Single Technology Appraisal

Daratumumab with bortezomib, lenalidomide and dexamethasone for untreated multiple myeloma when a stem cell transplant is unsuitable [ID3843]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Daratumumab with bortezomib, lenalidomide and dexamethasone for untreated multiple myeloma when a stem cell transplant is unsuitable [ID3843]

Contents:

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NICE National Institute for Health and Care Excellence

Daratumumab with bortezomib, lenalidomide and dexamethasone for untreated multiple myeloma when a stem cell transplant is unsuitable (ID3843)

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 30th January 2026. 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 recommendations sound and a suitable basis for guidance to the NHS? • are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation? 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):	Jonhson and Johnson Innovative Medicine (J&J)

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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.
Executive Summary	J&J welcome the opportunity to comment on the Draft Guidance Document (DGD) for daratumumab with bortezomib, lenalidomide and dexamethasone (DBLd) for untreated multiple myeloma when a stem cell transplant is unsuitable. J&J is disappointed with the draft guidance decision not to recommend DBLd which prevents patient access to a highly efficacious quadruplet regimen that indirect evidence demonstrates delivers significantly improved outcomes against current standard of care, daratumumab, lenalidomide and dexamethasone (DLd), and important uncaptured benefits because daratumumab can be delivered subcutaneously and is more convenient than some alternative treatments, such as isatuximab, that can only be delivered intravenously (DGD, page 18). There remains a significant unmet need for this generally elderly or frail patient population, often presenting with comorbidities, which DBLd has the potential to addresses; representing a novel treatment option that delivers deep, durable responses, and would be highly valued by both patients, caregivers and clinicians.

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	Following inclusion of all Committee-preferred assumptions, and addressing the Committee's request for additional analysis, DBLd remains dominant compared to DLd and isatuximab, bortezomib, lenalidomide and dexamethasone (IsaBLd), representing a cost-effective use of the NHS resources. J&J also acknowledge the potential uncertainties related to the evidence base noted by the Committee. As part of this response, the following uncertainties have been addressed: • **Comment 1: Evidence for the full CEPHEUS intention to treat (ITT) patient population** • **Comment 2: Uncertainty in the Indirect Treatment Comparison (ITC) methodology** • **Comment 3: Immaturity of CEPHEUS** • **Comment 4: Modelling overall survival: Implied HRs and alternative OS curves** • **Comment 5: Subsequent treatment distributions** Alongside the Comments above, the Company has also provided a revised base case which incorporates all of the Committee's preferred assumptions as outlined in the DGD (pages 17–18). A complete list of the changes made to the base case cost-effectiveness analysis, including the Committee-preferred assumptions, are presented in Appendix 1, with the revised base case results presented in Table 13 (probabilistic results) and Table 14 (deterministic results). A summary of the scenario analyses conducted by J&J as part of this response, including the scenario analyses conducted for the full ITT CEPHEUS population, is provided in Appendix 2, with the proportional hazards data from the network meta-analysis (NMA), requested by the Committee, presented in Appendix 3. Supportive clinical data from the CEPHEUS ITT population is further provided in Appendix 4. One factual inaccuracy identified within the DGD (page 18) is detailed in Appendix 5. Additional supporting information on the updated ITCs can be found in Appendix 6–Appendix 8. **There is limited uncertainty due to the robustness of evidence presented within the Company submission, Company addendum and this DGD response. Considering this minimal uncertainty alongside the unmet need, importance of reducing inequalities of treatment options capable of prolonged periods of remission compared with transplant eligible patients and uncaptured benefits, J&J consider that an ICER threshold towards the upper end of the NICE cost-effectiveness range to be appropriate.**

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	J&J are disappointed with the Committee's conclusion that "*an acceptable ICER would be towards the lower end of the range NICE considers a cost-effective use of NHS resources*" due to a "*high level of uncertainty*". Taking into account the disease burden and the unmet need for more efficacious treatments to treat NDMM (DGD, page 5–7), J&J consider that a willingness-to-pay threshold close to the upper end of the range normally considered cost-effective is appropriate for the following reasons: • Although J&J consider the CEPHEUS ITT analyses inappropriate for decision making, given the notably different populations, the impact on cost-effectiveness is minimal when using the DBLd ITT population in the ITCs (see **Comment 1** and Appendix 2.1), providing reassurance that this is not an area of uncertainty. • The rigorous and robust approach to the ITC methodology conducted against DLd (leveraging patient level data available from CEPHEUS and MAIA) and IsaBLd (extensive scenarios provided using NMAs and MAICs), detailed in **Comment 2**, demonstrates that this is not a key source of decision uncertainty. • CEPHEUS provides substantial follow-up of nearly 5 years, consistent with levels previously accepted by NICE in newly diagnosed multiple myeloma (NDMM; TA1098), detailed in **Comment 3**.[1] Additionally, any residual long-term uncertainty is addressed through calibration, ensuring that clinical plausibility is at the centre of decision making. • As detailed in **Comment 4**, the average modelled hazard ratios (HRs) from the independently fitted DBLd and DLd extrapolations for overall survival (OS) and progression-free survival (PFS) are more conservative than the ITC HRs across the model time horizon. This demonstrates a conservative OS modelling approach that mitigates the Committee's concerns about long-term survival uncertainty. • As detailed in **Comment 5**, the clinical expert-informed 2L/3L treatment distributions remain the most credible and up-to-date source to estimate subsequent treatment distributions, and any uncertainty has been robustly explored in scenario analysis (see Appendix 2.2). • J&J have also provided additional information on the ITC methodology versus IsaBLd to respond to "*uncertainty*" cited in the EAG critique on the Company Addendum, detailed in Appendix 8. In summary, J&J do not consider there to be high uncertainty in the evidence package for DBLd given the substantial follow-up provided in CEPHEUS, the rigorous and conservative approach to OS modelling, as well as the robust ITCs conducted against DLd and IsaBLd.

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	Given the unmet need, uncaptured health benefits of daratumumab and the additional evidence provided as part of this Draft Guidance response, J&J consider that an ICER threshold towards the upper end of the NICE cost-effectiveness range to be appropriate.
Comment 1	**Evidence for the full CEPHEUS ITT patient population (Section 3.6, 3.8, 3.9 and 3.15)** *"The committee concluded that it would like to see clinical evidence and economic analyses for the full CEPHEUS population alongside the ASCT-ineligible population."* *"It also recalled its previous conclusion that it would like to see scenario analyses using data from the whole CEPHEUS trial population."* *"The committee requested the following additional analyses: analyses that include the full trial population from CEPHEUS, alongside analyses for the ASCT-ineligible subpopulation updated based on committee preferences."* **At the Committee's request, J&J have provided clinical and cost-effectiveness results using the CEPHEUS ITT population against relevant comparators DLd and IsaBLd; however, this is not considered methodologically robust as they compare notably different populations and the results are less generalisable to the UK compared to the base-case ITC.** MAIA and IMROZ exclusively enrolled transplant-ineligible (TIE) patients, whereas the CEPHEUS ITT population includes both TIE and transplant-deferred (TD) patients. ITC methods such as inverse probability of treatment weighting (IPTW) and NMA rely on population similarity; therefore, including TD patients from CEPHEUS introduces heterogeneity and violates this assumption. **Characteristics of TIE vs TD patients in CEPHEUS** The TD patients in CEPHEUS are expected to have better outcomes than TIE patients as in the trial they were younger and fitter. This is shown in Table 1 which compares baseline characteristics of the TIE and TD patients. • **Age:** TD patients have a median age of [redacted] years, compared with 72 years for TIE patients • **Frailty:** [redacted]% of TD patients are classified as "fit," versus 59% in the TIE group • **Performance status:** ECOG 0 is observed in [redacted]% of TD patients compared with 38% of TIE patients

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These differences confirm that TD patients represent a younger and fitter population, who would be expected to have better outcomes than TIE patients, as they are more similar to a transplant-eligible (TE) cohort.

Table 1: Baseline characteristics for TIE and TD patients in CEPHEUS

Characteristic	TIE patients	TD patients
Age, years		
N	289	106
<65	4 (1.4%)	[redacted]
65–<70	66 (22.8%)	[redacted]
≥70	219 (75.8%)	[redacted]
Mean (SD)	[redacted]	[redacted]
Median	72.0	[redacted]
Range	[redacted]	[redacted]
Sex		
N	289	106
Female	142 (49.1%)	[redacted]
Male	147 (50.9%)	[redacted]
Race		
White	[redacted]	[redacted]
Black or African American	[redacted]	[redacted]
Asian	[redacted]	[redacted]
Native Hawaiian or other Pacific Islander	[redacted]	[redacted]
Other	[redacted]	[redacted]
Not reported	[redacted]	[redacted]
Baseline ECOG score		
0	109 (37.7%)	[redacted]
1	153 (52.8%)	[redacted]
2	27 (9.3%)	[redacted]
Total Additive (Frailty) Score		
Fit (score=0)	170 (58.8%)	[redacted]
Intermediate-fitness (score=1)	119 (41.2%)	[redacted]
ISS Stage		
I	98 (33.9%)	[redacted]
II	111 (38.4%)	[redacted]

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III	80 (27.7%)	[redacted]
Cytogenetic Risk		
Standard risk	216 (74.7%)	[redacted]
High risk	38 (13.1%)	[redacted]
Un-evaluable or missing	35 (12.1%)	[redacted]

Abbreviations: ECOG: Eastern Cooperative Oncology Group performance status; ISS: International Staging System; N: number of patients; SD: standard deviation; TD: transplant deferred; TIE: transplant ineligible.

TD patients in CEPHEUS

There were no UK patients recruited in the TD subgroup in CEPHEUS, reducing the generalisability of this population to UK clinical practice. UK clinical experts have also advised that they would very rarely (if ever) defer a patient for a transplant. Therefore, the ITT population (which includes 26% TD patients) disproportionately overrepresents this subgroup relative to UK clinical practice, limiting its relevance to UK decision making.

As seen in Table 2, in the CEPHEUS trial, Brazil and Poland recruited [redacted]% of TD participants. This differs to the TIE group where recruitment was generally well balanced between countries, with no single country providing more than [redacted]% of participants (Table 3).

Table 2: Countries of recruitment for TD patients in CEPHEUS

Region/Country	BLd (n=53)	DBLd (n=53)	Total (n=106)
Europe Region			
France	[redacted]	[redacted]	[redacted]
Israel	[redacted]	[redacted]	[redacted]
Netherlands	[redacted]	[redacted]	[redacted]
Poland	[redacted]	[redacted]	[redacted]
Spain	[redacted]	[redacted]	[redacted]
Turkey	[redacted]	[redacted]	[redacted]
Europe Region Total	[redacted]	[redacted]	[redacted]
North America			
Canada	[redacted]	[redacted]	[redacted]
United States	[redacted]	[redacted]	[redacted]
North America Total	[redacted]	[redacted]	[redacted]
Other			
Brazil	[redacted]	[redacted]	[redacted]
Japan	[redacted]	[redacted]	[redacted]
Other Total	[redacted]	[redacted]	[redacted]

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Abbreviations: BLd: bortezomib, lenalidomide, dexamethasone, DBLd: daratumumab, bortezomib, lenalidomide, dexamethasone; TD: transplant deferred.

Table 3: Countries of recruitment for TIE patients in CEPHEUS

Region/Country	BLd (n=145)	DBLd (n=144)	Total (n=298)
Europe Region			
Czech Republic	[redacted]	[redacted]	[redacted]
France	[redacted]	[redacted]	[redacted]
Germany	[redacted]	[redacted]	[redacted]
Israel	[redacted]	[redacted]	[redacted]
Netherlands	[redacted]	[redacted]	[redacted]
Poland	[redacted]	[redacted]	[redacted]
Spain	[redacted]	[redacted]	[redacted]
Turkey	[redacted]	[redacted]	[redacted]
United Kingdom	[redacted]	[redacted]	[redacted]
Europe Region Total	[redacted]	[redacted]	[redacted]
North America			
Canada	[redacted]	[redacted]	[redacted]
United States	[redacted]	[redacted]	[redacted]
North America Total	[redacted]	[redacted]	[redacted]
Other			
Brazil	[redacted]	[redacted]	[redacted]
Japan	[redacted]	[redacted]	[redacted]
Other Total	[redacted]	[redacted]	[redacted]

Abbreviations: BLd: bortezomib, lenalidomide, dexamethasone; DBLd: daratumumab, bortezomib, lenalidomide, dexamethasone; TIE: transplant ineligible.

Brazil and Poland were regions heavily impacted by the COVID-19 pandemic with many of these patients experiencing higher mortality unrelated to disease biology, driven by pandemic-related healthcare disruptions in these countries (see Section 2.10.2 in the original Company submission). There were [redacted] COVID-19 deaths in the DBLd TD arm (representing [redacted]% of total DBLd TD deaths) with all but [redacted] occurring in Brazil and Poland (see Table 4).

In addition to the direct impact of COVID-19 on the TD subgroup, the high proportion of patients recruited from Brazil ([redacted]%) limits the generalisability of this cohort to the UK. Notably, the Brazilian healthcare system offers fewer treatment options for multiple myeloma compared to the UK, driven by slower access to newer, expensive therapies. While private healthcare in Brazil has better access, significant disparities exist between public and private

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sectors with the public sector largely reliant on older foundational drugs like thalidomide and bortezomib. The disruption in the Brazilian healthcare system during the pandemic also likely led to delays and interruptions in cancer services that may have adversely affected patient care, treatment delivery, and outcomes for patients. Considering the high levels of recruitment in Brazil, the CEPHEUS trial results for the TD subgroup are less generalisable to the UK, compared to the TIE subgroup.

Table 4: Total and COVID-19-related deaths occurring in TD patients in CEPHEUS

	DBLd	BLd
Total deaths	[redacted]	[redacted]
COVID-19 deaths	[redacted]	[redacted]
Country of COVID-19 death		
Poland	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted] [redacted]	[redacted]	[redacted]
Brazil	[redacted]	[redacted]

Abbreviations: BLd: bortezomib, lenalidomide, dexamethasone; DBLd: daratumumab, bortezomib, lenalidomide, dexamethasone; TD: transplant deferred.

Comparison vs DLd:

In line with the Committee's preferred assumption, the base case ITC versus DLd uses IPTW to reweight patients and balance baseline characteristics between treatment arms. This method assumes that the populations being compared are conceptually aligned in terms of treatment intent and eligibility criteria and that all potentially relevant confounding factors are commonly available in the populations being compared. As a first step and key consideration in planning an ITC, the populations being compared should be aligned on the key clinically relevant eligibility criteria. Here, that necessitates excluding CEPHEUS TD patients, as MAIA, by design, did not enrol TD patients.

The TD patients in CEPHEUS were eligible for transplant but deferred for non-biological reasons (e.g. physician or patient choice). Because MAIA contains no TD patients, any prognostic differences associated with transplant deferral cannot be adjusted for if TD patients are included. As such, including TD patients in the IPTW analysis would introduce structural confounding because transplant eligibility reflects a different population and would therefore bias results due to underlying population heterogeneity, driven by the misalignment of eligibility criteria.

Although it is inappropriate to use the ITT population from CEPHEUS to compare against TIE patients in MAIA, at the Committee's request, J&J have provided results from an updated IPTW ITC comparing DBLd to DLd. The ITC follows the same approach as in the original

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company submission and additional supporting information can be found in Appendix 6. After reweighting, the SMD are close to 0, demonstrating that balance between arms has been achieved, see Figure 15 in Appendix 6. However, the balance achieved after reweighting does not extend to all clinically relevant characteristics: as highlighted above, it is not possible to balance for transplant deferral and it remains a potential source of residual confounding.

OS

When adjusting for COVID-19 (as per the base case), the DBLd ITT population (which includes TD patients) reduced the risk of death by [redacted]% (HR: [redacted], 95% CI: [redacted] p=[redacted]). These results are broadly consistent with the initial ITC results using the TIE patients in CEPHEUS presented in the original Company submission (HR: 0.63. 95% CI: 0.41-0.98; p=0.04).

PFS

Similar to OS, the PFS results for the ITT population (which includes TD patients) are highly consistent with those for the TIE population. When adjusting for COVID-19 (as per the base case), the DBLd ITT population reduced the risk of disease progression or death by [redacted]% (HR: [redacted], 95% CI: [redacted]; p=[redacted]). These results are comparable to a 45% reduction in the risk of disease progression or death for the ITC results using the TIE patients in CEPHEUS, as presented in the original Company submission (HR: 0.55, 95% CI: 0.38-0.79; p=0.001).

TTD

The time-to-treatment discontinuation (TTD) results for the ITT population (which includes TD patients) are highly consistent with the results using the TIE population. When adjusting for COVID-19 (as per the base-case), the DBLd ITT population reduced the risk of treatment discontinuation or death by [redacted]% (HR: [redacted], 95% CI: [redacted]; p=[redacted]). These results are comparable to a [redacted]% reduction in the risk of treatment discontinuation or death for the ITC results using the TIE patients in CEPHEUS, as presented in the original Company submission (HR: [redacted], 95% CI: [redacted]; p=[redacted])

Clinical summary

Whilst J&J do not consider this an appropriate analysis, as detailed earlier in this response, the PFS, OS and TTD results from the ITT population in CEPHEUS are consistent with the initial ITC results based on the TIE population. This consistency demonstrates that the results are robust and not a source of uncertainty. The Kaplan-Meier (KM) plots for OS, PFS and TTD for the ITT population in CEPHEUS, adjusted for COVID-19, are presented in Figure 12–Figure 14 in Appendix 4.

Moreover, as noted above, results including the TD subgroup are less generalisable to UK clinical practice considering the high levels of recruitment in Brazil and the composition of the ITT population, which consists of 74% TIE and 26% TD patients. In the UK, eligible patients

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would very rarely defer a transplant, making this population mix unrepresentative of routine clinical practice.

Cost-effectiveness results

As requested by the Committee, J&J have also provided updated cost-effectiveness results which compare DBLd in the full CEPHEUS ITT population to DLd. In these results, the base-case assumes the Company's original patient characteristics, as it is not appropriate to increase the age to 75 years, considering TD patients in CEPHEUS are much younger, as per Table 1.

The cost-effectiveness results for DBLd in the full CEPHEUS ITT population compared with DLd are presented in Table 15 of Appendix 2.1. The results are broadly similar to the original results in the TIE population, demonstrating that this is not an area of material uncertainty. However, J&J maintain that this approach is inappropriate due to the fundamental differences in patient populations, and that the resulting bias cannot be adequately addressed using an IPTW ITC. Moreover, this approach is not suitable for UK decision making given that around 26% of patients in CEPHEUS were TD (per Table 1) compared with a very small proportion in UK clinical practice and the high levels of recruitment from Brazil.

Comparison vs IsaBLd

In line with the Committee's preferred assumption, the base-case ITC versus IsaBLd is the NMA. A fundamental assumption underpinning NMAs is that the populations across contributing trials are sufficiently comparable. As described above, TD patients differ from TIE patients in baseline characteristics and prognosis. Consequently, including TD patients from CEPHEUS but using only TIE patients in IMROZ, violates the assumption of cross-trial comparability, introduces population heterogeneity, and biases the treatment effect estimates.

In addition, as outlined earlier, TD patients in CEPHEUS experienced a disproportionate negative impact of COVID-19 due to patient recruitment concentrating in Brazil and Poland. Comparing non-COVID-adjusted outcomes for DBLd from CEPHEUS with IsaBLd therefore introduces further bias. However, in line with the Committee's request, J&J have provided updated ITC results comparing DBLd in the ITT population to the TIE population in IMROZ.

NMA Results

J&J consider the results adjusted for COVID-19 more appropriate when comparing the ITT population in CEPHEUS to IsaBLd due to the disproportionate negative impact of COVID-19 on the TD group in CEPHEUS. Across the NMA results presented, there is overall broad consistency with the TIE results from the original NMA.

Table 5 shows the PFS and OS results (adjusted for COVID-19) of the ITT DBLd population compared with IsaBLd. A consistent numerical benefit in favour of DBLd can be seen across

both OS and PFS in the fixed effects (FE) and random effects (RE) model results. Details of the DIC fits are provided in Table 25 in Appendix 8.

Table 5: DBLd ITT population vs IsaBLd NMA results for OS (adjusted for COVID-19) and PFS (adjusted for COVID-19)

DBLd vs IsaBLd HR (95% CrI)	Fixed effects model	Random effects model
OS	[redacted]	[redacted]
PFS	[redacted]	[redacted]

Abbreviations: CrI: credible interval; DBLd: daratumumab, bortezomib, lenalidomide, and dexamethasone; HR; hazard ratio; IsaBLd: isatuximab, bortezomib, lenalidomide, and dexamethasone; ITT: intention-to-treat; NMA: network meta-analysis; OS: overall survival; PFS: progression-free survival.

Table 6 shows the PFS and OS results (unadjusted for COVID-19) of the ITT DBLd population compared with IsaBLd. As detailed earlier, these results are heavily biased against DBLd due to the disproportionate impact of COVID-19 on TD patients in CEPHEUS and the TD group in CEPHEUS representing ~26% of patients compared with negligible numbers in UK clinical practice, and are therefore considered inappropriate to use for decision making.

Table 6: DBLd ITT population vs IsaBLd NMA results for OS (unadjusted for COVID-19) and PFS (unadjusted for COVID-19)

DBLd vs IsaBLd HR (95% CrI)	Fixed effects model	Random effects model
OS	[redacted]	[redacted]
PFS	[redacted]	[redacted]

Abbreviations: CrI: credible interval; DBLd: daratumumab, bortezomib, lenalidomide, and dexamethasone; HR; hazard ratio; IsaBLd: isatuximab, bortezomib, lenalidomide, and dexamethasone; ITT: intention-to-treat; NMA: network meta-analysis; OS: overall survival; PFS: progression-free survival.

An additional NMA was conducted excluding patients recruited from Brazil and Poland. This supplementary analysis was undertaken because a high proportion of TD patients in CEPHEUS were recruited from these countries, and experienced a disproportionate negative impact of COVID-19, whereas IMROZ did not include comparable recruitment (notably, no patients were recruited from Brazil, the country most affected by COVID-19 within the TD population of CEPHEUS).[2] The resulting estimates (Table 7) are broadly consistent with those from the adjusted analyses, indicating that when the TD group is considered, this adjusted NMA provides a more appropriate comparison than the unadjusted for COVID-19 analysis, which is heavily biased against DBLd.

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Table 7: DBLd ITT population vs IsaBLd NMA results for OS (excluding patients from Brazil/Poland) and PFS (excluding patients from Brazil/Poland)

DBLd vs IsaBLd HR (95% CrI)	Fixed effects model	Random effects model
OS	[redacted]	[redacted]
PFS	[redacted]	[redacted]

Abbreviations: CrI: credible interval; DBLd: daratumumab, bortezomib, lenalidomide, and dexamethasone; HR; hazard ratio; IsaBLd: isatuximab, bortezomib, lenalidomide, and dexamethasone; ITT: intention-to-treat; NMA: network meta-analysis; OS: overall survival; PFS: progression-free survival.

MAIC results.

For completeness, J&J have also updated the results of the MAIC comparing the DBLd ITT population with IsaBLd; however, J&J agree with the Committee that the NMA should be considered as the appropriate base-case analysis. The covariates and methods for the MAIC are the same as described in the initial company addendum. Full details of the matching are provided in Appendix 7.

The results are broadly consistent to the original MAIC (see Table 8). As this analysis does not adjust for COVID-19, J&J maintain that it does not represent a fair comparison. The results are confounded by the disproportionate impact of COVID-19 on the TD patients in CEPHEUS, as well as by the mismatch in populations.

Table 8: Summary of MAIC results for DBLd (ITT population) versus IsaBLd

	PFS, HR (95% CI)	OS, HR (95% CI)
Base case MAIC	[redacted]	[redacted]
Sensitivity analysis MAIC	[redacted]	[redacted]

Abbreviations: CI: confidence interval; HR: hazard ratio; MAIC: matching-adjusted indirect comparison; OS: overall survival; PFS: progression-free survival.

Cost-effectiveness results

Despite J&J's concerns with the requested analysis noted above, for completeness and as requested by the Committee, J&J have provided updated cost-effectiveness results which compare DBLd in the full CEPHEUS ITT population with IsaBLd using the NMA in the COVID-19 unadjusted and adjusted analyses and the results which exclude Brazil/Poland in Table 16–Table 18 of Appendix 2.1.

Conclusion

To ensure methodological rigour and a fair comparison, only TIE patients from CEPHEUS should be included in ITCs and cost-effectiveness analyses versus MAIA and IMROZ, in line with the TIE inclusion criteria of the comparator trials. Including the broader ITT population from CEPHEUS, which encompasses TD patients, introduces population heterogeneity and

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	reduces generalisability to the UK. This is due to the disproportionate mix of TD versus TIE patients compared with UK clinical practice-where transplant deferral is uncommon-as well as the high level of recruitment from Brazil, where pandemic-related healthcare disruptions likely affected patient management and outcomes. The clinical and cost-effectiveness results presented in this response using the CEPHEUS ITT population are therefore provided solely for completeness at the Committee's request. J&J consider that the original TIE-based results are the appropriate basis for decision-making, as they ensure alignment between the populations of the intervention and comparator treatments.
Comment 2	**Uncertainty in the ITC methodology (Section 1.2 and 3.13)** *"There are uncertainties in the economic model, including: how the indirect comparisons with usual treatment have been undertaken."* *"The committee noted the high level of uncertainty, specifically: uncertainties in the ITC approaches."* **J&J have conducted extensive ITCs and sensitivity analyses, fully detailed in the Company submission, that confirm the robustness of the methods and consistency of results, demonstrating that this is not a key source of decision uncertainty.** J&J have provided full and comprehensive details on the various ITCs conducted that demonstrate their methodological robustness and appropriateness to support decision making. For the comparison against DLd, the availability of IPD from CEPHEUS and MAIA facilitated a robust IPTW ITC to be conducted, which demonstrated statistically significant and clinically meaningful benefits of DBLd versus the main comparator, DLd. Additionally, the results from the ITC were consistent across a range of sensitivity analyses exploring alternative prognostic variables, removal of COVID-19 adjustment, ITC methodologies and a supportive NMA. For the comparison against IsaBLd, J&J explored both NMAs and alternative ITC methods (which also included sensitivity analyses). Detailed information on the ITC methods can be found in the following parts of the Company documents: • Section 2.10.2 of the original Company submission provides comprehensive details on the ITC methodology and consistency of results across alternative methods • Clarification Questions A5 provides more details on the alternative ITC approaches • Appendix M of the Company submission and Clarification Questions A6-A12 provide comprehensive details of the NMA methodology and an NMA report • Section 2.2–2.3 of the Company Addendum provides details of the ITC against IsaBLd for the NMA and MAIC

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	In addition, as part of this Draft Guidance response, J&J have provided additional information to reduce any remaining uncertainty in the ITCs: • Proportional hazards tests from the NMA are presented in Appendix 3, as requested by the Committee • Further details on the ITC methodology versus IsaBLd in response to "*uncertainty*" cited in the EAG critique on the Company Addendum, presented in Appendix 8
Comment 3	**Immaturity of CEPHEUS (Section 1.2 and 3.4)** *"There are uncertainties in the economic model including: the estimates of how long people live and how long they have before their condition gets worse, because the trial data is immature."* *"The committee concluded that Dar-Bor-Len-Dex may be an effective treatment option for untreated multiple myeloma when an ASCT is unsuitable. But it noted the data from the trial was immature and did not compare Dar-Bor-Len-Dex with the relevant comparators, so the PFS and OS results were uncertain"* **CEPHEUS provides close to 5 years of follow-up, providing mature phase III randomised controlled trial (RCT) evidence which is consistent with previous trials in the NDMM disease area.** J&J acknowledge the Committee's view that survival data from CEPHEUS may be immature given that median OS and PFS were not reached; however, CEPHEUS provides substantial follow-up (median follow-up, ~58.7 months), which is consistent with other first-line NDMM trials. For instance, IMROZ reported a comparable median follow-up (~59.7 months), with medians also not reached; nevertheless, as part of TA1098, those results were deemed suitable for decision making by the Committee.[1] Additionally, in the first-line setting, where highly effective therapies such as DBLd drive high rates of MRD negativity and sustained MRD negativity with the potential for functional cure, it is inherently challenging to observe mature median OS and PFS within five years. Therefore, a substantially longer follow-up is typically required before medians emerge – this is an inherent and unavoidable feature of MM rather than a limitation of the clinical evidence. Crucially, the economic model addresses this long-term uncertainty conservatively through calibration: the statistically best-fitting PFS and OS curves for DBLd and DLd are intentionally attenuated to align with UK clinical experts' 10-, 15-, and 20-year survival expectations. By anchoring projections to expert-validated long-term estimates, this approach materially reduces reliance on extrapolation and de-risks long-term modelling uncertainty, ensuring that clinical plausibility is at the centre of decision making.

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Comment 4	**Modelling overall survival: Implied HRs (Section 3.9)** *"It also noted that for independently fitted extrapolations, it would like to see the plot of the implied hazard ratio between the modelled arms over time."* **The implied HRs between the Company's independently fitted DBLd and DLd extrapolations are more conservative than the ITC HRs for both PFS and OS, thereby reducing decision-making uncertainty in long-term survival projections.** As outlined in Comment 3, the base case model applies a calibration approach to ensure clinical face validity in the extrapolation of OS and PFS. The statistically best-fitting curves for DBLd and DLd are deliberately attenuated over time so that long-term survival aligns with estimates provided by UK clinical experts at the May 2025 Advisory Board.[3] This ensures consistency of approach across endpoints for both treatment arms and provides reassurance that long-term projections remain clinically plausible. In response to the Committee's request, plots of the implied HRs between the independently fitted DBLd and DLd extrapolations for OS and PFS have been generated (Figure 1 and Figure 2). Due to the calibration approach, the implied HR varies across 5-year increments, with time-varying hazard multipliers applied to each arm after Year 5 (and after Year 7 for DLd OS), in line with expert input. Despite this variation, the average implied HRs remain less favourable, and therefore more conservative, than the HRs derived from the ITC across the full model time horizon. This demonstrates that the calibrated OS approach is inherently conservative and materially reduces uncertainty in long-term survival estimates. **Figure 1: Implied HR between DBLd and DLd modelled OS extrapolations over model time horizon: with calibration**  **Footnote:** Plots are based on the Committee's preferred baseline assumptions: 75 years and 55% male. **Abbreviations:** DBLd; daratumumab, bortezomib, lenalidomide and dexamethasone; DLd; daratumumab, lenalidomide; HR: hazard ratio; OS: overall survival.

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Figure 2: Implied HR between DBLd and DLd modelled PFS extrapolations over model time horizon: with calibration

Footnote: Plots are based on the Committee's preferred baseline assumptions: 75 years and 55% male.
Abbreviations: DBLd; daratumumab, bortezomib, lenalidomide and dexamethasone; DLd; daratumumab, lenalidomide; HR: hazard ratio; OS: overall survival.

To better illustrate this, Table 9 presents a side-by-side comparison of the average implied HRs for PFS and OS over the first 20 years of the model versus the ITC-derived HRs. Across the full model time horizon, the implied HRs are less favourable than those from the ITC, providing reassurance that the calibration approach is conservative, reducing concern regarding long-term survival modelling uncertainty.

Table 9: Comparison of the base case ITC HRs and the average implied HRs over 20 years between DBLd and DLd

	Base case ITC HRs	Average modelled HRs over 20 years
PFS	0.55	[redacted]
OS	0.63	[redacted]

Abbreviations: DBLd; daratumumab, bortezomib, lenalidomide and dexamethasone; DLd; daratumumab, lenalidomide; HR: hazard ratio; ITC: indirect treatment comparison; OS: overall survival; PFS: progression-free survival.

Modelling overall survival: Alternative OS curves (Section 3.9 and 3.15)

"The committee concluded that, overall, the model was acceptable for decision making, but it recalled median OS and PFS were not reached in the CEPHEUS trial, so it would like to see scenario analyses exploring the use of alternative baseline OS curves with relative treatment effects applied. For example, using Systemic Anti-Cancer Therapy (SACT) data for Dar-Len-Dex as the baseline OS curve and the relevant hazard ratio applied to that."

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"The committee requested the following additional analyses: an exploration of different baseline OS curves used in the model"

Using the SACT dataset as an alternative data source for DLd OS would introduce additional, unquantifiable uncertainty due to the inherent immaturity of the available RWE.

J&J were unable to explore a scenario using SACT data to inform the baseline OS curve for DLd due to the unavailability of this dataset. Regardless, J&J consider that these data would remain too immature, reflecting only around two years of DLd follow-up since its NICE recommendation in September 2023 (TA917), to meaningfully reduce uncertainty in long-term survival modelling.[4] By contrast, the base case model uses mature OS data from MAIA, with nearly eight years of follow-up (median 89.3 months), providing a more robust and reliable foundation for characterising DLd's long-term survival profile.

In the absence of SACT data, and to further assess any uncertainty in the survival modelling, J&J compared the base case OS and PFS extrapolations for DLd with the Committee's preferred assumptions from TA917 (Table 10).[4] At 10 years, DLd PFS and OS in the model closely align with those assumptions. Beyond 10 years, the model's DLd OS projections become more optimistic than the TA917 assumptions, indicating that the extrapolations may overpredict long-term DLd survival. This confirms that the modelled DLd survival estimates are conservative and appropriate for decision-making, as they do not underestimate long-term benefit and provide a cautious basis for comparative cost-effectiveness.

Table 10: Comparison of OS and PFS extrapolations for DLd: TA917 Committee-preferred assumptions versus base case

Year	DLd: Committee-preferred assumptions from TA917[4]	DLd in CEPHEUS (Updated base case with Age = 75)
OS		
10	[redacted]	39.5%
15	[redacted]	19.9%
20	[redacted]	4.3%
PFS		
10	[redacted]	32.3%
15	[redacted]	14.9%
20	[redacted]	3.0%

Abbreviations: DLd; daratumumab, lenalidomide; OS: overall survival; PFS: progression-free survival; TA: technology appraisal.

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	In the absence of SACT data or a suitable alternative, J&J has been unable to explore use of an alternative baseline OS curve for DLd as suggested by the Committee. We note, however, that it would be inappropriate to apply a HR to the DLd baseline OS curve considering the violation of proportional hazards between DBLd and DLd as presented in the original Company submission (Appendix N). Thus, J&J maintain that the base case approach to modelling OS is the most appropriate and is one that places clinical plausibility at the centre of decision making. **Exploration of additional scenarios in the CEM** To explore any residual uncertainty in the OS modelling approach, J&J conducted an additional OS scenario using the second-best statistically fitting curves for OS (lognormal DBLd and Gompertz DLd). The results from this scenario analysis are presented in Table 19 in Appendix 2.2 and show that DBLd remains dominant to DLd. In summary, the current OS modelling approach is robust, leveraging relatively mature, trial-based evidence and established adjustment methods. Using SACT data as an alternative data source for DLd OS would introduce additional, unquantifiable uncertainty due to the inherent immaturity of the available RWE.
Comment 5	**Subsequent treatment distributions (Section 1.2, 3.12 and 3.15)** *"There are uncertainties in the economic model, including: the proportion of subsequent treatments offered in the NHS."* *"The committee concluded that the distributions of subsequent treatments at second and third line were uncertain, so it requested more evidence to demonstrate what would be expected in NHS practice and validation of the distributions used. This may include using SACT data to inform the proportion of subsequent treatments, particularly selinexor use at third line."* *"The committee requested the following additional analyses: more evidence to validate the distribution of second- and third-line treatments"* **In a rapidly evolving MM treatment landscape, the clinical expert-informed 2L/3L treatment distributions are the best available source of evidence to inform the base case; however, J&J have explored alternative subsequent treatment distributions to reduce decision-making uncertainty** J&J acknowledge the Committee's view that the second- and third-line (2L/3L) treatment distributions within the economic analysis are uncertain. As set out in the Company

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	submission (Section 3.5.1), the base case distributions were informed by treatment share estimates from five UK haematologists via an advisory board in May 2025.[3] The UK MM treatment landscape is evolving rapidly, with new treatments emerging across various lines of therapy. Given the extended median PFS observed with first-line regimens, there is inevitably a lag before robust real-world data on subsequent treatment patterns emerge. In MAIA, the median PFS with DLd was 61.9 months, and is expected to be even longer for DBLd as a quadruplet.[4] DLd was only recommended by NICE in 2023,[4] so most patients who received DLd at first-line will not yet have progressed. Consequently, there is currently no robust dataset that can inform UK subsequent treatment distributions after these regimens. This is compounded by recent changes to the treatment landscape, such as the reimbursement of belantamab mafodotin plus bortezomib (BeBd) at 2L in June 2025, for which there are limited data on real-world use, and use would be expected to increase over time as clinicians become more familiar managing associated AEs with this treatment.[5] In this context, clinical expert opinion is the most credible and up-to-date source to estimate subsequent treatment distributions following DLd, IsaBLd and DBLd in UK clinical practice, and therefore represents the best available evidence to inform this appraisal. In contrast to the Company's subsequent treatment distributions, the EAG's preferred distribution of 2L treatments is not clinically plausible or allowed per NICE guidance. The EAG estimated that 3–5% of patients would receive carfilzomib, lenalidomide and dexamethasone (CLd) after progressing on DLd, with 4% specified in their base case. However, the final NICE guidance for CLd specifies it is recommended if a patient has had only 1 prior line of therapy which includes bortezomib, and therefore it cannot be given after DLd.[6] Additionally, patients would likely be lenalidomide refractory after progressing on DLd/DBLd/IsaBLd, making treatment with a further lenalidomide containing regimen at 2L implausible. **Alternative subsequent treatment scenarios** J&J have explored additional evidence to understand subsequent treatments and have provided IQVIA market research data (from online surveys) to inform subsequent treatment distribution. This research was conducted in waves from each quarter of 2025 (with the Q4 research being completed between 10 September–27 October 2025).[7] Figure 3 shows the 2L treatment distribution for each quarter since BeBd was recommended by NICE in June 2025, for patients who have received both an anti-CD38 and lenalidomide at 1L. The data shows that the proportion of BeBd usage has increased quarter-on-quarter and would be expected to continue to increase in future months. The distribution of treatments at 2L for the most recent wave, only including treatments recommended and available at 2L, is shown in Table 11 below.

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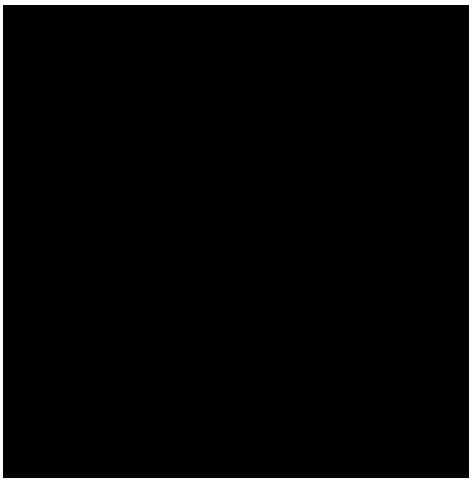
Due to the small sample size, it was not possible to derive a meaningful split for 3L treatments as there are only a very small number of patients who have progressed on DLd and a 2L therapy.

Figure 3: Market research treatment distributions at 2L for patients receiving both an anti-CD38 and lenalidomide at 1L (2025 Q2–Q4)



Source: J&J. Data on File. IQVIA Market Research. January 2026.[7]

Table 11: Market research treatment distributions at 2L, including only treatments NICE recommended and available at 2L in the UK (2025 Q4)

Treatment	Proportion
Cd	[redacted]
Selinexor combination	[redacted]
BeBd	[redacted]
Bd	[redacted]

Abbreviations: Bd: bortezomib and dexamethasone; BeBd: belantamab, bortezomib, and dexamethasone; Cd: carfilzomib and dexamethasone.
Source: J&J. Data on File. IQVIA Market Research. January 2026.[7]

In addition, J&J have also reviewed recent NHS pharmacy/ePrescribing datasets (VSTx) showing overall patient share in England at 2L.[8] These numbers were based on the latest data and evidence-based assumptions that were available at the time of analysis, Dec 2025. The VSTx dataset reflects all prevalent patients rather than new patient share, so it does not accurately reflect recent uptake, and it does not distinguish 2L treatments based on the 1L treatment previously received. However, when limiting the data to treatments allowed after DLd, the data shows rapid growth in BeBd use since funding approval, increasing from [redacted] patients in June to [redacted] patients in September (Table 12). This suggests that new patients

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initiating on BeBd at 2L are rising, while market share for other post-DLd options (Cd, SBd, and bortezomib) remain stable or are declining.

The VSTx dataset did not show 3L splits for treatments that would be received following DLd.

Table 12: Prevalent patient share in England at 2L based on the VSTx dataset

Treatment	June 25	July 25	August 25	Sep 25
Cd	[redacted]	[redacted]	[redacted]	[redacted]
SBd	[redacted]	[redacted]	[redacted]	[redacted]
BeBd	[redacted]	[redacted]	[redacted]	[redacted]
Bd/bortezomib	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: Bd; bortezomib and dexamethasone, BeBd; belantamab, bortezomib, and dexamethasone, Cd; carfilzomib and dexamethasone, SBd; selinexor, bortezomib, and dexamethasone.
Source: J&J. Data on File. VSTx dataset.[8]

Exploration of additional scenarios in the CEM

To reduce any residual uncertainty associated with subsequent treatments, J&J have explored additional modelling scenarios. These use the Committee preferred assumptions for baseline characteristics and proportion receiving 2L therapy.

- **Scenario 1**
  - **2L**: Based on the VSTx dataset and internal market research data, BeBd usage is rising in each month and quarter. To test uncertainty, in this scenario, the BeBd usage at 2L has been estimated at 50% with other shares reweighted across other treatments in the Company base case (SBd=12.4%, Cd=37.6%)
  - **3L**: There are limited data available at 3L, but in this scenario the SBd share has been reduced to 30%, increasing the shares of PBd and cyclophosphamide, respectively (cyclophosphamide = 49.05%, PBd=20.95%). Although the selinexor share for this scenario has been arbitrarily selected, it demonstrates the low uncertainty and limited impact of 3L treatments on the cost-effectiveness results.
- **Scenario 2**
  - **2L**: A more conservative scenario where market shares at 2L are aligned with the VSTx dataset (Cd=[redacted]%, SBd=[redacted]%, BeBd=[redacted]%, Bd=[redacted]%). This scenario heavily underestimates BeBd usage as the VSTx reports on prevalent patients rather than new patient uptake and does not distinguish 2L treatments based on the 1L regimen previously receievd
  - **3L**: This scenario reduces SBd share to 20% and increases the shares of PBd and cyclophosphamide respectively (cyclophosphamide= 56.1%, PBd=23.9%). As with scenario 1, although the selinexor share has been arbitrarily selected, it

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	demonstrates the low uncertainty and limited impact of 3L treatments on cost-effectiveness. These scenario results are presented in Table 19 and Table 20 in Appendix 2.2 and show the impact of alternative subsequent treatment distribution on the ICERs at list price. J&J expect the impact on the ICER to be lower when the actual (with PAS) price of subsequent treatments are considered, providing reassurance that the modelling of subsequent treatments represents a minimal source of uncertainty. J&J note the Committee's suggestion to use SACT data to inform subsequent treatment distributions. Even if SACT data were available, these results would be unlikely to be suitable for informing 2L/3L distributions due to immaturity and outdated practice patterns: • For DLd, SACT data would capture at most ~2 years of follow-up (see Comment 4), meaning few patients would have progressed to 2L within the SACT dataset[4] • For IsaBLd, given its recent introduction in UK practice, the SACT dataset would be unlikely to contain meaningful subsequent treatment data • Importantly, patients progressing in 2023–2024 within the SACT dataset would reflect a pre-2025 landscape and would not capture the impact of recent reimbursements, such as BeBd, limiting its applicability to current UK practice Accordingly, the SACT dataset would be of limited relevance for estimating subsequent treatment distributions following first-line triplet/quadruplet regimens at this time. In summary, J&J consider the expert-informed distributions to be the most appropriate reflection of current UK practice, with the clinical experts at the Committee meeting broadly aligning with these distributions. To test any uncertainty, J&J have explored multiple scenarios changing the subsequent treatment distribution using insights from internal market research and the VSTx dataset. As detailed above, both subsequent treatment scenarios represent highly conservative scenarios, given that BeBd usage is expected to increase rapidly in UK clinical practice. Of note, the model applies the same 2L/3L distributions to the DBLd, IsaBLd and DLd arms; therefore, no differential relative effects are anticipated to be introduced from these assumptions, with UK clinical experts confirming that it is appropriate to assume identical subsequent treatment distributions for these therapies at 2L/3L.[3]

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Appendices

Appendix 1. Committee-preferred assumptions applied in the cost-effectiveness analysis and updated Company base case

J&J have provided a revised Company base case which incorporates all of the Committee's preferred assumptions as outlined in the DGD (pages 17–18):

- Including DLd and IsaBLd as relevant comparators
- Using an IPTW ITC to inform the clinical effectiveness of the DLd comparison, and an NMA to inform the clinical effectiveness of the IsaBLd comparison
- Baseline characteristics in the model of 75 years and 55% male
- 75% of people in the model go on to have subsequent treatment after DBLd and IsaBLd

The revised base case results, including the Committee-preferred assumptions are presented in Table 13 (probabilistic results) and Table 14 (deterministic results).

Following inclusion of all Committee-preferred assumptions, DBLd remains dominant compared with DLd and IsaBLd, representing a cost-effective use of the NHS resources.

Table 13: Probabilistic DGD response base- case results (discounted daratumumab price)

Intervention	Total Costs	Total QALYs	Incremental Costs	Incremental QALYs	ICER	Incremental NHB at £20,000	Incremental NHB at £30,000
DBLd	[redacted]	[redacted]					
DLd	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]	[redacted]

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Intervention	Total Costs	Total QALYs	Incremental Costs	Incremental QALYs	ICER	Incremental NHB at £20,000	Incremental NHB at £30,000
IsaBLd	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]	[redacted]

Abbreviations: DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; DLd: daratumumab, lenalidomide and dexamethasone; ICER: incremental cost-effectiveness ratio; IsaBLd: isatuximab, bortezomib, lenalidomide and dexamethasone; LYs: life years; NHB: net health benefit; QALYs: quality-adjusted life years.

Table 14: Deterministic DGD response base- case results (discounted daratumumab price)

Intervention	Total Costs	Total QALYs	Incremental Costs	Incremental QALYs	ICER	Incremental NHB at £20,000	Incremental NHB at £30,000
DBLd	[redacted]	[redacted]					
DLd	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]	[redacted]
IsaBLd	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]	[redacted]

Abbreviations: DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; DLd: daratumumab, lenalidomide and dexamethasone; ICER: incremental cost-effectiveness ratio; IsaBLd: isatuximab, bortezomib, lenalidomide and dexamethasone; LYs: life years; NHB: net health benefit; QALYs: quality-adjusted life years.

Appendix 2. Summary of scenario analyses in the DGD response

Appendix 2.1 Scenario analyses using the full CEPHEUS ITT population

As requested by the Committee, J&J have provided updated cost-effectiveness results which compare DBLd in the full CEPHEUS ITT population to DLd and IsaBLd. In these results, the scenarios assume the Company's original patient baseline characteristics, as it is not appropriate to increase the age to 75 years, considering TD patients in CEPHEUS are much younger, as outlined in detail in Comment 1. However, these scenario analyses assume the Committee-preferred proportion of patients receiving 2L therapy after DBLd and IsaBLd (75%).

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The cost-effectiveness results for DBLd in the full CEPHEUS ITT population compared with DLd are presented in Table 15. The curve choice follows the same approach as the original Company submission, with the best statistically fitting curve chosen and calibrated to long-term projections with UK clinical experts' estimates. In this scenario, the TTD curve was also calibrated, to ensure clinical plausibility, given that none of the uncalibrated extrapolations aligned with the clinicians' long-term estimates. The settings for the model for the scenarios below can be found in the supporting reference "CEPHEUS ITT Population Settings".

The updated results which compare DBLd in the full CEPHEUS ITT population with IsaBLd using the NMA (both COVID-19 adjusted and unadjusted) and the results which exclude Brazil/Poland are presented in Table 16 – Table 18.

As outlined in Comment 1, these results are provided solely for completeness at the Committee's request. J&J do not consider them methodologically robust as they compare notably different populations which introduces heterogeneity. In addition, the TD subgroup in CEPHEUS over-represents the proportion of TD patients relative to the UK, and includes a high level of recruitment from Brazil (where pandemic related healthcare disruptions were significant) making the results less generalisable to the UK.

Table 15: Deterministic results versus DLd (discounted daratumumab price): CEPHEUS ITT population

Intervention	Total Costs	Total LYs	Total QALYs	Incremental Costs	Incremental LYs	Incremental QALYs	ICER (£/QALY)	Incremental NHB at £20,000	Incremental NHB at £30,000
DBLd	[redacted]	8.52	[redacted]						
DLd	[redacted]	7.49	[redacted]	[redacted]	1.03	[redacted]	Dominant	[redacted]	[redacted]

Footnote: Results are based on the Company's preferred patient characteristics (72 years and 50.9% male). Committee-preferred proportion receiving 2L therapy was assumed.
Abbreviations: DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; DLd: daratumumab, lenalidomide and dexamethasone; ICER: incremental cost-effectiveness ratio; LYs: life years; QALYs: quality-adjusted life years.

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Table 16: Deterministic results versus IsaBLd (discounted daratumumab price) using the COVID-19-adjusted NMA results: CEPHEUS ITT population

Intervention	Total costs	Total LYs	Total QALYs	Incremental Costs	Incremental LYs	Incremental QALYs	ICER (£/QALY)	Incremental NHB at £20,000	Incremental NHB at £30,000
DBLd	[redacted]	8.52	[redacted]						
IsaBLd	[redacted]	8.03	[redacted]	[redacted]	0.49	[redacted]	Dominant	[redacted]	[redacted]

Footnote: Results are based on the Company's preferred patient characteristics (72 years and 50.9% male). Committee-preferred proportion receiving 2L therapy was assumed.
Abbreviations: DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; ICER: incremental cost-effectiveness ratio; IsaBLd: isatuximab, bortezomib, lenalidomide and dexamethasone; ITT: intention-to-treat; LYs: life years; NMA: network meta-analysis; QALYs: quality-adjusted life years.

Table 17: Deterministic results versus IsaBLd (discounted daratumumab price) using the COVID-19-unadjusted NMA results: CEPHEUS ITT population

Intervention	Total costs	Total LYs	Total QALYs	Incremental Costs	Incremental LYs	Incremental QALYs	ICER (£/QALY)	Incremental NHB at £20,000	Incremental NHB at £30,000
DBLd	[redacted]	8.52	[redacted]						
IsaBLd	[redacted]	8.19	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]	[redacted]

Footnote: Results are based on the Company's preferred patient characteristics (72 years and 50.9% male). Committee-preferred proportion receiving 2L therapy was assumed.
Abbreviations: DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; ICER: incremental cost-effectiveness ratio; IsaBLd: isatuximab, bortezomib, lenalidomide and dexamethasone; ITT: intention-to-treat; LYs: life years; NMA: network meta-analysis; QALYs: quality-adjusted life years.

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Table 18: Deterministic results versus IsaBLd (discounted daratumumab price) using the NMA results excluding Brazil/Poland: CEPHEUS ITT population

Intervention	Total costs	Total LYs	Total QALYs	Incremental Costs	Incremental LYs	Incremental QALYs	ICER (£/QALY)	Incremental NHB at £20,000	Incremental NHB at £30,000
DBLd	[redacted]	8.52	[redacted]						
IsaBLd	[redacted]	7.65	[redacted]	[redacted]	0.86	[redacted]	Dominant	[redacted]	[redacted]

Footnote: Results are based on the Company's preferred patient characteristics (72 years and 50.9% male). Committee-preferred proportion receiving 2L therapy was assumed.
Abbreviations: DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; ICER: incremental cost-effectiveness ratio; IsaBLd: isatuximab, bortezomib, lenalidomide and dexamethasone; ITT: intention-to-treat; LYs: life years; NMA: network meta-analysis; QALYs: quality-adjusted life years.

Appendix 2.2 Scenario analyses conducted on the base case

A summary of the results of the scenario analyses conducted on the base case as part of this DGD response for DBLd versus DLd and DBLd versus IsaBLd are presented in Table 19 and Table 20, respectively. These scenarios use the Committee-preferred patient characteristics and proportion receiving 2L therapy.

As detailed in Comment 5, both subsequent treatment scenarios represent highly conservative scenarios. Additionally, J&J expect the impact on the ICER to be lower when the actual (with PAS) price of subsequent treatments is considered.

Table 19: Summary of revised base case and scenario analysis results – deterministic (discounted daratumumab price): DBLd versus DLd

Scenario	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Revised base case (using Committee-preferred assumptions)	[redacted]	[redacted]	Dominant

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Scenario		Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
1	Second-best statistically fitting curves for OS: Lognormal DBLd and Gompertz DLd (calibrated for both)	[redacted]	[redacted]	Dominant
2	BeBd usage of 50% at 2L (in line with market share data); SBd share of 30% at 3L	[redacted]	[redacted]	[redacted]
3	Market shares at 2L aligned with the VSTx dataset; SBd share of 20% at 3L	[redacted]	[redacted]	[redacted]

Footnote: Results are based on the Committee's preferred patient characteristics (75 years and 55% male). Committee-preferred proportion receiving 2L therapy was also assumed.
Abbreviations: 2L: second line; 3L: third line; BeBd: belantamab, bortezomib, and dexamethasone; DBLd; daratumumab, bortezomib, lenalidomide and dexamethasone DLd: daratumumab, lenalidomide; ICER: incremental cost-effectiveness ratio; OS: overall survival; QALY: quality-adjusted life year; SBd: selinexor, bortezomib, and dexamethasone.

Table 20: Summary of revised base case and scenario analysis results – deterministic (discounted daratumumab price): DBLd versus IsaBLd

Scenario		Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Revised base case (using Committee-preferred assumptions)		[redacted]	[redacted]	Dominant
1	BeBd usage of 50% at 2L (in line with market share data); SBd share of 30% at 3L	[redacted]	[redacted]	Dominant
2	Market shares at 2L aligned with the VSTx dataset; SBd share of 20% at 3L	[redacted]	[redacted]	Dominant

Footnote: Results are based on the Committee's preferred patient characteristics (75 years and 55% male). Committee-preferred proportion receiving 2L therapy was also assumed.
Abbreviations: 2L: second line; 3L: third line; BeBd: belantamab, bortezomib, and dexamethasone; DBLd; daratumumab, bortezomib, lenalidomide and dexamethasone; ICER: incremental cost-effectiveness ratio; IsaBLd: isatuximab, bortezomib, lenalidomide and dexamethasone; QALY: quality-adjusted life year; SBd: selinexor, bortezomib, and dexamethasone.

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Appendix 3. Proportional hazards data from the NMA

As requested by the Committee, J&J have provided the proportional hazards data for PFS and OS from MAIA and the SWOG S0777 trial used in the NMA (the key trials which connect DBLd to DLd), in Figure 4–Figure 11 below. The SWOG S0777 trial did not publish KM data for the transplant not intended subgroup, therefore the plots are only available for the full population.

Figure 4: SWOG OS log-log plot

Abbreviations: OS: overall survival.

Figure 5: SWOG OS Schoenfeld residuals plot

Abbreviations: OS: overall survival.

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Figure 6: SWOG PFS log-log plot

Abbreviations: PFS: progression-free survival.

Figure 7: SWOG PFS Schoenfeld residuals plot

Abbreviations: PFS: progression-free survival.

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Figure 8: MAIA OS log-log plot

Abbreviations: OS: overall survival.

Figure 9: MAIA OS Schoenfeld residuals plot

Abbreviations: OS: overall survival.

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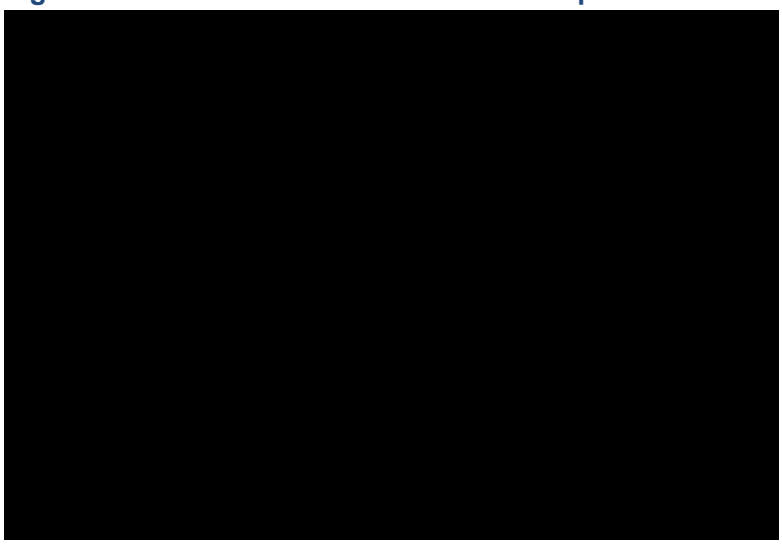
Figure 10: MAIA PFS log-log plot

Abbreviations: PFS: progression-free survival.

Figure 11: MAIA PFS Schoenfeld residuals plot



Abbreviations: PFS: progression-free survival.

As there is crossing in all the Loglog plots, particularly in MAIA, this indicates that the hazard rate is not constant over time, meaning the proportional hazards assumption is violated in the NMA. The IPTW ITC using patient level data from MAIA therefore remains the best source of evidence comparing DBLd to DLd.

The above information is only relevant to the comparison between DBLd and DLd. For the comparison against IsaBLd, as discussed in the Company addendum, proportional hazards are not violated in CEPHEUS or IMROZ (which connect DBLd to IsaBLd), MAIA and SWOG do not impact the NMA between DBLd and IsaBLd. Therefore, the NMA remains the best source of evidence for the comparison against IsaBLd, as agreed by the Committee.

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Appendix 4. Clinical data from CEPHEUS ITT population

A clinical summary of the OS, PFS TTD results from the ITT population in CEPHEUS, when adjusting for COVID-19, are presented in Figure 12–Figure 14 below. As outlined in Comment 1, these results are broadly consistent with the initial ITC results using the TIE patients in CEPHEUS presented in the original Company submission. Whilst J&J do not consider this an appropriate analysis, this consistency demonstrates that the results are robust and not a source of uncertainty.

Figure 12: KM plot of OS (full CEPHEUS ITT population; adjusted for COVID-19)

Abbreviations: CI: confidence interval; COVID-19: coronavirus disease 2019; HR: hazard ratio; ITT: intent-to-treat; KM: Kaplan-Meier; OS: overall survival.

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Figure 13: KM plot of PFS (full CEPHEUS ITT population; adjusted for COVID-19)

Abbreviations: CI: confidence interval; COVID-19: coronavirus disease 2019; HR: hazard ratio; ITT: intent-to-treat; KM: Kaplan-Meier; PFS: progression-free survival.

Figure 14: KM plot of TTD (full CEPHEUS ITT population; adjusted for COVID-19)

Abbreviations: CI: confidence interval; COVID-19: coronavirus disease 2019; HR: hazard ratio; ITT: intent-to-treat; KM: Kaplan-Meier; TTD: time-to-treatment discontinuation.

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Appendix 5. Factual inaccuracies

Page number	Quote from the DGD	Factual inaccuracy identified and rationale for requested correction	Correction requested
18	*"The committee noted that there was a notable difference between the probabilistic and deterministic ICERs"*	The current statement in the DGD that there is "*a notable difference between probabilistic and deterministic ICERs"* is factually incorrect. As shown in Tables 16 and 17 in Appendix A of the Company's clarification response, the deterministic and probabilistic ICERs for DBLd versus DLd at the discounted price for daratumumab are both dominant and aligned. The deterministic ICER is approximately -£16,000, and the probabilistic ICER approximately -£12,000. The Company does not consider this to be a notable difference, given that incremental QALYs are consistent across both analyses, with the total costs closely aligned: the probabilistic total costs for DBLd and DLd differ from the deterministic totals by only around £2,000. Furthermore, when applying the Committee's preferred assumptions (Appendix 1), the probabilistic and deterministic ICERs remain aligned and the conclusions of cost-effectiveness remain unchanged.	J&J request that the statement "*The committee noted that there was a notable difference between the probabilistic and deterministic ICERs"* to be removed.

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Appendix 6. Details of the ITT ITC versus DLd

The baseline characteristics of patients after weighting for the comparison of DBLd (ITT) compared to DLd are presented in Table 21 below.

Table 21: Post-weighting baseline characteristics

	DBLd	DLd	Standardised Difference	Total
ISS				
N	197	321	[redacted]	518
Stage I	[redacted]	[redacted]	–	[redacted]
Stage II	[redacted]	[redacted]	–	[redacted]
Stage III	[redacted]	[redacted]	–	[redacted]
Cytogenetic risk				
N	197	321	[redacted]	518
Standard	[redacted]	[redacted]	–	[redacted]
High	[redacted]	[redacted]	–	[redacted]
Not available	[redacted]	[redacted]	–	[redacted]
Extramedullary plasmacytomas				
N	197	321	[redacted]	518
No	[redacted]	[redacted]	–	[redacted]
Yes	[redacted]	[redacted]	–	[redacted]
Age				
N	197	321	[redacted]	518
<70	[redacted]	[redacted]	–	[redacted]
70-74	[redacted]	[redacted]	–	[redacted]
>=75	[redacted]	[redacted]	–	[redacted]
ECOG PS				
N	197	321	[redacted]	518
0	[redacted]	[redacted]	–	[redacted]
1	[redacted]	[redacted]	–	[redacted]
2+	[redacted]	[redacted]	–	[redacted]
eGFR (mL/min/1.73m2)				
N	197	321	[redacted]	518
<60	[redacted]	[redacted]	–	[redacted]

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	DBLd	DLd	Standardised Difference	Total
>=60	[redacted]	[redacted]	–	[redacted]
Sex				
N	197	321	[redacted]	518
Female	[redacted]	[redacted]	–	[redacted]
Male	[redacted]	[redacted]	–	[redacted]
Simplified frailty score				
N	197	321	[redacted]	518
0-1	[redacted]	[redacted]	–	[redacted]
>1	[redacted]	[redacted]	–	[redacted]
MM type				
N	197	321	[redacted]	518
IgG	[redacted]	[redacted]	–	[redacted]
Other	[redacted]	[redacted]	–	[redacted]
Hemoglobin (mg/L)				
N	197	321	[redacted]	518
<100	[redacted]	[redacted]	–	[redacted]
>=100 or missing	[redacted]	[redacted]	–	[redacted]
LDH (U/L)				
N	197	321	[redacted]	518
<=280 or missing	[redacted]	[redacted]	–	[redacted]
>280	[redacted]	[redacted]	–	[redacted]

Abbreviations: DBLd: daratumumab, bortezomib, lenalidomide, and dexamethasone; DLd: daratumumab, lenalidomide, and dexamethasone; ECOG PS: Eastern Cooperative Oncology Group Performance Status; eGFR: estimated Glomerular Filtration Rate; ISS: International Staging System; LDH: Lactate Dehydrogenase; MM: Multiple Myeloma.

The love plot for SMDs and the distribution of propensity scores, are presented in Figure 15 and Figure 16 below. The love plot shows that characteristics have been balanced with the weights with all the blue dots which represents after adjustment, lying close to 0.

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Figure 15: SMD Love plot

Red triangles = before adjustment, blue circle = after adjustment.
Abbreviations: ECOG PS: Eastern Cooperative Oncology Group Performance Status; eGFR: estimated Glomerular Filtration Rate; ISS: International Staging System; LDH: Lactate Dehydrogenase; MM: Multiple Myeloma; SMD: standardised mean difference.

Figure 16: Distribution of propensity scores

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Appendix 7. Details of the updated MAIC and NMA using the ITT

The DIC fits for the ITT NMA's can be found in Table 22 below.

Table 22: DIC fits for the ITT NMA

	COVID-19 adjusted NMA		Non COVID-19 adjusted NMA		NMA excluding Brazil and Poland	
	FE	RE	FE	RE	FE	RE
OS	−4,248	−2,656	−4,466	−2,899	−3,848	−2,274
PFS	−8,368	−7,001	−5,239	−3,868	−4,657	−3,256

Abbreviations: COVID: coronavirus disease; DIC: deviance information criterion; FE: fixed effects; ITT: intent-to-treat; NMA: network meta-analysis.

Updated MAIC supporting information (including TIE & TD patients in response to Committee requests in the DGD)

Table 23 shows the baseline characteristics and the SMD between the CEPHEUS ITT and IMROZ.

Table 23: Baseline characteristics and SMDs in the ITT MAIC

Characteristics		CEPHEUS (ITT)		IMROZ		SMD between CEPHEUS ITT and IMROZ
		DBLd (n=197)	BLd (n=198)	IsaBLd (n=265)	BLd (n=181)	
R-ISS, %	Stage I/II or missing	[redacted]	[redacted]	88.3	86.7	[redacted]
	Stage III	[redacted]	[redacted]	10.9	11.6	
Cytogenetic Risk, %	Unknown/missing	11.7	11.1	6.8	3.9	[redacted]
	Standard	75.6	75.3	78.1	77.3	[redacted]
	High	12.7	13.6	15.1	18.8	[redacted]
Age (years), %	<65 years	18.3	17.7	3	5	[redacted]
	65-69 years	26.4	26.8	26	27.5	[redacted]
	70-74 years	[redacted]	[redacted]	37.6	43.4	[redacted]
	75-80 years	[redacted]	[redacted]	26	31.5	[redacted]
ECOG performance status, %	0	36	42.4	46.4	43.6	[redacted]
	1	52.3	50.5	42.3	45.9	[redacted]
	⩾2 †	11.7	7.1	11.3	10.5	[redacted]
Type of MM, %	IgG	[redacted]	[redacted]	64.5	63.5	[redacted]
	Non-IgG	[redacted]	[redacted]	35.5	33.2	

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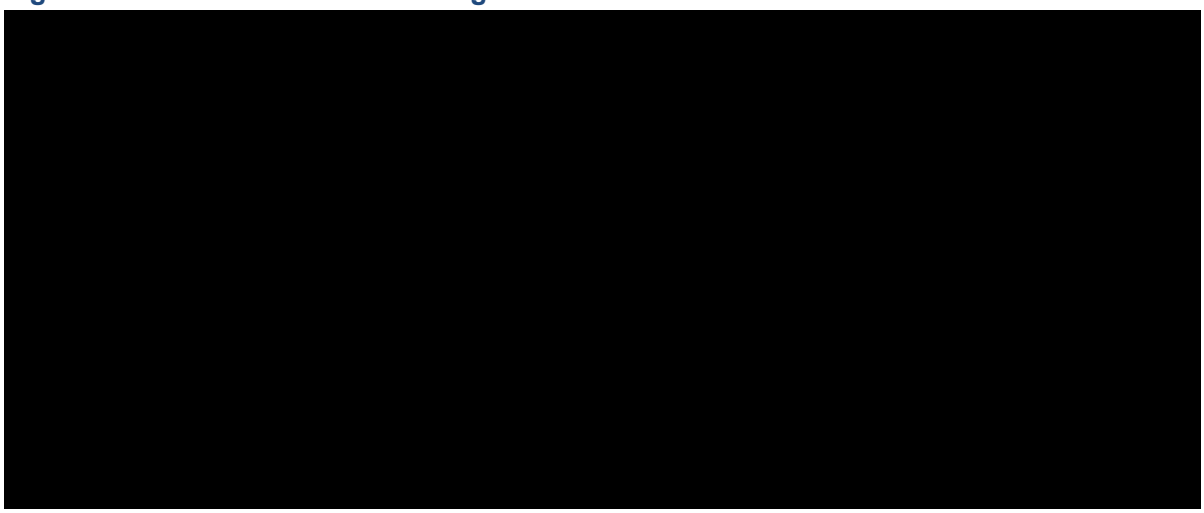
Characteristics		CEPHEUS (ITT)		IMROZ		SMD between CEPHEUS ITT and IMROZ
		DBLd (n=197)	BLd (n=198)	IsaBLd (n=265)	BLd (n=181)	
eGFR, %	<60 ml/min/1.73 m2	[redacted]	[redacted]	24.9	34.3	[redacted]
Extramedullary disease,%	EMD present	[redacted]	[redacted]	6.8	3.3	[redacted]
Sex, %	Male	44.2	56.1	54	51.9	[redacted]
Time since initial MM diagnosis (years)	Median, Range	0.1(0.0-0.5)	0.1(0.0-0.7)	0.1(0.0-4.1)	0.1(0.0-3.1)	[redacted]
Race, %	White	82.2	78.8	72.5	72.4	[redacted]
Frailty based on simplified IMWG frailty score, % 1	Frail	[redacted]	[redacted]	27.50	31.50	

Abbreviations: BLd: bortezomib; lenalidomide and dexamethasone; DBLd: daratumumab; bortezomib; lenalidomide and dexamethasone; ECOG: Eastern Cooperative Oncology Group Performance Status; eGFR: Estimated Glomerular Filtration Rate; EMD: Extramedullary Disease; IMWG: International Myeloma Working Group; IsaBLd: isatuximab; bortezomib; lenalidomide and dexamethasone; ITT: Intent-to-Treat; MM: Multiple Myeloma; R-ISS: Revised International Staging System.

Table 24 demonstrates the performance after matching for the MAIC that includes the transplant deferred population in CEPHEUS. The ESS was 80% of the original sample size retained. Starting with 395 patients, the analysis maintained an ESS of 314 patients after complete matching.

The MAIC demonstrated that the ESS was estimated at 314.06 patients in the base-case and 300.81 in the sensitivity analyses. The distribution of weights is shown in Figure 17 below.

Figure 17: Distribution of MAIC weights



Abbreviations: ECOG: Eastern Cooperative Oncology Group Performance Status; eGFR: Estimated Glomerular Filtration Rate; GFR: Glomerular Filtration Rate; IgG: Immunoglobulin G; ISS: International Staging System.

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Table 24: Performance after matching

Variable	Categories	AgD	IPD	IPD Adjusted										
		N	N	ISS	+risk	+Age	+ECOG	+IGG	+EMD	+frail	+male	+gfr	+DIAGYRS	+White
ESS (N)		446	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
R-ISS	I/II %	88.79	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	III %	11.21	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cytogenetic risk	Unknown %	5.61	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Standard %	77.80	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	High %	16.59	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age	<65 %	3.81	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	65-69 %	26.91	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	70-74 %	41.03	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	75+ %	28.25	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ECOG	0 %	45.30	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	1 %	43.70	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	2 & above %	11.00	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IgG	IgG %	64.13	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Non-IgG%	35.87	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Extramedullary disease	Yes %	5.38	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	No %	94.62	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Frail	Yes%	29.15	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	No%	70.85	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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NICE National Institute for Health and Care Excellence

Daratumumab with bortezomib, lenalidomide and dexamethasone for untreated multiple myeloma when a stem cell transplant is unsuitable [ID3843]

Draft guidance comments form

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Variable	Categories	AgD	IPD	IPD Adjusted										
		N	N	ISS	+risk	+Age	+ECOG	+IGG	+EMD	+frail	+male	+gfr	+DIAGYRS	+White
Male	Male %	53.14	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Female %	46.86	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
eGFR	Yes %	28.70	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
below <60 ml per minute per 1.73m^2	No %	71.30	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Year since diagnosis	Median	0.1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
White	Yes %	72.42	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	No %	27.58	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AgD: Aggregate Data; ECOG: Eastern Cooperative Oncology Group Performance Status; EMD: Extramedullary Disease; ESS: Effective Sample Size; GFR: Glomerular Filtration Rate; IgG: Immunoglobulin G; IPD: Individual Patient Data; ISS: International Staging System.

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Appendix 8. Response to EAG critique of Company Addendum

Original MAIC supporting information (including TIE patients only in response to EAG critique of company addendum)

J&J would like to provide additional information on the MAIC provided in the Company addendum on October 21st 2025 for the comparison against IsaBLd. While J&J agree with the Committee and the EAG that the MAIC serves as a supportive analysis to the NMA used in the base-case, the further detail provided here helps to reduce any residual uncertainty in the supporting ITC between DBLd and IsaBLd. J&J are providing this clarification because there was no opportunity to respond to the EAG's initial critique, which was only shared with J&J the afternoon before the 1st ACM.

<table>
<tr><th>EAG critique of Company Addendum</th><th>J&J response</th></tr>
<tr><td>Page 11 2.3.1

"We would have preferred to have seen the model fitting values for each outcome and a clear statement on which model was selected."</td><td>The DIC fits for the NMA are provided below in Table 25.

Table 25: DIC fits for non COVID-19 adjusted NMA
<table>
<tr><th></th><th>FE</th><th>RE (U[0,1])</th></tr>
<tr><td>OS</td><td>-4,134</td><td>-2,627</td></tr>
<tr><td>PFS</td><td>-4,975</td><td>-3,541</td></tr>
</table>
Abbreviations: COVID-19: coronavirus disease 2019; DIC: deviance information criterion; FE: fixed effects; ITT: intent-to-treat; NMA: network meta-analysis; OS: overall survival; PFS: progression-free survival; RE: random effects.

A FE model was chosen for the NMA for both endpoints (PFS and OS) due to a smaller DIC score compared to the RE model. Additionally, the FE model is deemed more appropriate given the small size of the network, which includes only one link connecting two treatments with multiple trials. Relying on the RE model with this network could introduce additional uncertainty, as the estimation of the random effects for most links is based on a single trial input. Therefore, the FE model provides a more reliable and parsimonious approach for this network.</td></tr>
<tr><td>Page 12 2.3.2

"The caveat to this is we could not independently appraise the individual components of the process</td><td>The choice of covariates in the MAIC followed the same approach as in the original company submission for the comparison against DLd. Selection of baseline covariates used for the ITCs was informed by two literature reviews, an empirical assessment of baseline characteristics' role as prognostic variables in CEPHEUS, MAIA, and ALCYONE, and input from</td></tr>
</table>

as little information had been given on these (except for details of the company's discussion with clinical experts)." *"The reason why the two additional two covariates (race and median duration since initial multiple myeloma diagnosis) were not included in the base model is not reported"* *"We observe general consistency between MAIC and the IPTW in terms of selected covariates, except for three covariates from the IPTW which are not mentioned in the MAIC (LDH, calcium levels and anaemia)."* *"However, further detail specific to the selection of the MAIC covariates would have been useful."*	clinical experts specialising in MM leading to the 11 covariates chosen. As per the original company submission, race and median duration since initial MM diagnosis, were included in the sensitivity analyses not the base case, as per expert feedback. This was the same approach used in the MAIC vs IsaBLd. In the base case ITC vs DLd, two covariates (LDH and anaemia) were included, and one additional covariate (calcium levels) was used in the sensitivity analysis. However, these covariates could not be included in the MAIC vs IsaBLd because IMROZ did not publish data for these variables. Without corresponding data from IMROZ, adjustment for these covariates was not possible. This explains the difference in covariates between the ITC vs DLd and the MAIC vs IsaBLd. Therefore, the list of covariates adjusted for in the MAIC versus IsaBLd, is where possible, the same as the covariates adjusted for in the IPTW ITC vs DLd.
Page 12, 2.3.2 *"Beyond the establishment of the covariates, the Addendum gives very* limited detail on the other *statistical characteristics of the MAIC. Notably, there is no comparison of patient characteristics (including the covariates) before and after matching, and hence whether there were any imbalances which could*	The ESS was well preserved throughout the matching process, with 87% of the original sample size retained, indicating minimal loss of statistical power while achieving appropriate population matching, see Table 26. The MAIC demonstrated that the ESS was estimated at 250.47 patients in the base-case (after starting with 289 patients). The sample size was not normally distributed and as expected, only a few patients were weighted above 2 which only contributed marginally to the ESS (Figure 18). Based on the weighted and unweighted ESS, the median weight was estimated at 0.86.

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cause confounding. Furthermore, the number of patients before and after matching (the effective sample size), is not stated, thus the degree of lost data is unknown."	**Figure 18: Distribution of MAIC weights** [redacted]

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Table 26: Performance after matching

Variable	Categories	AgD	IPD	IPD Adjusted										
		N	N	ISS	+risk	+Age	+ECOG	+IGG	+EMD	+ frail	+male	+gfr	+DIAGYRS	+White
ESS (N)		446	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
R-ISS	I/II %	88.79	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	III %	11.21	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cytogenetic risk	Unknown %	5.61	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Standard %	77.80	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	High %	16.59	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age	<65 %	3.81	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	65-69 %	26.91	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	70-74 %	41.03	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	75+ %	28.25	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ECOG	0 %	45.30	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	1 %	43.70	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	2 & above %	11.00	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IgG	IgG %	64.13	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Non-IgG%	35.87	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Extramedullary disease	Yes %	5.38	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	No %	94.62	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Frail	Yes%	29.15	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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Daratumumab with bortezomib, lenalidomide and dexamethasone for untreated multiple myeloma when a stem cell transplant is unsuitable [ID3843]

Draft guidance comments form

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Variable	Categories	AgD	IPD	IPD Adjusted										
		N	N	ISS	+risk	+Age	+ECOG	+IGG	+EMD	+ frail	+male	+gfr	+DIAGYRS	+White
	No%	70.85	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Male	Male %	53.14	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Female %	46.86	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
eGFR	Yes %	28.70	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
below <60 ml per minute per 1.73m²	No %	71.30	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Year since diagnosis	Median	0.10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
White	Yes %	72.42	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	No %	27.58	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AgD: Aggregate Data; ECOG: Eastern Cooperative Oncology Group Performance Status; EMD: Extramedullary Disease; ESS: Effective Sample Size; GFR: Glomerular Filtration Rate; IgG: Immunoglobulin G; IPD: Individual Patient Data; ISS: International Staging System.

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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):	NICE (Healthcare Data Analytics Team)

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NICE National Institute for Health and Care Excellence

Daratumumab with bortezomib, lenalidomide and dexamethasone for untreated multiple myeloma when a stem cell transplant is unsuitable [ID3843]

Draft guidance comments form

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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	The NICE Healthcare Data Analytics team were asked to provide SACT data on second line / third line treatments for the relevant cohort. Unfortunately, we could not provide a robust SACT extract for ID3843, for the following reasons:

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	1) The time frame is too recent to obtain sufficient second line data The information was requested for second and third line treatments for non-ASCT pathways. Since TA917 (October 2023), treatment pathways are expected to have changed, consequently the available relevant data is not yet mature enough to show sufficient second line and later treatments. The relevant data availability constraints are: • Diagnosis data in the National Disease Registration Service (NDRS) cancer analysis system is currently available to the end of calendar year 2023 only. • SACT treatment data are presently complete to summer 2025. Given typical time on first line treatment in the target cohort, exploratory analysis showed relatively few patients diagnosed since October 2023 who had reached second or subsequent line therapy within the available window of data. We would need a longer follow-up period before a sufficiently large post TA917 cohort exists in order to support reliable inference. **2) Difficulty reliably excluding ASCT eligible patients** Identifying Autologous Stem Cell Transplant (ASCT) relies on linkage to HES inpatient procedure codes within NDRS's data analysis environment. In exploratory queries we observed that induction/consolidation regimens often appear even when ASCT codes are excluded, suggesting a non-trivial degree of missingness in ASCT coding or linkages. Because the topic focuses on those who did not have ASCT, this uncertainty means we could not be confident of fully excluding ASCT recipients from the cohort. **3) Combination regimen identification would have been complex to do within the consultation timelines** Trusts record regimen combinations in varying ways in SACT. Some sites record explicit combination regimens, while others record the same components as separate contemporaneous 'individual' regimens. Accurately counting and analysing combination therapies would require bespoke amalgamation logic and validation, which is feasible but would have been challenging within the timeframe we had for this appraisal.
2	
3	
4	
5	
6	

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about funding from the company and links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into one response. We cannot accept more than one set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- In line with the NICE Health Technology Evaluation Manual (sections 5.4.4 to 5.4.21), if a comment contains confidential information, it is the responsibility of the responder to provide two versions, one complete and one with the confidential

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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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NICE National Institute for Health and Care Excellence

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

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NICE National Institute for Health and Care Excellence

Daratumumab with bortezomib, lenalidomide and dexamethasone for untreated multiple myeloma when a stem cell transplant is unsuitable [ID3843]

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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.

We have received funding from the drug manufacturer (Johnson & Johnson) in the last 12 months.

The table below shows the 2024 income from the relevant manufacturers and other pharmaceutical companies. 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

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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.
	Myeloma UK is very disappointed that NICE did not recommend daratumumab plus bortezomib, lenalidomide and dexamethasone for newly diagnosed myeloma patients who are not eligible for high-dose therapy and stem cell transplantation (HDT-SCT), for routine commissioning. This treatment has been shown to deliver significant benefits for HDT-SCT ineligible patients. It delivers deeper responses and longer remissions than the main comparator and is given in a more convenient and patient friendly way compared to IsaVRD the quadruplet recently approved for newly diagnosed myeloma patients (TA1098).
1	We are concerned about the committee's request to include the data from patients in the CEPHEUS trial who deferred stem cell transplantation because it does not reflect UK clinical practice. Deferred stem cell transplantations are not carried out in the UK. The processes and guidelines approved by NICE and NHS for the treatment of newly diagnosed myeloma patients rule out planned deferrals of SCT as an option. In NHS England, a patient can either be SCT eligible or ineligible. *"**Deferred transplants are not carried out routinely, or even frequently. Deferred transplants are not an approach endorsed by NICE/NHS England and are counter to their pathways. A decision not to embark on the SCT pathway in the first instance is a decision not to do a transplant at any stage"*** Prof. Graham Jackson, Consultant Haematologist, Freeman Hospital, Newcastle For a patient to access DVRD as per the indication under review in this appraisal [ID3843] they would be considered SCT ineligible. In the NHS there is no pathway or funding for a SCT ineligible patient to have stem cells harvested to allow a SCT later in the pathway. By choosing the SCT ineligible pathway the patient and clinician are making the decision that SCT is not a viable treatment option. Whilst there will be some patients who have their SCT later than planned due to non-response to initial treatment, other medical conditions, or specific circumstances, all these patients will have joined the pathway as SCT eligible patients and would not be eligible for the indication currently under assessment.

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Daratumumab with bortezomib, lenalidomide and dexamethasone for untreated multiple myeloma when a stem cell transplant is unsuitable [ID3843]

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	SCT eligible patients tend to be younger and fitter than SCT ineligible patients therefore patients selected for a deferred transplant are not representative of the patient population who would get the treatment being appraised. Furthermore, the available clinical data comparing upfront vs deferred SCT shows that upfront SCT delivers longer remissions times compared to deferred SCT. It also shows that 21% or the patients who did not get an upfront SCT did not get a SCT at second line. Therefore, deferred SCT would not be a recommended route for patients (1). 1. Attal, M., Lauwers-Cances, V., Hulin, C., Leleu, X., Caillot, D., Escoffre, M., Arnulf, B., Macro, M., Belhadj, K., Garderet, L. and Roussel, M., 2017. Lenalidomide, bortezomib, and dexamethasone with transplantation for myeloma. *New England Journal of Medicine*, *376*(14), pp.1311-1320.
2	We are concerned that the Committee did not fully consider the positive impact the differences in the administration route and dosing frequency for daratumumab compared to relevant comparator isatuximab (TA1098) would have on patient and carer quality of life. Firstly, isatuximab is given intravenously and daratumumab is given subcutaneously. Subcutaneous injections are faster and easier to administer than intravenous infusions. This difference could mean patients are in and out of the hospital faster on treatment days. Importantly, subcutaneous administration also opens the possibility of self-administration or administration by a community nurse. There are several hospitals which currently administer daratumumab in the community as part of their cancer care. This includes York and Scarborough Teaching Hospitals, Clatterbridge Hospital, and the Freeman Hospital, with others such as UCLH looking to expand options for at home administration of daratumumab (2, 3). Secondly, the dosing regimen and frequency is significantly different for IsaVRD (TA1089) and DVRD. For IsaVRD, isatuximab is given weekly for the first 6-week cycle, fortnightly for the next 3 six-week cycles and continues fortnightly for fourteen four-week cycles before moving to 4-weekly doses. This means that patients will have been getting treatment for 80 weeks (1.5 years) before moving to 4-weekly isatuximab. For DVRD, daratumumab is given weekly for the first two 3-week cycles, fortnightly for the next 6 three-week cycles before moving to four-week cycles with daratumumab given every four weeks. This means patients move to 4-weekly daratumumab after 24 weeks. This difference in dosing frequency significantly reduces the number of times patients need to attend clinic for treatment. Myeloma patients from our Advocacy Partner Panel shared the impact which frequent treatment has upon their quality of life: **" While treatment frequency may appear manageable on paper, in reality it represents a continuous physical, psychological, and logistical burden. Patients are required to structure large parts of their lives around treatment schedules, which leads to fatigue, anxiety, and loss of autonomy. 'Managing' treatment often means enduring it, rather than it being sustainable or patient centred."**

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	"Each clinic visit effectively removes a full day from normal life. This has a knock-on effect on family responsibilities, social interaction, employment, and the ability to plan ahead. Over months and years, the cumulative disruption erodes quality of life and contributes to isolation and reduced mental wellbeing. This impact is rarely captured in clinical outcomes but is very real for patients." ***"***It isn't just the treatment days it's also the having to go and get bloods done prior to treatment also! it means that some weeks you can literally be at hospital every day! it is impossible to lead a 'normal' life even if you feel well enough to do so". The frequency of tests and appointments also has substantial hidden costs, which patients and their family's face when accessing treatments **"The financial burden on patients and families is substantial and often underestimated. In my case, my wife attends appointments with me to be present during consultant discussions, which can result in lost income. Travel, parking, and associated costs accumulate quickly. For patients who lose employment or are forced into medical retirement, the financial impact can be severe and long-term. These pressures disproportionately affect working-age patients and those without financial resilience, creating inequity in the lived experience of care."** As members of the panel told us, having fewer clinic visits for an equally as effective treatment would make a tangible difference to their quality of life: ***"It would be transformational. Fewer clinic visits would reduce psychological stress associated with hospital attendance, improve treatment adherence, and allow patients to live more independently and normally."*** ***"When treatments offer comparable clinical effectiveness, convenience and reduced hospital dependency should be treated as essential outcomes"*** ***"There is also a big psychological benefit to having a longer break which allows a bit of normality to be established rather than the next hospital visit feeling like it is just around the corner"*** 2. York and Scarborough Teaching Hospitals NHS Foundation Trust (n.d.) *Giving yourself daratumumab subcutaneous injections: a step-by-step guide* [PDF]. Available at: https://www.yorkhospitals.nhs.uk/seecmsfile/?id=8455 (Last accessed: 28 January 2026). 3. The Clatterbridge Cancer Centre NHS Foundation Trust (2025) *Clatterbridge in the Community* [online]. Available at: https://www.clatterbridgecc.nhs.uk/patients-and-visitors/our-services/clatterbridge-community (Last accessed: 28 January 2026).
3	We are concerned that the Committee did not fully consider the significant patient benefit of increased progression-free survival compared to the main comparator DRD. As shown in the committee meeting DVRD delivers longer remission times than the main comparator DRD. We believe this is a key consideration that the committee should revisit and that

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	they should take into account the positive physical and mental health impact on patients and carers of a longer remission time associated with DVRD. In the CEPHEUS trial, 68% of patients who received DVRD were still in remission after 4.5 years (4). Having a long remission is very important for patients and their families. Patients describe remission as "*stability*," a time when "*life is more normal*" or "*they can more or less ignore the fact they have myeloma*." Relapse has a massive impact on the quality of lives of patients. It is hugely disruptive to patients and their families, and a significant source of stress and anxiety. Relapse completely disrupts the lives of patients and their families, symptoms (e.g., pain, fatigue), hospital visits and tests and uncertainty about the future increases. Switching treatments means adjusting to different side effects and new routines for hospital visits/treatment administration. *"**Unfortunately, I've switched treatment 3 times now and I think how you adjust depends on a number of factors: primarily what the new treatment is and how you experience the side effects but also, how well prepared you are for any potential side effects (and how well your team helps you to manage these).**" Person living with Myeloma* ***"Relapse is upsetting, devastating in fact and I always worry about what the next treatment will be like, particularly whether it will work and what impact the side effects might have on my QOL."** Person living with Myeloma* This period of instability typically lasts between 2-3 months due to the time needed to test and confirm relapse, book, and consent patients for treatment and for patients to respond and adjust to the new treatment. During this time, the patient's health often deteriorates. 4. Usmani, S.Z., Facon, T., Hungria, V., Bahlis, N.J., Venner, C.P., Braunstein, M., Pour, L., Martí, J.M., Basu, S., Cohen, Y.C. and Matsumoto, M., 2025. Daratumumab plus bortezomib, lenalidomide and dexamethasone for transplant-ineligible or transplant-deferred newly diagnosed multiple myeloma: the randomized phase 3 CEPHEUS trial. *Nature Medicine*, *31*(4), pp.1195-1202.
4	We are concerned that the Committee did not fully consider the significant patient benefit of increased depth of response compared to the main comparator DRD. DVRD delivers very deep responses and high levels of sustained MRD negativity (5). In the CEPHEUS trial, 81% of patients who had DVRD achieved a complete response or better. This means that 4 out of 5 patients would have no detectable signs of myeloma in their blood or bone marrow. Reaching and maintaining undetectable levels of myeloma and the blood and bone marrow has a significant positive impact on the mental wellbeing of people living with myeloma. Knowing that you have had the deepest response possible and that your cancer is undetectable / you are cancer-free is completely different to knowing it is there but controlled. Having no detectable signs of cancer often gives patients and their families an increased feeling of freedom, hope, and optimism for the future. The risk of relapse or infection risk feels lower. This means patients are more likely to plan for the future and increase social activities and engagements.

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	The full QoL impact of having no detectable levels of myeloma (paraproteins in regular blood tests) will not be picked up in the anxiety or depression utility scores. Firstly, the utility scores also do not consider the anxiety which partners and family can experience. Secondly the anxiety related to potential relapse is cyclical and linked to monthly blood tests or changes in health (e.g. a new pain) therefore it is highly likely that this impact would have been picked up in the QoL questionnaires used in the trial as they were only collected every 3 cycles and always on the first day of a new cycle. ***"When you have low levels of paraproteins getting your monthly blood test is more stressful. The levels fluctuate. When they are higher you start worrying about relapse. When your paraproteins are undetectable the results are clear."*** *Person living with Myeloma* ***5.*** Usmani, S.Z., Facon, T., Hungria, V., Bahlis, N.J., Venner, C.P., Braunstein, M., Pour, L., Martí, J.M., Basu, S., Cohen, Y.C. and Matsumoto, M., 2025. Daratumumab plus bortezomib, lenalidomide and dexamethasone for transplant-ineligible or transplant-deferred newly diagnosed multiple myeloma: the randomized phase 3 CEPHEUS trial. *Nature Medicine*, *31*(4), pp.1195-1202.
5	We are concerned that the Committee did not fully consider the significant patient benefit of receiving a quadruplet compared to DRD, the main comparator, which is a triplet. Quadruplets are considered the most effective treatments for myeloma. The complementary mechanisms of action work together to treat the biologically distinct subclones present in myeloma. Quadruplets also provide more flexibility to mitigate and manage side effects. There are four drugs to work with. If a patient experiences side effects due to one of the drugs, its dose can be easily adjusted. However, with monotherapies and doublets severe side effects, this often leads to treatment discontinuation, which is devastating for patients.
6	

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

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

Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
	The UKMS is disappointed in the decision not to recommend daratumumab with bortezomib, lenalidomide and dexamethasone (D-VRD) for newly diagnosed myeloma patients not eligible for autologous stem cell transplant. The reasons for this are outlined below.

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1	We disagree with the committee's request to include the data from patients in the CEPHEUS trial who deferred stem cell transplantation because it does not reflect UK clinical practice. CEPHEUS was a global study where many patients were recruited who live in the USA where deferred transplant is common due funding issues with private insurers. This is not the case in the UK and deferred transplant is almost never performed.
2	The newly diagnosed non-transplant eligible patient group make up the largest number of patients with myeloma as the median age of diagnosis remains around 70. Both on an individual patient basis and for the NHS at large it is important that patients have access to the most convenient and patient friendly treatments that are effective and support good quality of life. Although this group already has access to quadruplet therapy in the form of isatuximab-bortezomib-lenalidomide and dexamethasone (Isa-VRD) these two regimens are very different in terms of mode of delivery and quality of life impact. Subcutaneous daratumumab offers significant advantages over intravenous isatuximab for patients including speed of delivery, convenience and no requirement for painful cannulation for each dose. Also, the D-VRD regimen reverts to monthly daratumumab after 24 weeks, whereas patients receiving Isa-VRD only move to monthly dosing after 80 weeks. Finally, many sites are exploring and utilising out of hospital administration of daratumumab via homecare providers which will significantly relieve pressure on over stretched out patient day case treatment units for space. Intravenous isatuximab has not yet been given via the same route and patients must attend the hospital for treatment.
3	The committee report makes several references to DRD as an alternative treatment to D-VRD and the impression can be taken that the committee believes the two regimens to be 'equally effective'. This can be challenged for the following reasons, firstly D-VRD as a quadruplet will benefit those patients with myeloma who are particularly sensitive to proteosome inhibitor-based treatment as DRD does not contain a PI. Although there is opportunity to receive a PI later in the pathway outcomes are improved by using the best regimen first, rather than reserving treatments for a later point in time when the patient has unfortunately relapsed. Secondly, patients receiving D-VRD have a higher chance of achieving the deepest possible response (complete serological response, MRD negativity) compared to DRD. There has been significant progress towards 'functional cure' in myeloma which can be defined as a situation where the patient receives treatment that is sufficiently effective to maintain remission for the remainder of their natural lifespan. Quadruplet therapy offers this advantage over triplet therapy, as can be evidence by the finding that more patients in CEPHEUS achieved the deepest possible, MRD negative response than in the MAIA trial where DRD was tested. In the MAIA trial 14.9% of patients achieved sustained MRD negativity that lasted more than 6 months and 10.9% were MRD negative for more than 12 months (San Miguel et al, Blood 2022, Jan 27;139(4):492-501 In the CEPHEUS trial, the rate of sustained MRD negativity for > 12 months was 48.7% for D-VRD (Usmani S et al, Nature Medicine 2025:35;1195-1202) which is almost 5-fold higher than the above figures for DRD in MAIA. Finally, the quadruplet therapy offers advantages over triplet in that there is greater flexibility to titrate doses in the event of toxicity whilst still maintaining synergy between the agents than with a 3 drug regimen. For example, a significant dose reduction or even discontinuation of lenalidomide (due to skin rash in cycle 1 as commonly occurs) for a patient on DRD leads effectively to single

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	agent daratumumab maintenance and a high chance of early progression. In the same situation a patient receiving D-VRD would remain on multi-agent treatment for the first 8 cycles and is likely to achieve a deeper and more sustained response.

Insert extra rows as needed

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Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	Nothing to declare
Name of commentator person completing form:	[redacted]

Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	The cost code used in the model for subcutaneous (SC) administration (N10AF), applied to daratumumab, captures nurse time only and does not include chair time. In practice, a chair time slot is required and allocated for every SC administration of daratumumab. This covers patient assessment, observations, preparation of the injection, and the administration itself. As part of TA1098, feedback from myeloma nurse specialists confirmed that for the administration of

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	daratumumab SC, nurse time is typically 30–40 minutes, with chair time of a similar duration (up to 60 minutes to reflect variation in practice across hospitals). NHS guidance indicates that cost code SB12Z includes 30–60 minutes of chair time. In TA1098, the committee therefore considered SB12Z to be more appropriate than N10AF for SC administration and adopted SB12Z as the preferred assumption.
2	*"Insufficient TTD data were published for IsaBLd to allow a TTD ITC to be conducted between DBLd and IsaBLd. Therefore, in the absence of further information, an assumption was included in the economic analysis whereby the TTD curve for IsaBLd was set equal to the TTD curve for DBLd."* The base case appears to assume a similar duration of treatment between IsaVRd and DVRd, driven by the absence of published Time-To-Discontinuation (TTD) data for IsaVRd. As part of TA1098, a matching adjusted indirect comparison (MAIC) was conducted between the IMROZ IsaVRd TTD curve and the MAIA DRd TTD curve (https://doi.org/10.1007/s41669-024-00503-9; supplementary information, Figure S1). The results of this analysis indicated that, in a transplant-ineligible NDMM population, the IsaVRd and DRd TTD curves overlap throughout the entire follow-up period. Therefore, the committee considered equal duration of treatment between IsaVRd and DRd to be the most appropriate approach in TA1098. These results suggest that IsaVRd has a shorter duration of treatment than DVRd. Applying the same assumption in this appraisal does not require the availability of TTD data for IsaVRd, as it can be modelled using the DRd TTD curve. For completeness, details of the MAIC were provided but are considered confidential.
3	
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Insert extra rows as needed

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1. MAIC results for IsaVRd (IMROZ) vs DRd (MAIA) – TTD

Table 1: Patient baseline characteristics before and after weighting – IsaVRd vs DRd

Characteristic	IsaVRd: IMROZ		DRd (MAIA) N = 368
	Before matching N = 263	After matching ESS = 176 (67%)	
Age, years (mean)	71.68	[redacted]	73**
Male (%)	54%	[redacted]	51%
Race (%)			
White	73%	[redacted]	NR
Other	14%	[redacted]	NR
Missing/ not reported	13%	[redacted]	NR
ISS Stage (%)			
I	34%	[redacted]	27%
II	41%*	[redacted]	44%
III	25%	[redacted]	29%
ECOG PS (%)			
0 or 1	89%	[redacted]	85%
≥ 2	11%	[redacted]	17%
Cytogenetic risk (%)			
High	15%	[redacted]	15%
Standard	78%	[redacted]	85%
Missing	7%	[redacted]	0%
Multiple myeloma type (%)			
IgG	64%	[redacted]	61%
Non-IgG	36%	[redacted]	39%
Creatine clearance (%)			
≤ 60 mL/min	25%	[redacted]	44%
> 60 mL/min	75%*	[redacted]	56%
LDH levels, IU/L (mean)	199.1	[redacted]	NR
Time since diagnosis, months (mean)	1.99	[redacted]	1.4

Key: ECOG PS, Eastern Cooperative Oncology Group performance status; ESS, effective sample size, IgG, Immunoglobulin G; ISS, International Staging System; LDH, lactate dehydrogenase.

Notes: Matching characteristics are highlighted in blue, which included age, ISS stage, ECOG PS, cytogenetic risk and multiple myeloma type.
* Missing patients grouped into the largest category.
** Assumed based on the median.

Figure 1: Kaplan–Meier curve for TTD – IsaVRd (IMROZ) vs DRd (MAIA)

Key: DRd, daratumumab + lenalidomide + dexamethasone; IVRd, isatuximab + bortezomib + lenalidomide + dexamethasone; TTD, time to discontinuation.

Table 2: Kaplan-Meier summary of TTD – IsaVRd (IMROZ) vs DRd (MAIA)

Treatment (study)	N/ ESS	Events	Median TTD (95% CI)	Difference in restricted mean TTD up to 68.8* months (95% CI)
IsaVRd unadjusted (IMROZ)	263	[redacted]	[redacted]	[redacted]
IsaVRd weighted (IMROZ)	[redacted]	[redacted]	[redacted]	[redacted]
DRd (MAIA)	368	152	49.07 (42.39 to 57.45)	Reference

Key: CI, confidence interval; DRd, daratumumab + lenalidomide + dexamethasone; ESS, effective sample size; HR, hazard ratio; IsaVRd, isatuximab + bortezomib + lenalidomide + dexamethasone; NE, not evaluable; RMST, restricted mean survival time; TTD, time to discontinuation.
Notes: * Maximum TTD time for IsaVRd.

Table 3: HRs for TTD – IsaVRd (IMROZ) vs DRd (MAIA)

Method	Hazard ratio (95% CI)
HR (95% CI) from unadjusted Cox model	[redacted]
HR (95% CI) from weighted Cox model	[redacted]
HR (95% CI) from weighted Cox model (robust SE)	[redacted]
Bootstrap median HR (95% percentile CI)	[redacted]
Bootstrap median HR (95% BCa CI)	[redacted]

Key: BCa, bias-corrected and accelerated; CI, confidence interval; HR, hazard ratio; SE, standard error.

Notes: Results are considered statistically significant if 1 does not fall within the 95% CI. The bootstrapped HRs show an approximately normal distribution so the 95% CI based on the 2.5th and 97.5th percentiles is considered reliable for estimating the uncertainty (highlighted in blue).

Figure 2: Log cumulative hazard plot of TTD - IVRd (IMROZ) vs DRd (MAIA)

Key: DRd, daratumumab + lenalidomide + dexamethasone; IVRd, isatuximab + bortezomib + lenalidomide + dexamethasone; TTD, time to discontinuation.

Figure 3: Schoenfeld residual plot of TTD - IVRd (IMROZ) vs DRd (MAIA)

Key: DRd, daratumumab + lenalidomide + dexamethasone; IVRd, isatuximab + bortezomib + lenalidomide + dexamethasone; TTD, time to discontinuation.

Figure 4: Histogram rescaled weights - IVRd (IMROZ) vs DRd (MAIA)

Key: DRd, daratumumab + lenalidomide + dexamethasone; IVRd, isatuximab + bortezomib + lenalidomide + dexamethasone.

Figure 5: Bootstrapped Hazard Ratios for Time-to-discontinuation - IVRd (IMROZ) vs DRd (MAIA)

Key: DRd, daratumumab + lenalidomide + dexamethasone; IVRd, isatuximab + bortezomib + lenalidomide + dexamethasone.

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External Assessment Group Report commissioned by the NIHR Evidence Synthesis Programme on behalf of NICE

Multiple myeloma (untreated, stem cell transplant unsuitable) - daratumumab (with bortezomib, lenalidomide and dexamethasone) (ID3843)

External Assessment Group's critique of the company's response to Draft Guidance Document 1 (DGD1)

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Date completed	11th February 2026

Confidential information is underlined and highlighted blue

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1 INTRODUCTION

This document is the External Assessment Group (EAG)'s critique of the response by the company, J&J, to NICE Draft Guidance Document 1 (DGD1) (9th January 2026) for the technology appraisal of daratumumab (with bortezomib, lenalidomide and dexamethasone) for treating multiple myeloma (untreated, stem cell transplant unsuitable) (ID3843).

The EAG received the company's revised economic model and response document on 2nd February 2026, which included an updated model (dated 28-01-2026), hereafter, referred to as the company revised model and the company response.

2 EAG CRITIQUE OF THE COMPANY'S RESPONSE TO DGD1

In response to the committee's preferences the company has provided:

- A revised base case incorporating all the committee's preferred assumptions as outlined in the draft guidance (CS Appendix 1).
- Scenario analyses based on the CEPHUS trial ITT population for the comparison of DBLd versus DLd and versus DBLd versus IsaBLd, respectively. (CS Appendix 2.1)
- A set of scenario analyses on the company's revised base case (company Appendix 2.2)
- Proportional hazards data for comparator trials in the company's network meta analysis (NMA) (company Appendix 3)
- Kaplan Meier plots for overall survival (OS), progression free survival (PFS) and time to treatment discontinuation (TTD) from the CEPHEUS ITT population, adjusted for COVID-19 deaths (company Appendix 4)
- Further details of the indirect treatment comparison (ITC) for the comparison of DBLd versus DLD, based on the ITT population of the CEPHEUS trial (Appendix 6)
- Details of the updated matched adjusted indirect comparison (MAIC) and NMA based on the ITT population of the CEPHEUS trial (company Appendix 7)
- Response to the EAG critique of the MAIC in the company's addendum to their submission (21st October 2025). The addendum included the results of the comparison of DBLd versus IsaBLd. (company Appendix 8).

In the following sections we provide a critique of the company's revised analyses based on the above.

2.1 Evidence for the full CEPHEUS intention to treat (ITT) patient population

2.1.1 Baseline characteristics

Table 1 of the company's response reports selected baseline characteristics for the transplant ineligible (n=289) and transplant deferred sub-populations in the trial (n=106). Collectively these two sub-populations comprise the ITT population of the trial (defined as all

randomised patients, n=395). Previously baseline characteristics were presented in the CS for the ITT population and the transplant ineligible sub-population, but not for the transplant deferred population.

The company point out that there are notable differences in baseline characteristics between the two sub-populations in the trial. The EAG notes that only a limited number of baseline characteristics are given in company response Table 1 (age, sex, race, baseline ECOG score, frailty score, ISS stage, cytogenic risk). We assume that, in the main, these characteristics were chosen because they represent key prognostic factors / treatment effect modifiers. Based on these variables the company states that the transplant deferred population in the trial is younger, fitter and has lower ECOG scores than their transplant ineligible counterparts. Accordingly, the transplant deferred population is expected to have better outcomes than the transplant ineligible population. The EAG notes that it is not clear whether the marked differences in the characteristics between patients ineligible for transplant and those who chose not to have a transplant is an artefact of the clinical trial (e.g. eligibility criteria; disproportionately small transplant deferred sub-population) or whether it reflects the typical patient population in practice. Further, we note that this is at odds with expert clinical advice given to the appraisal committee that the transplant declined or deferred population would likely experience similar outcomes.

2.1.2 Generalisability

The EAG notes that whilst certain baseline characteristics differed between the two sub-populations of the trial (company response Table 1), these differences were less pronounced when comparing the ITT population and the transplant ineligible population. For example, median age in the transplant ineligible sub-population was [redacted] years, whilst in the transplant deferred sub-population it was markedly [redacted] ([redacted] years). In the ITT population median age was 70 years, which is more comparable with the transplant ineligible sub-population. This is to be expected given the higher proportion of ASCT ineligible patients in the trial (73%) compared to the ASCT deferred population (27%). This gives greater perspective and suggests that the ITT population is not substantively different to the transplant ineligible population.

The company reports that a high proportion of transplant deferred patients in the trial had been recruited from Brazil and Poland, and there were none in the UK. They cite differences in healthcare delivery and the heavy impact of Covid-19 in these countries as factors which reduces the generalisability of this sub-population to UK clinical practice. The EAG notes that UK patients comprised a relatively small proportion (8%) of the transplant ineligible sub-group and therefore this may also limit generalisability.

2.1.3 Indirect treatment comparisons

2.1.3.1 DBLd versus DLd

For the indirect comparison between BLd and DLd the committee expressed a preference (on this occasion) for the inverse probability of treatment weighting (IPTW) approach over the company's alternative NMA approach. Accordingly, the company has updated the IPTW method to estimate treatment effects for the scenario based on the CEPHEUS ITT population. However, the company explicitly highlight that the results are not considered methodologically robust, due to differences in the study populations in the key trials. They note that the MAIA trial[1, 2] included transplant ineligible patients only, whereas CEPHEUS includes both transplant ineligible and transplant deferred patients. Accordingly, this mismatch in trial patient inclusion criteria introduces heterogeneity and violates the assumption of similarity between trials.

The company notes that the transplant deferred patients in CEPHEUS were eligible for transplant but deferred for non-biological reasons (e.g. physician or patient choice). They explain the whilst the IPTW approach can achieve balance by reweighting clinically relevant characteristics, it cannot balance for transplant deferral and it remains a potential source of residual confounding. The EAG agrees with this in principle, however, we note that baseline differences between transplant ineligible and transplant deferred patients are less pronounced in the ITT population due to the preponderance of transplant ineligible patients in the trial (76%). Furthermore, the baseline characteristics which the company note as differing between the sub-populations of the trial (e.g. age, ECOG status, frailty - company response Table 1) are included in the weighting process in the IPTW indirect comparison and shown to be comparable to DLd patients in the MAIA trial (company response Table 21, Appendix 6).

The results of the IPTW indirect comparison of DBLd versus DLd, based on the ITT population of DBLd patients in the CEPHEUS trial (company response document page 10), overall, are broadly similar to results based on the transplant ineligible sub-population of the CEPHUS trial previously reported. This applies to OS, PFS and TTD outcomes. Despite the company's misgivings over the appropriateness of using the ITT population instead of the transplant ineligible sub-population, they regard the results of the revised ITC are "robust and not a source of uncertainty" (company response page 10). In the EAG's view the high proportion of transplant ineligible patients included in the CEPHEUS trial helps to reduce uncertainty arising from heterogeneity in the comparison with trials which exclusively recruited transplant ineligible patients. This likely explains the consistency in the time to event outcomes for the comparison of DBLd versus DLd when based on the ITT population

of the CEPHEUS trial compared to when based on transplant ineligible sub-population of the trial.

2.1.3.2 DBLd versus IsaBLD

In line with the committee's preferences the company have used the NMA for the comparison of DBLd versus IsaBLD. The company highlights that the same uncertainties discussed above for the ITC of DBLd versus DLd apply to this current comparison. Specifically, the mismatch between the ITT population of CEPHEUS (which includes transplant ineligible and transplant deferred patients) and the IMROZ trial[3] (which includes only transplant ineligible patients). The results (for the outcomes OS and PFS) of the NMA indirect comparison of DBLd versus IsaBLD, based on the ITT population of CEPHEUS, are reported in company response Table 5 (adjusted for Covid-19) and Table 6 (unadjusted for Covid-19). The company's preference is for the Covid-19 adjusted analyses. Across the NMA results presented, there is overall broad consistency with the results from the original NMA based on the transplant ineligible sub-population of CEPHEUS.

The company has also updated the MAIC for the comparison of DBLd versus IsaBLD, using the ITT population of the CEPHEUS trial (company response Appendix 7). The updated MAIC uses same methodology as used in the original MAIC included in the company's addendum to their submission in October 2025. In the company's current response document they provide more detail on the methods used in the MAIC, for example, reporting the effective sample size and the distribution of MAIC weights.

The EAG is reassured by the consistency between the NMA results between the original analysis (informed by the transplant ineligible population of CEPHEUS) and the updated analysis (informed by the ITT population)

2.1.4 Cost -effectiveness results

Company response Appendix 2.1 (Tables 15-18) show the cost effectiveness results of the scenarios using the full CEPHEUS ITT population. The company highlights that these scenarios use the company's original patient baseline characteristics (i.e. from CEPHEUS). The company did not consider it appropriate increase the modelled patient age to 75 years, because transplant-deferred (TD) patients in CEPHEUS were younger ([redacted] years) compared with the transplant-ineligible (TIE) patients (72 years; company response p.5). However, these scenario analyses do incorporate the committee-preferred proportion of patients receiving 2L therapy after DBLd and IsaBLd (75%). Given the age discrepancy between the two populations in CEPHEUS (TD and TIE) we consider it appropriate to use the original trial age in these scenarios.

We note that for the scenario comparing DBLd with DLd (company response Table 15), OS extrapolations differ between the arms: lognormal (new curve) for DBLd and the exponential for DLd (the same curve used in the model seen at ACM1). The company explain that the lognormal is the best statistical fit for DBLd when using the Covid-adjusted data in this scenario analysis.

The EAG agrees that the AIC/BIC data provided in the model (*DBLd* BH26:BN33) suggest that the lognormal curve is statistically the best fit for DBLd OS in this scenario. However, we note that the AIC/BIC results are close for the lognormal and exponential extrapolations. Consequently, we tested using the exponential (the curve used for DBLd in the model seen at ACM1) in a scenario analyses (4.2.1).

2.2 Modelling overall survival: Implied HRs and alternative OS curves

The committee requested the company explore the use of alternative baseline OS curves with relative treatment effects applied. For example, using Systemic Anti-Cancer Therapy (SACT) data for DLd as the baseline OS curve and the relevant hazard ratio applied to that (DGD1 section 3.9).

The company response explains that it was not possible to explore a scenario using SACT data to inform the baseline OS curve for DLd due to the unavailability of this dataset (comment 4, p.18) and the company explored a scenario using the second-best statistically fitting curves for OS (lognormal for DBLd and Gompertz for DLd) instead. Results are shown in company response Table 19.

We note that the choice of OS curve has little effect for DBLd, because the fit concerns the first five years of Kaplan-Meier data, after which curves are attenuated to align long-term modelled OS predictions with clinical expert expectations (Figure 1). For the DLd OS extrapolation, we note that while the Gompertz curve may match the Kaplan-Meier data well for the first 7 years, it has a notably worse long-term (> 7 years) OS prediction than the exponential curve (Figure 2).

Figure 1 DBLd overall survival – extrapolations with general population mortality cap applied
Source: Company model

Figure 2 DLd overall survival – extrapolations with general population mortality cap applied
Source: Company model

2.3 Subsequent treatment distributions

The committee requested the company provide more evidence to validate the distribution of second- and third-line treatments used in the economic model (DGD1 section 3.15), which may include using the proportion of subsequent treatments from SACT, particularly third-line selinexor use (DGD1 section 3.12). However, it was not possible to extract a robust dataset from SACT. Full details are given in the document 'ID3842 daratumumab – RJW comment re SACT data – 230126'.

In response to the committee's request, the company conducted scenarios testing:

1. BeBd usage estimated at 50% at second-line (other shares reweighted across other treatments: SBd = 12.4%, Cd = 37.6%); SBd share estimated at 30% at third-line (cyclophosphamide = 49.05%, PBd = 20.95%)
   Results are shown in company response Table 19 versus DLd and Table 20 versus IsaBLd

2. Market shares at second-line aligned with the VSTx dataset (NHS pharmacy/ePrescribing datasets); SBd share estimated at 20% at third-line (cyclophosphamide = 56.1%, PBd = 23.9%)
   Results are shown in company response Table 19 versus DLd and Table 20 versus IsaBLd

The company response (p.21) explains that it was not possible to calculate a split for third-line treatment using the IQVIA market research data because the sample size was small as very few patients had progressed on DLd and a second-line therapy. The EAG considers this explanation to be reasonable.

When limiting the VSTx dataset to treatments allowed after DLd, the EAG agrees that second-line BeBd use has increased over time, from [redacted] in June 2025 to [redacted] in September 2025 (company response, p.21; JJ Data on File VSTx Dataset). We note that the use of Cd declined and that SBd use remained stable over the same period (JJ Data on File VSTx Dataset). The company response (p.22) explains that the VSTx dataset did not provide 3L splits for treatments that would be received following DLd.

Table 1 below shows the proportions of patients receiving second-line treatment in the company's revised base case, in the IQVIA and VSTx data sets, and in scenario analyses 1 and 2. We consider that the company's base case and scenarios provide a good range of estimates of BeBd use. We note that the IQVIA and VSTx datasets do not estimate the proportion of patients receiving Bd/bortezomib/Velcade, this is just the patient proportion remainder.

Table 1 Subsequent treatment (second-line) distributions

Treatment	Proportion of patients				
	Company revised base case[a]	IQVIA market research	VSTx database	Scenario 1	Scenario 2
Cd	9.38%	[redacted]	[redacted]	37.6%	[redacted]
Selenexor combination/SBd	3.13%	[redacted]	[redacted]	12.4%	[redacted]
BeBd	87.50%	[redacted]	[redacted]	50%	[redacted]
Bd/bortezomib	0.00%	[redacted]	[redacted]	0%	[redacted]

Source: EAG created table

[a] Treatment share estimates from five UK haematologists at the company's advisory board in May 2025.

Bd; bortezomib and dexamethasone, BeBd; belantamab, bortezomib, and dexamethasone, Cd; carfilzomib and dexamethasone, SBd; selinexor, bortezomib, and dexamethasone; VSTx NHS pharmacy/ePrescribing datasets

3 EAG VALIDATION OF THE COMPANY'S REVISED COST-EFFECTIVENESS RESULTS

3.1 Company's revised base case cost-effectiveness results

The company provided a revised economic model (dated 28-01-2026), which the EAG successfully validated (Table *2*).

Table 2 Cumulative changes to the company base case seen at ACM1, and deterministic base case results of the company's revised model (pairwise comparison)

Description	Treatment	Total costs (£)	Total QALYs	Incr. Costs (£)	Incr. QALYs	ICER (£/QALY)
Company base case seen at ACM1	DBLd	[redacted]	[redacted]			
	DLd	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
	IsaBLd	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Use patient characteristics: age = 75 years; 55% male	DBLd	[redacted]	[redacted]			
	DLd	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
	IsaBLd	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
75% patients receive 2L subsequent treatment (DBLd and IsaBLd)	DBLd	[redacted]	[redacted]			
	DLd	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
	IsaBLd	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Company revised base case (dated 28-01-2026)	**DBLd**	[redacted]	[redacted]			
	DLd	[redacted]	[redacted]	[redacted]	[redacted]	**Dominant**
	IsaBLd	[redacted]	[redacted]	[redacted]	[redacted]	**Dominant**

Source: EAG created table
Abbreviations: 2L, second-line; ACM, Appraisal Committee Meeting; DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; DLd: daratumumab, lenalidomide and dexamethasone; ICER, incremental cost-effectiveness ratio; Incr., incremental; IsaBLd: isatuximab, bortezomib, lenalidomide and dexamethasone; QALY, quality-adjusted life-year

All results in this critique refer to the company's revised model dated 28-01-2026 and include the PAS discount for daratumumab. Analyses including appropriate Medicines Procurement and Supply Chain (MPSC) costs are presented in a separate confidential addendum.

In the company's revised base case, DBLd dominates both DBLd and IsaBLd (Table *2*). Company response Table 13 presents the probabilistic results of the company's revised base case. We note that the deterministic and probabilistic results are consistent for both DBLd compared with DLd, and with IsaBLd.

4 EAG ANALYSES

4.1 EAG preferred assumptions

The company's revised base case includes all of the committee's preferred assumptions as outlined in DGD1 section 3.14; the EAG has made no further changes. ICER results are presented in company response Table 13 (probabilistic analyses) and Table 14 (deterministic analyses) for DBLd compared with DLd and IsaBLd.

4.2 EAG scenario analyses on the company base case

4.2.1 Alternative OS curve for DBLd

Table 3: Deterministic results versus DLd: CEPHEUS ITT population, exponential curve for DBLd OS

Intervention	Total Costs	Total QALYs	Incremental Costs	Incremental QALYs	ICER (£/QALY)
DBLd	[redacted]	[redacted]			
DLd	[redacted]	[redacted]	[redacted]	[redacted]	Dominant

Adapted from Company response Table 15
Results are based on the Company's preferred patient characteristics (72 years and 50.9% male); committee-preferred proportion receiving 2L therapy was assumed.
Abbreviations: DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; DLd: daratumumab, lenalidomide and dexamethasone; ICER: incremental cost-effectiveness ratio; QALYs: quality-adjusted life years.

4.2.2 Stakeholder comments

4.2.2.1 Subcutaneous administration cost

A stakeholder highlighted that the cost code used in the model for subcutaneous administration (N10AF; Specialist nursing, cancer related, adult, face to face; National Schedule of NHS Costs 2023/24) captures nurse time only and does not include chair time (Comment 1, ID3843 daratumumab – Sanofi – DG comments A form).

Section 3.12 of the committee discussion in TA1098 (Isatuximab in combination for untreated multiple myeloma when a stem cell transplant is unsuitable, 24 September 2025) states that the "*SB12Z [cost code] included nurse time (30 minutes) and chair time (up to 60 minutes), as per NHS guidelines. The chair time included time to observe people having the treatment and to administer the subcutaneous treatment. N10AF factors in the nurse time, but not chair time.*" The committee concluded that the cost code SB12Z applied in the TA1098 economic model was acceptable.

We conducted a scenario using the latest cost for SB12Z of £152 (Deliver simple parenteral chemotherapy at first attendance; outpatient; National Schedule of NHS Costs 2023/24) for subcutaneous administrations in the company's revised model (Table *4*).

Table 4 Use SB12Z 2023/24 cost (£152) for subcutaneous administrations, pairwise comparisons

Intervention	Total Costs	Total QALYs	Incremental Costs	Incremental QALYs	ICER (£/QALY)
DBLd	[redacted]	[redacted]			
DLd	[redacted]	[redacted]	[redacted]	[redacted]	-£1,730
IsaBLd	[redacted]	[redacted]	[redacted]	[redacted]	Dominant

EAG created table
Abbreviations: DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; DLd: daratumumab, lenalidomide and dexamethasone; ICER: incremental cost-effectiveness ratio; IsaBLd: isatuximab, bortezomib, lenalidomide and dexamethasone; QALYs: quality-adjusted life years.

4.2.2.2 Time to treatment discontinuation (TTD) of IsaBLd

Due to lack of published data, the company were unable to conduct a TTD indirect treatment comparison between DBLd and IsaBLD and so their base case assumes that TTD for IsaBLd is the same as DBLd.

A stakeholder provided evidence demonstrating that IsaBLd (IMROZ trial) and DLd (MAIA trial) TTD curves overlap throughout the entire follow-up period of the two trials (ID3843 daratumumab – Sanofi – DG comments B appendix [MAIC results], Figure 1). The EAG agree that the TTD Kaplan-Meier curves for IsaBLD and DLd overlap. We conducted a scenario analysis setting the IsaBLD TTD equal to that of DLd (Table *5*).

Table 5 IsaBLD TTD equal to DLd TTD

Intervention	Total Costs	Total QALYs	Incremental Costs	Incremental QALYs	ICER (£/QALY)
DBLd	[redacted]	[redacted]			
IsaBLd	[redacted]	[redacted]	[redacted]	[redacted]	Dominant

EAG created table
Abbreviations: DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; DLd: daratumumab, lenalidomide and dexamethasone; ICER: incremental cost-effectiveness ratio; IsaBLd: isatuximab, bortezomib, lenalidomide and dexamethasone; QALYs: quality-adjusted life years; TTD, time to treatment discontinuation

4.3 Economic analysis summary

The company's revised model incorporates the committee's preferred assumptions from DGD1 and presents the results of the company's base case as pairwise comparisons of

DBLd compared with DLd and IsaBLd. We reviewed and successfully validated the company's revised model (Table 2). The company have conducted scenario analyses, meeting the committee's requests where possible and providing reasonable alternative scenarios otherwise.

4.4 Post-PMB analyses (3rd March 2026)

Following the ACM pre-meeting briefing (held 2nd March 2026), NICE requested the EAG run additional scenarios to explore remaining uncertainty.

Table 6 IsaBLD TTD calculated using hazard ratio

Technologies	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)
DBLd	[redacted]	[redacted]			
IsaBLd	[redacted]	[redacted]	[redacted]	[redacted]	Dominant

Source: EAG created table
Abbreviations: DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; DLd: daratumumab, lenalidomide and dexamethasone; ICER, incremental cost effectiveness ratio; Incr., incremental; IsaBLd: isatuximab, bortezomib, lenalidomide and dexamethasone; QALY, quality adjusted life year; TTD, time to treatment discontinuation

Table 7 Alternative second-line subsequent treatments: Cd 17.08%, SBd 9.10%, BeBd 73.82%; pairwise comparisons

Technologies	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)
DBLd	[redacted]	[redacted]			
DLd	[redacted]	[redacted]	[redacted]	[redacted]	£2,280
IsaBLd	[redacted]	[redacted]	[redacted]	[redacted]	Dominant

Source: EAG created table
Abbreviations: DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; DLd: daratumumab, lenalidomide and dexamethasone; ICER, incremental cost effectiveness ratio; Incr., incremental; IsaBLd: isatuximab, bortezomib, lenalidomide and dexamethasone; QALY, quality adjusted life year; TTD, time to treatment discontinuation

Table 8 Alternative second-line subsequent treatments: Cd 46.69%, SBd 33.02%, BeBd 20.29%; pairwise comparisons

Technologies	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)
DBLd	[redacted]	[redacted]			
DLd	[redacted]	[redacted]	[redacted]	[redacted]	£29,092
IsaBLd	[redacted]	[redacted]	[redacted]	[redacted]	Dominant

Source: EAG created table

Abbreviations: DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; DLd: daratumumab, lenalidomide and dexamethasone; ICER, incremental cost effectiveness ratio; Incr., incremental; IsaBLd: isatuximab, bortezomib, lenalidomide and dexamethasone; QALY, quality adjusted life year; TTD, time to treatment discontinuation

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