Single Technology Appraisal

Daratumumab with bortezomib, lenalidomide and dexamethasone for untreated multiple myeloma when an autologous stem cell transplant is suitable [ID6249]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

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Contents:

The following documents are made available to stakeholders:

Documents submitted during consultation on the first Draft Guidance document and shared with the Committee for the second Committee meeting

1. **Comments on the Draft Guidance from Johnson and Johnson Innovative Medicine (J&J)**
   a. Company response to Draft Guidance
   b. Company Additional Analyses

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 **Consultee and commentator comments on the Draft Guidance** from: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

3. **Systemic Anti-Cancer Therapy (SACT) Report**

4. **External Assessment Group critique of company comments on the Draft Guidance**
   a. EAG Critique
   b. EAG Addendum

Information requested following the second Committee meeting which will be shared with the Committee for the third Committee meeting:

5. **Additional Analysis Requested by the Committee following the second Committee meeting**

6. **Company Additional Scenarios Requested following the second Committee meeting**

7. **Company Follow-up Additional Scenarios requested following the second Committee meeting**

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

NICE National Institute for Health and Care Excellence

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Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 4 February 2026.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 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):	Johnson 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.	No disclosure
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	No disclosure
Name of commentator person completing form:	Tinevimbo Shiri

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.
	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 an autologous stem cell transplant is suitable. J&J is disappointed with the draft guidance decision not to recommend DBLd within its marketing authorisation. Whilst J&J acknowledge concerns raised by the Committee with respect to the full treatment sequence including maintenance, and request for additional analysis, we are disappointed that the Committee was unable to make an initial optimised recommendation for DBLd induction and consolidation given the compelling clinical and cost-effectiveness evidence submitted as part of this appraisal against the current standard of care, DBTd. J&J note that this would have been consistent with the pragmatic

	approach taken by other HTAs in the UK and would have supported timely patient access to a more tolerable, thalidomide-free, quadruplet regimen. Despite the availability of DBTd since the positive NICE recommendation in February 2022, transplant-eligible patients with newly diagnosed multiple myeloma still face high relapse risk and limited durability with standard of care treatment strategies. As recognised by patient experts, multiple myeloma has a large psychological impact because of the constant fear of relapse. Each additional line of treatment is associated with worse outcomes and myeloma can evolve over time and become more resistant to treatment. The impact on patient's quality of life and their families can be profound and there remains a persistent unmet need for more effective first-line therapies that induce remission and delay progression by achieving deep and durable responses. Minimal residual disease (MRD) represents the most sensitive measure of disease burden and depth of response in myeloma with its prognostic utility for progression-free survival (PFS) and overall survival (OS) well established across a range of disease settings including front-line transplant-eligible patients. J&J is pleased that the Committee concluded that the PERSEUS trial is suitable for decision making and acknowledged that there would be clinical benefits to MRD guided treatment. J&J note that the Committee was unable to conclude on an appropriate ICER threshold for this appraisal due to a "*high level of uncertainty*". We outline below the additional information and analysis provided as part of this draft guidance response which J&J believe supports an ICER threshold towards the upper-end of the range NICE normally considered cost-effective: • J&J acknowledge the **Committee's preference to use the reweighted IPTW analysis from PERSEUS for the relative effectiveness of DL versus L maintenance to inform the cost-effectiveness model**. As requested by Committee, J&J provide full details of the inverse probability of treatment weighting (IPTW) analysis and explored alternative statistical methods, leveraging patient level data from PERSEUS including doubly robust and multivariate regression methods. The results from alternative methods are broadly consistent with the IPTW analysis, with minimal impact on overall cost-effectiveness, providing reassurance that this is not a key area of residual uncertainty (see Comment 1 and Additional Analyses document accompanying this response). • **Lack of long-term OS and PFS data for the full sequence of daratumumab in combination with bortezomib, lenalidomide and dexamethasone (DBTd) followed by lenalidomide maintenance**: As requested by Committee, J&J has updated the survival modelling for standard of care by applying the hazard ratios generated from the IPTW of the PERSEUS trial to the DBLd-DL reference curve. For this analysis, we have considered the full range of parametric curves which continue to support the exponential and generalised gamma distributions for DBTd-L OS and PFS, respectively (see Comment 2 and Additional Analyses document accompanying this response). • J&J acknowledge the Committee's concerns regarding the **feasibility for MRD testing to become routine practice in the NHS and whether this would be applied exactly as in the PERSEUS trial**. As part of this draft guidance response, J&J provide full details of the UK Clinical Advisory Boad (CAB) held in July 2025 which supports the Company base case and feasibility for routine

MRD testing based on Next Generation Flow (NGF) within existing NHS infrastructure and practice.

[redacted] This would represent a significant step forward for the myeloma community with both patient and clinical experts at the first appraisal committee meeting expressing a strong preference for MRD guided therapy that would help reduce inequity with other haematological malignancies (e.g. chronic lymphocytic leukaemia, CLL) where MRD testing in the UK has been routine for a number of years.[1]

Cognisant of the perceived risk relating to implementation of an MRD based stopping rule, J&J has also explored a range of scenarios to quantify and minimise risk by providing options for recommendations that still allow patient access. These scenarios include: Next Generation Sequencing (NGS) and, a two-year fixed stopping rule (including a scenario that assumes high-risk patients, representing a particularly vulnerable subset of NDMM transplant-eligible patients, continue on DL maintenance until disease progression) which removes the reliance on MRD testing to guide maintenance treatment. All scenarios continue to demonstrate that DBLd remains a cost-effective use of NHS resources (see Comment 3 and Additional Analyses document accompanying this response (Section A, pages 2-6)).

- **Whether the modelled subsequent treatments are representative of what would be seen in NHS clinical practice:** Uncertainty regarding the modelling of subsequent treatments, including the proportion of patients modelled to receive belantamab mafodotin at second line, has been extensively explored via scenario analysis. We analysed the most recent NHS pharmacy/ePrescribing (VSTx) datasets, which provide the monthly distribution of subsequent treatments from October 2024 to September 2025[2]. Recognising that uptake of new treatments is likely to change over time, we combined the observed distributions with clinical expert judgement to produce projected future treatment distributions. In addition, we also considered a conservative scenario in which the subsequent treatment distribution remains consistent with the observed VSTx data where the uptake of belantamab mafodotin at second line remains low. Results continue to demonstrate that DBLd followed by DL maintenance remains a cost-effective use of NHS resources even when considering highly conservative market share assumptions not expected to reflect future prescribing behaviour following recent changes to the NICE recommended pathway.

In the remainder of this response, J&J focus on the key areas of uncertainty identified in the DGD. Additional analyses are provided in a separate accompanying document and, when considered together, are intended to reduce any residual decision-making uncertainty and support a positive final draft guidance recommendation for DBLd for untreated multiple myeloma when an autologous stem cell transplant is suitable. Importantly, DBLd remains a cost-effective use of NHS resources for all scenarios explored – indeed DBLd is dominant, representing improved efficacy at lower overall cost to the NHS. In addition, any concern regarding the feasibility to implement routine MRD testing in the NHS to guide discontinuation of daratumumab maintenance treatment is mitigated by inclusion of a scenario exploring a two-year fixed stopping rule which J&J hope will help avoid any unnecessary delays to patient access.

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1	**Indirect and direct treatment comparisons (DGD, Section 3.4)** *"The committee noted some generalisability issues with the AURIGA trial. It queried if the low proportion of people who received subsequent anti-CD38 treatments (daratumumab or isatuximab) after LEN maintenance in AURIGA would be representative of what would happen in the NHS. A clinical expert stated that it is likely people would be treated with daratumumab if they had not received it previously. So, AURIGA might not be representative of NHS practice. Another considered PERSEUS to be more relevant to clinical practice as more people who had not received daratumumab at first line went on to receive it at subsequent lines."* *"The committee concluded that reweighted IPTW analysis from the PERSEUS trial should be used for the relative effectiveness to inform the cost-effectiveness estimates. The committee concluded it would consider the uncertainties with the approach in its decision-making."* J&J note the Committee's preference to use the reweighted IPTW analysis from PERSEUS for the relative effectiveness of DL versus L maintenance to inform the cost-effectiveness model. We also note the Committee's request for further details of the ITC conducted and presentation of alternative ITC adjustment methods. Full details of the inverse probability of treatment weighting (IPTW) approach, including the balance of covariates before and after reweighting, assessment of overlap between populations before and after reweighting, distribution of propensity scores, and distribution of average treatment effect in the treated (ATT) weights (for both base case covariates and sensitivity covariates) are provided in the Additional Analyses document that supports this response (Section B, page 7 and Annex, page 33). Briefly, these results show that most variables were well balanced before reweighting with the exception of post-consolidation MRD status with a higher proportion of patients MRD-negative on the DL maintenance arm (DL: 62.1%; L: 40.1%). All variables were balanced after reweighting which was reflected in the propensity score distribution which showed improved overlap after matching patients to the DL arm. The distribution of weights for the base case ATT weighting resulted in over 30% of L patients down weighted. Following the Committee's request to explore alternate treatment comparison methods, J&J have performed doubly robust and multivariate regression analyses to isolate the treatment benefit of DL versus L in the PERSEUS trial (Additional Analyses, Section B, pages 7-9). The results are broadly consistent with the IPTW-ATT method for both PFS and OS, providing reassurance regarding the relative effect estimates used to inform the economic model. Furthermore, J&J have provided updated cost-effectiveness results based on the IPTW reweighted analysis from PERSEUS, along with additional scenario analyses exploring results based on the doubly robust and multivariate regression methods (Additional Analyses, Section B, pages 20-22).
2	**Modelling PFS and OS (DGD, Section 3.6)** *"The committee concluded that its preferred method to model PFS and OS for the DAR+BOR+THA+DEX followed by LEN maintenance arm would be to apply the hazard ratios generated from the IPTW of the PERSEUS trial. They noted long term OS and PFS estimates after applying the hazard ratios from PERSEUS had not been presented. As a result, the clinical experts could not comment on whether the long-term estimates of OS and PFS for the comparator arm were similar to what would be expected in the NHS. So, the committee was not able to conclude on the most appropriate OS and PFS parametric distributions."* In response to the Committee's preference to use the reweighted hazard ratios from PERSEUS to inform the relative effectiveness of DL versus L maintenance (rather than AURIGA), J&J has updated the survival modelling for DBTd-L. Specifically, we have applied the reweighted OS and PFS hazard ratios to adjust the chosen extrapolation of the DBLd-DL arm of the PERSEUS trial from the onset of maintenance. This

	generated a proxy OS and PFS extrapolation for DBTd induction and consolidation followed by L maintenance in the absence of trial data for the full (comparator) treatment sequence. To support Committee decision making, J&J has explored the full range of standard parametric models for the DBLd-DL reference curve and compared the resultant long-term modelled estimates for DBTd-L OS and PFS against clinical expert estimates at 10-, 15- and 25-years. The results continue to support the exponential and generalised gamma distributions for OS and PFS respectively. Refer to the Additional Analyses document for further details (Section B, page 9 – 15), including a scenario analysis exploring a more conservative Gompertz distribution for PFS which shows that DBLd-DL remains dominant when compared against DBTd-L (Section B, page 22-23).
3	**MRD-negativity stopping rule (DGD, Section 3.7)** *"The EAG stated that assuming all people continue daratumumab maintenance until progression has a large impact on cost-effectiveness."* The intervention arm of PERSEUS investigated an MRD-guided, response-adapted treatment strategy during the maintenance phase. Specifically, after a minimum of two years of maintenance therapy, patients who met the MRD guided stopping criteria discontinued daratumumab and continuing only with lenalidomide monotherapy until disease progression. Only patients who did not meet the MRD-guided stopping criteria continued with daratumumab plus lenalidomide (DL) maintenance until disease progression. J&J is not aware of any clinical evidence evaluating the efficacy and safety of DL maintenance until disease progression in an unselected patient population. Consequently, this EAG scenario is not considered appropriate or informative for NICE decision-making, as it is not evidence-based and primarily serves to extend treatment duration and associated costs unnecessarily, without any evidence or consideration for how health outcomes would be affected by continued treatment.
	MRD-negativity stopping rule (DGD, Section 3.7) *"The committee acknowledged that there would be clinical benefits to MRD guided treatment but that it was unclear whether MRD testing would be feasible in the NHS. It had concerns around how many MRD tests would be required to allow the discontinuation of daratumumab and if some people would decline testing in clinical practice. The committee was unclear on if it was feasible for all treatment centres to undertake MRD testing and where the tests would be processed. They also had concerns on if delays to MRD testing would result in daratumumab discontinuation later than the two-year time point. So, the committee was not able to conclude whether an MRD stopping rule was appropriate in the model which leads to uncertainty in the cost effectiveness estimates."* J&J note the Committee's concern regarding the feasibility to implement MRD testing nationally within the NHS. Insights gathered from a UK Clinical Advisory Boad (CAB) held in July 2025, involving myeloma clinicians and Heads of NHS diagnostic laboratory services with expertise in Next Generation Flow (NGF), Next Generation Sequencing (NGS) and related technologies, provides reassurance that MRD testing to support a daratumumab stopping rule is feasible within the existing NHS infrastructure and practice. <u>NHS system readiness and laboratory infrastructure</u> The CAB confirmed that the NHS already has established infrastructure to deliver high quality, high sensitivity MRD testing for myeloma. In particular, Leeds Teaching Hospitals NHS Trust and The Royal Marsden NHS Foundation Trust operate accredited laboratories that are recognised nationally for MRD assessment using standardised NGF assays. These laboratories meet sensitivity thresholds of 10^{-5} and operate to quality standards aligned with those used in large international clinical trials. In addition, CAB participants confirmed that approximately eight NHS laboratories currently participating in UK NEQAS schemes have the necessary capability to deliver MRD testing at equivalent analytical

standards. NEQAS participation provides assurance of assay validation, performance monitoring and inter-laboratory consistency. The availability of multiple accredited centres indicates that MRD testing capability is not limited to isolated specialist sites.

Feasibility across treatment centres and test processing model

J&J note the Committee's concerns about whether MRD testing could be undertaken across all treatment centres and where tests would be processed. The CAB advised that a centralised testing model is both feasible and already routine within NHS haematology services. Under this model, bone marrow samples are collected locally at treating centres and transferred to specialist laboratories for analysis. This approach is routinely used in standard NHS care for other haematological malignancies, such as chronic lymphocytic leukaemia (CLL). In addition, CAB participants cited the RADAR study[3] as an example of clinical trial use, in which patients were recruited from approximately 80 NHS sites nationally using centralised MRD testing pathways. Laboratory leads from Leeds and The Royal Marsden confirmed that they regularly receive bone marrow samples from geographically distant NHS sites and that sample integrity and analytic validity are maintained following transport, provided established protocols are followed.

Logistic pathways and Trust-level SOPs

The CAB confirmed that standardised pathways for bone marrow sampling, packaging and transport are already embedded within NHS Trust SOPs.

Specifically:

- Bone marrow aspirates are obtained by haematologists or appropriately trained clinicians, supported by trained nursing staff.
- Samples are labelled with full patient identifiers and securely packaged in sterile, temperature-controlled containers.
- Transport is coordinated by designated clinical or laboratory staff using NHS-approved courier services in accordance with national protocols for inter-hospital specimen handling.

These processes are identical to those already used for other complex haematological diagnostics. J&J is committed to supporting pathway education and the sharing of best practice to ensure clarity of roles and responsibilities across Trusts and to minimise unwarranted variation. For example, to support feasibility and consistent implementation of the MRD testing pathway in routine NHS practice,

[redacted]

If recommended by NICE, it is notable that the first NGF test required to inform the MRD-based stopping criteria for DL maintenance would be approximately 21-months after the first patients start DBLd induction therapy (9-months for the initial induction/transplant/consolidation - factoring-in recovery time - followed by 12-months maintenance). J&J consider this sufficient time to provide the necessary education and training to support consistent implementation of routine MRD testing pathways for transplant-eligible NDMM patients across the NHS. This also represents an advantage of NGF over NGS technology which has the requirement for an additional baseline test, thus necessitating the availability of established MRD testing pathways and services from initial diagnosis (refer to commentary below for further discussion on NGS).

Laboratory capacity and volume of testing

The Committee's concern about whether sufficient capacity exists to deliver MRD testing at scale and within required timelines can be contextualised using NHS England Blueteq data submitted in the Budget Impact Submission for ID6249. Over the 12-month period from July 2024 to June 2025:

- 1,565 patients were registered for daratumumab based induction therapy (DBTd), and-based induction therapy (DBTd), and
- 1,005 patients were registered for lenalidomide maintenance.

This population represents those eligible for daratumumab plus lenalidomide (DL) maintenance and therefore for MRD testing to inform treatment discontinuation. At the CAB, lead clinical scientists from both Leeds and the Royal Marsden confirmed that the expected testing demand associated with these NHSE patient numbers would fall within the combined capacity of their two centres.

Risk of testing delays and impact on the stopping rule

CAB feedback indicated that the risk of testing delays is low in routine practice due to:

- Established and predictable sample transport pathways;
- Validated laboratory workflows with defined turnaround times; and
- Ongoing quality assurance mechanisms, including NEQAS participation.

When MRD testing is planned prospectively as part of the treatment pathway, laboratories are able to schedule capacity accordingly. Recent and continual operational improvements, including streamlined sample collection protocols and logistics, further reduce the likelihood of systematic delays sufficient to materially affect the daratumumab stopping rule.

Patient acceptance of MRD testing

Clinicians at the CAB advised that bone marrow assessment is already a familiar component of myeloma management within the NHS. When MRD testing is presented as a tool to inform treatment de-escalation and potentially reduce long-term exposure to therapy, it was viewed as acceptable in routine clinical practice, with no expectation of widespread refusal. This view was supported by patient expert feedback per the draft guidance which notes, *"if MRD testing could tailor their treatment and enable them to stop treatment, they would be more likely to want the testing done"*.

Conclusion

Based on input from UK clinical and laboratory experts, MRD testing using validated NGF technology delivered through established centralised services at Leeds Teaching Hospitals NHS Trust and The Royal Marsden NHS Foundation Trust is operationally feasible within current NHS infrastructure. Both centres operate accredited laboratories with standardised, high sensitivity NGF assays and established referral and logistics pathways that are routinely used by NHS treatment centres nationwide. The anticipated volume of MRD testing required to support a daratumumab stopping rule is within existing laboratory capacity, and potential risks related to access, turnaround times, and patient acceptance are considered manageable within current clinical practice and 21-month lead time for further optimisation. On this basis, J&J considers that the inclusion of an NGF based MRD stopping rule in the economic model is appropriate and represents a realistic and implementable NHS delivery scenario.

J&J does, however, recognise and support the goals of the NHS 10 Year Health Plan and the National Cancer Plan which includes the delivery of comprehensive and ubiquitous genomic profiling for solid cancers and haematological malignancies.[4, 5] Whilst this technology goes beyond the requirements of what's necessary to inform the MRD-based stopping rule in PERSEUS, J&J recognise that in the future it is expected to deliver enhanced benefit to patients including provision of comprehensive genomic analysis and molecular profiling to guide precision treatment decisions and access to clinical trials. This broader ambition of the NHS is expected to lead to a transition over the next one to two years toward next generation sequencing (NGS) for MRD assessment delivered through the Genomic Laboratory Hub (GLH) network.

While NGS offers higher analytical sensitivity (10^{-6}) than the accepted IMWG standard (10^{-5}) that underpins the evidence for stopping in the PERSEUS trial, it is not yet routinely deployable at scale across the NHS due to ongoing infrastructural, regulatory, and cost considerations. By contrast, flow cytometry is

already embedded within NHS haematology services, supported by validated protocols, accredited laboratories, robust logistics, and rapid turnaround times, and delivers a clinically appropriate sensitivity (10^{-5}) to inform current treatment decisions. Clinical and laboratory experts therefore anticipate there to be a period of transition from NGF to NGS where both technologies will coexist as the NHS capability evolves to meet the objectives of the 10 Year Health Plan. If recommended by NICE, J&J therefore anticipate a phased transition from NGF to NGS-based testing. In rare instances where neither test is available, J&J consider a two-year fixed duration for DL maintenance preferrable to no access (see below), ensuring that all newly diagnosed transplant-eligible patients have the opportunity to benefit from deeper, more durable remissions and the hope of a functional cure from their myeloma.

To support Committee decision making, we consider the following scenarios:

1. MRD testing conducted using NGS technology delivered by the NHS Genomic Medicine Service, with testing performed across their network of seven GLHs. Under an NGS-based approach, a baseline MRD assessment at diagnosis is required to enable subsequent longitudinal testing. As a result, all patients would undergo a minimum of three MRD tests, with an additional test required for a subset of patients who achieve MRD negativity at a later time point, as detailed in the Company submission.

   Standard diagnostic procedures for multiple myeloma include a bone marrow biopsy. Consequently, the additional baseline lab test required for MRD assessment by NGS will not require the patient to be subjected to an additional bone marrow biopsy.

2. Two-year fixed treatment duration (all patients): daratumumab plus lenalidomide maintenance is given for a fixed treatment duration of two years for all patients following induction and consolidation therapy with DBLd. Clinical efficacy data for this scenario is informed by the phase II GRIFFIN study[6] (refer company submission Appendix N).

   J&J has provided this scenario should the Committee conclude that, despite the additional evidence presented, MRD-guided tailored maintenance is not feasible to deliver in the NHS within the 21-month timeframe following initiation of induction therapy. Whilst two-year fixed duration is still expected to deliver significant improved efficacy over current standard of care, it would deny patients who remain MRD-positive (or MRD-negative but non-sustained), the opportunity to continue DL maintenance beyond two-years including high-risk patients who, arguably, stand to benefit most from intensified maintenance therapy. Notwithstanding, J&J understand that this is preferred by clinical experts as compared to not having any access to DL maintenance.

3. Two-year fixed treatment duration (excl. high-risk patients): daratumumab plus lenalidomide maintenance is given for a fixed treatment duration of two-years for all patients, excluding high-risk patients who continue to receive DL maintenance until clinical progression, following induction and consolidation therapy with DBLd. Clinical efficacy data for this scenario is informed by the phase II GRIFFIN study[6] (refer company submission Appendix N).

DBLd remains a cost-effective use of NHS resources for all scenarios explored, providing reassurance that the overall conclusions are robust to the choice of MRD technology (NGF versus NGS). Regardless of the testing method, J&J are committed to working with all relevant stakeholders including NICE, NHS England, local NHS trusts and health care professionals including laboratory pathologists to ensure that there is no unnecessary delay to patient access to the PERSEUS regimen. This includes consideration of a two-year fixed treatment duration in the unlikely event an MRD test is not available. Please refer to the Additional Analysis document for further details of these scenarios (Section B, pages 25-32).

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4	**Modelling time to treatment discontinuation (DGD, Section 3.8)** *"The committee concluded that the same source should be used to model treatment discontinuation and effectiveness. They recalled their preference for using hazard ratios using the PERSEUS data to estimate the effectiveness of LEN maintenance. So, concluded that the TTD Kaplan-Meier from PERSEUS should be used to inform lenalidomide discontinuation in the DAR+BOR+THA+DEX followed by LEN arm. They noted that as different induction and consolidation treatments were received in PERSEUS, the outcomes may not fully reflect what would be expected in NHS clinical practice. The committee concluded it would take this uncertainty into account in decision-making.* In line with the Committee's preferred modelling assumption for TTD, J&J have updated the economic model to use the Kaplan-Meier data from PERSEUS to inform lenalidomide discontinuation. Uncertainty regarding this assumption has been explored via scenario analyses using the most optimistic (log-normal) and pessimistic (Gompertz) TTD curve selections which shows that the incremental costs change by [redacted]% and [redacted]% from the base case, respectively. This demonstrates that TTD modelling for lenalidomide maintenance is not a key driver of cost-effectiveness or area of decision-making uncertainty. Furthermore, similar to efficacy, J&J has explored the reweighted TTD curve for L patients who were matched with the DL patients in PERSEUS. Results are comparable to the unweighted TTD curve, although it suggests that patients who respond well to treatment will stay a bit longer on maintenance treatment (Figure 1). J&J has retained the exponential curve selection as our preferred base-case. We note, however, that the more optimistic log-normal distribution which closely matches the reweighted TTD curve would improve overall cost-effectiveness due to an increase in incremental costs for the comparator treatment sequence. *Figure 1. Comparison of TTD curves for patients who received lenalidomide monotherapy maintenance between unweighted and reweighted patients in the PERSEUS trial.* [redacted] **Abbreviations:** BLd: bortezomib with lenalidomide and dexamethasone; KM: Kaplan Meier; L: lenalidomide; TTD: time to treatment discontinuation
5	**Subsequent treatment costs (DGD, Section 3.9)** *"The committee acknowledged that there was significant uncertainty around how well the proportions modelled to receive subsequent treatments reflected NHS practice. It was particularly concerned about the*

proportion modelled to receive belantamab mafodotin at second line. It also had concerns about how many people in each arm were modelled to progress to each line of therapy. It noted that some of the subsequent treatments in the model were very expensive which had a large impact on cost-effectiveness. So, there was too much uncertainty to conclude if the modelled subsequent treatments were representative of NHS clinical practice."

Distribution of subsequent treatments

The multiple myeloma (MM) treatment pathway in the UK is evolving rapidly with a number of recent NICE recommended treatment options including belantamab mafodotin at second-line (2L) and teclistamab at fourth-line (4L). Most recently, belantamab mafodotin in combination with pomalidomide and dexamethasone (BePd) and talquetamab have been recommended at 2L and 4L, respectively.

To address the Committee's concern regarding the modelling of subsequent treatments, J&J has reviewed recent NHS pharmacy/ePrescribing datasets (VSTx) showing the latest monthly distribution of subsequent treatments from October 2024 to September 2025.[2] Whilst the uptake of new treatment options remains limited, J&J understand that the situation is likely to rapidly evolve over the coming months as local protocols are established and clinicians gain experience using the new treatments and managing related toxicities. The VSTx datasets also represent all prevalent patients and does not give an accurate perspective of new patient share. As such, J&J sought to combine the observed distribution with clinical expert opinion to derive projected future treatment distributions to inform the economic model (Additional Analyses, Section B, pages 16 – 19, 24 - 25).

From a modelling perspective, cost-effectiveness is most sensitive to the distribution and cost of belantamab mafodotin at 2L. Following the positive NICE recommendation of belantamab mafodotin in combination with bortezomib and dexamethasone (BeBd) in June 2025, its market share has grown steadily month-on-month and clinical insights received by J&J indicate it is expected to displace daratumumab plus bortezomib and dexamethasone (DBd) given the comparative head-to-head clinical efficacy[7]. As such and acknowledging that current market share estimates for BeBd remains low, J&J has revised down its market share estimate for belantamab mafodotin from 80% to 50%, with [redacted] of patients anticipated to remain on DBd representing the balance after other 2L treatment options are accounted for. To fully explore uncertainty, a scenario analysis was also conducted where we assume the current distribution of subsequent treatments ([redacted] BeBd and [redacted] DBd at 2L). Reassuringly, this resulted in a dominant ICER in all scenarios.

Current market share estimates for teclistamab at 4L similarly remains low ([redacted]) reflecting the recency of the positive NICE recommendation in November 2024. J&J has revised its base case market share estimate from 50% to 60%, in line with the clinical expert feedback at the first appraisal committee meeting however, we also consider a scenario with lower share for teclistamab in line with current market share estimates.

Please refer to the Additional Analyses document submitted alongside this response for further details regarding the modelling of subsequent treatments for the revised base-case and scenarios (Section B, pages 24 - 25).

Proportion of patients modelled to receive a subsequent treatment

J&J note the Committee's concern regarding the proportion of people in each arm who were modelled to progress to each line of therapy.

In the model, the proportion receiving subsequent treatment increases with follow-up (over time) and is driven by PFS and OS. Progression into 2L treatment is governed by the DBLd-DL or DBTd-L PFS curves, while progression into further subsequent lines (i.e., third-line (3L) and fourth-line (4L)) is determined by

	the weighted median PFS of the relevant treatments in that line of therapy. To reduce uncertainty and support Committee decision making, J&J report the proportion of patients in each arm modelled to progress to successive lines of therapy. In the base case, the model predicts that [redacted] and [redacted] of patients (calculated as those who progress minus those who die) in the DBTd-L arm will progress to 2L, 3L and 4L, respectively; in the DBLd-DL arm the corresponding proportions are, [redacted], [redacted] and [redacted] (Additional Analyses, Section B, pages 20 – 21). Within the first five years, the model predicts that [redacted], [redacted] and [redacted] of patients in the DBTd-L arm progress to 2L, 3L and 4L, respectively, whereas in the DBLd-DL arm the figures are [redacted], [redacted] and [redacted], respectively. These results are in line with observations from PERSEUS trial, where, at the data cutoff of 01 August 2023, only 9.4% of patients in the DBLd-DL arm and 26.8% in the BLd-L arm had received at least one subsequent treatment. Median PFS for DBLd-DL ([redacted] years) is almost twofold that for DBTd-L ([redacted] years), which is mirrored by the difference in the proportions modelled to receive subsequent therapy. Moreover, J&J note that the modelled proportion receiving subsequent treatment following DBTd-L is [redacted], which may be conservative relative to TA763, where [redacted] of alive patients in the DBTd-L arm progressed to second line therapy. The difference is driven by the modelled PFS curve, which is above the PFS curve in TA763 after 10 years, resulting in fewer patients progressing.
6	**Utility values (DGD, Section 3.10)** *"The committee noted that ideally a different utility value would be applied for each line of treatment in the progressed disease state. The committee concluded that applying a single utility value post progression was acceptable but acknowledged that was a simplifying assumption and that applying a utility value weighted by the line of treatment could be an alternative approach."* J&J agree that applying a single utility value to the post-progression health state is a simplifying assumption. As such, we also explore a scenario that assigns a different utility value for each line of treatment in the progressed disease health state. Specifically, we apply a utility value weighted by line of treatment as suggested by the EAG, which results in a decrease in total QALYs in the DBTd-L arm. Please refer to the Additional Analyses document submitted alongside this response for further details (Section B, page 23 – 24). Thus, whilst a simplifying assumption, applying a single utility value to the post-progression health state is also a conservative assumption that results in an overestimation of QALYs for the comparator is positive uncertainty and is not a key area of decision-making uncertainty.
7	**Areas needing clarification (DGD, Section 3.13)** "*The committee considered that there were many areas of uncertainty (see section 3.11) and would like to see clarification on: whether there is further clinical evidence for the full treatment sequence of DAR+BOR+THA+DEX followed by LEN maintenance including if real-world evidence from the SACT dataset is available.*" There is limited real-world evidence (RWE) reporting clinical effectiveness and outcomes for DBTd followed by lenalidomide maintenance since the positive NICE recommendation for TA763 in February 2022. As part of the ongoing appraisal for DBLd, NICE, in partnership with the National Disease and Registration Service (NDRS), commissioned a systemic anti-cancer therapy (SACT) report exploring age, gender, overall survival and time on treatment for those receiving lenalidomide maintenance therapy following an autologous stem cell transplant and an induction/consolidation regimen containing daratumumab (cohort 2). A second cohort agnostic to the induction/consolidation regimen received (cohort 1) was also explored, however we do not comment further here given the high overlap (94%) and recognition of DBTd-L as the most relevant comparator for this appraisal (DGD, page 8). Whilst J&J support NICE's ambition on RWE, it is important that any RWE analysis adheres to a high degree of methodological robustness and aligns with the NICE RWE framework.[8] Whilst the SACT report

provides details of the methods followed, and cohort inclusion/exclusion criteria, J&J have the following concerns regarding the use and interpretation of this dataset:

- Cohort definition: the use of the NDRS myeloma group codes (defined by ICD10 C969 or D479 AND ICD03 morphology codes of 9732/3) mean the cohort is likely to include patients diagnosed with Myelomatosis, Plasma cell myeloma and myeloma (NOS) or plasmacytic leukemia. There is a risk that patients included within the cohort do not belong to the relevant indication and therefore there is a selection bias and the patient cohort may not be representative of the intended population.

- Lack of a target trial emulation (TTE) approach: the NICE RWE Framework highlights the necessity in taking a target trial emulation approach to account for selection and confounding bias when attempting to compare outcomes between cohorts. The absence of a TTE approach in this analysis restricts any attempt to indirectly compare outcomes in the SACT cohorts versus modelled estimates for DBTd-L in clinical trial data.

- Patient characteristics: the SACT report only reports the age and gender distribution of the cohort with no details of important prognostic variables for multiple myeloma including, for example, ISS (or R-ISS) staging, and performance status. Even in appropriately defined cohorts where a target trial emulation approach is employed any attempt to indirectly compare outcomes versus modelled estimates for DBTd-L would be highly susceptible to bias unless these potential confounding clinical factors are reported and appropriately used to achieve population balance.

- Data immaturity: The median follow-up time for cohort 2 OS was 22.7 months (treatment duration median follow-up not reported). This limited follow-up, and high number of censored events after 12-months for both OS and treatment duration, substantially restricts the dataset's usefulness for informing long-term model projections.

- Time on treatment reporting: the SACT report does not provide outcome definitions for time on treatment which limits interpretation of results. The SACT report does not provide details of any rules applied regarding the handling of dose reductions or dose interruptions, rules on treatment gaps to define treatment persistence versus treatment discontinuation which is critical for a robust definition and limits its usefulness to inform this appraisal. The NICE RWE Framework is very specific about ensuring operational definitions are reported for endpoints in protocols to avoid misclassification bias.

- Lack of data reporting progression-free survival (PFS): an operational definition for PFS cannot be robustly constructed using SACT data.

<u>Patient characteristics</u>
The proportion of male patients in SACT was 59.3% (n = 450), which is similar to the proportion of male patients in PERSEUS of 58.7% (n = 416). In SACT, mean age, standard deviation, median age and interquartile range (IQR) were similar between males and females. The median age at the onset of maintenance from SACT was 63 years, IQR 56 - 68 years, which is broadly consistent with the median age in the PERSEUS trial at randomisation of 60 years, IQR 31 – 70 years. These findings support the generalisability of the PERSEUS trial population to NHS NDMM patients.

<u>Overall survival</u>
Overall survival (OS) data for cohort 2 from SACT remains immature with median survival not reached. Whilst J&J does not consider the SACT data a suitable dataset to inform the decision problem, and note high censoring after 12 months which increases susceptibility to informative censoring, we note that that a

naïve comparison of overall survival from the onset of maintenance among patients who received DBTd-L is in line with the reweighted analysis curves from PERSEUS. Overlayed curves are presented in Figure 2.

Figure 2. Naïve comparison of OS curves for patients who received lenalidomide monotherapy maintenance between reweighted patients in the PERSEUS trial and SACT patients

Note: The Kaplan Meier curve for DBTd-L from the SACT report was digitized using the WebPlotDigitizer.[9]

In addition, long-term extrapolations from seven fitted parametric models indicate that 10-year survival from maintenance ranges from 75% to 88%, with the best statistically fitting curve (exponential) predicting 79.3% of patients alive at 10 years (Table 1). This broadly aligns with the Company's base case estimate of [redacted] for DBTd-L survival at 10 years, although the Company base case was fitted from randomisation which may partly explain the lower estimate (Additional Analyses, Section B: page 12).

Table 1. Estimated 10-year survival from the onset of lenalidomide maintenance

Parametric model	10-year survival	AIC	BIC
Exponential	79.3%	480.62	**485.25**
Weibull	76.1%	482.29	491.56
Log-normal	82.4%	479.93	489.2
Log-logistic	77.6%	482.09	491.36
Gamma	75.2%	482.23	491.49
Generalised Gamma	87.5%	**479.28**	493.17
Gompertz	87.8%	482.23	491.5

Key: AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion. Note that the 10-year survival was calculated based on the parameter estimates per SACT report.

Time on treatment

Similar to OS, the median time on treatment for cohort 2 from SACT was not reached at the end of study follow-up. Moreover, the SACT report does not adequately describe patient characteristics, nor provide a

	definition for time on treatment to allow a comparison against the TTD definition in PERSEUS. As such, J&J does not consider a naive comparison of the time on treatment data from SACT and TTD data from PERSEUS appropriate. We note, however, that due to the generic cost of lenalidomide, this is not a key driver of cost-effectiveness. Progression-free survival As noted above, the SACT report does not include an analysis of PFS which we understand cannot be reliably derived based on SACT data. J&J note, however, a recent UK RWE study based on a retrospective analysis of patients treated with DBTd (or BTd) at the Royal Marsden.[10] Included in this study were a total of 173 patients (DBTd: 103; BTd: 70) who received an autologous stem cell transplant (ASCT) between 1st January 2021 and 31 May 2024. Almost all patients in both groups received maintenance therapy with lenalidomide (DBTd: 98%; BTd: 98.6%). PFS in this study was defined as the time from the date of stem cell reinfusion to progression, according to IMWG criteria, or death from any cause. Whilst the median follow-up from ASCT for DBTd patients was short (10.9 months), the 24-month PFS rate was reported as 89.7% which is broadly consistent with the modelled PFS curve for DBTd-L ([redacted]) fitted from randomisation. In summary, despite the aforementioned limitations, SACT data supports generalisability of the PERSEUS study to UK clinical practice and provides reassurance regarding the OS model projections for the front-line treatment sequence DBTd-L. Whilst SACT does not report PFS, we were able to compare the 24-month PFS rate in the model for DBTd-L against Bertuglia et al. 2025[10] which shows a high degree of consistency, helping to reduce uncertainty related to the clinical plausibility of model projections for UK standard of care.

Insert extra rows as needed

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Daratumumab with bortezomib, lenalidomide and dexamethasone for untreated multiple myeloma when an autologous stem cell transplant is suitable [ID6249]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 4 February 2026. Please submit via NICE Docs.

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Single Technology Appraisal

Daratumumab with bortezomib, lenalidomide and dexamethasone for untreated multiple myeloma when an autologous stem cell transplant is suitable [ID6249]

Company Additional Analyses

[February 2025]

File name	Version	Contains confidential information	Date
ID6249_Daratumumab_Additional_Analyses_[noCON].docx	V1	Yes	February 2025

Introduction

These supplementary analyses explore the Committee's preferred assumptions per the NICE draft guidance for ID6249. Specifically, this includes:

- equal efficacy in PFS and OS between DBLd and DBTd during the induction and consolidation phase;
- reweighted hazard ratios using the PERSEUS data for the maintenance phase of DBTd followed by lenalidomide maintenance;
- single utility value in the progressed disease state; and
- TTD using PERSEUS data for lenalidomide discontinuation in the DBTd followed by lenalidomide maintenance arm.

In addition, Johnson & Johnson (J&J) note the Committee's concern regarding the distribution of subsequent treatments and proportion of people having subsequent treatments in the model. To further explore this uncertainty, J&J has reviewed Electronic Healthcare Record (EHR) and Commissioning Data (CoDa) along with Secondary Care Medicines Data (SCMD) to inform the distribution of subsequent treatments in the model.[1]

Section A: Summary of the updated base case and additional scenarios

J&J have updated the Company base case in line with the Committee's preferred assumptions and an update on the distribution of subsequent treatment based on the recent NHS pharmacy/ePrescribing datasets (October 2024 - September 2025) combined with clinical expert opinion.

Additional scenario analyses were conducted exploring results from multivariable regression and double robust methods for DL versus L comparison, use of the Gompertz for extrapolating DBLd-DL PFS, the impact of lower utility values applied to subsequent treatment lines, use of different utility values from previous TA763, the proportion modelled to receive belantamab mafodotin and selinexor at second & third-

line respectively, using next-generation sequencing MRD testing cost and a two-year fixed treatment duration for daratumumab maintenance. A PAS of [redacted] is applied in all scenarios. Deterministic and probabilistic results of the updated analyses are presented in Table 1 and Table 2, respectively. A user guide describing the key changes to the model and providing step-by-step instructions for running all scenarios is provided.[2]

Table 1. Deterministic analyses based on the Committee's preferred assumptions and results from additional scenarios to address uncertainty

	Total outcomes by treatment			Incremental outcomes			
	Costs	**LYs**	**QALYs**	**Costs**	**LYs**	**QALYs**	**ICER**
Base case							
DBTd-L	[redacted]	[redacted]	[redacted]	-	-	-	-
DBLd-DL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Scenario 1: DL vs L comparison using multivariable regression							
DBTd-L	[redacted]	[redacted]	[redacted]	-	-	-	-
DBLd-DL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Scenario 2: DL vs L comparison using doubly robust							
DBTd-L	[redacted]	[redacted]	[redacted]	-	-	-	-
DBLd-DL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Scenario 3: Gompertz distribution for PFS							
DBTd-L	[redacted]	[redacted]	[redacted]	-	-	-	-
DBLd-DL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Scenario 4: Utility value in the progressed disease state weighted by the line of treatment							
DBTd-L	[redacted]	[redacted]	[redacted]	-	-	-	-
DBLd-DL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Scenario 5: Utility values from TA763							
DBTd-L	[redacted]	[redacted]	[redacted]	-	-	-	-
DBLd-DL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Scenario 6(a): Subsequent treatment distribution: Current distribution with BeBd 4.1% and DBd 63.3% at 2L							
DBTd-L	[redacted]	[redacted]	[redacted]	-	-	-	-
DBLd-DL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Scenario 6(b): Subsequent treatment distribution: Inclusion of SBd at 3L with 8% market share							

DBTd-L	[redacted]	[redacted]	[redacted]	-	-	-	-
DBLd-DL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Scenario 7: MRD testing using NGS							
DBTd-L	[redacted]	[redacted]	[redacted]	-	-	-	-
DBLd-DL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Scenario 8(a): Daratumumab maintenance based on a 2-year fixed treatment duration							
DBTd-L	[redacted]	[redacted]	[redacted]	-	-	-	-
DBLd-DL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Scenario 8(b): Daratumumab maintenance based on a 2-year fixed treatment duration for all patients except for high-risk patients (21.7%)							
DBTd-L	[redacted]	[redacted]	[redacted]	-	-	-	-
DBLd-DL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Scenario 8(c): Daratumumab maintenance based on a 2-year fixed treatment duration (Pooled PERSEUS & GRIFFIN)							
DBTd-L	[redacted]	[redacted]	[redacted]	-	-	-	-
DBLd-DL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Scenario 8(d): Daratumumab maintenance based on a 2-year fixed treatment duration: PFS HR = 0.661							
DBTd-L	[redacted]	[redacted]	[redacted]	-	-	-	-
DBLd-DL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant

Abbreviations: 2L, second line; BeBd, belantamab mafodotin with bortezomib and dexamethasone, DBd, daratumumab with bortezomib and dexamethasone; DBLd, daratumumab with bortezomib, lenalidomide and dexamethasone; DBTd, daratumumab with bortezomib, thalidomide and dexamethasone; DL, daratumumab with lenalidomide; ICER, Incremental cost-effectiveness ratio; L, lenalidomide; LY, Life years; MRD, minimal residual disease; NGS, next generation sequencing; QALY, Quality adjusted life year; OS, Overall survival; PFS, progression-free survival

Table 2. Probabilistic analyses based on the Committee's preferred assumptions and results from additional scenarios to address uncertainty

	Total outcomes by treatment			**Incremental outcomes**			
	Costs	**LYs**	**QALYs**	**Costs**	**LYs**	**QALYs**	**ICER**
Base case							
DBTd-L	[redacted]	[redacted]	[redacted]	-	-	-	-
DBLd-DL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Scenario 1: DL vs L comparison using multivariable regression							
DBTd-L	[redacted]	[redacted]	[redacted]	-	-	-	-
DBLd-DL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Scenario 2: DL vs L comparison using doubly robust							
DBTd-L	[redacted]	[redacted]	[redacted]	-	-	-	-
DBLd-DL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant

Scenario 3: Gompertz distribution for PFS						
DBTd-L	[redacted]	[redacted]	[redacted]	-	-	-
DBLd-DL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Scenario 4: Utility value in the progressed disease state weighted by the line of treatment						
DBTd-L	[redacted]	[redacted]	[redacted]	-	-	-
DBLd-DL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Scenario 5: Utility values from TA763						
DBTd-L	[redacted]	[redacted]	[redacted]	-	-	-
DBLd-DL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Scenario 6(a): Subsequent treatment distribution: Current distribution with BeBd 4.1% and DBd 63.3% at 2L						
DBTd-L	[redacted]	[redacted]	[redacted]	-	-	-
DBLd-DL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Scenario 6(b): Subsequent treatment distribution: Inclusion of SBd at 3L with 8% market share						
DBTd-L	[redacted]	[redacted]	[redacted]	-	-	-
DBLd-DL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Scenario 7: MRD testing using NGS						
DBTd-L	[redacted]	[redacted]	[redacted]	-	-	-
DBLd-DL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Scenario 8(a): Daratumumab maintenance based on a 2-year fixed treatment duration						
DBTd-L	[redacted]	[redacted]	[redacted]	-	-	-
DBLd-DL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Scenario 8(b): Daratumumab maintenance based on a 2-year fixed treatment duration for all patients except for high-risk patients (21.7%)						
DBTd-L	[redacted]	[redacted]	[redacted]	-	-	-
DBLd-DL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Scenario 8(c): Daratumumab maintenance based on a 2-year fixed treatment duration (Pooled PERSEUS & GRIFFIN)						
DBTd-L	[redacted]	[redacted]	[redacted]	-	-	-
DBLd-DL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Scenario 8(d): Daratumumab maintenance based on a 2-year fixed treatment duration: PFS HR = 0.661						
DBTd-L	[redacted]	[redacted]	[redacted]	-	-	-
DBLd-DL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant

Abbreviations: 2L, second line; BeBd, belantamab mafodotin with bortezomib and dexamethasone, DBd, daratumumab with bortezomib and dexamethasone; DBLd, daratumumab with bortezomib, lenalidomide and dexamethasone; DBTd, daratumumab with bortezomib, thalidomide and dexamethasone; DL, daratumumab with lenalidomide; ICER, Incremental cost-effectiveness ratio; L, lenalidomide; LY, Life years; MRD, minimal residual disease; NGS, next generation sequencing; QALY, Quality adjusted life year; OS, Overall survival; PFS, progression-free survival

Section B: Additional evidence requested by the committee

Reweighted hazard ratios for the PERSEUS data for the maintenance phase of DBTd followed by lenalidomide maintenance

Efficacy data

In order to isolate the effect of DL versus L maintenance on progression-free survival (PFS) and overall survival (OS) following DBLd induction, HDT-ASCT, and DBLd consolidation, an inverse probability of treatment weighting (IPTW) analysis was performed using individual patient-level data from the PERSEUS trial[3]. The analysis included DBLd-DL patients and BLd-L patients who initiated maintenance therapy (DL (n=322) or L monotherapy (n=299)) and who had not progressed prior to the start of maintenance therapy.

Both PFS and OS from the start of maintenance therapy were then evaluated for DL maintenance versus L maintenance under three scenarios:

- L maintenance as observed in patients who had not progressed at the start of maintenance (i.e., without weighting) in PERSEUS,
- L maintenance with patients re-weighted to resemble DL patients with respect to post-consolidation MRD-negativity status and the base case baseline covariate set, and
- L maintenance with patients re-weighted to resemble DL patients with respect to post-consolidation MRD-negativity status and the sensitivity analysis baseline covariate set.

Additional details such as the balance of covariates before and after reweighting, assessment of overlap between populations before and after reweighting, distribution of propensity scores, and distribution of average treatment effect in the treated (ATT) weights (for both base case variables and sensitivity) are provided in the Annex.

Following the Committee's request to explore alternative methods, we have included the multivariable regression and the doubly robust methods. Regression adjustment

approach uses a Cox proportional hazard regression model conditional on covariates to predict outcomes. By including patient-level variables that may influence treatment outcomes in the regression model, the aim is to adjust for their potential confounding effects, i.e., estimate the treatment effects for each treatment group, adjusting for differences in patient characteristics. This allows for a fairer than otherwise comparison between the treatments, as the regression adjustment has accounted for potential imbalances in the patient populations. The doubly robust estimator specifies regression models for the outcome and the exposure as a function of covariates. It provides double protection from model misspecification[4, 5] and allows to model the exposure as a function of covariates to estimate the PS (or predicted probability of exposure conditional on covariates) for each individual, using the observed data.

Results from the doubly robust and multivariate regression analyses have been included and are broadly in line with the IPTW-ATT results. Results are presented in Table 3.

Table 3. Overview of PFS and OS results (before and after re-weighting) for DL versus L maintenance therapy in PERSEUS

Comparison	**PFS** **HR (95% CI)**	**OS** **HR (95% CI)**
DL vs L maintenance (unweighted)	[redacted]	[redacted]
IPTW-ATT	[redacted]	[redacted]
DL vs L maintenance (weighted; base case baseline covariate set)	[redacted]	[redacted]
DL vs L maintenance (weighted; sensitivity analysis baseline covariate set)	[redacted]	[redacted]
Doubly robust		

DL vs L maintenance (weighted; base case baseline covariate set)	[redacted]	[redacted]
DL vs L maintenance (weighted; sensitivity analysis baseline covariate set)	[redacted]	[redacted]
Multivariable regression		
DL vs L maintenance (weighted; base case baseline covariate set)	[redacted]	[redacted]
DL vs L maintenance (weighted; sensitivity analysis baseline covariate set)	[redacted]	[redacted]

Abbreviations: ATT: average treatment effect in the treated; CI: confidence interval; DL: daratumumab and lenalidomide; HR: hazard ratio; IPTW: inverse probability of treatment weighting; L: lenalidomide; OS: overall survival; PFS: progression-free survival.

In the base case economic model, the HRs derived using the base covariate set in the IPTW-ATT analysis were applied. The proportional hazards (PH) assumption was assessed via Schoenfeld residuals of the survival outcome data from the IPTW-ATT analysis. No evidence of violation of the PH assumption was observed, indicating that the use of a HR as a summary measure for treatment effect in terms of both PFS and OS was appropriate. Full details of the PH assessments can be found in the Annex. Scenario analyses were conducted using the HRs derived from both the doubly robust and multivariable methods.

Extrapolation of overall survival

DBLd with DL maintenance

Per the original Company submission, long-term OS extrapolations for DBLd-DL were obtained by fitting standard parametric distributions to observed OS data from the intervention arm of the PERSEUS trial (Figure 1). Comparison of predicted survival rates for DBLd-DL OS extrapolations capped by the general population mortality is presented in Table 4.

Figure 1. Extrapolations of OS for DBLd-DL using IPD from the PERSEUS trial

Abbreviations: DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; DL: daratumumab with lenalidomide; IPD: individual patient data; KM: Kaplan-Meier; OS: overall survival.

Table 4. Comparison of predicted survival rates for DBLd-DL OS extrapolations (with GPM cap)

Survival model	DBLd-DL			
	Mean OS (months)	OS survival rates (%, mean [range])		
		10 years	15 years	25 years
Clinical expert estimates				
Clinical expert estimates	NA	77 [75, 80]	67 [65,70]	38 [25, 53]
Extrapolations				
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]
Generalised Gamma	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; DL: daratumumab with lenalidomide; GPM: general population mortality; NA: not applicable; OS: overall survival.

The exponential distribution for DBLd-DL OS was selected as the base case extrapolation as it had the best statistical fit, aligned best with the observed hazards, and had the closest fit to clinician estimates (refer company submission Section 3.3.1.4). J&J note the exponential distribution for OS was also considered the most appropriate curve choice by the EAG.

DBTd with L maintenance

J&J has updated the survival modelling for DBTd-L in line with the Committee's preference to use the reweighted hazard ratios from PERSEUS to inform the relative effectiveness of DL versus L maintenance (rather than AURIGA). Specifically, the reweighted OS hazard ratio from PERSEUS was applied to adjust the chosen extrapolation of the DBLd-DL arm of the PERSEUS trial from the onset of maintenance therapy (~9.7 months from randomisation). This generated a proxy OS extrapolation (presented in Figure 2) for DBTd induction and consolidation followed by L maintenance in the absence of trial data for the full treatment sequence.

Long-term estimates of OS estimated by clinicians and the predicted estimates by DBTd-L extrapolation (derived from the application of the reweighted PERSEUS HR on the chosen DBLd-DL OS extrapolation) are presented in Table 5. The long-term OS estimates derived for DBTd-L, using the exponential distribution as the reference curve for DBLd-DL, are therefore within the range of clinical expert estimates provided across two landmark timepoints (15 and, 25 years), confirming its clinical validity. The DBTd-L extrapolation generated is therefore considered a suitable proxy for modelling DBTd-L OS in the absence of trial data investigating the full standard of care (SoC) treatment sequence.

Figure 2. OS exponential extrapolation for DBLd-DL, and DBTd-L derived from application of the relative treatment effect (for maintenance phase) derived from the reweighted analysis of PERSEUS on the selected DBLd-DL extrapolation

Abbreviations: DBTd: daratumumab, bortezomib, thalidomide and dexamethasone; DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; DL: daratumumab-lenalidomide; KM: Kaplan-Meier; GPM: general population mortality; L: lenalidomide; OS: overall survival.

Table 5. Comparison of predicted survival rates for DBTd-L OS extrapolations (with GPM cap)

Survival model	DBTd-L			
	Mean OS (months)	OS survival rates (%, mean [range])		
		10 years	15 years	25 years
Clinical expert estimates				
Clinical expert estimates	NA	68 [60, 70]	55 [45, 65]	30 [15, 45]
Extrapolations				
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]
Generalised Gamma	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; L: lenalidomide; GPM: general population mortality; NA: not applicable; OS: overall survival.

Extrapolation of progression-free survival

DBLd with DL maintenance

Per the original Company submission, long-term PFS extrapolations for DBLd-DL were obtained by fitting standard parametric distributions to observed PFS data from the intervention arm of the PERSEUS trial (Figure 3). The PFS extrapolations implemented in the model include a cap to ensure that PFS did not exceed OS for DBLd-DL to ensure clinical plausibility. Long-term estimates of PFS for each parametric extrapolation are provided in Table 6.

Figure 3. Extrapolations of PFS for DBLd-DL using IPD from the PERSEUS trial

Abbreviations: DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; DL: daratumumab with lenalidomide; IPD: individual patient data; KM: Kaplan-Meier; PFS: progression-free survival.

Table 6. Comparison of predicted survival rates for DBLd-DL PFS extrapolations (with OS cap)

Survival model	DBLd-DL			
	Mean OS (months)	PFS survival rates (%, mean [range])		
		10 years	15 years	25 years
Clinical expert estimates				
Clinical expert estimates	NA	64 [60, 65]	48 [45, 55]	21 [15, 35]
Extrapolations				
Exponential	[redacted]	[redacted]	[redacted]	[redacted]

Survival model	DBLd-DL			
	Mean OS (months)	PFS survival rates (%, mean [range])		
		10 years	15 years	25 years
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]
Generalised Gamma	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; DL: daratumumab with lenalidomide; GPM: general population mortality; NA: not applicable; PFS: progression-free survival.

The generalised gamma distribution for DBLd-DL PFS was selected as the base case extrapolation as it had the closest fit to clinician estimates and observed hazards (refer Company submission Section 3.3.1.5).

DBTd with L maintenance

The relative treatment benefit of DL versus L maintenance, derived from the reweighted PERSEUS analysis, was applied to adjust the chosen extrapolation of the DBLd-DL arm of the PERSEUS trial from the onset of maintenance therapy (~9.7 months from randomisation). This generated a proxy PFS extrapolation (presented in Figure 4) for DBTd induction and consolidation followed by L maintenance in the absence of trial data for the full treatment sequence.

Long-term estimates of PFS estimated by clinicians and the predicted estimates by DBTd-L extrapolation (derived from the application of the reweighted PERSEUS HR on the chosen DBLd-DL PFS extrapolation) are presented in Table 7. The long-term PFS estimates derived for DBTd-L, using the Generalised Gamma distribution as the reference curve for DBLd-DL, are therefore within the range of clinical expert estimates provided across two landmark timepoints (10 and, 25 years), confirming its clinical validity. The DBTd-L extrapolation generated is therefore considered a suitable proxy for modelling DBTd-L PFS in the absence of trial data investigating the full treatment sequence. As mentioned above, we also consider a scenario exploring a more conservative Gompertz distribution as the reference curve for DBLd-DL (lower-end of clinician estimates). Refer to Scenario analyses section below for further details.

Figure 4. PFS exponential extrapolation for DBLd-DL, and DBTd-L derived from application of the relative treatment effect (for maintenance phase) derived from the reweighted analysis of PERSEUS on the selected DBLd-DL extrapolation

Abbreviations: DBTd: daratumumab, bortezomib, thalidomide and dexamethasone; DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; DL: daratumumab-lenalidomide; KM: Kaplan-Meier; GPM: general population mortality; L: lenalidomide; PFS: progression-free survival.

Table 7. Comparison of predicted survival rates for DBTd-L PFS extrapolations (with OS cap)

Survival model	DBTd-L			
	Mean PFS (months)	PFS survival rates (%, mean [range])		
		10 years	15 years	25 years
Clinical expert estimates				
Clinical expert estimates	NA	34 [25, 40]	10 [0, 15]	3 [0, 5]
Extrapolations				
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]
Generalised Gamma	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: DBLd: daratumumab, bortezomib, lenalidomide and dexamethasone; L: lenalidomide; OS: overall survival; NA: not applicable; PFS: progression-free survival.

Distribution of subsequent treatments

J&J utilised data from NHS organisations in England to derive the proportion of patients on each subsequent treatment (VSTx dataset). VSTx is informed by NHS prescribing, pharmacy and commissioning datasets covering the period from October 2024 to September 2025[1]. The figures in Table 8 below were based on data available and evidence-based assumptions at the time of analysis, December 2025.

Given the recency of the NICE recommendation for belantamab mafodotin at second line (2L), we used as snapshot of patient numbers recorded in September 2025 representing the latest available data point to inform current market share estimates. We note that for established treatments, the market share was stable across the 12-month period, whilst for recently approved treatments, the uptake is shown to increase month-on-month.[1]

The distribution of patients on 2L, third line (3L) and fourth line (4L) treatment is presented in Table 8. This shows that the majority ([redacted]) of patients continue to receive daratumumab at 2L with bortezomib and dexamethasone (DBd) with limited uptake of belantamab mafodotin with bortezomib and dexamethasone (BeBd), albeit increasing, following its positive NICE recommendation in June 2025. It's important to note that this data represents market share estimates for all prevalent patients, rather than new patient share. The future estimate for BeBd is also expected to be higher given the Committee's conclusion of superior head-to-head efficacy versus DBd[6].

Table 8. Distribution of second line (2L), third line (3L) and fourth line (4L) treatments in patients where transplant is suitable[1]

Treatment by line	N (%)
2L regimen	
Daratumumab + Bortezomib + Dexamethasone (DBd)	[redacted]
Carfilzomib + Lenalidomide + Dexamethasone (CaLd)	[redacted]
Carfilzomib + Dexamethasone (Cad)	[redacted]
Selinexor + Bortezomib + Dexamethasone (SBd)	[redacted]
Lenalidomide + Dexamethasone (Ld)	[redacted]
Belantamab Mafodotin + Bortezomib + Dexamethasone (BeBd)	[redacted]
Other 2L*	[redacted]
3L regimen	

Ixazomib + Lenalidomide + Dexamethasone (ILd)	[redacted]
Panobinostat + Bortezomib + Dexamethasone (PanoBd)	[redacted]
4L regimen	**N (%)**
Daratumumab (D)	[redacted]
Isatuximab + Pomalidomide + Dexamethasone (IsaPd)	[redacted]
Elranatamab	[redacted]
Pomalidomide + Dexamethasone (Pd)	[redacted]
Teclistamab (Tec)	[redacted]
Talquetamab (Tal)	[redacted]

Abbreviations: 2L: second line regimens; 3L: third line regimens; 4L: fourth line regimens; *Bortezomib, Bortezomib + Dexamethasone, Bortezomib + Dexamethasone + Pomalidomide, Daratumumab + Dexamethasone + Pomalidomide, Dexamethasone + Elotuzumab + Lenalidomide

The distribution of patients on 3L treatment shows that the majority of patients received ixazomib with lenalidomide and dexamethasone (ILd) as a third-line treatment option. Only, a small proportion received panobinostat with bortezomib and dexamethasone (PanoBd).

The distribution of patients on 4L treatments shows that the majority of patients received daratumumab monotherapy and isatuximab with pomalidomide and dexamethasone (IsaPd) as a combination. Following the recent approvals of teclistamab and talquetamab, more patients are expected to receive these new regimens soon. IsaPd (n = 553) and elranatamab monotherapy (n = 261) are available through managed access and therefore have not been included in the analysis.

Current and future distributions used in the model

We have reweighted the distribution of treatments by considering only relevant treatments (Table 9). As described above, the VSTx data represents a snapshot of treatment distributions, however the MM pathway is fast evolving. Due to recency of MM pathway changes, the current distribution of subsequent treatments will significantly change in the near future. After excluding treatments not recommended and/or only available through managed access, we have combined the *current distribution* with clinical expert opinion to derive *future treatment distributions* used in the updated Company base case (Table 9). Scenario analysis based on the current observed market shares of BeBd and DBd in VSTx data are also explored.

2L

Removing the combined group of different treatments (*Other 2L*) from 2L treatments, the reweighted current proportion of DBd is [redacted] (Table 9, Current column). Whilst BeBd is expected to take a significant share of DBd at 2L, we have revised the market share estimate down from 80% to 50% following clinical expert feedback at the first committee meeting, noting its use may not be as high. Based on the VSTx data, we expect the majority of the BeBd share to be taken from DBd, reducing it from [redacted] to [redacted] in the future.

3L

The current and future proportions for 3L treatments: ILd and PanoBd are assumed to remain the same, with ILd taking the largest share as is in the VSTx data. It is expected that some patients would use selinexor with bortezomib and dexamethasone (SBd) at 3L, therefore we also considered a scenario where a small proportion ([redacted] based on IQVIA market research data[7]) receive SBd at 3L, such that ILd market share reduces to [redacted] with PanoBd remaining at [redacted]

4L

For the current distribution at 4L, we removed IsaPd and elranatamab monotherapy from 4L treatments and reweighted the proportion of the remaining treatments. For future distribution, we have increased the teclistamab market share estimate in the Company base case from 50% to 60% in line with clinical expert feedback at the first committee meeting. We also expect the market share for talquetamab to increase and to achieve this we adjusted down the market share for daratumumab monotherapy from [redacted] to [redacted] and Pd from [redacted] to [redacted]

Table 9. Comparison of current and predicted future distribution of subsequent treatments

Treatment	Current (%)	Future (%)
2L regimen		
Daratumumab + Bortezomib + Dexamethasone (DBd)	[redacted]	[redacted]
Carfilzomib + Lenalidomide + Dexamethasone (CaLd)	[redacted]	[redacted]
Carfilzomib + Dexamethasone (Cad)	[redacted]	[redacted]
Selinexor + Bortezomib + Dexamethasone (SBd)	[redacted]	[redacted]
Lenalidomide + Dexamethasone (Ld)	[redacted]	[redacted]
Belantamab Mafodotin + Bortezomib + Dexamethasone (BeBd)	[redacted]	[redacted]

3L regimen		
Ixazomib + Lenalidomide + Dexamethasone (ILd)	[redacted]	[redacted]
Panobinostat + Bortezomib + Dexamethasone (PanoBd)	[redacted]	[redacted]
Selinexor + Bortezomib + Dexamethasone (SBd)*	[redacted]	[redacted]
4L regimen		
Daratumumab (D)	[redacted]	[redacted]
Pomalidomide + Dexamethasone (Pd)	[redacted]	[redacted]
Teclistamab (Tec)	[redacted]	[redacted]
Talquetamab (Tal)	[redacted]	[redacted]

Abbreviations: 2L: second line regimens; 3L: third line regimens; 4L: fourth line regimens. *It's expected that some patients would use SBd at 3L

As a simplifying assumption, we assumed that the proportion of patients receiving subsequent treatments was the same regardless of prior treatment exposure (note, this was necessary as market share data based on prior treatment exposure was not available in VSTx). An identical approach of applying the same distribution of treatments after disease progression was adopted in TA11203.[8]

Base case results

The company base case now includes the following:

- Application of the HRs from the IPTW-ATT weighting based on base covariates to derive the proxy OS/PFS curves for DBTd-L,
- Subsequent treatment distributions based on the *predicted future* (Table 9, Future column) where BeBd will take a significant share of the DBd share at 2L based on clinical expert feedback
- Equal efficacy in PFS and OS between DBLd and DBTd during induction and consolidation phases
- Incidence of Grade 3/4 adverse events occurring during maintenance in 5% of patients in PERSEUS trial. Included adverse events are neutropenia (25.5% in the DL arm versus 36.0% in the L arm) and diarrhoea (8.1% in the DL arm versus 2.7% in the L arm)
- Single utility value in the progressed disease state
- DBLd-DL OS extrapolation using the exponential distribution

- DBLd-DL PFS extrapolation using the Generalised Gamma distribution
- TTD using PERSEUS data for lenalidomide discontinuation in the DBTd-L maintenance arm

The cost-effectiveness results based on the Committee's preferred assumptions and updated distribution of subsequent treatments are shown in Table 10. These results show that DBLd-DL dominates DBTd-L.

Table 10. Base case cost-effectiveness results

	Total outcomes by treatment			**Incremental outcomes**			
	Costs	**LYs**	**QALYs**	**Costs**	**LYs**	**QALYs**	**ICER**
DBTd-L	[redacted]	[redacted]	[redacted]	-	-	-	-
DBLd-DL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant

Abbreviations: DBLd, daratumumab with bortezomib, lenalidomide and dexamethasone; DBTd, daratumumab with bortezomib, thalidomide and dexamethasone; DL, daratumumab with lenalidomide; ICER, Incremental cost-effectiveness ratio; L, lenalidomide; LY, Life years; QALY, Quality adjusted life year

In the model, the proportion receiving subsequent treatment increases with follow-up (over time) and is driven by PFS and OS. Progression into 2Ltreatment is governed by the DBLd-DL or DBTd-L PFS curves, while progression into further subsequent lines (i.e., 3L and 4L) is determined by the weighted median PFS of the relevant treatments in that line of therapy.

The proportion of patients in each arm modelled to progress to each line of therapy are presented in Table 11. In the base case, the model predicts that [redacted]%, [redacted]% and [redacted]% of patients in the DBTd-L arm will progress to 2L, 3L and 4L, respectively; in the DBLd-DL arm the corresponding proportions are [redacted]%, [redacted]% and [redacted]%. Within the first five years, the model predicts that [redacted]%, [redacted]% and [redacted]% of patients in the DBLd-DL arm progress to 2L, 3L and 4L, respectively, whereas in the DBTd-L arm the corresponding proportions are [redacted]%, [redacted]% and [redacted]%, respectively. These results are in line with observations from PERSEUS trial, where after a median follow-up of 47.8 months 9.4% of patients in the DBLd-DL arm and 26.8% in the BLd-L arm had received at least one subsequent treatment. The proportion modelled to receive a subsequent treatment following DBTd-L ([redacted]%) may represent a

conservative estimate as in TA763, the proportion of alive patients progressing to second line therapy in the DBTd-L arm was [redacted]%.

Table 11. Incident subsequent treatment in the base case

Treatment arm	**1L->2L**	**2L->3L**	**3L->4L**
Overall			
DBLd-DL	[redacted]	[redacted]	[redacted]
DBTd-L	[redacted]	[redacted]	[redacted]
By time period			
DBLd-DL	**1L->2L**	**2L->3L**	**3L->4L**
<5years	[redacted]	[redacted]	[redacted]
5-10years	[redacted]	[redacted]	[redacted]
10-15years	[redacted]	[redacted]	[redacted]
15-20years	[redacted]	[redacted]	[redacted]
20+years	[redacted]	[redacted]	[redacted]
DBTd-L	**1L->2L**	**2L->3L**	**3L->4L**
<5years	[redacted]	[redacted]	[redacted]
5-10years	[redacted]	[redacted]	[redacted]
10-15years	[redacted]	[redacted]	[redacted]
15-20years	[redacted]	[redacted]	[redacted]
20+years	[redacted]	[redacted]	[redacted]

Abbreviations: DBLd, daratumumab with bortezomib, lenalidomide and dexamethasone; DBTd, daratumumab with bortezomib, thalidomide and dexamethasone; DL, daratumumab with lenalidomide; 1L: first line; 2L: second line; 3L: third line; 4L: fourth line

Scenario analyses

J&J has explored a number of scenario analyses to assess the impact of model inputs, and assumptions on the plausibility of the cost-effectiveness results.

Alternative methods to derive efficacy data for DBTd-L

We also considered other alternative methods to derive the HRs for both OS and PFS. In Table 12 and Table 13, we present cost-effectiveness results when HRs for OS are informed by multivariable and doubly robust methods, respectively.

Table 12. Scenario 1: DL vs L comparison informed by multivariable regression

	Total outcomes by treatment	**Incremental outcomes**

	Costs	LYs	QALYs	Costs	LYs	QALYs	ICER
DBTd-L	[redacted]	[redacted]	[redacted]	-	-	-	-
DBLd-DL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant

Abbreviations: DBLd, daratumumab with bortezomib, lenalidomide and dexamethasone; DBTd, daratumumab with bortezomib, thalidomide and dexamethasone; DL, daratumumab with lenalidomide; HR: hazard ratio; ICER, Incremental cost-effectiveness ratio; L, lenalidomide; LY, Life years; OS: overall survival; PFS: progression-free survival; QALY, Quality adjusted life year

Table 13. Scenario 2: DL vs L comparison informed by doubly robust method

	Total outcomes by treatment			Incremental outcomes			
	Costs	LYs	QALYs	Costs	LYs	QALYs	ICER
DBTd-L	[redacted]	[redacted]	[redacted]	-	-	-	-
DBLd-DL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant

Abbreviations: DBLd, daratumumab with bortezomib, lenalidomide and dexamethasone; DBTd, daratumumab with bortezomib, thalidomide and dexamethasone; DL, daratumumab with lenalidomide; HR: hazard ratio; ICER, Incremental cost-effectiveness ratio; L, lenalidomide; LY, Life years; OS: overall survival; PFS: progression-free survival; QALY, Quality adjusted life year

Gompertz distribution for PFS

In line with the EAG's preferred curve selection, we also considered the Gompertz distribution for PFS, with the corresponding cost-effectiveness results provided in Table 14.

Table 14. Scenario 3: Gompertz distribution for PFS

	Total outcomes by treatment			Incremental outcomes			
	Costs	LYs	QALYs	Costs	LYs	QALYs	ICER
DBTd-L	[redacted]	[redacted]	[redacted]	-	-	-	-
DBLd-DL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant

Abbreviations: DBLd, daratumumab with bortezomib, lenalidomide and dexamethasone; DBTd, daratumumab with bortezomib, thalidomide and dexamethasone; DL, daratumumab with lenalidomide; ICER, Incremental cost-effectiveness ratio; L, lenalidomide; LY, Life years; QALY, PFS: progression-free survival; Quality adjusted life year

Using efficacy inputs derived from alternative methods and by varying the selected PFS curves, the proportion of patients modelled to progress to second-line treatment

ranged from [redacted]% to [redacted]% in the DBTd-L arm and from [redacted]% to [redacted]% in the DBLd-DL arm (Table 15).

Table 15. Incident subsequent treatment in scenarios

Treatment arm	1L->2L	2L->3L	3L->4L
Base case			
DBLd-DL	[redacted]	[redacted]	[redacted]
DBTd-L	[redacted]	[redacted]	[redacted]
Scenario 1: DL vs L comparison using multivariable regression			
DBLd-DL	[redacted]	[redacted]	[redacted]
DBTd-L	[redacted]	[redacted]	[redacted]
Scenario 2: DL vs L comparison using doubly robust			
DBLd-DL	[redacted]	[redacted]	[redacted]
DBTd-L	[redacted]	[redacted]	[redacted]
Scenario 3: Gompertz distribution for PFS			
DBLd-DL	[redacted]	[redacted]	[redacted]
DBTd-L	[redacted]	[redacted]	[redacted]

Abbreviations: DBLd, daratumumab with bortezomib, lenalidomide and dexamethasone; DBTd, daratumumab with bortezomib, thalidomide and dexamethasone; DL, daratumumab with lenalidomide; 1L: first line; 2L: second line; 3L: third line; 4L: fourth line

Utility value in the progressed disease state weighted by the line of treatment

The Committee noted that the impact of multiple myeloma on health-related quality of life varies between individuals. It considered the utility values used for the progression-free state in the Company's base-case model to be an oversimplification that would likely overestimate utility. As suggested by the EAG, we modelled a scenario applying the observed difference in utility between progression-free maintenance and second-line treatment—calculated as [redacted]-[redacted] = [redacted]) to 3L and 4L treatment, giving utility values of [redacted] and [redacted], respectively. The corresponding cost-effectiveness results are provided in Table 16.

Table 16. Scenario 4: Utility value in the progressed disease state weighted by the line of treatment

	Total outcomes by treatment			Incremental outcomes			
	Costs	**LYs**	**QALYs**	**Costs**	**LYs**	**QALYs**	**ICER**
DBTd-L	[redacted]	[redacted]	[redacted]	-	-	-	-
DBLd-DL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant

Abbreviations: DBLd, daratumumab with bortezomib, lenalidomide and dexamethasone; DBTd, daratumumab with bortezomib, thalidomide and dexamethasone; DL, daratumumab with lenalidomide; ICER, Incremental cost-effectiveness ratio; L, lenalidomide; LY, Life years; QALY, Quality adjusted life year

Utility values from TA763

We also considered a scenario using the utility values used in TA763, and this resulted in the cost-effectiveness results provided in Table 17.

Table 17. Scenario 5: Utility values from TA763

	Total outcomes by treatment			Incremental outcomes			
	Costs	**LYs**	**QALYs**	**Costs**	**LYs**	**QALYs**	**ICER**
DBTd-L	[redacted]	[redacted]	[redacted]	-	-	-	-
DBLd-DL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant

Abbreviations: DBLd, daratumumab with bortezomib, lenalidomide and dexamethasone; DBTd, daratumumab with bortezomib, thalidomide and dexamethasone; DL, daratumumab with lenalidomide; ICER, Incremental cost-effectiveness ratio; L, lenalidomide; LY, Life years; QALY, Quality adjusted life year

Subsequent treatment distribution

We also considered a scenario using the *current distribution* (Table 9, Current column) of subsequent treatments, in which BeBd has a low market share at 2L of [redacted]% while DBd is dominant at [redacted]%. This is a highly conservative scenario as the VSTx data reflects all prevalent patients, rather than new patient share, and shows an increase in BeBd uptake month-on-month following its positive NICE recommendation. It is therefore not considered a true reflection of the expected future prescribing habits. The corresponding cost-effectiveness results are presented in Table 18.

Table 18. Scenario 6(a): Subsequent treatment distribution: Current distribution with BeBd [redacted]% and DBd [redacted]% at 2L

	Total outcomes by treatment			Incremental outcomes			
	Costs	**LYs**	**QALYs**	**Costs**	**LYs**	**QALYs**	**ICER**
DBTd-L	[redacted]	[redacted]	[redacted]	-	-	-	-
DBLd-DL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant

Abbreviations: BeBd, belantamab mafodotin with bortezomib and dexamethasone; DBd, daratumumab with bortezomib and dexamethasone; DBLd, daratumumab with bortezomib, lenalidomide and dexamethasone; DBTd, daratumumab with bortezomib, thalidomide and dexamethasone; DL, daratumumab with lenalidomide; ICER, Incremental cost-effectiveness ratio; L, lenalidomide; LY, Life years; QALY, Quality adjusted life year

It is expected that some patients would use SBd at 3L, therefore we also considered another scenario where [redacted] of the patients receive SBd at 3L, resulting in ILd market share of [redacted] and PanoBd of [redacted] (Table 19).

Table 19. Scenario 6(b): Subsequent treatment distribution: Inclusion of SBd at 3L with [redacted]% market share

	Total outcomes by treatment			Incremental outcomes			
	Costs	**LYs**	**QALYs**	**Costs**	**LYs**	**QALYs**	**ICER**
DBTd-L	[redacted]	[redacted]	[redacted]	-	-	-	-
DBLd-DL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant

Abbreviations: DBLd, daratumumab with bortezomib, lenalidomide and dexamethasone; DBTd, daratumumab with bortezomib, thalidomide and dexamethasone; DL, daratumumab with lenalidomide; ICER, Incremental cost-effectiveness ratio; L, lenalidomide; LY, Life years; QALY, Quality adjusted life year

MRD testing using NGS

In the base-case model we included the cost of a flow cytometry test to determine MRD-negativity. Flow cytometry is currently available, but we recognize the goals of the NHS 10 Year Health Plan and National Cancer plan which includes the delivery of comprehensive and ubiquitous genomic profiling for both solid cancers and hematological malignancies. This broader ambition of the NHS is expected to lead to the future delivery of MRD testing via a network of Genomic Laboratory Hubs (GLHs) using next-generation sequencing (NGS). For illustrative purposes, we therefore considered a scenario in which NGS is adopted in the future. NGS requires a

baseline MRD test at diagnosis, resulting in three tests for all patients and an additional test for a subset of patients who convert to MRD-negativity later, as explained in the Company submission. At the first committee meeting, the NHS lead estimated the cost of an NGS MRD test at £1,100–£1,400, and we therefore used the midpoint value of £1,250 per test. The cost-effectiveness results for the NGS testing scenario are presented in Table 20.

Table 20. Scenario 7: MRD testing using NGS

	Total outcomes by treatment			Incremental outcomes			
	Costs	**LYs**	**QALYs**	**Costs**	**LYs**	**QALYs**	**ICER**
DBTd-L	[redacted]	[redacted]	[redacted]	-	-	-	-
DBLd-DL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant

Abbreviations: DBLd, daratumumab with bortezomib, lenalidomide and dexamethasone; DBTd, daratumumab with bortezomib, thalidomide and dexamethasone; DL, daratumumab with lenalidomide; ICER, Incremental cost-effectiveness ratio; L, lenalidomide; LY, Life years; MRD, minimal residual disease; NGS, next generation sequencing; QALY, Quality adjusted life year

Fixed treatment duration for daratumumab maintenance

The GRIFFIN trial is an ongoing randomised, open-label, multicentre, Phase II trial in transplant eligible NDMM patients.[9] For more details, see Appendix N in the Company Submission. Daratumumab was given for a maximum of 24 months in the intervention arm regardless of MRD-negativity status and patients could continue with their standard of care according to local guidelines. Most patients (>85%)[10] in the trial continued with lenalidomide after 24 months fixed duration daratumumab maintenance, consistent with current UK standard of care maintenance.

Time to event outcomes, mainly OS and PFS in GRIFFIN and PERSEUS were similar despite all patients in the DBLd-DL arm discontinuing the daratumumab component after 24 months of maintenance (Figure 5 and Figure 6, respectively). This is not unexpected, since the majority of patients in PERSEUS had a comparable daratumumab exposure to those in GRIFFIN; two thirds of PERSEUS participants discontinued daratumumab after 2 years of maintenance.

Accordingly, and given the concordance of the observed OS and PFS curves between the two trials, this modelling scenario assumes that the efficacy in patients

who discontinue daratumumab after 24 months of maintenance treatment is reflected by the Company's selected OS and PFS extrapolations in the base case.

Figure 5. OS KM curves for the DBLd-DL in PERSEUS and GRIFFIN

Abbreviations: DBLd, daratumumab with bortezomib, lenalidomide and dexamethasone; DL, daratumumab with lenalidomide; KM, Kaplan Meier; OS, overall survival

Figure 6. PFS KM curves for the DBLd-DL in PERSEUS and GRIFFIN

Abbreviations: DBLd, daratumumab with bortezomib, lenalidomide and dexamethasone; DL, daratumumab with lenalidomide; KM, Kaplan Meier; PFS, progression-free survival

Mature time to treatment discontinuation (TTD) data were available for the cohort of patients who discontinued daratumumab maintenance therapy after 24 months.

Observed TTD KM data were therefore applied in the model for these patients, as presented in Figure 7 below.

Figure 7. Observed Kaplan-Meier TTD data for patients who discontinued daratumumab maintenance therapy after 24 months

Abbreviations: DVRd (DBLd), daratumumab with bortezomib, lenalidomide and dexamethasone; KM, Kaplan Meier; TTD: time to treatment discontinuation

Treatment duration for patients who received DL maintenance but discontinued lenalidomide maintenance therapy in GRIFFIN and PERSEUS are presented in Figure 8. TTD for patients who received DL maintenance following DBLd induction and consolidation, but discontinued lenalidomide during the maintenance phase, was modelled by fitting extrapolations to TTD data from the GRIFFIN trial (Figure 9), with goodness-of-fit statistics of each of the extrapolations presented in Table 21. When comparing the fitted model statistics, the exponential extrapolation showed the best statistical fit with the observed data in terms of both Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC).

Figure 8. Observed Kaplan-Meier TTD data for patients who received DL maintenance but discontinued lenalidomide maintenance therapy in GRIFFIN and PERSEUS trials

Abbreviations: DBLd, daratumumab with bortezomib, lenalidomide and dexamethasone; DL: daratumumab with lenalidomide; L: lenalidomide; KM, Kaplan Meier; TTD: time to treatment discontinuation

Figure 9. Extrapolation of TTD from the GRIFFIN trial for DBLd-DL patients who discontinued lenalidomide maintenance therapy

Abbreviations: DBLd, daratumumab with bortezomib, lenalidomide and dexamethasone; DL: daratumumab with lenalidomide; KM, Kaplan Meier; TTD: time to treatment discontinuation; L: lenalidomide

Table 21. Goodness-of-fit statistics for TTD extrapolations for DBLd-DL patients who discontinued lenalidomide maintenance therapy

Survival model	Lenalidomide discontinuation			
	AIC	BIC	AIC rank	BIC rank
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]
Generalised Gamma	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; DBLd: daratumumab, bortezomib, lenalidomide, dexamethasone; DL: daratumumab with lenalidomide; TTD: time to discontinuation.

Four scenarios were explored based on a two-year fixed daratumumab treatment duration:

a. Daratumumab maintenance with a fixed two-year treatment duration in which all patients discontinue daratumumab after 24 months.

b. Daratumumab maintenance with a fixed two-year treatment duration except for high-risk patients. In the PERSEUS trial, a total of 154 (21.7%) participants had a high-risk cytogenetic abnormality (presence of del[17p] [redacted], t[4;14] [redacted] or t[4;16] [redacted]). Under this scenario, 78.3% (standard risk) patients discontinue daratumumab after two years of maintenance treatment and 21.7% (high risk) patients continue to receive DL. We assume the efficacy of DL in these high-risk patients is similar to that observed in PERSEUS patients who did not achieve sustained MRD-negativity.

c. Daratumumab maintenance with a fixed two-year treatment duration, with DBLd-DL efficacy informed by extrapolations based on the pooled PERSEUS and GRIFFIN analysis of OS and PFS.

d. Daratumumab maintenance with a fixed two-year treatment duration and a diminished PFS HR of [redacted], corresponding to the upper bound of the 95% confidence interval from the IPTW-ATT analysis. Although OS and PFS were highly concordant between PERSEUS and GRIFFIN over the observed

follow-up, divergence in the medium to long term remains possible because some patients in PERSEUS continued to receive daratumumab maintenance beyond two years which is reasonably expected to translate to long-term efficacy benefit versus 2-year fixed duration.

Incidence of Grade 3/4 adverse events occurring during maintenance in 5% of patients in GRIFFIN were included in these scenario analyses[10]. Based on the PERSEUS trial, only neutropenia and diarrhoea were included in the model. By contrast, the GRIFFIN study reported more varied adverse-event rates, including neutropenia (46.5% in DL versus 22.6% in L), lymphopenia (23.5% DL versus 22.6% L), thrombocytopenia (16.2% DL versus 8.8% L), anaemia (9.1% DL versus 5.9% L), pneumonia (12.1% DL versus 13.7% L) and leukopenia (17.2% DL versus 7.8% L).

The cost-effectiveness results are presented in Table 22 and Table 23, corresponding to a fixed two-year daratumumab maintenance duration applied to all patients receiving DL and to standard-risk patients only, respectively. Table 24 reports the cost-effectiveness results for a scenario in which the PFS and OS extrapolations are informed by pooled data from GRIFFIN and PERSEUS. Applying the PFS HR for DL versus L based on the upper bound of the 95% confidence interval indicates that DBLd-DL remains dominant over DBTd-L (Table 25).

Table 22. Scenario 8(a): Daratumumab maintenance based on a 2-year fixed treatment duration

	Total outcomes by treatment			**Incremental outcomes**			
	Costs	**LYs**	**QALYs**	**Costs**	**LYs**	**QALYs**	**ICER**
DBTd-L	[redacted]	[redacted]	[redacted]	-	-	-	-
DBLd-DL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant

Abbreviations: DBLd, daratumumab with bortezomib, lenalidomide and dexamethasone; DBTd, daratumumab with bortezomib, thalidomide and dexamethasone; DL, daratumumab with lenalidomide; ICER, Incremental cost-effectiveness ratio; L, lenalidomide; LY, Life years; QALY, Quality adjusted life year

Table 23. Scenario 8(b): Daratumumab maintenance based on a 2-year fixed treatment duration except for high-risk patients (21.7%)

	Total outcomes by treatment			**Incremental outcomes**			
	Costs	**LYs**	**QALYs**	**Costs**	**LYs**	**QALYs**	**ICER**

DBTd-L	[redacted]	[redacted]	[redacted]	-	-	-	-
DBLd-DL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant

Abbreviations: DBLd, daratumumab with bortezomib, lenalidomide and dexamethasone; DBTd, daratumumab with bortezomib, thalidomide and dexamethasone; DL, daratumumab with lenalidomide; ICER, Incremental cost-effectiveness ratio; L, lenalidomide; LY, Life years; QALY, Quality adjusted life year

Table 24. Scenario 8(c): Daratumumab maintenance based on a 2-year fixed treatment duration (Pooled PERSEUS and GRIFFIN)

	Total outcomes by treatment			**Incremental outcomes**			
	Costs	**LYs**	**QALYs**	**Costs**	**LYs**	**QALYs**	**ICER**
DBTd-L	[redacted]	[redacted]	[redacted]	-	-	-	
DBLd-DL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant

Abbreviations: DBLd, daratumumab with bortezomib, lenalidomide and dexamethasone; DBTd, daratumumab with bortezomib, thalidomide and dexamethasone; DL, daratumumab with lenalidomide; ICER, Incremental cost-effectiveness ratio; L, lenalidomide; LY, Life years; QALY, Quality adjusted life year

Table 25. Scenario 8(d): Daratumumab maintenance based on a 2-year fixed treatment duration: PFS HR = 0.661

	Total outcomes by treatment			**Incremental outcomes**			
	Costs	**LYs**	**QALYs**	**Costs**	**LYs**	**QALYs**	**ICER**
DBTd-L	[redacted]	[redacted]	[redacted]	-	-	-	
DBLd-DL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant

Abbreviations: DBLd, daratumumab with bortezomib, lenalidomide and dexamethasone; DBTd, daratumumab with bortezomib, thalidomide and dexamethasone; DL, daratumumab with lenalidomide; ICER, Incremental cost-effectiveness ratio; L, lenalidomide; LY, Life years; QALY, Quality adjusted life year

Annex: IPTW analyses

Balance of populations

Characteristics before and after weighting of the patients who received L maintenance to resemble patients who received DL maintenance are presented in Table 26. Generally, all variables were balanced after re-weighting.

Table 26. Characteristics before and after reweighting for DL versus L maintenance in PERSEUS.

Covariate grouping	Baseline Covariate	Target population	L maintenance unweighted	L maintenance reweighted on MRD+	
		DL maintenance (N=322)	L maintenance (N=299)	Base case covariate set (Weighted N=322.6)	Sensitivity analysis covariate set (Weighted N=322.5)
MRD status	Post-consolidation MRD status: MRD+	[redacted]	[redacted]	[redacted]	[redacted]
MRD status	Post-consolidation MRD status: MRD-	[redacted]	[redacted]	[redacted]	[redacted]
Base case	Age: <50 years	[redacted]	[redacted]	[redacted]	[redacted]
Base case	Age: ≥50 years	[redacted]	[redacted]	[redacted]	[redacted]
Base case	Sex: Female	[redacted]	[redacted]	[redacted]	[redacted]
Base case	Sex: Male	[redacted]	[redacted]	[redacted]	[redacted]
Base case	ECOG PS: 0	[redacted]	[redacted]	[redacted]	[redacted]
Base case	ECOG PS: 1	[redacted]	[redacted]	[redacted]	[redacted]
Base case	ECOG PS: 2	[redacted]	[redacted]	[redacted]	[redacted]
Base case	ISS: Stage I	[redacted]	[redacted]	[redacted]	[redacted]
Base case	ISS: Stage II	[redacted]	[redacted]	[redacted]	[redacted]
Base case	ISS: Stage III	[redacted]	[redacted]	[redacted]	[redacted]
Base case	Cytogenetics: High risk	[redacted]	[redacted]	[redacted]	[redacted]
Base case	Cytogenetics: Standard risk	[redacted]	[redacted]	[redacted]	[redacted]
Base case	Myeloma isotype: Non-IgG	[redacted]	[redacted]	[redacted]	[redacted]
Base case	Myeloma isotype: IgG	[redacted]	[redacted]	[redacted]	[redacted]
Base case	Haemoglobin: ≥10 g/dL	[redacted]	[redacted]	[redacted]	[redacted]
Base case	Haemoglobin: <10 g/dL	[redacted]	[redacted]	[redacted]	[redacted]
Sensitivity	LDH: <280 U/L	[redacted]	[redacted]	[redacted]	[redacted]
Sensitivity	LDH: ≥280 U/L	[redacted]	[redacted]	[redacted]	[redacted]
Sensitivity	Creatinine clearance: ≥90 mL/min	[redacted]	[redacted]	[redacted]	[redacted]
Sensitivity	Creatinine clearance: <90 mL/min	[redacted]	[redacted]	[redacted]	[redacted]
Sensitivity	MM SLiM-CRAB criteria at Dx: ≥1 CRAB features present	[redacted]	[redacted]	[redacted]	[redacted]
Sensitivity	MM SLiM-CRAB criteria at Dx: SLiM features only	[redacted]	[redacted]	[redacted]	[redacted]
Sensitivity	Plasmacytomas: None	[redacted]	[redacted]	[redacted]	[redacted]

Sensitivity	Plasmacytomas: ≥1 plasmacytoma	[redacted]	[redacted]	[redacted]	[redacted]
Sensitivity	Serum calcium: ≥2.75 mmol/L	[redacted]	[redacted]	[redacted]	[redacted]
Sensitivity	Serum calcium: <2.75 mmol/L	[redacted]	[redacted]	[redacted]	[redacted]
Sensitivity	Bone lesions: None	[redacted]	[redacted]	[redacted]	[redacted]
Sensitivity	Bone lesions: ≥1	[redacted]	[redacted]	[redacted]	[redacted]
Sensitivity	Platelets: ≥150 x 10E9/L	[redacted]	[redacted]	[redacted]	[redacted]
Sensitivity	Platelets: <150 x 10E9/L	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CRAB: hyperCalcemia, DL: daratumumab with lenalidomide; Renal, Anemia, Bone; ECOG PS: Eastern Cooperative Oncology Group Performance Status; g/dL: grams per decilitre; IgG: immunoglobulin G; ISS: International Staging System; LDH: lactate dehydrogenase; L: lenalidomide; MRD: minimal disease residual; MM: multiple myeloma; SLiM: ≥60% clonal plasma cells in the bone marrow, involved/uninvolved free light chain ratio of 100 or more with the involved serum free light chain being ≥100 mg/L, and Magnetic Resonance Imaging with more than one focal marrow lesion; U/L: units per litre.

Assessment of overlap

To assess the extent of overlap between populations based on the included variables before and after adjustment, the propensity score (PS) distributions between patients in DL and L arms were assessed. Histograms of the PSs from the two arms were plotted (Figure 10) and the degree of overlap compared: the significant overlapping region suggested that, without adjustment, L patients may generalise well to the DL population.

Figure 10. Distribution of PSs for patients in DL and L before reweighting for base case covariates

Abbreviations: DR (DL): daratumumab with lenalidomide; IPTW: inverse probability of treatment weighting; MRD: minimal disease residual; PS: propensity score; R (L): lenalidomide

After adjusting using ATT weights, the overlap between populations improved as depicted by the reweighted distribution of PSs (Figure 11).

Figure 11. Distribution of PSs for patients in DL and L after reweighting + base case covariates

Abbreviations: DR (DL): daratumumab with lenalidomide; IPTW: inverse probability of treatment weighting; MRD: minimal disease residual; PS: propensity score; R (L): lenalidomide

Figure 12 presents the distribution of weights for the base case ATT weighting, which weighted L patients to match DL patients' characteristics. Every patient with a weight >1 is down weighted, resulting in over 30% of L patients down weighted.

Figure 12. Distribution of ATT weights

Abbreviations: ATT: average treatment effect in the treated; DR (DL): daratumumab with lenalidomide; IPTW: inverse probability of treatment weighting; MRD: minimal disease residual; PS: propensity score; R (L): lenalidomide. **Note**: All DL-treated patients have an ATT weight of 1; in the histogram, the ATT weights for the L-treated patients are rounded to the nearest integer.

Similarly, the distribution of PSs for patients in DL and L when all variables are included before and after reweighting and the distribution of ATT weights are given in Figure 13, Figure 14 and Figure 15, respectively.

Figure 13. Distribution of PSs for patients in DL and L before reweighting for base case covariates

Abbreviations: DR (DL): daratumumab with lenalidomide; IPTW: inverse probability of treatment weighting; MRD: minimal disease residual; PS: propensity score; R (L): lenalidomide

Figure 14. Distribution of PSs for patients in DL and L after reweighting + sensitivity covariates

Abbreviations: DR (DL): daratumumab with lenalidomide; IPTW: inverse probability treatment weighting; MRD: minimal disease residual; PS: propensity score; R (L): lenalidomide

Figure 15. Distribution of ATT weights for sensitivity covariates

Abbreviations: ATT: average treatment effect in the treated; DR (DL): daratumumab with lenalidomide; IPTW: inverse probability of treatment weighting; MRD: minimal disease residual; PS: propensity score; R (L): lenalidomide. Note: All DL-treated patients have an ATT weight of 1; in the histogram, the ATT weights for the R-treated patients are rounded to the nearest integer

Test for proportional hazards

The proportional hazards assumption for the base-case ATT-weighted Cox model was evaluated with the Grambsch-Therneau test[11] based on scaled Schoenfeld residuals (using the default Kaplan–Meier time transformation) for both OS and PFS.

For OS, the test yielded a p-value of 0.47, providing no evidence of time-varying effects. The Schoenfeld residuals plot is shown in Figure 16. For PFS the test retained a p-value of 0.42, providing no evidence of time-varying effects. The Schoenfeld residuals plot is presented in Figure 17.

Figure 16. OS Schoenfield test plot (DL versus L for the base case ATT)

Figure 17. PFS Schoenfield test plot (DL versus L for the base case ATT)

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Daratumumab with bortezomib, lenalidomide and dexamethasone for untreated multiple myeloma when an autologous stem cell transplant is suitable [ID6249]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 4 February 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 provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Myeloma UK

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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

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	Sebia				11192	11,192	
	Sanofi			720	33,990	34710	
	Takeda	20000		880	15389	36269	
	Totals	79400	59891	4584	77984	221,859	

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

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	Myeloma UK is very disappointed that NICE did not recommend daratumumab plus bortezomib, lenalidomide and dexamethasone for newly diagnosed myeloma patients who are eligible for high-dose therapy and stem cell transplantation (HDT-SCT) for routine commissioning. This treatment could deliver significant benefits for HDT-SCT eligible patients. If this use had been approved, DVRD would have been the first tailored treatment for newly diagnosed patients due to the unique amendments to DVRD's maintenance phase based on the patient's minimal residual disease (MRD) status. It would also have allowed the much-anticipated switch from thalidomide to lenalidomide during induction and given stem cell transplant (SCT)-eligible patients access to doublet maintenance of daratumumab and lenalidomide for the first time.
2	Given the unique and innovative nature of the MRD-related stopping rule we are requesting that the NICE committee invites a MRD specialist to attend the second committee meeting for this appraisal. There are several laboratory experts who regularly conduct MRD tests for myeloma in the UK, including those for the large national RADAR and Myeloma XI clinical trials. We believe these experts are best placed to provide testimony and evidence on the appropriateness on the companies' proposals for MRD testing, how it would and could be used in clinical practice.
3	We are concerned that the discussion on MRD testing at the first committee meeting exceeded the scope of this appraisal focusing on the future potential of MRD testing in myeloma rather than the specific testing requirements for the use of DRVD.

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Daratumumab with bortezomib, lenalidomide and dexamethasone for untreated multiple myeloma when an autologous stem cell transplant is suitable [ID6249]

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	This appraisal is assessing the use of DVRD in SCT-eligible patients. Only around 1600-1800 myeloma patients in the UK get SCT as initial treatment (2). Looking at the PERSEUS clinical trial 88% of patients reached complete response and were eligible for MRD testing (3). This allows us to estimate that approximately 1400-1600 myeloma patients would be eligible for MRD testing. This number is comparable to the number of patients in the RADAR clinical trial which had a recruitment target of 1400 patients. It also important to note, when flow cytometry is used that the first test would only be given after the patient has been on maintenance for 12 months. Over 18 months after a patient has started treatment. This will give the NHS sufficient time to make any improvements to capacity. Every tertiary hospital has a flow cytometry lab that could, if given sufficient training, conduct MRD tests. Although MRD testing is not routinely used in clinical practice, the main method currently used to assess MRD in the UK is flow cytometry. It is the main method used for sequential MRD monitoring in large national clinical trials including Myeloma XI, XII (ACCoRd) and RADAR (3, 4). 1. British Society of Blood and Marrow Transplantation and Cellular Therapies (2026) BSBMTCT registry data, accessed via https://bsbmtct.org/about-the-registry/# 2. Sonneveld, P., Dimopoulos, M.A., Boccadoro, M., Quach, H., Ho, P.J., Beksac, M., Hulin, C., Antonioli, E., Leleu, X., Mangiacavalli, S. and Perrot, A., 2024. Daratumumab, bortezomib, lenalidomide, and dexamethasone for multiple myeloma. *New England journal of medicine*, *390*(4), pp.301-313. 3. Jackson, G., Pawlyn, C., Davies, F.E., et al. (2024) 'MRD and molecular risk status help to define optimal maintenance delivery strategies after ASCT: long term outcomes of the UK MRA Myeloma XI trial comparing lenalidomide to observation', *Blood*, 144 (Supplement 1), p. 3375. https://doi.org/10.1182/blood-2024-205871 4. Striha, A., Ashcroft, A. J., Hockaday, A, et al. (2018). The role of ixazomib as an augmented conditioning therapy in salvage autologous stem cell transplant (ASCT) and as a post-ASCT consolidation and maintenance strategy in patients with relapsed multiple myeloma (ACCoRd [UK-MRA Myeloma XII] trial): study protocol for a Phase III randomised controlled trial. *Trials*, *19*(1), p.169. https://doi.org/10.1186/s13063-018-2524-8
4	We believe the proposed stopping rule and the method and frequency of MRD testing as outlined in the model by the company is appropriate and consistent with patient preferences. Time of treatment is a key unmet need for myeloma patients. Most treatment for myeloma is continuous, with patients receiving treatment from diagnosis to relapse. Continuous treatment often means living with side effects and regular trips to hospital for treatment. This can have a significant impact on patients and their families. **"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."** Person living with Myeloma

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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." Person living with Myeloma **"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."** Person living with Myeloma The proposed stopping rule is a step change for patients. It gives patients with stable myeloma the opportunity to reduce their treatment burden and helps ensure they are not getting more treatment than they need. The use of MRD status as the basis for the clinical decision to stop daratumumab gives patients reassurance that the decision to stop is based in the status of their myeloma, that it is stable and undetectable. **"If an MRD negative test at some point were to have indicated that I could have lowered the dose or even stopped the treatment, I would have jumped at the chance."** Person living with Myeloma The method and frequency as outline in the proposal is consistent with what we hear from patients. At the moment, MRD testing requires a bone marrow biopsy which is an invasive and sometimes painful procedure. Bone marrow biopsies are routinely used in the diagnosis and management for myeloma (5) and whilst patients are willing to have them to inform clinical decisions about their treatment and care they do not want to have more than is necessary. Members of our Advocacy Partner Panel (a panel of people with lived experience of Myeloma), told us that they would accept MRD testing to inform and look at how well treatment was working. However, the painful nature of biopsies and sometimes insufficient pain relief associated with them meant they would not want more biopsies than necessary. **"I'm in favour of MRD tests which inform treatment decisions... ...but I'm not so convinced about using MRD testing for [non-treatment specific] regular monitoring, it's invasive".** Person living with Myeloma **"Pain relief is key when it comes to bone marrow biopsies – it's the pain that is unmanageable, not that there are issues with the tests in and of themselves"** Person living with Myeloma The company has proposed flow cytometry as the main method for testing. Most patients do not care or think about how a test is conducted in a lab, they care about how the sample is taken, analgesics and pain relief for the biopsy, the quality and accuracy of the results, and how long the results take. All available methods can test to the sensitivity (10^{-5}) required for the stopping rule and therefore would be considered the same quality and accuracy. However, the flow cytometry route does not require base line biopsies meaning one less biopsy for patients. The summary of product characteristics for daratumumab defines the criteria for stopping daratumumab as >12 months sustained MRD negativity and at least 24 months on maintenance.

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	The company's proposal for two tests one 12 months after starting maintenance and another 12 months after is the minimum possible to meet the stopping criteria. Unlike other blood cancer, myeloma can be monitored via monthly blood tests that detect the presence of paraprotein, a known biomarker for myeloma. Therefore, MRD tests do not need to be used to check for disease progression/relapse. 5. NICE (2018) *Myeloma: diagnosis and management,* NICE guideline NG35. Available at: Myeloma: diagnosis and management (Last accessed 30-01-2026)
5	We are concerned that the Committee did not fully consider the innovative nature of this treatment. Although DVRD is a combination of drugs already used to treat myeloma, the way that they are used in this appraisal is a step-change for myeloma patients. DVRD is the first tailored myeloma treatment to be appraised by NICE. It is the first regimen to use MRD status to inform clinical decisions about ongoing treatment. Myeloma is a very complex and individual cancer and there is a clear need for more tailored treatments to improve both the length and quality of the lives of people affected by myeloma. This treatment regimen paves the way for an evidence-based, more personalised approach to myeloma treatment.
6	We are concerned that the Committee did not fully consider the significant patient benefit of increased progression-free survival due to the use of doublet maintenance. As shown in the committee meeting DVRD delivers longer remission times than the current standard of care. In the PERSEUS trial, 84% of patients who received DVRD were still in remission after 4 years (6). 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

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	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. 6. Sonneveld, P., Dimopoulos, M.A., Boccadoro, M., Quach, H., Ho, P.J., Beksac, M., Hulin, C., Antonioli, E., Leleu, X., Mangiacavalli, S. and Perrot, A., 2024. Daratumumab, bortezomib, lenalidomide, and dexamethasone for multiple myeloma. *New England journal of medicine*, *390*(4), pp.301-313.

Insert extra rows as needed

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- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
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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):	The UK Myeloma Society

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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.	Johnson and Johnson are a Premium Sponsor of the UKMS and as such pay the society £15,000 sponsorship per year which is used to fund educational events.
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted]

Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	The UKMS is very disappointed that NICE did not recommend daratumumab plus bortezomib, lenalidomide and dexamethasone for newly diagnosed myeloma patients who are eligible for high-dose therapy and stem cell transplantation (HDT-SCT) for routine commissioning. This patient group represents the youngest group of newly diagnosed myeloma patients who currently have no access to combined anti-CD38 monoclonal antibody (MoAb) and

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	Immunomodulatory drug maintenance and can only access single agent lenalidomide. This represents a very unfair situation compared to the older patient group who can access dual agent maintenance either via DRD or Isa-VRD. It is well known that single agent lenalidomide does not maintain durable remission for many patients and in the UK Myeloma XI trial 35.7% of patients who relapsed within 12 months of transplant were on lenalidomide maintenance (Bygrave C et al, BJH, 2021, British Journal of Haematology | Wiley Online Library). This group of functional high-risk patients have a poor outcome compared to later relapsing patients and there is data to show that dual agent maintenance can reduce the population of patients who are functionally high risk. Currently approved regimens incorporating up-front anti-CD38 MoAbs have significantly reduced the risk of early relapse at 12 to 24 months to approximately less than 10% in transplant-eligible (Gay F et al, A rational approach to functional high-risk myeloma | Hematology, ASH Education Program | American Society of Hematology)
2	The D-VRD regimen is superior to the existing D-VTD approval as the combination of lenalidomide with bortezomib is significantly less likely to cause painful peripheral neuropathy than when bortezomib is combined with thalidomide. Patients with severe PN suffer a significant negative impact on their quality of life with many having symptoms that limit their ability to walk, maintain balance and drive when symptoms are severe.
3	There was a significant amount of discussion in the committee around MRD testing to guide MRD driven discontinuation of DR maintenance after 2 years of sustained MRD negativity. Our view on this is: 1. This would be a prudent approach as those patients in the deepest possible, MRD negative - remission, can stop daratumumab which will deliver a cost saving compared to unlimited daratumumab that is currently available to frontline non-transplant eligible patients or patients with relapsed myeloma receiving DVD 2nd line or Dara mono 4th line. In this regard, investment in MRD testing will deliver a cost saving to the NHS drugs budget. 2. Stopping treatment is not only prudent but is also attractive to patients who can regain freedom from visits to day unit for their injections of daratumumab. This will also release capacity in busy day unit facilities to treat other patients and maintain flow through units. 3. Many blood cancer patients now have access to MRD testing for disease monitoring, such as CML, AML and ALL and in some cases MRD data drives treatment decision. We feel that myeloma patients deserve the same system and acknowledge that funding for MRD testing has been achieved via a step wise approach in these diseases, without requirement for the manufacture to pay. 4. The UKMS is actively working with the existing FLOW cytometry labs in Leeds and the Royal Marsden to deliver FLOW based MRD in the short term, with sufficient capacity evidenced by the successful recruitment of almost 1400 patients to the MXV/RADAR trial where MRD testing was standard. 5. In addition the UKMS is working with providers of NGS based MRD to implement this technology in the UK as quickly as possible. This can be delivered within the next 2 years.
6	The newly diagnosed transplant eligible (TE) patient group will lose more life years to myeloma than those diagnosed at an older age and will benefit most from access to treatments that can prolonged remission. Whilst in remission this group are more likely to

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	be able to continue to work and care for their families and maintain a more normal quality of life. As shown in the committee meeting DVRD delivers longer remission times than the current standard of care. In the PERSEUS trial, 84% of patients who received DVRD were still in remission after 4 years (Sonneveld, P. et al, 2024. Daratumumab, bortezomib, lenalidomide, and dexamethasone for multiple myeloma. *New England journal of medicine*, *390*(4), pp.301-313. D-VTD followed by transplantation and lenalidomide maintenance is not a treatment pathway that has ever been tested in a clinical trial and experience of the clinical community finds that outcomes can be very heterogeneous. It is not uncommon for patients to develop progressive disease prior to transplant (that could be mitigated by the substitution of thalidomide for lenalidomide) or during maintenance and this is a time of significant anxiety and reduced quality of life. The D-VRD combination as used in PERSEUS represents a new standard of care for newly diagnosed TE patients and those in the UK require access through this appraisal.

Insert extra rows as needed

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NDRS-NICE partnership report

Background

This report was produced in partnership by the National Disease and Registration Service (NDRS) and National Institute for Health and Care Excellence (NICE). NDRS and NICE have established a partnership focused on routinely collected data to support NICE decision making on the appraisals of cancer treatments. The partnership uses NDRS datasets, including the information submitted by trusts to the Systemic Anti-Cancer Therapy (SACT) dataset,[1] to provide an understanding of current practice.

This partnership is focused on producing demographic and survival information using NDRS data, alongside supplementary information tailored to each technology appraisal. These may include, for example, the time patients spend on particular treatments, genetic data where this is available, or other information on real-world care pathways. Interpretation of the data is not included in this report. Detail on how NICE health technology appraisals use this data can be found in the NICE health technology evaluations manual,[2] with specific information relating to the survival analysis modelling available in Technical Support Document (TSD).[3]

The focus of this report is the indication **ID6249 Daratumumab with bortezomib, lenalidomide and dexamethasone for untreated multiple myeloma when a stem cell transplant is suitable.**

Two cohorts were assessed for this indication:

- Those receiving first line lenalidomide maintenance therapy after autologous stem cell transplant
- Those receiving first line lenalidomide maintenance therapy after autologous stem cell transplant where the induction / consolidation regimen included daratumumab (a subset containing 94% of the first cohort)

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[1] Chloe J. Bright et al., "Data Resource Profile: The Systemic Anti-Cancer Therapy (SACT) dataset," *International Journal of Epidemiology* 49, no. 1 (February 2020): 15–15l, https://dx.doi.org/10.1093/ije/dyz137.

[2] *NICE health technology evaluations: the manual (2025) NICE process and methods PMG36. Last updated 23 October 2025*, n.d., https://www.nice.org.uk/process/pmg36.

[3] Latimer Nicholas, *NICE DSU Technical Support Document 14: Undertaking survival analysis for economic evaluations alongside clinical trials - extrapolation with patient-level data*, 2011, http://www.nicedsu.org.uk/.

The latter cohort was picked in order to differentiate between induction/consolidation regimens approved under NICE TA763 that contain daratumumab in addition to bortezomib, thalidomide and dexamethasone, and other induction/consolidation regimens, for example bortezomib, dexamethasone and thalidomide approved under NICE TA311.

Age, gender, overall survival and time on treatment for those receiving lenalidomide maintenance therapy following an autologous stem cell transplant (cohort 1)

Introduction

This report was produced in partnership by the National Disease and Registration Service (NDRS) and National Institute for Health and Care Excellence (NICE). It presents overall survival, gender split, age distribution and time on treatment among patients with multiple myeloma who have received lenalidomide maintenance at first line following an autologous stem cell transplant.

Method

A snapshot of SACT data was taken on 7th December 2025 and made available for analysis on 19th December 2025. SACT treatment data is only considered complete when 90% of trusts have submitted data, which at the time of analysis was 31st March 2025. This date is used for censoring of time on treatment. Patient death dates were last updated on the 5th October 2025, which is the censoring date for the overall survival analysis.

Overall survival is measured from commencement of first lenalidomide maintenance treatment to death (if date recorded) or censoring date (if death date not present). Time-on-treatment was measured by the difference between a patient's first and last recorded lenalidomide maintenance treatment, plus 28 days (standard gap between administrations). If a patient died before the nominal cycle end, the end date was revised to the date of death. If the treatment end date extends beyond the treatment censoring date (31st March 25), the patient was censored.

Cohort inclusions / exclusions

Patients were included if they met all of the following conditions:

- Diagnosed between 1st Feb 2022 and 31st December 2023 (inclusive). Diagnoses and treatment pathways prior to this point would be before publication of NICE Technology Appraisal TA763 — "Daratumumab in combination for untreated multiple myeloma" and would not reflect subsequent changes to the expected pathway resulting from commissioners being required to fund the approved treatment
- Gender recorded as male or female
- Country code was 'England', based on postcode of residence at diagnosis
- NDRS cancer group definition of 'Myeloma'
- An autologous stem cell transplant was carried out as part of treatment after diagnosis

- Lenalidomide was initiated within 6 months after the stem cell transplant (based on both regimen and drug administration descriptions), and the lenalidomide regimen did not include dexamethasone.

and were excluded if

- Any SACT treatments after diagnosis (not only lenalidomide) were recorded as being given as part of a trial

Identification of autologous stem cell transplant

The presence of an autologous stem cell transplant (ASCT) in the treatment pathway was determined by linkage of the registration record to HES, specifically where the post-diagnosis HES inpatient record contained an OPCS code of 'X33.4 - autologous peripheral blood stem cell transplant'. A sensitivity analysis explored how many additional records would be added by including other related codes in case significant numbers were recorded under related codes. All other restrictions were kept in place whilst codes were varied. Varying the codelist gave the following results: No additional cases were identified by including bone marrow graft codes (W34*). One additional record was found recorded as an allogenic stem cell transplant (X33.6), and no further cases were associated with the code for a syngeneic stem cell transplant (X33.5). Sixteen cases would be added if the definition was expanded to include X33.8 'Other specified blood transfusion' and X33.9 'Unspecified other blood transfusion'. Given the risk of including non-ASCT cases and minimal gain in sample size, X33.4 was selected as the sole ASCT defining code.

Observed ASCT rates (c. 16%) were lower than expected (25-30%), based on previous modelling work for NICE TA680. The identified cases therefore likely understate the true number of applicable procedures, reflecting under-recording or miscoding. We assume that ASCTs that are unrecorded or coded under alternative OPCS codes are not systematically associated with the outcomes analysed below (e.g., overall survival or time on treatment), given that coding missingness is likely a function of hospital administration and documentation rather than anything associated with clinical treatment. On this basis, any bias from missing ASCT data is expected to be minimal.

Identification of lenalidomide maintenance

Lenalidomide monotherapy is recommended as first-line maintenance following stem cell transplant. Owing to variation in SACT recording practices and the structure of SACT tables, it can be challenging to algorithmically distinguish first-line lenalidomide from second and subsequent lines, where lenalidomide may be used in combination (for example, carfilzomib + dexamethasone + lenalidomide [KRd], lenalidomide + dexamethasone [Rd], or ixazomib + lenalidomide + dexamethasone [Ixa-Rd]). These combinations may be grouped at the regimen level in SACT or recorded as contemporaneous but separate ('split') regimens.

To reduce misclassification of second-line uses, we: (i) count only regimens where the NDRS-categorised description ("benchmark group") mentions lenalidomide only; (ii) include only cases where the earliest lenalidomide use occurs within six months of the

ASCT date; and (iii) exclude cases where dexamethasone appears in the drug-level tables for lenalidomide monotherapy regimens. Dexamethasone was selected as the common element for combination therapies that are given at second line (and subsequently). Therefore, excluding based on dexamethasone should remove second line therapies not of interest.

Where split regimens occur, time-on-treatment may be overstated if the lenalidomide end date is taken from a combination containing lenalidomide. However, the observed time-on-treatment pattern would not imply a median survival exceeding the 53-month progression-free survival reported in a published meta-analysis.[4] We therefore consider potential overstatement of time on treatment from the incidental inclusion of combination regimens to be limited.

Flow chart

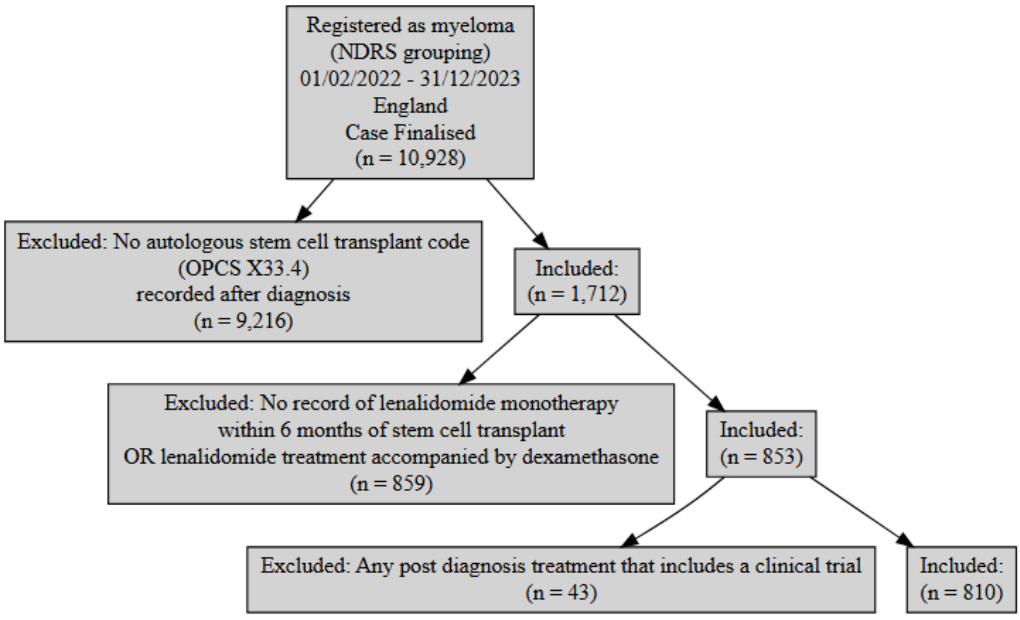

Figure 1: Inclusion / Exclusion Flow Chart

[4] Philip L. McCarthy et al., "Lenalidomide maintenance after autologous stem-cell transplantation in newly diagnosed multiple myeloma: A meta-analysis," *Journal of Clinical Oncology* 35, no. 29 (2017): 3279–3289, https://ascopubs.org/doi/abs/10.1200/JCO.2017.72.6679.

Patient acknowledgement

This work uses data that has been provided by patients and collected by the NHS as part of their care and support. The data is collated, maintained and quality assured by the National Cancer Registration and Analysis Service, which is part of NHS England.

Results

Age at start of treatment

The table below sets out the mean age, standard deviation, median age and interquartile range (IQR) of patients who have received lenalidomide monotherapy maintenance treatment for multiple myeloma following an ASCT. Age is measured at the commencement of lenalidomide.

Characteristic	**Female** N = 326[1]	**Male** N = 484[1]
Age at start of treatment	62, (8) : 63 (56, 68)	62, (8) : 63 (56, 68)

[1]Mean, (SD) : Median (Q1, Q3)

Table 1: Mean age, standard deviation, median age and IQR of patients who have received lenalidomide maintenance

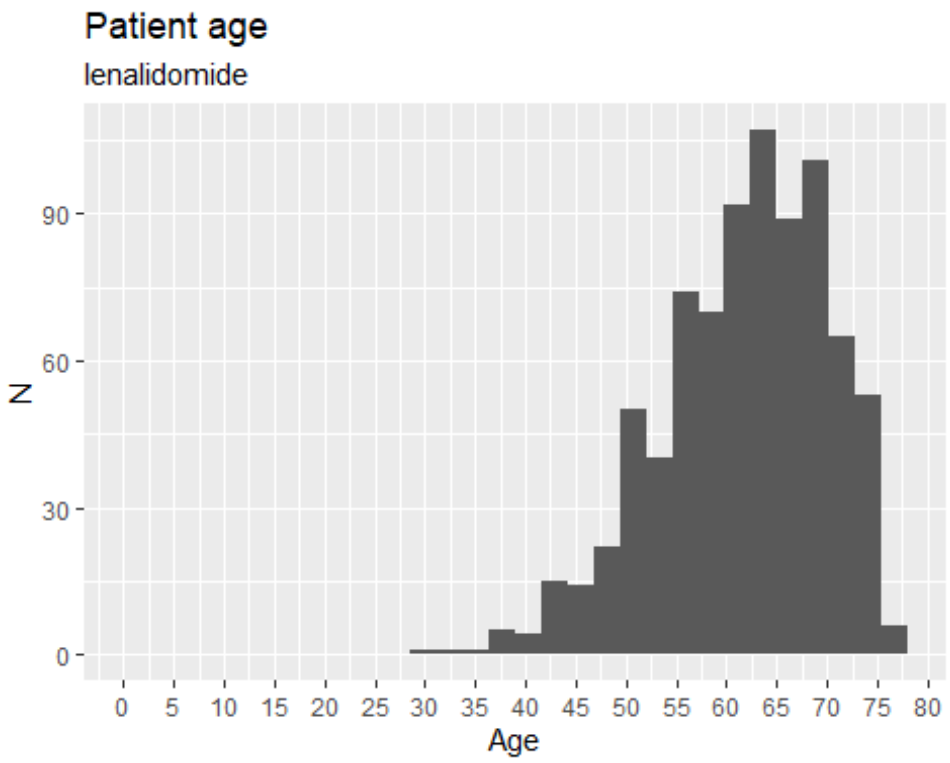

Figure 1: Age distribution of patients who have received lenalidomide maintenance

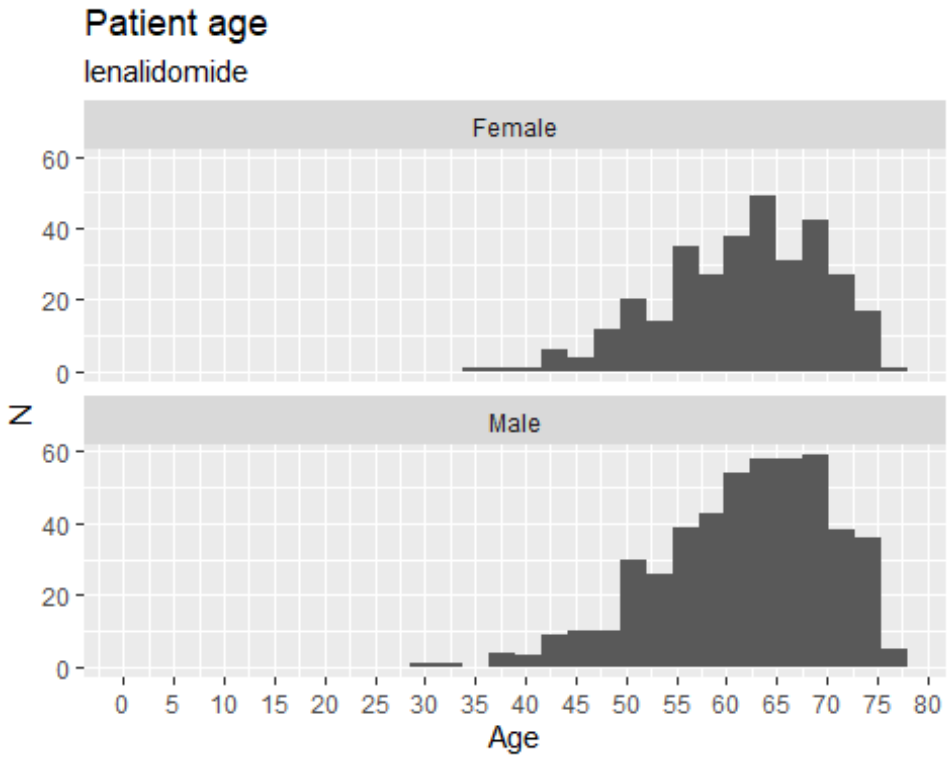

Figure 2: Age distribution of patients who have received lenalidomide maintenance

Overall Survival

Base K-M plot

The Kaplan-Meier plot below shows survival over time for those receiving a maintenance regimen of lenalidomide monotherapy after an ASCT and associated induction/consolidation regimen.

Median survival was not reached, restricted mean survival (over the whole curve) was 32.93 months. The minimum follow-up time was 1.6 months, median 22.9 months, and maximum follow-up time of 34 months. Subsequent graphs with fitted parametric survival curves have an extended X axis to allow differentiation of longer-term projections.

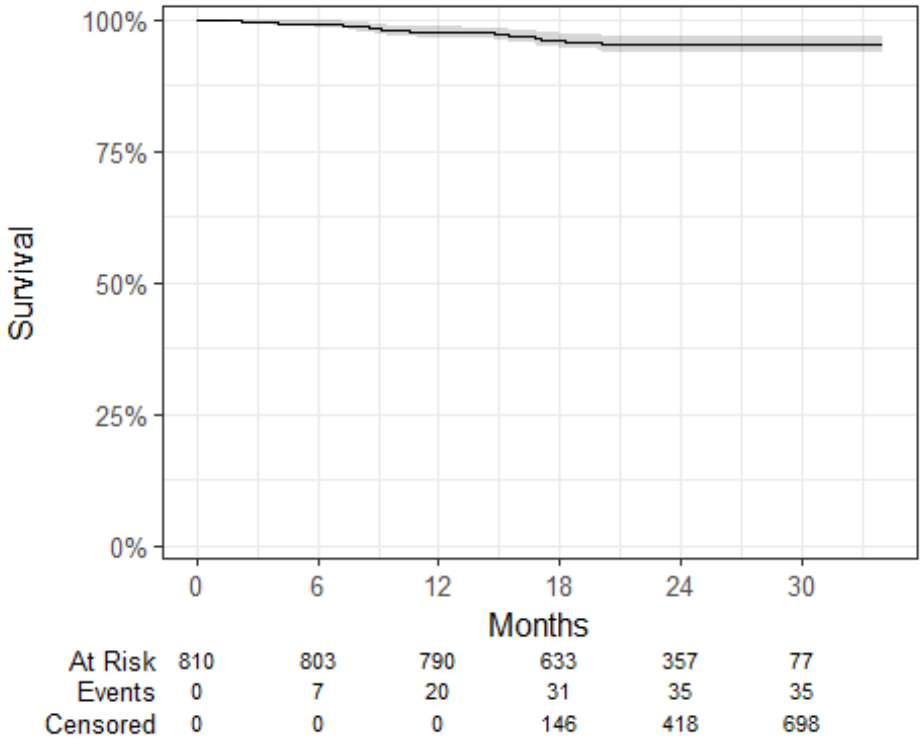

Figure 3: Overall survival amongst patients who have received lenalidomide maintenance therapy for multiple myeloma

Exponential

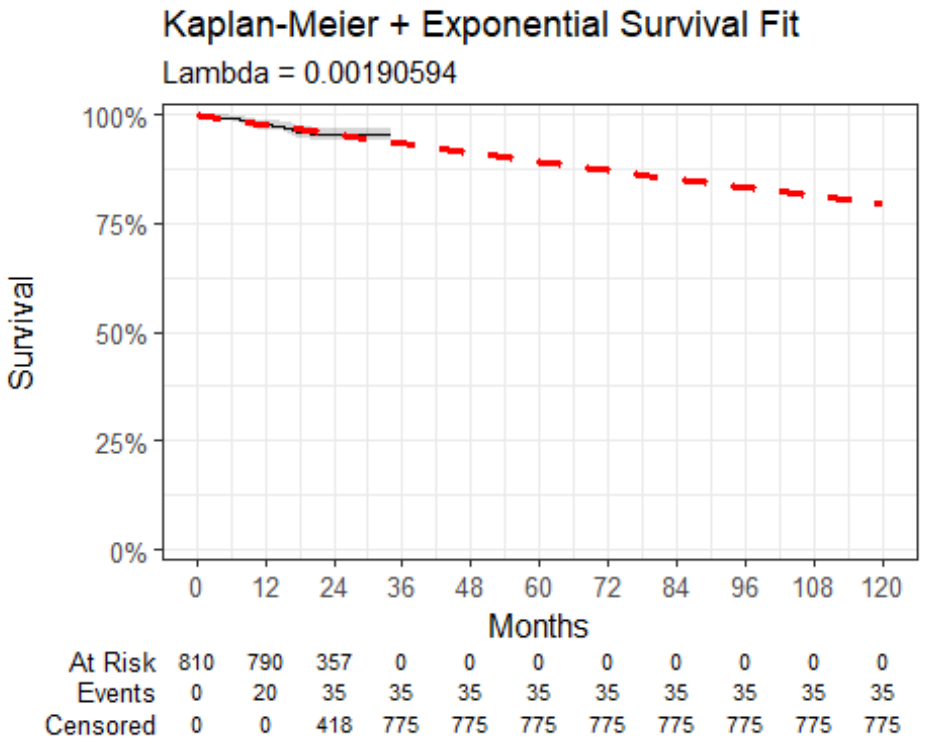

Figure 4: Overall survival against exponential survival function

Parameter	Estimate	Std. Error	z	p-value
(Intercept)	6.263	0.169	37.0511	1.723937e-300

log-likelihood = -254.197278697312

AIC = 510.394557394624

BIC = 515.09159164229

Table 2: Survival Model Fit Summary (Exponential distribution)

Weibull

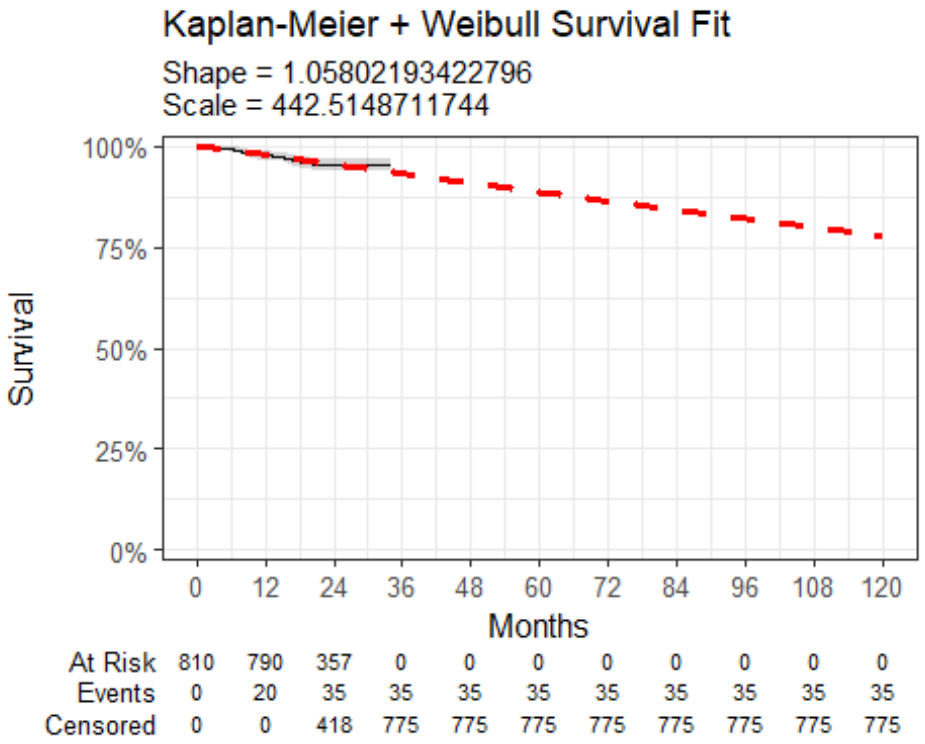

Figure 5: Overall survival against Weibull survival function

Parameter	Estimate	Std. Error	z	p-value
(Intercept)	6.092	0.506	12.0309863	2.442255e-33
Log(scale)	-0.056	0.164	-0.3443074	7.306151e-01

log-likelihood = -254.139211094705

AIC = 512.278422189409

BIC = 521.672490684742

Table 3: Survival Model Fit Summary (Weibull distribution)

Log-normal

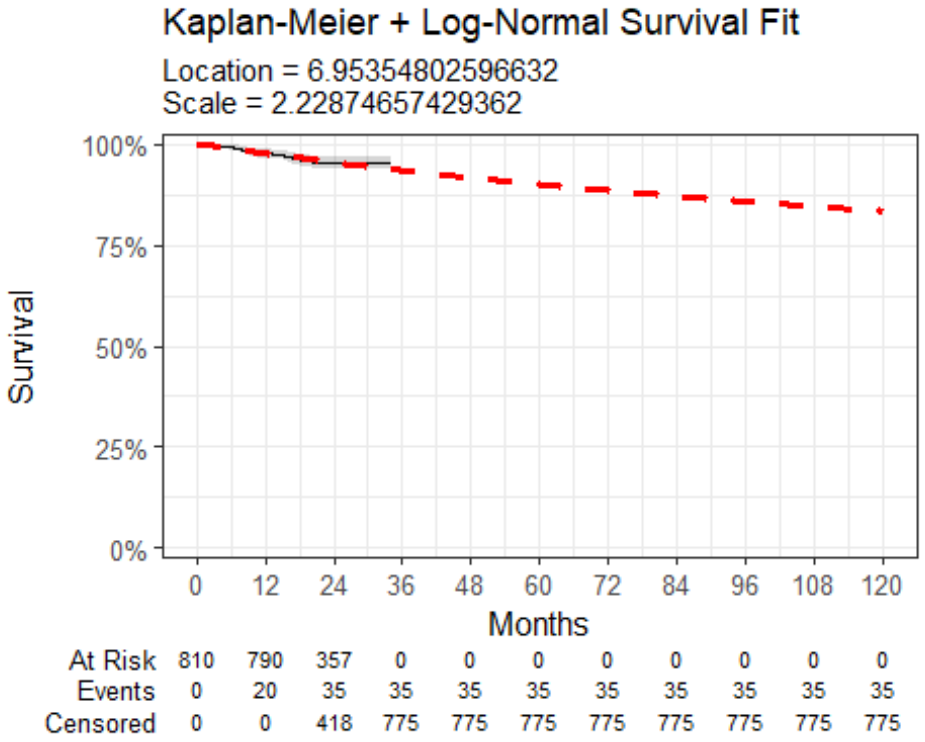

Figure 6: Overall survival against Log-normal survival function

Parameter	Estimate	Std. Error	z	p-value
(Intercept)	6.954	0.622	11.172431	5.563677e-29
Log(scale)	0.801	0.150	5.354432	8.582579e-08

log-likelihood = -253.017726380271

AIC = 510.035452760542

BIC = 519.429521255875

Table 4: Survival Model Fit Summary (Log-normal distribution)

Log-logistic

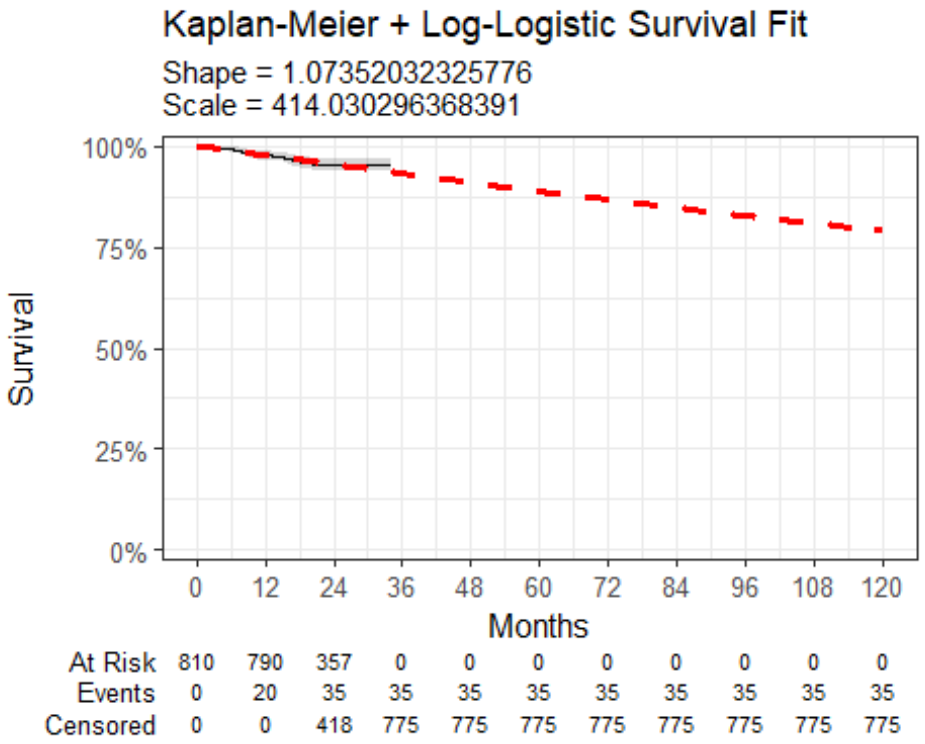

Figure 7: Overall survival against Log-Logistic survival function

Parameter	Estimate	Std. Error	z	p-value
(Intercept)	6.026	0.497	12.1312100	7.217506e-34
Log(scale)	-0.071	0.163	-0.4353301	6.633229e-01

log-likelihood = -254.043063917263

AIC = 512.086127834527

BIC = 521.48019632986

Table 5: Survival Model Fit Summary (Log-Logistic distribution)

Gaussian

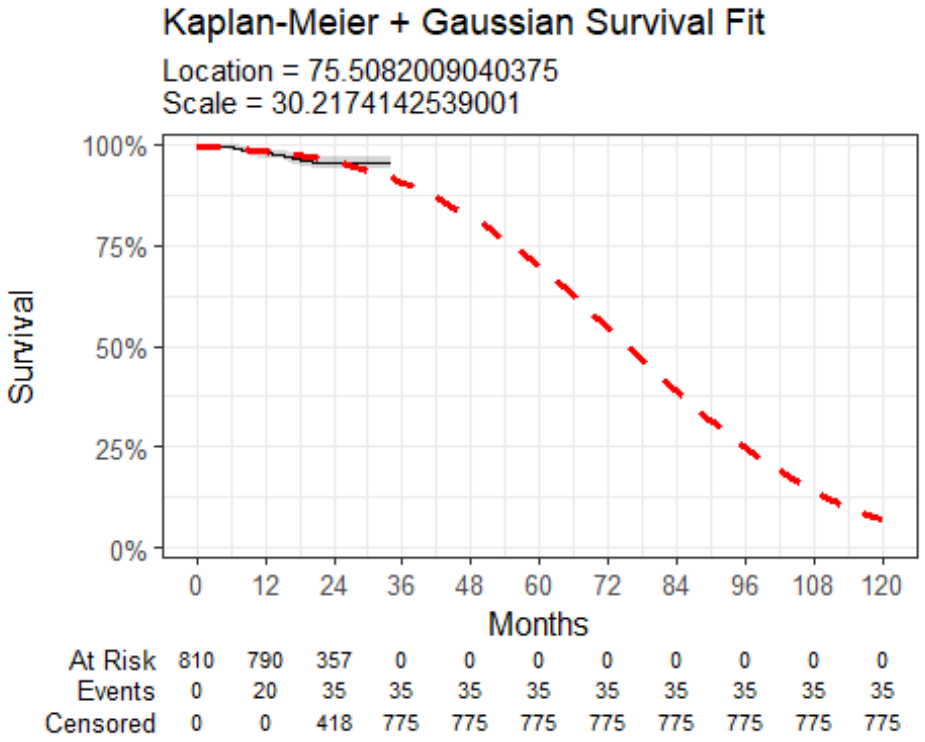

Figure 8: Overall survival against Gaussian survival function

Parameter	Estimate	Std. Error	z	p-value
(Intercept)	75.508	8.350	9.042938	1.525163e-19
Log(scale)	3.408	0.149	22.919514	2.968703e-116

log-likelihood = -266.598284641717

AIC = 537.196569283434

BIC = 546.590637778767

Table 6: Survival Model Fit Summary (Gaussian distribution)

Gamma

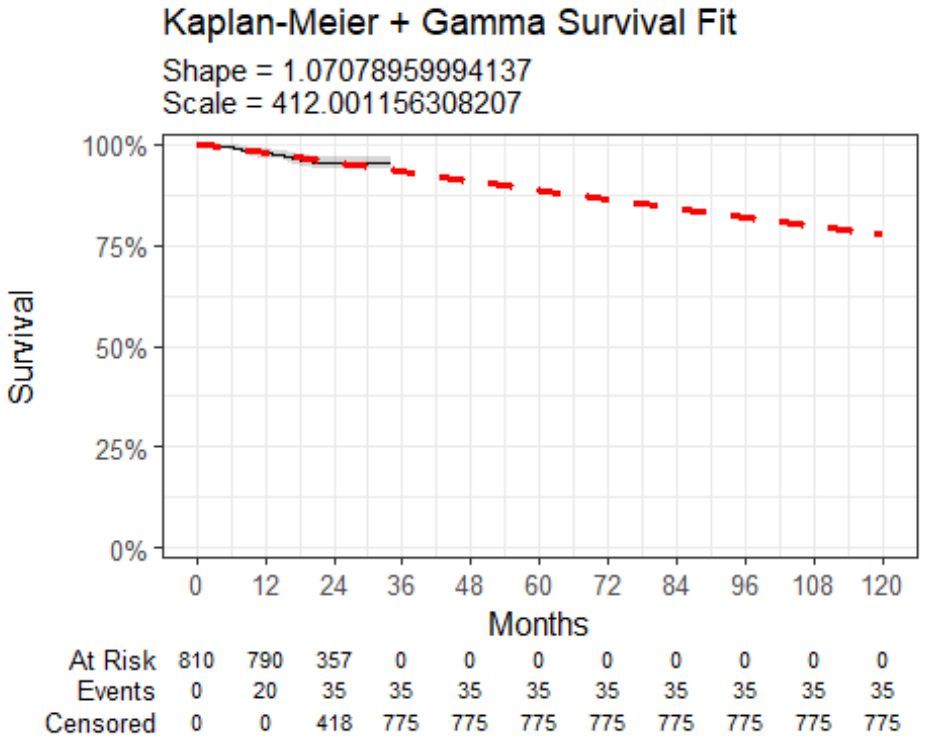

Figure 9: Overall survival against gamma survival function

Parameter	Estimate	Std. Error	L95.	U95.
shape	1.071	0.187	0.7610084923	1.506672237
rate	0.002	0.002	0.0007186083	0.008198056

log-likelihood = -254.121503720937

AIC = 512.243007441874

BIC = 521.637075937207

Table 7: Survival Model Fit Summary (Gamma distribution)

Generalised gamma

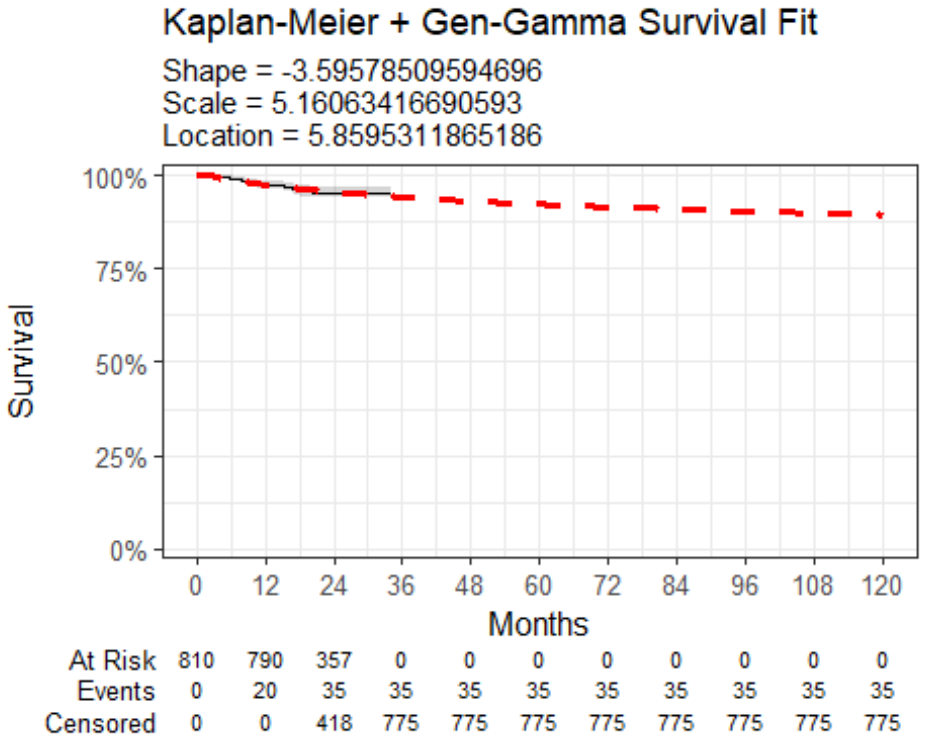

Figure 10: Overall survival against Generalised Gamma survival function

Parameter	Estimate	Std. Error	L95.	U95.
mu	5.860	1.791	2.349881	9.369182
sigma	5.161	0.956	3.589803	7.418832
Q	-3.596	2.812	-9.108147	1.916577

log-likelihood = -251.94243604773

AIC = 509.88487209546

BIC = 523.975974838459

Table 8: Survival Model Fit Summary (Generalised Gamma distribution)

Gompertz

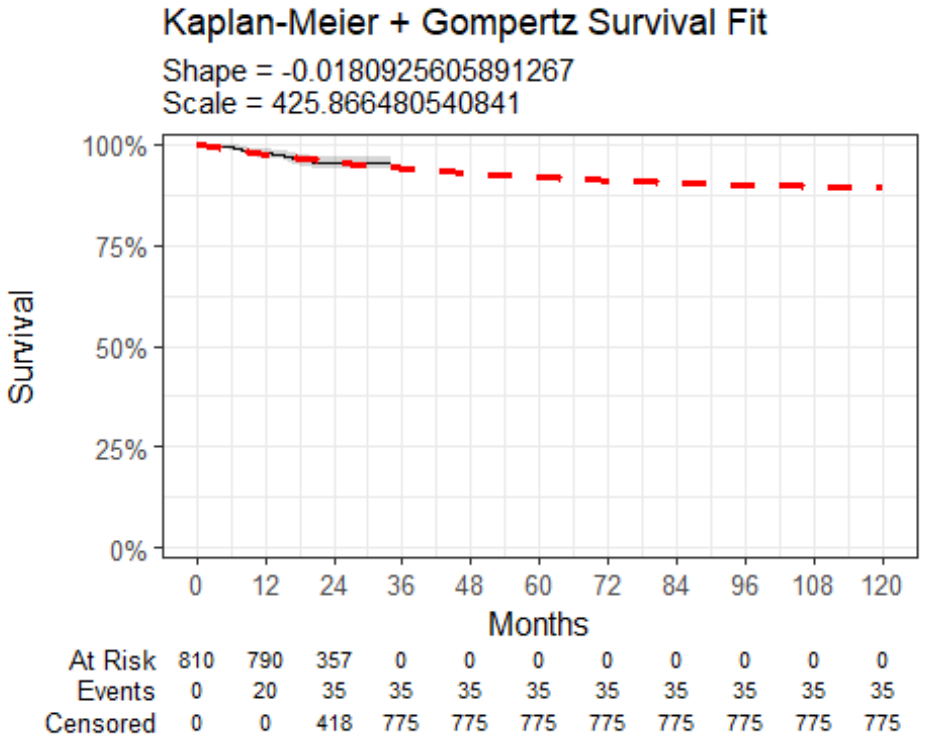

Figure 11: Overall survival against Gompertz survival function

Parameter	Estimate	Std. Error	L95.	U95.
shape	-0.018	0.023	-0.063050362	0.026865241
rate	0.002	0.001	0.001292897	0.004264706

log-likelihood = -253.883807531669

AIC = 511.767615063337

BIC = 521.16168355867

Table 9: Survival Model Fit Summary (Gompertz distribution)

Time on Treatment

The Kaplan-Meier plot below shows time-on-treatment (ToT) for patients receiving lenalidomide maintenance after an ASCT and associated induction/consolidation regimen. The median ToT was not reached.

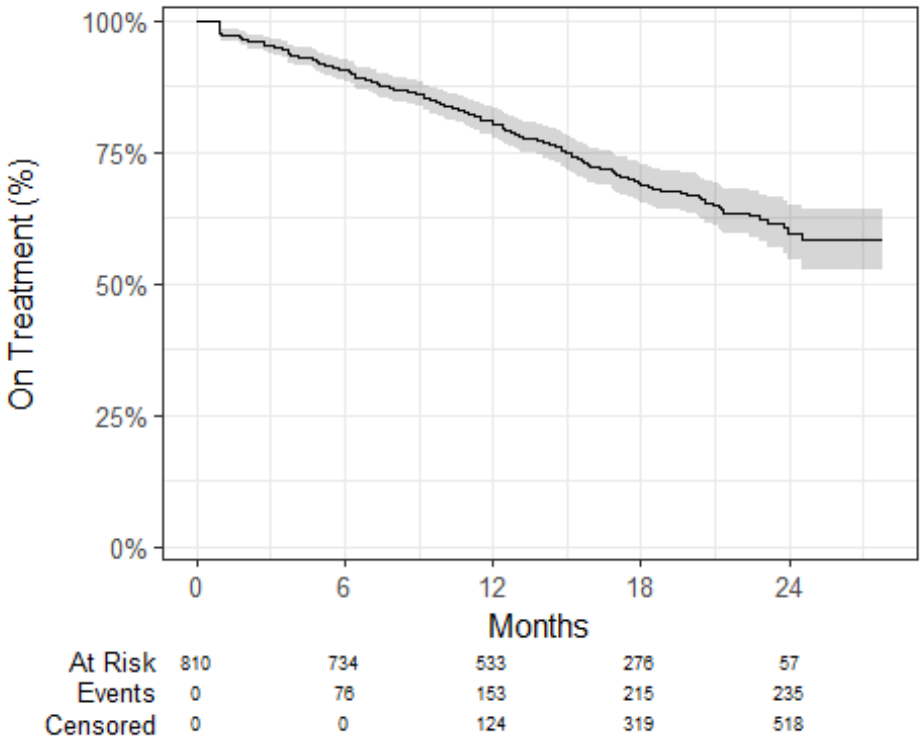

Figure 12: Time-on-treatment for patients receiving lenalidomide maintenance

Age, gender, overall survival and time on treatment for those receiving lenalidomide maintenance therapy following an autologous stem cell transplant and an induction/consolidation regimen containing daratumumab (cohort 2)

Introduction

This report was produced in partnership by the National Disease and Registration Service (NDRS) and National Institute for Health and Care Excellence (NICE). It presents overall survival, gender split, age distribution and time on treatment among patients with multiple myeloma who have received lenalidomide maintenance at first line following an autologous stem cell transplant and an induction/consolidation regimen containing daratumumab.

Method

A snapshot of SACT data was taken on 7th December 2025 and made available for analysis on 19th December 2025. SACT data is only considered complete when 90% of trusts have submitted data, which at the time of analysis was 31st March 2025. This date is used for censoring of time on treatment. Patients were traced for their vital status on 5th October 2025, which is the censoring date for the overall survival analysis.

Overall survival is measured from commencement of first lenalidomide maintenance treatment to death (if date recorded) or censoring date (if death date not present). Time-on-treatment was measured by the difference between a patient's first and last recorded lenalidomide maintenance treatment, plus 28 days (standard gap between administrations). If a patient died before the nominal cycle end, the end date was revised to the date of death. If the treatment end date extends beyond the treatment censoring date (31st March 25), the patient was censored.

Cohort inclusions / exclusions

Patients were included if they met all of the following conditions:

- Diagnosed between 1st Feb 2022 and 31st December 2023 (inclusive). Diagnoses and treatment pathways prior to this point would be before publication of NICE Technology Appraisal TA763 — "Daratumumab in combination for untreated multiple myeloma" and would not reflect subsequent changes to the expected pathway resulting from commissioners being required to fund the approved treatment
- Gender recorded as male or female
- Country code was 'England', based on postcode of residence at diagnosis
- NDRS cancer group definition of 'Myeloma'

- An autologous stem cell transplant was carried out as part of treatment after diagnosis
- Lenalidomide was initiated within 6 months after the stem cell transplant (based on both regimen and drug administration descriptions), and the lenalidomide regimen did not include dexamethasone.
- Daratumumab was recorded as being administered in the window between the diagnosis date and two months after the autologous stem cell transplant date (proxy for induction/consolidation of daratumumab, bortezomib, thalidomide and dexamethasone ['VTd'])

and were excluded if

- Any SACT treatments after diagnosis (not only lenalidomide) were recorded as being given as part of a trial

Identification of autologous stem cell transplant

The presence of an autologous stem cell transplant (ASCT) in the treatment pathway was determined by linkage of the registration record to HES, specifically where the post-diagnosis HES inpatient record contained an OPCS code of 'X33.4 - autologous peripheral blood stem cell transplant'. A sensitivity analysis explored how many additional records would be added by including other related codes in case significant numbers were recorded under related codes. All other restrictions were kept in place whilst codes were varied. Varying the codelist gave the following results: No additional cases were identified by including bone marrow graft codes (W34*). One additional record was found recorded as an allogenic stem cell transplant (X33.6), and no further cases were associated with the code for a syngeneic stem cell transplant (X33.5). Sixteen cases would be added if the definition was expanded to include X33.8 'Other specified blood transfusion' and X33.9 'Unspecified other blood transfusion'. Given the risk of including non-ASCT cases and minimal gain in sample size, X33.4 was selected as the sole ASCT defining code.

Observed ASCT rates (c. 16%) were lower than expected (25-30%), based on previous modelling work for NICE TA680. The identified cases therefore likely understate the true number of applicable procedures, reflecting under-recording or miscoding. We assume that ASCTs that are unrecorded or coded under alternative OPCS codes are not systematically associated with the outcomes analysed below (e.g., overall survival or time on treatment), given that coding missingness is likely a function of hospital administration and documentation rather than anything associated with clinical treatment. On this basis, any bias from missing ASCT data is expected to be minimal.

Identification of lenalidomide maintenance

Lenalidomide monotherapy is recommended as first-line maintenance following stem cell transplant. Owing to variation in SACT recording practices and the structure of SACT tables, it can be challenging to algorithmically distinguish first-line lenalidomide from second and subsequent lines, where lenalidomide may be used in combination (for example, carfilzomib + dexamethasone + lenalidomide [KRd], lenalidomide + dexamethasone [Rd], or ixazomib + lenalidomide + dexamethasone [Ixa-Rd]). These combinations may be

grouped at the regimen level in SACT or recorded as contemporaneous but separate ('split') regimens.

To reduce misclassification of second-line uses, we: (i) count only regimens where the NDRS-categorised description ("benchmark group") mentions lenalidomide only; (ii) include only cases where the earliest lenalidomide use occurs within six months of the ASCT date; and (iii) exclude cases where dexamethasone appears in the drug-level tables for lenalidomide monotherapy regimens.

Where split regimens occur, time-on-treatment may be overstated if the lenalidomide end date is taken from a combination containing lenalidomide. However, the observed time-on-treatment pattern would not imply a median survival exceeding the 53-month progression-free survival reported in a published meta-analysis.[5] We therefore consider potential overstatement of time on treatment from the incidental inclusion of combination regimens to be limited.

Identification of induction/consolidation regimens containing daratumumab

We searched the SACT regimen-and drug-level tables for entries indicating daratumumab administered between the diagnosis date and up to two months after the ASCT date. This window, informed by the VTd pathway described in MHRA licensing, was selected to capture the induction/consolidation phase—maximising identification of relevant regimens while minimising inclusion of second-line and later regimens containing daratumumab.

We conducted a sensitivity analysis by varying the post-ASCT window and reviewing treatment pathways regimens that fell outside that boundary boundaries, starting with a reduced boundary of 4 months prior and 2 months post ASCT. This returned 75% of patients with a recorded daratumumab administration in the period. Having reviewed a selection of patient pathways in the 25% of remaining diagnosis, we found regimen descriptions indicative of VTd induction outside of that window, chiefly earlier than the recorded ASCT date minus 4 months. Sequentially expanding the initial boundary back to 6 months brought in more of these cases, to the point of including 86% of cases, though induction regimens starting earlier than that were still found in the remaining 14% of the population. Expanding the admissible daratumumab administration window from the diagnosis date to two-months post ASCT date took the proportion of inductions / consolidations containing daratumumab to 94% of ASCT cases. We concluded the diagnosis date to two-month post-ASCT boundary was the most appropriate window to capture relevant regimens and was internally consistent with the pathway description, licensing

[5] Philip L. McCarthy et al., "Lenalidomide maintenance after autologous stem-cell transplantation in newly diagnosed multiple myeloma: A meta-analysis," *Journal of Clinical Oncology* 35, no. 29 (2017): 3279–3289, https://ascopubs.org/doi/abs/10.1200/JCO.2017.72.6679.

authorisation, and clinical expectations for the proportion receiving VTd induction/consolidation.

Flow chart

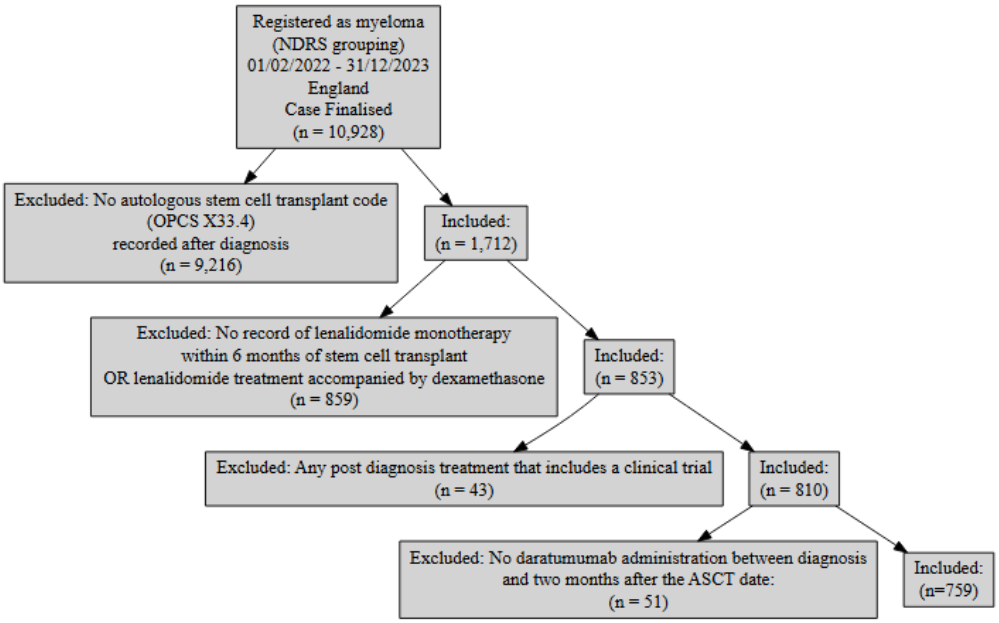

Figure 1: Inclusion / Exclusion Flow Chart

Patient acknowledgement

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Results

Age at start of treatment

The table below sets out the mean age, standard deviation, median age and interquartile range (IQR) of patients who have received lenalidomide monotherapy maintenance treatment for multiple myeloma following an ASCT. Age is measured at the commencement of lenalidomide.

Characteristic	**Female** N = 309[1]	**Male** N = 450[1]
Age at start of treatment	62, (8) : 63 (56, 68)	62, (8) : 63 (56, 68)

[1]Mean, (SD) : Median (Q1, Q3)

Table 10: Mean age, standard deviation, median age and IQR of patients who have received lenalidomide maintenance

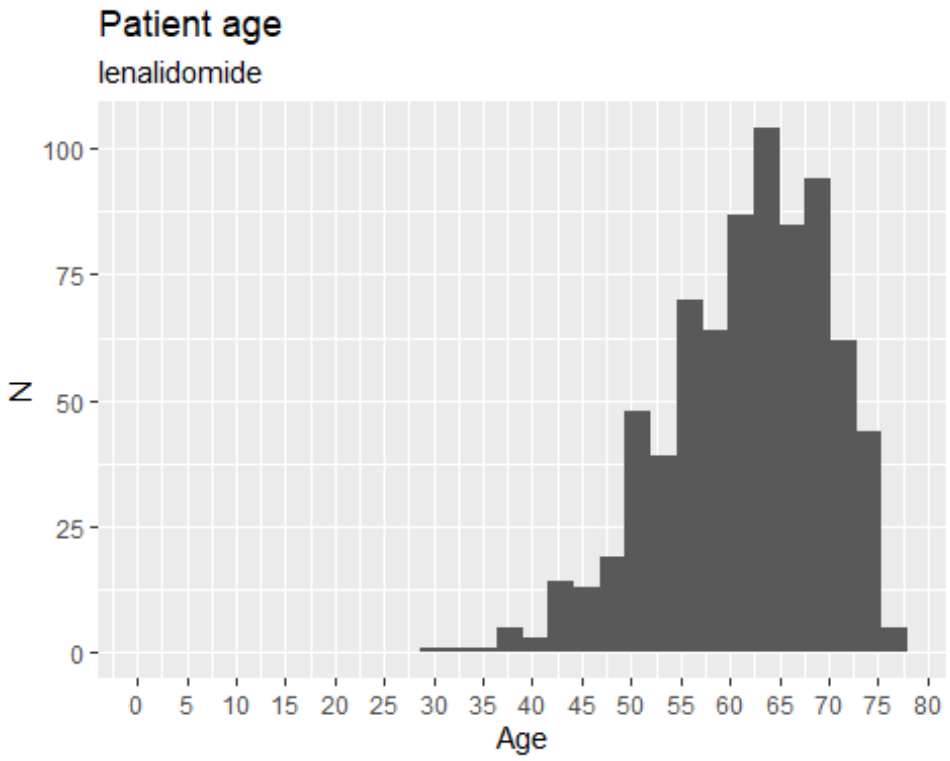

Figure 13: Age distribution of patients who have received lenalidomide maintenance

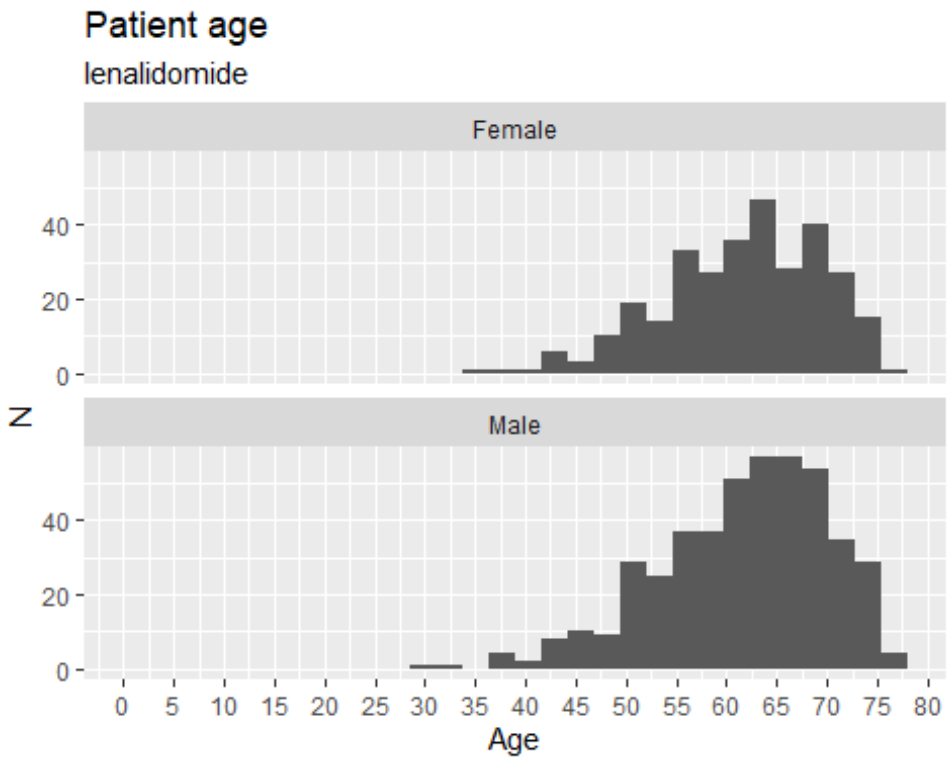

Figure 14: Age distribution of patients who have received lenalidomide maintenance

Overall Survival

Base K-M plot

The Kaplan-Meier plot below shows survival over time for those receiving a treatment regimen of lenalidomide monotherapy after ASCT and induction/consolidation regimen containing daratumumab.

Median survival was not reached, restricted mean survival (over the whole curve) was 32.93 months. The minimum follow-up time was 1.8 months, median 22.7 months, and maximum follow-up time of 34 months. Subsequent graphs with fitted parametric survival curves have an extended X axis to allow differentiation of longer-term projections.

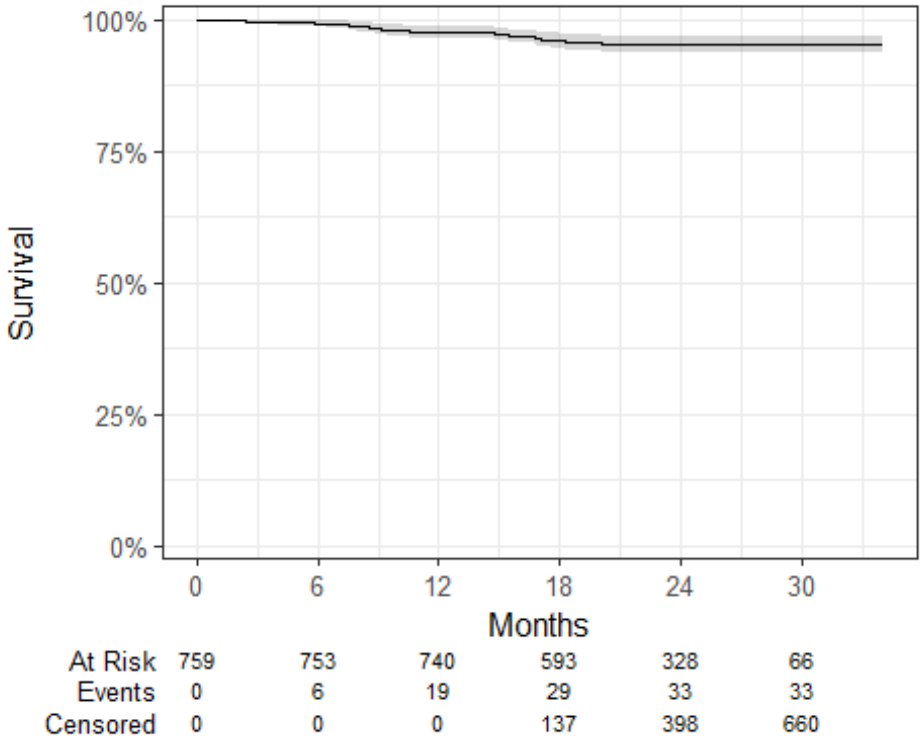

Figure 15: Overall survival amongst patients who have received lenalidomide maintenance therapy for multiple myeloma

Exponential

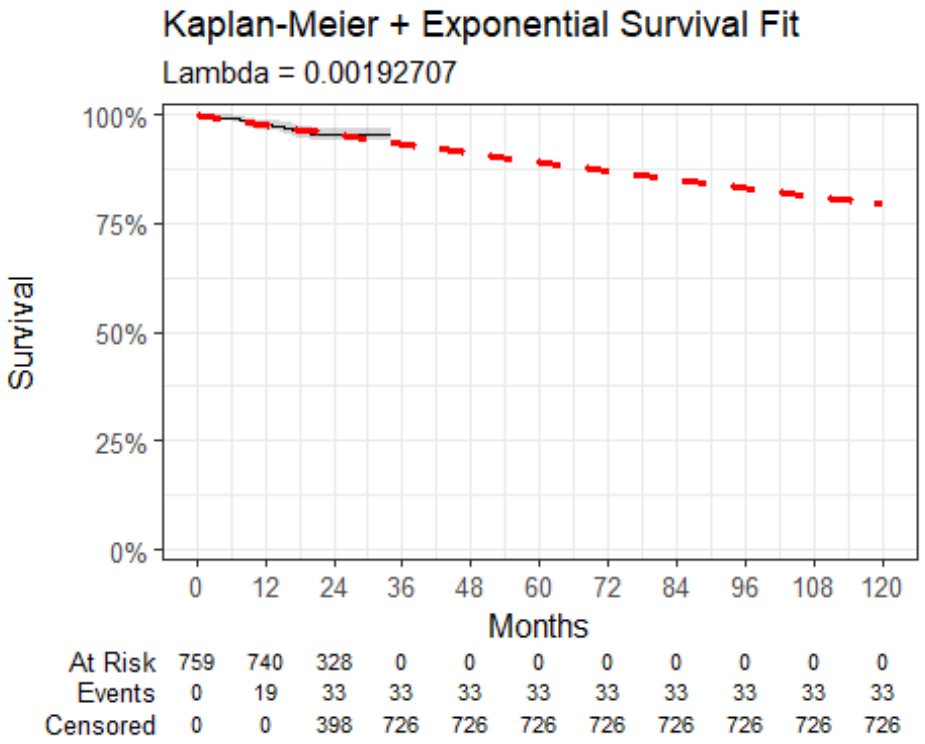

Figure 16: Overall survival against exponential survival function

Parameter	Estimate	Std. Error	z	p-value
(Intercept)	6.252	0.174	35.91359	1.874405e-282

log-likelihood = -239.307875639097

AIC = 480.615751278195

BIC = 485.24775305559

Table 11: Survival Model Fit Summary (Exponential distribution)

Weibull

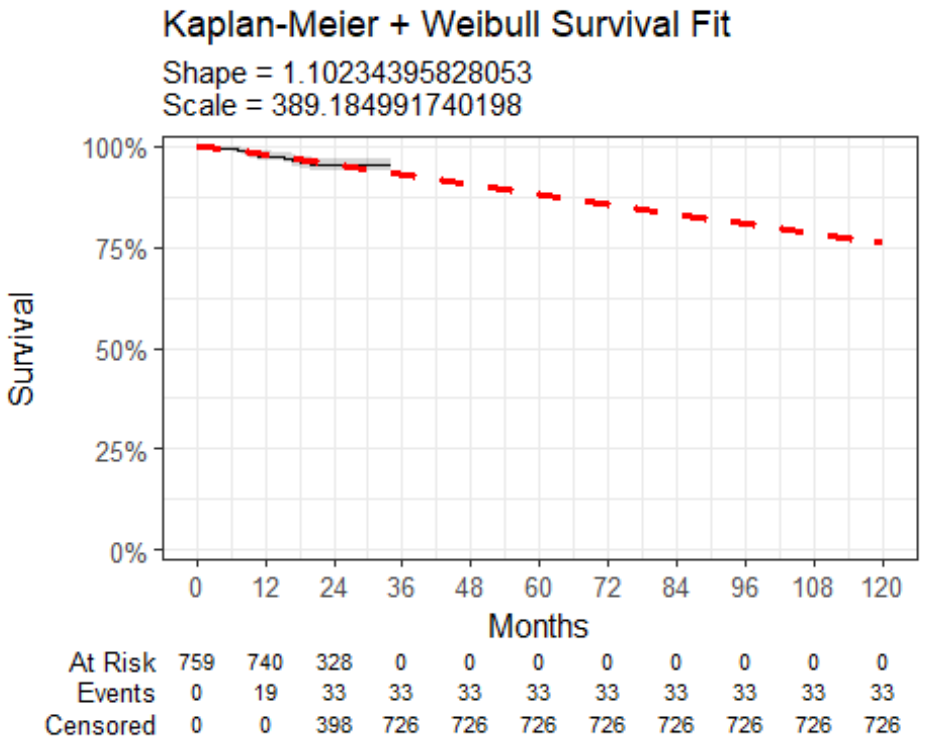

Figure 17: Overall survival against Weibull survival function

Parameter	Estimate	Std. Error	z	p-value
(Intercept)	5.964	0.499	11.9624924	5.585974e-33
Log(scale)	-0.097	0.168	-0.5786208	5.628451e-01

log-likelihood = -239.146323166856

AIC = 482.292646333713

BIC = 491.556649888504

Table 12: Survival Model Fit Summary (Weibull distribution)

Log-normal

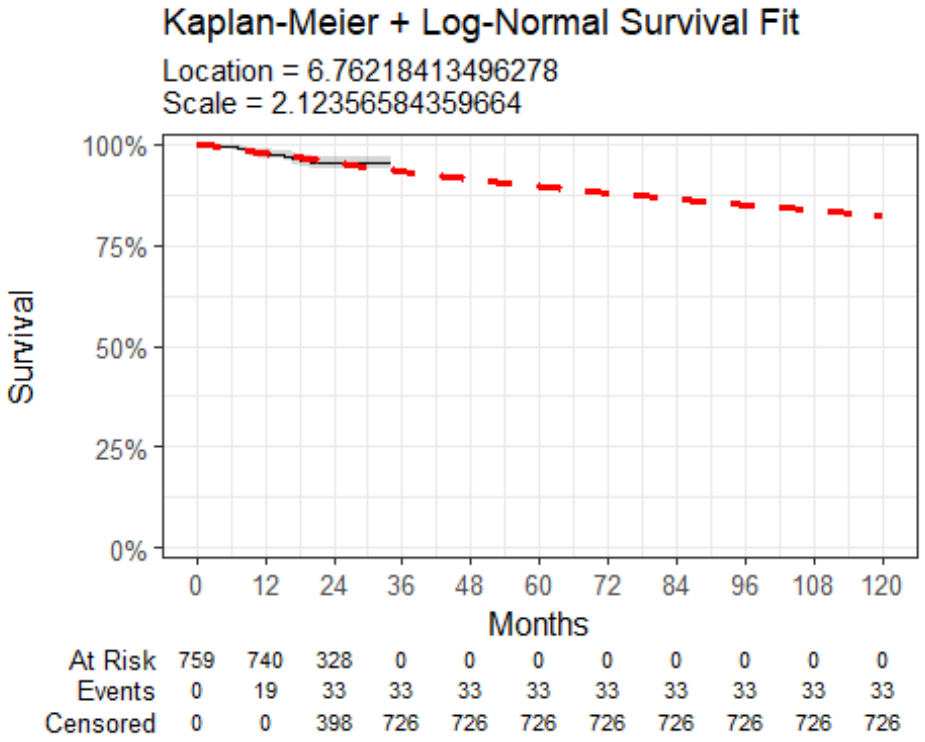

Figure 18: Overall survival against Log-normal survival function

Parameter	Estimate	Std. Error	z	p-value
(Intercept)	6.762	0.610	11.085156	1.480927e-28
Log(scale)	0.753	0.154	4.883469	1.042356e-06

log-likelihood = -237.967017351041

AIC = 479.934034702082

BIC = 489.198038256874

Table 13: Survival Model Fit Summary (Log-normal distribution)

Log-logistic

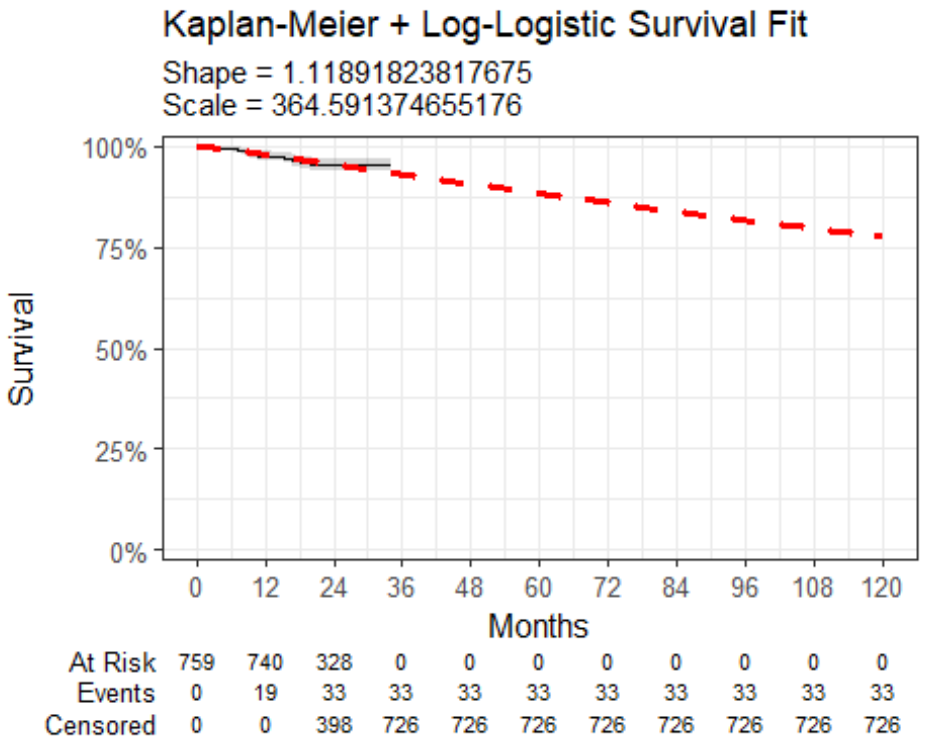

Figure 19: Overall survival against Log-Logistic survival function

Parameter	Estimate	Std. Error	z	p-value
(Intercept)	5.899	0.489	12.0671385	1.575167e-33
Log(scale)	-0.112	0.168	-0.6707908	5.023538e-01

log-likelihood = -239.045904763936

AIC = 482.091809527872

BIC = 491.355813082663

Table 14: Survival Model Fit Summary (Log-Logistic distribution)

Gaussian

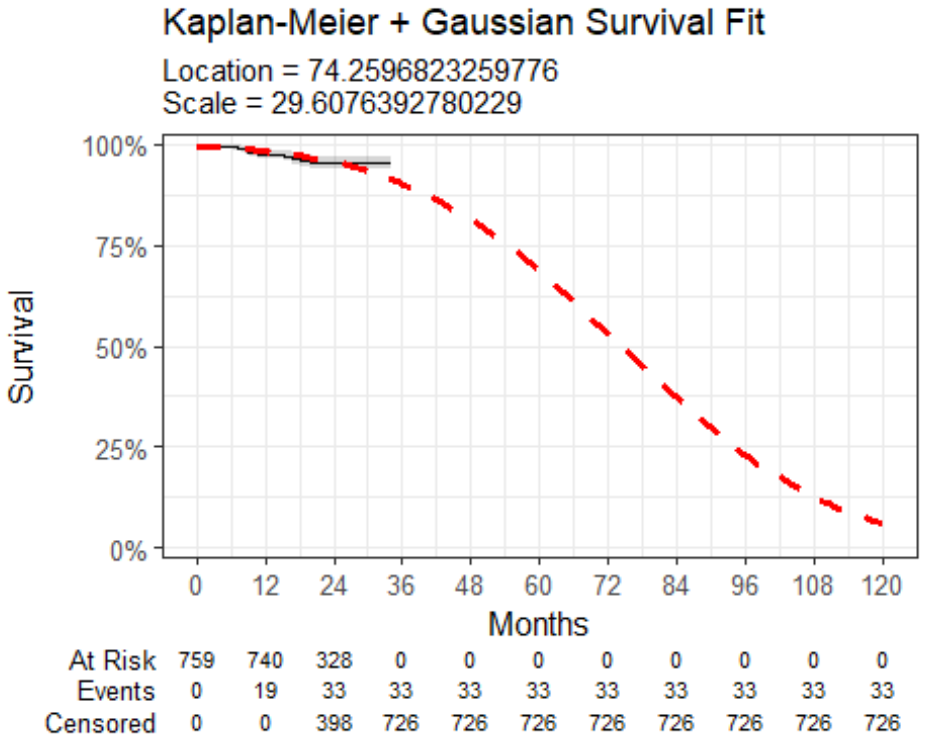

Figure 20: Overall survival against Gaussian survival function

Parameter	Estimate	Std. Error	z	p-value
(Intercept)	74.260	8.409	8.83074	1.039858e-18
Log(scale)	3.388	0.153	22.13523	1.447861e-108

log-likelihood = -250.496759783642

AIC = 504.993519567285

BIC = 514.257523122076

Table 15: Survival Model Fit Summary (Gaussian distribution)

Gamma

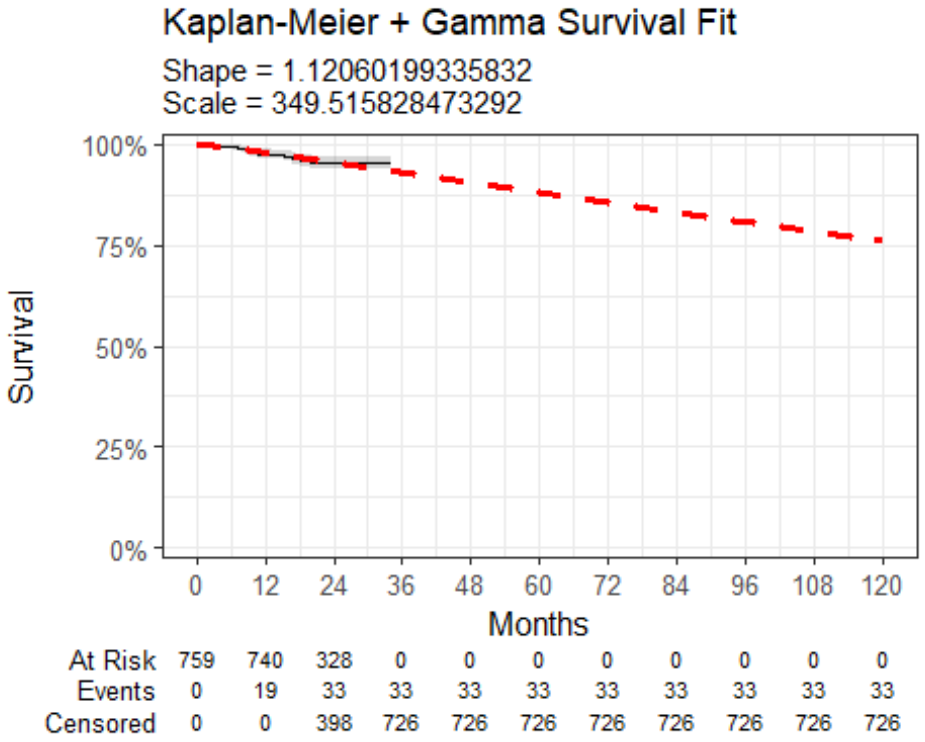

Figure 21: Overall survival against gamma survival function

Parameter	Estimate	Std. Error	L95.	U95.
shape	1.121	0.202	0.7868263364	1.595966949
rate	0.003	0.002	0.0008476806	0.009656818

log-likelihood = -239.113996853114

AIC = 482.227993706228

BIC = 491.49199726102

Table 16: Survival Model Fit Summary (Gamma distribution)

Generalised gamma

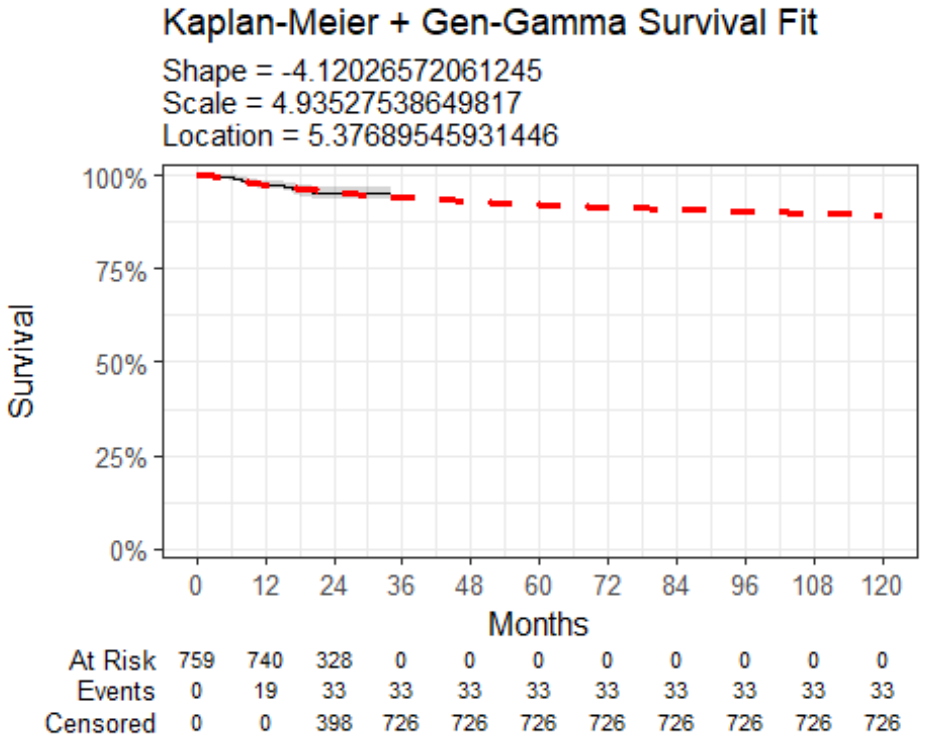

Figure 22: Overall survival against Generalised Gamma survival function

Parameter	Estimate	Std. Error	L95.	U95.
mu	5.377	1.627	2.188143	8.565648
sigma	4.935	0.758	3.651754	6.669930
Q	-4.120	2.809	-9.625500	1.384969

log-likelihood = -236.638289820402

AIC = 479.276579640805

BIC = 493.172584972991

Table 17: Survival Model Fit Summary (Generalised Gamma distribution)

Gompertz

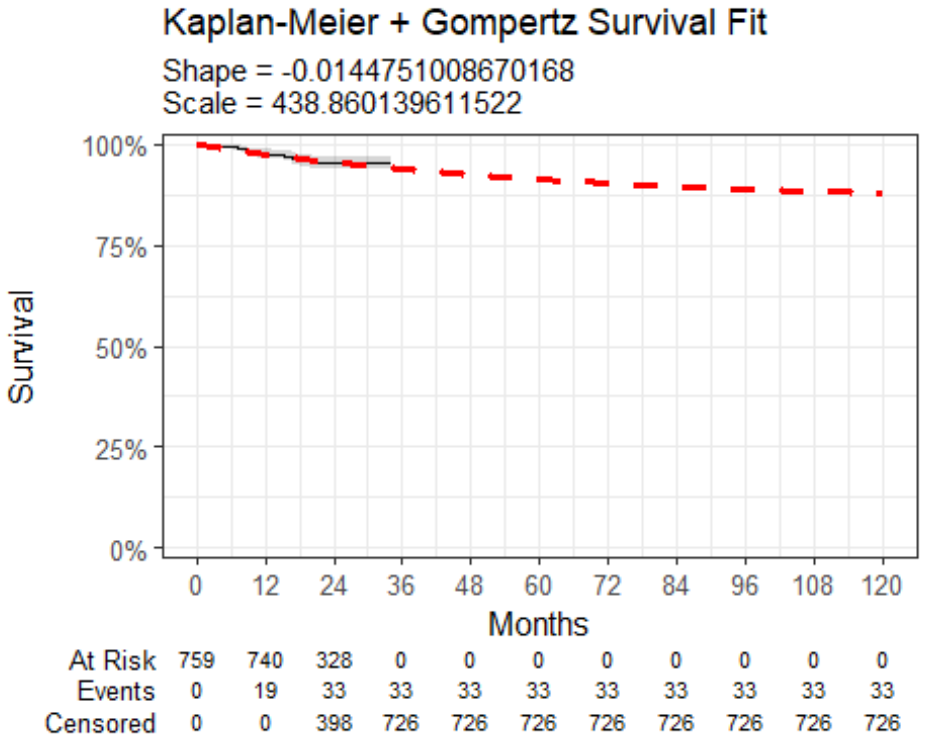

Figure 23: Overall survival against Gompertz survival function

Parameter	Estimate	Std. Error	L95.	U95.
shape	-0.014	0.024	-0.060769236	0.031819034
rate	0.002	0.001	0.001226006	0.004235018

log-likelihood = -239.117243522846

AIC = 482.234487045692

BIC = 491.498490600483

Table 18: Survival Model Fit Summary (Gompertz distribution)

Time on Treatment

The Kaplan-Meier plot below shows time-on-treatment (ToT) for patients receiving lenalidomide maintenance after an ASCT and an induction/consolidation regimen containing daratumumab. The median ToT was not reached.

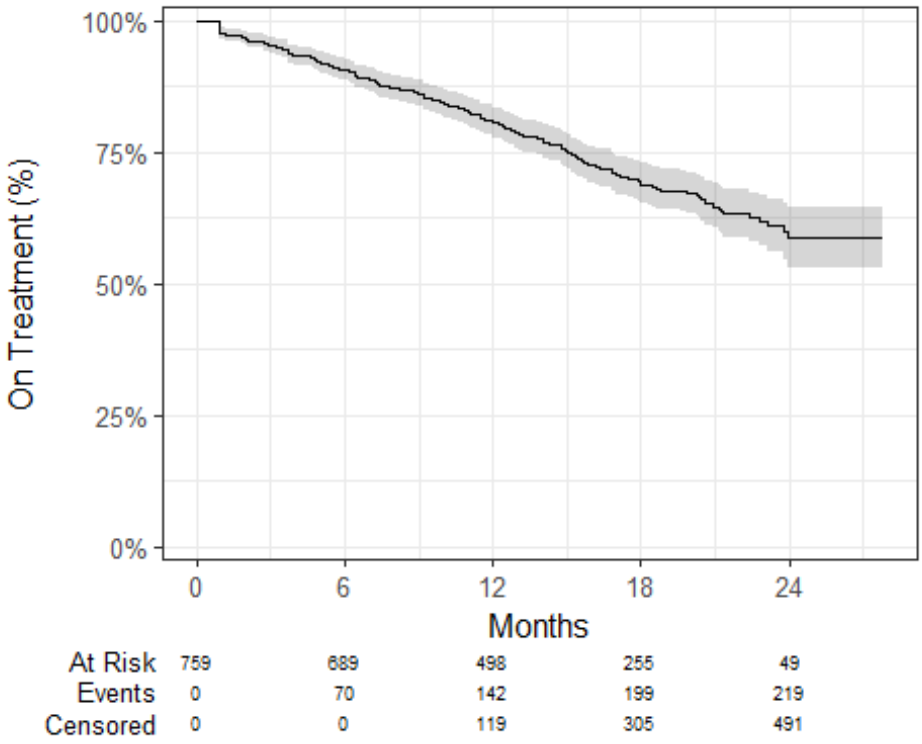

Figure 24: Time-on-treatment for patients receiving lenalidomide maintenance

in collaboration with:

Erasmus School of Health Policy & Management

Maastricht University

Daratumumab in combination for newly diagnosed multiple myeloma when stem cell transplant is suitable [ID6249]

EAG critique of the company response to the draft guidance

Produced by Kleijnen Systematic Reviews (KSR) Ltd. in collaboration with Erasmus University Rotterdam (EUR) and Maastricht University

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1. EAG critique of the company response to the draft guidance

This report contains the EAG critique of the company response to the draft guidance (DG) produced following the first appraisal committee meeting (ACM).[1-3] The EAG also provide an addendum containing a summary of the cost effectiveness analyses provided by the company as part of the Additional Analyses document in comparison to those post-clarification from the EAG report, supplemented by the EAG's additional analyses.[2, 4]

1.1 Indirect and direct treatment comparisons (DGD [draft guidance document], Section 3.4)

Given the committee's preference for the reweighted inverse probability of treatment weighting (IPTW) analysis from PERSEUS in order to estimate the effect of daratumumab plus lenalidomide (DL) versus lenalidomide (L) in the maintenance phase, the company have provided further details (comparison of covariate values and assessment of overlap of the propensity score (PS) weights) in the Additional Analyses document.[2] In this, also in response to the committee's request, alternative methods i.e. multivariable regression and the doubly robust methods have been explored. The weighting was based on MRD status at the start of the maintenance phase and a set of baseline covariates (either a base case set or including additional covariates as a sensitivity analysis). The results for OS and PFS are shown below.

Table 1. Overview of PFS and OS results (before and after re-weighting) for DL versus L maintenance therapy in PERSEUS

Comparison	PFS HR (95% CI)	OS HR (95% CI)
DL vs L maintenance (unweighted)	[redacted]	[redacted]
IPTW-ATT		
DL vs L maintenance (weighted; base case baseline covariate set)	[redacted]	[redacted]
DL vs L maintenance (weighted; sensitivity analysis baseline covariate set)	[redacted]	[redacted]
Doubly robust		
DL vs L maintenance (weighted; base case baseline covariate set)	[redacted]	[redacted]
DL vs L maintenance (weighted; sensitivity analysis baseline covariate set)	[redacted]	[redacted]
Multivariable regression		
DL vs L maintenance (weighted; base case baseline covariate set)	[redacted]	[redacted]
DL vs L maintenance (weighted; sensitivity analysis baseline covariate set)	[redacted]	[redacted]

Source: Table 3, Additional analyses.[2]

ATT: average treatment effect in the treated; CI: confidence interval; DL: daratumumab and lenalidomide; HR: hazard ratio; IPTW: inverse probability of treatment weighting; L: lenalidomide; OS: overall survival; PFS: progression-free survival.

EAG comment: The company have provided what the committee requested, as expressed in the DG. The comparison of covariate values (not reproduced here for brevity) seems to show little difference in baseline covariate values, which is unsurprising given the randomised design of the trial, although some small differences might have arisen due to the censoring of those who had progressed prior to the start of maintenance, and those have mostly been reduced by weighting. There were more substantial differences in MRD status, which all but disappeared by weighting. Assessment of overlap (figures not shown for brevity) also shows that, although it could be regarded as not lacking beforehand, is much improved after weighting.

The results then show that the HRs for both PFS and OS all increase with weighting, except in the sensitivity analysis when using regression, where the HR for PFS is unchanged and the HR for OS decreases. It therefore appears that less biased estimates of the HRs are probably a little higher than the unweighted, lying in a range somewhere between [redacted] and [redacted] for PFS and between [redacted] and [redacted] for OS.

1.2 Modelling PFS and OS (DGD, Section 3.6)

In response to the committee's preferred approach for modelling OS and PFS for the DBTd induction followed by L maintenance arm (DBTd-L), the company have updated the survival modelling methodology to incorporate the reweighted OS and PFS HRs presented in Table 1 of Section 1.1. Incorporation of the reweighted HRs allowed estimation of OS and PFS for the DBTd-L arm based on the survival data of the DBLd-DL arm of the PERSEUS trial, aligning with the committee's preferred approach. In the updated base case, the IPTW-ATT HRs have been used (i.e. [redacted]). The company have further referred to the evaluation of standard parametric models for the DBLd-DL reference curve that were presented in the original company submission, whilst in their additional analysis compared the updated long-term DBTd-L projections against clinical expert estimates at 10, 15, and 25 years (Additional Analyses, Section B: Table 5, pp. 12; Table 7, pp.15). From these analyses the company have concluded that the exponential distribution for OS and the generalized gamma for PFS would be the most appropriate options for their base case (Additional Analyses, Section B, pp. 9–15). A scenario analysis has also been conducted using the Gompertz PFS distribution, confirming that DBLd-DL remained dominant over DBTd-L (Additional Analyses, Section B, pp. 22–23).

EAG comment: The company have updated their OS/PFS modelling approach aligning with the committee's request in the DG.

Considering the updated OS predictions for the DBTd-L arm, the exponential model appears to overestimate the 10-year OS, while predictions at 15 and 25 years align more closely with clinical experts' expectations (Additional Analyses; Table 5, pp. 12).[2] As highlighted in the EAG report, the exponential model assumes a constant hazard over time, which may be a strong assumption. The observed hazard from the DBLd-DL arm (shown in Figure 4.3 of the EAG report) appears to increase modestly over time, which may not be adequately captured by the exponential distribution and could lead to overestimation of long-term OS. Nevertheless, the EAG does not think any of the alternative extrapolations proposed by the company provide a better fit.

Considering the updated PFS predictions for the DBTd-L arm, the generalised gamma model appears to overestimate the 15-year PFS, while predictions at 10 and 25 years align more closely with clinical experts' expectations (Additional Analyses; Table 7, pp. 15).[2] It is also noted that apart from the Gompertz, all other parametric models overestimate 10, 15 and 25-year PFS. The Gompertz curve

overestimates the 10-year PFS when compared to clinicians-elicited predictions. As mentioned in the EAG report, the Gompertz scores better in terms of AIC/BIC criteria compared to the generalised gamma. Nonetheless, the company has explored the impact of using a Gompertz parametric model in a scenario analysis, which showed that DBLd-DL remained dominant over DBTd-L. The EAG finds this approach appropriate for the purpose.

1.3 MRD-negativity stopping rule (DGD, Section 3.7)

Regarding the MRD-negativity stopping rule, the DG stated*:*

- "*The EAG stated that assuming all people continue daratumumab maintenance until progression has a large impact on cost-effectiveness.*
- *The committee acknowledged that there would be clinical benefits to MRD guided treatment but that it was unclear whether MRD testing would be feasible in the NHS. It had concerns around how many MRD tests would be required to allow the discontinuation of daratumumab and if some people would decline testing in clinical practice. The committee was unclear on if it was feasible for all treatment centres to undertake MRD testing and where the tests would be processed. They also had concerns on if delays to MRD testing would result in daratumumab discontinuation later than the two-year time point. So, the committee was not able to conclude whether an MRD stopping rule was appropriate in the model which leads to uncertainty in the cost effectiveness estimates."*

In response to the first point the company indicated that in PERSEUS, maintenance was MRD-guided: after at least two years, patients meeting MRD stopping criteria discontinued daratumumab and continued lenalidomide alone until progression, while patients who did not meet the MRD-guided stopping criteria continued daratumumab plus lenalidomide (DL) until progression. The company stated there is no evidence on the efficacy or safety of DL maintenance until progression in an unselected population and considered an EAG scenario assuming DL maintenance until progression to be not evidence based, extending costs without evidence of additional health benefit, and therefore not informative for NICE decision making.

Regarding the feasibility of MRD testing in the NHS, based on UK clinical and laboratory expert input, MRD testing using validated NGF technology at Leeds Teaching Hospitals NHS Trust and The Royal Marsden NHS Foundation Trust is considered operationally feasible within current NHS infrastructure, with accredited laboratories, established referral pathways, sufficient capacity, and manageable risks. The company therefore considers an NGF-based MRD stopping rule appropriate and implementable. The company recognises NHS ambitions under the 10 Year Health Plan and National Cancer Plan to expand genomic profiling, with an expected transition over 1–2 years to NGS-based MRD testing via the Genomic Laboratory Hub (GLH) network.[5, 6] Although NGS offers higher sensitivity (10^{-6} vs IMWG standard 10^{-5}), it is not yet routinely deployable at scale due to infrastructural, regulatory, and cost constraints. NGF (10^{-5}) is currently embedded in NHS services and considered clinically appropriate. A phased transition from NGF to NGS is anticipated. Where no MRD test is available, a two-year fixed DL maintenance duration is considered preferable to no access. Three scenarios were presented to support the committee on this point:

1. MRD testing using NGS would be delivered through the NHS Genomic Medicine Service across seven GLHs. A baseline MRD assessment at diagnosis is required to enable longitudinal testing. Therefore, all patients would undergo at least three MRD tests, with an additional test for a subset achieving MRD negativity later, as described in the Company submission. Because

bone marrow biopsy is part of standard multiple myeloma diagnostics, the baseline NGS MRD assessment would not require an additional biopsy.

2. Two-year fixed treatment duration (all patients) of DL maintenance is given following induction and consolidation with DBLd. Clinical efficacy is informed by the phase II GRIFFIN study (CS Appendix N).[7] This scenario is proposed if MRD-guided maintenance is not considered feasible within the 21-month timeframe. Although two-year fixed duration is expected to improve efficacy versus current standard care, it would prevent MRD-positive or non-sustained MRD-negative patients, including high-risk patients, from continuing DL beyond two years. The company notes that clinical experts prefer this approach over no access to DL maintenance.
3. Two-year fixed duration (excluding high-risk patients) DL maintenance is given after induction and consolidation with DBLd for all patients except high-risk patients, who continue DL until progression. Clinical efficacy inputs are based on the phase II GRIFFIN study (CS Appendix N).[7]

The company states that DBLd remains cost effective across all scenarios explored, indicating that conclusions are robust to the choice of MRD technology (NGF versus NGS). The company commits to working with NICE, NHS England, local NHS trusts and laboratory professionals to avoid delays in access to the PERSEUS regimen, including use of a two-year fixed treatment duration if MRD testing is unavailable. Further details are provided in the Additional Analysis document (Section B, pages 25–32).[2]

EAG comment: The EAG notes that assuming all patients continue daratumumab maintenance until disease progression has a substantial impact on the cost-effectiveness results. However, the EAG has not assessed the clinical plausibility of this scenario. The appropriateness of assuming DL maintenance until progression should be determined by clinical experts. Nevertheless, the EAG considers the scenario informative for decision making. It demonstrates that the model results are highly sensitive to assumptions about treatment duration, and therefore highlights the importance of robust evidence and justification for the stopping rule applied in the base case.

The EAG would like to thank the company for providing additional information on the operational feasibility of MRD testing within the NHS. The description of existing NGF infrastructure and anticipated transition to NGS is noted. The EAG considers that the practical feasibility of implementing MRD-guided stopping, including capacity, turnaround times and service configuration, is primarily a matter for NHS experts to determine.

The EAG also thanks the company for presenting additional scenarios exploring alternative testing approaches and fixed-duration treatment strategies. The EAG considers these scenarios relevant for Committee decision making, as they help characterise structural uncertainty related to testing strategy and treatment duration. The clinical plausibility and anticipated uptake of these scenarios should be confirmed by experts.

1.4 Modelling time to treatment discontinuation (DGD, Section 3.8)

The committee concluded in the DG that the survival data used to inform the time to treatment discontinuation (TTD) for L maintenance therapy in the DBTd-L arm should be derived by the PERSEUS trial, i.e. the same source that was used for the relative effectiveness estimates. In response to this request, the company in their updated base case have used the PERSEUS Kaplan-Meier data from the BLd-L arm of the PERSEUS trial to inform TTD for L maintenance therapy. Scenario analyses

using the most optimistic (log-normal) and pessimistic (Gompertz) TTD curves have been explored showing incremental costs changes of [redacted]% and [redacted]% from the base case, respectively, indicating that TTD assumptions are not a key driver of cost-effectiveness. Similar to the company's approach for defining HRs based on the reweighted trial data, use of a reweighted TTD curve estimated from L patients who were matched with the DL patients in the PERSEUS trial has been explored in an additional scenario analysis. In their updated base case, the company have maintained in using the exponential model.

EAG comment: The company's base case approach includes survival data from the BLd-L arm of the PERSEUS trial to inform TTD for L maintenance therapy in the DBTd-L arm, aligning with the committee's preferred approach.

The company reported a set of scenario analyses. However, the EAG noted that these were not included in the scenario analyses section of the Additional Analyses document.[2] Consequently, the EAG used the economic model to replicate the company's results from these scenarios as these were reported above. When applying the log-normal and Gompertz TTD curves for L maintenance, instead of the exponential model, the resulting changes in incremental costs differed from those reported in the company's response to the DG document. Specifically, the log-normal curve produced a change of [redacted]% rather than [redacted]%, while the Gompertz curve produced a change of [redacted]% rather than [redacted]%. The EAG further confirmed that using the reweighted BLd-L data from the PERSEUS trial had minimal impact on the cost-effectiveness outcomes.

1.5 Subsequent treatment costs (DGD, Section 3.9)

According to the DG, "*the committee acknowledged that there was significant uncertainty around how well the proportions modelled to receive subsequent treatments reflected NHS practice. It was particularly concerned about the proportion modelled to receive belantamab mafodotin at second line. It also had concerns about how many people in each arm were modelled to progress to each line of therapy. It noted that some of the subsequent treatments in the model were very expensive which had a large impact on cost-effectiveness. So, there was too much uncertainty to conclude if the modelled subsequent treatments were representative of NHS clinical practice*".

In relation to the distribution of subsequent treatments, the company highlighted that the UK multiple myeloma pathway is evolving, with recent NICE recommendations including belantamab mafodotin at second line (2L) and teclistamab at fourth line (4L), and more recently belantamab mafodotin with pomalidomide and dexamethasone (BePd) at 2L and talquetamab at 4L. To address Committee concerns, the company reviewed NHS pharmacy/ePrescribing (VSTx) data (October 2024–September 2025).[8] Uptake of new treatments remains limited but is expected to increase as local protocols and experience develop. Because VSTx reflects prevalent patients rather than new patient share, the company combined observed data with clinical expert opinion to project future treatment distributions for modelling (Additional Analyses, Section B, pages 16–19, 24–25). Cost effectiveness is most sensitive to the distribution and cost of belantamab mafodotin at 2L. Following NICE recommendation of belantamab mafodotin with bortezomib and dexamethasone (BeBd) in June 2025, market share has increased and is expected to displace daratumumab with bortezomib and dexamethasone (DBd) based on head-to-head efficacy.[9]The company reduced its base-case BeBd share from 80% to 50%, with the remaining proportion allocated mainly to DBd. A scenario using current lower shares was also explored and resulted in a dominant ICER. At 4L, teclistamab uptake remains low following NICE recommendation in November 2024. The company revised its base-case share from 50% to 60% in line

with clinical feedback and explored a lower-share scenario. Further details are provided in Additional Analyses (Section B, pages 24–25).[2]

The company addressed Committee concerns regarding the proportion of patients progressing to subsequent lines of therapy. In the model, progression to 2L is driven by DBLd-DL or DBTd-L PFS curves, while progression to 3L and 4L is determined by the weighted median PFS of treatments used in each line. The proportion receiving subsequent therapy increases over time and depends on PFS and OS. In the base case, [redacted] and [redacted] of patients in the DBTd-L arm are modelled to progress to 2L, 3L and 4L, respectively, compared with [redacted], [redacted] and [redacted] in the DBLd-DL arm (Additional Analyses, Section B, pages 20–21).[2] Within five years, [redacted], [redacted] and [redacted] (DBTd-L) and [redacted], [redacted] and [redacted] (DBLd-DL) are predicted to progress to successive lines. These estimates are consistent with PERSEUS data (cut-off 01 August 2023), where 9.4% of patients in the DBLd-DL arm and 26.8% in the BLd-L arm had received at least one subsequent treatment. Median PFS for DBLd-DL ([redacted] years) is nearly twice that of DBTd-L ([redacted] years), reflected in lower progression rates. The modelled proportion progressing after DBTd-L ([redacted]) may be conservative relative to TA763, where [redacted] of alive DBTd-L patients progressed to 2L; this difference arises because the modelled PFS curve exceeds that used in TA763 beyond 10 years, resulting in fewer patients progressing.

EAG comment: The EAG would like to thank the company for providing updated information on the distribution of subsequent treatments, including review of NHS pharmacy/ePrescribing (VSTx) data (October 2024–September 2025)2 and the additional analyses presented in Section B (pages 16–19, 24–25).[2] The EAG acknowledges that the multiple myeloma pathway is evolving following recent NICE recommendations. However, the EAG considers that the base case should reflect established NHS practice at the time of decision making. While future uptake of belantamab mafodotin at 2L and teclistamab at 4L may increase, projected market shares based partly on expert opinion may introduce structural uncertainty. The EAG therefore considers that current observed treatment distributions are more appropriate for the base case, with forward-looking assumptions explored in scenario analyses. The EAG notes that cost effectiveness is still highly sensitive to the assumed uptake of 2L treatments. Although the company reduced the base-case share from 80% to 50% and explored a scenario based on current lower shares, assumptions about displacement of DBd based on head-to-head efficacy remain uncertain. This represents a key structural driver of results.

The validity of the proportion of patients progressing to subsequent lines of therapy should be confirmed by published data or clinical experts.

1.6 Utility values (DGD, Section 3.10)

The DG stated that the "*committee noted that ideally a different utility value would be applied for each line of treatment in the progressed disease state. The committee concluded that applying a single utility value post progression was acceptable but acknowledged that was a simplifying assumption and that applying a utility value weighted by the line of treatment could be an alternative approach*".

The company acknowledged that applying a single utility value in the post-progression health state is a simplifying assumption. A scenario analysis was conducted applying line-of-treatment–weighted utilities in the progressed state, as suggested by the EAG, which reduced total QALYs in the DBTd-L arm (Additional Analyses, Section B, pages 23–24).[2] The company stated that, although simplified, the single-utility approach is conservative because it overestimates QALYs for the comparator. It therefore considered this uncertainty and not a key driver of decision-making uncertainty.

EAG comment: The EAG agrees that applying a single utility value in the post-progression state is a simplifying assumption. Whether and to what extent this assumption is conservative depends on the relative distribution of subsequent treatments and time spent in later lines across arms. The EAG agrees that this structural assumption does not appear to be a primary driver of cost-effectiveness results, based on the scenario presented. Nonetheless, applying line-specific utilities is methodologically preferable where data permit, as it better reflects differences in health-related quality of life across lines of therapy and reduces structural uncertainty.

1.7 Areas needing clarification (DGD, Section 3.13)

The company have presented a critique of the SACT data, an analysis of which was supplied at the request of the committee, identifying that cohort 2 are the patients relevant to this appraisal i.e. those who are supposed to have received receiving lenalidomide maintenance therapy following an autologous stem cell transplant and an induction/consolidation regimen containing daratumumab. They question the methodological robustness of the analysis, identifying some concerns, including the possibility of including patients with the wrong condition e.g. myelomatosis; lack of target trial emulation (TTE); lack of key patient characteristics; data immaturity; lack of definition of ToT; and no data to estimate PFS.

Nevertheless, they do make some comparisons with PERSEUS in sex and age, and OS (through digitisation of the Kaplan Meier curve), although refraining from a comparison between ToT and TTD in PERSEUS. They find comparability in sex and age. For OS, they also find comparability, stating:[2] *"In addition, long-term extrapolations from seven fitted parametric models indicate that 10-year survival from maintenance ranges from 75% to 88%, with the best statistically fitting curve (exponential) predicting 79.3% of patients alive at 10 years (Table 1). This broadly aligns with the Company's base case estimate of* [redacted] *for DBTd-L survival at 10 years, although the Company base case was fitted from randomisation which may partly explain the lower estimate (Additional Analyses, Section B: page 12)."*

They also provide a comparison of PFS between PERSEUS and another recent real world evidence dataset, which included patients treated with DBTd followed by 98% with L, which showed a 24-month PFS of 89.7% (from date of ASCT), versus the company modelled value of [redacted] (from randomisation).

EAG comment: The EAG appreciate the concerns of the company regarding the SACT data, although it does seem to have been useful in demonstrating some comparability with PERSEUS and one of the company's OS estimates. Therefore, it might also be informative to provide comparisons between other OS statistics e.g. the median, and survival to other timepoints in addition to 10 years (e.g. 15 and 25 years, as shown in Figure 2 of the DG response. A comparison between the economic model outputs using the SACT data vs. those from PERSEUS might also be valuable.

2. References

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in collaboration with:

Erasmus School of Health Policy & Management

Maastricht University

Addendum: additional analyses after company's DG response

Daratumumab in combination for newly diagnosed multiple myeloma when stem cell transplant is suitable [ID6249]

Produced by Kleijnen Systematic Reviews (KSR) Ltd. in collaboration with Erasmus University Rotterdam (EUR) and Maastricht University

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[redacted]

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1. Company's cost-effectiveness results

1.1 Company's deterministic base-case results

Table 1.1 shows the company's deterministic base-case CE results as they were presented in the main EAR report after clarification (after accounting for corrections to inputs and calculations during the clarification phase), as well as the updated results provided in response to the draft guidance (DG) document. As there is a commercial access agreement (CAA) in place for daratumumab, in the CS [redacted].

The company's updated base case in their response to the DG included:

- Application of the HRs from the IPTW-ATT weighting based on base covariates to derive the proxy OS/PFS curves for DBTd-L.
- Subsequent treatment distributions based on the predicted future (Table 9 in additional analyses document, Future column) where BeBd is expected to take a significant share of the DBd share at 2L based on clinical expert feedback.
- Equal efficacy in PFS and OS between DBLd and DBTd during induction and consolidation phases.
- Incidence of Grade 3/4 adverse events occurring during maintenance in 5% of patients in PERSEUS trial. Included adverse events are neutropenia (25.5% in the DL arm versus 36.0% in the L arm) and diarrhoea (8.1% in the DL arm versus 2.7% in the L arm).
- Single utility value in the progressed disease state.
- DBLd-DL OS extrapolation using the exponential distribution.
- DBLd-DL PFS extrapolation using the Generalised Gamma distribution.
- TTD using PERSEUS data for lenalidomide discontinuation in the DBTd-L maintenance arm.

The results from the updated base case in the DG show that DBLd-DL dominates DBTd-L.

Table 1.1: Company base-case deterministic CE results (DBLd-DL vs. DBTd-L, discounted)

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. Costs (£)	Inc. LYG	Inc. QALYs	ICER (£/QALY)
Company's post-clarification base case, copy main EAG report							
DBTd-L	[redacted]	[redacted]	[redacted]	-	-	-	-
DBLd-DL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	25,888
Company's post-DG base case							
DBTd-L	[redacted]	[redacted]	[redacted]	-	-	-	-
DBLd-DL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	DBLd-DL dominates

Based on Table 5.1 of the EAR and the additional analyses document submitted alongside the company's response to the DG.
CE = cost-effectiveness; DBLd = daratumumab, bortezomib, lenalidomide and dexamethasone; DBTd = daratumumab, bortezomib, thalidomide and dexamethasone; DL = daratumumab with lenalidomide; ICER =

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. Costs (£)	Inc. LYG	Inc. QALYs	ICER (£/QALY)
incremental cost-effectiveness ratio; Inc. = incremental; LYG = life years gained; QALY = quality-adjusted life year							

1.2 Company's probabilistic sensitivity analysis

Table 1.2 shows the company's probabilistic base-case CE results as they were presented in the main EAR report after clarification and the update probabilistic results provided in response to the draft guidance (DG) document.

Table 1.2: Company base-case probabilistic CE results (DBLd-DL vs. DBTd-L, discounted)

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. Costs (£)	Inc. LYG	Inc. QALYs	ICER (£/QALY)
Company's post-clarification base case, copy main EAG report							
DBTd-L	[redacted]	[redacted]	[redacted]	-	-	-	-
DBLd-DL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	27,699
Company's post-DG base case							
DBTd-L	[redacted]	[redacted]	[redacted]	-	-	-	-
DBLd-DL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	DBLd-DL dominates
Based on Table 5.5 of the EAR and the additional analyses document submitted alongside the company's response to the DG. CE = cost-effectiveness; DBLd = daratumumab, bortezomib, lenalidomide and dexamethasone; DBTd = daratumumab, bortezomib, thalidomide and dexamethasone; DL = daratumumab with lenalidomide; ICER = incremental cost-effectiveness ratio; Inc. = incremental; LYG = life years gained; QALY = quality-adjusted life year							

1.3 Company's scenario analyses in response to DG

The company presented the results of a set of scenario analyses to assess the robustness of the model against alternative model inputs and assumptions. In these scenarios, the impact of using results from multivariable regression and double robust methods for DL versus L comparison was explored, as well as the use of the Gompertz for extrapolating DBLd-DL PFS, the impact of lower utility values applied to subsequent treatment lines, the use of different utility values from previous TA763, the proportion modelled to receive belantamab mafodotin and selinexor at second and third-line respectively, the potential use of next-generation sequencing MRD testing cost and a two-year fixed treatment duration for daratumumab maintenance. A PAS of [redacted]% has been applied in all scenarios for [redacted] as explained in Section 1.2. In all scenarios, the ICERs for DBLd-DL compared to DBTd-L produced more QALYs at a lower cost, indicating DBLd-DL is dominant compared to DBTd-L.

Table 1.3: Company scenario analyses results in response to DG (DBLd-DL vs. DBTd-L)

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. Costs (£)	Inc. LYG	Inc. QALYs	ICER (£/QALY)
Company's post-DG base case							
DBTd-L	[redacted]	[redacted]	[redacted]	-	-	-	-

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. Costs (£)	Inc. LYG	Inc. QALYs	ICER (£/QALY)
DBLd-DL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	DBLd-DL dominates
Scenario 1: DL vs L comparison using multivariable regression							
DBTd-L	[redacted]	[redacted]	[redacted]	-	-	-	-
DBLd-DL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	DBLd-DL dominates
Scenario 2: DL vs L comparison using doubly robust							
DBTd-L	[redacted]	[redacted]	[redacted]	-	-	-	-
DBLd-DL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	DBLd-DL dominates
Scenario 3: Gompertz distribution for PFS							
DBTd-L	[redacted]	[redacted]	[redacted]	-	-	-	-
DBLd-DL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	DBLd-DL dominates
Scenario 4: Utility value in the progressed disease state weighted by the line of treatment							
DBTd-L	[redacted]	[redacted]	[redacted]	-	-	-	-
DBLd-DL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	DBLd-DL dominates
Scenario 5: Utility values from TA763							
DBTd-L	[redacted]	[redacted]	[redacted]	-	-	-	-
DBLd-DL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	DBLd-DL dominates
Scenario 6(a): Subsequent treatment distribution: Current distribution with BeBd 4.1% and DBd 63.3% at 2L							
DBTd-L	[redacted]	[redacted]	[redacted]	-	-	-	-
DBLd-DL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	DBLd-DL dominates
Scenario 6(b): Subsequent treatment distribution: Inclusion of SBd at 3L with 8% market share							
DBTd-L	[redacted]	[redacted]	[redacted]	-	-	-	-
DBLd-DL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	DBLd-DL dominates
Scenario 7: MRD testing using NGS							
DBTd-L	[redacted]	[redacted]	[redacted]	-	-	-	-
DBLd-DL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	DBLd-DL dominates
Scenario 8(a): Daratumumab maintenance based on a 2-year fixed treatment duration							
DBTd-L	[redacted]	[redacted]	[redacted]	-	-	-	-
DBLd-DL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	DBLd-DL dominates
Scenario 8(b): Daratumumab maintenance based on a 2-year fixed treatment duration for all patients except for high-risk patients (21.7%)							

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. Costs (£)	Inc. LYG	Inc. QALYs	ICER (£/QALY)
DBTd-L	[redacted]	[redacted]	[redacted]	-	-	-	-
DBLd-DL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	DBLd-DL dominates
Scenario 8(c): Daratumumab maintenance based on a 2-year fixed treatment duration (Pooled PERSEUS & GRIFFIN)							
DBTd-L	[redacted]	[redacted]	[redacted]	-	-	-	-
DBLd-DL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	DBLd-DL dominates
Scenario 8(d): Daratumumab maintenance based on a 2-year fixed treatment duration: PFS HR = 0.661							
DBTd-L	[redacted]	[redacted]	[redacted]	-	-	-	-
DBLd-DL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	DBLd-DL dominates

Based on Table 1 of the additional analyses document submitted alongside the company's response to the DG. 2L = second line; BeBd = belantamab mafodotin with bortezomib and dexamethasone; CE = cost-effectiveness; DBd = daratumumab with bortezomib and dexamethasone; DBLd = daratumumab, bortezomib, lenalidomide and dexamethasone; DBTd = daratumumab, bortezomib, thalidomide and dexamethasone; DL = daratumumab with lenalidomide; ICER = incremental cost-effectiveness ratio; Inc. = incremental; L = lenalidomide; LYG = life years gained; MRD = minimal residual disease; NGS = next generation sequencing; QALY = quality-adjusted life year; OS = Overall survival; PFS = progression-free survival;

2. EAG's additional analyses

2.1 EAG's exploratory analyses using company's base case in response to DG

The EAG performed the following exploratory scenario analyses to investigate the impact of alternative assumptions conditional on the company's base-case in its response to the DG document. Table 2.1 shows the results of the EAG's exploratory analyses changing one assumption at the time from the company's base-case in its response to the DG document. All scenarios presented are deterministic. As shown in Table 2.1, DBLd-DL produces cost savings compared to DBTd-L (indicating it remains dominant when compared with DBTd-L) in all scenarios apart from the scenarios which use the lower bound of the OS HR, where TTD for D within the DBLd-DL arm is informed from the treat to progression option, and the scenario in which the second line treatment mix is informed from the PERSEUS data. Under these scenarios the ICERs were £6,045, £73,525 and £156,653 per QALY gained, respectively.

Table 2.1: Results of EAG's exploratory analyses using company's base-case in its response to the DG document

Exploratory analysis number	Scenario applied to company's base-case	Incremental costs (£)	Incremental QALYs	ICER £/QALY
0	Company's base-case (in its DG response)	[redacted]	[redacted]	DBLd-DL dominates
1	OS Weibull	[redacted]	[redacted]	DBLd-DL dominates
2	OS log-logistic	[redacted]	[redacted]	DBLd-DL dominates
3	OS log-normal	[redacted]	[redacted]	DBLd-DL dominates
4	OS Gamma	[redacted]	[redacted]	DBLd-DL dominates
5	OS CI lower bound: HR = [redacted]	[redacted]	[redacted]	6,045
6	OS CI upper bound: HR = [redacted]	[redacted]	[redacted]	483,877*
7	PFS CI lower bound: HR = [redacted]	[redacted]	[redacted]	DBLd-DL dominates
8	PFS CI upper bound: HR = [redacted]	[redacted]	[redacted]	DBLd-DL dominates
9	Tx effect waning (start = cycle 66 [5 years], duration 50 cycles [3.8 years])	[redacted]	[redacted]	DBLd-DL dominates
10	Tx effect waning (start = cycle 132 [10 years], duration 50 cycles [3.8 years])	[redacted]	[redacted]	DBLd-DL dominates
10	Tx effect waning (start = cycle 132 [10 years], duration 100 cycles [7.6 years])	[redacted]	[redacted]	DBLd-DL dominates
12	TTD – Treat to progression (D within DL)	[redacted]	[redacted]	73,525

Exploratory analysis number	Scenario applied to company's base-case	Incremental costs (£)	Incremental QALYs	ICER £/QALY
13	TTD – D within DL for MRD+ log-normal	[redacted]	[redacted]	DBLd-DL dominates
14	TTD – D within DL for MRD+ gen Gamma	[redacted]	[redacted]	DBLd-DL dominates
15	TTD – D within DL for MRD+ treat to progression	[redacted]	[redacted]	DBLd-DL dominates
16	TTD – L within DL treat to progression	[redacted]	[redacted]	DBLd-DL dominates
17	TTD – L within L treat to progression	[redacted]	[redacted]	DBLd-DL dominates
18	Second line treatment mix from PERSEUS	[redacted]	[redacted]	156,653

Based on Table 5.9 of the EAR and the electronic model in the company's response to the DG document.
* ICER in the SW quadrant of the CE plane.
CE = cost-effectiveness; DBLd = daratumumab, bortezomib, lenalidomide and dexamethasone; D = daratumumab; DL = dexamethasone with lenalidomide; EAG = External Assessment Group; HR = hazard ratio; ICER = incremental cost-effectiveness ratio; L = lenalidomide; NICE = National Institute for Health and Care Excellence; OS = overall survival; PFS = progression-free survival; QALY = quality-adjusted life year; TTD = time to treatment discontinuation

2.2 EAG's preferred assumptions

Considering the company's updated approach to informing the OS and PFS HRs from reweighted data of the PERSEUS trial, in line with the committee's preferred assumptions, and to using the BLd arm of PERSEUS to derive the TTD curve for lenalidomide maintenance in the DBTd-L comparator arm, the EAG has no further preferred adjustments to the current company's base-case analysis.

2.3 EAG's scenario analyses using EAG's preferred assumptions

As there are no new EAG's preferred assumptions, the EAG considers that no additional scenario analyses are needed to illustrate the uncertainties that are still present in the economic model.

Additional scenarios request post-ACM2

Subsequent treatments

- 2nd line treatments informed by distributions from the VSTx dataset (table 8 in the company Additional Analysis). Exclude CAR+LEN+DEX and LEN+DEX (removed from the total patients). Other 2L excluded and redistributed across CAR+DEX and SEL+BOR+DEX according to their relative proportions. DAR+BOR+DEX excluded and assume patients receive BEL+BOR+DEX instead.

- Scenario 1 assumes 3L and 4L are unchanged from company/EAG base case at ACM2.

- Scenario 2 assumes 3L and 4L are the same as company base case in ID3843

	Scenario 1	Scenario 2
Treatment	**2L aligned with scenario 3 in ID3843, 3L and 4L unchanged from company and EAG base case**	**All lines aligned with scenario 3 in ID3843**
2nd Line		
DAR+BOR+DEX	[redacted]	[redacted]
CAR+LEN+DEX	[redacted]	[redacted]
CAR+DEX	[redacted]	[redacted]
SEL+BOR+DEX	[redacted]	[redacted]
LEN+DEX	[redacted]	[redacted]
BEL+BOR+DEX	[redacted]	[redacted]
Other 2L	[redacted]	[redacted]
3 L		
IXA+LEN+DEX	[redacted]	[redacted]
PAN+BOR+DEX	[redacted]	[redacted]
Cyclophosphamide	[redacted]	[redacted]
SEL+BOR+DEX	[redacted]	[redacted]
4 L		
DAR	[redacted]	[redacted]
POM+DEX	[redacted]	[redacted]
TEC	[redacted]	[redacted]
TAL	[redacted]	[redacted]

MRD stopping rule

Assume 95% receive MRD testing, then:

- Scenario 3: 5% continue DAR until progression
- Scenario 4: Of the 5%, 21.7% (high risk) continue DAR until progression, 78.3% stop DAR at 2 years
- Scenario 5: 5% stop DAR at 2 years

LEN TTD in DAR+LEN modelled as per base case (exponential) in all scenarios

DAR TTD (who don't meet stopping rule criteria)

- Scenario 6: TTD DAR (MRD+) extrapolated using log normal
- Scenario 7: TTD DAR (MRD+) extrapolated using log logistic

Can these combinations be run together:

1. Scenario 1 + 3 + 6
2. Scenario 1 + 4 + 6
3. Scenario 1 + 5 + 6
4. Scenario 1 + 3 + 7
5. Scenario 1 + 4 + 7
6. Scenario 1 + 5 + 7
7. Scenario 2 + 3 + 6
8. Scenario 2 + 4 + 6
9. Scenario 2 + 5 + 6
10. Scenario 2 + 3 + 7
11. Scenario 2 + 4 + 7
12. Scenario 2 + 5 + 7

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Daratumumab with bortezomib, lenalidomide and dexamethasone for untreated multiple myeloma when an autologous stem cell transplant is suitable [ID6249]

Additional Scenarios Requested Post-ACM2

[April 2025]

File name	Version	Contains confidential information	Date
ID6249_Daratumumab_Additional_Requests_Post-ACM2_[CON].docx	V1	Yes	April 2025

Additional scenarios requested post ACM-2

Company position

We have modelled all scenario permutations as requested by NICE. To the best of our knowledge ICERs all remain under £25,000/QALY, even when confidential PASes are incorporated.

With regards to Scenario 3 that assumes 5% of patients not tested continue on DL maintenance until disease progression, it's important to recognise that this decouples treatment cost and efficacy (costs increase with no commensurate uplift in efficacy). Moreover, as mentioned previously, the log-normal distribution for daratumumab TTD (Scenario 6) sits notably higher than the observed Kaplan Meier (KM) at end of study follow-up (approximately 10% higher) and implies that nearly 10% of non-sustained responders (I.e., poorer responders) remain on daratumumab maintenance beyond 30 years.

We consider this scenario clinically implausible. We acknowledge that in clinical practice daratumumab may be given longer than lenalidomide; however rarely if ever to patients in clinical practice stay on treatment longer than in a trial setting. The combined scenarios that include Scenarios 3 + Scenario 6 (i.e. combined scenarios 1 and 7) are therefore considered implausibly extreme going beyond the upper-bound to decision making uncertainty.

Subsequent treatments

- 2nd line treatments informed by distributions from the VSTx dataset (Table 8 in the company Additional Analysis). CAR+LEN+DEX and LEN+DEX are excluded and therefore removed from the total patients). Other 2L group are excluded and redistributed across CAR+DEX and SEL+BOR+DEX according to their relative proportions. DAR+BOR+DEX excluded, assuming that patients receive BEL+BOR+DEX instead.
- **Scenario 1**: 3L and 4L are unchanged from company/EAG base case at ACM2;
- **Scenario 2**: 3L and 4L are the same as company base case in ID3843;

Table 1. Distribution of subsequent treatments

	Base case	Scenario 1	Scenario 2
Treatment	**Future (RWE + expert opinion) unchanged from company and EAG base case**	**2L aligned with scenario 3 in ID3843, 3L and 4L unchanged from company and EAG base case**	**All lines aligned with scenario 3 in ID3843**
2nd Line			
DAR+BOR+DEX	[redacted]	[redacted]	[redacted]
CAR+LEN+DEX	[redacted]	[redacted]	[redacted]
CAR+DEX	[redacted]	[redacted]	[redacted]
SEL+BOR+DEX	[redacted]	[redacted]	[redacted]
LEN+DEX	[redacted]	[redacted]	[redacted]
BEL+BOR+DEX	[redacted]	[redacted]	[redacted]
Other 2L	[redacted]	[redacted]	[redacted]
3 L			
IXA+LEN+DEX	[redacted]	[redacted]	[redacted]
PAN+BOR+DEX	[redacted]	[redacted]	[redacted]
Cyclophosphamide	[redacted]	[redacted]	[redacted]
SEL+BOR+DEX	[redacted]	[redacted]	[redacted]
4 L			
DAR	[redacted]	[redacted]	[redacted]
POM+DEX	[redacted]	[redacted]	[redacted]
TEC	[redacted]	[redacted]	[redacted]
TAL	[redacted]	[redacted]	[redacted]

MRD stopping rule

This assumes that 95% of the patients receive MRD testing, with the 5% not tested handled according to the following scenarios:

- **Scenario 3**: 5% continue DAR until progression
- **Scenario 4**: Of the 5%, 21.7% (high risk) continue DAR until progression, 78.3% stop DAR at 2 years
- **Scenario 5**: 5% stop DAR at 2 years

Lenalidomide TTD in DAR + LEN modelled as per base case (exponential) in all scenarios

DAR TTD (for those who don't meet stopping rule criteria)

- **Scenario 6**: TTD DAR (MRD+) extrapolated using the log normal
- **Scenario 7**: TTD DAR (MRD+) extrapolated using the log-logistic

Summary of the base case and additional scenarios requested

Additional scenario analyses were conducted exploring results from inverse probability of treatment weighting – average treatment effect on the treated (IPTW-ATT) reweighted base case variables for DL versus L comparison, use of the generalised gamma and exponential distributions for extrapolating DBLd-DL PFS and OS, respectively, and the flow cytometry MRD testing cost.

A PAS of [redacted] for daratumumab at 1L is applied in all scenarios. Deterministic and probabilistic results of the updated analyses are presented in Table 2 and Table 3, respectively. A user guide describing the key changes to the model and providing step-by-step instructions for running all scenarios is provided.[1]

Table 2. Deterministic analyses based on the Committee's preferred assumptions and results from additional scenarios

	Total outcomes by treatment			Incremental outcomes			
	Costs	**LYs**	**QALYs**	**Costs**	**LYs**	**QALYs**	**ICER**
Base case							
DBTd-L	[redacted]	[redacted]	[redacted]	-	-	-	-
DBLd-DL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-£618,105 (Dominant)
Scenario 1 + 3 + 6							
DBTd-L	[redacted]	[redacted]	[redacted]	-	-	-	-
DBLd-DL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-£870,153 (Dominant)
Scenario 1 + 4 + 6							
DBTd-L	[redacted]	[redacted]	[redacted]	-	-	-	-
DBLd-DL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-£881,744 (Dominant)
Scenario 1 + 5 + 6							
DBTd-L	[redacted]	[redacted]	[redacted]	-	-	-	-
DBLd-DL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-£884,969 (Dominant)
Scenario 1 + 3 + 7							
DBTd-L	[redacted]	[redacted]	[redacted]	-	-	-	-
DBLd-DL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-£901,402 (Dominant)
Scenario 1 + 4 + 7							
DBTd-L	[redacted]	[redacted]	[redacted]	-	-	-	-
DBLd-DL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-£910,069 (Dominant)
Scenario 1 + 5 + 7							
DBTd-L	[redacted]	[redacted]	[redacted]	-	-	-	-
DBLd-DL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-£912,474 (Dominant)
Scenario 2 + 3 + 6							

DBTd-L	[redacted]	[redacted]	[redacted]	-	-	-	-
DBLd-DL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-£837,830 (Dominant)
Scenario 2 + 4 + 6							
DBTd-L	[redacted]	[redacted]	[redacted]	-	-	-	-
DBLd-DL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-£849,421 (Dominant)
Scenario 2 + 5 + 6							
DBTd-L	[redacted]	[redacted]	[redacted]	-	-	-	-
DBLd-DL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-£852,646 (Dominant)
Scenario 2 + 3 + 7							
DBTd-L	[redacted]	[redacted]	[redacted]	-	-	-	-
DBLd-DL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-£869,079 (Dominant)
Scenario 2 + 4 + 7							
DBTd-L	[redacted]	[redacted]	[redacted]	-	-	-	-
DBLd-DL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-£877,746 (Dominant)
Scenario 2 + 5 + 7							
DBTd-L	[redacted]	[redacted]	[redacted]	-	-	-	-
DBLd-DL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-£880,151 (Dominant)

Abbreviations: DBLd, daratumumab with bortezomib, lenalidomide and dexamethasone; DBTd, daratumumab with bortezomib, thalidomide and dexamethasone; DL, daratumumab with lenalidomide; ICER, Incremental cost-effectiveness ratio; L, lenalidomide; LY, Life years; QALY, Quality adjusted life year.

Table 3. Probabilistic analyses based on the Committee's preferred assumptions and results from additional scenarios

	Total outcomes by treatment			Incremental outcomes			
	Costs	**LYs**	**QALYs**	**Costs**	**LYs**	**QALYs**	**ICER**
Base case							
DBTd-L	[redacted]	[redacted]	[redacted]	-	-	-	-
DBLd-DL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-£606,260 (Dominant)
Scenario 1 + 3 + 6							
DBTd-L	[redacted]	[redacted]	[redacted]	-	-	-	-
DBLd-DL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-£853,966 (Dominant)
Scenario 1 + 4 + 6							
DBTd-L	[redacted]	[redacted]	[redacted]	-	-	-	-
DBLd-DL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-£865,397 (Dominant)
Scenario 1 + 5 + 6							
DBTd-L	[redacted]	[redacted]	[redacted]	-	-	-	-
DBLd-DL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-£868,580 (Dominant)
Scenario 1 + 3 + 7							
DBTd-L	[redacted]	[redacted]	[redacted]	-	-	-	-
DBLd-DL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-£883,662 (Dominant)
Scenario 1 + 4 + 7							
DBTd-L	[redacted]	[redacted]	[redacted]	-	-	-	-
DBLd-DL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-£892,334 (Dominant)
Scenario 1 + 5 + 7							
DBTd-L	[redacted]	[redacted]	[redacted]	-	-	-	-
DBLd-DL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-£894,742 (Dominant)
Scenario 2 + 3 + 6							

DBTd-L	[redacted]	[redacted]	[redacted]	-	-	-	-
DBLd-DL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-£822,476 (Dominant)
Scenario 2 + 4 + 6							
DBTd-L	[redacted]	[redacted]	[redacted]	-	-	-	-
DBLd-DL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-£833,908 (Dominant)
Scenario 2 + 5 + 6							
DBTd-L	[redacted]	[redacted]	[redacted]	-	-	-	-
DBLd-DL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-£837,090 (Dominant)
Scenario 2 + 3 + 7							
DBTd-L	[redacted]	[redacted]	[redacted]	-	-	-	-
DBLd-DL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-£852,172 (Dominant)
Scenario 2 + 4 + 7							
DBTd-L	[redacted]	[redacted]	[redacted]	-	-	-	-
DBLd-DL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-£860,843 (Dominant)
Scenario 2 + 5 + 7							
DBTd-L	[redacted]	[redacted]	[redacted]	-	-	-	-
DBLd-DL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-£863,252 (Dominant)

Abbreviations: DBLd, daratumumab with bortezomib, lenalidomide and dexamethasone; DBTd, daratumumab with bortezomib, thalidomide and dexamethasone; DL, daratumumab with lenalidomide; ICER, Incremental cost-effectiveness ratio; L, lenalidomide; LY, Life years; QALY, Quality adjusted life year.

References

1. J&J, *Data on File. ID6249 Post ACM2 CEM User guide.* 2026.

Table 1. Deterministic analyses based on the Committee's preferred assumptions and results from additional scenarios. TTD curves for the 5% informed by PFS

	Total outcomes by treatment			Incremental outcomes			
	Costs	**LYs**	**QALYs**	**Costs**	**LYs**	**QALYs**	**ICER**
Base case							
DBTd-L	[redacted]	[redacted]	[redacted]	-	-	-	-
DBLd-DL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-£618,105 (Dominant)
Scenario 1 + 3 + 6							
DBTd-L	[redacted]	[redacted]	[redacted]	-	-	-	-
DBLd-DL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-£834,237 (Dominant)
Scenario 1 + 4 + 6							
DBTd-L	[redacted]	[redacted]	[redacted]	-	-	-	-
DBLd-DL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-£873,128 (Dominant)
Scenario 1 + 5 + 6							
DBTd-L	[redacted]	[redacted]	[redacted]	-	-	-	-
DBLd-DL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-£884,345 (Dominant)
Scenario 1 + 3 + 7							
DBTd-L	[redacted]	[redacted]	[redacted]	-	-	-	-
DBLd-DL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-£861,742 (Dominant)
Scenario 1 + 4 + 7							
DBTd-L	[redacted]	[redacted]	[redacted]	-	-	-	-
DBLd-DL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-£900,634 (Dominant)
Scenario 1 + 5 + 7							
DBTd-L	[redacted]	[redacted]	[redacted]	-	-	-	-
DBLd-DL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-£911,850 (Dominant)

Scenario 2 + 3 + 6							
DBTd-L	[redacted]	[redacted]	[redacted]	-	-	-	-
DBLd-DL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-£801,914 (Dominant)
Scenario 2 + 4 + 6							
DBTd-L	[redacted]	[redacted]	[redacted]	-	-	-	-
DBLd-DL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-£840,805 (Dominant)
Scenario 2 + 5 + 6							
DBTd-L	[redacted]	[redacted]	[redacted]	-	-	-	-
DBLd-DL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-£852,022 (Dominant)
Scenario 2 + 3 + 7							
DBTd-L	[redacted]	[redacted]	[redacted]	-	-	-	-
DBLd-DL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-£829,419 (Dominant)
Scenario 2 + 4 + 7							
DBTd-L	[redacted]	[redacted]	[redacted]	-	-	-	-
DBLd-DL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-£868,311 (Dominant)
Scenario 2 + 5 + 7							
DBTd-L	[redacted]	[redacted]	[redacted]	-	-	-	-
DBLd-DL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-£879,527 (Dominant)

Abbreviations: DBLd, daratumumab with bortezomib, lenalidomide and dexamethasone; DBTd, daratumumab with bortezomib, thalidomide and dexamethasone; DL, daratumumab with lenalidomide; ICER, Incremental cost-effectiveness ratio; L, lenalidomide; LY, Life years; QALY, Quality adjusted life