Single Technology Appraisal

Daratumumab with lenalidomide and dexamethasone for untreated multiple myeloma when stem cell transplant is unsuitable [ID4014]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Daratumumab with lenalidomide and dexamethasone for untreated multiple myeloma when stem cell transplant is unsuitable [ID4014]

Contents:

The following documents are made available to stakeholders:

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

Daratumumab with lenalidomide and dexamethasone for untreated multiple myeloma when stem cell transplant is unsuitable

Single Technology Appraisal

Response to consultee, commentator and public comments on the Draft Guidance Document (DGD)

Type of stakeholder:

Consultees – Organisations that accept an invitation to participate in the appraisal including the companies, national professional organisations, national patient organisations, the Department of Health and Social Care and the Welsh Government and relevant NHS organisations in England. Consultees can make a submission and participate in the consultation on the appraisal consultation document (ACD; if produced). All non-company consultees can nominate clinical experts and/or patient experts to verbally present their personal views to the Appraisal Committee. Company consultees can also nominate clinical experts. Representatives from NHS England and clinical commissioning groups invited to participate in the appraisal may also attend the Appraisal Committee as NHS commissioning experts. All consultees have the opportunity to consider an appeal against the final recommendations, or report any factual errors, within the final appraisal document (FAD).

Clinical and patient experts and NHS commissioning experts – The Chair of the Appraisal Committee and the NICE project team select clinical experts and patient experts from nominations by consultees and commentators. They attend the Appraisal Committee meeting as individuals to answer questions to help clarify issues about the submitted evidence and to provide their views and experiences of the technology and/or condition. Before they attend the meeting, all experts must either submit a written statement (using a template) or indicate they agree with the submission made by their nominating organisation..

Commentators – Commentators can participate in the consultation on the ACD (if produced), but NICE does not ask them to make any submission for the appraisal. Non-company commentator organisations can nominate clinical experts and patient experts to verbally present their personal views to the Appraisal Committee. Commentator organisations representing relevant comparator technology companies can also nominate clinical experts. These organisations receive the FAD and have opportunity to report any factual errors. These organisations include comparator technology companies, Healthcare Improvement Scotland any relevant National Collaborating Centre (a group commissioned by NICE to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups such as the NHS Confederation, the NHS Commercial Medicines Unit, the Scottish Medicines Consortium, the Medicines and Healthcare Products Regulatory Agency, the Department of Health and Social Care, Social Services and Public Safety for Northern Ireland).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but NICE reserves the right to summarise and edit comments received during consultations, or not to publish them at all, where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful or publication would be otherwise inappropriate.

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
1	Consultee (company)	Janssen-Cilag Ltd	Janssen welcomes the opportunity to comment on the provisional Draft Guidance for daratumumab in combination with lenalidomide and dexamethasone. We are committed to working with the National Institute for Health and Care Excellence (NICE) to address the Committee's outstanding concerns, as outlined in the Draft Guidance document, in order for patients to gain access to this life extending and highly innovative treatment. Janssen note that the Committee concluded that the MAIA trial has shown DLd to be a clinically effective treatment. In addition, the Committee recognise that DLd would be a welcomed treatment option in the UK by clinicians and people with multiple myeloma, and would address the current inequity in access to effective treatments between those patients eligible and those ineligible for transplant. Janssen agree with the Committee that for newly diagnosed multiple myeloma, patients who are ineligible for an autologous stem cell transplant have the highest unmet need, as these patients are typically older/frailer and have more comorbidities than those who are eligible for transplant. As such, it is important that these patients have access to the most efficacious treatment options available to reduce the current inequity in access. The evidence base for this appraisal is primarily from MAIA, a phase 3, direct head-to-head trial comparing DLd to Ld, the most relevant comparator in the NHS. Since the original company submission, additional evidence from MAIA is now available for the Committee's consideration and to inform this appraisal. A summary of the new evidence from MAIA and impact on cost-effectiveness are included below, with further details provided in Appendix A. We believe this new evidence is informative to several points of the committee discussion, which are summarised below: • With the updated data from MAIA, there is now over 7-years of observed data (6-years median follow-up). The updated OS results from MAIA are consistent with the previous data cut, with the DLd arm continuing to demonstrate a statistically significant reduction in the risk of death compared with Ld. **For TTD, the additional follow-up from MAIA has narrowed the range of plausible curves and helped to reduce uncertainty for the Committee.**	Thank you for your comment. The committee considered the new evidence from MAIA. Please see comments 2-7 for the NICE response to each of the points raised.

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			• Regarding the long-term treatment effect for OS, Janssen acknowledge there remains residual uncertainty when modelling a lifetime time horizon. However, such uncertainty is unavoidable when modelling front-line outcomes for a step-change therapy and we consider the latest data cut from MAIA, with over 6-years median follow-up, suitably mature and robust to inform Committee decision making. **Importantly, the latest data cut from MAIA demonstrates a consistent trend with the OS HR for DLd vs Ld continuing to improve (decrease) over time**. This observation is also consistent with clinical expert feedback at the 1st ACM which noted the biological plausibility for a continued improvement in treatment effect driven by deeper responses. Whilst the totality of evidence and latest data cut from MAIA supports the original company base case approach, to explore uncertainty further, a number of scenarios are provided to help inform Committee decision making. • Finally, the Committee concluded that, given the uncertainty in the appraisal, the ICER would need to be substantially below £30,000 per QALY to be considered a cost-effective use of NHS resources. Janssen consider the inclusion of the **latest data cut from MAIA, with over 6-years median follow-up for OS and TTD, has helped to reduce residual modelling uncertainty and narrow the range of plausible scenarios**. In addition, a number of wider benefits of introducing DLd, such as reducing the current health inequity between patients eligible and not eligible for transplant, should also be considered (see Comment 6 below). As such, Janssen consider it appropriate for the Committee to consider an ICER threshold towards the upper end of the cost-effectiveness range. Further details for each of these points and a revised company base case are presented below.	
2	Consultee (company)	Janssen-Cilag Ltd	**Additional data from MAIA supports the OS benefit for DLd and reduces overall uncertainty in the appraisal** Draft Guidance, Section 3.5: *"The committee accepted that from the current follow up MAIA showed a survival benefit. But it noted that with the current data cut, median overall survival was only just being reached in the lenalidomide plus dexamethasone arm. Because of this, the overall survival modelling was uncertain and would benefit from longer follow-up data from MAIA. It recalled that further data that could be incorporated into the appraisal is now available and that this may reduce uncertainty"* As per the provisional Draft Guidance, a further data cut for OS and TTD is now available from MAIA with a median follow-up of over 6-years (73.6 months). A summary of the updated OS (and TTD) data is included within the main body of this response, with full details provided in Appendix A.	Thank you for your comment. The committee considered that the additional evidence provided did not resolve the uncertainty in the OS modelling (see FDG (final draft guidance) - section 3.6). The committee concluded that of the curves presented the generalised gamma curve resulted in the most plausible long term survival

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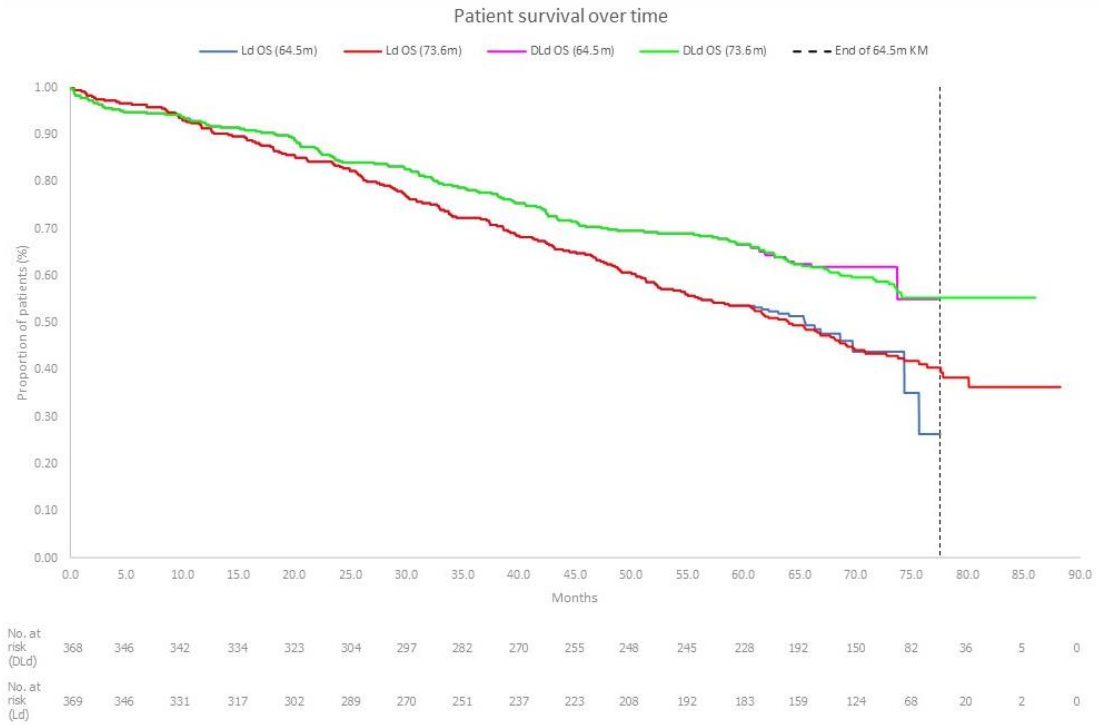
			The 73.6 month data cut provides a further 8.7 months of study follow-up (to give a total of 86 months follow up) and includes an additional [redacted] OS events for DLd and [redacted] OS events for Ld. The total number of OS events is now [redacted] and [redacted] on the DLd and Ld arms respectively. The Kaplan-Meier chart in Figure 1 compares the updated overall survival function plots for DLd and Ld against the previous MAIA data cut (median follow-up of 64.5 months). **Figure 1: Kaplan–Meier estimates of OS in the MAIA trial (ITT population) (73.6 months median follow-up)**  **Abbreviations:** CI: confidence interval; DLd: daratumumab, lenalidomide and dexamethasone, HR: hazard ratio; NR: not reached; Ld: lenalidomide and dexamethasone (referred to as Ld throughout this submission). Source: Janssen Data on file. Adapted from Kumar et al. 2022. The latest data cut from MAIA continues to demonstrate an OS benefit for DLd compared with Ld in newly diagnosed transplant-ineligible multiple myeloma. DLd was associated with a statistically	estimates (see FDG – section 3.11).

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			significant 35% reduction in the risk of death compared with Ld (HR: 0.65; 95% CI: 0.52-0.80; p<0.0001). The 73.6 month data cut also supports the trend for an improved treatment effect with longer study follow-up with a lower HR and increased precision around the point estimate reflected by a narrower confidence interval. **Updated MAIA 73.6m OS extrapolations** Figure 2 provides the updated parametric extrapolations for DLd OS using the latest MAIA data cut. **Figure 2: Extrapolation of OS for DLd using IPD from MAIA 73.6m data cut (with GPM cap)**  **Abbreviations**: DLd: daratumumab, lenalidomide and dexamethasone; GPM: general population mortality; IPD: individual patient data; KM: Kaplan-Meier; OS: overall survival. The Exponential curve has best statistical fit (lowest AIC/BIC) across both the 64.5 and 73.6 month data cuts (refer to Appendix A). During Technical Engagement (using the 64.5m data cut), Janssen noted that both the Exponential and Gompertz were plausible, acknowledging similarity	

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			in the long-term estimates with mean predicted OS of 116.7 months and 115.1 months respectively. As such, Janssen revised its base case selection from Exponential to Gompertz to align with the EAG preferred curve. However, with the latest MAIA data cut, there is increased divergence between the two curves with the Exponential and Gompertz providing mean OS estimates of 114.2 and 108.2 months respectively. Whilst both distributions remain clinically plausible, Gompertz is considered a conservative estimate. To align with the Committee's preferred assumption following the first ACM, Janssen retain the Gompertz selection for DLd OS. A scenario analysis exploring the impact on cost-effectiveness selecting the best-fitting Exponential curve for DLd OS is also explored. For Ld, the Gompertz extrapolation remains the best fitting curve, with a negligible difference in the estimated total mean OS across the two data cuts (69.54 months vs 69.19 months) (refer to Appendix A). As such, Gompertz is retained as the base case curve selection for Ld OS. In summary, the consistency of the OS results with the latest MAIA data cut reflects maturity of the data with over 6-years median follow-up and provides reassurance with regards stability of the cost-effectiveness estimates. Whilst Janssen acknowledge inherent modelling uncertainty in the context of a lifetime time horizon, the Gompertz curve selection for DLd OS is considered conservative with residual uncertainty fully explored via scenario analysis.	
3	Consultee (company)	Janssen-Cilag Ltd	**New data available from MAIA for TTD supports the Generalised Gamma and the Gompertz, but not Exponential** Draft Guidance, Section 3.9: *"Based on the appraised evidence, the committee concluded that the exponential curve was most appropriate for decision making. But it said that it would reconsider its decision if evaluation of the most recent data cut suggested another extrapolation is more appropriate."* Previously, based on the MAIA 64.5 month data cut, the clinically plausible range for DLd TTD was between the Generalised Gamma (lowest AIC) and the exponential (lowest BIC), with the Gompertz sitting as a midpoint in the range. Janssen considered the statistical fit for the Generalised Gamma, Gompertz and Exponential to be broadly comparable, with a preference for the Gompertz in the base case. Janssen did not consider there was sufficient evidence to select the upper bound (Exponential) or lower bound (Generalised Gamma) from the plausible range as a base case input for decision making. The EAG and Committee preferred the exponential for DLd TTD, based on the lowest BIC, although acknowledged that further data could inform decision	Thank you for your comment. The committee concluded that it would consider scenarios using generalised gamma and Gompertz curves to extrapolate TTD because they were both clinically plausible (see FDG – section 3.10).

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			making. This is despite the exponential representing an upper bound of the clinically plausible range and the rationale for the lowest BIC being inconsistent with the approach considered for other survival extrapolations. As noted above, additional TTD data is now available from MAIA based on the 73.6 month data cut. The updated Kaplan-Meier chart for TTD is presented in Figure 3, with full details available in Appendix A. **Figure 3: Updated TTD for DLd and Ld in the MAIA trial (ITT population; median follow-up = 73.6m)**  **Abbreviations**: DLd: daratumumab, lenalidomide and dexamethasone, Ld: lenalidomide and dexamethasone **Source**: Janssen Data on File. MAIA 73.6m data cut. **<u>Updated MAIA 73.6m TTD extrapolations</u>** Figure 4 and Figure 5 provides the updated parametric extrapolations for DLd and Ld TTD	

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			respectively, using the latest MAIA data cut. The associated statistical fit for each distribution (DLd and Ld) is provided in Table 1. **Figure 4: Extrapolation of TTD for DLd using IPD from MAIA 73.6m data cut**  **Figure 5: Extrapolation of TTD for Ld using IPD from MAIA 73.6m data cut**	

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			 **Abbreviations:** Ld: lenalidomide and dexamethasone; IPD: individual patient data; KM: Kaplan-Meier TTD: time to discontinuation. **Table 1: Goodness-of-fit statistics for DLd and Ld TTD survival models using MAIA 73.6m data cut** **Survival model** / **DLd** / **Ld** **AIC** / **BIC** / **AIC** / **BIC** Exponential: 2623.9 / 2627.8 / 2963.3 / **2967.2** Weibull: 2625.4 / 2633.2 / 2963.6 / 2971.4 Loglogistic: 2649.5 / 2657.3 / 3001.5 / 3009.3 Lognormal: 2679.8 / 2687.6 / 3030.5 / 3038.3 Generalised Gamma: **2614.0** / **2625.7** / **2961.2** / 2972.9 Gompertz: 2619.2 / 2627.0 / 2965.2 / 2973.0 Visual inspection of the updated TTD extrapolations for DLd support both the Generalised	

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			Gamma and Gompertz. Notably, the updated TTD data does not support the exponential distribution with a clear separation and divergence with the observed Kaplan-Meier with longer study follow-up. In terms of statistical fit, the Generalised Gamma now has the lowest AIC/BIC with the Gompertz ranked second, and exponential third. In summary, the 73.6 month data cut from MAIA has helped to significantly reduce uncertainty regarding the expected treatment duration for DLd, with the plausible range now lying between the Generalised Gamma and Gompertz. Based on best visual and statistical fit, Janssen has updated the company base case selection to Generalised Gamma. A scenario analysis using Gompertz is provided to explore the range of uncertainty and impact on overall cost-effectiveness. Similarly, for Ld, Janssen has updated the company base case selection from Weibull to Generalised Gamma based on visual and statistical fit. This, however, has a minimal impact on the overall estimated TTD (see Appendix A) and cost-effectiveness results.	
4	Consultee (company)	Janssen-Cilag Ltd	**Scenarios exploring long-term extrapolation of OS treatment effect** Draft Guidance, Section 3.10: *"…the committee concluded that the company's base case could potentially be plausible, but it is highly optimistic and associated with high uncertainty. It noted that the most recent MAIA data cut (October 2022) could provide a small amount of additional evidence to help inform the extrapolation, but recalled this data cut was not currently included within this appraisal."* *"The scenario with constant treatment effect was supported by the company's piecewise Cox model, which showed that overall survival hazard ratios remained stable over the 4- to 6-year period, indicating a constant survival benefit."* As per the Draft Guidance document (Section 3.10), the economic model used independently fitted parametric curves to estimate long-term OS for DLd and Ld. This was appropriate given the observed violation of proportional hazards, and the approach to curve selection was consistent with guidance provided in NICE DSU TSD 14. The full range of parametric models were assessed, and alternative, more flexible survival models were also explored which indicated overall consistency in the results. Nonetheless, Janssen understand the concern of the Committee with regard to the long-term treatment effect when considering a lifetime time horizon. To explore this issue further, Janssen has updated the Piecewise Cox analysis previously conducted using the latest data cut from MAIA (Refer to Table 2). As noted above, the OS hazard ratio has continued to improve with each successive data cut including the latest (73.6 month) data cut from MAIA (HR: 0.65; 95% CI: 0.52-	Thank you for your comment. The updated piecewise Cox analysis and additional scenarios were considered by the committee. The committee concluded that it preferred scenario 1. (see FDG – section 3.14).

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			0.80; p<0.0001). Although the hazard ratio has improved at a reduced rate over the last ~2-years, analysis of the hazard ratio over time indicates a 'stepped' downward trend. The hazard ratio remained close to 1 for the first 2-years before a marked step-down after 24-months. There then followed a period of stabilisation before a further step-down beyond 4-years. **Table 2: Updated Piecewise Cox analysis of MAIA OS data (73.6m) over time** *MAIA Follow up duration (months)* / *OS HR* / *95% CI* / *P value* *≤6* *≤12* *≤18* *≤24* *≤30* *≤36* *≤42* *≤48* *≤54* *≤60* *≤66* *≤72* *≤78* *≤84* A continued improvement in treatment effect was also supported by clinical experts at the 1st ACM, underpinned by biological plausibility of the impact of deeper responses on the disease and overall health state for transplant-ineligible patients. As noted in the original company submission (Section B.1.3.5 and the company response to Technical Engagement, Key issue 9, p18), achieving deep and durable responses is recognised as one of the primary goals of front-line treatment, resulting in a fundamental shift in the trajectory of the disease course and long-term outcomes for patients. This is particularly true for transplant-ineligible patients with the deep/sustained responses not only helping to better control their myeloma, but also helping to improve their overall health state given the complex range of comorbidities often present at diagnosis for this elderly/frail population (e.g. better bone disease control and preserved kidney function). In MAIA, the rate of minimal residual disease (MRD) negativity at sensitivity 10^{-5} was significantly higher and approximately 3-fold for the DLd group (32.1%) compared with the Ld group (11.1%)	

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(odds ratio [OR]: 3.78; 95% CI: 2.55, 5.59; p<0.0001), with patients achieving MRD negativity in the DLd group resembling general population mortality (GPM) (Document B, Section B.2.6.2.10). DLd also achieved greater than 4-fold higher ≥12-month and ≥18-month sustained MRD rates (≥12-month sustained MRD-negative: 18.8% vs 4.1%; p<0.0001) (≥18-month sustained MRD-negative: 16.8% vs 3.3%; p<0.0001). The prognostic significance of MRD and its association with improved PFS/OS is well established in newly diagnosed MM (including transplant-ineligible patients) with results from MAIA supporting the continued improvement in the DLd treatment effect observed.[1]

In summary, the totality of evidence available from MAIA, clinical expert feedback at the 1st ACM and biological understanding of the disease supports the original company base case. We do, however, understand the inherent uncertainty when modelling a lifetime time horizon. As such, we have explored a range of scenarios either fixing the hazard ratio or considering an attenuation of the DLd treatment effect.

Additional scenarios exploring the long-term modelled treatment effect

To help inform Committee decision making, a range of scenarios are provided to explore the long-term modelling uncertainty between the upper and lower bounds on DLd efficacy defined by the company base case and Committee's fixed hazard ratio scenario. Per the Committee's conclusions in the Draft Guidance, we have included attenuation scenarios where the relative treatment effect reduces over time but where the hazard ratio for DLd versus Ld does not reach 1 (Scenarios 5 and 6).

A description of each scenario is provided below in Table 3, with full model inputs in Appendix B.

Table 3: Additional scenarios exploring OS HR uncertainty
<table>
<tr><th>Scenario</th><th>Approach</th><th>Assumption</th></tr>
<tr><td>1</td><td>Fix OS HR from end of observed KM</td><td>• Fix the modelled hazard ratio from the end of observed MAIA period (7.16 years in the 73.6m data cut) onwards</td></tr>
<tr><td>2</td><td>Fix OS HR at 12-years</td><td>• Model independently fitted OS survival curves until 12-years</td></tr>
</table>
</td><td></td></tr>
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[1] Munshi, N. et al. Expanded Meta-Analysis Confirms the Association Between MRD and Long-term Survival Outcomes in Multiple Myeloma (MM). Poster presented at American Society of Hematology (ASH). 2019

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		• Fix the hazard ratio from 12-years onwards
3	Fix OS HR at 15-years	• Model independently fitted OS survival curves until 15-years • Fix the modelled hazard ratio from 15-years onwards
4	Reduced OS HR improvement until fix at 12-years	• Model a reduced rate of OS improvement from 7.16 years until 12-years • Assume the OS benefit at 12-years is fixed onwards (at the midpoint between generated OS HR at 12-years and OS HR at 7.16 years)
5	Exploratory attenuation scenario: from 12-years	• Assume the OS HR generated at 12-years attenuates from 12-19 years by 25%
6	Exploratory attenuation scenario: from 15-years	• Assume the OS HR generated at 15-years attenuates from 15-25 years by 25%

A visual representation of the exploratory OS HR scenarios is provided in Figure 6:

Figure 6: Visual representation of scenarios exploring modelled OS HRs over time

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			 BC: base case *Note: The OS HR depicted above represents the modelled treatment effect at specific timepoints (calculated from per cycle hazards) and contrasts with the reported HR from MAIA which represents a summary measure of the average treatment effect across the entire (observed) follow-up period.* Janssen note that the downward trend in the modelled OS HR continues to be supported by the base case curve selections for DLd and Ld (with Gompertz considered a conservative selection for DLd OS) and improvement in the overall hazard ratio.	
5	Consultee (company)	Janssen-Cilag Ltd	**Inclusion of treatments only available through the Cancer Drugs Fund** **NICE Draft Guidance, Section 3.12:** *"The committee concluded that treatments recommended for use in the Cancer Drugs Fund should not be considered as subsequent treatments. But it said that if treatments currently*	Thank you for your comment. The committee concluded that both treatments should be incorporated into the modelling for this appraisal

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			included within the Cancer Drugs Fund are recommended for routine practice after their respective ongoing reviews and are considered established clinical practice, the modelling could be updated to incorporate these as subsequent treatments." Janssen note that, since the 1st ACM and the release of the Draft Guidance for this appraisal, • Positive NICE guidance has been published for ixazomib with lenalidomide and dexamethasone for treating relapsed or refractory multiple myeloma (TA870) • Committee B has considered daratumumab with bortezomib and dexamethasone for previously treated multiple myeloma (ID4057) for routine commissioning. It is expected that these two treatments will be available in routine commissioning by the time of the second NICE committee meeting for this appraisal. As such, all scenarios and updated company base case ICERs provided below are when including 'DBd at 2L and IxaLd at 3L' in the economic model.	(see FDG – section 3.16).
6	Consultee (company)	Janssen-Cilag Ltd	**Generalisability of subsequent treatments in MAIA compared to UK clinical practice** **NICE Draft Guidance, Section 3.4:** *"The committee agreed that the population in MAIA is generalisable to NHS clinical practice. However, it also noted that the subsequent treatments used in MAIA were likely to differ from those offered in NHS clinical practice. The committee considered that this would impact generalisability and lead to uncertainty in the long-term treatment effect of daratumumab plus lenalidomide and dexamethasone (see section 3.10). Despite the uncertainty, the committee considered that the MAIA trial represented the best available evidence."* MAIA is an international phase III randomised controlled trial which enrolled patients in 176 hospitals, across 14 countries including the UK. As such, MAIA included a number of subsequent treatments not routinely available in NHS clinical practice. In the original company submission Janssen performed an inverse probability of censoring weights (IPCW) analysis to adjust for subsequent treatments not routinely available in England and to reduce any potential bias (Document B, Section B.2.6.2.6). The results demonstrated a higher OS benefit for DLd versus Ld with a hazard ratio of [redacted]. Given these analyses, the EAG concluded that unadjusted results from MAIA may be conservative (ID4014 Draft Guidance Document, Section 3.4). Following publication of the positive Final Appraisal Document (FAD) for ixazomib plus lenalidomide and dexamethasone at 3rd line, and the expected transition from the Cancer Drugs Fund (CDF) to baseline commissioning for DVd at 2nd line, Janssen has updated the IPCW results to include both	Thank you for your comment. The committee considered the updated IPCW results. The committee concluded that there was uncertainty about the generalisability of the OS data from MAIA to NHS clinical practice (see FDG – section 3.5).

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			treatments. Results continue to demonstrate a higher OS benefit for DLd compared with the unadjusted results (updated IPCW OS HR: [redacted]) suggesting the unadjusted results from MAIA remain a conservative estimate. Despite concerns raised by the Committee in relation to the generalisability of subsequent treatments administered in MAIA, Janssen note that the UK Myeloma Forum (UKMF) consider that the outcomes for the control arm reflect expected outcomes in UK clinical practice for this patient population (ID4014 Committee Papers). The generalisability of subsequent treatments administered within an international clinical trial context to a UK setting is a common issue faced across multiple HTA appraisals, particularly in the MM setting. In this case, however, the generalisability concerns should be reduced for the Committee because: • the inclusion of patients from the UK within MAIA • the validation of the observed long-term absolute outcomes for Ld being generalisable to the UK setting • The observed MAIA outcomes for the standard of care (Ld) arm in the UK are better than other comparable trials (FIRST trial) **Additional treatments used in MAIA which may improve outcomes in Ld arm** There were a total of [redacted] different treatment combinations used as 2nd or 3rd line treatments in MAIA (the full list of treatments was previously provided by Janssen during the Clarification Process). Janssen consider there to be high generalisability for the subsequent treatments used in the DLd arm of MAIA. In current UK clinical practice, it is expected that patients who receive frontline DLd would likely change treatment class, and receive a bortezomib based treatment at second line. This is reflected in the MAIA trial, as the majority (75%) of 2nd and 3rd line treatments administered after DLd were bortezomib-based. In the Ld arm of MAIA, aligned with what would be expected in UK practice, the most frequently used combination after Ld at 2L and 3L was daratumumab in combination with bortezomib and	

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<tr><td></td><td></td><td></td><td>dexamethasone (n=36). Daratumumab was also given at 2L and 3L for patients in the Ld arm either as monotherapy (n=10), or with a wide variety of other treatment combinations, including combinations such as daratumumab + lenalidomide + dexamethasone (n=8), daratumumab + pomalidomide + dexamethasone (n=8) and carfilzomib + daratumumab + dexamethasone (n=5). In addition, pomalidomide + dexamethasone (n=16) and a number of investigational treatments, including antineoplastic drugs and other monoclonal antibodies were included as subsequent treatments at 2L and 3L for the Ld arm. It is expected that these treatment combinations would uplift the MAIA Ld outcomes, relative to treatments routinely available in the UK.

As such, whilst there may be concerns regarding the generalisability of subsequent treatments used in MAIA, the direction of any potential bias remains unclear with the IPCW results suggesting overall conservative nature of the unadjusted results.</td><td></td></tr>
<tr><td>7</td><td>Consultee (company)</td><td>Janssen-Cilag Ltd</td><td>Additional benefits not captured in the QALY framework, additional data from MAIA and exploratory scenarios provided should reduce decision making uncertainty for the Committee

NICE Draft Guidance, Section 3.13:

“The committee considered the uncertainty, particularly relating to the long-term treatment attenuation. It concluded that the ICER would have to be substantially below £30,000 per QALY gained to be considered a cost-effective use of NHS resources and accepted for routine commissioning.”

In Section 3.13, in terms of the acceptable ICER for decision making, the Committee noted a number of uncertainties in this appraisal, as per Table 4 below. However, the additional evidence from MAIA, with now over 7-years of observed data available, as well as additional scenarios provided, should reduce the decision uncertainty for the Committee.

Table 4: Reduction of uncertainties for Committee decision making
<table>
<tr><th>Uncertainty named in Draft Guidance</th><th>Addressed in appraisal process</th></tr>
<tr><td>• “the relative immaturity of the overall survival data for daratumumab plus lenalidomide and dexamethasone”</td><td>• Additional OS data from MAIA, with follow up of over 7 years, now available to reduce uncertainty in appraisal</td></tr>
<tr><td>• “the relative effectiveness of bortezomib combination treatments”</td><td>• Committee recognise that uncertainty on appropriate approach to compare to bortezomib did not materially impact the fully incremental analysis cost-effectiveness results, and so is not relevant when considering the</td></tr>
</table></td><td>Thank you for your comment. The committee considered the additional evidence from MAIA and the additional scenarios as well as the proposed uncaptured benefits. The committee concluded that the ICER would need to be below £30,000 per QALY gained. (see FDG – section 3.17)</td></tr>
</table>

<table>
<tr><th>Comment number</th><th>Type of stakeholder</th><th>Organisation name</th><th>Stakeholder comment
Please insert each new comment in a new row</th><th>NICE Response
Please respond to each comment</th></tr>
<tr><td></td><td></td><td></td><td>
<table>
<tr><td></td><td>decision making ICER.</td></tr>
<tr><td>• “the appropriate parametric curve for time to treatment discontinuation for daratumumab plus lenalidomide and dexamethasone”</td><td>• Additional TTD data from MAIA reduces the uncertainty of the appropriate parametric curve for DLd TTD, which now supports the Gen Gamma and the Gompertz.</td></tr>
<tr><td>• “the attenuation of the treatment effect”</td><td>• Observed data from MAIA of more than 7 years of follow up supporting the company’s original base case approach
• Updated company base case, additional exploratory and attenuation scenarios provided in this response to explore uncertainty for Committee decision making</td></tr>
<tr><td>• “the market share of second- and third-line treatments”</td><td>• Conclusion that the company’s estimates of market share of second line and third line were acceptable for decision making</td></tr>
</table>

Janssen also note the number of additional benefits not captured in the QALY calculation (see Document B, Section 3.12), which are appropriate when considering the uncertainty associated with this appraisal:

• Providing benefits, such as prolonged remission and reduction in anxiety associated with relapse, which are aligned to MM patient preferences and are not explicitly considered in the QALY framework,

• Providing a positive impact on carers, such as reduction in burden of care as a direct result of the reduction in the rate of deterioration of the disease.

• Removal of a present day NHS inequity in access of effective treatments between transplant-eligible and transplant ineligible patients, the benefit of which supports non-health objectives (see Section B.1.4 of Document B).

• Additional benefits from providing access to an anti-CD38 treatment in newly diagnosed, transplant ineligible MM patients, as this will provide future innovative treatment options for patients both in terms of enrolment into clinical trials and in terms of access to therapies whose marketing authorisations will specify anti-CD38 exposure. This benefit of having access to DLd is not captured in the QALY framework.</td><td></td></tr>
</table>

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			The Committee have listed the residual uncertainty as a reason for the acceptable ICER needing to be substantially below £30,000 per QALY. However, the additional wider benefits provided from DLd, as well as additional evidence provided in this response should be considered when considering the appropriate decision making threshold for the Committee. As such, Janssen consider it appropriate for the Committee to consider an ICER threshold towards the upper end of the cost-effectiveness range.	
8	Consultee (Professional group)	UK Myeloma Society	Attenuation of treatment effect. We state again that we think there is no case for treatment waning. The issue of "treatment waning" is not appropriate in the myeloma space, as discussed at several NICE HTA meetings. In the setting of the current appraisal, the question is why would you include treatment waning? What is the evidence to support its inclusion? There is no clinical evidence or even rational to include a segregated treatment waning effect on the experimental arm only, if it exists (and that is a big "if"), then it would impact both arms. Treatment waning starting at 12 years (for a period of 7 years) should not be included in this appraisal.	Thank you for your comment. Waning of treatment effect was discussed by the committee (see FDG – section 3.13).
9	Consultee (Professional group)	UK Myeloma Society	Subsequent treatments. Variation in subsequent treatments for patients in the MAIA clinical trial are expected in a large multi-national clinical trial, with different access to subsequent therapies. It is our view that these are generalisable to UK practice and represent the best available evidence.	Thank you for your comment. The generalisability of the data from MAIA was discussed by the committee (see FDG – section 3.4).
10	Consultee (Professional group)	UK Myeloma Society	Indirect comparison with Bortezomib Cyclophosphamide Dexamethasone (BCD). Cyclophosphamide is the alkylator of choice for outpatient treatment in the UK (rather than low dose Melphalan). It is our view that there is clinical equivalence of BCD with Bortezomib Melphalan Prednisolone (BMP). It is therefore appropriate to model using BMP, where there is more published comparative data.	Thank you for your comment. The indirect comparison with BCD was discussed by the committee. The committee concluded that the decision did not materially impact the fully incremental analysis cost-effectiveness results (see FDG – section 3.8)
11	Consultee (Patient/carer group)	Myeloma UK	Myeloma UK is very disappointed that NICE did not recommend daratumumab plus lenalidomide and dexamethasone for newly diagnosed myeloma patients who are not eligible for high-dose therapy and stem cell transplantation (HDT-SCT) for routine commissioning. This treatment is a game-changer for HDT-SCT ineligible patients and has been available in the	Thank you for your comment. Both clinical and patient experts were invited to the second committee meeting.

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			US and Europe for nearly four years. We ask that NICE invite clinical experts and Myeloma UK to the second committee meeting.	
12	Consultee (Patient/carer group)	Myeloma UK	**We are concerned that the Committee did not fully consider the disparity in progression-free and overall survival between HDT-SCT-eligible and HDT-SCT-ineligible myeloma patients.** • Most myeloma patients are HDT-SCT ineligible. Around two-thirds of the people diagnosed with myeloma annually are ineligible for HDT-SCT due to old age, poor health, or frailty. • HDT-SCT ineligible patients have significantly lower remission times and overall survival rates than those eligible for HDT-SCT. • Although age, frailty and co-morbidities contribute to the difference in survival rates, the disparity in survival has increased in recent years as innovative treatments (e.g., DVTD induction) have become available to HDT-SCT eligible patients but not to HDT-SCT ineligible patients. References: *"The average remission times are approximately 4–5 years after transplant if maintenance lenalidomide is used, 2–3 years after transplant if no maintenance is used and 1–2 years if patients are not transplanted, although there is great variation in these outcomes." [Bird SA, Boyd K. Palliat Care Soc Pract. 2019; 13:1178224219868235.]* *The median overall survival of HDT-SCT eligible patients ranges from over 140 months to 42 months depending on stage at diagnosis. In HDT-SCT median overall survival ranges from 91 months to 22 months depending on stage at diagnosis. [*D'agostino M. et. al. Journal of clinical oncology. 2022; 40(29):3406.	Thank you for your comment. The committee considered how people have fewer treatment options when stem cell transplant is unsuitable (see FDG – sections 3.17 and 3.19).
13	Consultee (Patient/carer group)	Myeloma UK	**We are concerned that the Committee did not fully consider the significant patient benefit of increased progression-free survival.** In the MAIA trial, daratumumab plus lenalidomide and dexamethasone delivers a median PFS of over five years. • DLd delivers over two years more remission time than the patients who received lenalidomide and dexamethasone experienced. • The remission times observed for DLd are comparable to the median overall survival	Thank you for your comment. The committee considered the benefits of increased progression free survival. (see FDG – section 3.17)

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			times delivered in standard care. 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 completely disrupts the lives of patients and their families. • Symptoms increase (e.g., pain, fatigue). • Hospital visits and tests increase. • Switching treatments means adjusting to different side effects and new routines for hospital visits/treatment administration. • Uncertainty about the future, whether the new treatment will work and how well they will tolerate it. Reference: Draft guidance section 3.3 *"Median progression-free survival was 61.9 months in the daratumumab plus lenalidomide and dexamethasone (DLd) group and 34.4 months in the lenalidomide plus dexamethasone (Ld) group."* *"Median overall survival was not reached in the daratumumab plus lenalidomide and dexamethasone group and was 65.5 months in the lenalidomide plus dexamethasone group."*	
14	Consultee (Patient/carer group)	Myeloma UK	**We are concerned that the Committee did not fully consider the importance of a quality first remission.** The first remission is often the deepest, longest remission and the period when a patient's quality of life is highest. Myeloma is a relapsing and remitting cancer where each additional line of treatment is associated with worse outcomes; remission times decrease, and side effects increase. Treatments often become less effective and harder to tolerate with every relapse. Over time, myeloma evolves, becoming more resistant to treatment, and patients get older, frailer and have more comorbidities. First remission is therefore widely held as the best opportunity to gain the best response with the	Thank you for your comment. The committee considered the importance of a quality first remission (see FDG – section 3.17)

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			longest time until disease progression. It is also the point in their disease where many patients will have the best quality of life post-diagnosis because their burden of treatment and illness is less than patients who are multiply relapsed. It is also important to note that not all patients receive treatments beyond first line. A real-world analysis of myeloma patient outcomes found that 95% of patients received first-line treatment, but only 61%, 38%, and 15% received second, third and fourth-line treatments, respectively. Reference: Yong K. et. al. Br J Haematol. 2016; 175(2):252	
15	Consultee (Patient/carer group)	Myeloma UK	**We disagree that the overall data is immature, and it is not clear what the threshold for maturity would be.** The median follow-up for the data submitted to the committee was 5.4 years (64.5 months). The follow-up is comparable to the median life expectancy for myeloma patients; the UK cancer registry shows that 52% of patients live for five years or more. Myeloma is an incurable, heterogeneous cancer with a continually evolving and changing treatment pathway; therefore, there will always be uncertainty. The treatment has been available in other countries for almost four years and was considered ineligible for the Cancer Drugs Fund. Reference: Office for National Statistics, Cancer survival by stage at diagnosis for England(link is external), 2019.	Thank you for your comment. The committee considered that MAIA has a long follow up and has shown that daratumumab plus lenalidomide and dexamethasone is a clinically effective treatment (see FDG – section 3.17).

Document processed	Organisation name – Stakeholder or respondent	Disclosure on tobacco funding / links	Number of comments extracted	Comments

NICE National Institute for Health and Care Excellence

Daratumumab with lenalidomide and dexamethasone for untreated multiple myeloma when stem cell transplant is unsuitable [ID4014]

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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):	Janssen-Cilag Ltd
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	N/A
Name of commentator person completing form:	Timothy Ming

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	Janssen welcomes the opportunity to comment on the provisional Draft Guidance for daratumumab in combination with lenalidomide and dexamethasone. We are committed to working with the National Institute for Health and Care Excellence (NICE) to address the Committee's outstanding concerns, as outlined in the Draft Guidance document, in order for patients to gain access to this life extending and highly innovative treatment. Janssen note that the Committee concluded that the MAIA trial has shown DLd to be a clinically effective treatment. In addition, the Committee recognise that DLd would be a welcomed treatment option in the UK by clinicians and people with multiple myeloma, and would address the current inequity in access to effective treatments between those patients eligible and those ineligible for transplant. Janssen agree with the Committee that for newly diagnosed multiple myeloma, patients who are ineligible for an autologous stem cell transplant have the highest unmet need, as these patients are typically older/frailer and have more comorbidities than those who are eligible for transplant. As such, it is important that these patients have access to the most efficacious treatment options available to reduce the current inequity in access. The evidence base for this appraisal is primarily from MAIA, a phase 3, direct head-to-head trial comparing DLd to Ld, the most relevant comparator in the NHS. Since the original company submission, additional evidence from MAIA is now available for the Committee's consideration and to inform this appraisal. A summary of the new evidence from MAIA and impact on cost-effectiveness are included below, with further details provided in Appendix A. We believe this new evidence is informative to several points of the committee discussion, which are summarised below: • With the updated data from MAIA, there is now over 7-years of observed data (6-years median follow-up). The updated OS results from MAIA are consistent with the previous data cut, with the DLd arm continuing to demonstrate a statistically significant reduction in the risk of death compared with Ld. **For TTD, the additional follow-up from MAIA has narrowed the range of plausible curves and helped to reduce uncertainty for the Committee.** • Regarding the long-term treatment effect for OS, Janssen acknowledge there remains residual uncertainty when modelling a lifetime time horizon. However, such uncertainty is unavoidable when modelling front-line outcomes for a step-change therapy and we consider the latest data cut from MAIA, with over 6-years median follow-up, suitably mature and robust to inform Committee decision making. **Importantly, the latest data cut from MAIA demonstrates a consistent trend with the OS HR for DLd vs Ld continuing to improve (decrease) over time**. This observation is also consistent with clinical expert feedback at the 1st ACM which noted the biological plausibility for a continued improvement in treatment effect driven by deeper responses. Whilst the totality of evidence and latest data cut from MAIA supports the original company base case approach, to explore uncertainty further, a number of scenarios are provided to help inform Committee decision making. • Finally, the Committee concluded that, given the uncertainty in the appraisal, the ICER would need to be substantially below £30,000 per QALY to be considered a cost-effective use of NHS resources. Janssen consider the inclusion of the **latest data cut from MAIA, with over**

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	6-years median follow-up for OS and TTD, has helped to reduce residual modelling uncertainty and narrow the range of plausible scenarios. In addition, a number of wider benefits of introducing DLd, such as reducing the current health inequity between patients eligible and not eligible for transplant, should also be considered (see Comment 6 below). As such, Janssen consider it appropriate for the Committee to consider an ICER threshold towards the upper end of the cost-effectiveness range. Further details for each of these points and a revised company base case are presented below.
1	**Additional data from MAIA supports the OS benefit for DLd and reduces overall uncertainty in the appraisal** Draft Guidance, Section 3.5: *"The committee accepted that from the current follow up MAIA showed a survival benefit. But it noted that with the current data cut, median overall survival was only just being reached in the lenalidomide plus dexamethasone arm. Because of this, the overall survival modelling was uncertain and would benefit from longer follow-up data from MAIA. It recalled that further data that could be incorporated into the appraisal is now available and that this may reduce uncertainty"* As per the provisional Draft Guidance, a further data cut for OS and TTD is now available from MAIA with a median follow-up of over 6-years (73.6 months). A summary of the updated OS (and TTD) data is included within the main body of this response, with full details provided in Appendix A. The 73.6 month data cut provides a further 8.7 months of study follow-up (to give a total of 86 months follow up) and includes an additional [redacted] OS events for DLd and [redacted] OS events for Ld. The total number of OS events is now [redacted] and [redacted] on the DLd and Ld arms respectively. The Kaplan-Meier chart in Figure 1 compares the updated overall survival function plots for DLd and Ld against the previous MAIA data cut (median follow-up of 64.5 months).

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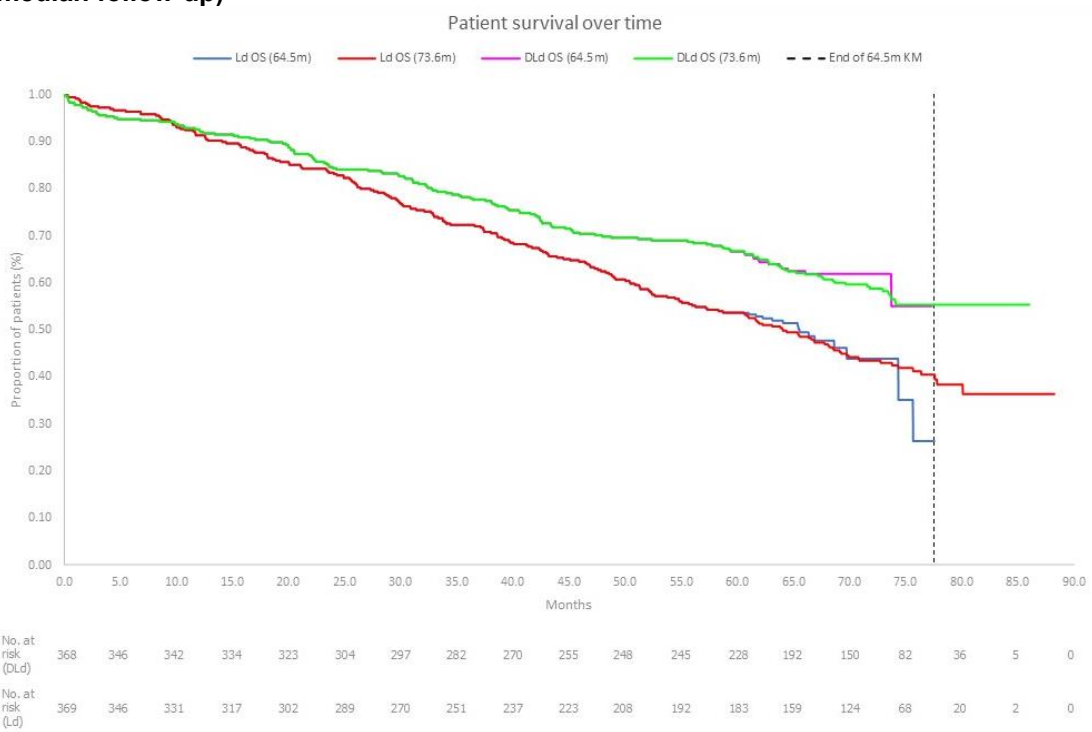
Figure 1: Kaplan–Meier estimates of OS in the MAIA trial (ITT population) (73.6 months median follow-up)



Abbreviations: CI: confidence interval; DLd: daratumumab, lenalidomide and dexamethasone, HR: hazard ratio; NR: not reached; Ld: lenalidomide and dexamethasone (referred to as Ld throughout this submission).
Source: Janssen Data on file. Adapted from Kumar et al. 2022.

The latest data cut from MAIA continues to demonstrate an OS benefit for DLd compared with Ld in newly diagnosed transplant-ineligible multiple myeloma. DLd was associated with a statistically significant 35% reduction in the risk of death compared with Ld (HR: 0.65; 95% CI: 0.52-0.80; p<0.0001). The 73.6 month data cut also supports the trend for an improved treatment effect with longer study follow-up with a lower HR and increased precision around the point estimate reflected by a narrower confidence interval.

Updated MAIA 73.6m OS extrapolations

Figure 2 provides the updated parametric extrapolations for DLd OS using the latest MAIA data cut.

Figure 2: Extrapolation of OS for DLd using IPD from MAIA 73.6m data cut (with GPM cap)

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	 **Abbreviations**: DLd: daratumumab, lenalidomide and dexamethasone; GPM: general population mortality; IPD: individual patient data; KM: Kaplan-Meier; OS: overall survival. The Exponential curve has best statistical fit (lowest AIC/BIC) across both the 64.5 and 73.6 month data cuts (refer to Appendix A). During Technical Engagement (using the 64.5m data cut), Janssen noted that both the Exponential and Gompertz were plausible, acknowledging similarity in the long-term estimates with mean predicted OS of 116.7 months and 115.1 months respectively. As such, Janssen revised its base case selection from Exponential to Gompertz to align with the EAG preferred curve. However, with the latest MAIA data cut, there is increased divergence between the two curves with the Exponential and Gompertz providing mean OS estimates of 114.2 and 108.2 months respectively. Whilst both distributions remain clinically plausible, Gompertz is considered a conservative estimate. To align with the Committee's preferred assumption following the first ACM, Janssen retain the Gompertz selection for DLd OS. A scenario analysis exploring the impact on cost-effectiveness selecting the best-fitting Exponential curve for DLd OS is also explored. For Ld, the Gompertz extrapolation remains the best fitting curve, with a negligible difference in the estimated total mean OS across the two data cuts (69.54 months vs 69.19 months) (refer to Appendix A). As such, Gompertz is retained as the base case curve selection for Ld OS. In summary, the consistency of the OS results with the latest MAIA data cut reflects maturity of the data with over 6-years median follow-up and provides reassurance with regards stability of the cost-effectiveness estimates. Whilst Janssen acknowledge inherent modelling uncertainty in the context of a lifetime time horizon, the Gompertz curve selection for DLd OS is considered conservative with residual uncertainty fully explored via scenario analysis.
2	**New data available from MAIA for TTD supports the Generalised Gamma and the Gompertz, but not Exponential** Draft Guidance, Section 3.9: *"Based on the appraised evidence, the committee concluded that the exponential curve was most appropriate for decision making. But it said that it would reconsider its decision if evaluation of the most recent data cut suggested another extrapolation is more appropriate."*

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Previously, based on the MAIA 64.5 month data cut, the clinically plausible range for DLd TTD was between the Generalised Gamma (lowest AIC) and the exponential (lowest BIC), with the Gompertz sitting as a midpoint in the range. Janssen considered the statistical fit for the Generalised Gamma, Gompertz and Exponential to be broadly comparable, with a preference for the Gompertz in the base case. Janssen did not consider there was sufficient evidence to select the upper bound (Exponential) or lower bound (Generalised Gamma) from the plausible range as a base case input for decision making. The EAG and Committee preferred the exponential for DLd TTD, based on the lowest BIC, although acknowledged that further data could inform decision making. This is despite the exponential representing an upper bound of the clinically plausible range and the rationale for the lowest BIC being inconsistent with the approach considered for other survival extrapolations.

As noted above, additional TTD data is now available from MAIA based on the 73.6 month data cut. The updated Kaplan-Meier chart for TTD is presented in Figure 3, with full details available in Appendix A.

Figure 3: Updated TTD for DLd and Ld in the MAIA trial (ITT population; median follow-up = 73.6m)

Abbreviations: DLd: daratumumab, lenalidomide and dexamethasone, Ld: lenalidomide and dexamethasone
Source: Janssen Data on File. MAIA 73.6m data cut.

Updated MAIA 73.6m TTD extrapolations

Figure 4 and Figure 5 provides the updated parametric extrapolations for DLd and Ld TTD respectively, using the latest MAIA data cut. The associated statistical fit for each distribution (DLd and Ld) is provided in Table 1.

Figure 4: Extrapolation of TTD for DLd using IPD from MAIA 73.6m data cut

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Figure 5: Extrapolation of TTD for Ld using IPD from MAIA 73.6m data cut

Abbreviations: Ld: lenalidomide and dexamethasone; IPD: individual patient data; KM: Kaplan-Meier TTD: time to discontinuation.

Table 1: Goodness-of-fit statistics for DLd and Ld TTD survival models using MAIA 73.6m data cut

Survival model	DLd		Ld	
	AIC	BIC	AIC	BIC
Exponential	2623.9	2627.8	2963.3	**2967.2**
Weibull	2625.4	2633.2	2963.6	2971.4
Loglogistic	2649.5	2657.3	3001.5	3009.3
Lognormal	2679.8	2687.6	3030.5	3038.3

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Generalised Gamma	**2614.0**	**2625.7**	**2961.2**	2972.9
Gompertz	2619.2	2627.0	2965.2	2973.0

Visual inspection of the updated TTD extrapolations for DLd support both the Generalised Gamma and Gompertz. Notably, the updated TTD data does not support the exponential distribution with a clear separation and divergence with the observed Kaplan-Meier with longer study follow-up. In terms of statistical fit, the Generalised Gamma now has the lowest AIC/BIC with the Gompertz ranked second, and exponential third.

In summary, the 73.6 month data cut from MAIA has helped to significantly reduce uncertainty regarding the expected treatment duration for DLd, with the plausible range now lying between the Generalised Gamma and Gompertz. Based on best visual and statistical fit, Janssen has updated the company base case selection to Generalised Gamma. A scenario analysis using Gompertz is provided to explore the range of uncertainty and impact on overall cost-effectiveness.

Similarly, for Ld, Janssen has updated the company base case selection from Weibull to Generalised Gamma based on visual and statistical fit. This, however, has a minimal impact on the overall estimated TTD (see Appendix A) and cost-effectiveness results.

3

Scenarios exploring long-term extrapolation of OS treatment effect

Draft Guidance, Section 3.10:

"…the committee concluded that the company's base case could potentially be plausible, but it is highly optimistic and associated with high uncertainty. It noted that the most recent MAIA data cut (October 2022) could provide a small amount of additional evidence to help inform the extrapolation, but recalled this data cut was not currently included within this appraisal."
"The scenario with constant treatment effect was supported by the company's piecewise Cox model, which showed that overall survival hazard ratios remained stable over the 4- to 6-year period, indicating a constant survival benefit."

As per the Draft Guidance document (Section 3.10), the economic model used independently fitted parametric curves to estimate long-term OS for DLd and Ld. This was appropriate given the observed violation of proportional hazards, and the approach to curve selection was consistent with guidance provided in NICE DSU TSD 14. The full range of parametric models were assessed, and alternative, more flexible survival models were also explored which indicated overall consistency in the results.

Nonetheless, Janssen understand the concern of the Committee with regard to the long-term treatment effect when considering a lifetime time horizon. To explore this issue further, Janssen has updated the Piecewise Cox analysis previously conducted using the latest data cut from MAIA (Refer to Table 2). As noted above, the OS hazard ratio has continued to improve with each successive data cut including the latest (73.6 month) data cut from MAIA (HR: 0.65; 95% CI: 0.52-0.80; p<0.0001). Although the hazard ratio has improved at a reduced rate over the last ~2-years, analysis of the hazard ratio over time indicates a 'stepped' downward trend. The hazard ratio remained close to 1 for the first 2-years before a marked step-down after 24-months. There then followed a period of stabilisation before a further step-down beyond 4-years.

Table 2: Updated Piecewise Cox analysis of MAIA OS data (73.6m) over time

MAIA Follow up duration (months)	*OS HR*	*95% CI*	*P value*
≤6	[redacted]	[redacted]	[redacted]

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≤12		[redacted]			[redacted]			[redacted]
≤18		[redacted]			[redacted]			[redacted]
≤24		[redacted]			[redacted]			[redacted]
≤30		[redacted]			[redacted]			[redacted]
≤36		[redacted]			[redacted]			[redacted]
≤42		[redacted]			[redacted]			[redacted]
≤48		[redacted]			[redacted]			[redacted]
≤54		[redacted]			[redacted]			[redacted]
≤60		[redacted]			[redacted]			[redacted]
≤66		[redacted]			[redacted]			[redacted]
≤72		[redacted]			[redacted]			[redacted]
≤78		[redacted]			[redacted]			[redacted]
≤84		[redacted]			[redacted]			[redacted]

A continued improvement in treatment effect was also supported by clinical experts at the 1st ACM, underpinned by biological plausibility of the impact of deeper responses on the disease and overall health state for transplant-ineligible patients. As noted in the original company submission (Section B.1.3.5 and the company response to Technical Engagement, Key issue 9, p18), achieving deep and durable responses is recognised as one of the primary goals of front-line treatment, resulting in a fundamental shift in the trajectory of the disease course and long-term outcomes for patients. This is particularly true for transplant-ineligible patients with the deep/sustained responses not only helping to better control their myeloma, but also helping to improve their overall health state given the complex range of comorbidities often present at diagnosis for this elderly/frail population (e.g. better bone disease control and preserved kidney function).

In MAIA, the rate of minimal residual disease (MRD) negativity at sensitivity 10^{-5} was significantly higher and approximately 3-fold for the DLd group (32.1%) compared with the Ld group (11.1%) (odds ratio [OR]: 3.78; 95% CI: 2.55, 5.59; p<0.0001), with patients achieving MRD negativity in the DLd group resembling general population mortality (GPM) (Document B, Section B.2.6.2.10). DLd also achieved greater than 4-fold higher ≥12-month and ≥18-month sustained MRD rates (≥12-month sustained MRD-negative: 18.8% vs 4.1%; p<0.0001) (≥18-month sustained MRD-negative: 16.8% vs 3.3%; p<0.0001). The prognostic significance of MRD and its association with improved PFS/OS is well established in newly diagnosed MM (including transplant-ineligible patients) with results from MAIA supporting the continued improvement in the DLd treatment effect observed.[1]

In summary, the totality of evidence available from MAIA, clinical expert feedback at the 1st ACM and biological understanding of the disease supports the original company base case. We do, however, understand the inherent uncertainty when modelling a lifetime time horizon. As such, we have explored a range of scenarios either fixing the hazard ratio or considering an attenuation of the DLd treatment effect.

Additional scenarios exploring the long-term modelled treatment effect

To help inform Committee decision making, a range of scenarios are provided to explore the long-term modelling uncertainty between the upper and lower bounds on DLd efficacy defined by the company base case and Committee's fixed hazard ratio scenario. Per the Committee's

[1] Munshi, N. et al. Expanded Meta-Analysis Confirms the Association Between MRD and Long-term Survival Outcomes in Multiple Myeloma (MM). Poster presented at American Society of Hematology (ASH). 2019

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conclusions in the Draft Guidance, we have included attenuation scenarios where the relative treatment effect reduces over time but where the hazard ratio for DLd versus Ld does not reach 1 (Scenarios 5 and 6).

A description of each scenario is provided below in Table 3, with full model inputs in Appendix B.

Table 3: Additional scenarios exploring OS HR uncertainty

Scenario	Approach	Assumption
1	Fix OS HR from end of observed KM	• Fix the modelled hazard ratio from the end of observed MAIA period (7.16 years in the 73.6m data cut) onwards
2	Fix OS HR at 12-years	• Model independently fitted OS survival curves until 12-years • Fix the hazard ratio from 12-years onwards
3	Fix OS HR at 15-years	• Model independently fitted OS survival curves until 15-years • Fix the modelled hazard ratio from 15-years onwards
4	Reduced OS HR improvement until fix at 12-years	• Model a reduced rate of OS improvement from 7.16 years until 12-years • Assume the OS benefit at 12-years is fixed onwards (at the midpoint between generated OS HR at 12-years and OS HR at 7.16 years)
5	Exploratory attenuation scenario: from 12-years	• Assume the OS HR generated at 12-years attenuates from 12-19 years by 25%
6	Exploratory attenuation scenario: from 15-years	• Assume the OS HR generated at 15-years attenuates from 15-25 years by 25%

A visual representation of the exploratory OS HR scenarios is provided in Figure 6:

Figure 6: Visual representation of scenarios exploring modelled OS HRs over time

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	 BC: base case *Note: The OS HR depicted above represents the modelled treatment effect at specific timepoints (calculated from per cycle hazards) and contrasts with the reported HR from MAIA which represents a summary measure of the average treatment effect across the entire (observed) follow-up period.* Janssen note that the downward trend in the modelled OS HR continues to be supported by the base case curve selections for DLd and Ld (with Gompertz considered a conservative selection for DLd OS) and improvement in the overall hazard ratio.
4	**Inclusion of treatments only available through the Cancer Drugs Fund** **NICE Draft Guidance, Section 3.12:** *"The committee concluded that treatments recommended for use in the Cancer Drugs Fund should not be considered as subsequent treatments. But it said that if treatments currently included within the Cancer Drugs Fund are recommended for routine practice after their respective ongoing reviews and are considered established clinical practice, the modelling could be updated to incorporate these as subsequent treatments."* Janssen note that, since the 1st ACM and the release of the Draft Guidance for this appraisal, • Positive NICE guidance has been published for ixazomib with lenalidomide and dexamethasone for treating relapsed or refractory multiple myeloma (TA870) • Committee B has considered daratumumab with bortezomib and dexamethasone for previously treated multiple myeloma (ID4057) for routine commissioning. It is expected that these two treatments will be available in routine commissioning by the time of the second NICE committee meeting for this appraisal. As such, all scenarios and updated company base case ICERs provided below are when including 'DBd at 2L and IxaLd at 3L' in the economic model.
5	**Generalisability of subsequent treatments in MAIA compared to UK clinical practice** **NICE Draft Guidance, Section 3.4:**

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	"The committee agreed that the population in MAIA is generalisable to NHS clinical practice. However, it also noted that the subsequent treatments used in MAIA were likely to differ from those offered in NHS clinical practice. The committee considered that this would impact generalisability and lead to uncertainty in the long-term treatment effect of daratumumab plus lenalidomide and dexamethasone (see section 3.10). Despite the uncertainty, the committee considered that the MAIA trial represented the best available evidence." MAIA is an international phase III randomised controlled trial which enrolled patients in 176 hospitals, across 14 countries including the UK. As such, MAIA included a number of subsequent treatments not routinely available in NHS clinical practice. In the original company submission Janssen performed an inverse probability of censoring weights (IPCW) analysis to adjust for subsequent treatments not routinely available in England and to reduce any potential bias (Document B, Section B.2.6.2.6). The results demonstrated a higher OS benefit for DLd versus Ld with a hazard ratio of [redacted]. Given these analyses, the EAG concluded that unadjusted results from MAIA may be conservative (ID4014 Draft Guidance Document, Section 3.4). Following publication of the positive Final Appraisal Document (FAD) for ixazomib plus lenalidomide and dexamethasone at 3rd line, and the expected transition from the Cancer Drugs Fund (CDF) to baseline commissioning for DVd at 2nd line, Janssen has updated the IPCW results to include both treatments. Results continue to demonstrate a higher OS benefit for DLd compared with the unadjusted results (updated IPCW OS HR: [redacted]) suggesting the unadjusted results from MAIA remain a conservative estimate. Despite concerns raised by the Committee in relation to the generalisability of subsequent treatments administered in MAIA, Janssen note that the UK Myeloma Forum (UKMF) consider that the outcomes for the control arm reflect expected outcomes in UK clinical practice for this patient population (ID4014 Committee Papers). The generalisability of subsequent treatments administered within an international clinical trial context to a UK setting is a common issue faced across multiple HTA appraisals, particularly in the MM setting. In this case, however, the generalisability concerns should be reduced for the Committee because: • the inclusion of patients from the UK within MAIA • the validation of the observed long-term absolute outcomes for Ld being generalisable to the UK setting • The observed MAIA outcomes for the standard of care (Ld) arm in the UK are better than other comparable trials (FIRST trial) **Additional treatments used in MAIA which may improve outcomes in Ld arm** There were a total of [redacted] different treatment combinations used as 2nd or 3rd line treatments in MAIA (the full list of treatments was previously provided by Janssen during the Clarification Process). Janssen consider there to be high generalisability for the subsequent treatments used in the DLd arm of MAIA. In current UK clinical practice, it is expected that patients who receive frontline DLd would likely change treatment class, and receive a bortezomib based treatment at second line. This is reflected in the MAIA trial, as the majority (75%) of 2nd and 3rd line treatments administered after DLd were bortezomib-based.

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<table>
<tr><td></td><td>In the Ld arm of MAIA, aligned with what would be expected in UK practice, the most frequently used combination after Ld at 2L and 3L was daratumumab in combination with bortezomib and dexamethasone (n=36). Daratumumab was also given at 2L and 3L for patients in the Ld arm either as monotherapy (n=10), or with a wide variety of other treatment combinations, including combinations such as daratumumab + lenalidomide + dexamethasone (n=8), daratumumab + pomalidomide + dexamethasone (n=8) and carfilzomib + daratumumab + dexamethasone (n=5). In addition, pomalidomide + dexamethasone (n=16) and a number of investigational treatments, including antineoplastic drugs and other monoclonal antibodies were included as subsequent treatments at 2L and 3L for the Ld arm. It is expected that these treatment combinations would uplift the MAIA Ld outcomes, relative to treatments routinely available in the UK.

As such, whilst there may be concerns regarding the generalisability of subsequent treatments used in MAIA, the direction of any potential bias remains unclear with the IPCW results suggesting overall conservative nature of the unadjusted results.</td></tr>
<tr><td>6</td><td>Additional benefits not captured in the QALY framework, additional data from MAIA and exploratory scenarios provided should reduce decision making uncertainty for the Committee

NICE Draft Guidance, Section 3.13:

“The committee considered the uncertainty, particularly relating to the long-term treatment attenuation. It concluded that the ICER would have to be substantially below £30,000 per QALY gained to be considered a cost-effective use of NHS resources and accepted for routine commissioning.”

In Section 3.13, in terms of the acceptable ICER for decision making, the Committee noted a number of uncertainties in this appraisal, as per Table 4 below. However, the additional evidence from MAIA, with now over 7-years of observed data available, as well as additional scenarios provided, should reduce the decision uncertainty for the Committee.

Table 4: Reduction of uncertainties for Committee decision making
<table>
<tr><th>Uncertainty named in Draft Guidance</th><th>Addressed in appraisal process</th></tr>
<tr><td>• “the relative immaturity of the overall survival data for daratumumab plus lenalidomide and dexamethasone”</td><td>• Additional OS data from MAIA, with follow up of over 7 years, now available to reduce uncertainty in appraisal</td></tr>
<tr><td>• “the relative effectiveness of bortezomib combination treatments”</td><td>• Committee recognise that uncertainty on appropriate approach to compare to bortezomib did not materially impact the fully incremental analysis cost-effectiveness results, and so is not relevant when considering the decision making ICER.</td></tr>
<tr><td>• “the appropriate parametric curve for time to treatment discontinuation for daratumumab plus lenalidomide and dexamethasone”</td><td>• Additional TTD data from MAIA reduces the uncertainty of the appropriate parametric curve for DLd TTD, which now supports the Gen Gamma and the Gompertz.</td></tr>
<tr><td>• “the attenuation of the treatment effect”</td><td>• Observed data from MAIA of more than 7 years of follow up supporting the company’s original base case approach</td></tr>
</table></td></tr>
</table>

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		• Updated company base case, additional exploratory and attenuation scenarios provided in this response to explore uncertainty for Committee decision making
	• *"the market share of second- and third-line treatments"*	• Conclusion that the company's estimates of market share of second line and third line were acceptable for decision making

Janssen also note the number of additional benefits not captured in the QALY calculation (see Document B, Section 3.12), which are appropriate when considering the uncertainty associated with this appraisal:

- Providing benefits, such as prolonged remission and reduction in anxiety associated with relapse, which are aligned to MM patient preferences and are not explicitly considered in the QALY framework,
- Providing a positive impact on carers, such as reduction in burden of care as a direct result of the reduction in the rate of deterioration of the disease.
- Removal of a present day NHS inequity in access of effective treatments between transplant-eligible and transplant ineligible patients, the benefit of which supports non-health objectives (see Section B.1.4 of Document B).
- Additional benefits from providing access to an anti-CD38 treatment in newly diagnosed, transplant ineligible MM patients, as this will provide future innovative treatment options for patients both in terms of enrolment into clinical trials and in terms of access to therapies whose marketing authorisations will specify anti-CD38 exposure. This benefit of having access to DLd is not captured in the QALY framework.

The Committee have listed the residual uncertainty as a reason for the acceptable ICER needing to be substantially below £30,000 per QALY. However, the additional wider benefits provided from DLd, as well as additional evidence provided in this response should be considered when considering the appropriate decision making threshold for the Committee.

As such, Janssen consider it appropriate for the Committee to consider an ICER threshold towards the upper end of the cost-effectiveness range.

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is 'commercial in confidence' in turquoise and information that is 'academic in confidence' in yellow. If confidential information is submitted, please submit a second version of your comments form with that information replaced with the

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following text: 'academic / commercial in confidence information removed'. See the NICE Health Technology Evaluation Manual (section 5.4) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the draft guidance document, please submit these separately.

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

Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Model Assumptions

Revised base case

Janssen have provided a revised base case covering the issues in comments 1-6 of this document, as follows:
- Incorporating the updated OS and TTD data using MAIA 73.6m data cut
- Updated TTD base case extrapolations, changing to Generalised Gamma for DLd and Ld TTD

In addition to the revised base case, Janssen has provided scenario analyses applied to the company base case as follows:
- DLd OS exponential
- DLd TTD Generalised Gamma
- Additional exploratory OS HR scenarios (scenarios 1-6)

Revised economic analyses

Table 5 summarises the revised company base case plus additional scenario analyses. The committee acknowledged that uncertainty in the indirect comparison versus bortezomib did not materially impact the fully incremental analysis results. As such, only ICERs versus Ld are presented.

The revised company base-case is presented in Table 6. The probabilistic scatterplot is presented in Figure 7 and cost-effectiveness acceptability curve in Figure 8.

Table 5: Updated cost-effectiveness results (Gompertz OS, with [redacted] PAS)

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Scenario		Inc. costs	Inc. QALYs	ICER
Post Technical Engagement company base case (64.5m MAIA data) • 64.5m OS: Gompertz • 64.5m TTD: Gompertz		[redacted]	[redacted]	[redacted]
Availability of updated MAIA data (73.6m data)				
Company Revised Base case: • Incorporating updated MAIA 73.6m OS and TTD data • Generalised Gamma for DLd TTD and Ld TTD		[redacted]	[redacted]	[redacted]
Additional scenarios (applied to the company revised base-case)				
DLd OS exponential (best statistical fit)		[redacted]	[redacted]	[redacted]
DLd TTD Gompertz		[redacted]	[redacted]	[redacted]
Additional exploratory OS HR scenarios (applied to the company revised base-case)				
1	Fixed OS HR from end of observed KM	[redacted]	[redacted]	[redacted]
2	Fixed OS HR from 12-year timepoint	[redacted]	[redacted]	[redacted]
3	Fixed OS HR from 15-year timepoint	[redacted]	[redacted]	[redacted]
4	Reduced OS improvement until fix at 12-years	[redacted]	[redacted]	[redacted]
5	Attenuation scenarios: 12-19 years, 25% reduction	[redacted]	[redacted]	[redacted]
6	Attenuation scenarios: 15-25 years, 25% reduction	[redacted]	[redacted]	[redacted]
Additional exploratory OS HR scenarios (applied to the company revised base-case, including DLd Exponential OS)				
1a	Fixed OS HR from end of observed KM	[redacted]	[redacted]	[redacted]
2a	Fixed OS HR from 12-year timepoint	[redacted]	[redacted]	[redacted]
3a	Fixed OS HR from 15-year timepoint	[redacted]	[redacted]	[redacted]
4a	Reduced OS improvement until fix at 12-years	[redacted]	[redacted]	[redacted]
5a	Attenuation scenarios: 12-19 years, 25% reduction	[redacted]	[redacted]	[redacted]
6a	Attenuation scenarios: 15-25 years, 25% reduction	[redacted]	[redacted]	[redacted]
Additional exploratory OS HR scenarios (applied to the company revised base-case, including DLd Gompertz TTD)				
1b	Fixed OS HR from end of observed KM	[redacted]	[redacted]	[redacted]
2b	Fixed OS HR from 12-year timepoint	[redacted]	[redacted]	[redacted]
3b	Fixed OS HR from 15-year timepoint	[redacted]	[redacted]	[redacted]
4b	Reduced OS improvement until fix at 12-years	[redacted]	[redacted]	[redacted]
5b	Attenuation scenarios: 12-19 years, 25% reduction	[redacted]	[redacted]	[redacted]
6b	Attenuation scenarios: 15-25 years, 25% reduction	[redacted]	[redacted]	[redacted]

Table 6: Revised company base-case results (with [redacted] PAS)

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER (£/QALY)
Deterministic							
DLd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ld	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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Probabilistic							
DLd	[redacted]		[redacted]				
Ld	[redacted]		[redacted]	[redacted]		[redacted]	[redacted]

Figure 7: Cost-effectiveness plane for DLd versus Ld, revised company base-case results (with PAS)

Abbreviations: DLd: daratumumab, lenalidomide and dexamethasone; Ld: lenalidomide and dexamethasone; PAS: patient access scheme; PSA: probabilistic sensitivity analysis.

Note: the variance-covariance matrix for generalised gamma resulted in sampling parameter values far outside of the uncertainty around the KM survival estimates, and survival curves starting at zero where the scale parameter had a negative value. As such, an alternative 'bootstrapping' approach was taken to assess the sensitivity of results to parameter uncertainty.

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Figure 8: Cost-effectiveness acceptability curve, revised company base-case results (with PAS)

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Appendix A: Company Evidence: Additional follow up from MAIA 73.6 month data cut

A1.1Appendix A: Introduction

This appendix provides additional evidence informing the NICE Committee appraisal of daratumumab (Darzalex®) in combination with lenalidomide and dexamethasone (DLd) untreated multiple myeloma when stem cell transplant (ASCT) is unsuitable (ID4014).

This appendix contains updated overall survival (OS) and time to treatment discontinuation (TTD) data from the MAIA clinical trial (MMY3008). As described in Document B (Section B 2.2), MAIA is a randomised, open-label, active controlled, parallel-group, multicentre, Phase 3 clinical trial, which assessed the efficacy and tolerability of DLd versus lenalidomide and dexamethasone (Ld) in patients with ASCT-ineligible newly diagnosed multiple myeloma (NDMM).

The evidence presented in Document B (May 2022) represented the most recent results available at the time of submission from MAIA, with a clinical cut-off of 21st October 2021 (64.5 months median follow-up). Since then, more mature OS and TTD data from MAIA has become available, with median follow-up of 73.6 months.

The updated clinical data from MAIA are provided below in Section A.2, with updated base case OS and TTD extrapolations informing the economic analysis found in Section A.3.

A2 Additional OS and TTD data from MAIA 73.6m data cut

Additional OS data are now available from MAIA. At a median follow-up of 73.6 months, a total of [redacted] death events had occurred in the MAIA trial. The total number of events in each arm were [redacted] patients ([redacted]%) in the DLd group and [redacted] patients ([redacted]%) in the Ld group, representing an additional [redacted] OS events in the DLd arm, and an additional [redacted] OS events in the Ld arm compared to the previous data cut (64.5 months follow-up).

The new data from MAIA continues to show OS was significantly improved with DLd and was associated with a 35% reduction in the risk of death compared with Ld (HR: 0.65; 95% CI: 0.52-0.80; p<0.0001). The median OS was not reached for the DLd group and was 64.07 months for the Ld group. With over 6-years of median follow-up, these results represent both a statistically significant and clinically meaningful improvement in life expectancy for patients treated with DLd compared with current UK standard of care, aligned with key patient preferences.

A summary of OS from MAIA at a median follow-up of 73.6 months compared to the previous follow-up of 64.5 months, is presented in Table 1 and the associated Kaplan Meier plot in Figure 1.

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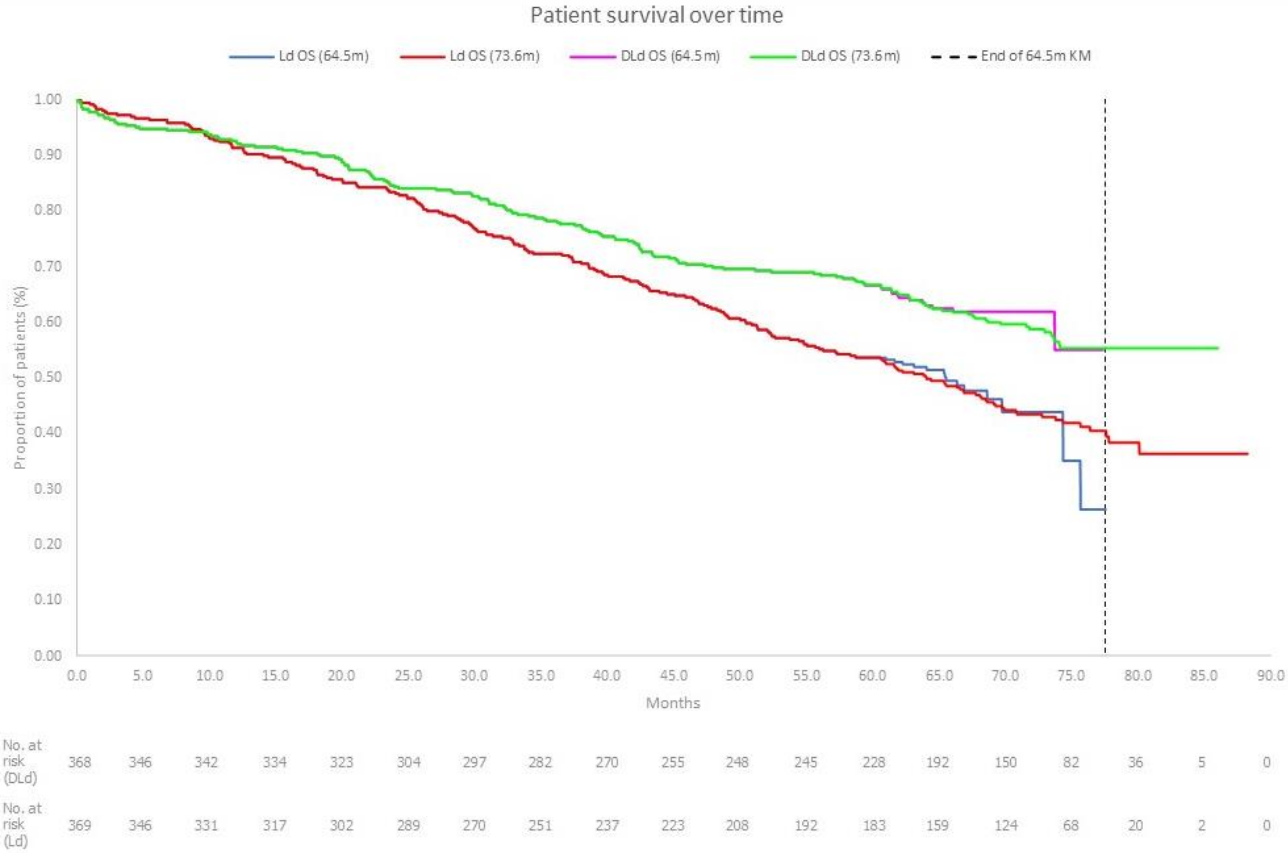
Table 1: Summary of OS in the MAIA trial (ITT population) (73.6m vs 64.5m median follow-up)

	MAIA: 73.6 months data cut		MAIA: 64.5 months data cut	
	DLd (n=368)	Ld (n=369)	DLd (n=368)	Ld (n=369)
Number of events (%)	[redacted]	[redacted]	[redacted]	[redacted]
Median (95% CI)	NE ([redacted])	64.07 ([redacted])	NE (73.72, NE)	65.54 (55.98, 75.66)
HR (95% CI)	0.65 (0.52, 0.80)		0.66 (0.53, 0.83)	
p–value	0.0001		0.0003	
60-month OS rate, %	66.7	53.7	66.6	53.6

Abbreviations: CI: confidence interval ; DLd: daratumumab, lenalidomide and dexamethasone; HR: hazard ratio; ITT: intention-to-treat; Ld: lenalidomide and dexamethasone; NE: not estimable; OS: overall survival
Source: **Janssen Data on File. MAIA 73.6m data cut.**

Figure 1: Kaplan–Meier estimates of OS in the MAIA trial (ITT population) (73.6 months follow-up)



Abbreviations: CI: confidence interval; DLd: daratumumab, lenalidomide and dexamethasone, HR: hazard ratio; NR: not reached; Ld: lenalidomide and dexamethasone (referred to as Ld throughout this submission).
Source: Janssen Data on file**.** Adapted from Kumar *et al.* 2022.

Relative to the 64.5m data cut, the latest OS data from MAIA support the trend for an improved treatment effect in favour of DLd with a lower HR and narrower confidence interval with longer study follow-up. This trend for improvement with each successive data cut from MAIA has been consistently observed over the last 6-years, with

a reduction in the OS HR implying an improved treatment effect in favour of the daratumumab triplet versus the lenalidomide doublet (Table 2).

Table 2: Improvement in MAIA OS results over time (updated with 73.6m data cut)

MAIA data cut	Clinical cut-off	Median follow-up	OS HR
Primary PFS analysis (pre specified interim analysis)	Sept 2018	28.0 months	[redacted]
9m snapshot (conference data cut)	June 2019	36.4 months	[redacted]
ASH 2020 (conference data cut)	June 2020	47.9 months	[redacted]
263 OS events (prespecified interim analysis)	Feb 2021	56.2 months	0.68 (0.53, 0.86)
Updated analysis (regulatory data cut)	Oct 2021	64.5 months	0.66 (0.53, 0.83)
ASH 2022 (conference data cut)	**Oct 2022**	**73.6 months**	**0.65 (0.52, 0.80)**

Abbreviations: ASH: American Society of Haematology; HR: hazard ratio; OS: overall survival; PFS: progression-free survival.
Source: Facon *et al*. (2019);[103] Facon *et al*. (2021);[104] MAIA CSR (September 2018 data cut). [Data on File]. 2019;[8] MAIA Abbreviated CSR. [Data on File] 2021;[106] Kumar et al. 2020.[109] MAIA HEMAR report. [Data on file] 2022;[9] MAIA CSR (October 2021 data cut). [Data on file]. 2022. [102] Kumar *et al.* 2022 (2)

A2.1 MAIA 73.6m data cut: OS subgroups

Consistent with the previous data cut (64.5m follow-up), OS subgroup analyses similarly demonstrated that the treatment effect of DLd over Ld was consistent across the pre-specified, clinically relevant subgroups including patients of 75 years of age or older, and patients with a poor prognosis such as those with advanced-stage disease (ISS Staging III) or renal impairment, with the exception of the subgroup analysis of patients with impaired hepatic function at baseline (Figure 2). As with the previous data cut, the interpretation for this subgroup is limited by the small sample size (31 and 29 patients in the DLd and Ld groups, respectively) and wide CI (0.64, 2.60).

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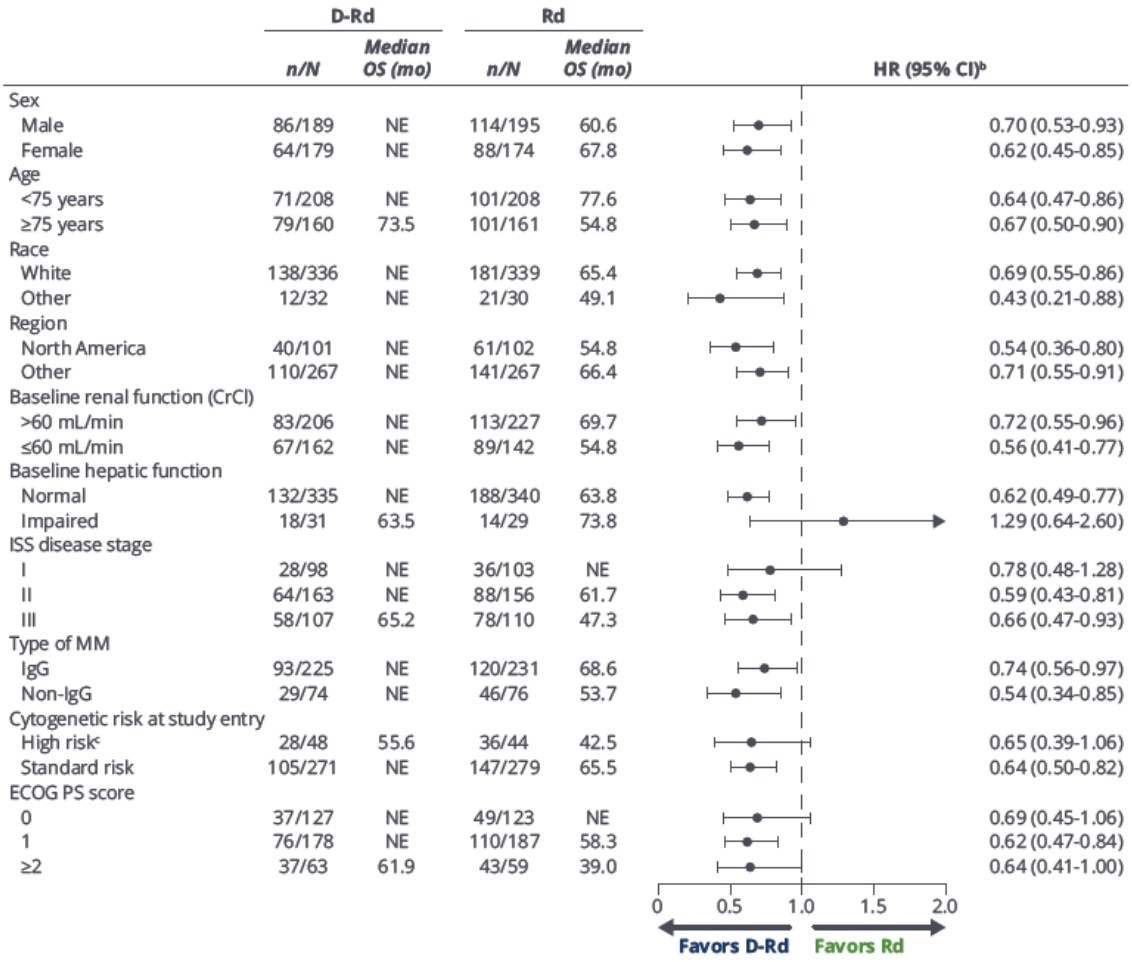
Figure 2: Forest plots of subgroup analyses on OS in the MAIA trial (ITT population) (73.6m median follow-up)



Abbreviations: CI: confidence interval; CrCl: creatine clearance; D-Rd: daratumumab, lenalidomide and dexamethasone (referred to as DLd throughout this submission); ECOG: Eastern Cooperative Oncology Group; EVT: event; Igg: immunoglobin G; ISS: international staging system; Rd: lenalidomide and dexamethasone (referred to as Ld throughout this submission); OS: overall survival.
Source: Kumar *et al.* 2022 (2)

OS by MRD status was also reported in the latest (73.6m) data cut from MAIA for both DLd and Ld. As noted in Section B1.3.5 of Document B, MRD is the most sensitive measure of response currently available in multiple myeloma and has been recommended in IMWG response assessment criteria.

MRD negativity was assessed at the sensitivity threshold of 10^{-5}. The 60-month (5-year) OS rate for MRD-negative patients was 88.9% for the DLd group compared to 78.0% for the Ld group. For those that were MRD-positive, the 60-month OS was 55.9% for the DLd group and 50.4% for the Ld group (2). For those patients who achieve MRD negativity following DLd treatment, the depth of response allows long-term disease control as demonstrated by the 5-year OS rates.

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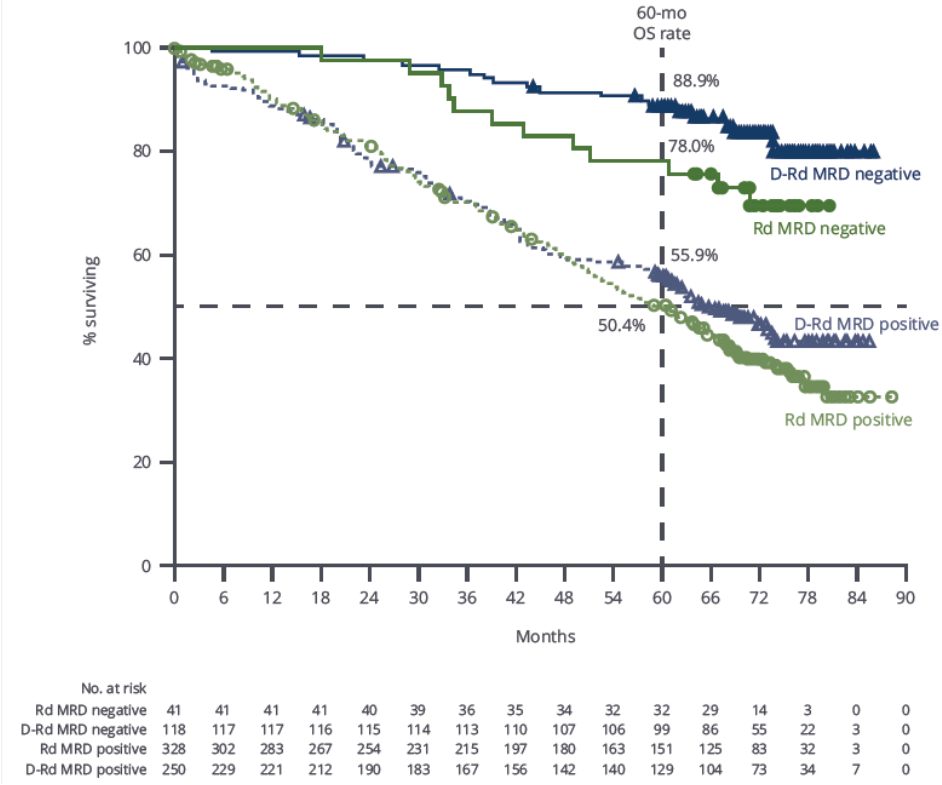
The Kaplan Meier plot for OS by MRD status at 73.6 months median follow-up is presented in Figure 3.

Figure 3: Kaplan–Meier estimates of OS by MRD status in the MAIA trial (73.6 months median follow-up)



Abbreviations: CI: confidence interval; D-Rd: daratumumab, lenalidomide and dexamethasone (referred to as DLd throughout this submission); HR: hazard ratio; NR: not reached; Rd: lenalidomide and dexamethasone (referred to as Ld throughout this submission).
Source: Kumar *et al.* 2022 (2)

A2.2 MAIA Time to Treatment Discontinuation (TTD): 73.6m data cut

In addition to updated OS data, updated TTD data was also collected from the MAIA 73.6 month data cut. This conference data cut was presented at the 2022 American Society for Haematology (ASH) Annual Meeting, and focused on overall survival. The prespecified final TTD analysis is expected to be available at the time of the final OS Analysis/End of Study (when approximately 390 deaths have occurred;) Protocol 54767414 MMY3008; Phase 3 Amendment 9, 20 July 2021).

At a median follow-up of 73.6 months, a total of [redacted] ([redacted] %) patients had discontinued DLd treatment, and a total of [redacted] ([redacted] %) patients had discontinued Ld treatment. The median TTD was [redacted] months ([redacted]) for DLd and [redacted] months ([redacted]) for Ld. The Kaplan Meier for DLd and Ld TTD is presented in Figure 4.

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Figure 4: Updated TTD for DLd and Ld in the MAIA trial (ITT population (73.6m median follow-up)

Abbreviations: DLd: daratumumab, lenalidomide and dexamethasone, Ld: lenalidomide and dexamethasone
Source: Janssen Data on File. MAIA 73.6m data cut.

A3. Impact of MAIA 73.6m data on OS and TTD base case survival extrapolations

The updated results from the MAIA 73.6m data cut for OS and TTD have been incorporated into the economic model for this submission. Unless noted differently below, all other inputs/ assumptions for the model are consistent with the initial company base case.

A3.1 Updated extrapolations of OS using MAIA 73.6m

As per the original approach outlined in Document B (Section B.3.3.1.1), extrapolation for OS was performed in accordance with the guidance provided in the NICE DSU Technical Support Document (TSD) 14. Extrapolation of OS for DLd and Ld were updated using patient-level data from the 73.6m data cut of the ITT population of MAIA. The extrapolation of the BMP curve using the ALCYONE population remains consistent as the original approach, as detailed in Section B.3.3.1.

For the updated DLd and Ld OS data, a similar approach to curve fitting was followed for the MAIA 73.6m data cut, as detailed in Document B.3.3.1.3. The full range of parametric distributions were explored (exponential, Weibull, loglogistic, lognormal, Gompertz, and generalised gamma), with each model assessed in terms of goodness-of-fit statistics (Akaike information criterion [AIC] and the Bayesian information criteria [BIC]), visual inspection of the hazard function and survival curves to the observed data from the MAIA trial, and clinical plausibility of long-term survival predictions.

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As the assumption of proportional hazards was demonstrated to be violated (Section B.3.3.1.1), independent models were fitted separately to the OS Kaplan-Meier data for DLd and Ld (Figure 5 and Figure 6).

With the updated data cut from MAIA, now there is over six years of median follow up available. As such, the choice of curve was mainly informed by the best statistical fit using the AIC and BIC values (Table 3). However, choice of distribution for the base case for OS was also informed considering graphical assessment of fit (how well the predicted curve captured the shape of the observed Kaplan-Meier data).

Table 3: Goodness-of-fit statistics for DLd, Ld, and BMP OS survival models

Survival model	DLd		Ld		BMP*	
	AIC	BIC	AIC	BIC	AIC	BIC
Exponential	**1804.1**	**1808.0**	2,264.7	2,268.6	1374.4	1378.3
Weibull	1805.9	1813.7	2,254.3	2,262.1	1370.3	1378.1
Loglogistic	1811.6	1819.4	2,262.9	2,270.7	1376.0	1383.8
Lognormal	1831.6	1839.5	2,287.5	2,295.3	1396.7	1404.6
Generalised gamma	1804.3	1816.0	2,253.9	2,265.6	1367.6	1379.4
Gompertz	1805.3	1813.1	**2,251.9**	**2,259.7**	**1361.3**	**1369.0**

Bold indicates lowest AIC/BIC value
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; BMP: bortezomib, melphalan and prednisone; DLd: daratumumab, lenalidomide and dexamethasone; Ld: lenalidomide and dexamethasone; OS: overall survival.
*BMP OS has not been updated with the MAIA 73.6m data cut

Consistent with the previous data cut, the exponential for DLd OS and Gompertz for Ld OS remain the best fitting curves, based on lowest AIC/BIC.

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Figure 5: Extrapolation of OS for DLd using IPD from MAIA 73.6m data cut (with GPM cap)

Abbreviations: DLd: daratumumab, lenalidomide and dexamethasone; GPM: general population mortality; IPD: individual patient data; KM: Kaplan-Meier; OS: overall survival.

Figure 6: Extrapolation of OS for Ld using IPD from MAIA 73.6m data cut (with GPM cap)

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Abbreviations: Ld: lenalidomide and dexamethasone; GPM: general population mortality; IPD: individual patient data; KM: Kaplan-Meier; OS: overall survival.

A comparison of the estimated mean OS for each survival curve between the 64.5 month and 73.6 month data cuts for DLd and Ld are provided in Table 4 below.

For DLd, all survival models provide similar long-term mean OS estimates, with the exception of generalised gamma which, consistent with the previous data cut, remains a notable outlier. In addition, the overall mean OS estimates for DLd from the best statistical fitted model (Exponential) is consistent across the 64.5 month and the 73.6 month data cuts (116.68 months vs 114.21 months respectively). This is also the case for the overall mean estimated OS for Ld for the Gompertz curve (69.54 months vs 69.19 months). The stability of estimated OS results for both arms across data cuts provides reassurance that the long-term OS estimates remain robust, with over 6-years of median follow-up now available from MAIA.

Table 4: Comparison of DLd mean OS with new MAIA data cut

	DLd mean estimated OS over model horizon (months)		**Ld mean estimated OS over model horizon (months)**	
Survival model	**Mean OS (MAIA 64.5m data)**	**Mean OS (MAIA 73.6m data)**	**Mean OS (MAIA 64.5m data)**	**Mean OS (MAIA 73.6m data)**
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Loglogistic	[redacted]	[redacted]	[redacted]	[redacted]
Lognormal	[redacted]	[redacted]	[redacted]	[redacted]
Generalised Gamma	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]

Bold indicates lowest AIC/BIC value

Janssen note that the Exponential curve for DLd remains the best statistical fitting curve across both the MAIA 64.5m and the 73.6m data cuts. During Technical Engagement for this appraisal, Janssen revised its original base case selection from Exponential to Gompertz, acknowledging that both curves gave clinically plausible long-term estimates, with less than a 2-month difference in the mean predicted OS (Gompertz mean = [redacted] months; Exponential mean = [redacted] months).

Using the latest MAIA 73.6m data cut, the difference in mean predicted OS between the Exponential ([redacted] months) and the Gompertz ([redacted] months) curves is more pronounced. Whilst Janssen consider that both remain clinically plausible, Gompertz represents a more conservative estimate. Janssen also note that the exponential from the latest (73.6m) data cut results in a similar mean OS estimate ([redacted] months) compared with the previous Committee preferred curve (64.5m data cut, Gompertz mean = [redacted] months).

A3.2 Updated extrapolations of TTD using MAIA 73.6m data

As noted above, in addition to updated OS data from the 73.6m data cut, updated TTD data were available from MAIA. As per Document B.3.3.1.4, extrapolation of TTD for DLd and Ld was updated using patient-level data from the 73.6m data cut of the ITT population of MAIA. The approach for BMP TTD was unchanged from the original submission (Section B.3.3.1.4).

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Goodness-of-fit statistics for each parametric distribution for TTD explored are presented in Table 6, and the extrapolated curves are presented in Figure 7 for DLd, and Figure 8 for Ld.

Table 6: Goodness-of-fit statistics for DLd and Ld TTD survival models using MAIA 73.6m data cut

Survival model	DLd		Ld	
	AIC	BIC	AIC	BIC
Exponential	2623.9	2627.8	2963.3	**2967.2**
Weibull	2625.4	2633.2	2963.6	2971.4
Loglogistic	2649.5	2657.3	3001.5	3009.3
Lognormal	2679.8	2687.6	3030.5	3038.3
Generalised Gamma	**2614.0**	**2625.7**	**2961.2**	2972.9
Gompertz	2619.2	2627.0	2965.2	2973.0

Footnote: Bold indicates lowest AIC/BIC value
Abbreviations: AIC: Akaike information criterion; DLd: daratumumab, lenalidomide and dexamethasone; Ld: lenalidomide and dexamethasone; TTD: time to discontinuation.

Figure 7: Extrapolation of TTD for DLd using IPD from MAIA 73.6m data cut

Abbreviations: DLd: daratumumab, lenalidomide and dexamethasone; IPD: individual patient data; KM: Kaplan-Meier; TTD: time to discontinuation.

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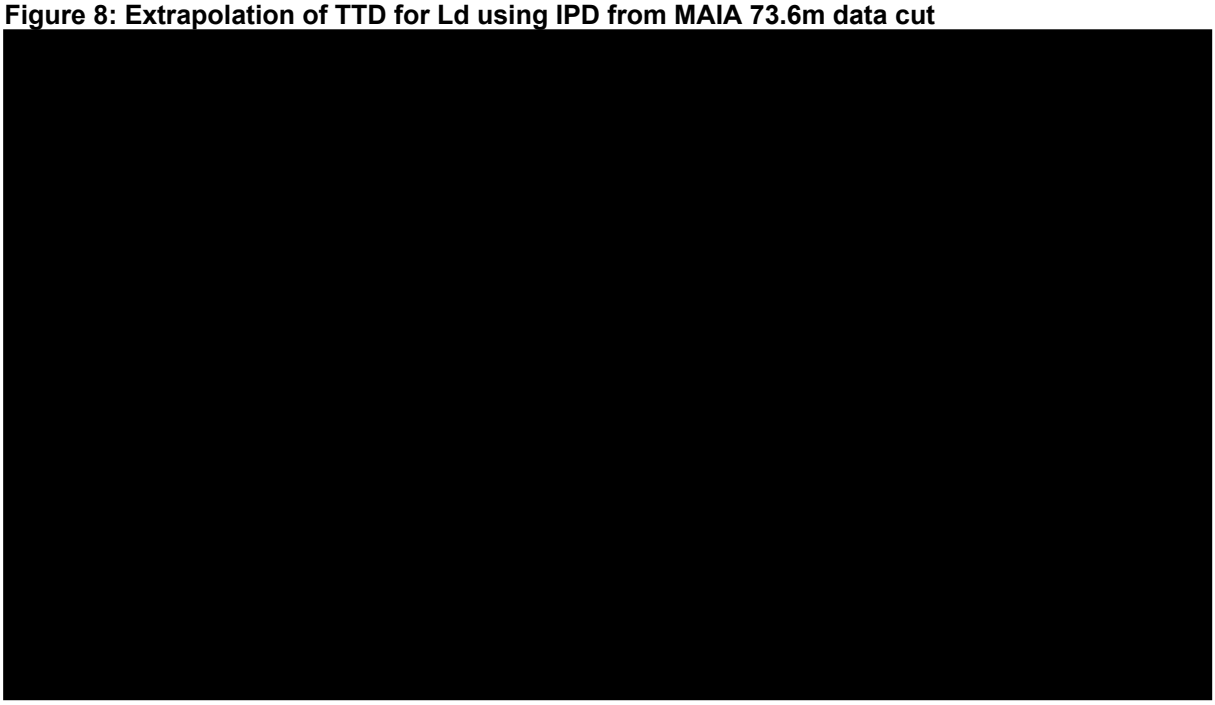
Figure 8: Extrapolation of TTD for Ld using IPD from MAIA 73.6m data cut



Abbreviations: Ld: lenalidomide and dexamethasone; IPD: individual patient data; KM: Kaplan-Meier TTD: time to discontinuation.

With over 6-years of median follow up now available from MAIA, curve selection was informed from statistical and visual fit.

In terms of statistical fit, the Generalised Gamma now has the lowest AIC and BIC with the Gompertz ranked second, and exponential third. Based on this assessment, the Generalised Gamma, or the Gompertz for DLd are appropriate, with the Generalised Gamma selected in the revised company base case. The Generalised Gamma extrapolation for Ld were selected in the base case.

Refer to Table 7 for a comparison of curve selection criteria for DLd and Ld:

Table 7: Comparison of TTD curve selection criteria

	DLd		Ld	
	MAIA 64.5m data cut	**MAIA 73.6m data cut**	**MAIA 64.5m data cut**	**MAIA 73.6m data cut**
Exponential	- 1st best BIC - 2nd best AIC	- 3rd best AIC & BIC - Poor visual fit	- 1st best BIC - 2nd best AIC	- 1st best BIC - 2nd best AIC
Weibull	-	-	-2nd best AIC -2nd best BIC	-2nd best BIC -3rd best AIC
Loglogistic	-	-	-	-
Lognormal	-	-	-	-
Generalised Gamma	- 1st best AIC - 3rd best BIC	- 1st best AIC & 1st best BIC	- 1st best AIC	- 1st best AIC - 3rd best BIC

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		- Best visual fit		- Best visual fit
Gompertz	-2nd best BIC -3rd best AIC	- 2nd best AIC & 2nd best BIC - Good visual fit	- 3rd best BIC - 3rd best AIC	-

Previously, the company base case for TTD for DLd and Ld using the MAIA 64.5m data cut were the Gompertz and Weibull extrapolations for DLd and Ld, respectively. With the previous 64.5m results, the Committee preferred the Exponential for DLd TTd, based on best BIC fit. For DLd TTD, the additional follow-up now available from MAIA clearly shows the exponential no longer has a good fit with the observed data (Figure 7) and no longer has the best BIC. With the new data, the Generalised Gamma and Gompertz remain plausible options for DLd TTD, with the data strongly supporting the Generalised Gamma based on visual and statistical fit.

For Ld, there is a minor change to the TTD curve with the updated choice of the Generalised Gamma, compared to Weibull as chosen previously. This is due to the better statistical fit (Table 7). However, there is a minimal impact to the results; with the exception of the Lognormal and Loglogistic, all TTD extrapolations for Ld predict similar mean TTD (Table 8).

A comparison of the estimated mean TTD for DLd and Ld per survival model are provided in Table 8 below.

Table 8: Comparison of mean DLd TTD with new MAIA data cut

	DLd mean estimated TTD over model horizon (months)		**Ld mean estimated TTD over model horizon (months)**	
Survival model	**Mean TTD (MAIA 64.5m)**	**Mean TTD (MAIA 73.6m)**	**Mean TTD: MAIA 64.5m extrapolations**	**Mean TTD: MAIA 73.6m extrapolations**
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
GenGamma	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
LogLogistic	[redacted]	[redacted]	[redacted]	[redacted]
Lognormal	[redacted]	[redacted]	[redacted]	[redacted]

Bold indicates updated company base case

A4. Summary of updated OS and TD extrapolations with MAIA 73.6m data cut

In summary, incorporating the updated OS and TTD data from the MAIA 73.6m data into the economic model has resulted in:

- Maintaining OS Gompertz for DLd and Ld (based on current Committee preference)
    - Scenarios reflecting OS Exponential for DLd as best statistical fitting curve
- Change base case selection for DLd TTD from Gompertz to Generalised Gamma
    - Scenarios reflecting DLd Gompertz TTD as alternative clinically plausible curve
- Change base case selection for Ld TTD from Weibull to Generalised Gamma (based on best statistical fit)

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As noted above, the base case curve selection for Dld TTD and Ld TTD have been amended compared to the Company base case Post Technical Engagement, as per **Error! Reference source not found.** below. All other model inputs have remained as per the original submission.

Table 9: Summary of base case inputs applied in economic model (using MAIA 73.6m data cut)

	Post Technical Engagement Company base case survival inputs (MAIA 64.5m data cut)		Updated base case survival inputs (MAIA 73.6m data cut)	
	OS	**TTD**	**OS**	**TTD**
Extrapolation for DLd	Gompertz	Gompertz	Gompertz	Generalised Gamma
Extrapolation for Ld	Gompertz	Weibull	Gompertz	Generalised Gamma
Extrapolation for BMP	Gompertz	N/A (KM data)	Gompertz	N/A (KM data)

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Appendix B: Additional model details to replicate exploratory OS HR scenarios

This appendix contains additional details for the settings within the economic model for the scenarios presented in the main response.

	Scenario	**Apply treatment attenuation**	**Attenuation start point**	**Attenuation duration**	**User-specified HR at attenuation start point**	**User-specified target HR at end of attenuation duration**
		Settings, cell I52	**Settings, cell I69**	**Settings, I70**	**Settings, I72**	**Settings, I73**
Revised company base case	Independently fitted OS curves	No	N/A	N/A	N/A	N/A
1	Fixed OS HR from end of observed KM	Yes (user specified constant HR)	7.1 years (end of MAIA observed period)	N/A	0.42	N/A
2	Fixed OS HR from 12-year timepoint	Yes (user specified constant HR)	12-years	N/A	0.25*	N/A
3	Fixed OS HR from 15-year timepoint	Yes (user specified constant HR)	15-years	N/A	0.18	N/A
4	Reduced OS improvement until fix at 12 years	Yes (user specified varying HR)	7.1 years	4.9 years (until 12 years)	0.42	0.335 (applied from 12 years onwards) (0.42-((0.42-0.25)/2))
5, 5b	Attenuation scenarios: 12-19 years, 25% reduction	Yes (user specified varying HR)	12 years	7 years	0.25	0.4375 A 25% reduction in OS benefit is derived from: (0.25+ 25% of 0.75)
6,6b	Attenuation scenarios: 15-25 years, 25% reduction	Yes (user specified varying HR)	15 years	10 years	0.18	0.385 A 25% reduction in OS benefit is derived from: (0.18+ 25% of 0.82)
4a	Reduced OS improvement until fix at 12 years	Yes (user specified varying HR)	7.1 years	4.9 years (until 12 years)	0.35	0.26 (applied from 12 years onwards)

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						(0.35-((0.35-0.17)/2))
5a	Attenuation scenarios: 12-19 years, 25% reduction	Yes (user specified varying HR)	12 years	7 years	0.17	0.3775 A 25% reduction in OS benefit is derived from: (0.17 + 25% of 0.83 = 0.3775)
6a	Attenuation scenarios: 15-25 years, 25% reduction	Yes (user specified varying HR)	15 years	10 years	0.11	0.3325 A 25% reduction in OS benefit is derived from: (0.11 + 25% of 0.89 = 0.3325)

*In the model, the 'User specified HR at attenuation start point' ('Settings', cell I72) is equal to 'extrapolated HR at attenuation start point' ('Settings, cell I73) to avoid any errors in rounding

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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):	**Myeloma UK**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

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Name of commentator person completing form:	xxxxxxxx
Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	Myeloma UK is very disappointed that NICE did not recommend daratumumab plus lenalidomide and dexamethasone for newly diagnosed myeloma patients who are not eligible for high-dose therapy and stem cell transplantation (HDT-SCT) for routine commissioning. This treatment is a game-changer for HDT-SCT ineligible patients and has been available in the US and Europe for nearly four years. We ask that NICE invite clinical experts and Myeloma UK to the second committee meeting.
2	**We are concerned that the Committee did not fully consider the disparity in progression-free and overall survival between HDT-SCT-eligible and HDT-SCT-ineligible myeloma patients.** • Most myeloma patients are HDT-SCT ineligible. Around two-thirds of the people diagnosed with myeloma annually are ineligible for HDT-SCT due to old age, poor health, or frailty. • HDT-SCT ineligible patients have significantly lower remission times and overall survival rates than those eligible for HDT-SCT. • Although age, frailty and co-morbidities contribute to the difference in survival rates, the disparity in survival has increased in recent years as innovative treatments (e.g., DVTD induction) have become available to HDT-SCT eligible patients but not to HDT-SCT ineligible patients. References: *"The average remission times are approximately 4–5 years after transplant if maintenance lenalidomide is used, 2–3 years after transplant if no maintenance is used and 1–2 years if patients are not transplanted, although there is great variation in these outcomes." [Bird SA, Boyd K. Palliat Care Soc Pract. 2019; 13:1178224219868235.]* *The median overall survival of HDT-SCT eligible patients ranges from over 140 months to 42 months depending on stage at diagnosis. In HDT-SCT median overall survival ranges from 91 months to 22 months depending on stage at diagnosis. [*D'agostino M. et. al. Journal of clinical oncology. 2022; 40(29):3406.
3	**We are concerned that the Committee did not fully consider the significant patient benefit of increased progression-free survival.**

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	In the MAIA trial, daratumumab plus lenalidomide and dexamethasone delivers a median PFS of over five years. • DLd delivers over two years more remission time than the patients who received lenalidomide and dexamethasone experienced. • The remission times observed for DLd are comparable to the median overall survival times delivered in standard care. 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 completely disrupts the lives of patients and their families. • Symptoms increase (e.g., pain, fatigue). • Hospital visits and tests increase. • Switching treatments means adjusting to different side effects and new routines for hospital visits/treatment administration. • Uncertainty about the future, whether the new treatment will work and how well they will tolerate it. Reference: Draft guidance section 3.3 *"Median progression-free survival was 61.9 months in the daratumumab plus lenalidomide and dexamethasone (DLd) group and 34.4 months in the lenalidomide plus dexamethasone (Ld) group."* *"Median overall survival was not reached in the daratumumab plus lenalidomide and dexamethasone group and was 65.5 months in the lenalidomide plus dexamethasone group."*
2	**We are concerned that the Committee did not fully consider the importance of a quality first remission.** The first remission is often the deepest, longest remission and the period when a patient's quality of life is highest. Myeloma is a relapsing and remitting cancer where each additional line of treatment is associated with worse outcomes; remission times decrease, and side effects increase. Treatments often become less effective and harder to tolerate with every relapse. Over time, myeloma evolves, becoming more resistant to treatment, and patients get older, frailer and have more comorbidities. First remission is therefore widely held as the best opportunity to gain the best response with the longest time until disease progression. It is also the point in their disease where many patients will have the best quality of life post-diagnosis because their burden of treatment and illness is less than patients who are multiply relapsed. It is also important to note that not all patients receive treatments beyond first line. A real-world analysis of myeloma patient outcomes found that 95% of patients received first-line treatment, but only 61%, 38%, and 15% received second, third and fourth-line treatments, respectively.

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	Reference: Yong K. et. al. Br J Haematol. 2016; 175(2):252
3	**We disagree that the overall data is immature, and it is not clear what the threshold for maturity would be.** The median follow-up for the data submitted to the committee was 5.4 years (64.5 months). The follow-up is comparable to the median life expectancy for myeloma patients; the UK cancer registry shows that 52% of patients live for five years or more. Myeloma is an incurable, heterogeneous cancer with a continually evolving and changing treatment pathway; therefore, there will always be uncertainty. The treatment has been available in other countries for almost four years and was considered ineligible for the Cancer Drugs Fund. Reference: Office for National Statistics, Cancer survival by stage at diagnosis for England(link is external), 2019.

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Daratumumab with lenalidomide and dexamethasone for untreated multiple myeloma when stem cell transplant is unsuitable [ID4014]

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Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	UK Myeloma Society has received an unrestricted educational grant from Janssen-Cilag (£14,000 per annum). UK Myeloma Society has also received unrestricted educational grants from other pharmaceutical companies.

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Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	Attenuation of treatment effect. We state again that we think there is no case for treatment waning. The issue of "treatment waning" is not appropriate in the myeloma space, as discussed at several NICE HTA meetings. In the setting of the current appraisal, the question is why would you include treatment waning? What is the evidence to support its inclusion? There is no clinical evidence or even rational to include a segregated treatment waning effect on the experimental arm only, if it exists (and that is a big "if"), then it would impact both arms. Treatment waning starting at 12 years (for a period of 7 years) should not be included in this appraisal.
2	Subsequent treatments. Variation in subsequent treatments for patients in the MAIA clinical trial are expected in a large multi-national clinical trial, with different access to subsequent therapies. It is our view that these are generalisable to UK practice and represent the best available evidence.
3	Indirect comparison with Bortezomib Cyclophosphamide Dexamethasone (BCD). Cyclophosphamide is the alkylator of choice for outpatient treatment in the UK (rather than low dose Melphalan). It is our view that there is clinical equivalence of BCD with Bortezomib Melphalan Prednisolone (BMP). It is therefore appropriate to model using BMP, where there is more published comparative data.
4	
5	
6	

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EAG Response to Company Comments on Appraisal Consultation Document (ACD)

Produced by: Bristol Technology Assessment Group, University of Bristol

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

[redacted]

[redacted]

Abbreviations

Abbreviations	Definition
AIC	Akaike Information Criteria
BIC	Bayesian Information Criterion
BNF	British National Formulary
CMU	Commercial Medicines Unit
DBd	Daratumumab, Bortezomib, and Dexamethasone
DLd	Daratumumab with Lenalidomide and dexamethasone
DSU	Decision Support Unit
eMIT	electronic Market Information Tool
EAG	Evidence Assessment Group
HR	Hazard Ratio
IxaLd	ixazomib with lenalidomide and dexamethasone
ICER	Incremental Cost Effectiveness Ratio
IPCW	Inverse Probability of Censoring Weighting
IPD	Individual Participant Data
KM	Kaplan-Meier
Ld	Lenalidomide and dexamethasone
MAIC	Matching Adjusted Indirect Comparison
MM	Multiple Myeloma
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
OS	Overall Survival
PAS	Patient Access Scheme
QALY	Quality-Adjusted Life Year
TSD	Technical Support Document
TTD	Time To Treatment Discontinuation

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1 Introduction

This report provides the evidence assessment group (EAG) review of the additional evidence, analyses, and results provided by Janssen-Cilag Ltd (company) in response to the appraisal consultation document (ACD) for daratumumab with lenalidomide and dexamethasone (DLd) for untreated multiple myeloma (MM) when stem cell transplant is unsuitable. The company identified an error in a utility value and subsequently sent a corrected version of their consultation comments document and a corrected executable model which the EAG received on the 14/04/2023. The company sent a further updated consultation comments and model on 2/05/23 incorporating an updated patient access scheme (PAS) price for daratumumab, and it is this updated version that we review in this report.

2 Review of Company's Consultation Response

The company arranged their response into six issues which we review in turn below.

2.1 Additional data from MAIA on overall survival benefit of DLd

In their response to the ACD the company have provided updated results, based on a new data cut with a median follow up time of 73.6 months. The original company submission was based on a median follow up of 64.5 months. At the 64.5 months data cut the hazard ratio (HR) for overall survival (OS) benefit of Dld relative to Ld was 0.66 (95% CI: 0.53 to 0.83) and at 73.6 months data cut the HR is 0.65 (95% CI: 0.52 to 0.80). The company state that this supports "*the trend for an improved treatment effect with longer study follow-up with a lower HR and increased precision around the point estimate reflected by a narrower confidence interval.*" (Company response, page 4).

The EAG agree that the latest data cut demonstrates that the treatment effect of DLd compared with Ld is maintained for OS at 73.6 months median follow up. However, the EAG does not consider the results to support a trend for improved treatment effect - instead the estimated HR has remained stable with a small increase in precision. Note that the p-value ($p<0.0001$) reported in the company response document relates to the OS 73.6 months point estimate only and is not a test for a trend in improved treatment effect.

The company also provide updated OS extrapolations for DLd, using the 73.6 months data cut (Figure 1), together with model fit statistics for DLd and Ld (Table 1). The company note that the Exponential now gives the lowest AIC and BIC for DLd, and argues that although both Exponential and Gompertz distributions are clinically plausible, they consider the Gompertz to provide a conservative estimate of the survival benefits of DLd. The Gompertz still gives the lowest AIC and BIC for Ld. The company retain the Gompertz for both DLd and Ld in their base-case, but run a scenario analysis using the Exponential for DLd.

The EAG considers that there is still uncertainty as to the most appropriate distributions for extrapolation of OS. The EAG agree that the Exponential is preferred based on BIC (which tends to select simpler models), whereas there is very little to choose between the Exponential, Gompertz, Weibull, and Generalised Gamma, based on AIC (which tends to select more complex models) (Table 1). The EAG still prefers to use a common distribution for both treatments, as recommended in Decision Support Unit TSD14 unless there is a strong rationale otherwise. The Gompertz (used in the companys base-case) is the distribution with overall best fit across treatments and model fit measures and the EAG prefers this in its base-case, but agrees with the company that a scenario using the Exponential for DLd is clinically plausible.

FIGURE 1: EXTRAPOLATION OF OS FOR DLD USING IPD FROM MAIA 73.6M DATA CUT (WITH GENERAL POPULATION MORTALITY CAP) (REPRODUCED FROM FIGURE 2 OF COMPANY RESPONSE)

TABLE 1: GOODNESS-OF-FIT STATISTICS FOR DLD, AND LD OS SURVIVAL MODELS (REPRODUCED FROM TABLE 3 IN COMPANYS CONSULTATION COMMENTS)

Survival model	DLd		Ld	
	AIC	BIC	AIC	BIC
Exponential	1804.1	1808.0	2,264.7	2,268.6
Weibull	1805.9	1813.7	2,254.3	2,262.1
Loglogistic	1811.6	1819.4	2,262.9	2,270.7
Lognormal	1831.6	1839.5	2,287.5	2,295.3
Generalised gamma	1804.3	1816.0	2,253.9	2,265.6
Gompertz	1805.3	1813.1	2,251.9	2,259.7

Bold indicates lowest AIC/BIC value
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; BMP: bortezomib, melphalan and prednisone; DLd: daratumumab, lenalidomide and dexamethasone; Ld: lenalidomide and dexamethasone; OS: overall survival.

2.2 Additional data from MAIA on time to treatment discontinuation (TTD)

The company provide updated time to treatment discontinuation (TTD) extrapolations using the 73.6 months data cut (Figure 2 and Figure 3), together with model fit statistics (Table 2). The company note that for DLd both AIC and BIC are lowest for the Generalised Gamma followed by the Gompertz, and so they now use the Generalised Gamma in their base-case with a scenario using the Gompertz. For Ld, the company also prefer the Generalised Gamma, which gives the lowest AIC, but note that extrapolations for Ld are not sensitive to the choice of distribution.

The EAG agree with the company that the 73.6 months data cut provides support for the Generalised Gamma over the Exponential (previously used in the EAG base-case) for DLd. The EAG notes that visually the extrapolation of the Generalised Gamma has a steep trajectory, and that the Gompertz may also be plausible based on statistical and visual fit. The EAG considers that there is still uncertainty in the extrapolation of TTD for DLd, but that the Generalised Gamma (used in the company's base-case) is the distribution with overall best fit across treatments and model fit measures. Note however, that based on the Generalised Gamma, there are no patients still taking DLd after 10 years, which may have implications for the plausibility of extrapolations for OS.

FIGURE 2: EXTRAPOLATION OF TTD FOR DLD USING IPD FROM MAIA 73.6M DATA CUT (REPRODUCED FROM FIGURE 4 IN COMPANYS CONSULTATION COMMENTS)

FIGURE 3: EXTRAPOLATION OF TTD FOR LD USING IPD FROM MAIA 73.6M DATA CUT (REPRODUCED FROM FIGURE 5 IN COMPANYS RESPONSE)

Abbreviations: Ld: lenalidomide and dexamethasone; IPD: individual patient data; KM: Kaplan-Meier TTD: time to discontinuation.

TABLE 2 GOODNESS-OF-FIT STATISTICS FOR DLD AND LD TTD SURVIVAL MODELS USING MAIA 73.6M DATA CUT (REPRODUCED FROM TABLE 1 IN COMPANYS RESPONSE)

Survival model	DLd		Ld	
	AIC	BIC	AIC	BIC
Exponential	2623.9	2627.8	2963.3	2967.2
Weibull	2625.4	2633.2	2963.6	2971.4
Loglogistic	2649.5	2657.3	3001.5	3009.3
Lognormal	2679.8	2687.6	3030.5	3038.3
Generalised Gamma	2614.0	2625.7	2961.2	2972.9
Gompertz	2619.2	2627.0	2965.2	2973.0

2.3 Long-term extrapolation of OS treatment effect

The extrapolations for OS in the company's base-case model imply that the HR for DLd vs Ld continues to fall over time from around 0.4 at the end of MAIA to below 0.1 by 23 years. The company argue that this is plausible based on the deep and durable responses to DLd seen in MAIA (measured by minimal residual disease). They provide an updated piecewise Cox analysis of the MAIA study based on the 73.6 months data cut, which they argue supports the continued reduction in the HR (Table 3).

The EAG agree that DLd is clinically effective, that the survival benefit of DLd over Ld is maintained into the long-term, and that the depth and durability of response may mediate the long-term survival benefit. However, the EAG does not believe that the data from MAIA support the HR continuing to decrease into the long term. Error! Reference source not found. shows the HR up to different follow-up times, and whilst these initially decline, they are relatively stable beyond 60 months. These are cumulative HRs rather than piecewise HRs, but we would expect the piecewise HRs to show the same pattern.

Table 3 Updated piecewise Cox analysis of MAIA OS data (73.6m) over time (reproduced from table 2 of companys consultation comments)

MAIA Follow up duration (months)	OS HR	95% CI	P value
≤6	[redacted]	[redacted]	[redacted]
≤12	[redacted]	[redacted]	[redacted]
≤18	[redacted]	[redacted]	[redacted]
≤24	[redacted]	[redacted]	[redacted]
≤30	[redacted]	[redacted]	[redacted]
≤36	[redacted]	[redacted]	[redacted]
≤42	[redacted]	[redacted]	[redacted]
≤48	[redacted]	[redacted]	[redacted]
≤54	[redacted]	[redacted]	[redacted]
≤60	[redacted]	[redacted]	[redacted]
≤66	[redacted]	[redacted]	[redacted]
≤72	[redacted]	[redacted]	[redacted]
≤78	[redacted]	[redacted]	[redacted]
≤84	[redacted]	[redacted]	[redacted]

The company acknowledge the inherent uncertainty in the extrapolation of the treatment effect, and provide a range of scenario analyses to explore different assumptions on the HR beyond the end of MAIA (Company Consultation Comments, Table 3), displayed graphically in Figure 5. The company's base-case assumes that the HR continues to fall (bottom curve), and scenarios are provided for the HR stabilising at different points in the curve (Scenarios 1-3), falling at a reduced rate before stabilising (Scenario 4), or increasing before stabilising (Scenarios 5-6).

The EAG consider scenarios 1 and 4 to be most plausible based on the updated data from MAIA (Figure 1, Table 3), which supports a stabilisation of the HR (Scenario 1) or at the most a small reduction in the HR (Scenario 4). Given that no patients remain on DLd beyond 10 years under the company's preferred assumptions for TTD (Figure 2), stabilisation of the HR by 12 years (as in Scenario 4) is considered by the EAG to be optimistic. The EAG prefers Scenario 1 in its updated base-case, with Scenario 4 as the most optimistic plausible scenario.

Figure 4: Visual representation of scenarios exploring modelled OS HRs over time (reproduced from Figure 6 Company's Consultation Comments)

2.4 Inclusion of treatments only available through the Cancer Drugs Fund

All scenarios in the updated company base case include 'DBd at 2nd line and ixazomib with lenalidomide and dexamethasone (IxaLd) at 3rd line in the economic model.

The EAG agrees that IxaLd should be included in the model at 3rd line following the publication of NICE guidance for treating relapsed or refractory multiple myeloma (TA870), and includes it in the EAG updated base-case.

The EAG has been advised by NICE to include daratumumab plus bortezomib and dexamethasone at 2nd line (ID4057- ongoing), and it is included in the EAG updated base-case.

2.5 Generalisability of subsequent treatments in MAIA compared to UK clinical practice

The company consultation comments note that the EAG considered the unadjusted results from MAIA, as reported in the original company submission, to be conservative compared to the IPCW analysis. The IPCW analysis was conducted to adjust for subsequent treatments not routinely available in England. As part of their consultation response, the company have updated their IPCW analysis to include ixazomib plus lenalidomide and dexamethasone at

3rd line (TA870) and daratumumab plus bortezomib and dexamethasone at 2nd line (ID4057-ongoing). The updated IPCW HR for OS is [redacted] and the EAG agree with the company that the unadjusted results from MAIA remain a conservative estimate.

The EAG have not been able to verify the proportion (75%) reported in the company consultation comments receiving a bortezomib based regimen following DLd at 1st line. Based on the subsequent treatment data provided to the EAG after clarification, we calculate that after receiving DLd at 1st line, [redacted] (64%) of patients received a bortezomib based regimen at 2nd line and [redacted] (23%) at 3rd line (after first receiving daratumumab). On the basis of the data available, the EAG cannot confirm if any patients received a bortezomib based regimen at both 2nd and 3rd line. However, we agree with the company that, for patients initially treated with DLd, the majority of regimens administered at 2nd or 3rd line were bortezomib-based.

2.6 Additional benefits not captured in the QALY framework and decision-making uncertainty

The company highlight areas where their latest data cut from MAIA and their additional scenarios have reduced decision uncertainty, specifically the uncertainty around the extrapolation of OS, the extrapolation of the treatment effect (HR) for OS, and the extrapolation of time until treatment discontinuation on DLd.

The EAG agree that the additional data from MAIA has been helpful to identify the most plausible assumptions. The EAG accept the company's revised assumptions on time to treatment discontinuation, but consider that the updated data support a stabilised HR (Scenario 1) rather than a continued reduction in the HR as in the companys base-case.

The company note several areas where there are additional benefits of DLd that are not captured by the QALY framework:

- Reduction in anxiety associated with relapse
- Reduction in burden of carers due to the reduction in the rate of deterioration of the disease
- Resolving inequity in access to effective treatments between transplant-eligible and transplant ineligible patients
- Enabling enrolment into future clinical trials for therapies whose marketing authorisations will specify anti-CD38 exposure

The EAG agrees that these benefits are not captured in the company's existing model, although notes that the top two points could have been modelled by the company and the fourth is speculative.

3 EAGs Preferred Assumptions

The EAG checked the company's model, and noted that the company uses an updated method to calculate subsequent treatment costs from their original submission. This differs from the cost calculation method and formulas used by the EAG, and a different estimate is calculated for third-line PBd treatment. However, both the EAG and company's methods produce similar estimates for second- and third-line treatment acquisition costs. The EAG prefers to include its calculations to avoid rounding errors, although acknowledge that differing methodology does not make a big difference to the ICERs.

The EAG updated its preferred base-case using the MAIA 73.6m data cut, adopting the Generalised Gamma distribution for TTD for both DLd and Ld (as in the company base-case), including IxaLd at 3L and DBd at 2L, and assuming Scenario 1 for the extrapolation of the OS HR (Figure 4). The EAGs updated base-case therefore differs from the company's updated base-case in the correction to the subsequent treatment cost calculations and the assumption for extrapolating the HR for OS.

4 Results

The company's updated model results are given in Table 5 of the company's consultation comments document, which include an [redacted] PAS. The key results are reproduced in Table 4, together with the EAG's preferred assumptions (EAG updated base-case).

TABLE 4: UPDATED DETERMINISTIC COST-EFFECTIVENESS RESULTS (GOMPERTZ OS, WITH [redacted] PAS) FOR THE COMPANY'S UPDATE BASE-CASE AND KEY SCENARIOS (REPRODUCED FROM TABLE 5 OF COMPANY'S CONSULTATION COMMENTS). THE EAG'S UPDATED DETERMINISTIC BASE-CASE IS ALSO GIVEN ALONG WITH THE COMPANYS UPDATED BASE-CASE AND SCENARIO 4 WITH CORRECTED SUBSEQUENT TREATMENT COSTS.

SCENARIO		INC. COSTS	INC. QALYS	ICER
Company Revised Base case using updated MAIA data (73.6m data)				
• Incorporating updated MAIA 73.6m OS and TTD data • Generalised Gamma for DLd TTD and Ld TTD		[redacted]	[redacted]	[redacted]
Additional scenarios (applied to the company revised base-case)				
DLd OS exponential (best statistical fit)		[redacted]	[redacted]	[redacted]
DLd TTD Gompertz		[redacted]	[redacted]	[redacted]
Additional exploratory OS HR scenarios (applied to the company revised base-case)				
1	Fixed OS HR from end of observed KM	[redacted]	[redacted]	[redacted]
2	Fixed OS HR from 12-year timepoint	[redacted]	[redacted]	[redacted]

3	Fixed OS HR from 15-year timepoint	[redacted]	[redacted]	[redacted]
4	Reduced OS improvement until fix at 12-years	[redacted]	[redacted]	[redacted]
5	Attenuation scenarios: 12-19 years, 25% reduction	[redacted]	[redacted]	[redacted]
6	Attenuation scenarios: 15-25 years, 25% reduction	[redacted]	[redacted]	[redacted]
EAG Scenarios				
Company Revised Base-Case • Correcting subsequent treatment cost calculations		[redacted]	[redacted]	[redacted]
Company Revised Base case • Fixed OS HR from end of observed KM (Scenario 1) • Correcting subsequent treatment cost calculations		[redacted]	[redacted]	[redacted]
Company Revised Base case • Reduced OS improvement until fix at 12-years (Scenario 4) • Correcting subsequent treatment cost calculations		[redacted]	[redacted]	[redacted]
EAG Updated Base-Case				
• Incorporating updated MAIA 73.6m OS and TTD data • Generalised Gamma for DLd TTD and Ld TTD • Fixed OS HR from end of observed KM (Scenario 1) • Correcting subsequent treatment cost calculations		[redacted]	[redacted]	[redacted]

The probabilistic results for the Company's updated base-case are provided in Table 6, Figure 7, and Figure 8 of the Company's Consultation Comments document.

The probabilistic results for the EAGs updated base-case are provided in Table 5, and Figure 5.

TABLE 5 DETERMINISTIC AND PROBABILISTIC PAIRWISE ANALYSES BETWEEN DLD AND LD - EAG BASE CASE WITH UPDATED [redacted]

Technologies	Total costs (£)	Total QALYs	Inc. costs (£)	Inc. QALYs	ICER (£/QALY)
Deterministic					
DLd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ld	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Probabilistic					
DLd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ld	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

FIGURE 5 INCREMENTAL COST-EFFECTIVENESS PLANE DLD VS LD - EAG BASE CASE WITH UPDATED [redacted]

Results with PAS prices for Carfilzomib, Pomalidomide, Panobinostat, and Ixazomib, together with Commercial Medicines Unit (CMU) price for Melphalan (CS uses British National Formulary (BNF) price), and electronic Market Information Tool (eMIT) price for Cyclophosphamide (CS uses BNF price) are provided in a confidential appendix.

5 References

Latimer N. NICE DSU Technical Support Document 14: Undertaking survival analysis for economic evaluations alongside clinical trials - extrapolation with patient-level data. 2011. https://www.sheffield.ac.uk/nice-dsu/tsds/survival-analysis