NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Daratumumab in combination for untreated multiple myeloma when stem cell transplant is suitable [ID1510]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Daratumumab in combination for untreated multiple myeloma when stem cell transplant is suitable [ID1510]

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3. **Consultee and commentator comments on the Appraisal Consultation Document** from:
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5. **Evidence Review Group critique of company comments on the ACD**

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

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Single Technology Appraisal

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

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	NICE Response
1	Clinical Expert	NHS consultant	Iam concerned whether robust process has been followed here. Committee has requested further modelling including lenalidomide maintenance. Lenalidomide maintenance guidance was issued on 1st March 2021. The committee had over 6 weeks to decide if this had to be incorporated in the model before the papers were sent out end of April 2021 for the appraisal meeting. In addition new maintenance therapies are in development including one within the current trial that is being considered within this appraisal (CASSIOPEIA) which may be considered by NICE in the next 6-12 months. As induction and maintenance therapies are developed separately in trials, the current interpretation induces undue penalty on induction regimens that would be considered for myeloma.	Thank you for your comment. The committee acknowledged that there is no direct evidence of daratumumab followed by lenalidomide maintenance but noted that lenalidomide is now widely used in NHS practice. Given its use in NHS practice the committee would prefer a scenario is presented that includes both the costs and benefits of lenalidomide. See sections 3.5 and 3.16 of the ACD.
2	Clinical Expert	NHS consultant	3.2 Iam concerned that Bortezomib and dexamethasone is considered as a comparator when in clinical practice only handful of patients will have this induction (i.e bad neuropathy). NHSE dataset should be able to validate this statement.	Thank you for your comment. The committee discussed several potential comparators including bortezomib and dexamethasone but concluded bortezomib plus thalidomide and dexamethasone is the most relevant comparator. See section 3.3 of the ACD.
3	Clinical Expert	NHS consultant	3.14 Treatment waning is not observed during 10-year actual follow up in the GIMEMA trial considered by NICE TA311 and approve VTD. It is hard to conceive how treatment waning would happen within this time frame when clinical outcomes (ORR, PFS) for DVTD are better than VTD	Thank you for your comment. Based on the evidence presented to it the committee concluded that it had not seen enough evidence to

Comment number	Type of stakeholder	Organisation name	Stakeholder comment	NICE Response
				support changing its original conclusion that the treatment effect of daratumumab would likely last 10 years or less after consolidation. See section 3.15 of the ACD.
4	Clinical Expert	NHS consultant	3.15 PHE datasets do not reflect the actual patients transplanted, often patients over 65 experience toxicities during induction and don't get to transplant. Therefore the median age at transplant is often 65 as in Myeloma XI trial.	Thank you for your comment. The company revised its base case for the second committee meeting to include a mean age at the start of induction from the Public Health England data. See section 3.17 of the ACD.
5	Consultee	UK MYELOMA FORUM (UKMF)	We are concerned that subsequent therapy change (Lenalidomide maintenance) is impacting on ability to appraise induction regimens for myeloma. Whilst we recognise the modelling assumptions do change, so do Maintenance regimens, which change with time and several are under investigation including Daratumumab within the Cassiopeia trial and Ixazomib. This interpretation could significantly impact new induction regimens for myeloma considered by NICE and unintentionally favours maintenance therapy appraisal.	Thank you for your comment. The committee acknowledged that there is no direct evidence of daratumumab followed by lenalidomide maintenance but noted that lenalidomide is now widely used in NHS practice. Given its use in NHS practice the committee would prefer a scenario is presented that includes both the costs and benefits of lenalidomide. See sections 3.5 and 3.16 of the ACD.
6	Consultee	UK MYELOMA FORUM (UKMF)	Treatment pathway, 3.2. Bortezomib in combination with thalidomide or cyclophosphamide are both appropriate and widely used in clinical practice. The committee stated that bortezomib dexamethasone should also be used as comparator. Whilst this is in keeping with NICE guidance (TA311) this does not reflect clinical practice. Treating clinicians would always prefer to give a 3 rather than 2 drug combinations to improve depth of response and outcomes. This data should be available from NHSE SACT datasets.	Thank you for your comment. The committee discussed several potential comparators including bortezomib and dexamethasone but concluded bortezomib plus thalidomide and dexamethasone is the most relevant comparator. See section 3.3 of the

Comment number	Type of stakeholder	Organisation name	Stakeholder comment	NICE Response
				ACD
7	Consultee	UK MYELOMA FORUM (UKMF)	Treatment waning 3.14. This is difficult due to the lack of long-term data (i.e > 5 yrs) with Daratumumab in the frontline setting. Patients receiving transplants are younger and fitter. Published data with BTd compared to Td, with a 10 year median follow up, (Lancet Haematol 2020; 7: e861–73) shows a sustained effect of BTd therapy at 10 years. It is conceivable that the improved MRD rate seen with the addition of Daratumumab (D-BTd) may show similar (if not better) improvements at 10 years. We therefore think that if treatment waning were to occur this would be beyond 10 years, and not at 5 years as suggested.	Thank you for your comment. Based on the evidence presented to it the committee concluded that it had not seen enough evidence to support changing its original conclusion that the treatment effect of daratumumab would likely last 10 years or less after consolidation. See section 3.15 of the ACD.
8	Consultee	Myeloma UK	*Has all of the relevant evidence been taken into account?* We are not aware of any omissions in the evidence base.	Thank you for your comment. No action required
9	Consultee	Myeloma UK	*Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?* Partly. As set out in our evidence submission there remains a significant unmet need for myeloma patients eligible for stem cell transplant, who need more effective treatments that will induce a longer and more durable period of remission. We therefore note and welcome the Committee's findings that: •patients with untreated multiple myeloma would welcome a new first-line treatment option. •daratumumab, bortezomib, thalidomide and dexamethasone (DVTD) improve progression-free and overall survival. •the adverse event profile of DVTD is acceptable. • minimal residual disease (MRD) negativity is likely to better predict survival outcomes than conventional response. •patients who are MRD negative would have a complete response over time. •clinical consolidation can be easily adapted into NHS practice. We particularly welcome the ACD finding that it has been established in clinical practice that MRD negativity is associated with better progression-free survival and overall survival. Our main concern is around the Committee's request that lenalidomide maintenance should be incorporated into the economic model. We are concerned at this inclusion given that lenalidomide maintenance was not included in the final scope for this appraisal and was therefore not part of the appraisal that the company and other consultees were asked to submit evidence on as part of the decision problem. We recognise the committee's desire to reflect real world practice in its deliberations but comment that there is a	Thank you for your comments. Please see responses to individual issues below. <u>Lenalidomide maintenance:</u> Clinical and patient experts were invited to attend the second committee meeting to provide their insight and experience relating to this issue and other issues discussed at the meeting. The committee noted that lenalidomide is now widely used in NHS practice. Given its use in NHS practice the committee would prefer a scenario is presented that includes both the costs and benefits of lenalidomide. See sections 3.5 and 3.16 of the ACD.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment	NICE Response
			balance to be struck between this and preserving the integrity of the appraisal process (as is recognised in other elements of NICE methods and process, e.g., the exclusion of CDF treatments from appraisals as comparators.) We therefore have questions about the fairness of introducing lenalidomide maintenance into consideration at this stage. **Given the significance of introducing new data and modelling on lenalidomide maintenance we think it essential that clinical and patient experts be invited to attend the second Committee meeting.** We believe that potentially widening the scope of the decision problem merits expert attendance. For example, there are important patient insight and experience issues relating to the duration of treatment with lenalidomide maintenance, including the reasons why a patient may not wish to continue with lenalidomide maintenance to progression. Patients, in consultation with their clinician, may wish to stop maintenance treatment with lenalidomide before they become refractory in order to be able to access combinations including lenalidomide later in the pathway, or they may wish to take a treatment break for other reasons. (Current clinical trials are researching whether maintenance can be stopped after two years (SWOG and GMMG-MM5 trial) or even adjusted based on MRD status (OPTIMUM Trial)). Further to this, we know from engagement with our patients that a treatment free period is highly valued by patients. If DVTD, with associated deeper response, was offered as induction and consolidation for patients eligible for ASCT, some patients may choose not to receive lenalidomide maintenance in order to have an extended treatment free period. Finally, we recognise that there are a range of concerns around modelling and uncertainty on issues such as treatment effect waning and overall survival (OS). We do not intend to comment on each of these in detail, other than to emphasise. as we have in other appraisals, that it is increasingly challenging to deliver OS within the timelines of a clinical trial and that this fact must not prevent patients from accessing the most promising new treatments. The CDF is the key policy mechanism for delivering access to treatments in this category and we are therefore obviously disappointed that this does not seem to be an option that will help resolve the key uncertainties for DVTD. Despite this we hope that all avenues will be explored by the company, NICE and NHS England to enable a positive recommendation, whether those be methodological or commercial.	<u>Modelling overall survival:</u> NICE recognise that modelling is usually required to extrapolate costs and health benefits over an extended time horizon. See section 5.7 of the NICE Guide to the methods of technology appraisal 2013.
10	Consultee	Myeloma UK	*Are the recommendations sound and a suitable basis for guidance to the NHS?* For the reasons set out above, particularly around the inclusion of lenalidomide maintenance in the appraisal, no.	Thank you for your comment. See the NICE response to comment number 9.
11	Consultee	Myeloma UK	*Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?* We agree with the Committee's position that DVTD should not be restricted to patients under the age of 65 despite this being criteria within the CASSEIOPIA trial.	Thank you for your comment. No action required

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<tr><th>Comment number</th><th>Type of stakeholder</th><th>Organisation name</th><th>Stakeholder comment</th><th>NICE Response</th></tr>
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<tr><td>12</td><td>Consultee</td><td>Janssen-Cilag Limited</td><td>
The committee agreed that the results of the landmark analysis were likely biased because of informative censoring. However, it deemed that the direction of the bias was unclear because it affected both treatment arms. The committee concluded that the company's censoring approach had limitations, and that its effect on the results of the landmark analysis was uncertain."
The updated landmark analysis submitted as part of Janssen's technical engagement response applied a censoring approach to patients re-randomised to daratumumab maintenance therapy. This was because Janssen did not have access to patient-level data for patients re-randomised to daratumumab maintenance therapy. As such, it was not possible to perform an adjusted landmark analysis similar to the prespecified inverse probability weighting (IPW) PFS and OS analysis performed for the intention-to-treat (ITT) population. Whilst the number of patients re-randomised on both arms was high, Janssen acknowledge the risk of selection bias that may have been introduced because patients with less than a partial response were not subject to re-randomisation.
To address the AC's concern regarding potential bias and uncertainty in the landmark analysis results, Janssen has now been able to perform an inverse probability censoring weights (IPCW) adjusted landmark analysis (on the August 2020 datacut) following recent publication of the CASSIOPEIA Part 2 results, [redacted].[i] Further detail of the IPCW methodology is provided in Appendix A.
A comparison of the Cox proportional hazard model results for PFS and OS from the original, updated and revised (IPCW adjusted) landmark analysis is presented in Table 1. The Kaplan-Meier plots for the revised landmark analysis (PFS and OS), along with the associated tests for proportional hazards, are included in Appendix B and Appendix C respectively.
Table 1: Cox proportional hazard model results
<table>
<tr><th></th><th>Original landmark analysis (median follow-up = 29.2 months)</th><th>Updated landmark analysis (median follow-up = 44.5 months, censoring for maintenance)</th><th>Revised IPCW adjusted landmark analysis (median follow-up = 44.5 months)</th></tr>
<tr><td>PFS</td><td></td><td></td><td></td></tr>
<tr><td>DBTd MRD+ versus BTd MRD+ HR (95% CI)</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>n/N (%)</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>DBTd MRD- versus BTd MRD-) HR (95% CI)</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>n/N (%)</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
</table>
</td><td>Thank you for your comment. The committee concluded that the company's IPCW-adjusted landmark analysis was likely less biased than the censoring-adjusted landmark analysis and more appropriate for decision making, but that residual confounding may remain. See section 3.7 of the ACD.</td></tr>
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Comment number	Type of stakeholder	Organisation name	Stakeholder comment	NICE Response
			[redacted]	
			OS	
			DBTd MRD+ versus BTd MRD+ HR (95% CI)	
			n/N (%)	
			DBTd MRD- versus BTd MRD-) HR (95% CI)	
			n/N (%)	
			Key: CI = confidence interval; BTd = bortezomib, thalidomide and dexamethasone; DBTd = daratumumab, bortezomib, thalidomide and dexamethasone; HR = hazard ratio; IPCW = inverse probability censoring weights; MRD = minimal residual disease; n = number of events; OS = overall survival; PFS = progression-free survival.	
			Whilst results from the revised IPCW adjusted landmark analysis are broadly comparable to the censoring approach for PFS, there is variability shown for OS with a stronger depth of response effect (and marginally reduced confidence interval) for MRD-positive patients, and a weaker effect (and wider confidence interval) for MRD-negative patients. Janssen note however that the overall impact on the ICER is negligible, increasing from £17,957[1] per quality adjusted life year (QALY) to £18,694 per QALY (applying base case settings per technical engagement, Gompertz for PFS and exponential for OS BTd MRD-positive extrapolations).	
13	Consultee	Janssen-Cilag Limited	**Daratumumab 'treatment effect' waning** *"[The committee] considered that the daratumumab treatment effect was likely to decline gradually over time, but the timepoints at which this decline would start and finish were highly uncertain. The committee concluded that treatment effect waning should be included in the model, but that the duration of the daratumumab treatment effect was highly uncertain. The committee considered it reasonable to consider scenarios with a treatment effect lasting 5 and 10 years after consolidation therapy."* Janssen acknowledge the relative immaturity of survival data from CASSIOPEIA in the context of modelling survival outcomes over a lifetime time-horizon. That said, results from the original, updated and revised (IPCW adjusted) landmark analyses, consistently demonstrate a depth of response effect in favour of DBTd with no evidence to suggest a possible waning of effect over time with median follow-up approaching 4 years. This is compelling, since DBTd is a fixed treatment of 6 cycles; meaning that patients will have received no active	Thank you for your comment. Based on the evidence presented to it the committee concluded that it had not seen enough evidence to support changing its original conclusion that the treatment effect of daratumumab would likely last 10 years or less after consolidation. See section 3.15 of the ACD.

[1] Note, a formula error of median treatment duration used in the calculation of subsequent therapy costs was identified in the economic model submitted during technical engagement. Correcting for this error, the technical engagement base case is £17,704.

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treatment for ~3 years and yet no waning of effect has been observed.

During technical engagement Janssen presented wider contextual evidence from CASSIOPEIA that supports maintenance of a depth of response effect favouring DBTd versus BTd in the long-term, with an almost doubling of MRD negative response rates at a deeper sensitivity threshold of 10^{-6} using Next Generation Sequencing (NGS 10^{-6}: 39.1% vs 22.8%; OR: 2.18; 95% CI: 1.58, 3.01; p<0.0001),[ii] higher rates of sustained MRD negativity, more pronounced deepening of response rates over time, and higher rates of MRD negativity conversion. These data reflect daratumumab's unique mechanism of action which is to modulate the body's own immune system to better fight the disease.[iii] Furthermore, PFS2 results continue to demonstrate the lasting benefit of upfront daratumumab exposure beyond progression. PFS2 results were broadly consistent before and after adjusting to exclude patients re-randomised to daratumumab maintenance with a [redacted] reduction in the risk of progression or death on next line of therapy after median follow-up of 44.5 months.

Janssen also presented recently published results from the GIMEMA study after 10-years median follow-up which further supports maintenance of a treatment effect driven by deeper responses with no evidence of treatment effect waning for bortezomib, thalidomide and dexamethasone (BTd) versus thalidomide and dexamethasone (Td).[iv] As such, Janssen consider the waning effect scenarios at 5- and 10-years for DBTd presented as scenarios in the company's original submission to be both highly conservative and not evidence-based.

Nonetheless, to explore uncertainty further, and considering the AC's preferred modelling assumption of a treatment effect for daratumumab lasting 5- to 10-years after consolidation, Janssen has updated the cost-effectiveness model to include a scenario that assumes a gradual waning of effect at a constant rate between 5- and 10-years and also a treatment effect lasting 7.5 years representing the 5- and 10-year mid-point. Results from these analyses, along with the original scenario analysis, are presented in Table 2.

Table 2: Treatment effect waning scenarios (with PAS)
<table>
<tr><th>Scenario</th><th>Inc. costs</th><th>Inc. QALYs</th><th>ICER (£ per QALY)</th></tr>
<tr><td>Updated IPCW adjusted landmark analysis (with PAS)</td><td>[redacted]</td><td>[redacted]</td><td>£18,694</td></tr>
<tr><td>No additional treatment effect of DBTd after 5 years (MRD+ and MRD-)</td><td>[redacted]</td><td>[redacted]</td><td>£36,752</td></tr>
<tr><td>No additional treatment effect of DBTd after 10 years (MRD+ and MRD-)</td><td>[redacted]</td><td>[redacted]</td><td>£25,185</td></tr>
<tr><td>Gradual waning of treatment effect of DBTd between 5- and 10-years (MRD+ and MRD-)</td><td>[redacted]</td><td>[redacted]</td><td>£29,793</td></tr>
<tr><td>No additional treatment effect of DBTd after 7.5</td><td>[redacted]</td><td>[redacted]</td><td>£29,354</td></tr>
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Comment number	Type of stakeholder	Organisation name	Stakeholder comment	NICE Response
			years (MRD+ and MRD-) | | | | Key: DBTd = daratumumab, bortezomib, thalidomide and dexamethasone; ICER = incremental cost-effectiveness ratio; Inc. = incremental; IPCW = inverse probability censoring weights; MRD = minimal residual disease; PAS = patient access scheme; QALY = quality-adjusted life year. These results indicate that DBTd remains a cost-effective use of NHS resources under all scenarios except the highly conservative 5-year treatment waning. Given the broader contextual evidence from CASSIOPEIA supporting deeper and more sustained responses for DBTd, along with external evidence from the GIMEMA study with 10-years median follow-up, Janssen does not consider 5-year treatment waning to be clinically plausible. Indeed, a 5-year treatment waning scenario was not supported by clinical experts at the first appraisal committee meeting.	
14	Consultee	Janssen-Cilag Limited	**Lenalidomide maintenance** *"The clinical experts explained that lenalidomide maintenance was now widely used in clinical practice and this was likely to increase in future. The clinical lead for the Cancer Drugs Fund stated that adding daratumumab to induction (and consolidation) treatment would likely increase the duration of lenalidomide maintenance. The effect of including lenalidomide maintenance on the cost effectiveness of daratumumab plus bortezomib, thalidomide and dexamethasone was therefore unclear. The committee concluded that a scenario analysis incorporating lenalidomide maintenance as a subsequent treatment should be provided to represent current NHS clinical practice."* The standard NICE process set out in the 'Guide to the processes of technology appraisal' (the Guide) emphasises the importance of the final scope.[v] The final scope, as specified in the Guide, provides a framework for the appraisal by defining important aspects including the population, intervention and comparators of interest following extensive consultation with relevant stakeholders including the manufacturer and NHS England. Janssen understand that the NICE appraisal process operates within an external environment and treatment landscape that is constantly evolving, particularly in this disease area. Given this changing landscape, Janssen appreciate the final scope as defined by NICE to provide a 'true north' and relevant point of reference throughout the appraisal process. In line with section 2.1.2 of the Methods Guide, we understand the scope to establish the boundaries of the work that is required to demonstrate the case for cost effectiveness for the appraisal committee.[vi] Lenalidomide maintenance is considered a front-line therapy, albeit subsequent to induction/ASCT/consolidation. Lenalidomide maintenance was not recommended by NICE for routine commissioning until after the company submission, and post technical engagement with the ERG and NICE technical team. Indeed, were it not for the fact that the first appraisal committee meeting was delayed 2-months due to the impact of COVID-19 on NICE capacity, lenalidomide maintenance would not have been recommended at the time of the committee meeting. Changes in the external environment after the final scope has been defined are not generally considered relevant for decision making. As such, Janssen notes that the AC's request for a scenario analysis incorporating lenalidomide maintenance is somewhat off process. Moreover, inclusion of a treatment pathway change at this stage of the appraisal is highly challenging.	Thank you for your comment. The committee acknowledged that there is no direct evidence of daratumumab followed by lenalidomide maintenance but noted that lenalidomide is now widely used in NHS practice. Given its use in NHS practice the committee would prefer a scenario is presented that includes both the costs and benefits of lenalidomide. See sections 3.5 and 3.16 of the ACD

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Several studies have been published investigating the synergistic immune-mediated relationship between daratumumab and IMiDs (such as lenalidomide).[vii,viii,ix,x,xi] To summarise, daratumumab increases the number of cytotoxic T cells upon which IMiDs act. As such, it may reasonably be assumed that lenalidomide maintenance therapy will be more efficacious post DBTd than post BTd. From a modelling perspective, however, Janssen is not aware of any clinical evidence (RCT or observational real-world studies) to explicitly inform the efficacy of lenalidomide maintenance following daratumumab. Nonetheless, to help address the AC's concern that patients may stay on lenalidomide maintenance longer following daratumumab, Janssen has performed a highly conservative scenario analysis incorporating <u>the costs of lenalidomide maintenance with no consideration of improved clinical outcomes.</u> For this analysis, Janssen has used time to treatment discontinuation (TTD) data from the Myeloma XI study which was the main source of clinical evidence in NICE TA680.[xii] Specifically, Janssen consider a scenario where the median TTD from Myeloma XI (in the transplant-eligible subgroup) is assumed for both arms ([redacted] months equivalent to ~[redacted] model cycles), and also a scenario which assumes treatment duration of lenalidomide following BTd and DBTd is in line with the observed ratio between median TTD and PFS (57 months) for the transplant-eligible subgroup from Myeloma XI.[xiii,xiv] Costs are then calculated in the model based on a 28-day dosing schedule, with treatment administered at 10 mg per day on days 1 - 21 (in line with recommended NICE guidance)[vii] and applying an exponential distribution, thereby assuming a constant rate of treatment discontinuation. Janssen is aware of the imminent patent expiry for lenalidomide expected 18th of January 2022 therefore a generic price, representing a [redacted] discount to list, has been assumed using bortezomib as a recent analogue for the associated impact on price following genericisation. Refer to Appendix E for details. In addition, Janssen has applied a relative dose intensity adjustment (89%), representing an average between the company and ERG estimates, consistent with the AC's conclusion in TA680.[vii] Results from the scenario analysis are presented in Table 3 with the ICER increasing from £18,694 to £25,734 per QALY when longer treatment duration following DBTd (relative to BTd) and a generic price of lenalidomide is assumed. The ICER associated with a longer treatment duration following daratumumab and list price for lenalidomide is significantly above £30k per QALY. This does not, however, account for the net price of lenalidomide, nor the incremental clinical benefit of lenalidomide post DBTd versus post BTd.
Table 3: Lenalidomide maintenance scenarios (with PAS)
<table>
<tr><th></th><th colspan="3">List Price for Lenalidomide</th><th colspan="3">Generic Lenalidomide</th></tr>
<tr><th>Scenario</th><th>Inc. costs</th><th>Inc. QALYs</th><th>ICER (£ per QALY)</th><th>Inc. costs</th><th>Inc. QALYs</th><th>ICER (£ per QALY)</th></tr>
<tr><td>Updated company base case using revised IPCW adjusted landmark analysis (with PAS))</td><td>[redacted]</td><td>[redacted]</td><td>£18,694</td><td></td><td></td><td></td></tr>
<tr><td>Median TTD per Myeloma XI ([redacted] both arms)</td><td>[redacted]</td><td>[redacted]</td><td>£43,039</td><td>[redacted]</td><td>[redacted]</td><td>£22,931</td></tr>
<tr><td>Median TTD</td><td>[redacted]</td><td>[redacted]</td><td>£71,073</td><td>[redacted]</td><td>[redacted]</td><td>£25,734</td></tr>
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<tr><td>derived as observed ratio between median treatment duration and PFS per Myeloma XI (DBTd: [redacted]; BTd; [redacted])</td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td colspan="7">Key: DBTd = daratumumab, bortezomib, thalidomide and dexamethasone; ICER = incremental cost-effectiveness ratio; Inc. = incremental; PAS = patient access scheme; PFS = progression-free survival; QALY = quality-adjusted life year.</td></tr>
</table>

It is notable that the majority of transplant-eligible patients in Myeloma XI stopped treatment with lenalidomide maintenance prior to progression; only [redacted] of patient discontinuations were due to a progression event, with the next most common reason being [redacted] ([redacted]), followed by [redacted] ([redacted]).[viii] As noted in the Final Appraisal Determination (FAD) for TA680, clinicians are mindful of the toxicity profile of lenalidomide.[vii] Stopping treatment prior to a patient becoming refractory also gives clinicians the attractive option to retreat with lenalidomide at later lines. As noted in the original company submission, there is evidence that myeloma patients value a treatment-free interval which is likely to be particularly true for individuals achieving the deepest levels of post-consolidation response.[xv,xvi] Indeed, the role of MRD to inform the optimum treatment strategy based on a risk stratification approach, and stopping rules based on MRD status, continues to be investigated as part of a number of ongoing clinical trials including RADAR and Myeloma XI.[xvii,xviii] Given this, Janssen consider the ratio modelled between TTD and PFS to be conservative as it does not necessarily follow that longer PFS after DBTd induction/consolidation will lead to a longer time on treatment with lenalidomide maintenance. In addition to this, scenarios incorporating the cost of lenalidomide maintenance may be considered conservative as they do not account for a lower proportion of patients receiving maintenance following DBTd (for example patients who are MRD negative).

In summary, there is no clinical evidence to demonstrate the efficacy of lenalidomide maintenance following daratumumab. Cost-effectiveness analysis of DBTd versus BTd including the cost of lenalidomide maintenance is therefore entirely speculative and not evidence-based. Despite these inherent limitations, scenario analysis with generic lenalidomide demonstrate that DBTd remains well within the £20k-£30k per QALY range normally considered to be a cost-effective use of NHS resources. Janssen also consider these results highly conservative in the sense they do not assume any incremental clinical benefit of lenalidomide post DBTd versus post BTd.</td><td></td></tr>
<tr><td>15</td><td>Consultee</td><td>Janssen-Cilag Limited</td><td>Non response-based approach (standard PSM)

“The committee noted the uncertainties associated with the different elements of the company’s approach; these included the choice of extrapolations for people with minimal residual disease having bortezomib plus thalidomide and dexamethasone (see section 3.13), and the results of the meta-analysis (see section 3.11) and landmark analysis (see section 3.6). The committee was unsure if the company’s approach to the long-term survival modelling reduced the uncertainty. It would have preferred that a scenario be provided using a conventional approach of fitting models directly to the ITT data from CASSIOPEIA.”</td><td>Thank you for your comment. The committee considered the company’s updated economic model. It noted that both approaches have uncertainty but concluded that the company’s approach to modelling</td></tr>
</table>

<table>
<tr><th>Comment number</th><th>Type of stakeholder</th><th>Organisation name</th><th>Stakeholder comment</th><th>NICE Response</th></tr>
<tr><td></td><td></td><td></td><td>
As per the original company submission, a response-based modelling approach leveraging post-consolidation MRD status was preferred due to the immaturity of OS data from CASSIOPEIA, and wide variation in survival outcomes predicted using conventional modelling approaches for both DBTd and BTd (refer company submission Document B, Section B.3.3.2). The evidence review group (ERG) also concluded in their report that OS data from CASSIOPEIA is too immature for simple extrapolation with parametric survival functions to be robust and that there was good rational for taking a response-based approach to survival modelling.

In response to the AC's concern whether a response-based approach helped to reduce uncertainty, Janssen has updated the economic model to include functionality to compare outcomes by fitting standard parametric models directly to the IPCW adjusted ITT data for Part 1. After median follow-up of 44.5 months, results from the standard partitioned survival model (PSM) analysis show median OS for DBTd ranging from 11.4 years (Gompertz) to 27.0 years (Generalised Gamma) across the 45-year time horizon of the model. Results were similarly uncertain for BTd, with median OS ranging from 11.3 years (Gompertz) to 22.7 years (log normal), demonstrating the significant variability in predicted survival outcomes dependent on the particular model distribution chosen. By contrast, uncertainty with regards long-term survival predictions was reduced adopting a response-based modelling approach, with median OS ranging between 22.5 and 26.8 years for DBTd, and between 14.3 and 24.4 years for BTd dependent on the choice of survival distribution for the base 'reference' curve (BTd MRD-positive).

Table 4: Median overall survival (years)
<table>
<tr><th></th><th colspan="2">BTd</th><th colspan="2">DBTd</th></tr>
<tr><th></th><th>Response-based PSM</th><th>Standard PSM</th><th>Response-based PSM</th><th>Standard PSM</th></tr>
<tr><td>Exponential</td><td>14.3</td><td>19.0</td><td>22.5</td><td>25.9</td></tr>
<tr><td>Weibull</td><td>17.1</td><td>13.8</td><td>24.8</td><td>17.6</td></tr>
<tr><td>Log normal</td><td>24.1</td><td>22.7</td><td>26.8</td><td>25.7</td></tr>
<tr><td>Log logistic</td><td>21.5</td><td>16.5</td><td>26.0</td><td>21.4</td></tr>
<tr><td>Gompertz</td><td>24.4</td><td>11.4</td><td>26.8</td><td>11.3</td></tr>
<tr><td>Generalised gamma</td><td>23.3</td><td>22.0</td><td>26.5</td><td>27.0</td></tr>
<tr><td colspan="5">Key: BTd = bortezomib, thalidomide and dexamethasone; DBTd = daratumumab, bortezomib, thalidomide and dexamethasone; PSM = partitioned survival model</td></tr>
</table>

Whilst Janssen acknowledge that residual uncertainty remains regarding the hazard ratios incorporated from the MRD meta-analysis and CASSIOPEIA landmark analysis, this uncertainty has been extensively explored in both sensitivity and scenario analysis. Janssen also note the consistency of results between the two models with an ICER of £21,891 from the standard PSM (applying base case settings per technical engagement, Weibull extrapolations for PFS and OS) providing further compelling evidence supporting the cost-effectiveness of DBTd versus BTd (refer to Table 5).

Table 5: Comparison of modelled cost-effectiveness results
<table>
<tr><th>Scenario</th><th>Inc. costs</th><th>Inc. QALYs</th><th>ICER (£ per QALY)</th></tr>
<tr><td>Response-based model</td><td>[redacted]</td><td>[redacted]</td><td>£18,694</td></tr>
</table>
</td><td>long-term survival, using a landmark analysis, is acceptable for decision making. See section 3.11 of the ACD.</td></tr>
</table>

Comment number	Type of stakeholder	Organisation name	Stakeholder comment	NICE Response
			Standard PSM [redacted] £21,891 Key: ICER = incremental cost-effectiveness ratio; Inc = incremental; PSM = partitioned survival model; QALY = quality-adjusted life year Note: assumes Weibull curve selection for both BTd and DBTd PFS/OS based on an assessment of statistical goodness-of-fit, visual inspection of the survival curves to the observed data from CASSIOPEIA, and clinical plausibility of long-term survival predictions. The prognostic significance of MRD in multiple myeloma including front-line transplant-eligible patients is well established.[xx,xxi,xxii] By leveraging MRD as a surrogate marker for survival outcomes, the response-based approach has helped to reduce uncertainty related to long-term OS predictions, a key driver of cost-effectiveness in the economic model.	
16	Consultee	Janssen-Cilag Limited	**Survival for bortezomib, thalidomide and dexamethasone (BTd)** *"The committee agreed with the ERG that the company's censoring approach would likely underestimate survival for patients having bortezomib plus thalidomide and dexamethasone. The committee concluded that the company's extrapolations likely underestimated survival for patients having bortezomib plus thalidomide and dexamethasone"* Janssen do not agree with the AC's conclusion that the OS extrapolations in the company base case likely underestimate survival for patients treated with BTd. As per the ACD, the ERG considered the exponential distribution for modelling BTd MRD-positive OS to be "reasonable", predicting 69.6% and 48.4% of patients alive at 5- and 10-years respectively. The OS outcomes predicted by the model for BTd, weighted by the proportion of patients achieving post-consolidation MRD negativity, were marginally higher than the clinical expert prediction at 5-years (76% versus 70% respectively) and within the range predicted by clinical experts at 10-years (57% versus 50-60% respectively). However, as noted above, to address the AC's concern regarding potential bias, Janssen has updated the survival analysis based on results from a revised IPCW landmark analysis incorporating the August 2020 data-cut from CASSIOPEIA (median follow-up, 44.5 months). Consistent with the original company submission and technical engagement response, extrapolation of PFS and OS for BTd patients with a post-consolidation MRD-positive response was performed in accordance with the guidance provided in the NICE DSU Technical Support Document (TSD) 14.[xix] Refer to Appendix D for further details, including the goodness-of-fit statistics for each parametric distribution explored and the extrapolated survival curves. Based on an assessment of statistical goodness-of-fit, visual inspection of the survival curves to the observed data from the CASSIOPEIA trial, and clinical plausibility of long-term survival predictions, the gompertz and exponential distributions were selected for PFS and OS respectively. The updated	Thank you for your comment. The committee noted that the revised inverse probability of censoring weighting - adjusted landmark analysis was likely less subject to bias than the censoring-adjusted landmark analysis. It concluded that survival for people having bortezomib plus thalidomide and dexamethasone should be modelled using curves fitted to the inverse probability of censoring weighting -adjusted data from the landmark analysis. See sections 3.7 and 3.14 of the ACD.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment	NICE Response
			OS and PFS outcomes predicted by the model for the overall cohort (i.e. BTd MRD-negative and MRD-positive combined, weighted by the proportion of patients achieving post-consolidation MRD negativity), are presented in Figure 1 with a comparison of survival predictions against the original and updated model submitted during technical engagement presented in Table 6. **Figure 1: Comparison of modelled survival predictions for BTd versus CASSIOPEIA (MRD+ and MRD- combined)**	

Comment number	Type of stakeholder	Organisation name	Stakeholder comment	NICE Response

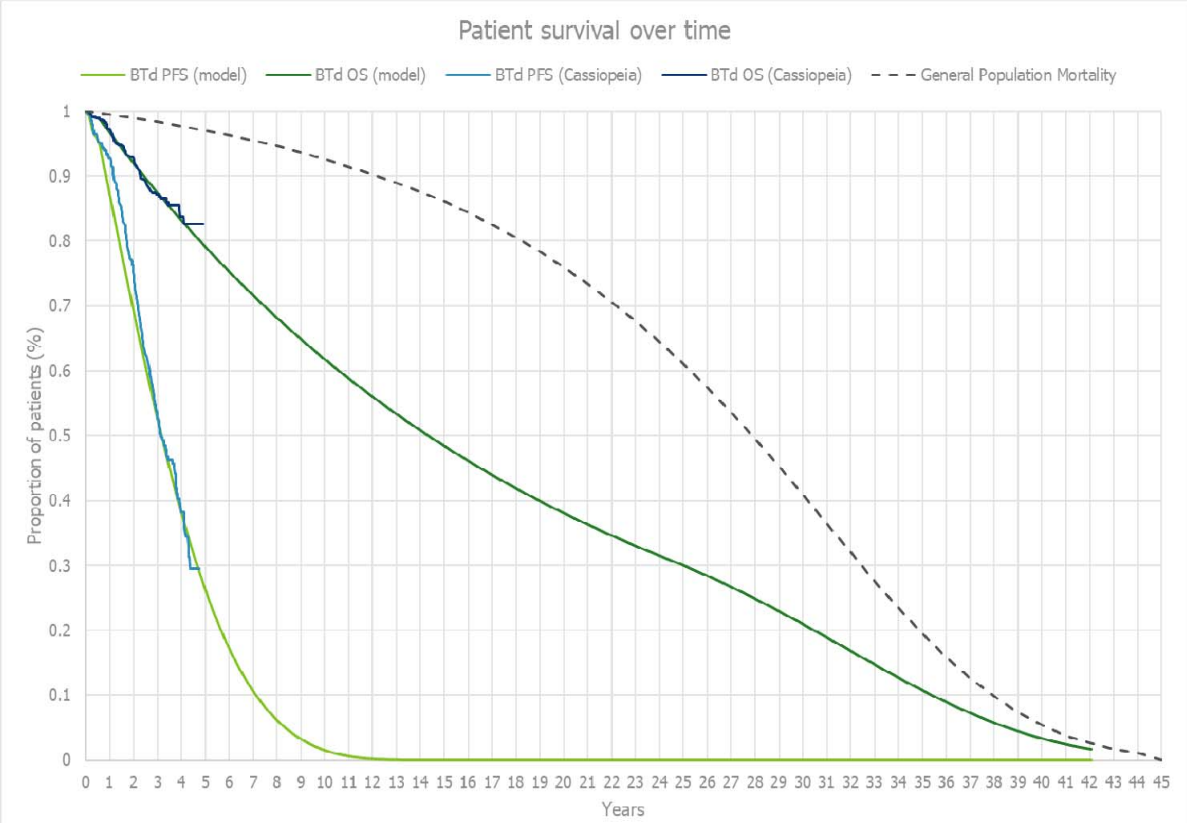

Table 6: BTd survival predictions (months) – comparison of original, updated and revised economic models

Treatment	Median PFS	Mean PFS	Median OS	Mean OS
Original model	47	70	162	197

<table>
<tr><th>Comment number</th><th>Type of stakeholder</th><th>Organisation name</th><th>Stakeholder comment</th><th>NICE Response</th></tr>
<tr><td></td><td></td><td></td><td>
<table>
<tr><td>Updated model (incorporating landmark analysis, censoring for maintenance)</td><td>37</td><td>59</td><td>146</td><td>185</td></tr>
<tr><td>Revised model (incorporating IPCW adjusted landmark analysis)</td><td>38</td><td>44</td><td>172</td><td>205</td></tr>
<tr><td>CASSIOPEIA IPCW adjusted Kaplan-Meier</td><td>[redacted]</td><td>n/a</td><td>n/a</td><td>n/a</td></tr>
<tr><td colspan="5">Key: BTd = bortezomib, thalidomide and dexamethasone; n/a = not available OS = overall survival; PFS = progression-free survival</td></tr>
</table>

The revised IPCW adjusted landmark analysis has resulted in an upward shift in survival outcomes for BTd (and DBTd) with 5- and 10-year OS rates of 79% and 62% respectively. Whilst the issue of selective censoring has been addressed, survival outcomes continue to be modelled based on post-consolidation, rather than post-ASCT, response. As noted in Sections B.1.3.4 and B.2.13 of the original company submission (Document B), BTd patients currently receive 4-6 cycles of induction-only treatment in clinical practice in England. BTd patients therefore do not benefit from deeper responses achieved by ‘mopping up’ residual myeloma cells during consolidation which reduces the risk of clonal and subclonal mutations, leading to early relapse. This was illustrated in the company submission where both conventional and MRD response rates in CASSIOPEIA deepen significantly across the different treatment phases with 14.6% of BTd patients ≥CR post-transplant compared with 26.0% post-consolidation (refer company submission, Document B, Section B.2.6.1). In this respect, the relative treatment effect modelled is likely biased against daratumumab in favour of BTd with the cost-effectiveness results representing a conservative estimate.</td><td></td></tr>
<tr><td>17</td><td>Consultee</td><td>Janssen-Cilag Limited</td><td>Comparison versus bortezomib and dexamethasone (Bd)

“the committee noted that bortezomib plus dexamethasone is cheaper than bortezomib plus</td><td>Thank you for your comment. The committee considered the exploratory</td></tr>
</table>

Comment number	Type of stakeholder	Organisation name	Stakeholder comment	NICE Response
			thalidomide and dexamethasone. As such, it does not necessarily follow that showing cost effectiveness against bortezomib plus thalidomide and dexamethasone would also show cost effectiveness against bortezomib plus dexamethasone. The committee concluded that bortezomib plus thalidomide and dexamethasone was a relevant comparator, but it would have preferred bortezomib plus dexamethasone to be included as a comparator in the model." As per the original company submission, a comparison of DBTd versus Bd was not possible and therefore excluded from the original cost-utility analysis because equivalent efficacy parameter inputs to inform the economic model (MRD negativity rates 100 days post autologous stem cell transplant) were not available following a systematic literature review of the available clinical evidence (both randomised control trial and observational studies). Janssen therefore proposed a pragmatic approach to cost-effectiveness of DBTd versus Bd on the grounds that there is consistent evidence that Bd is inferior to BTd across matching adjusted indirect comparison (MAIC), real-world evidence from Public Health England (PHE) cohort, and clinical expert opinion, while costs are broadly comparable. To help address the AC's concern regarding differential costs between BTd and Bd, and therefore the relative cost-effectiveness of DBTd versus Bd, Janssen conducted a crude exploratory analysis to incorporate the costs associated with Bd as front-line induction therapy, with efficacy assumed equivalent to BTd. Janssen consider this simplified modelling approach highly conservative however has been included to help address uncertainty related to comparative effectiveness of DBTd versus Bd. Results from the analysis indicate an ICER of £21,263 (IPCW adjusted landmark analysis, Gompertz for PFS and exponential for OS BTd MRD positive extrapolations, other base case settings per technical engagement) demonstrating DBTd remains a highly cost-effective front-line treatment option for transplant-eligible multiple myeloma patients.	analysis provided. It concluded bortezomib plus thalidomide and dexamethasone is the most relevant comparator reflecting NHS practice. See section 3.3 of the ACD.

[i] Moreau et al. Daratumumab Maintenance or Observation After Treatment With Bortezomib, Thalidomide, and Dexamethasone ± Daratumumab and Autologous Stem Cell Transplant in Patients With Newly Diagnosed Multiple Myeloma: CASSIOPEIA Part 2. ASCO Annual Meeting. June 8, 2021.
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[viii] Adams et al. 2019. High-Parameter Mass Cytometry Evaluation of Relapsed/Refractory Multiple Myeloma Patients Treated with Daratumumab Demonstrates Immune Modulation as a Novel Mechanism of Action. Cytometry. 95(3): 279-289
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[xiii] Janssen. [Data on File] Myeloma XI. SCT-eligible subgroup analysis. 2021
[xiv] Jackson et al. 2019. Lenalidomide maintenance versus observation for patients with newly diagnosed multiple myeloma (Myeloma XI): a multicentre, open-label, randomised, phase 3 trial. Lancet Oncology. 2019; 20:57-73
[xv] He et al. 2020. Patient Perceptions Regarding Multiple Myeloma and Its Treatment: Qualitative Evidence From Interviews With Newly Diagnosed and Relapsed/Refractory Patients in the United Kingdom, France, and Germany. Presented at virtual ISPOR; May 18–20, 2020.
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[xvii] Diamond et al. Dynamics of minimal residual disease in patients with multiple myeloma on continuous lenalidomide maintenance: a single-arm, single-centre, phase 2 trial. Lancet Haematology. 2021; 8: e422-32
[xviii] Clinicaltrialsregiser.eu. 2019-001258-25. Risk-Adapted therapy Directed According to Response comparing treatment escalation and de-escalation strategies in newly diagnosed patients with multiple myeloma (NDMM) suitable for stem cell transplant (TE). Available at: https://www.clinicaltrialsregister.eu/ctr-search/trial/2019-001258-25/GB
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NICE National Institute for Health and Care Excellence

Daratumumab in combination for untreated multiple myeloma when stem cell transplant is suitable [ID1510]

Consultation on the appraisal consultation document – deadline for comments 5pm on Friday 18 June 2021 email: NICE DOCS

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

Comment number	Comments

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Daratumumab in combination for untreated multiple myeloma when stem cell transplant is suitable [ID1510]

Consultation on the appraisal consultation document – deadline for comments 5pm on Friday 18 June 2021 email: NICE DOCS

	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.
	Janssen welcomes the opportunity to comment on the preliminary recommendation made by the appraisal committee (AC) detailed in the appraisal consultation document (ACD). We are disappointed that the AC's preliminary decision is to not recommend daratumumab in combination with bortezomib, thalidomide and dexamethasone (DBTd) within its marketing authorisation. We are, however, committed to working with the National Institute for Health and Care Excellence (NICE) to address the AC's key concerns, as outlined in the ACD, in order to gain access for patients to this highly innovative and effective fixed duration treatment. The treatment goal of front-line therapy is to induce remission and delay progression by achieving deep and durable responses. Minimal residual disease (MRD) represents the most sensitive measure of disease burden and depth of response in myeloma with its prognostic utility for progression-free survival (PFS) and overall survival (OS) well established across a range of disease settings including front-line transplant eligible patients.[1,2,3] Janssen is pleased that the AC recognise the broad clinical support for the prognostic significance of MRD and conclude that it represents an appropriate approach to model long-term survival. As recognised by patient experts, with each line of therapy a substantial proportion of patients stop having treatment because they become too ill or have complications. This highlights the need to treat patients with the most effective treatments as early as possible in the pathway when they are at their fittest. Updated results from CASSIOPEIA Part 1 demonstrate a significant PFS and OS benefit for DBTd relative to BTd with median follow-up of 44.5 months (PFS HR: 0.58; 95% CI 0.47,0.72; p<0.0001) (OS HR: 0.54; 95% CI 0.37 0.79; p=0.0012).[4] Janssen is pleased that the AC concluded adding daratumumab to BTd induction improves both PFS and OS and that consolidation could be incorporated into NHS clinical practice with few challenges. In the remainder of this response, Janssen focus discussion on the key areas of uncertainty highlighted in the ACD.

1	**Landmark analysis** *"The committee agreed that the results of the landmark analysis were likely biased because of informative censoring. However, it deemed that the direction of the bias was unclear because it affected both treatment arms. The committee concluded that the company's censoring approach had limitations, and that its effect on the results of the landmark analysis was uncertain."* The updated landmark analysis submitted as part of Janssen's technical engagement response applied a censoring approach to patients re-randomised to daratumumab maintenance therapy. This was because Janssen did not have access to patient-level data for patients re-randomised to daratumumab maintenance therapy. As such, it was not possible to perform an adjusted landmark analysis similar to the prespecified inverse probability weighting (IPW) PFS and OS analysis performed for the intention-to-treat (ITT) population. Whilst the number of patients re-randomised on both arms was high, Janssen acknowledge the risk of selection bias that may have been introduced because patients with less than a partial response were not subject to re-randomisation. To address the AC's concern regarding potential bias and uncertainty in the landmark analysis results, Janssen has now been able to perform an inverse probability censoring weights (IPCW) adjusted landmark analysis (on the August 2020 datacut) following recent publication of the CASSIOPEIA Part 2 results, [redacted].[4] Further detail of the IPCW methodology is provided in Appendix A. A comparison of the Cox proportional hazard model results for PFS and OS from the original, updated and revised (IPCW adjusted) landmark analysis is presented in Table 1. The Kaplan-Meier plots for the revised landmark analysis (PFS and OS), along with the associated tests for proportional hazards, are included in Appendix B and Appendix C respectively.

Daratumumab in combination for untreated multiple myeloma when stem cell transplant is suitable [ID1510]

Consultation on the appraisal consultation document – deadline for comments 5pm on Friday 18 June 2021 email: NICE DOCS

Table 1: Cox proportional hazard model results

	Original landmark analysis (median follow-up = 29.2 months)	Updated landmark analysis (median follow-up = 44.5 months, censoring for maintenance)	Revised IPCW adjusted landmark analysis (median follow-up = 44.5 months)
PFS			
DBTd MRD+ versus BTd MRD+ HR (95% CI)	[redacted]	[redacted]	[redacted]
n/N (%)	[redacted]	[redacted]	[redacted]
DBTd MRD- versus BTd MRD-) HR (95% CI)	[redacted]	[redacted]	[redacted]
n/N (%)	[redacted]	[redacted]	[redacted]
OS			
DBTd MRD+ versus BTd MRD+ HR (95% CI)	[redacted]	[redacted]	[redacted]
n/N (%)	[redacted]	[redacted]	[redacted]
DBTd MRD- versus BTd MRD-) HR (95% CI)	[redacted]	[redacted]	[redacted]
n/N (%)	[redacted]	[redacted]	[redacted]

Key: CI = confidence interval; BTd = bortezomib, thalidomide and dexamethasone; DBTd = daratumumab, bortezomib, thalidomide and dexamethasone; HR = hazard ratio; IPCW = inverse probability censoring weights; MRD = minimal residual disease; n = number of events; OS = overall survival; PFS = progression-free survival.

Whilst results from the revised IPCW adjusted landmark analysis are broadly comparable to the censoring approach for PFS, there is variability shown for OS with a stronger depth of response effect (and marginally reduced confidence interval) for MRD-positive patients, and a weaker effect (and wider confidence interval) for MRD-negative patients. Janssen note however that the overall impact on the ICER is negligible, increasing from £17,957[1] per quality adjusted life year (QALY) to £18,694 per QALY (applying base case settings per technical engagement, Gompertz for PFS and exponential for OS BTd MRD-positive extrapolations).

2 **Daratumumab 'treatment effect' waning**

"[The committee] considered that the daratumumab treatment effect was likely to decline gradually over time, but the timepoints at which this decline would start and finish were highly uncertain. The committee concluded that treatment effect waning should be included in the model, but that the duration of the daratumumab treatment effect was highly uncertain. The committee considered it reasonable to consider scenarios with a treatment effect lasting 5 and 10 years after consolidation therapy."

Janssen acknowledge the relative immaturity of survival data from CASSIOPEIA in the context of modelling survival outcomes over a lifetime time-horizon. That said, results from the original, updated and revised (IPCW adjusted) landmark analyses, consistently demonstrate a depth of response effect in favour of DBTd with no evidence to suggest a possible waning of effect over time with median follow-up approaching 4 years. This is compelling, since DBTd is a fixed treatment of 6 cycles; meaning that patients will have

[1] Note, a formula error of median treatment duration used in the calculation of subsequent therapy costs was identified in the economic model submitted during technical engagement. Correcting for this error, the technical engagement base case is £17,704.

received no active treatment for ~3 years and yet no waning of effect has been observed.

During technical engagement Janssen presented wider contextual evidence from CASSIOPEIA that supports maintenance of a depth of response effect favouring DBTd versus BTd in the long-term, with an almost doubling of MRD negative response rates at a deeper sensitivity threshold of 10^{-6} using Next Generation Sequencing (NGS 10^{-6}: 39.1% vs 22.8%; OR: 2.18; 95% CI: 1.58, 3.01; p<0.0001),[5] higher rates of sustained MRD negativity, more pronounced deepening of response rates over time, and higher rates of MRD negativity conversion. These data reflect daratumumab's unique mechanism of action which is to modulate the body's own immune system to better fight the disease.[6] Furthermore, PFS2 results continue to demonstrate the lasting benefit of upfront daratumumab exposure beyond progression. PFS2 results were broadly consistent before and after adjusting to exclude patients re-randomised to daratumumab maintenance with a [redacted] reduction in the risk of progression or death on next line of therapy after median follow-up of 44.5 months.

Janssen also presented recently published results from the GIMEMA study after 10-years median follow-up which further supports maintenance of a treatment effect driven by deeper responses with no evidence of treatment effect waning for bortezomib, thalidomide and dexamethasone (BTd) versus thalidomide and dexamethasone (Td).[7] As such, Janssen consider the waning effect scenarios at 5- and 10-years for DBTd presented as scenarios in the company's original submission to be both highly conservative and not evidence-based.

Nonetheless, to explore uncertainty further, and considering the AC's preferred modelling assumption of a treatment effect for daratumumab lasting 5- to 10-years after consolidation, Janssen has updated the cost-effectiveness model to include a scenario that assumes a gradual waning of effect at a constant rate between 5- and 10-years and also a treatment effect lasting 7.5 years representing the 5- and 10-year mid-point. Results from these analyses, along with the original scenario analysis, are presented in Table 2.

Table 2: Treatment effect waning scenarios (with PAS)

Scenario	Inc. costs	Inc. QALYs	ICER (£ per QALY)
Updated revised IPCW adjusted landmark analysis (with PAS)	[redacted]	[redacted]	£18,694
No additional treatment effect of DBTd after 5 years (MRD+ and MRD-)	[redacted]	[redacted]	£36,752
No additional treatment effect of DBTd after 10 years (MRD+ and MRD-)	[redacted]	[redacted]	£25,185
Gradual waning of treatment effect of DBTd between 5- and 10-years (MRD+ and MRD-)	[redacted]	[redacted]	£29,793
No additional treatment effect of DBTd after 7.5 years (MRD+ and MRD-)	[redacted]	[redacted]	£29,354

Key: DBTd = daratumumab, bortezomib, thalidomide and dexamethasone; ICER = incremental cost-effectiveness ratio; Inc. = incremental; IPCW = inverse probability censoring weights; MRD = minimal residual disease; PAS = patient access scheme; QALY = quality-adjusted life year.

These results indicate that DBTd remains a cost-effective use of NHS resources under all scenarios except the highly conservative 5-year treatment waning. Given the broader contextual evidence from CASSIOPEIA supporting deeper and more sustained responses for DBTd, along with external evidence from the GIMEMA study with 10-years median follow-up, Janssen does not consider 5-year treatment waning to be clinically plausible. Indeed, a 5-year treatment waning scenario was not supported by clinical experts at the first appraisal committee meeting.

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3	**Lenalidomide maintenance** *"The clinical experts explained that lenalidomide maintenance was now widely used in clinical practice and this was likely to increase in future. The clinical lead for the Cancer Drugs Fund stated that adding daratumumab to induction (and consolidation) treatment would likely increase the duration of lenalidomide maintenance. The effect of including lenalidomide maintenance on the cost effectiveness of daratumumab plus bortezomib, thalidomide and dexamethasone was therefore unclear. The committee concluded that a scenario analysis incorporating lenalidomide maintenance as a subsequent treatment should be provided to represent current NHS clinical practice."* The standard NICE process set out in the 'Guide to the processes of technology appraisal' (the Guide) emphasises the importance of the final scope.[8] The final scope, as specified in the Guide, provides a framework for the appraisal by defining important aspects including the population, intervention and comparators of interest following extensive consultation with relevant stakeholders including the manufacturer and NHS England. Janssen understand that the NICE appraisal process operates within an external environment and treatment landscape that is constantly evolving, particularly in this disease area. Given this changing landscape, Janssen appreciate the final scope as defined by NICE to provide a 'true north' and relevant point of reference throughout the appraisal process. In line with section 2.1.2 of the Methods Guide, we understand the scope to establish the boundaries of the work that is required to demonstrate the case for cost effectiveness for the appraisal committee.[9] Lenalidomide maintenance is considered a front-line therapy, albeit subsequent to induction/ASCT/consolidation. Lenalidomide maintenance was not recommended by NICE for routine commissioning until after the company submission, and post technical engagement with the ERG and NICE technical team. Indeed, were it not for the fact that the first appraisal committee meeting was delayed 2-months due to the impact of COVID-19 on NICE capacity, lenalidomide maintenance would not have been recommended at the time of the committee meeting. Changes in the external environment after the final scope has been defined are not generally considered relevant for decision making. As such, Janssen notes that the AC's request for a scenario analysis incorporating lenalidomide maintenance is somewhat off process. Moreover, inclusion of a treatment pathway change at this stage of the appraisal is highly challenging. Several studies have been published investigating the synergistic immune-mediated relationship between daratumumab and IMiDs (such as lenalidomide).[10,11,12,13,14] To summarise, daratumumab increases the number of cytotoxic T cells upon which IMiDs act. As such, it may reasonably be assumed that lenalidomide maintenance therapy will be more efficacious post DBTd than post BTd. From a modelling perspective, however, Janssen is not aware of any clinical evidence (RCT or observational real-world studies) to explicitly inform the efficacy of lenalidomide maintenance following daratumumab. Nonetheless, to help address the AC's concern that patients may stay on lenalidomide maintenance longer following daratumumab, **Janssen has performed a highly conservative scenario analysis incorporating <u>the costs of lenalidomide maintenance with no consideration of improved clinical outcomes.</u>** For this analysis, Janssen has used time to treatment discontinuation (TTD) data from the Myeloma XI study which was the main source of clinical evidence in NICE TA680.[15] Specifically, Janssen consider a scenario where the median TTD from Myeloma XI (in the transplant-eligible subgroup) is assumed for both arms ([redacted] months equivalent to ~[redacted] model cycles), and also a scenario which assumes treatment duration of lenalidomide following BTd and DBTd is in line with the observed ratio between median TTD and PFS (57 months) for the transplant-eligible subgroup from Myeloma XI.[16,17] Costs are then calculated in the model based on a 28-day dosing schedule, with treatment administered at 10 mg per day on days 1 - 21 (in line with recommended NICE guidance)[15] and applying an exponential distribution, thereby assuming a constant rate of treatment discontinuation. Janssen is aware of the imminent patent expiry for lenalidomide expected 18th of January 2022 therefore a generic price, representing a [redacted] discount to list, has been assumed using bortezomib as a recent analogue for the associated impact on price following genericisation. Refer to

Appendix E for details. In addition, Janssen has applied a relative dose intensity adjustment (89%), representing an average between the company and ERG estimates, consistent with the AC's conclusion in TA680.[15] Results from the scenario analysis are presented in Table 3 with the ICER increasing from £18,694 to £25,734 per QALY when longer treatment duration following DBTd (relative to BTd) and a generic price of lenalidomide is assumed. The ICER associated with a longer treatment duration following daratumumab and list price for lenalidomide is significantly above £30k per QALY. This does not, however, account for the net price of lenalidomide, nor the incremental clinical benefit of lenalidomide post DBTd versus post BTd.

Table 3: Lenalidomide maintenance scenarios (with PAS)

	List Price for Lenalidomide			Generic Lenalidomide		
Scenario	**Inc. costs**	**Inc. QALYs**	**ICER (£ per QALY)**	**Inc. costs**	**Inc. QALYs**	**ICER (£ per QALY)**
Updated company base case using revised IPCW adjusted landmark analysis (with PAS))	[redacted]	[redacted]	£18,694			
Median TTD per Myeloma XI ([redacted] both arms)	[redacted]	[redacted]	£43,039	[redacted]	[redacted]	£22,931
Median TTD derived as observed ratio between median treatment duration and PFS per Myeloma XI (DBTd: [redacted]; BTd; [redacted])	[redacted]	[redacted]	£71,073	[redacted]	[redacted]	£25,734

Key: DBTd = daratumumab, bortezomib, thalidomide and dexamethasone; ICER = incremental cost-effectiveness ratio; Inc. = incremental; PAS = patient access scheme; PFS = progression-free survival; QALY = quality-adjusted life year.

It is notable that the majority of transplant-eligible patients in Myeloma XI stopped treatment with lenalidomide maintenance prior to progression; only [redacted] of patient discontinuations were due to a progression event, with the next most common reason being [redacted] ([redacted]), followed by [redacted] ([redacted]).[16] As noted in the Final Appraisal Determination (FAD) for TA680, clinicians are mindful of the toxicity profile of lenalidomide.[15] Stopping treatment prior to a patient becoming refractory also gives clinicians the attractive option to retreat with lenalidomide at later lines. As noted in the original company submission, there is evidence that myeloma patients value a treatment-free interval which is likely to be particularly true for individuals achieving the deepest levels of post-consolidation response.[18,19] Indeed, the role of MRD to inform the optimum treatment strategy based on a risk stratification approach, and stopping rules based on MRD status, continues to be investigated as part of a number of ongoing clinical trials including RADAR and Myeloma XI.[20,21] Given this, Janssen consider the ratio modelled between TTD and PFS to be conservative as it does not necessarily follow that longer PFS after DBTd induction/consolidation will lead to a longer time on treatment with lenalidomide maintenance. In addition to this, scenarios incorporating the cost of lenalidomide maintenance may be considered conservative as they do not account for a lower proportion of patients receiving maintenance following DBTd (for example patients who are MRD negative).

In summary, there is no clinical evidence to demonstrate the efficacy of lenalidomide maintenance following

daratumumab. Cost-effectiveness analysis of DBTd versus BTd including the cost of lenalidomide maintenance is therefore entirely speculative and not evidence-based. Despite these inherent limitations, scenario analysis with generic lenalidomide demonstrate that DBTd remains well within the £20k-£30k per QALY range normally considered to be a cost-effective use of NHS resources. Janssen also consider these results highly conservative in the sense they do not assume any incremental clinical benefit of lenalidomide post DBTd versus post BTd.

4 **Non response-based approach (standard PSM)**

"The committee noted the uncertainties associated with the different elements of the company's approach; these included the choice of extrapolations for people with minimal residual disease having bortezomib plus thalidomide and dexamethasone (see section 3.13), and the results of the meta-analysis (see section 3.11) and landmark analysis (see section 3.6). The committee was unsure if the company's approach to the long-term survival modelling reduced the uncertainty. It would have preferred that a scenario be provided using a conventional approach of fitting models directly to the ITT data from CASSIOPEIA."

As per the original company submission, a response-based modelling approach leveraging post-consolidation MRD status was preferred due to the immaturity of OS data from CASSIOPEIA, and wide variation in survival outcomes predicted using conventional modelling approaches for both DBTd and BTd (refer company submission Document B, Section B.3.3.2). The evidence review group (ERG) also concluded in their report that OS data from CASSIOPEIA is too immature for simple extrapolation with parametric survival functions to be robust and that there was good rational for taking a response-based approach to survival modelling.

In response to the AC's concern whether a response-based approach helped to reduce uncertainty, Janssen has updated the economic model to include functionality to compare outcomes by fitting standard parametric models directly to the IPCW adjusted ITT data for Part 1. After median follow-up of 44.5 months, results from the standard partitioned survival model (PSM) analysis show median OS for DBTd ranging from 11.4 years (Gompertz) to 27.0 years (Generalised Gamma) across the 45-year time horizon of the model. Results were similarly uncertain for BTd, with median OS ranging from 11.3 years (Gompertz) to 22.7 years (log normal), demonstrating the significant variability in predicted survival outcomes dependent on the particular model distribution chosen. By contrast, uncertainty with regards long-term survival predictions was reduced adopting a response-based modelling approach, with median OS ranging between 22.5 and 26.8 years for DBTd, and between 14.3 and 24.4 years for BTd dependent on the choice of survival distribution for the base 'reference' curve (BTd MRD-positive).

Table 4: Median overall survival (years)

	BTd		DBTd	
	Response-based PSM	**Standard PSM**	**Response-based PSM**	**Standard PSM**
Exponential	14.3	19.0	22.5	25.9
Weibull	17.1	13.8	24.8	17.6
Log normal	24.1	22.7	26.8	25.7
Log logistic	21.5	16.5	26.0	21.4
Gompertz	24.4	11.4	26.8	11.3
Generalised gamma	23.3	22.0	26.5	27.0

Key: BTd = bortezomib, thalidomide and dexamethasone; DBTd = daratumumab, bortezomib, thalidomide and dexamethasone; PSM = partitioned survival model

Whilst Janssen acknowledge that residual uncertainty remains regarding the hazard ratios incorporated from the MRD meta-analysis and CASSIOPEIA landmark analysis, this uncertainty has been extensively explored in both sensitivity and scenario analysis. Janssen also note the consistency of results between the two models with an ICER of £21,891 from the standard PSM (applying base case settings per technical engagement, Weibull extrapolations for PFS and OS) providing further compelling evidence supporting the cost-effectiveness of DBTd versus BTd (refer to Table 5).

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Table 5: Comparison of modelled cost-effectiveness results

Scenario	Inc. costs	Inc. QALYs	ICER (£ per QALY)
Response-based model	[redacted]	[redacted]	£18,694
Standard PSM	[redacted]	[redacted]	£21,891

Key: ICER = incremental cost-effectiveness ratio; Inc = incremental; PSM = partitioned survival model; QALY = quality-adjusted life year

Note: assumes Weibull curve selection for both BTd and DBTd PFS/OS based on an assessment of statistical goodness-of-fit, visual inspection of the survival curves to the observed data from CASSIOPEIA, and clinical plausibility of long-term survival predictions.

The prognostic significance of MRD in multiple myeloma including front-line transplant-eligible patients is well established.[1,2,3] By leveraging MRD as a surrogate marker for survival outcomes, the response-based approach has helped to reduce uncertainty related to long-term OS predictions, a key driver of cost-effectiveness in the economic model.

5 **Survival for bortezomib, thalidomide and dexamethasone (BTd)**

"The committee agreed with the ERG that the company's censoring approach would likely underestimate survival for patients having bortezomib plus thalidomide and dexamethasone. The committee concluded that the company's extrapolations likely underestimated survival for patients having bortezomib plus thalidomide and dexamethasone"

Janssen do not agree with the AC's conclusion that the OS extrapolations in the company base case likely underestimate survival for patients treated with BTd. As per the ACD, the ERG considered the exponential distribution for modelling BTd MRD-positive OS to be "reasonable", predicting 69.6% and 48.4% of patients alive at 5- and 10-years respectively. The OS outcomes predicted by the model for BTd, weighted by the proportion of patients achieving post-consolidation MRD negativity, were marginally higher than the clinical expert prediction at 5-years (76% versus 70% respectively) and within the range predicted by clinical experts at 10-years (57% versus 50-60% respectively).

However, as noted above, to address the AC's concern regarding potential bias, Janssen has updated the survival analysis based on results from a revised IPCW landmark analysis incorporating the August 2020 data-cut from CASSIOPEIA (median follow-up, 44.5 months). Consistent with the original company submission and technical engagement response, extrapolation of PFS and OS for BTd patients with a post-consolidation MRD-positive response was performed in accordance with the guidance provided in the NICE DSU Technical Support Document (TSD) 14.[22] Refer to Appendix D for further details, including the goodness-of-fit statistics for each parametric distribution explored and the extrapolated survival curves.

Based on an assessment of statistical goodness-of-fit, visual inspection of the survival curves to the observed data from the CASSIOPEIA trial, and clinical plausibility of long-term survival predictions, the gompertz and exponential distributions were selected for PFS and OS respectively. The updated OS and PFS outcomes predicted by the model for the overall cohort (i.e. BTd MRD-negative and MRD-positive combined, weighted by the proportion of patients achieving post-consolidation MRD negativity), are presented in Figure 1 with a comparison of survival predictions against the original and updated model submitted during technical engagement presented in Table 6.

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Figure 1: Comparison of modelled survival predictions for BTd versus CASSIOPEIA (MRD+ and MRD- combined)

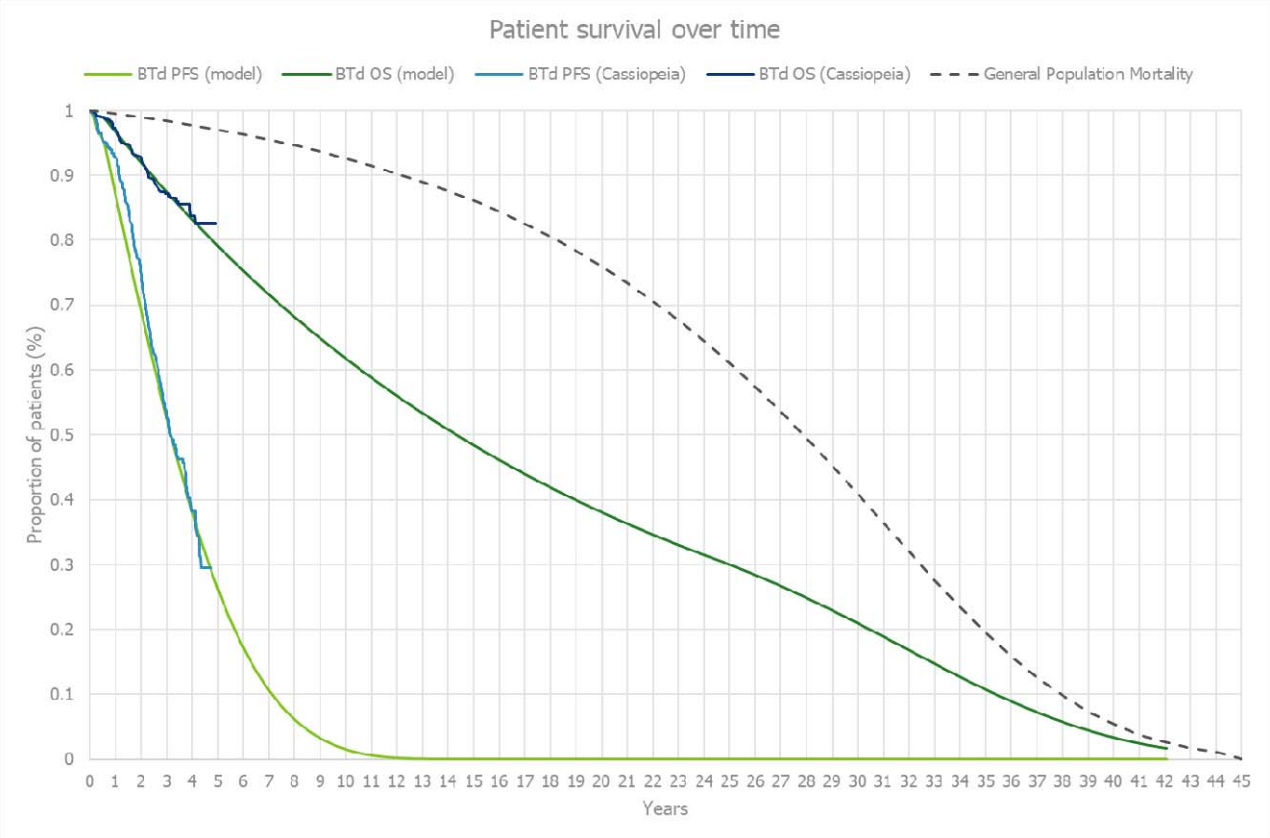

Table 6: BTd survival predictions (months) – comparison of original, updated and revised economic models

Treatment	Median PFS	Mean PFS	Median OS	Mean OS
Original model	47	70	162	197
Updated model (incorporating landmark analysis, censoring for maintenance)	37	59	146	185
Revised model (incorporating IPCW adjusted landmark analysis)	38	44	172	205
CASSIOPEIA IPCW adjusted Kaplan-Meier	[redacted]	n/a	n/a	n/a

Key: BTd = bortezomib, thalidomide and dexamethasone; n/a = not available OS = overall survival; PFS = progression-free survival

The revised IPCW adjusted landmark analysis has resulted in an upward shift in survival outcomes for BTd (and DBTd) with 5- and 10-year OS rates of 79% and 62% respectively. Whilst the issue of selective censoring has been addressed, survival outcomes continue to be modelled based on post-consolidation,

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	rather than post-ASCT, response. As noted in Sections B.1.3.4 and B.2.13 of the original company submission (Document B), BTd patients currently receive 4-6 cycles of induction-only treatment in clinical practice in England. BTd patients therefore do not benefit from deeper responses achieved by 'mopping up' residual myeloma cells during consolidation which reduces the risk of clonal and subclonal mutations, leading to early relapse. This was illustrated in the company submission where both conventional and MRD response rates in CASSIOPEIA deepen significantly across the different treatment phases with 14.6% of BTd patients ≥CR post-transplant compared with 26.0% post-consolidation (refer company submission, Document B, Section B.2.6.1). In this respect, the relative treatment effect modelled is likely biased against daratumumab in favour of BTd with the cost-effectiveness results representing a conservative estimate.
6	**Comparison versus bortezomib and dexamethasone (Bd)** *"the committee noted that bortezomib plus dexamethasone is cheaper than bortezomib plus thalidomide and dexamethasone. As such, it does not necessarily follow that showing cost effectiveness against bortezomib plus thalidomide and dexamethasone would also show cost effectiveness against bortezomib plus dexamethasone. The committee concluded that bortezomib plus thalidomide and dexamethasone was a relevant comparator, but it would have preferred bortezomib plus dexamethasone to be included as a comparator in the model."* As per the original company submission, a comparison of DBTd versus Bd was not possible and therefore excluded from the original cost-utility analysis because equivalent efficacy parameter inputs to inform the economic model (MRD negativity rates 100 days post autologous stem cell transplant) were not available following a systematic literature review of the available clinical evidence (both randomised control trial and observational studies). Janssen therefore proposed a pragmatic approach to cost-effectiveness of DBTd versus Bd on the grounds that there is consistent evidence that Bd is inferior to BTd across matching adjusted indirect comparison (MAIC), real-world evidence from Public Health England (PHE) cohort, and clinical expert opinion, while costs are broadly comparable. To help address the AC's concern regarding differential costs between BTd and Bd, and therefore the relative cost-effectiveness of DBTd versus Bd, Janssen conducted a crude exploratory analysis to incorporate the costs associated with Bd as front-line induction therapy, with efficacy assumed equivalent to BTd. Janssen consider this simplified modelling approach highly conservative however has been included to help address uncertainty related to comparative effectiveness of DBTd versus Bd. Results from the analysis indicate an ICER of £21,263 (IPCW adjusted landmark analysis, Gompertz for PFS and exponential for OS BTd MRD positive extrapolations, other base case settings per technical engagement) demonstrating DBTd remains a highly cost-effective front-line treatment option for transplant-eligible multiple myeloma patients.

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7. Model Assumptions

Revised base case

Considering the AC's stated wishes, alongside the issues covered in comments 1-6 of this document, Janssen provide a revised base case, as follows:

- Using an approach less subject to bias than simple censoring to adjust the landmark analysis for re-randomisation to daratumumab maintenance
- A mean age at the start of induction based on the real-world evidence from Public Health England
- Omitting panobinostat plus bortezomib and dexamethasone as a subsequent treatment at third or fourth line

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In addition to the revised base case and in acknowledgement of the AC's request for scenario analyses, Janssen has provided scenario analyses as follows:

- A treatment effect lasting 5 to 10 years after consolidation therapy
- Incorporating lenalidomide maintenance as a subsequent treatment to reflect current NHS clinical practice
- Using a conventional approach of fitting progression-free and overall survival models directly to the ITT data from CASSIOPEIA

8. Revised economic analyses

Table 7 summarises the revised company base case incorporating committee preferred assumptions plus additional scenario analyses requested in the ACD. The revised company base-case is presented in Table 8. Probabilistic scatterplot is presented in Figure 2 and cost effectiveness acceptability curve in Figure 3.

Table 7. Updated cost-effectiveness results (with PAS)

Scenario	Inc. costs	Inc. QALYs	ICER
Post technical engagement company base-case	[redacted]	[redacted]	£17,957
Correction for median treatment duration used in the calculation of subsequent therapy costs	[redacted]	[redacted]	£17,704
IPCW adjusted landmark analysis (on the August 2020 datacut)[a]	[redacted]	[redacted]	£18,694
Mean age at the start of induction based on the real-world evidence from Public Health England	[redacted]	[redacted]	£21,029
No PBd at 3L	[redacted]	[redacted]	£22,331
Company Revised base case	[redacted]	[redacted]	£22,331
Additional scenarios (applied to the company revised base-case)			
No additional treatment effect of DBTd after 5 years (MRD+ and MRD-)	[redacted]	[redacted]	£40,534
No additional treatment effect of DBTd after 10 years (MRD+ and MRD-)	[redacted]	[redacted]	£28,139
Gradual waning of treatment effect of DBTd between 5- and 10-years (MRD+ and MRD-)	[redacted]	[redacted]	£33,069
No additional treatment effect of DBTd after 7.5 years (MRD+ and MRD-)	[redacted]	[redacted]	£32,617
Len maintenance, Median TTD per Myeloma XI ([redacted] both arms), list price for len	[redacted]	[redacted]	£49,214
Len maintenance, Median TTD per Myeloma XI ([redacted] both arms), generic price for len	[redacted]	[redacted]	£28,141
Len maintenance, Median TTD derived as observed ratio between median TTD and PFS per Myeloma XI (DBTd: [redacted]; BTd; [redacted]), list price for len	[redacted]	[redacted]	£80,169
Len maintenance, Median TTD derived as observed ratio between median treatment duration and PFS per Myeloma XI (DBTd: [redacted]; BTd; [redacted]), generic price for len	[redacted]	[redacted]	£31,236
Using a conventional approach of fitting progression-free and overall survival models directly to the ITT data from CASSIOPEIA[b]	[redacted]	[redacted]	£25,332

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Abbreviations: 3L, third-line; BTd, bortezomib, thalidomide and dexamethasone; DBTd, daratumumab, bortezomib, thalidomide and dexamethasone; ICER, incremental cost-effectiveness ratio; Inc, incremental; IPCW, Inverse probability of censoring weights; ITT, intention to treat; Len, lenalidomide; MRD, minimal residual disease; PAS, patient access scheme; PBd, Panobinostat, bortezomib and dexamethasone; PFS, progression free survival; TTD, time to treatment duration; QALYs, quality-adjusted life years

Notes: a: Gompertz for BTd MRD+ PFS; Exponential for BTd MRD+ OS; b: assumes Weibull curve selection for both BTd and DBTd PFS/OS based on an assessment of statistical goodness-of-fit, visual inspection of the survival curves to the observed data from CASSIOPEIA, and clinical plausibility of long-term survival predictions

Table 8. Revised company base-case results (with PAS)

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER (£/QALY)
Deterministic							
DBTd	[redacted]	[redacted]	[redacted]				
BTd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£22,331
Probabilistic							
DBTd	[redacted]	N/A	[redacted]				
BTd	[redacted]	N/A	[redacted]	[redacted]	N/A	[redacted]	£20,719

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Abbreviations: BTd, bortezomib, thalidomide and dexamethasone; DBTd, daratumumab, bortezomib, thalidomide and dexamethasone; ICER, incremental cost-effectiveness ratio; Inc, incremental; LYG, life years gained; N/A = not available; PAS, patient access scheme; QALYs, quality-adjusted life years

Figure 2. Cost-effectiveness plane for DBTd versus BTd, revised company base-case results (with PAS)

Abbreviations: BTd, bortezomib, thalidomide and dexamethasone; DBTd, daratumumab, bortezomib, thalidomide and dexamethasone; PAS, patient access scheme; PSA, probabilistic sensitivity analysis; QALYs, quality-adjusted life years; WTP, willingness to pay.

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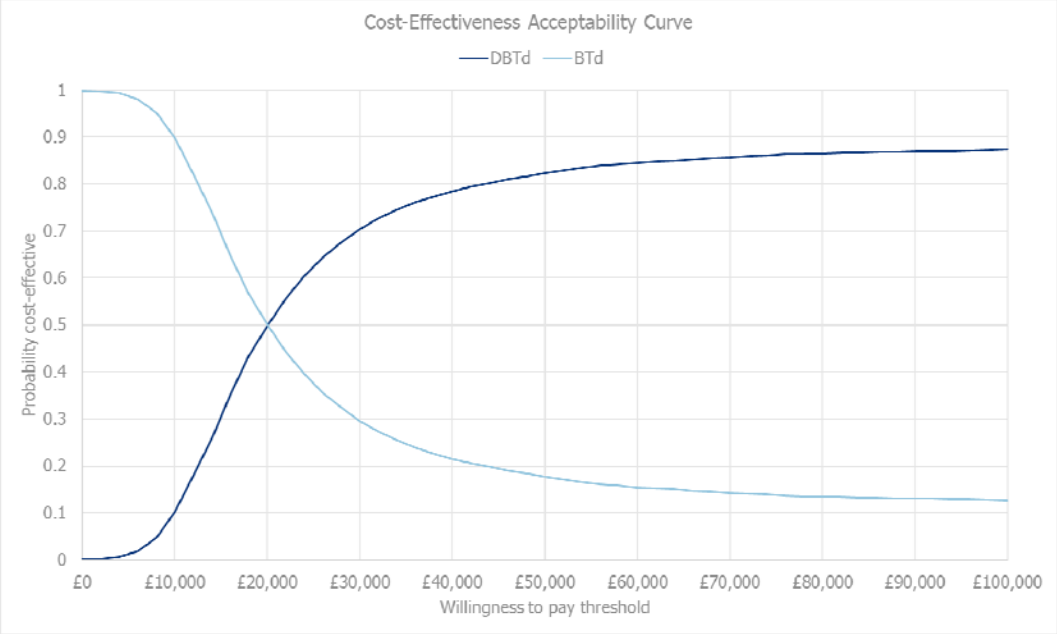
Figure 3. Cost-effectiveness acceptability curve, revised company base-case results (with PAS)



Abbreviations: BTd, bortezomib, thalidomide and dexamethasone; DBTd, daratumumab, bortezomib, thalidomide and dexamethasone; PAS, patient access scheme

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Daratumumab in combination for untreated multiple myeloma when stem cell transplant is suitable [ID1510]

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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
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Appendix A: IPCW Methodology

In general, inverse probability of censoring weights (IPCW) can be used to adjust for the impact of treatment switching happening over time by including time varying weights. However, in this instance, assumptions related to time varying confounders were not necessary for the purpose of the landmark analysis as the switching to daratumumab maintenance was based on random assignment and occurred at a similar timepoint for all patients.

The IPCW adjusted landmark analysis upweighted the DBTd+OBS and BTd+OBS cohorts to represent similar patients to those re-randomised to DBTd+DARA and BTd+DARA respectively. In this reweighting, the following available prognostic patient characteristics available at time of re-randomisation (ECOG) and at initial randomisation (ISS stage, cytogenetic risk, and site affiliation) were taken into account, including consideration of reduced patient numbers.

A logistic regression including these factors estimating the probability of being a patient re-randomised to observation arm was then used to generate propensity scores, which were translated into (inverse probability) weights. Finally, these IPW weights were used in a weighted Cox regression to estimate the hazard ratio between the treatment in the different cohorts of interest, which were used to inform the cost-effectiveness model.

The weighted Cox regression took into account these weights as time-dependent. All patients received a weight of 1 until re-randomisation to maintenance treatment. From re-randomisation, OBS patients were upweighted to represent similar patients in the censored daratumumab maintenance group. This estimation of the weights was done for each MRD status within each treatment arm separately.

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Appendix B: IPCW adjusted landmark analysis

Figure 1: IPCW adjusted landmark analysis: PFS by treatment arm; MRD-negative at the time of the post-consolidation assessment (ITT population, median follow-up = 44.5 months)

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Figure 2: IPCW adjusted landmark analysis: PFS by treatment arm; MRD-positive at the time of the post-consolidation assessment (ITT population, median follow-up = 44.5 months)

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Figure 3: IPCW adjusted landmark analysis: OS by treatment arm; MRD-negative at the time of the post-consolidation assessment (ITT population, median follow-up = 44.5 months)

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Figure 4: IPCW adjusted landmark analysis: OS by treatment arm; MRD-positive at the time of the post-consolidation assessment (ITT population, median follow-up = 44.5 months)

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Appendix C: Revised IPCW adjusted landmark analysis - tests of proportional hazards

C.1. MRD status by treatment arm

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C.2. Treatment by MRD status

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C.3 Schoenfeld residuals

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Appendix D: Extrapolation of BTd MRD+ OS and PFS

Table 1: Goodness-of-fit statistics for BTd MRD+ OS (revised IPCW adjusted landmark analysis) survival models

Survival model	AIC	BIC
Exponential	**617.818**	**622.033**
Weibull	619.138	627.568
Lognormal	618.686	627.115
Loglogistic	619.022	627.451
Gompertz	619.065	627.494
Generalised Gamma	620.597	633.241

Key: AIC = Akaike's information criterion; BIC = Bayesian information criterion; BTd = bortezomib, thalidomide and dexamethasone; MRD = minimal residual disease; OS = overall survival.

Table 2: Comparison of predicted survival rates for BTd MRD+ OS (revised IPCW adjusted landmark analysis) survival models

Survival model	OS survival rates			
	5 years	10 years	20 years	30 years
Clinician estimate	≤70%[a]	44%[b]	-	-
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Lognormal	[redacted]	[redacted]	[redacted]	[redacted]
Loglogistic	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Generalised Gamma	[redacted]	[redacted]	[redacted]	[redacted]

Key: BTd = bortezomib, thalidomide and dexamethasone; MRD = minimal residual disease; OS = overall survival.

[a] Feedback from UK clinician, not part of the clinical advisory board meeting for DBTd [i]

[b] Feedback from clinical advisory board meeting for DBTd with reference to the all patient estimate for newly diagnosed MM including mixed population of transplant-eligible and ineligible patients from the Office for National Statistics (ONS)[ii]

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Figure 3: Extrapolation of OS for BTd MRD+ (revised IPCW adjusted landmark analysis)

Table 3: Goodness-of-fit statistics for BTd MRD+ PFS (revised IPCW adjusted landmark analysis) survival models

Survival model	AIC	BIC
Exponential	1489.107	1493.274
Weibull	1488.694	1497.029
Lognormal	1537.101	1545.436
Loglogistic	1501.929	1510.264
Gompertz	**1484.889**	**1493.224**
Generalised Gamma	1486.059	1498.561

Key: AIC = Akaike's information criterion; BIC = Bayesian information criterion; BTd = bortezomib, thalidomide and dexamethasone; MRD = minimal residual disease; PFS = progression-free survival.

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Table 4: Comparison of predicted survival rates for BTd MRD+ PFS (revised IPCW adjusted landmark analysis) survival models

Survival model	PFS survival rates		
	5 years	10 years	20 years
Clinician estimate	20–30%[a]	<10%[b]	<1%[b]
Exponential	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]
Lognormal	[redacted]	[redacted]	[redacted]
Loglogistic	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]
Generalised Gamma	[redacted]	[redacted]	[redacted]

Key: BTd = bortezomib, thalidomide and dexamethasone; MRD = minimal residual disease; PFS = progression-free survival.

[a] Feedback from UK clinician, not part of the clinical advisory board meeting for DBTd[i]

[b] Feedback from clinical advisory board meeting for DBTd[ii]

Figure 4: Extrapolation of PFS for BTd MRD+ (revised IPCW adjusted landmark analysis)

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Appendix E: Bortezomib loss of exclusivity (LOE)

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- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
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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.

[i] Janssen. Personal Communication with Consultant Haematologist in the UK. May 2020.
[ii] Janssen. [Data on File] Clinical Advisory Board Meeting Minutes. August 2020

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Myeloma UK
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**N/A**
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	Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	*Has all of the relevant evidence been taken into account?* We are not aware of any omissions in the evidence base.
2	*Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?* Partly. As set out in our evidence submission there remains a significant unmet need for myeloma patients eligible for stem cell transplant, who need more effective treatments that will induce a longer and more durable period of remission. We therefore note and welcome the Committee's findings that: • patients with untreated multiple myeloma would welcome a new first-line treatment option. • daratumumab, bortezomib, thalidomide and dexamethasone (DVTD) improve progression-free and overall survival. • the adverse event profile of DVTD is acceptable. • minimal residual disease (MRD) negativity is likely to better predict survival outcomes than conventional response. • patients who are MRD negative would have a complete response over time. • clinical consolidation can be easily adapted into NHS practice. We particularly welcome the ACD finding that it has been established in clinical practice that MRD negativity is associated with better progression-free survival and overall survival. Our main concern is around the Committee's request that lenalidomide maintenance should be incorporated into the economic model. We are concerned at this inclusion given that lenalidomide maintenance was not included in the final scope for this appraisal and was therefore not part of the appraisal that the company and other consultees were asked to submit evidence on as part of the decision problem. We recognise the committee's desire to reflect real world practice in its deliberations but comment that there is a balance to be struck between this and preserving the integrity of the appraisal process (as is recognised in other elements of NICE methods and process, e.g., the exclusion of CDF treatments from appraisals as

	comparators.) We therefore have questions about the fairness of introducing lenalidomide maintenance into consideration at this stage. **Given the significance of introducing new data and modelling on lenalidomide maintenance we think it essential that clinical and patient experts be invited to attend the second Committee meeting.** We believe that potentially widening the scope of the decision problem merits expert attendance. For example, there are important patient insight and experience issues relating to the duration of treatment with lenalidomide maintenance, including the reasons why a patient may not wish to continue with lenalidomide maintenance to progression. Patients, in consultation with their clinician, may wish to stop maintenance treatment with lenalidomide before they become refractory in order to be able to access combinations including lenalidomide later in the pathway, or they may wish to take a treatment break for other reasons. (Current clinical trials are researching whether maintenance can be stopped after two years (SWOG and GMMG-MM5 trial) or even adjusted based on MRD status (OPTIMUM Trial)). Further to this, we know from engagement with our patients that a treatment free period is highly valued by patients. If DVTD, with associated deeper response, was offered as induction and consolidation for patients eligible for ASCT, some patients may choose not to receive lenalidomide maintenance in order to have an extended treatment free period. Finally, we recognise that there are a range of concerns around modelling and uncertainty on issues such as treatment effect waning and overall survival (OS). We do not intend to comment on each of these in detail, other than to emphasise. as we have in other appraisals, that it is increasingly challenging to deliver OS within the timelines of a clinical trial and that this fact must not prevent patients from accessing the most promising new treatments. The CDF is the key policy mechanism for delivering access to treatments in this category and we are therefore obviously disappointed that this does not seem to be an option that will help resolve the key uncertainties for DVTD. Despite this we hope that all avenues will be explored by the company, NICE and NHS England to enable a positive recommendation, whether those be methodological or commercial.
3	*Are the recommendations sound and a suitable basis for guidance to the NHS?* For the reasons set out above, particularly around the inclusion of lenalidomide maintenance in the appraisal, no.

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4	*Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual* orientation, age, *gender reassignment, pregnancy and maternity?* We agree with the Committee's position that DVTD should not be restricted to patients under the age of 65 despite this being criteria within the CASSEIOPIA trial.
5	
6	

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	UK MYELOMA FORUM (UKMF)
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	UKMF has received an unrestricted educational grant from Janssen-Cilag (£10,000 per annum), and Celgene (BMS, £10,000 per annum). UKMF has also received unrestricted educational grants from other pharmaceutical companies.
Name of commentator person completing form:	DR NEIL RABIN, VICE CHAIR UK MYELOMA FORUM
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Example 1	We are concerned that this recommendation may imply that ……..
1	We are concerned that subsequent therapy change (Lenalidomide maintenance) is impacting on ability to appraise induction regimens for myeloma. Whilst we recognise the modelling assumptions do change, so do Maintenance regimens, which change with time and several are under investigation including Daratumumab within the Cassiopeia trial and Ixazomib. This interpretation could significantly impact new induction regimens for myeloma considered by NICE and unintentionally favours maintenance therapy appraisal.
2	Treatment pathway, 3.2. Bortezomib in combination with thalidomide or cyclophosphamide are both appropriate and widely used in clinical practice. The committee stated that bortezomib dexamethasone should also be used as comparator. Whilst this is in keeping with NICE guidance (TA311) this does not reflect clinical practice. Treating clinicians would always prefer to give a 3 rather than 2 drug combinations to improve depth of response and outcomes. This data should be available from NHSE SACT datasets.
3	Treatment waning 3.14. This is difficult due to the lack of long-term data (i.e > 5 yrs) with Daratumumab in the frontline setting. Patients receiving transplants are younger and fitter. Published data with BTd compared to Td, with a 10 year median follow up, (Lancet Haematol 2020; 7: e861–73) shows a sustained effect of BTd therapy at 10 years. It is conceivable that the improved MRD rate seen with the addition of Daratumumab (D-BTd) may show similar (if not better) improvements at 10 years. We therefore think that if treatment waning were to occur this would be beyond 10 years, and not at 5 years as suggested.
4	
5	
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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	[**Dr Karthik Ramasamy**]
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Daratumumab in combination for untreated multiple myeloma when stem cell transplant is suitable [ID1510]

Consultation on the appraisal consultation document – deadline for comments 5pm on Friday 18 June 2021 email: NICE DOCS

	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	Iam concerned whether robust process has been followed here. Committee has requested further modelling including lenalidomide maintenance. Lenalidomide maintenance guidance was issued on 1st March 2021. The committee had over 6 weeks to decide if this had to be incorporated in the model before the papers were sent out end of April 2021 for the appraisal meeting. In addition new maintenance therapies are in development including one within the current trial that is being considered within this appraisal (CASSIOPEIA) which may be considered by NICE in the next 6-12 months. As induction and maintenance therapies are developed separately in trials, the current interpretation induces undue penalty on induction regimens that would be considered for myeloma.
2	3.2 Iam concerned that Bortezomib and dexamethasone is considered as a comparator when in clinical practice only handful of patients will have this induction (i.e bad neuropathy). NHSE dataset should be able to validate this statement.
3	3.14 Treatment waning is not observed during 10-year actual follow up in the GIMEMA trial considered by NICE TA311 and approve VTD. It is hard to conceive how treatment waning would happen within this time frame when clinical outcomes (ORR, PFS) for DVTD are better than VTD
4	3.15 PHE datasets do not reflect the actual patients transplanted, often patients over 65 experience toxicities during induction and don't get to transplant. Therefore the median age at transplant is often 65 as in Myeloma XI trial.
5	
6	

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about 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.
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- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) 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.
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Evidence Review Group's critique of the company's response to the ACD

Produced by Southampton Health Technology Assessments Centre (SHTAC)

Authors Joanne Lord, David Scott, Lorna Hazell, Neelam Kalita

Date completed 28 June 2021

Commercial in confidence (CIC) information in blue

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1. Summary of company's response and ERG critique

Table 1 Summary of response to committee's preferred assumptions

Preferred assumptions (ACD 3.17)	Company response	ERG comments
Landmark analysis (ACD 3.6) *Using an approach less subject to bias than simple censoring to adjust the landmark analysis for re-randomisation to daratumumab maintenance*	IPCW adjusted landmark analysis conducted with individual patient data from the August 2020 data cut (CR point 1 and appendices A-C). Revised OS and PFS curves fitted to MRD+ IPCW data for comparator arm (BTd) (CR appendix D) Adjusted HRs and OS/PFS extrapolations included in revised base case analysis	IPCW adjusted landmark analysis is appropriate and results appear reasonable (although ERG cannot fully validate). Some uncertainties: • Potential prognostic factors not included • Proportional hazards not met See section 2.1 below. See also 2.3 for discussion of OS and PFS survival models.
Waning of treatment effects (ACD 3.14) *A treatment effect lasting 5 to 10 years after consolidation therapy*	Waning not included in the revised base case, but four scenarios are reported: gradual waning between 5 and 10 years, and sudden loss of effect at 5, 7.5 and 10 years (CR point 2). Argues that 5-year waning is not clinically plausible and reiterates 'contextual evidence' from TE.	Scenario with gradual waning between 5 and 10 years reflects committee's preferred assumptions and should be included in the revised base case. We also report an ERG scenario with loss of OS effect at 5 years for the MRD- subgroup, which we believe better reflects trial data. See section 2.2 below.
Mean age of population (ACD 3.15) *Mean age at start of induction based on real-world evidence from Public Health England*	Included in revised base case	No further comments
Subsequent treatments (ACD 3.16) *Omitting panobinostat plus bortezomib and dexamethasone as subsequent treatment at third or fourth line*	Included in revised base case	No further comments

Table 2 Summary of response to requested scenarios

Requested scenarios (ACD 3.17)	Company response	ERG comments
Lenalidomide maintenance (ACD 3.4) *A scenario incorporating lenalidomide maintenance as a subsequent treatment to reflect current NHS clinical practice*	Lack of clinical evidence to model lenalidomide maintenance treatment after daratumumab. Four scenarios reported with lenalidomide maintenance costs (CR Table 3). Treatment duration assumed: [redacted] cycles (median TTD in Myeloma XI); and [redacted] cycles for DBTd/BTd (ratios between median TTD and PFS in Myeloma XI). Scenarios at list price or assumed generic reduction ([redacted]) for lenalidomide.	Scenarios with costs but no effects of lenalidomide maintenance are subject to uncertainty. One might expect these scenarios to be conservative, as they assume equal or longer lenalidomide maintenance after daratumumab induction and consolidation.
Non response-based approach (ACD 3.10) *A scenario using a conventional approach of fitting progression-free and overall survival models directly to the ITT data from CASSIOPEIA*	Standard parametric survival models fitted to IPCW adjusted data (CR issue 4). One scenario is reported, assuming Weibull distributions for OS and PFS in both treatment groups (CR Table 5).	Evidence to support the choice of Weibull extrapolations in the scenario is not presented. For illustration, we report additional scenarios with: Gompertz for PFS and Weibull for OS; and with Gompertz for PFS and exponential for OS (as in the company's revised base case model). See section 2.4.

Table 3 Summary of response to other uncertainties

Additional uncertainties	Company response	ERG comments
Survival extrapolations (ACD 3.13) *Clinical experts predicted around 70% of people on bortezomib plus thalidomide and dexamethasone would be alive after 5 years, and 50%-60% after 10 years.* *The committee concluded that the company's extrapolations likely underestimated survival for patients having bortezomib plus thalidomide and dexamethasone.*	Parametric survival models were fitted to the IPCW adjusted landmark data for the MRD+ BTd group (CR appendix D). The base case uses Gompertz for PFS and exponential for OS. Overall predictions of 5- and 10-year OS are 79% and 62% respectively for BTd including both MRD subgroups (CR Figure 1). The company argue that the better survival than predicted by clinical experts is due to consolidation treatment in the trial.	The choice of baseline survival extrapolations for the revised base case is reasonable, based on model fit statistics and comparison of extrapolations with clinical opinion. The resulting survival extrapolation for the comparator (BTd) exceeds clinical expectations. See section 2.3 below.
Comparison with Bd (ACD 3.2) *The committee noted that bortezomib plus thalidomide and dexamethasone was a relevant comparator, but it would have preferred bortezomib plus dexamethasone to be included as a comparator in the model*	Exploratory analysis including costs for Bd as first-line induction therapy with efficacy assumed equal to BTd (CR issue 6)	No further comment

2. ERG critique of revised analysis

2.1. Landmark analysis

The Company have revised their previous landmark analysis, in which subjects re-randomised to daratumumab maintenance therapy were censored, following committee concerns over informative censoring. The revised approach uses the IPCW method to inform the landmark analysis, reweighting control arms to be similar to treatment arms by MRD status (CR appendix A).

The company state that ECOG, ISS stage, cytogenetic risk, and site affiliation were used to generate the IPCW scores and respective subject weights. Nevertheless, the ERG considers there are other prognostic factors which could potentially have been included in the propensity weighting including renal function, comorbidities, extent of extramedullary disease, and high-risk FISH abnormalities. The distribution of these potential prognostic factors between arms for the MRD+ and MRD- subgroups is unclear and comparisons of prognostic factors pre- and post-weighting are not reported.

That aside, as far as the ERG can judge the IPCW analysis has been correctly implemented. Results are broadly similar to the previous Landmark analysis using censoring (CR Table 1). Hazard ratios for OS and PFS improved slightly for the daratumumab combination in the MRD+ subgroup. In the MRD- subgroup, the hazard ratio for PFS was unchanged, but that for OS worsened for the daratumumab combination. With or without the IPCW adjustment, the effect of the daratumumab combination on PFS appears to be robust in both subgroups ([redacted]) (CR appendix Figures 1 and 2). However, high uncertainty over the effects on OS remains (CR appendix Figures 3 and 4).

The ERG notes that the tests for proportional hazards in the MRD status subgroups show potential violation (CR appendix C). This adds uncertainty to the cost-effectiveness results because the model uses fixed hazard ratios from the landmark analysis to adjust PFS and OS extrapolations for the daratumumab combination in both MRD subgroups.

The company have also used the IPCW landmark analysis to revise the baseline OS and PFS extrapolations used in the economic model. See section 2.3 below.

2.2. Daratumumab 'treatment effect' waning

Waning is not included in the company's revised base case, although they present cost-effectiveness results with four waning scenarios (CR Table 2). The ERG considers that the assumption of gradual waning between 5 and 10 years is a fair interpretation of committee's

preferred assumption and should be included in the revised base case. Results are similar with a sudden loss of effect at 7.5 years.

The company states that they do not consider 5-year treatment waning to be plausible and reiterates 'wider contextual evidence' from CASSIOPEIA and from the GIMEMA study that they believe supports long-term maintenance of better response for the daratumumab combination. The ERG acknowledges these points, but we also highlight the high remaining uncertainty over the direct evidence of a daratumumab survival benefit from CASSIOPEIA (CR Table 1), particularly in the MRD- subgroup (CR appendix Figure 3). We therefore report an additional scenario, with gradual waning between 5 and 10 years, but with a loss of effect for OS at 5 years.

2.3. Survival for bortezomib, thalidomide and dexamethasone (BTd)

The company disagree that the OS extrapolations in their previous base case analysis underestimated survival for patients in the BTd arm, based on comparisons with predictions of 5 and 10-year survival from their clinical experts.

The baseline OS and PFS extrapolations have now been revised by fitting standard parametric survival models to IPCW landmark data for MRD+ patients in the control arm (see CR appendix D). For their base case analysis, the company chose the following survival models:

- **Exponential for OS** – This has the best AIC/BIC model fit statistics and produces the least favourable projections; closest to the company's clinical expert survival estimates (CR appendix Tables 1 and 2).
- **Gompertz for PFS** – This also has the best AIC/BIC model fit statistics and gives the second least favourable 5-year projections of progression free survival (CR appendix Tables 3 and 4). We note that there is an error in CR Figure 4: which shows OS rather than PFS results.

The resulting base case extrapolations for the whole patient population (including MRD+ and MRD- patients) are shown in Figure 1 below (and CR Figure 1). Overall predictions of 5- and 10-year OS are 79% and 62% respectively for BTd. These compare with the clinical expert estimates of 70% and 50-60% respectively, cited in the ACD (paragraph 3.13). The company argue that the better survival than predicted by clinical experts is due to consolidation treatment in the trial.

The ERG considers that these extrapolations provide a reasonable fit to the trial data. Although survival exceeds clinical expectations with current treatment, alternative baseline

OS survival models (e.g. Weibull) would be more optimistic. This may relate to the nature of the population and interventions in the trial and/or to the way in which survival for the MRD-subgroup is estimated in the model (with a constant HR).

Figure 1 Response-based extrapolations, revised base case model

2.4. Non response-based approach (standard partitioned survival model)

The company outline their approach to fitting standard parametric survival models to IPCW adjusted data from the CASSIOPEIA trial (CR issue 4). They state that Weibull curves were selected for both PFS and OS based on assessment of goodness-of-fit statistics, visual inspection and clinical plausibility of long-term projections (CR Table 5 footnote). Further information to support this choice is not presented.

For illustration, we show IPCW adjusted PFS and OS extrapolations from the company's model (Figure 2 and **Figure 3**). We also show the resulting model predictions for two scenarios: Figure 4 with Weibull for PFS and OS (as in the company's non response-based scenario); Figure 5 with Gompertz PFS and Exponential OS (as in the revised base case model). Note that the latter two figures include adjustment to prevent mortality rates becoming more favourable than for people of the same age in the general population.

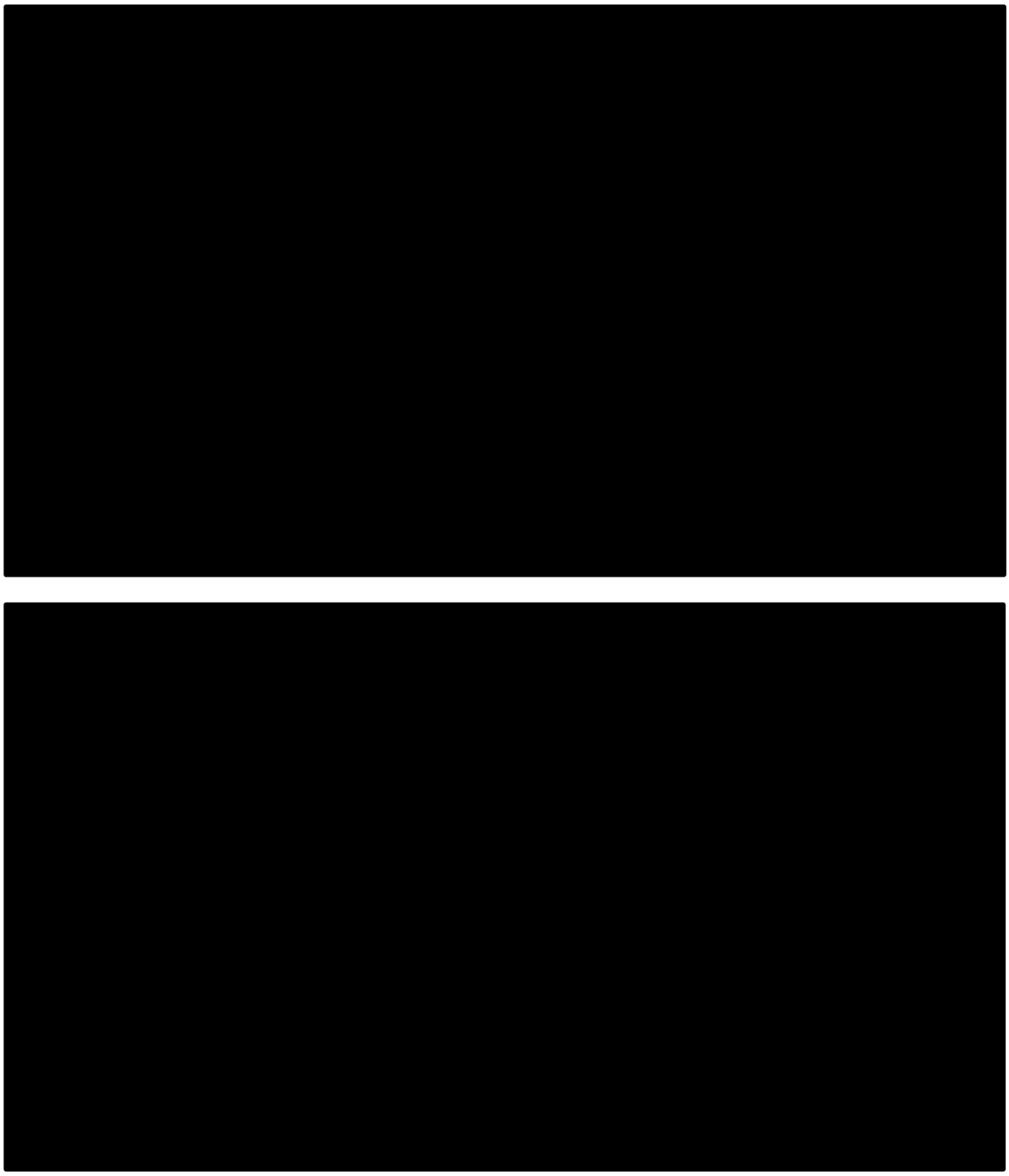

Figure 2 Conventional PFS extrapolations: IPCW adjusted data cut August 2020

Figure 3 Conventional OS extrapolations: IPCW adjusted data cut August 2020

Figure 4 Non response-based extrapolations: Weibull for PFS and OS

Figure 5 Non response-based extrapolations: Gompertz PFS and Exponential OS

3. ERG check of revised economic analysis

The ERG successfully replicated the company's base case and scenario results reported in Table 7 of the ACD response (with PAS discount for daratumumab, all other treatments at list price). The probabilistic analysis gave similar to the deterministic results.

Additional ERG scenarios applied to the company's revised base case are shown in Table 4 below. Table 5 reports results with the assumption of gradual waning of treatment effects for the daratumumab combination between 5 and 10 years after consolidation therapy added to the company's base case analysis. The ERG considers that this analysis best reflects the committee's preferred assumptions (ACD 3.17). We show selected scenarios applied to this 'committee preferred' analysis in Table 6.

Table 4 Additional ERG scenarios applied to revised base case, deterministic (daratumumab PAS, all other drugs at list price)

Scenario	Inc. costs	Inc. QALYs	ICER
Company's revised base case	[redacted]	[redacted]	£22,331
Loss of treatment effect at 5 years for OS MRD-, gradual waning from 5 to 10 years for PFS (MRD+ and MRD-) and OS MRD+	[redacted]	[redacted]	£36,961
Conventional survival models fitted to ITT data from CASSIOPEIA: PFS Gompertz; OS Weibull	[redacted]	[redacted]	£28,735
Conventional survival models fitted to ITT data from CASSIOPEIA: PFS Gompertz; OS Exponential	[redacted]	[redacted]	£26,082

Source: obtained from company model by ERG

Table 5 Committee preferred analysis: company's revised base-case plus gradual waning over 5-10 years (daratumumab PAS, all other drugs at list price)

Technologies	Total costs (£)	Total QALYs	Inc. costs (£)	Inc. QALYs	ICER (£/QALY)
Deterministic					
BTd	[redacted]	[redacted]			
DBTd	[redacted]	[redacted]	[redacted]	[redacted]	£33,069
Probabilistic					
BTd	[redacted]	[redacted]			
DBTd	[redacted]	[redacted]	[redacted]	[redacted]	£32,757

Source: Obtained from company model by ERG

Table 6 ERG scenario analysis applied to committee preferred analysis, deterministic (daratumumab PAS, all other drugs at list price)

Scenario	Inc. costs	Inc. QALYs	ICER
Committee preferred analysis: company's revised scenario + gradual waning between 5 and 10 years	[redacted]	[redacted]	£33,069
Loss of OS effect at 5 years for MRD-	[redacted]	[redacted]	£36,961
Lenalidomide maintenance, median TTD per Myeloma XI ([redacted] both arms), list price	[redacted]	[redacted]	£62,153
Lenalidomide maintenance, median TTD derived as observed ratio between median TTD and PFS per Myeloma XI (DBTd: [redacted]; BTd; [redacted]), list price	[redacted]	[redacted]	£101,085
Conventional survival models fitted to ITT data from CASSIOPEIA: PFS Gompertz and OS Weibull (*model does not include waning for this scenario*)	[redacted]	[redacted]	£28,735
Costs for bortezomib + dexamethasone, effects assumed equal to bortezomib + thalidomide + dexamethasone	[redacted]	[redacted]	£37,076

Source: Obtained from company model by ERG