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

NICE National Institute for Health and Care Excellence

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

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

Contents:

The following documents are made available to consultees and commentators:

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

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

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	Consultee	UK MYELOMA FORUM (UKMF)	The committee has stated that the duration of Daratumumab effect is uncertain. They have concluded that the treatment effect of Daratumumab would likely last 10 years or less. We do not agree that there will be a treatment waning effect. Newly diagnosed myeloma patients will be given a highly effective treatment for a short fixed duration (4 cycles of D-BTd pre transplant and 2 cycles of D-BTd afterward), with a high response rate. There will be two groups of patients (D-BTd or BTd alone) that will have different outcomes based on their depth of response (higher MRD negative rate in the D-BTd group). As this treatment is given for a short duration there is less likelihood of developing resistant disease that would alter long term outcomes. This is supported by the fact that there is no evidence of treatment waning in the CASSIOPEA trial after 4 years follow up. As mentioned previously there is no evidence of treatment waning in other trials that have published data beyond 10 years (GIMMEMA trial comparing BTd vs Td induction/consolidation).	Thank you for your comment. The committee considered all the evidence provided and the views of clinical experts and concluded that it is reasonable to assume that the treatment effect for daratumumab in combination will be maintained long term. (See FAD section 3.17)
2	Consultee	UK MYELOMA FORUM (UKMF)	Lenalidomide maintenance. As mentioned there is no data evaluating Lenalidomide maintenance after Daratumumab induction therapy. We welcome the use of the large UK based Myeloma XI trial data in this appraisal, although there remains uncertainty combining data from 2 separate trials. The Myeloma XI trial data was used to support the approval of Lenalidomide maintenance by NICE (TA680). In this appraisal it was assumed there was a gradual treatment waning effect over 10-25 years. If treatment waning is accepted by the committee, despite our concerns mentioned above, we would support a gradual waning effect as used in TA680 over 10-25 years as this represents both a clinically plausible and pragmatic approach consistent with previous NICE technology appraisals in the same part of the patient pathway.	Thank you for your comment. The company provided a revised base case that included both costs and benefits of lenalidomide maintenance using data from the Myeloma XI study. The committee concluded that this approach was reasonable for decision making. (See FAD section 3.18). The committee also concluded that it is reasonable to assume that the treatment effect for daratumumab in combination will be maintained long term. (See FAD section 3.17)

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3	Consultee	UK MYELOMA FORUM (UKMF)	Beyond QALY benefits. We note the ACD did not acknowledge any additional benefits of D-BTd. Given Daratumumab's innovative mechanism of action and an extension in the treatment free period, we feel this will have a positive impact on quality of life for both he patient and care giver.	Thank you for your comment. The committee considered that it had not been presented with strong evidence that daratumumab in combination adds benefits of a substantial nature not adequately captured in the reference case QALY measure. (See FAD section 3.23)
4	Consultee	UK MYELOMA FORUM (UKMF)	We would welcome giving clinical input at any future committee meetings.	Thank you for your comment. If additional clinical input is needed in this disease area in the future, NICE will welcome your input.
5	Consultee	Myeloma UK	We note the progress made following the first Appraisal Consultation Document (ACD) and the agreement reached on issues such as: consolidation being adopted into NHS practice; MRD negativity being likely to predict survival outcomes better than stringent complete response; and that the company's landmark analysis approach to modelling long term survival is appropriate.	Thank you for your comment. No action required.
6	Consultee	Myeloma UK	However we do not believe that the • the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence or that • the provisional recommendations are a sound and suitable basis for guidance to the NHS. The reasons for these conclusions are set out below.	Thank you for your comment. Please see responses to individual issues below.
7	Consultee	Myeloma UK	In our view, the evidence summaries do not fully reflect the strength of clinical opinion on the weaknesses in the ERG's approach to treatment waning. If treatment waning is to be applied then a realistic, evidence based approach which is consistent across myeloma appraisals should be applied. We highlight the fact that no treatment waning was observed for daratumumab patients in the CASSIOPEIA trial after almost four years of follow up. We do not believe the evidence supports the Committee's conclusion that the treatment effect of daratumumab would likely last 10 years or less after consolidation. We note that in TA680 the Committee applied a 10 – 25 year waning assumption of lenalidomide maintenance. If treatment waning is to be applied in this appraisal, it should be consistent with this decision, which is at the same part of the treatment pathway (first line.)	Thank you for your comment. The committee considered all the evidence that was provided and the views of clinical experts and concluded that it was reasonable to assume that the impact of deepening a response would be maintained over a lifetime for daratumumab in combination. (See FAD section 3.17)
8	Consultee	Myeloma UK	Another area of concern is the approach to including lenalidomide maintenance in modelling cost effectiveness.	Thank you for your

Comment number	Type of stakeholder	Organisation name	Stakeholder comment	NICE Response
			First of all we note that lenalidomide maintenance was not included in the final scope of the appraisal and that its inclusion post technical engagement is not standard NICE process. We do understand the desire to reflect real world clinical practice in the Committee's considerations, but there is a balance to be struck in doing this with protecting the integrity of the appraisal process. (We note that the exclusion of Cancer Drugs Fund (CDF) approved treatments as comparators is an instance of where real world clinical practice is not taken into account by Committees.) We note and agree with the second ACD's observation that modelling the effects of lenalidomide maintenance on cost effectiveness is challenging. We hope that Janssen will have done everything possible to "mine" existing data such as Myeloma XI for relevant evidence but we would also encourage the committee to take a pragmatic and proportionate approach to this uncertainty. Otherwise the approval of lenalidomide maintenance will place unreasonable barriers in the way of approving effective new induction regimens.	comment. The committee understood that lenalidomide maintenance is now established practice in the NHS. The company provided a revised base case that included both costs and benefits of lenalidomide maintenance using data from the Myeloma XI study. The committee concluded that this approach was reasonable for decision making. (See FAD section 3.18)
9	Consultee	Myeloma UK	While noting that patients would welcome the approval of this treatment option, we do not believe that the ACD fully recognises the innovative nature of daratumumab as an addition to induction treatment, including the psychological benefit to patients in knowing that they are receiving an innovative treatment with improved chances of achieving MRD negative status. Also, while we agree with clinical opinion that the majority of patients will go on to receive lenalidomide maintenance, the MRD negative benefits may over time enable some patients to decide to have a treatment free period, leaving the opportunity of accessing lenalidomide further down the treatment pathway.	Thank you for your comment. The committee considered that it had not been presented with strong evidence that daratumumab plus bortezomib, thalidomide and dexamethasone adds benefits of a substantial nature not adequately captured in the reference case QALY measure. (See FAD section 3.23)
10	Consultee	Myeloma UK	Finally, while we are relieved that the possibility of a positive decision is still present, we are frustrated at the length of time this appraisal has taken. We realise that the speed of the appraisal is not within the control of NICE alone and that companies have a key role to play in supporting earlier positive decisions. However, we are now around one year past our initial submission to this appraisal and in that time many patients have missed the opportunity of accessing a treatment which can deliver longer remissions. We encourage all parties, including the company, to do all they can to deliver a solution that will enable patients to access this treatment as soon as possible.	Thank you for your comment. Comment noted.
11	Consultee	Janssen-Cilag Limited	Janssen welcomes the opportunity to comment on the preliminary recommendation made by the appraisal committee (AC) detailed in the second appraisal consultation document (ACD). We are disappointed that the AC's preliminary recommendation is not to recommend daratumumab in combination with bortezomib, thalidomide and dexamethasone (DBTd) as induction and consolidation treatment for untreated multiple myeloma in adults, when an autologous stem cell transplant is suitable. We remain committed, however, to working with the National Institute for Health and Care Excellence (NICE) to address the AC's key concerns, as outlined in the second ACD, in order to gain access for patients to this highly innovative and effective fixed duration front-line treatment.	Thank you for your comment. Please see responses to individual issues below.

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			Following the second committee meeting, Janssen is pleased that the AC have accepted that bortezomib, thalidomide and dexamethasone (BTd) is the most relevant comparator to DBTd and concluded that the response-based modelling approach and inverse probability censoring weights (IPCW)-adjusted landmark analysis are appropriate for decision-making. Janssen agree with the Committee that the IPCW-adjusted landmark analysis is less susceptible to selection bias than naïve censoring. We consider it important to note, however, that survival extrapolations for BTd continue to exceed predictions from clinical experts. This is due to the use of post-consolidation response rates in the model which is not representative of current UK clinical practice. In terms of modelling for DBTd, Janssen is pleased that the AC acknowledge the reasonableness to consider a scenario with no treatment effect waning for daratumumab. Janssen is, however, disappointed with the AC's preference to model lenalidomide maintenance as a subsequent therapy within the base case despite acknowledging the lack of clinical evidence and considerable uncertainty associated with this. Further, we are highly concerned by the AC's preference to combine modelling lenalidomide maintenance with treatment waning for daratumumab, which is not evidence-based nor aligned with TA680.[1] Thus, in this response, Janssen focus discussion on the following key areas: • Modelling lenalidomide maintenance as a subsequent therapy • The appropriateness of applying treatment waning for daratumumab • The overall conservative nature of the company cost-effectiveness model with regards to survival for BTd Janssen has provided a revised base case cost-effectiveness analysis within this response utilising evidence-based inputs and assumptions where possible (see **Error! Reference source not found.** section below). Importantly, we have aimed to avoid speculation, which we consider only serves to add, rather than help reduce, uncertainty. These updated results also incorporate a new patient access scheme (PAS) of [redacted]% for daratumumab, which has been submitted to the patient access schemes liaison unit (PASLU).	
12	Consultee	Janssen-Cilag Limited	**Lenalidomide maintenance as a subsequent therapy** *"The committee acknowledged that the lack of clinical evidence exploring the use of lenalidomide maintenance following daratumumab plus bortezomib, thalidomide and dexamethasone made incorporating it into the model challenging, but not impossible. It considered that the model should reflect current NHS practice, and was aware that practice changes over time. At the second meeting, the company included lenalidomide maintenance in their model, but only included the costs and did not consider any clinical benefits (see section 3.16). The committee concluded that both the costs and benefits of lenalidomide maintenance should be incorporated as a subsequent treatment in the model to represent current NHS practice."* As noted in our previous ACD response, lenalidomide maintenance as a subsequent therapy was not described in the final scope for this appraisal. As such, Janssen considers the AC's request for incorporating lenalidomide maintenance to be above and beyond the boundary of work set out in the final scope. Moreover, inclusion of a treatment pathway change at this stage of the appraisal is highly challenging, not least given the lack of efficacy data to support cost/benefit assumptions with lenalidomide maintenance following daratumumab specifically.	Thank you for your comment. The committee understood that lenalidomide maintenance is now established practice in the NHS. The committee considered the revised base case that included both costs and benefits of lenalidomide maintenance using data from the Myeloma XI study. The committee considered that the scenario that included a

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			However, given the AC's preference to include lenalidomide maintenance in the base case, Janssen has revised the company base case to model the impact of lenalidomide maintenance using an evidence-based approach. When providing results for this revised base case, both costs and efficacy are considered for lenalidomide maintenance as requested by the AC. Whilst Janssen is not aware of any clinical evidence (from either randomised controlled trials [RCTs] or observational real-world studies) to directly inform the efficacy of lenalidomide maintenance following daratumumab, Janssen has used data from the Myeloma XI study which was the main source of clinical evidence in NICE TA680.[1, 2] Specifically, from a cost perspective, Janssen has assumed the same duration of lenalidomide maintenance therapy following both DBTd and BTd using data for median time to treatment discontinuation (TTD) from Myeloma XI (in the transplant-eligible subgroup; [redacted] months equivalent to ~[redacted] model cycles) to avoid speculating on a difference in lenalidomide maintenance duration between the DBTd and BTd treatment arms.[2, 3] 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) 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 the list price, has been assumed for lenalidomide in the revised base case using bortezomib as a recent analogue for the associated impact on price following genericisation.[4] 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.[1] From an efficacy perspective, Janssen has modelled an efficacy uplift for both DBTd and BTd based on the observed hazard ratio (HR) by minimal residual disease (MRD) status for lenalidomide maintenance versus observation in Myeloma XI. To ensure the clinical plausibility of modelled outcomes are maintained, the efficacy benefit is applied to progression-free survival (PFS) only, with modelled overall survival (OS) for BTd already noted to surpass that observed for the lenalidomide maintenance arm in Myeloma XI (refer to comment 4 below for further details). Further, the HRs for OS were not significant and associated with wide confidence intervals ([redacted] for MRD-positive and [redacted] for MRD-negative). For PFS, the HRs applied in the revised base case are [redacted] for MRD-positive patients and [redacted] for MRD-negative patients.[3] Notably, when applying efficacy for lenalidomide maintenance therapy in the revised base case, treatment waning for lenalidomide is applied from 10–25 years in line with TA680.[1] To explore uncertainty, and in line with committee preferred assumptions, a scenario analysis is presented below, which assumes a longer treatment duration on lenalidomide maintenance for daratumumab patients. In this scenario, 18 additional cycles (equivalent to an ~20% increase in drug acquisition costs for lenalidomide) are applied to DBTd MRD-negative patients consistent with discussions from the second committee meeting for this appraisal. To balance costs with effects, Janssen has assumed a survival benefit by adjusting the PFS and OS HRs downward by 20% for DBTd MRD-negative versus BTd MRD-negative patients (equivalent to a 0.24 [2.63%] quality adjusted life year [QALY] gain). The rational for this is that, in clinical practice, patients would likely not receive additional cycles of lenalidomide maintenance unless an associated survival benefit was anticipated as a result. Furthermore, as noted above, the model does not otherwise capture any OS benefit associated with lenalidomide maintenance.	longer treatment duration on lenalidomide maintenance for the subgroup who were minimal residual disease negative in the daratumumab in combination arm was more likely to reflect clinical practice. (See FAD section 3.18)

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13	Consultee	Janssen-Cilag Limited	**Daratumumab 'treatment effect' waning** *"The committee considered the possibility that because people have first-line daratumumab for a fixed, short treatment duration, its treatment effect may be less likely to wane than if they had it for longer. This is because the entire benefit of first-line daratumumab would have been delivered, with no opportunity for a gradual loss of effect over time. This difference in prescribing compared with NICE appraisals of daratumumab monotherapy for treating relapsed and refractory multiple myeloma and daratumumab with bortezomib and dexamethasone for previously treated multiple myeloma mean that it may be more reasonable to consider a scenario with no treatment effect waning. However, the committee considered that the treatment effect of daratumumab was likely to wane at some point, and that when this would happen remained uncertain. It decided 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."* Janssen do not consider a 10-year treatment effect for daratumumab to be either evidence-based or clinically plausible. Whilst we acknowledge inherent uncertainty in modelling a lifetime effect, improved long-term outcomes for daratumumab patients are driven by deeper post-consolidation responses rather than a conventional treatment effect per se, and there is substantial evidence demonstrating the association between MRD negativity with improved PFS/OS in newly diagnosed transplant-eligible multiple myeloma.[5-7] External evidence from the GIMEMA study comparing BTd versus thalidomide and dexamethasone (Td) induction/consolidation therapy also provides compelling evidence of maintenance of a treatment effect driven by deeper responses with 10-years median follow-up.[8] It therefore does not make biological or clinical sense to assume that the survival benefit of significantly deeper responses will immediately stop at 10-years. As described in the company response to the first ACD for this appraisal, results from the IPCW-adjusted landmark analyses 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. In addition, 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), higher rates of sustained MRD negativity, more pronounced deepening of response rates over time, and higher rates of MRD negativity conversion.[9] Furthermore, PFS2 results continue to demonstrate the lasting benefit of upfront daratumumab exposure beyond progression with a ~[redacted] reduction in the risk of progression or death on next line of therapy after median follow-up of 44.5 months (before and after adjusting to exclude patients re-randomised to daratumumab maintenance). As noted at the second committee meeting by the clinical lead of the Cancer Drugs Fund, results from CASSIOPEIA Part 2 further support maintenance of a treatment effect driven by deeper post-consolidation responses. Moreover, as requested by the AC, the revised company base case includes lenalidomide maintenance as a subsequent therapy, with patients now assumed to be on continuous therapy. Whilst data from CASSIOPEIA demonstrates continued benefit of DBTd following initial induction/consolidation in terms of more pronounced deepening of response rates over time due to the immunomodulatory effect of daratumumab, the treatment effect of lenalidomide maintenance is now considered the most important factor in determining long-term outcomes (since the full benefit of DBTd has already been delivered as fixed duration therapy). As such, the	Thank you for your comment. The committee considered all the evidence that was provided and the views of clinical experts and concluded that it was reasonable to assume that the impact of deepening a response would be maintained over a lifetime for daratumumab in combination. (See FAD section 3.17)

Comment number	Type of stakeholder	Organisation name	Stakeholder comment	NICE Response
			question is no longer around the persistence of a daratumumab treatment effect, rather the persistence of a lenalidomide maintenance treatment effect. Given changes to the treatment pathway modelled with the inclusion of lenalidomide maintenance as a subsequent therapy, and consistent and compelling evidence supporting maintenance of a treatment effect for daratumumab grounded on both biological and clinical plausibility, daratumumab treatment waning has not been incorporated into the company revised base case. However, in order to explore uncertainty and to demonstrate the effect of waning on the cost-effectiveness results, Janssen has presented two scenarios in **Error! Reference source not found.** below incorporating daratumumab waning assumptions. The first (scenario 2) assumes waning between 10–25 years (in line with the committee's conclusion in the final appraisal document [FAD] for TA680), and the second (scenario 3) waning from 10 years. As described above, in the revised base case, treatment waning for lenalidomide maintenance is applied from 10–25 years in line with TA680.[1]	
14	Consultee	Janssen-Cilag Limited	**Survival outcomes for BTd** *"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."* *"The company considered that its revised analysis likely overestimated overall survival for people having bortezomib plus thalidomide and dexamethasone. It suggested that this was because people in CASSIOPEIA had consolidation treatment, which was not currently part of NHS practice (see section 3.4). Consolidation treatment could have produced a deeper response than induction treatment alone, and therefore longer survival. The ERG considered that the extrapolations used by the company in its revised base case reasonably fit the CASSIOPEIA trial data. However, the ERG agreed with the company that the predictions of overall survival exceeded those from clinical experts. The ERG suggested that this could be due to the nature of the population and interventions in the trial, and the use of a constant hazard ratio to estimate overall survival for people without minimal residual disease."* Janssen acknowledge that the revised IPCW-adjusted landmark analysis is less susceptible to selection bias than naïve censoring. However, we disagree that there remains any risk of residual confounding as all patients followed-up in Part 2 were re-randomised. Moreover, and as noted in the original company submission and prior ACD response, there is an inherent bias against DBTd in favour of BTd within the cost-effectiveness model as survival estimates for BTd are based on post-consolidation response rates, which is not representative of current UK clinical practice. This leads to modelled survival predictions for BTd which exceed clinical expert opinion, with 79% and 62% of patients estimated to be alive at 5- and 10-years respectively compared with clinician estimates of 70% and 50–60% as noted in the first ACD. Indeed, the ERG agreed that the modelled OS represents an overestimate. The overestimation of modelled survival for BTd is also clearly demonstrated when compared against survival outcomes from the Myeloma XI study (see **Error! Reference source not found.**). **Table 1: Estimated and observed overall survival for BTd**	Thank you for your comment. The committee considered all the estimated and observed overall survival data presented. The committee concluded that modelled estimates for long term survival for people who have bortezomib plus thalidomide and dexamethasone are likely to be reflective of clinical practice. (See FAD section 3.16).

Comment number	Type of stakeholder	Organisation name	Stakeholder comment	NICE Response

Data Source		Time (months)					
	12	18	24	36	48	60	120
BTd							
CASSIOPEIA	98%	95%	93%	-	-	-	-
Company revised base case (excl. efficacy uplift for lenalidomide maintenance)	97%	95%	92%	88%	83%	79%	62%
SoC with lenalidomide maintenance							
MYELOMA XI[a] (estimated from KM, transplant-eligible)	96%	94%	92%	88%	79%	73%	-

[e] Estimated from Kaplan-Meier curve (Figure 5B) presented in Jackson *et al.* (2019).[2]

Abbreviations: BTd: bortezomib, thalidomide and dexamethasone; SoC, standard of care.

In Myeloma XI, less than 80% of transplant-eligible patients were alive after 4-years on lenalidomide maintenance with approximately 73% alive at 5-years.[2] By contrast, 83% and 79% of BTd patients are modelled to be alive at 4- and 5-years respectively (see **Error! Reference source not found.**). This is despite the intensive pathway of Myeloma XI including a quadruplet combination of carfilzomib, cyclophosphamide, lenalidomide and dexamethasone (KCLd). In this respect, the relative treatment effect modelled is biased against daratumumab in favour of BTd with the cost-effectiveness results representing a conservative estimate. The overestimation of modelled survival for BTd also precludes clinically plausible OS estimates being derived if an efficacy benefit associated with lenalidomide maintenance is applied, as described in comment 2 above.

References

1. National Institute of Health and Care Excellence (NICE). TA680. Lenalidomide maintenance treatment after an autologous stem cell transplant for newly diagnosed multiple myeloma. 2021.
2. Jackson GH, Davies FE, Pawlyn C, et al. Lenalidomide maintenance versus observation for patients with newly diagnosed multiple myeloma (Myeloma XI): a multicentre, open-label, randomised, phase 3 trial. The Lancet Oncology 2019;20:57-73.
3. Janssen. [Data on File] Myeloma XI. SCT-eligible subgroup analysis. 2021.
4. Janssen. [Data on File] Bortezomib loss of exclusivity. March 2021.
5. Munshi, N. et al. Expanded Meta-Analysis Confirms the Association Between MRD and Long-term Survival Outcomes in Multiple Myeloma (MM). Poster presented at American Society of Hematology (ASH). 2019
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7. Munshi NC, Avet-Loiseau H, Anderson KC, et al. A large meta-analysis establishes the role of MRD negativity in long-term survival outcomes in patients with multiple myeloma. Blood advances 2020;4:5988-5999.
8. Tacchetti P, Pantani L, Patriarca F, et al. Bortezomib, thalidomide, and dexamethasone followed by double autologous haematopoietic stem-cell transplantation for newly diagnosed multiple myeloma (GIMEMA-MMY-3006): long-term follow-up analysis of a randomised phase 3, open-label study. The Lancet Haematology 2020;7:e861-e873.
9. Janssen. [Data on File] MMY3006. Clinical Study Report: Part 1. 2019.

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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 17 September 2021. Please submit via NICE Docs.

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

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Consultation on the appraisal consultation document – deadline for comments 5pm on 17 September 2021. Please submit via NICE Docs.

Comment number	**Comments**
1	Janssen welcomes the opportunity to comment on the preliminary recommendation made by the appraisal committee (AC) detailed in the second appraisal consultation document (ACD). We are disappointed that the AC's preliminary recommendation is not to recommend daratumumab in combination with bortezomib, thalidomide and dexamethasone (DBTd) as induction and consolidation treatment for untreated multiple myeloma in adults, when an autologous stem cell transplant is suitable. We remain committed, however, to working with the National Institute for Health and Care Excellence (NICE) to address the AC's key concerns, as outlined in the second ACD, in order to gain access for patients to this highly innovative and effective fixed duration front-line treatment. Following the second committee meeting, Janssen is pleased that the AC have accepted that bortezomib, thalidomide and dexamethasone (BTd) is the most relevant comparator to DBTd and concluded that the response-based modelling approach and inverse probability censoring weights (IPCW)-adjusted landmark analysis are appropriate for decision-making. Janssen agree with the Committee that the IPCW-adjusted landmark analysis is less susceptible to selection bias than naïve censoring. We consider it important to note, however, that survival extrapolations for BTd continue to exceed predictions from clinical experts. This is due to the use of post-consolidation response rates in the model which is not representative of current UK clinical practice. In terms of modelling for DBTd, Janssen is pleased that the AC acknowledge the reasonableness to consider a scenario with no treatment effect waning for daratumumab. Janssen is, however, disappointed with the AC's preference to model lenalidomide maintenance as a subsequent therapy within the base case despite acknowledging the lack of clinical evidence and considerable uncertainty associated with this. Further, we are highly concerned by the AC's preference to combine modelling lenalidomide maintenance with treatment waning for daratumumab, which is not evidence-based nor aligned with TA680.[1] Thus, in this response, Janssen focus discussion on the following key areas: • Modelling lenalidomide maintenance as a subsequent therapy • The appropriateness of applying treatment waning for daratumumab • The overall conservative nature of the company cost-effectiveness model with regards to survival for BTd Janssen has provided a revised base case cost-effectiveness analysis within this response utilising evidence-based inputs and assumptions where possible (see **Error! Not a valid result for table.** section below). Importantly, we have aimed to avoid speculation, which we consider only serves to add, rather than help reduce, uncertainty. These updated results also incorporate a new patient access scheme (PAS) of [redacted]% for daratumumab, which has been submitted to the patient access schemes liaison unit (PASLU).
2	**Lenalidomide maintenance as a subsequent therapy** *"The committee acknowledged that the lack of clinical evidence exploring the use of lenalidomide maintenance following daratumumab plus bortezomib, thalidomide and dexamethasone made incorporating it into the model challenging, but not impossible. It considered that the model should reflect current NHS practice, and was aware that practice changes over time. At the second meeting, the company included lenalidomide maintenance in their model, but only included the costs and did not consider any clinical benefits (see section 3.16). The committee concluded that both the costs and benefits of*

lenalidomide maintenance should be incorporated as a subsequent treatment in the model to represent current NHS practice."

As noted in our previous ACD response, lenalidomide maintenance as a subsequent therapy was not described in the final scope for this appraisal. As such, Janssen considers the AC's request for incorporating lenalidomide maintenance to be above and beyond the boundary of work set out in the final scope. Moreover, inclusion of a treatment pathway change at this stage of the appraisal is highly challenging, not least given the lack of efficacy data to support cost/benefit assumptions with lenalidomide maintenance following daratumumab specifically.

However, given the AC's preference to include lenalidomide maintenance in the base case, Janssen has revised the company base case to model the impact of lenalidomide maintenance using an evidence-based approach.

When providing results for this revised base case, both costs and efficacy are considered for lenalidomide maintenance as requested by the AC. Whilst Janssen is not aware of any clinical evidence (from either randomised controlled trials [RCTs] or observational real-world studies) to directly inform the efficacy of lenalidomide maintenance following daratumumab, Janssen has used data from the Myeloma XI study which was the main source of clinical evidence in NICE TA680.[1, 2]

Specifically, from a cost perspective, Janssen has assumed the same duration of lenalidomide maintenance therapy following both DBTd and BTd using data for median time to treatment discontinuation (TTD) from Myeloma XI (in the transplant-eligible subgroup; [redacted] months equivalent to ~[redacted] model cycles) to avoid speculating on a difference in lenalidomide maintenance duration between the DBTd and BTd treatment arms.[2, 3] 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) 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 the list price, has been assumed for lenalidomide in the revised base case using bortezomib as a recent analogue for the associated impact on price following genericisation.[4] 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.[1]

From an efficacy perspective, Janssen has modelled an efficacy uplift for both DBTd and BTd based on the observed hazard ratio (HR) by minimal residual disease (MRD) status for lenalidomide maintenance versus observation in Myeloma XI. To ensure the clinical plausibility of modelled outcomes are maintained, the efficacy benefit is applied to progression-free survival (PFS) only, with modelled overall survival (OS) for BTd already noted to surpass that observed for the lenalidomide maintenance arm in Myeloma XI (refer to comment 4 below for further details). Further, the HRs for OS were not significant and associated with wide confidence intervals ([redacted] for MRD-positive and [redacted] for MRD-negative). For PFS, the HRs applied in the revised base case are [redacted] for MRD-positive patients and [redacted] for MRD-negative patients.[3] Notably, when applying efficacy for lenalidomide maintenance therapy in the revised base case, treatment waning for lenalidomide is applied from 10–25 years in line with TA680.[1]

To explore uncertainty, and in line with committee preferred assumptions, a scenario analysis is presented below, which assumes a longer treatment duration on lenalidomide maintenance for daratumumab patients. In this scenario, 18 additional cycles (equivalent to an ~20% increase in drug acquisition costs for lenalidomide) are applied to DBTd MRD-negative patients consistent with discussions from the second committee meeting for this

	appraisal. To balance costs with effects, Janssen has assumed a survival benefit by adjusting the PFS and OS HRs downward by 20% for DBTd MRD-negative versus BTd MRD-negative patients (equivalent to a 0.24 [2.63%] quality adjusted life year [QALY] gain). The rational for this is that, in clinical practice, patients would likely not receive additional cycles of lenalidomide maintenance unless an associated survival benefit was anticipated as a result. Furthermore, as noted above, the model does not otherwise capture any OS benefit associated with lenalidomide maintenance.
3	**Daratumumab 'treatment effect' waning** *"The committee considered the possibility that because people have first-line daratumumab for a fixed, short treatment duration, its treatment effect may be less likely to wane than if they had it for longer. This is because the entire benefit of first-line daratumumab would have been delivered, with no opportunity for a gradual loss of effect over time. This difference in prescribing compared with NICE appraisals of daratumumab monotherapy for treating relapsed and refractory multiple myeloma and daratumumab with bortezomib and dexamethasone for previously treated multiple myeloma mean that it may be more reasonable to consider a scenario with no treatment effect waning. However, the committee considered that the treatment effect of daratumumab was likely to wane at some point, and that when this would happen remained uncertain. It decided 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."* Janssen do not consider a 10-year treatment effect for daratumumab to be either evidence-based or clinically plausible. Whilst we acknowledge inherent uncertainty in modelling a lifetime effect, improved long-term outcomes for daratumumab patients are driven by deeper post-consolidation responses rather than a conventional treatment effect per se, and there is substantial evidence demonstrating the association between MRD negativity with improved PFS/OS in newly diagnosed transplant-eligible multiple myeloma.[5-7] External evidence from the GIMEMA study comparing BTd versus thalidomide and dexamethasone (Td) induction/consolidation therapy also provides compelling evidence of maintenance of a treatment effect driven by deeper responses with 10-years median follow-up.[8] It therefore does not make biological or clinical sense to assume that the survival benefit of significantly deeper responses will immediately stop at 10-years. As described in the company response to the first ACD for this appraisal, results from the IPCW-adjusted landmark analyses 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. In addition, 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), higher rates of sustained MRD negativity, more pronounced deepening of response rates over time, and higher rates of MRD negativity conversion.[9] Furthermore, PFS2 results continue to demonstrate the lasting benefit of upfront daratumumab exposure beyond progression with a ~[redacted] reduction in the risk of progression or death on next line of therapy after median follow-up of 44.5 months (before and after adjusting to exclude patients re-randomised to daratumumab maintenance). As noted at the second committee meeting by the clinical lead of the Cancer Drugs Fund, results from CASSIOPEIA Part 2 further support maintenance of a treatment effect driven by deeper post-consolidation responses. Moreover, as requested by the AC, the revised company base case includes lenalidomide maintenance as a subsequent therapy, with patients now assumed to be on continuous

	therapy. Whilst data from CASSIOPEIA demonstrates continued benefit of DBTd following initial induction/consolidation in terms of more pronounced deepening of response rates over time due to the immunomodulatory effect of daratumumab, the treatment effect of lenalidomide maintenance is now considered the most important factor in determining long-term outcomes (since the full benefit of DBTd has already been delivered as fixed duration therapy). As such, the question is no longer around the persistence of a daratumumab treatment effect, rather the persistence of a lenalidomide maintenance treatment effect. Given changes to the treatment pathway modelled with the inclusion of lenalidomide maintenance as a subsequent therapy, and consistent and compelling evidence supporting maintenance of a treatment effect for daratumumab grounded on both biological and clinical plausibility, daratumumab treatment waning has not been incorporated into the company revised base case. However, in order to explore uncertainty and to demonstrate the effect of waning on the cost-effectiveness results, Janssen has presented two scenarios in Table 2 below incorporating daratumumab waning assumptions. The first (scenario 2) assumes waning between 10–25 years (in line with the committee's conclusion in the final appraisal document [FAD] for TA680), and the second (scenario 3) waning from 10 years. As described above, in the revised base case, treatment waning for lenalidomide maintenance is applied from 10–25 years in line with TA680.[1]
4	**Survival outcomes for BTd** *"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."* *"The company considered that its revised analysis likely overestimated overall survival for people having bortezomib plus thalidomide and dexamethasone. It suggested that this was because people in CASSIOPEIA had consolidation treatment, which was not currently part of NHS practice (see section 3.4). Consolidation treatment could have produced a deeper response than induction treatment alone, and therefore longer survival. The ERG considered that the extrapolations used by the company in its revised base case reasonably fit the CASSIOPEIA trial data. However, the ERG agreed with the company that the predictions of overall survival exceeded those from clinical experts. The ERG suggested that this could be due to the nature of the population and interventions in the trial, and the use of a constant hazard ratio to estimate overall survival for people without minimal residual disease."* Janssen acknowledge that the revised IPCW-adjusted landmark analysis is less susceptible to selection bias than naïve censoring. However, we disagree that there remains any risk of residual confounding as all patients followed-up in Part 2 were re-randomised. Moreover, and as noted in the original company submission and prior ACD response, there is an inherent bias against DBTd in favour of BTd within the cost-effectiveness model as survival estimates for BTd are based on post-consolidation response rates, which is not representative of current UK clinical practice. This leads to modelled survival predictions for BTd which exceed clinical expert opinion, with 79% and 62% of patients estimated to be alive at 5- and 10-years respectively compared with clinician estimates of 70% and 50–60% as noted in the first ACD. Indeed, the ERG agreed that the modelled OS represents an overestimate. The overestimation of modelled survival for BTd is also clearly demonstrated when compared against survival outcomes from the Myeloma XI study (see **Error! Reference source not found.**).

Table 1: Estimated and observed overall survival for BTd

Data Source		Time (months)					
	12	18	24	36	48	60	120
BTd							
CASSIOPEIA	98%	95%	93%	-	-	-	-
Company revised base case (excl. efficacy uplift for lenalidomide maintenance)	97%	95%	92%	88%	83%	79%	62%
SoC with lenalidomide maintenance							
MYELOMA XI[a] (estimated from KM, transplant-eligible)	96%	94%	92%	88%	79%	73%	-

[e] Estimated from Kaplan-Meier curve (Figure 5B) presented in Jackson *et al.* (2019).[2]

Abbreviations: BTd: bortezomib, thalidomide and dexamethasone; SoC, standard of care.

In Myeloma XI, less than 80% of transplant-eligible patients were alive after 4-years on lenalidomide maintenance with approximately 73% alive at 5-years.[2] By contrast, 83% and 79% of BTd patients are modelled to be alive at 4- and 5-years respectively (see **Error! Reference source not found.**). This is despite the intensive pathway of Myeloma XI including a quadruplet combination of carfilzomib, cyclophosphamide, lenalidomide and dexamethasone (KCLd). In this respect, the relative treatment effect modelled is biased against daratumumab in favour of BTd with the cost-effectiveness results representing a conservative estimate. The overestimation of modelled survival for BTd also precludes clinically plausible OS estimates being derived if an efficacy benefit associated with lenalidomide maintenance is applied, as described in comment 2 above.

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

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Revised base case

Considering the AC's preferred assumptions, alongside the issues covered in comments 1–4 of this document, Janssen provide a revised company base case as follows:

- Incorporating lenalidomide maintenance costs equivalent to [redacted] cycles for both DBTd and BTd, with an associated efficacy uplift applied to PFS only
- Lenalidomide maintenance treatment waning applied from 10–25 years
- Generic price for lenalidomide, assuming a [redacted]% discount from list price

In addition to the revised company base case, and in acknowledgement of the AC's request for scenario analyses, Janssen provide the following scenario analyses:

- Scenario 1 – Revised base case + an assumption of a longer lenalidomide maintenance duration for MRD-negative patients in the DBTd arm (18 additional cycles) and an associated efficacy benefit of 20%
- Scenario 2 – Scenario 1 + an assumption of treatment waning for daratumumab from 10–25 years
- Scenario 3 – Scenario 1 + an assumption of treatment waning for daratumumab from 10 years

Table 2 summarises the revised company base case plus additional scenario analyses requested in the ACD. The revised company base-case, including both deterministic and probabilistic results, is presented in Table 3. The probabilistic scatterplot is presented in Figure 1 and cost effectiveness acceptability curve in Figure 2.

Table 2: Updated cost-effectiveness results (with [redacted]% PAS)

Scenario	Inc. costs	Inc. QALYs	ICER
Company base case from first ACD response	[redacted]	[redacted]	£22,331
Include lenalidomide maintenance	[redacted]	[redacted]	£25,858
Revised daratumumab PAS	[redacted]	[redacted]	£23,061
Company revised base case	[redacted]	[redacted]	£23,061
Additional scenarios (applied to the company revised base-case)			
Scenario 1	[redacted]	[redacted]	£21,201
Scenario 2	[redacted]	[redacted]	£21,960
Scenario 3	[redacted]	[redacted]	£26,366

Abbreviations: ACD, appraisal consultation document; ICER, incremental cost-effectiveness ratio; Inc, incremental; PAS, patient access scheme; QALYs, quality-adjusted life years.

Table 3: Revised company base-case results (with [redacted]% 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]	£23,061
Probabilistic							
DBTd	[redacted]	N/A	[redacted]	-	-	-	-
BTd	[redacted]	N/A	[redacted]	[redacted]	N/A	[redacted]	£21,036

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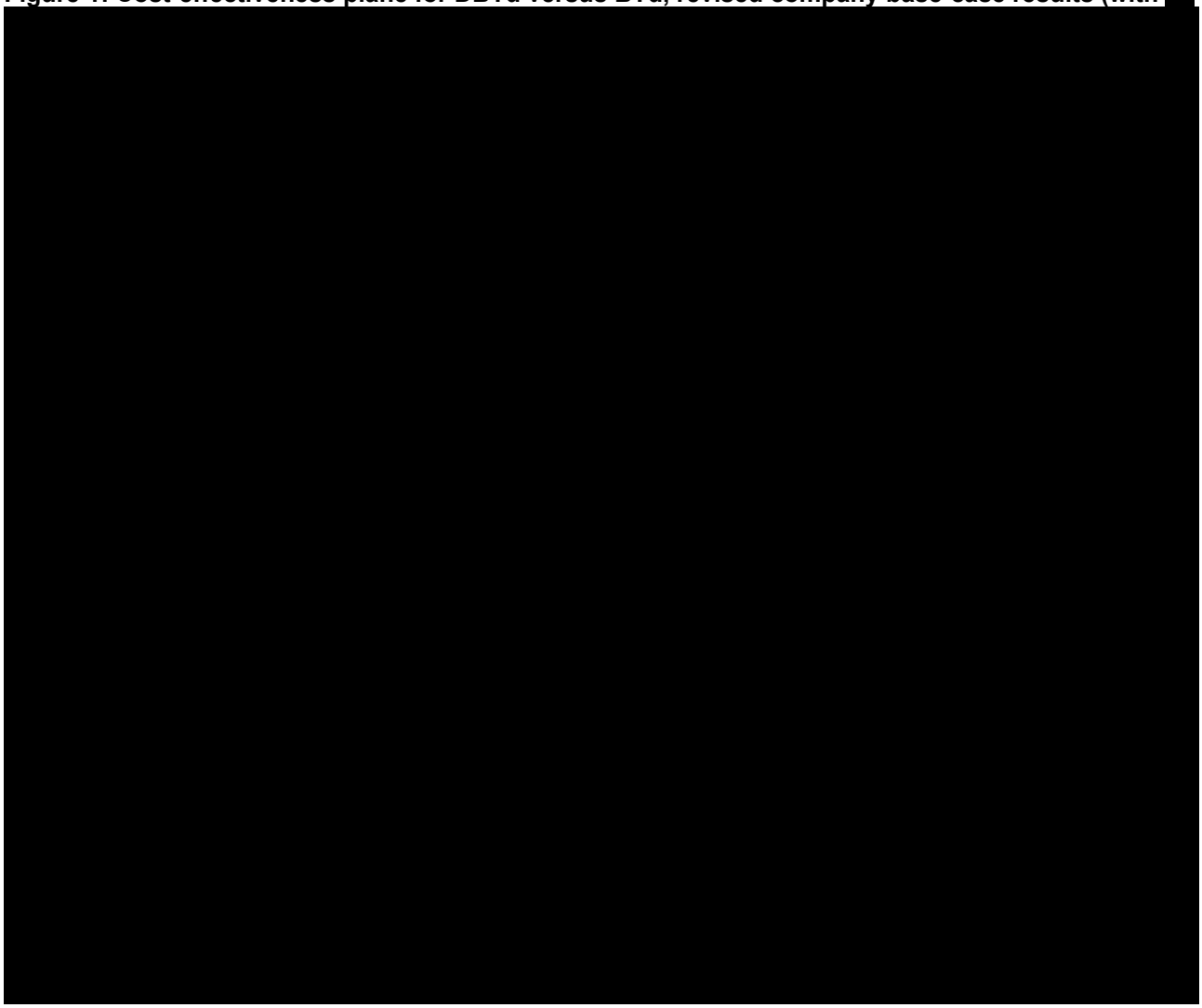
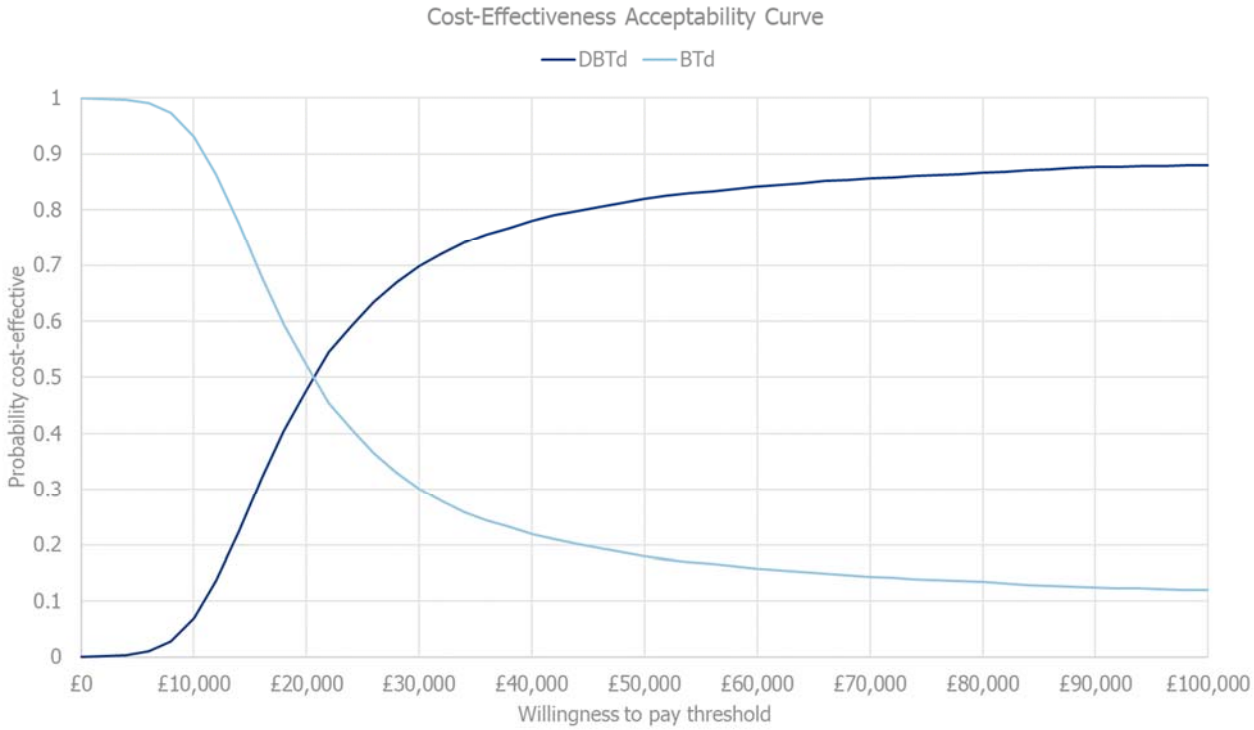
Abbreviations: BTd, bortezomib, thalidomide and dexamethasone; DBTd, daratumumab, bortezomib, thalidomide and dexamethasone; ICER, incremental cost-effectiveness ratio; Inc, incremental; LYG, life years gained; N/A = not available; PAS, patient access scheme; QALYs, quality-adjusted life years.

Figure 1: Cost-effectiveness plane for DBTd versus BTd, revised company base-case results (with [redacted] 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.

Figure 2: Cost-effectiveness acceptability curve, revised company base-case results (with [redacted]% PAS)



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

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1. National Institute of Health and Care Excellence (NICE). TA680. Lenalidomide maintenance treatment after an autologous stem cell transplant for newly diagnosed multiple myeloma. 2021.
2. Jackson GH, Davies FE, Pawlyn C, et al. Lenalidomide maintenance versus observation for patients with newly diagnosed multiple myeloma (Myeloma XI): a multicentre, open-label, randomised, phase 3 trial. The Lancet Oncology 2019;20:57-73.
3. Janssen. [Data on File] Myeloma XI. SCT-eligible subgroup analysis. 2021.
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9. Janssen. [Data on File] MMY3006. Clinical Study Report: Part 1. 2019.

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

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	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	We note the progress made following the first Appraisal Consultation Document (ACD) and the agreement reached on issues such as: consolidation being adopted into NHS practice; MRD negativity being likely to predict survival outcomes better than stringent complete response; and that the company's landmark analysis approach to modelling long term survival is appropriate.
2	However we do not believe that the • the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence or that • the provisional recommendations are a sound and suitable basis for guidance to the NHS. The reasons for these conclusions are set out below.
3	In our view, the evidence summaries do not fully reflect the strength of clinical opinion on the weaknesses in the ERG's approach to treatment waning. If treatment waning is to be applied then a realistic, evidence based approach which is consistent across myeloma appraisals should be applied. We highlight the fact that no treatment waning was observed for daratumumab patients in the CASSIOPEIA trial after almost four years of follow up. We do not believe the evidence supports the Committee's conclusion that the treatment effect of daratumumab would likely last 10 years or less after consolidation. We note that in TA680 the Committee applied a 10 – 25 year waning assumption of lenalidomide maintenance. If treatment waning is to be applied in this appraisal, it should be consistent with this decision, which is at the same part of the treatment pathway (first line.)
4	Another area of concern is the approach to including lenalidomide maintenance in modelling cost effectiveness. First of all we note that lenalidomide maintenance was not included in the final scope of the appraisal and that its inclusion post technical engagement is not standard NICE process. We do understand the desire to reflect real world clinical practice in the Committee's considerations, but there is a balance to be struck in doing this with protecting the integrity of the appraisal process. (We note that the exclusion of Cancer Drugs Fund (CDF) approved treatments as comparators is an instance of where real world clinical practice is not taken into account by Committees.) We note and agree with the second ACD's observation that modelling the effects of lenalidomide maintenance on cost effectiveness is challenging. We hope that Janssen will have done everything possible to "mine" existing data such as Myeloma XI for relevant evidence but we would also encourage the committee to take a pragmatic and proportionate approach to this uncertainty. Otherwise the approval of lenalidomide maintenance will place unreasonable barriers in the way of approving effective new induction regimens.
5	While noting that patients would welcome the approval of this treatment option, we do not believe that the ACD fully recognises the innovative nature of daratumumab as an addition to induction treatment, including the psychological benefit to patients in knowing that they are receiving an innovative treatment with improved chances of achieving MRD negative status. Also, while we agree with

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	clinical opinion that the majority of patients will go on to receive lenalidomide maintenance, the MRD negative benefits may over time enable some patients to decide to have a treatment free period, leaving the opportunity of accessing lenalidomide further down the treatment pathway.
6	Finally, while we are relieved that the possibility of a positive decision is still present, we are frustrated at the length of time this appraisal has taken. We realise that the speed of the appraisal is not within the control of NICE alone and that companies have a key role to play in supporting earlier positive decisions. However, we are now around one year past our initial submission to this appraisal and in that time many patients have missed the opportunity of accessing a treatment which can deliver longer remissions. We encourage all parties, including the company, to do all they can to deliver a solution that will enable patients to access this treatment as soon as possible.

Insert extra rows as needed

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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
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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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 17 September 2021. Please submit via 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	The committee has stated that the duration of Daratumumab effect is uncertain. They have concluded that the treatment effect of Daratumumab would likely last 10 years or less. We do not agree that there will be a treatment waning effect. Newly diagnosed myeloma patients will be given a highly effective treatment for a short fixed duration (4 cycles of D-BTd pre transplant and 2 cycles of D-BTd afterward), with a high response rate. There will be two groups of patients (D-BTd or BTd alone) that will have different outcomes based on their depth of response (higher MRD negative rate in the D-BTd group). As this treatment is given for a short duration there is less likelihood of developing resistant disease that would alter long term outcomes. This is supported by the fact that there is no evidence of treatment waning in the CASSIOPEA trial after 4 years follow up. As mentioned previously there is no evidence of treatment waning in other trials that have published data beyond 10 years (GIMMEMA trial comparing BTd vs Td induction/consolidation).
2	Lenalidomide maintenance. As mentioned there is no data evaluating Lenalidomide maintenance after Daratumumab induction therapy. We welcome the use of the large UK based Myeloma XI trial data in this appraisal, although there remains uncertainty combining data from 2 separate trials. The Myeloma XI trial data was used to support the approval of Lenalidomide maintenance by NICE (TA680). In this appraisal it was assumed there was a gradual treatment waning effect over 10-25 years. If treatment waning is accepted by the committee, despite our concerns mentioned above, we would support a gradual waning effect as used in TA680 over 10-25 years as this represents both a clinically plausible and pragmatic approach consistent with previous NICE technology appraisals in the same part of the patient pathway.
3	Beyond QALY benefits. We note the ACD did not acknowledge any additional benefits of D-BTd. Given Daratumumab's innovative mechanism of action and an extension in the treatment free period, we feel this will have a positive impact on quality of life for both he patient and care giver.
4	We would welcome giving clinical input at any future committee meetings.
5	
6	

Insert extra rows as needed

Checklist for submitting comments

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- Complete the disclosure about links with, or funding from, the tobacco industry.
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- Do not include medical information about yourself or another person from which you or the person could be identified.
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- If you have received agreement from NICE to submit additional evidence with your comments on the appraisal consultation document, please submit these separately.

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

Evidence Review Group's critique of the company's response to the second ACD

Produced by Southampton Health Technology Assessments Centre (SHTAC)

Authors Joanne Lord, Neelam Kalita

Date completed 29 September 2021

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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 (ACD2 section 3.19)	Company response	ERG comments
Including lenalidomide maintenance as a subsequent treatment, to reflect current NHS practice (ACD2 sections 3.5 and 3.16)	The company have presented a revised base case including lenalidomide maintenance, with the following assumptions: • [redacted] four-week model cycles ([redacted] months) of lenalidomide maintenance after induction/ consolidation treatment with the daratumumab combination (DBTd) or comparator (BTd) (company estimate of median time to treatment discontinuation in the Myeloma XI trial transplant-eligible subgroup).[1] • Treatment effect on PFS: HR (lenalidomide maintenance versus observation) [redacted] for MRD-positive and [redacted] for MRD-negative (company analysis of Myeloma XI Kaplan-Meier data).[1] • No change to OS with lenalidomide maintenance, as the modelled estimate for BTd exceeds that for lenalidomide maintenance in Myeloma XI (ACD2 response Table 1). The lenalidomide maintenance HRs for OS were also uncertain: [redacted] for MRD-	The company have responded to this request. The revised base case includes estimated costs and benefits of lenalidomide maintenance, assumed to be the same with or without prior treatment with daratumumab. A scenario with increased duration and better PFS and OS with lenalidomide maintenance after daratumumab is also presented (see below). The base case assumptions on lenalidomide maintenance duration and effects are appropriately based on Myeloma XI results, which was the main source of evidence in TA680. The decision not to model the effect of lenalidomide maintenance on overall survival in the revised base case is reasonable to reflect survival expectations with standard care. In Scenario 1, the company includes a lenalidomide maintenance survival benefit in the daratumumab arm only. We test the effect of excluding this in ERG additional analysis (Table 6). The regimen and dose intensity are consistent with TA680 committee conclusions. One inconsistency with TA680 is the continued inclusion of lenalidomide as a second and third line treatment option

	positive and [redacted] for MRD-negative). • 10 mg per day lenalidomide maintenance on days 1-21 of 28 day cycle (as in Myeloma XI trial and following TA680 committee conclusions).[2 3] • 89% relative dose intensity (based on committee conclusions in TA680).[3] The company also assume a [redacted] price discount for lenalidomide due to forthcoming patent expiry (based on experience with bortezomib).	(unchanged from the previous base case). We tested the effect of subsequent treatment with lenalidomide after first relapse (Table 5). However, we did not not exclude lenalidomide at third line, as it is the only remaining option after excluding CDF treatments and the panobinostat combination. It is not usual to assume price reductions for future patent expiry in NICE appraisals. Removing the assumed discount for lenalidomide causes a moderate increase in the ICER (Table 5 below). We also report results with all PAS and CMU discounts for comparators, concurrent and subsequent treatments in a separate addendum.
A landmark analysis adjusted for re-randomisation to daratumumab maintenance using the company's IPCW approach (ACD2 section 3.7). Basing the long-term survival modelling on the company's landmark analysis approach, split by minimal residual	The company welcome these conclusions but disagree with committee's conclusion that residual confounding may remain after adjustment for daratumumab maintenance in the CASSIOPEIA trial, as all patients included in the daratumumab maintenance phase were re-randomised. They also argue that overall survival extrapolations for standard care are overestimates, as patients in the CASSIOPEIA trial had post-transplant consolidation treatment, which is not current UK practice. To support this point, the company cite clinical expert opinion from ACD1 and draw a comparison with results from 5-year follow up from MYELOMA XI (ACD1 response Table 1).	We also agree with the decision to base survival estimates on the landmark analysis, split by MRD status, with IPCW adjustment for re-randomisation to daratumumab maintenance. We consider that there is still a risk of residual confounding, due to informative censoring of the patients who entered the CASSIOPEIA maintenance phase and missing prognostic factors in the IPCW adjustment, however this risk is clearly lower than with the previous naïve censoring approach. We disagree that overestimation of survival is 'clearly demonstrated'. Comparison of modelled extrapolations with clinical opinion and data from external sources is inevitably uncertain.

disease status (ACD2 section 3.11) Using the IPCW-adjusted landmark analysis to model survival for people having bortezomib plus thalidomide and dexamethasone (ACD2 section 3.14).		We consider that differences between the model estimates and survival outcomes from Myeloma are actually quite small: a 4 percentage point difference at month 48, and 6 percentage point difference at month 60. The company also fails to cite results for BTd in the GIMEMA study, which was discussed at ACM1 (slide 47). This reported 3, 5 and 10 year survival of 86%, 79% and 60%, respectively. These results are remarkably similar to extrapolations from the company's revised base case of 88%, 79% and 62%.
A daratumumab treatment effect lasting up to 10 years after consolidation treatment (ACD2 section 3.15).	The company argue that a 10-year treatment effect is not "evidence-based or clinically plausible". They reiterate arguments from their original submission, technical engagement and response to the first ACD regarding the depth of response over 4-year follow up of CASSIOPEIA, 10-year follow up from GIMEMA and other contextual evidence. The revised base case does not include treatment waning for daratumumab. It does include waning of the effects of lenalidomide maintenance between 10-25 years, as in TA680. The company do include daratumumab waning in two scenarios (see below).	The ERG does not agree with the company's decision to exclude waning from their base case. The company has not provided any additional evidence to support this case. We think it is important to reiterate two key counter-arguments for a more conservative approach. The model structure already 'hard wires' treatment effects from inducing and consolidating a MRD negative response. Evidence from CASSIOPEIA for additional survival benefits within the MRD groups are uncertain, with wide confidence intervals: HRs for DBTd vs. BTd are [redacted] for MRD-positive and [redacted] for MRD-negative (ACD2 slide 31). We report additional ERG scenarios on waning (Table 5)
A mean age at the start of induction treatment based on evidence from Public Health	Implemented in the previous and revised base case analyses.	This has been appropriately implemented.

England (ACD2 section 3.17)		
Omitting panobinostat plus bortezomib and dexamethasone as a treatment at third or fourth line (ACD2 section 3.18)	Implemented in the previous and revised base case analyses.	This has been appropriately implemented.

Table 2 Summary of response to requested scenarios

Requested scenarios (ACD2 section 3.19)	Company response	ERG comments
Lenalidomide maintenance (ACD2 section 3.16) *A scenario including maintenance with lenalidomide should include both its costs and benefits*	Scenario 1: • Additional 18 cycles of lenalidomide maintenance for MRD-negative patients after DBTd (calibrated to give a 20% increase in lenalidomide acquisition cost) • Additional 20% reduction in HRs (DBTd vs. BTd) for PFS and OS in MRD-negative patients	Scenario 1 reflects the committee's preference for a longer duration of lenalidomide maintenance after first line daratumumab (ACD 3.16). The company assumes that extended lenalidomide maintenance would be restricted to patients with an MRD-negative response and accompanied with survival benefits, which is reasonable. However, the magnitudes of these changes are highly uncertain. There is also no clear rationale for assuming the same 20% reduction for lenalidomide acquisition costs and for the hazard ratios. We test sensitivity of cost-effectiveness to these assumptions in Table 6.
Treatment effect waning The Committee decided that it had not	The company present two scenarios with daratumumab waning "to explore uncertainty and to	The waning assumption in Scenario 3 is consistent with the committee's preference for a daratumumab treatment effect lasting "up to 10 years" after consolidation treatment.

seen enough evidence to support changing its original conclusion that the treatment effect of daratumumab would likely last 10 years or less after consolidation.	demonstrate the effect of waning on the cost-effectiveness results". Scenario 2: • Scenario 1 plus gradual loss of daratumumab relative treatment effects (HRs for DBTd vs. BTd) starting at year 10 and ending at year 25. Scenario 3: • Scenario 1 plus sudden loss of daratumumab relative effects at year 10.	We report additional ERG scenarios in Table 5. This includes a scenario with gradual loss of daratumumab effects starting at year 5 and ending at year 10, which is an alternative interpretation of the committee's preferred assumption. For comparison, we also report a scenario with sudden loss of daratumumab effects at year 5, which is consistent with current evidence from four years of follow up from CASSIOPEIA.

Table 3 Summary of response to other uncertainties

Additional uncertainties	Company response	ERG comments
The duration of the daratumumab treatment effect	Discussion relating to treatment waning as above. No further evidence, but scenarios with alternative waning assumptions are provided.	Additional ERG waning scenarios to further explore uncertainty.
How the duration and benefits of lenalidomide maintenance may differ for people having daratumumab plus bortezomib, thalidomide and dexamethasone compared with people having bortezomib, thalidomide and dexamethasone without daratumumab.	The company notes that modelling lenalidomide maintenance is highly challenging due to the lack of clinical evidence to support cost/benefit assumptions following daratumumab. A scenario with longer lenalidomide maintenance treatment and enhanced OS and PFS benefits following daratumumab is provided.	We agree that this is highly uncertain. The company take a reasonable approach in their revised base case (with no difference in lenalidomide costs or benefits with or without previous daratumumab), and Scenario 1. We provide sensitivity analysis on the assumptions in this scenario.

2. ERG check of revised economic analysis

We replicated the company's revised base case analysis (Table 2 of their response to ACD2). The base case assumptions for lenalidomide maintenance include an assumed [redacted] reduction in the list price of lenalidomide. We show this separately because this assumption on its own causes an increase in the previous base case ICER. This is caused by the effect of the assumed discount on costs for second and third line lenalidomide: the model predicts a smaller cost reduction for daratumumab than for the comparator (see Table 4 below).

The ERG also replicated the company's scenario analyses (Table 4). Scenario 1 has a higher ICER than the revised base case due to the combined effect of assumptions about the duration of lenalidomide maintenance treatment (18 months longer) and improved overall and progression-free survival (20% reduction in HRs) for MRD-negative patients following daratumumab. The addition of assumptions about waning of the daratumumab treatment effect in Scenarios 2 and 3 increase the ICER.

Table 4: ERG check of company base case and scenario analyses, deterministic

Scenarios		Total costs	Total QALYs	Incr. costs	Incr. QALYs	ICER
Cumulative change to company's base case						
Company base case from first ACD response	DBTd BTd	[redacted]	[redacted]	[redacted]	[redacted]	£22,331
Assumed lenalidomide price reduction ([redacted]%)	DBTd BTd	[redacted]	[redacted]	[redacted]	[redacted]	£25,452
Include lenalidomide maintenance	DBTd BTd	[redacted]	[redacted]	[redacted]	[redacted]	£25,858
Revised daratumumab PAS ([redacted]%) – Revised base case	DBTd BTd	[redacted]	[redacted]	[redacted]	[redacted]	£23,061
Company scenario analyses						
Scenario 1: longer lenalidomide maintenance for DBTd MRD-	DBTd BTd	[redacted]	[redacted]	[redacted]	[redacted]	£21,201
Scenario 2: + daratumumab waning from 10-25 years	DBTd BTd	[redacted]	[redacted]	[redacted]	[redacted]	£21,960
Scenario 3: + daratumumab waning at 10 years	DBTd BTd	[redacted]	[redacted]	[redacted]	[redacted]	£26,366

Source: Company response to ACD2 Table 2, with additional results obtained by the ERG from the company model (dated 18/09/21)

3. Additional ERG analysis

We conducted three sets of scenarios on the company's revised base case (Table 5):

- Removing the assumed price discount for lenalidomide causes a moderate increase in the base case ICER. The ICER increase is larger in company scenarios 1-3, which assume a longer duration of lenalidomide maintenance after daratumumab.
- The ICER increases with earlier waning of the daratumumab effect (sudden loss of relative effect at 5 years or gradual decrease between 5 and 10 years). These scenarios reflect the committee's conclusion
- Removing lenalidomide as a treatment option after first relapse has a negligible impact on the ICER.

Table 5 Additional ERG scenarios on revised company base case, deterministic

Scenarios		Total costs	Total QALYs	Incr. costs	Incr. QALYs	ICER
Company revised base case	DBTd BTd	[redacted]	[redacted]	[redacted]	[redacted]	£23,061
No price reduction for lenalidomide						
Company revised base case	DBTd BTd	[redacted]	[redacted]	[redacted]	[redacted]	£25,957
Company Scenario 1	DBTd BTd	[redacted]	[redacted]	[redacted]	[redacted]	£40,046
Company Scenario 2	DBTd BTd	[redacted]	[redacted]	[redacted]	[redacted]	£40,227
Company Scenario 3	DBTd BTd	[redacted]	[redacted]	[redacted]	[redacted]	£45,104
Alternative assumption about waning of daratumumab treatment effect						
Waning from 5 to 10 years	DBTd BTd	[redacted]	[redacted]	[redacted]	[redacted]	£33,360
Waning at 5 years	DBTd BTd	[redacted]	[redacted]	[redacted]	[redacted]	£40,608
Use of lenalidomide as subsequent treatment						
None after first relapse	DBTd BTd	[redacted]	[redacted]	[redacted]	[redacted]	£23,142

Source: Obtained by the ERG from the company model (dated 18/09/21)

We also tested the sensitivity of results for Scenario 1 to the assumptions about the additional duration and survival effects of lenalidomide maintenance after daratumumab (Table 6). The ICER is not very sensitive to changes in the assumed duration of lenalidomide maintenance for people who are MRD-negative after daratumumab. It is more sensitive to assumptions about the effect of lenalidomide on survival outcomes in this group.

Table 6 ERG sensitivity analysis on company scenario 1, deterministic

Scenarios		Total costs	Total QALYs	Incr. costs	Incr. QALYs	ICER
Company Scenario 1	DBTd BTd	[redacted]	[redacted]	[redacted]	[redacted]	£21,201
Sensitivity to duration of lenalidomide maintenance (DBTd MRD-)						
Additional 12 months	DBTd BTd	[redacted]	[redacted]	[redacted]	[redacted]	£20,679
Additional 24 months	DBTd BTd	[redacted]	[redacted]	[redacted]	[redacted]	£21,657
Sensitivity to effect of lenalidomide maint. (HR for DBTd vs. BTd, MRD-)						
20% reduction PFS only	DBTd BTd	[redacted]	[redacted]	[redacted]	[redacted]	£24,245
10% reduction PFS & OS	DBTd BTd	[redacted]	[redacted]	[redacted]	[redacted]	£23,027
30% reduction PFS & OS	DBTd BTd	[redacted]	[redacted]	[redacted]	[redacted]	£19,576

Source: Obtained by the ERG from the company model (dated 18/09/21)

1. Janssen. [Data on File] Myeloma XI. SCT-eligible subgroup analysis. 2021.
2. Jackson GH, Davies FE, Pawlyn C, et al. Lenalidomide maintenance versus observation for patients with newly diagnosed multiple myeloma (Myeloma XI): a multicentre, open-label, randomised, phase 3 trial. *The Lancet Oncology* 2019;20(1):57-73. doi: 10.1016/S1470-2045(18)30687-9
3. National Institute of Health and Care Excellence (NICE). TA680. Lenalidomide maintenance treatment after an autologous stem cell transplant for newly diagnosed multiple myeloma. 2021