NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Daratumumab in combination for untreated systemic amyloid light-chain amyloidosis [ID3748]

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 systemic amyloid light-chain amyloidosis
[ID3748]

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 treating newly diagnosed systemic amyloid light-chain amyloidosis

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 Please insert each new comment in a new row	NICE Response Please respond to each comment
1	Patient group	Myeloma UK	We welcome that the committee have acknowledged that AL Amyloidosis is a serious, incurable condition, and that its mental and physical effects can be overwhelming. We also welcome that the committee has agreed that there is an unmet need for effective licensed treatments options for AL Amyloidosis and that Daratumumab in combination improves the haematological response for patients whilst having tolerable side effects. We are also pleased that NICE will consider daratumumab in combination within its full licensed population regardless of disease severity. We understand that there are several uncertainties to be resolved including on the data source for extrapolation of overall survival and the timeline for assessing haematological response. We are concerned that the first committee meeting did not include a clinical expert who was a haematologist. In NHS clinical practice a haematologist would be the lead consultant for patients with AL Amyloidosis. The clinical experts invited to the first committee meeting included cardiologists and nephrologists. The experts' contributions to the discussion were significant and important, including on the inclusion of patients with cardiac 3b disease severity in the full licensed indication. However, they would not normally be the lead consultants for patients with AL Amyloidosis. We feel that a haematologist would be better placed to answer committee questions on significant issues such as the generalisability of patient population data to UK NHS clinical practice and on the timelines for assessing haematological response. Both of which are key issues of uncertainty the committee highlighted in the appraisal consultation document.	While the committee recognised AL amyloidosis is a serious incurable condition and there is an unmet need because there are no licensed treatments, daratumumab in combination could not be recommended because of the uncertainties in the evidence and because the cost-effectiveness estimates are higher than what NICE considers to be an effective use of NHS resources. Although, the company attempted to address issues surrounding the data source for extrapolating overall survival, uncertainties remain (see section 3.13 of the FAD). At the second committee meeting, both patient and clinical experts including a consultant haematologist attended.

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			We would therefore request that both clinical and patient experts be invited to the second committee meeting. We would also request that at the second committee meeting a haematologist be invited as a clinical expert to help answer the committee's questions. We understand that the submitting company have nominated a clinical expert who is a haematologist and would welcome their invitation to the second committee meeting. Alternatively, the committee could reach out to the UK Myeloma Society for a clinical expert as many haematologists who specialise in myeloma also treat a significant number of patients with AL Amyloidosis. There are currently no licensed treatments for AL Amyloidosis available through the NHS and this is the first time a treatment for AL Amyloidosis that has come to NICE for HTA. We feel that by having a haematologist in the second meeting the committee will be better placed to answer key questions in this appraisal. If this were to be approved, then it would be the very first treatment for newly diagnosed AL Amyloidosis which would be a significant milestone for AL Amyloidosis patients and their families.	
2	Clinical expert	Jennifer Pinney	• Has all of the relevant evidence been taken into account? yes • Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? The cost effectiveness modelling is potentially flawed as there was no incorporation of costs related to progression to end stage renal failure. Dialysis is expensive with a range of costs estimated between £15,000 to £60,000 per year depending on frequency, modality and hospital admissions. The benefit from delay of disease progression to end stage renal failure or prevention of progression was not included in any of the modelling. This should be considered as part of the cost effectiveness modelling. • Are the provisional recommendations sound and a suitable basis for guidance to the NHS? The recommendation is disappointing; it was surprising that a haematologist was not on the expert panel. Haematologists are the physicians who deliver	At the second committee meeting, the Evidence Review Group confirmed that the company model includes progression to end-stage organ failure and assumes that some people need haemodialysis and peritoneal dialysis and transplant or surgical intervention with related costs. A consultant haematologist attended the second committee meeting as a clinical expert. While the committee recognised AL amyloidosis is a serious incurable condition and there is an unmet need because there are no licensed treatments, daratumumab in combination could not be recommended because of the uncertainties in the evidence and because the cost-effectiveness

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			the treatment and have most experience with the use of Daratumumab. I would strongly recommend involvement in future reviews.	estimates are higher than what NICE considers to be an effective use of NHS resources.
3	Company	Janssen	Janssen thank NICE for the opportunity to comment on the Appraisal Consultation Document (ACD) for daratumumab in combination with bortezomib, cyclophosphamide and dexamethasone (DBCd) for treating newly diagnosed systemic amyloid light-chain (AL) amyloidosis [ID3748] published on the 20 January 2022.[1] Janssen are pleased that the Appraisal Committee (AC) have recognised that AL amyloidosis is a life-threatening, incurable condition and that there is an unmet need for an effective treatment option for this condition.[1] In particular, Janssen are pleased that the AC concluded: • The correct comparator for decision making is BCd (ACD, page 6) • The relevant positioning for DBCd in UK clinical practice is as a front-line therapy for newly diagnosed adults with AL amyloidosis, regardless of severity, and that if recommended, NICE would consider DBCd for use within its approved full licensed indication (ACD, page 7) • The ANDROMEDA trial population is likely to be broadly generalisable to typical clinical practice in England, despite the exclusion of people with severe complications such as Stage IIIb cardiac disease (ACD, page 8) • The primary endpoint of the ANDROMEDA trial, complete haematologic response, is a surrogate endpoint for overall survival (ACD, page 9) • DBCd is an effective treatment for improving haematologic response, and reducing major organ deterioration in individuals with AL amyloidosis (ACD, page 10) • The adverse events (AEs) associated with DBCd observed in the ANDROMEDA trial were generally well tolerated by patients and	While the committee recognised AL amyloidosis is a serious incurable condition and there is an unmet need because there are no licensed treatments, daratumumab in combination could not be recommended because of the uncertainties in the evidence and because the cost-effectiveness estimates are higher than what NICE considers to be an effective use of NHS resources. The committee noted that the end-of-life criteria was not met for the full population for which the company was positioning daratumumab in combination (see section 3.18 of the FAD). Despite the company's ACD response, at the second committee meeting uncertainties still remained about the best data source to inform the economic model (see section 3.11 of the FAD), potential confounding factors between haematological response and overall survival (see section 3.12 of the FAD) and validity of the utility values (see section 3.15 of the FAD). In addition, the committee considered the company's approach to modelling sustained benefit of daratumumab was not appropriate (see section 3.14 of the FAD), that the administrative cost of daratumumab and bortezomib to be the same for the first 6 cycles at £1,127 per cycle for both daratumumab and standard care arms (see section 3.17 of the FAD).

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			appropriately represented in the economic analysis (ACD, page 10) • DBCd is an innovative therapy associated with benefits which are not captured in the cost per QALY framework, such as the benefits to people with concomitant myeloma (ACD, page 20) Janssen are, however, disappointed with the AC's preliminary decision not to recommend DBCd within its marketing authorisation for the treatment of adult patients with newly diagnosed AL amyloidosis in England.[1] DBCd is the first and only treatment licensed for patients with AL amyloidosis and is both highly innovative and highly effective thus addressing a considerable unmet need. Janssen remain committed to working with NICE throughout the subsequent stages of this appraisal to secure a positive outcome which will enable patient access to DBCd. To support the case for access to DBCd for newly diagnosed AL amyloidosis patients, Janssen wish to highlight the following points pertaining to topics discussed during the ACM and ACD: • Greater flexibility in the acceptable incremental cost-effectiveness ratio (ICER) is supported by a substantial proportion of the eligible patient population being end-of-life and the existence of benefits associated with DBCd not captured in the cost per QALY framework • Following re-categorisation and adjustment, data from the UK cohort of the EMN23 study represents the most robust source of real-world evidence to inform the economic model • Additional analysis investigating the association between haematologic response and overall survival in ANDROMEDA has confirmed no evidence of confounding • Data from ANDROMEDA demonstrates higher levels of sustained response for DBCd versus BCd which has already translated to a survival benefit at 20.3 months median follow-up. The benefit of daratumumab maintenance therapy in this regard was not captured in	

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			the economic model • DBCd represents an effective treatment for patients with end-stage cardiac disease, and use of NHS resources in this patient group is expected to provide substantial clinical benefits given their very high level of unmet need • SF36v2 data from the ALchemy trial are unavailable, precluding their use to validate the utility dataset currently used in the economic model • The administration cost of £332 for daratumumab subcutaneous injection significantly overestimates the true cost to the NHS Detailed discussion of the above points is provided in Points 1–7 below. To further support access, Janssen have revised the PAS for daratumumab, increasing the simple discount to a [redacted], thus offering additional value for money to the NHS. All changes to the economic base case implemented in order to address the concerns of the AC, alongside the updated base case and scenario results, are outlined in **Error! Reference source not found.**. In conclusion, Janssen have endeavoured to secure robust real-world evidence data that are reflective of UK clinical practice and aligned with the haematologic response categories implemented in the ANDROMEDA trial. These data have been implemented in the updated company base case, presented in **Error! Reference source not found.**, in order to reflect the AC's preferences and reduce uncertainty associated with the decision problem. The updated economic model results indicate daratumumab in combination to be a cost-effective use of NHS resources when considering the cost-effectiveness range typically considered by NICE for rare diseases such as AL amyloidosis, and taking into account, the extent of clinical unmet need and elements of value not captured in the QALY. Flexibility in the acceptable ICER is supported by the direction of travel of the new NICE guidance development manual towards greater acceptance of uncertainty in	

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			rare diseases and conditions with a high unmet need.[2] Furthermore, while the decision for positioning DBCd for routine commissioning responds to a high unmet need, discussions with NHSE have confirmed that daratumumab in combination is eligible for entry to the Cancer Drugs Fund (CDF).	
4	Company	Janssen	**Greater flexibility in the acceptable ICER is supported by a substantial proportion of the eligible patient population being end-of-life and the existence of insufficiently captured benefits associated with DBCd treatment. This is further supported by the direction of travel of the new NICE guidance development manual regarding acceptance of uncertainty in rare diseases and high unmet need conditions** **Section 3.20, page 20:** The ACD states: "*The uncertainty means an acceptable incremental cost-effectiveness ratio (ICER) is £20,000 per quality-adjusted years (QALY) gained*". Janssen consider this to be an exceptionally low ICER threshold for an innovative treatment in a rare disease setting with a high unmet need and no other licensed therapies. The innovative nature of DBCd is underscored by clinical experts, who have described daratumumab as "*a welcome giant leap without a doubt*".[3] In particular, Janssen ask the AC to take the following into account during decision-making: ***The social value of treating a rare disease*** The introduction of DBCd as the first and only licensed option for patients with AL amyloidosis would represent a step-change in the management of this rare disease in the UK, offering patients a highly effective and tolerable treatment option which can prolong survival, reduce organ deterioration and improve quality of life. Although DBCd for AL amyloidosis met only three of the seven criteria necessary to qualify for the NICE highly specialised technology (HST) pathway, the social value judgement on the importance of treating patients diagnosed with a rare condition such as AL amyloidosis nevertheless remains and warrants flexibility in the acceptable ICER.	While the committee recognised AL amyloidosis is a serious incurable condition and there is an unmet need because there are no licensed treatments and that daratumumab in combination is innovative, it could not be recommended because of the uncertainties in the evidence and because the cost-effectiveness estimates are higher than what NICE considers to be an effective use of NHS resources. The committee noted that the end-of-life criteria was not met for the full population for which the company was positioning daratumumab in combination (see section 3.18 of the FAD).

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			Previous decisions by NICE have upheld the principle of a social value to treating rare diseases, over-and-above their ordinary cost-effectiveness criteria. For example, in TA586, lenalidomide plus dexamethasone was recommended despite uncertainty and a most plausible ICER above £30,000 per QALY because myeloma is an orphan condition and the AC considered that there was an unmet need for an alternative option to toxic chemotherapy.[4] As such, Janssen consider that the current appraisal warrants the flexibility that has previously been given to other rare conditions with a high unmet need. In addition, the new guidance development manual recently published by NICE (PMG36) provides more insight into how greater levels of uncertainty may be considered. In particular, Section 6.2.34 of this guidance outlines that greater levels of uncertainty around the ICER may be acceptable for therapies which are indicated for the treatment of a rare disease and thus are associated with more uncertainty in the clinical and economic evidence base.[2] This direction of travel supports that greater flexibility in the acceptable ICER is warranted and appropriate in appraisals of treatments in rare diseases, such as daratumumab in AL amyloidosis. In summary, there are clear clinical benefits associated with DBCd, a NICE precedent for considering a higher threshold despite higher uncertainty in a rare disease and clarification in the new manual around cases where the Committee can accept higher uncertainty, particularly in rare diseases. Together, these factors support Janssen's position that exercising flexibility with the acceptable ICER is appropriate for this innovative medicine that has the potential to address a significant unmet need for a rare condition. ***A significant proportion of eligible patients are end of life*** Cardiac stage IIIb patients have been identified by the European Staging system as those with the most severe cardiac amyloidosis and poor survival.[5] It has been suggested that, at the National Amyloidosis Centre (NAC), 18% to 20% of patients seen are cardiac stage IIIb. Following transition to bortezomib-based therapies in the post-2010 period, survival improvements	

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			were observed in patients with cardiac stages II and IIIa, but not for patients with cardiac stage IIIb, where median survival is 5 months, this is, these patients remain with the highest unmet need.[6] Recent published results of an ongoing Phase 2 study evaluating the efficacy and safety of daratumumab monotherapy used off-label in newly diagnosed patients with cardiac stage IIIb AL amyloidosis[7] indicated that daratumumab monotherapy has induced rapid and deep haematologic responses and no new safety signals on participant individuals whilst surpassing the expected overall survival of 5 months for this subgroup of patients who have achieved a median overall survival of 9 months,[7] demonstrating that daratumumab meets end-of-life criteria for these subgroup of patients. ***Some health-related benefits associated with DBCd are not captured within the cost per QALY framework*** In Section 6.3.3 of the guide to the methods of technology appraisal (PMG9, 2013), it is stated that "*strong reasons to indicate that the assessment of the change in health-related quality of life has been inadequately captured, and may therefore misrepresent the health utility gained*" is a factor which should be considered when deciding the acceptability of a technology as an effective use of NHS resources when the most plausible ICER is above £20,000 per QALY.[8] This was considered in TA605, where an ICER in the region of £45,000 per QALY gained led to a final positive recommendation in consideration that health-related quality of life benefits have not been fully captured in the cost-per-QALY framework. Janssen propose that this factor should be considered when judging the cost-effectiveness of DBCd for the following reasons: • Feedback from a clinical expert from the UK NAC was that the improvement in quality of life expected following the initiation of a successful treatment takes time, with data collected at the UK NAC indicating that for BCd-treated patients in the UK who achieve a CHR or VGPR, quality of life improvements are typically not observed	

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			before the one-year timepoint.[9] In contrast, the median follow-up time for the utility data derived from the ANDROMEDA trial was 11.4 months. This suggests that the utility benefits associated with daratumumab treatment implemented in the economic model may be conservative estimations of the true quality of life benefits that can be expected in clinical practice. • As outlined in Section B.1.3 of the Company Submission (CS), an additional benefit of the introduction of DBCd to UK clinical practice would be an increase in awareness of this rare disease. This has the potential to shorten diagnosis times (and thus positively impact patients' outcomes and survival rates due to patients being diagnosed more quickly). It is not possible to capture this QALY benefit in the economic model. • The availability of an effective licensed treatment with an acceptable safety profile, such as daratumumab would increase peace of mind and give hope to patients newly diagnosed with AL amyloidosis. No utility was applied to the DBCd arm in the economic model to capture this psychological benefit in the QALY calculation, representing a conservative approach. • As acknowledged on page 20 of the ACD, the introduction of DBCd as a treatment option for patients with AL amyloidosis would have benefits for patients with concomitant multiple myeloma. This additional benefit is not captured within the current cost-per-QALY analysis. • As discussed in the Janssen response to Issue 12 at Technical Engagement, an improvement associated with daratumumab treatment in the efficacy of autologous stem cell transplantation (ASCT), and thus in the long-term survival of patients who receive ASCT, is expected with daratumumab treatment. This benefit is not captured within the cost-per-QALY framework. ***Conclusion*** AL amyloidosis is a rare condition with a considerable unmet need, particularly in end-of-life patients with Stage IIIb cardiac disease for whom	

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			current standard of care has not translated in to survival improvements. Several quality-of-life benefits are not captured within the presented economic model framework meaning the cost-effectiveness of DBCd has been underestimated. As such, Janssen consider that exercising flexibility with the acceptable ICER is suitable for this appraisal.	
5	Company	Janssen	**Following re-categorisation and adjustment, data from the UK cohort of the EMN23 study represents the most robust source of real-world evidence to inform the economic model** **Section 3.21, page 22:** The ACD states the committee's preferred assumptions were to: "*assess haematological response at 3 months in the base case but explore a scenario using 6 months, adjusting analyses to ensure consistency in response categorisation between the 2 data sources, ANDROMEDA and ALchemy*."g Following discussion with the UK NAC, it was confirmed that haematologic response data from either the ALchemy study or the EMN23 study UK cohort would need to be re-categorised to ensure alignment with ANDROMEDA, specifically in terms of: a) The approach to the response categorisation of patients who had switched treatments, and b) The criteria used to define each response category In the absence of access to patient-level data from ALchemy, re-categorisation of the UK cohort data from the EMN23 study was performed as a pragmatic alternative. The following sections describe the rationale for use of the EMN23 study UK cohort as the external data source for the economic model, and the process by which data from UK-based patients in the EMN23 study were re-categorised to align the response definitions with the ANDROMEDA study without confounding by treatment switching.	Despite the company's ACD response, at the second committee meeting uncertainties still remained about the best data source to inform the economic model (see section 3.11 of the FAD).

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			1. Considerable overlap exists in the patient populations recruited to the two external data sources under consideration for use in the model In order to inform the long-term survival of newly diagnosed AL amyloidosis patients in the economic model, two external data sources were considered, namely the ALchemy and EMN23 studies. The ALchemy study is an ongoing, prospective, observational study of 1,194 newly diagnosed patients with AL amyloidosis in the UK. The EMN23 study is an ongoing, retrospective, observational, multicentre study on the management and outcomes of AL amyloidosis patients from 10 European countries, including a cohort of 1,166 UK-based patients that initiated treatment between 2011–2018. Baseline characteristics of the UK EMN23 cohort, alongside those of the ANDROMEDA ITT population, are presented in **Error! Reference source not found.**. As noted in the Janssen response to Technical Engagement Key Issue 6, a substantial degree of overlap is observed between the UK-based patient populations recruited to the EMN23 and ALchemy trials. Approximately 95% overlap between the two study populations was confirmed during engagement with the UK NAC. ***2. Summary of Appraisal Committee conclusions*** In their preliminary decision, the AC concluded that the UK-based ALchemy study was more representative of NHS clinical practice compared to EMN23 (ACD, pages 12–13), and raised concerns regarding the consistency between the response categorisation used in the ANDROMEDA trial and ALchemy study in relation to patients that had switched treatments (ACD, pages 13–14). In particular, the AC noted that in ANDROMEDA, any patients who switched treatments before six months were categorised as non-responders at the six-month time point. However, in ALchemy, response status at six months was reported irrespective of previous treatment changes – for instance, a person who switched treatments after three months and whose	

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			condition subsequently responded would be reported as having a response. ***3. Inconsistency in categorisation of response at six months between ALchemy and ANDROMEDA also affects the EMN23 UK cohort*** Janssen confirm that the inconsistency in response categorisation at six months observed between the ALchemy study and ANDROMEDA trial with regards to treatment switching is also relevant in the EMN23 study (including the UK cohort specifically). ***4. Identification of a further inconsistency in haematologic response categorisation between ANDROMEDA and ALchemy/EMN23 UK cohort data*** Following receipt of the ACD in December 2021, Janssen entered into discussions with the lead consultant in the ALchemy study, with the aim of responding to the AC's preferred assumptions. The discussion focussed on the adjustment of analyses needed to ensure consistency in response categorisation between ALchemy and ANDROMEDA in terms of treatment switching. During this discussion, an **additional point** of misalignment in haematologic response categorisation between the ALchemy and ANDROMEDA trials was noted. It was confirmed that published ALchemy results utilised response criteria to assess haematologic response that were not aligned with those used in ANDROMEDA,[10] and that UK data from EMN23 were similarly affected. Assessment of haematologic response in ANDROMEDA emphasised the absolute value of free light-chains and was based on more recent criteria and in line with current clinical practice guidelines.[11] Patients with a positive serum immunofixation and confirmed daratumumab immunofixation interference who met all other clinical criteria for CHR were considered to have achieved CR. Further details of the response criteria used in ANDROMEDA are presented in **Error! Reference source not found.**. By comparison, the criteria used to assess response in ALchemy and the UK	

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			cohort from EMN23 are more closely aligned with older versions of response criteria.[12-14] As such, Janssen were advised by the ALchemy study steering group that re-categorisation of response data from the chosen external data source to align with that in ANDROMEDA would be required prior to incorporating this data in the economic model. ***5. Due to the inaccessibility of ALchemy data required for re-categorisation of response data, the decision was taken to utilise the EMN23 study (UK cohort data) instead*** During discussions with Janssen, the ALchemy lead consultant confirmed that unpublished data from the ALchemy study could not be shared. Given that ALchemy is an ongoing investigator-initiated study with an existing protocol and ethical approval, any request to access unpublished data or the results of analyses conducted would require amendments to the existing protocol, ethical approval and for patients to re-consent. As a result, it was confirmed that accessing unpublished ALchemy data was not a viable option for Janssen. An alternative solution that utilised EMN23 study UK cohort data was instead proposed and received support from the ALchemy study lead consultant. As noted under Part 1 of this response, there is approximately a 95% overlap in patients recruited to each study, and as such both populations may be considered inter-changeable and generalisable to the UK. Accordingly, EMN23 UK cohort data which had been adjusted to ensure that six-month response data were not confounded by treatment switching (see Part 7 of this response) then underwent a re-categorisation process to ensure alignment with the response criteria used in ANDROMEDA. ***6. Process followed to re-categorise EMN23 UK cohort data to align with response criteria in ANDROMEDA***	

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			A number of steps were followed to facilitate re-categorisation of response data. Any additional patient-level data required for this re-categorisation were identified and a request for these data to be provided was submitted to the UK NAC. Following transfer of the data to the EMN23 study group, responses were re-categorised to align with ANDROMEDA response criteria. Further details describing the process in full, including methodological details, are provided in **Error! Reference source not found.**. Upon completion of this process, the economic model was updated with the new input data. ***7. Re-categorised EMN23 UK cohort at 6-month landmark analysis data are no longer confounded by treatment switching*** As noted above, a proportion of patients at the six-month landmark assessment timepoint in both the EMN23 UK cohort and ALchemy studies had switched treatment, potentially confounding the haematologic response results. To address the AC's concern, and remove risk of confounding, the EMN23 UK cohort data were further adjusted to ensure that the XXXXX and XXXXX patients who had switched treatment at the three- and six-month timepoints, respectively, were censored from the analyses. The adjustment was possible as the dataset provided by the UK NAC included information on the timepoint at which patients began second-line treatment. ***Updated clinical data and cost-effectiveness results (EMN23 UK cohort)*** The distributions of patients by response category at the three- and six-month timepoints in the updated EMN23 UK cohort following re-categorisation are presented in Table 1. The same approach, previously used, that involves the application of ANDROMEDA-based relative risks (DBCd versus BCd) to response rates from EMN23 was implemented in the newly updated UK cohort. The conditioning order, as before, was as preferred by the ERG: alive, CR, VGPR. Full response data by cycle and the updated Kaplan-Meier graphs of the overall survival landmark analysis by haematologic response at	

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<tr><td></td><td></td><td></td><td>three- and six-months following the re-categorisation are presented in Error! Reference source not found..

Table 1: Response data at three- and six-month
<table>
<tr><th></th><th colspan="2">Three months</th><th colspan="2">Six months</th></tr>
<tr><th></th><th>DBCd</th><th>BCd</th><th>DBCd</th><th>BCd</th></tr>
<tr><td>CR</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>VGPR</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
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Abbreviations: BCd: bortezomib, cyclophosphamide and dexamethasone; CR: complete response; DBCd: daratumumab SC in combination with bortezomib, cyclophosphamide and dexamethasone; NR: no response; PR: partial response; VGPR: very good partial response.

Updated cost-effectiveness results, which incorporate the re-categorised haematologic response data and revised landmark analyses, are presented in Error! Reference source not found..</td><td></td></tr>
<tr><td>6</td><td>Company</td><td>Janssen</td><td>Additional analysis investigating potential confounders in the association between haematologic response and overall survival reveal no evidence of confounding

Section 3.12, page 16: The ACD states: “The committee concluded that, because the company used haematological response as a surrogate for overall survival, the committee would prefer to see analyses that show whether the extrapolations are sensitive to potential confounders of the relationship between haematological response and death.”

In response to this, Janssen developed multivariate analyses using data from the 11.4 months median follow-up data cut-off of the ANDROMEDA trial to assess the impact of baseline patient characteristics on overall survival for patients who achieved a CHR at three months and six months. These analyses were explored for the whole patient population, independent of</td><td>Despite the company’s ACD response, at the second committee meeting uncertainties still remained about potential confounding factors between haematological response and overall survival (see section 3.12 of the FAD).</td></tr>
</table>

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			treatment arm, and per treatment arm. Model instability in the BCd-only arm, however, means that results are available for the whole population and DBCd-only population. The results of these analyses are presented in **Error! Reference source not found.** and demonstrate that no confounding issues were identified. In addition, feedback from a UK clinical expert confirmed that haematologic response is a consistent, reliable and independent predictor of survival in AL amyloidosis and that based on their clinical experience of the disease, they would expect that confounding between haematologic response and the overall survival predictions in ANDROMEDA would not be meaningfully impactful.	
7	Company	Janssen	**Data from ANDROMEDA demonstrates higher levels of sustained response for DBCd versus BCd which has already translated to a survival benefit at 20.3 months median follow-up. The benefit of daratumumab maintenance therapy in this regard was not captured in the economic model** As highlighted by the ERG during the first ACM, the model structure did not capture the survival benefit expected to accrue from deeper / more sustained responses associated with daratumumab maintenance therapy. In this sense, the long-term survival estimates for DBCd are considered to represent a conservative estimate. In the DBCd treatment arm, individuals are modelled to receive a maximum of 18 cycles of daratumumab monotherapy following the six cycles of DBCd treatment (i.e. 24 cycles in total). Whilst the model captured the costs associated with daratumumab monotherapy in cycles 7 to 24, the expected benefits in terms of survival were not previously modelled. Post hoc analysis from ANDROMEDA data (18-month landmark analysis[1]) with a median 25.8 months follow-up[15] demonstrate that a higher proportion	The committee considered that the company's approach to modelling sustained benefit of daratumumab was not appropriate (see section 3.14 of the FAD).

[1] ANDROMEDA 18-month landmark analysis data cut-off, with a median 25.8 months follow-up, updated analyses for haematologic response, organ response and safety, as indicated in Section A.1 of the Clarification questions document.

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<tr><th>Comment number</th><th>Type of stakeholder</th><th>Organisation name</th><th>Stakeholder comment
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Please respond to each comment</th></tr>
<tr><td></td><td></td><td></td><td>
of patients receiving DBCd (65.4% and 66.3% at 3 months and 6 months respectively) sustained their response until month 24 as compared with patients receiving BCd (54.2% and 51.9% at 3 months and 6 months respectively), highlighting that the continuous use of daratumumab is associated with higher levels of sustained response (see Appendix 3,Error! Reference source not found.).

To adjust the economic model to incorporate the expected survival benefit of daratumumab monotherapy, Janssen has used ANDROMEDA safety data results at a median follow up of 20.3 months[16]. The expected long-term survival benefit of daratumumab monotherapy was modelled by multiplying the per-cycle overall survival probability for each haematologic response group (based on recategorised EMN23 data) with a factor informed by the observed survival in the ANDROMEDA trial (at 20.3 months median follow-up).[16]

The observed ratio of surviving patients in ANDROMEDA at a median follow-up of 20.3 months was calculated to be 1.066, indicating a 6.6% higher survival in patients treated with DBCd as compared with patients on BCd only (Table 2).

This observed ratio was subsequently compared with the equivalent ratio between the treatment arms in the model (in Cycle 22, corresponding to a follow up of 20.2 months), which was 1.021. Per-cycle survival probabilities for all response states in the DBCd arm (from Cycle 7) were then multiplied by a factor of 1.044 (calculated as 1.066 divided by 1.021) in order to align modelled long-term survival in the DBCd arm with the expected survival benefit from both deeper and more sustained responses associated with daratumumab monotherapy, as observed in ANDROMEDA.

Table 2: ANDROMEDA safety population patient disposition at median 20.3-month follow-up
<table>
<tr><th></th><th>DBCd (N=193)</th><th>BCd (N=188)</th></tr>
<tr><td>Alive patients, n (%)</td><td>162 (83.9)</td><td>148 (78.7)</td></tr>
</table>
</td><td></td></tr>
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Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			<table><tr><td>Survival ratio (DBCd/BCd)</td><td>-</td><td>**1.066**</td></tr></table> Updated cost-effectiveness results, which incorporate the **1.044** multiplier are presented in **Error! Reference source not found.**, **Error! Reference source not found.**. **It is important to note that the adjustment described above may be conservative given that it is based on survival data at 20.3 months follow-up (12.4 months landmark analysis). Please note the 20.3 month follow-up data was used given no outcome data, other than response, are available from the most recent 18-month data cut off.**	
8	Company	Janssen	**DBCd represents an effective treatment for patients with end-stage cardiac disease** **Section 3.20, page 21:** The ACD states: "*The company presented no trial evidence for people with more severe complications*." (page 21) Janssen are pleased to read the conclusion of the AC that it would consider daratumumab in combination within its full licensed indication (i.e., as a first-line treatment for newly diagnosed systemic AL amyloidosis, regardless disease severity) (ACD, page 7).[1] As discussed in Section B.1.1 of the original Company Submission, Mayo Clinical Cardiac Stage IIIb patients were excluded from the ANDROMEDA trial. As such, Janssen wish to highlight that, in order to gain insight into the haematologic response rates that would be required for DBCd to be a cost-effective option for patients in this subgroup, these patients are included in the updated EMN23 base case cost-effectiveness analysis, presented in **Error! Reference source not found.**. Furthermore, subgroup data for patients in the ANDROMEDA trial stratified by cardiac disease stage are available and demonstrate that the relative treatment effect of DBCd increases with increasing severity of cardiac disease according to the Mayo Clinic Cardiac Staging system. As such, as discussed in response to Key	Please see sections 3.4 and 3.5 of the FAD.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			Issue 1 at the Technical Engagement stage (Technical Engagement Response Document, page 4), Janssen consider the assumption that the relative treatment benefit of DBCd versus BCd observed in the ANDROMEDA trial is generalisable to patients with Cardiac Stage IIIb disease, which is made in the updated EMN23 base case (**Error! Reference source not found.**), to be conservative. Accordingly, the EMN23 base case analysis of cost-effectiveness in a population that includes patients with Cardiac Stage IIIb disease is considered conservative. Furthermore, as indicated in Point 1, recent published results of an ongoing Phase 2 study [7] indicated that daratumumab monotherapy has induced rapid and deep haematologic responses and no new safety signals on participant individuals whilst surpassing the expected overall survival of 5 months for this subgroup of patients who have achieved a median overall survival of 9 months.[7] Therefore, Janssen consider that the available evidence supports DBCd being a cost-effective treatment for end-of-life AL amyloidosis patients with end-stage cardiac disease, despite their exclusion from the ANDROMEDA trial.	
9	Company	Janssen	**SF36v2 data from the ALchemy trial are unavailable, precluding their use to validate the utility dataset currently used in the economic model** **Section 3.13, page 17:** The ACD states: "*The committee concluded that the company should have used SF36v2 data from ALchemy to validate its utility set derived from ANDROMEDA*." As discussed in response to Point 2 above, although further publications reporting ALchemy HRQoL data are expected in Q3 2022, Janssen are unable to access patient-level or unpublished data from the ALchemy study at this time. As such, Janssen confirm that it has not been possible to perform a new scenario analysis using the ALchemy SF36v2 utility set to validate the economic model results. However, as discussed further in response to Point 1 above, Janssen wish to emphasise that the submitted economic approach implements EQ-5D data with limited follow-up whereas clinicians and clinical data from the UK NAC indicate that improvements in	Despite the company's ACD response, at the second committee meeting uncertainties still remained about the validity of the utility values (see section 3.15 of the FAD).

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			quality of life are typically not observed before the one-year timepoint.[9] As such, the current economic approach is conservative given that it is expected not to capture the true quality of life benefits associated with daratumumab treatment. For this reason, health state utility values estimated by UK-based clinicians at an advisory board were implemented in a scenario analysis and presented in Section B.3.8.3 of the Company Submission. The lowered ICER resulting from this scenario analysis reflects the conservative nature of the base case approach.	
10	Company	Janssen	**The administration cost of £332 for daratumumab subcutaneous injection significantly overestimates the true cost** **Section 3.15, page 18:** The ACD concluded that: "…*the company's choice of administration costs underestimated the true costs and should instead be £332*." Reference cost data provided by the National Tariff Payment System does not distinguish between intravenous infusion (IV) or subcutaneous (SC) administration of cancer treatment. This is despite significant difference in the level of service activity associated with each procedure. The HRG code preferred by the committee (SB15Z), and referred in the ACD, is identified under the class of parenteral chemotherapies which principally relate to infusional treatments that involve complex monitoring and extended chair time. The description of simple parenteral chemotherapy provided in Annex B states, *"Overall time of 30 minutes nurse time and 30 to 60 minutes chair time for delivery of a complete cycle."* This is between six and twenty times longer than the chair time necessary to administer SC daratumumab which is a 3–5-minute injection[17], and therefore significantly overestimates the associated drug administration costs. Additionally, Janssen experience with daratumumab IV suggests that preparation time by a pharmacist can be as long as 45 minutes per administration for the IV, whilst preparation time for the SC is not required. As such, and in the absence of a specific tariff for subcutaneous drug administration, Janssen consider the specialist nursing tariff for cancer treatment (N10AF) more appropriate and reflective of the service delivery costs actually incurred. Janssen note that this tariff was also recently accepted by NICE in the appraisal of daratumumab in combination for untreated multiple myeloma when stem cell transplant is suitable (TA763).	The committee considered that the administrative cost of daratumumab and bortezomib to be the same for the first 6 cycles at £1,127 per cycle for both daratumumab and standard care arms (see section 3.17 of the FAD).

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			To further investigate service delivery costs associated with the provision of SC daratumumab in clinical practice, Janssen conducted a micro-costing exercise in the UK, using a Discrete Event Simulation tool to model treatment delivery in the hospital setting. Inputs relating to hospital capacity, time for treatment, and patient characteristics were collected from a quantitative survey of treatment providers, including 60 health care professionals (20 haematologists or haemato-oncologists, 20 haemato-oncologist nurses, 10 hospital payers and 10 hospital pharmacists) in general hospitals, teaching / academic hospital and specialist treatment centres in the UK.[18] Simulations (10 repeats) were run using parameters for a typical NHS hospital over a 5-year timeframe, and 27 new patients were treated with daratumumab SC every year. Results showed that average administration cost of daratumumab SC in the hospital setting is £123 per dose. The micro-costing exercise broadly supports the HRG code N10AF used in the updated company base case results (see Appendix 1, Error! Reference source not found.). However, in line with the committee preferred assumptions, we include a scenario using an administration cost of £332 although, as noted above, Janssen considers that this significantly overestimates the actual associated cost to the NHS (refer to Appendix 1, Error! Reference source not found.). For information, we also provide a scenario using the average cost of £123 resulting from the micro-costing analysis (refer to Appendix 1, Error! Reference source not found.).	

	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:	Cristina Penaloza

Comment number	Comments
Summary	Janssen thank NICE for the opportunity to comment on the Appraisal Consultation Document (ACD) for daratumumab in combination with bortezomib, cyclophosphamide and dexamethasone (DBCd) for treating newly diagnosed systemic amyloid light-chain (AL) amyloidosis [ID3748] published on the 20 January 2022.[1] Janssen are pleased that the Appraisal Committee (AC) have recognised that AL amyloidosis is a life-threatening, incurable condition and that there is an unmet need for an effective treatment option for this condition.[1] In particular, Janssen are pleased that the AC concluded: • The correct comparator for decision making is BCd (ACD, page 6) • The relevant positioning for DBCd in UK clinical practice is as a front-line therapy for newly diagnosed adults with AL amyloidosis, regardless of severity, and that if recommended, NICE would consider DBCd for use within its approved full licensed indication (ACD, page 7) • The ANDROMEDA trial population is likely to be broadly generalisable to typical clinical practice in England, despite the exclusion of people with severe complications such as Stage IIIb cardiac disease (ACD, page 8) • The primary endpoint of the ANDROMEDA trial, complete haematologic response, is a surrogate endpoint for overall survival (ACD, page 9) • DBCd is an effective treatment for improving haematologic response, and reducing major organ deterioration in individuals with AL amyloidosis (ACD, page 10) • The adverse events (AEs) associated with DBCd observed in the ANDROMEDA trial were generally well tolerated by patients and appropriately represented in the economic analysis (ACD, page 10) • DBCd is an innovative therapy associated with benefits which are not captured in the cost per QALY framework, such as the benefits to people with concomitant myeloma (ACD, page 20) Janssen are, however, disappointed with the AC's preliminary decision not to recommend DBCd within its marketing authorisation for the treatment of adult patients with newly diagnosed AL amyloidosis in England.[1] DBCd is the first and only treatment licensed for patients with AL amyloidosis and is both highly innovative and highly effective thus addressing a considerable unmet need. Janssen remain committed to working with NICE throughout the subsequent stages of this appraisal to secure a positive outcome which will enable patient access to DBCd. To support the case for access to DBCd for newly diagnosed AL amyloidosis patients, Janssen wish to highlight the following points pertaining to topics discussed during the ACM and ACD: • Greater flexibility in the acceptable incremental cost-effectiveness ratio (ICER) is supported by a substantial proportion of the eligible patient population being end-of-life and the existence of benefits associated with DBCd not captured in the cost per QALY framework

	• Following re-categorisation and adjustment, data from the UK cohort of the EMN23 study represents the most robust source of real-world evidence to inform the economic model • Additional analysis investigating the association between haematologic response and overall survival in ANDROMEDA has confirmed no evidence of confounding • Data from ANDROMEDA demonstrates higher levels of sustained response for DBCd versus BCd which has already translated to a survival benefit at 20.3 months median follow-up. The benefit of daratumumab maintenance therapy in this regard was not captured in the economic model • DBCd represents an effective treatment for patients with end-stage cardiac disease, and use of NHS resources in this patient group is expected to provide substantial clinical benefits given their very high level of unmet need • SF36v2 data from the ALchemy trial are unavailable, precluding their use to validate the utility dataset currently used in the economic model • The administration cost of £332 for daratumumab subcutaneous injection significantly overestimates the true cost to the NHS Detailed discussion of the above points is provided in Points 1–7 below. To further support access, Janssen have revised the PAS for daratumumab, increasing the simple discount to a [redacted], thus offering additional value for money to the NHS. All changes to the economic base case implemented in order to address the concerns of the AC, alongside the updated base case and scenario results, are outlined in Appendix 1. In conclusion, Janssen have endeavoured to secure robust real-world evidence data that are reflective of UK clinical practice and aligned with the haematologic response categories implemented in the ANDROMEDA trial. These data have been implemented in the updated company base case, presented in Appendix 1, in order to reflect the AC's preferences and reduce uncertainty associated with the decision problem. The updated economic model results indicate daratumumab in combination to be a cost-effective use of NHS resources when considering the cost-effectiveness range typically considered by NICE for rare diseases such as AL amyloidosis, and taking into account, the extent of clinical unmet need and elements of value not captured in the QALY. Flexibility in the acceptable ICER is supported by the direction of travel of the new NICE guidance development manual towards greater acceptance of uncertainty in rare diseases and conditions with a high unmet need.[2] Furthermore, while the decision for positioning DBCd for routine commissioning responds to a high unmet need, discussions with NHSE have confirmed that daratumumab in combination is eligible for entry to the Cancer Drugs Fund (CDF).
Point 1	**Greater flexibility in the acceptable ICER is supported by a substantial proportion of the eligible patient population being end-of-life and the existence of insufficiently captured benefits associated with DBCd treatment. This is further supported by the direction of travel of the new**

NICE guidance development manual regarding acceptance of uncertainty in rare diseases and high unmet need conditions

Section 3.20, page 20: The ACD states: "*The uncertainty means an acceptable incremental cost-effectiveness ratio (ICER) is £20,000 per quality-adjusted years (QALY) gained*".

Janssen consider this to be an exceptionally low ICER threshold for an innovative treatment in a rare disease setting with a high unmet need and no other licensed therapies. The innovative nature of DBCd is underscored by clinical experts, who have described daratumumab as "*a welcome giant leap without a doubt*".[3] In particular, Janssen ask the AC to take the following into account during decision-making:

The social value of treating a rare disease

The introduction of DBCd as the first and only licensed option for patients with AL amyloidosis would represent a step-change in the management of this rare disease in the UK, offering patients a highly effective and tolerable treatment option which can prolong survival, reduce organ deterioration and improve quality of life. Although DBCd for AL amyloidosis met only three of the seven criteria necessary to qualify for the NICE highly specialised technology (HST) pathway, the social value judgement on the importance of treating patients diagnosed with a rare condition such as AL amyloidosis nevertheless remains and warrants flexibility in the acceptable ICER.

Previous decisions by NICE have upheld the principle of a social value to treating rare diseases, over-and-above their ordinary cost-effectiveness criteria. For example, in TA586, lenalidomide plus dexamethasone was recommended despite uncertainty and a most plausible ICER above £30,000 per QALY because myeloma is an orphan condition and the AC considered that there was an unmet need for an alternative option to toxic chemotherapy.[4] As such, Janssen consider that the current appraisal warrants the flexibility that has previously been given to other rare conditions with a high unmet need.

In addition, the new guidance development manual recently published by NICE (PMG36) provides more insight into how greater levels of uncertainty may be considered. In particular, Section 6.2.34 of this guidance outlines that greater levels of uncertainty around the ICER may be acceptable for therapies which are indicated for the treatment of a rare disease and thus are associated with more uncertainty in the clinical and economic evidence base.[2] This direction of travel supports that greater flexibility in the acceptable ICER is warranted and appropriate in appraisals of treatments in rare diseases, such as daratumumab in AL amyloidosis.

In summary, there are clear clinical benefits associated with DBCd, a NICE precedent for considering a higher threshold despite higher uncertainty in a rare disease and clarification in the new manual around cases where the Committee can accept higher uncertainty, particularly in rare diseases. Together, these factors support Janssen's position that exercising flexibility

with the acceptable ICER is appropriate for this innovative medicine that has the potential to address a significant unmet need for a rare condition.

A significant proportion of eligible patients are end of life

Cardiac stage IIIb patients have been identified by the European Staging system as those with the most severe cardiac amyloidosis and poor survival.[5] It has been suggested that, at the National Amyloidosis Centre (NAC), 18% to 20% of patients seen are cardiac stage IIIb. Following transition to bortezomib-based therapies in the post-2010 period, survival improvements were observed in patients with cardiac stages II and IIIa, but not for patients with cardiac stage IIIb, where median survival is 5 months, this is, these patients remain with the highest unmet need.[6]

Recent published results of an ongoing Phase 2 study evaluating the efficacy and safety of daratumumab monotherapy used off-label in newly diagnosed patients with cardiac stage IIIb AL amyloidosis[7] indicated that daratumumab monotherapy has induced rapid and deep haematologic responses and no new safety signals on participant individuals whilst surpassing the expected overall survival of 5 months for this subgroup of patients who have achieved a median overall survival of 9 months,[7] demonstrating that daratumumab meets end-of-life criteria for these subgroup of patients.

Some health-related benefits associated with DBCd are not captured within the cost per QALY framework

In Section 6.3.3 of the guide to the methods of technology appraisal (PMG9, 2013), it is stated that "*strong reasons to indicate that the assessment of the change in health-related quality of life has been inadequately captured, and may therefore misrepresent the health utility gained*" is a factor which should be considered when deciding the acceptability of a technology as an effective use of NHS resources when the most plausible ICER is above £20,000 per QALY.[8] This was considered in TA605, where an ICER in the region of £45,000 per QALY gained led to a final positive recommendation in consideration that health-related quality of life benefits have not been fully captured in the cost-per-QALY framework.

Janssen propose that this factor should be considered when judging the cost-effectiveness of DBCd for the following reasons:

- Feedback from a clinical expert from the UK NAC was that the improvement in quality of life expected following the initiation of a successful treatment takes time, with data collected at the UK NAC indicating that for BCd-treated patients in the UK who achieve a CHR or VGPR, quality of life improvements are typically not observed before the one-year timepoint.[9] In contrast, the median follow-up time for the utility data derived from the ANDROMEDA trial was 11.4 months. This suggests that the utility benefits associated with daratumumab treatment implemented in the economic model may be conservative estimations of the true quality of life benefits that can be expected in clinical practice.
- As outlined in Section B.1.3 of the Company Submission (CS), an additional benefit of the introduction of DBCd to UK clinical practice

	would be an increase in awareness of this rare disease. This has the potential to shorten diagnosis times (and thus positively impact patients' outcomes and survival rates due to patients being diagnosed more quickly). It is not possible to capture this QALY benefit in the economic model. • The availability of an effective licensed treatment with an acceptable safety profile, such as daratumumab would increase peace of mind and give hope to patients newly diagnosed with AL amyloidosis. No utility was applied to the DBCd arm in the economic model to capture this psychological benefit in the QALY calculation, representing a conservative approach. • As acknowledged on page 20 of the ACD, the introduction of DBCd as a treatment option for patients with AL amyloidosis would have benefits for patients with concomitant multiple myeloma. This additional benefit is not captured within the current cost-per-QALY analysis. • As discussed in the Janssen response to Issue 12 at Technical Engagement, an improvement associated with daratumumab treatment in the efficacy of autologous stem cell transplantation (ASCT), and thus in the long-term survival of patients who receive ASCT, is expected with daratumumab treatment. This benefit is not captured within the cost-per-QALY framework. ***Conclusion*** AL amyloidosis is a rare condition with a considerable unmet need, particularly in end-of-life patients with Stage IIIb cardiac disease for whom current standard of care has not translated in to survival improvements. Several quality-of-life benefits are not captured within the presented economic model framework meaning the cost-effectiveness of DBCd has been underestimated. As such, Janssen consider that exercising flexibility with the acceptable ICER is suitable for this appraisal.
Point 2	**Following re-categorisation and adjustment, data from the UK cohort of the EMN23 study represents the most robust source of real-world evidence to inform the economic model** **Section 3.21, page 22:** The ACD states the committee's preferred assumptions were to: "*assess haematological response at 3 months in the base case but explore a scenario using 6 months, adjusting analyses to ensure consistency in response categorisation between the 2 data sources, ANDROMEDA and ALchemy*." Following discussion with the UK NAC, it was confirmed that haematologic response data from either the ALchemy study or the EMN23 study UK cohort would need to be re-categorised to ensure alignment with ANDROMEDA, specifically in terms of: a) The approach to the response categorisation of patients who had switched treatments, and b) The criteria used to define each response category

	In the absence of access to patient-level data from ALchemy, re-categorisation of the UK cohort data from the EMN23 study was performed as a pragmatic alternative. The following sections describe the rationale for use of the EMN23 study UK cohort as the external data source for the economic model, and the process by which data from UK-based patients in the EMN23 study were re-categorised to align the response definitions with the ANDROMEDA study without confounding by treatment switching. ***1. Considerable overlap exists in the patient populations recruited to the two external data sources under consideration for use in the model*** In order to inform the long-term survival of newly diagnosed AL amyloidosis patients in the economic model, two external data sources were considered, namely the ALchemy and EMN23 studies. The ALchemy study is an ongoing, prospective, observational study of 1,194 newly diagnosed patients with AL amyloidosis in the UK. The EMN23 study is an ongoing, retrospective, observational, multicentre study on the management and outcomes of AL amyloidosis patients from 10 European countries, including a cohort of 1,166 UK-based patients that initiated treatment between 2011–2018. Baseline characteristics of the UK EMN23 cohort, alongside those of the ANDROMEDA ITT population, are presented in Appendix 2.1.1. As noted in the Janssen response to Technical Engagement Key Issue 6, a substantial degree of overlap is observed between the UK-based patient populations recruited to the EMN23 and ALchemy trials. Approximately 95% overlap between the two study populations was confirmed during engagement with the UK NAC. ***2. Summary of Appraisal Committee conclusions*** In their preliminary decision, the AC concluded that the UK-based ALchemy study was more representative of NHS clinical practice compared to EMN23 (ACD, pages 12–13), and raised concerns regarding the consistency between the response categorisation used in the ANDROMEDA trial and ALchemy study in relation to patients that had switched treatments (ACD, pages 13–14). In particular, the AC noted that in ANDROMEDA, any patients who switched treatments before six months were categorised as non-responders at the six-month time point. However, in ALchemy, response status at six months was reported irrespective of previous treatment changes – for instance, a person who switched treatments after three months and whose condition subsequently responded would be reported as having a response. ***3. Inconsistency in categorisation of response at six months between ALchemy and ANDROMEDA also affects the EMN23 UK cohort*** Janssen confirm that the inconsistency in response categorisation at six months observed between the ALchemy study and ANDROMEDA trial with

regards to treatment switching is also relevant in the EMN23 study (including the UK cohort specifically).

4. Identification of a further inconsistency in haematologic response categorisation between ANDROMEDA and ALchemy/EMN23 UK cohort data

Following receipt of the ACD in December 2021, Janssen entered into discussions with the lead consultant in the ALchemy study, with the aim of responding to the AC's preferred assumptions. The discussion focussed on the adjustment of analyses needed to ensure consistency in response categorisation between ALchemy and ANDROMEDA in terms of treatment switching.

During this discussion, an **additional point** of misalignment in haematologic response categorisation between the ALchemy and ANDROMEDA trials was noted. It was confirmed that published ALchemy results utilised response criteria to assess haematologic response that were not aligned with those used in ANDROMEDA,[10] and that UK data from EMN23 were similarly affected. Assessment of haematologic response in ANDROMEDA emphasised the absolute value of free light-chains and was based on more recent criteria and in line with current clinical practice guidelines.[11] Patients with a positive serum immunofixation and confirmed daratumumab immunofixation interference who met all other clinical criteria for CHR were considered to have achieved CR. Further details of the response criteria used in ANDROMEDA are presented in Appendix 2.1.2. By comparison, the criteria used to assess response in ALchemy and the UK cohort from EMN23 are more closely aligned with older versions of response criteria.[12-14]

As such, Janssen were advised by the ALchemy study steering group that re-categorisation of response data from the chosen external data source to align with that in ANDROMEDA would be required prior to incorporating this data in the economic model.

5. Due to the inaccessibility of ALchemy data required for re-categorisation of response data, the decision was taken to utilise the EMN23 study (UK cohort data) instead

During discussions with Janssen, the ALchemy lead consultant confirmed that unpublished data from the ALchemy study could not be shared. Given that ALchemy is an ongoing investigator-initiated study with an existing protocol and ethical approval, any request to access unpublished data or the results of analyses conducted would require amendments to the existing protocol, ethical approval and for patients to re-consent.

As a result, it was confirmed that accessing unpublished ALchemy data was not a viable option for Janssen. An alternative solution that utilised EMN23 study UK cohort data was instead proposed and received support from the ALchemy study lead consultant. As noted under Part 1 of this response, there is approximately a 95% overlap in patients recruited to each study, and as such

both populations may be considered inter-changeable and generalisable to the UK.

Accordingly, EMN23 UK cohort data which had been adjusted to ensure that six-month response data were not confounded by treatment switching (see Part 7 of this response) then underwent a re-categorisation process to ensure alignment with the response criteria used in ANDROMEDA.

6. Process followed to re-categorise EMN23 UK cohort data to align with response criteria in ANDROMEDA

A number of steps were followed to facilitate re-categorisation of response data. Any additional patient-level data required for this re-categorisation were identified and a request for these data to be provided was submitted to the UK NAC. Following transfer of the data to the EMN23 study group, responses were re-categorised to align with ANDROMEDA response criteria. Further details describing the process in full, including methodological details, are provided in Appendix 2.1.3.

Upon completion of this process, the economic model was updated with the new input data.

7. Re-categorised EMN23 UK cohort at 6-month landmark analysis data are no longer confounded by treatment switching

As noted above, a proportion of patients at the six-month landmark assessment timepoint in both the EMN23 UK cohort and ALchemy studies had switched treatment, potentially confounding the haematologic response results. To address the AC's concern, and remove risk of confounding, the EMN23 UK cohort data were further adjusted to ensure that the [redacted] and [redacted] patients who had switched treatment at the three- and six-month timepoints, respectively, were censored from the analyses. The adjustment was possible as the dataset provided by the UK NAC included information on the timepoint at which patients began second-line treatment.

Updated clinical data and cost-effectiveness results (EMN23 UK cohort)

The distributions of patients by response category at the three- and six-month timepoints in the updated EMN23 UK cohort following re-categorisation are presented in Table 1. The same approach, previously used, that involves the application of ANDROMEDA-based relative risks (DBCd versus BCd) to response rates from EMN23 was implemented in the newly updated UK cohort. The conditioning order, as before, was as preferred by the ERG: alive, CR, VGPR. Full response data by cycle and the updated Kaplan-Meier graphs of the overall survival landmark analysis by haematologic response at three- and six-months following the re-categorisation are presented in Appendix 2.1.4.

Table 1: Response data at three- and six-month

	Three months		Six months	
	DBCd	BCd	DBCd	BCd

CR	[redacted]	[redacted]	[redacted]	[redacted]	
VGPR	[redacted]	[redacted]	[redacted]	[redacted]	
PR	[redacted]	[redacted]	[redacted]	[redacted]	
NR	[redacted]	[redacted]	[redacted]	[redacted]	
Dead	[redacted]	[redacted]	[redacted]	[redacted]	

Abbreviations: BCd: bortezomib, cyclophosphamide and dexamethasone; CR: complete response; DBCd: daratumumab SC in combination with bortezomib, cyclophosphamide and dexamethasone; NR: no response; PR: partial response; VGPR: very good partial response.

Updated cost-effectiveness results, which incorporate the re-categorised haematologic response data and revised landmark analyses, are presented in Appendix 1.

Point 3

Additional analysis investigating potential confounders in the association between haematologic response and overall survival reveal no evidence of confounding

Section 3.12, page 16: The ACD states: "*The committee concluded that, because the company used haematological response as a surrogate for overall survival, the committee would prefer to see analyses that show whether the extrapolations are sensitive to potential confounders of the relationship between haematological response and death*."

In response to this, Janssen developed multivariate analyses using data from the 11.4 months median follow-up data cut-off of the ANDROMEDA trial to assess the impact of baseline patient characteristics on overall survival for patients who achieved a CHR at three months and six months. These analyses were explored for the whole patient population, independent of treatment arm, and per treatment arm. Model instability in the BCd-only arm, however, means that results are available for the whole population and DBCd-only population. The results of these analyses are presented in Appendix 4 and demonstrate that no confounding issues were identified.

In addition, feedback from a UK clinical expert confirmed that haematologic response is a consistent, reliable and independent predictor of survival in AL amyloidosis and that based on their clinical experience of the disease, they would expect that confounding between haematologic response and the overall survival predictions in ANDROMEDA would not be meaningfully impactful.

Point 4

Data from ANDROMEDA demonstrates higher levels of sustained response for DBCd versus BCd which has already translated to a survival benefit at 20.3 months median follow-up. The benefit of daratumumab maintenance therapy in this regard was not captured in the economic model

As highlighted by the ERG during the first ACM, the model structure did not capture the survival benefit expected to accrue from deeper / more sustained responses associated with daratumumab maintenance therapy. In this sense, the long-term survival estimates for DBCd are considered to represent a conservative estimate.

In the DBCd treatment arm, individuals are modelled to receive a maximum of 18 cycles of daratumumab monotherapy following the six cycles of DBCd treatment (i.e. 24 cycles in total). Whilst the model captured the costs associated with daratumumab monotherapy in cycles 7 to 24, the expected benefits in terms of survival were not previously modelled.

Post hoc analysis from ANDROMEDA data (18-month landmark analysis[1]) with a median 25.8 months follow-up[15] demonstrate that a higher proportion of patients receiving DBCd (65.4% and 66.3% at 3 months and 6 months respectively) sustained their response until month 24 as compared with patients receiving BCd (54.2% and 51.9% at 3 months and 6 months respectively), highlighting that the continuous use of daratumumab is associated with higher levels of sustained response (see Appendix 3,Table 16).

To adjust the economic model to incorporate the expected survival benefit of daratumumab monotherapy, Janssen has used ANDROMEDA safety data results at a median follow up of 20.3 months[16]. The expected long-term survival benefit of daratumumab monotherapy was modelled by multiplying the per-cycle overall survival probability for each haematologic response group (based on recategorised EMN23 data) with a factor informed by the observed survival in the ANDROMEDA trial (at 20.3 months median follow-up).[16]

The observed ratio of surviving patients in ANDROMEDA at a median follow-up of 20.3 months was calculated to be 1.066, indicating a 6.6% higher survival in patients treated with DBCd as compared with patients on BCd only (Table 2).

This observed ratio was subsequently compared with the equivalent ratio between the treatment arms in the model (in Cycle 22, corresponding to a follow up of 20.2 months), which was 1.021. Per-cycle survival probabilities for all response states in the DBCd arm (from Cycle 7) were then multiplied by a factor of **1.044** (calculated as 1.066 divided by 1.021) in order to align modelled long-term survival in the DBCd arm with the expected survival benefit from both deeper and more sustained responses associated with daratumumab monotherapy, as observed in ANDROMEDA.

Table 2: ANDROMEDA safety population patient disposition at median 20.3-month follow-up

	DBCd (N=193)	BCd (N=188)
Alive patients, n (%)	162 (83.9)	148 (78.7)
Survival ratio (DBCd/BCd)	-	**1.066**

Updated cost-effectiveness results, which incorporate the **1.044** multiplier are presented in Appendix 1, Table 4.

[1] ANDROMEDA 18-month landmark analysis data cut-off, with a median 25.8 months follow-up, updated analyses for haematologic response, organ response and safety, as indicated in Section A.1 of the Clarification questions document.

	It is important to note that the adjustment described above may be conservative given that it is based on survival data at 20.3 months follow-up (12.4 months landmark analysis). Please note the 20.3 month follow-up data was used given no outcome data, other than response, are available from the most recent 18-month data cut off.
Point 5	**DBCd represents an effective treatment for patients with end-stage cardiac disease** **Section 3.20, page 21:** The ACD states: "*The company presented no trial evidence for people with more severe complications*." (page 21) Janssen are pleased to read the conclusion of the AC that it would consider daratumumab in combination within its full licensed indication (i.e., as a first-line treatment for newly diagnosed systemic AL amyloidosis, regardless disease severity) (ACD, page 7).[1] As discussed in Section B.1.1 of the original Company Submission, Mayo Clinical Cardiac Stage IIIb patients were excluded from the ANDROMEDA trial. As such, Janssen wish to highlight that, in order to gain insight into the haematologic response rates that would be required for DBCd to be a cost-effective option for patients in this subgroup, these patients are included in the updated EMN23 base case cost-effectiveness analysis, presented in Appendix 1. Furthermore, subgroup data for patients in the ANDROMEDA trial stratified by cardiac disease stage are available and demonstrate that the relative treatment effect of DBCd increases with increasing severity of cardiac disease according to the Mayo Clinic Cardiac Staging system. As such, as discussed in response to Key Issue 1 at the Technical Engagement stage (Technical Engagement Response Document, page 4), Janssen consider the assumption that the relative treatment benefit of DBCd versus BCd observed in the ANDROMEDA trial is generalisable to patients with Cardiac Stage IIIb disease, which is made in the updated EMN23 base case (Appendix 1), to be conservative. Accordingly, the EMN23 base case analysis of cost-effectiveness in a population that includes patients with Cardiac Stage IIIb disease is considered conservative. Furthermore, as indicated in Point 1, recent published results of an ongoing Phase 2 study [7] indicated that daratumumab monotherapy has induced rapid and deep haematologic responses and no new safety signals on participant individuals whilst surpassing the expected overall survival of 5 months for this subgroup of patients who have achieved a median overall survival of 9 months.[7] Therefore, Janssen consider that the available evidence supports DBCd being a cost-effective treatment for end-of-life AL amyloidosis patients with end-stage cardiac disease, despite their exclusion from the ANDROMEDA trial.

Point 6	**SF36v2 data from the ALchemy trial are unavailable, precluding their use to validate the utility dataset currently used in the economic model** **Section 3.13, page 17:** The ACD states: "*The committee concluded that the company should have used SF36v2 data from ALchemy to validate its utility set derived from ANDROMEDA*." As discussed in response to Point 2 above, although further publications reporting ALchemy HRQoL data are expected in Q3 2022, Janssen are unable to access patient-level or unpublished data from the ALchemy study at this time. As such, Janssen confirm that it has not been possible to perform a new scenario analysis using the ALchemy SF36v2 utility set to validate the economic model results. However, as discussed further in response to Point 1 above, Janssen wish to emphasise that the submitted economic approach implements EQ-5D data with limited follow-up whereas clinicians and clinical data from the UK NAC indicate that improvements in quality of life are typically not observed before the one-year timepoint.[9] As such, the current economic approach is conservative given that it is expected not to capture the true quality of life benefits associated with daratumumab treatment. For this reason, health state utility values estimated by UK-based clinicians at an advisory board were implemented in a scenario analysis and presented in Section B.3.8.3 of the Company Submission. The lowered ICER resulting from this scenario analysis reflects the conservative nature of the base case approach.
Point 7	**The administration cost of £332 for daratumumab subcutaneous injection significantly overestimates the true cost** **Section 3.15, page 18:** The ACD concluded that: "…*the company's choice of administration costs underestimated the true costs and should instead be £332*." Reference cost data provided by the National Tariff Payment System does not distinguish between intravenous infusion (IV) or subcutaneous (SC) administration of cancer treatment. This is despite significant difference in the level of service activity associated with each procedure. The HRG code preferred by the committee (SB15Z), and referred in the ACD, is identified under the class of parenteral chemotherapies which principally relate to infusional treatments that involve complex monitoring and extended chair time. The description of simple parenteral chemotherapy provided in Annex B states, *"Overall time of 30 minutes nurse time and 30 to 60 minutes chair time for delivery of a complete cycle."* This is between six and twenty times longer than the chair time necessary to administer SC daratumumab which is a 3–5-minute injection[17], and therefore significantly overestimates the associated drug administration costs. Additionally, Janssen experience with daratumumab IV suggests that preparation time by a pharmacist can be as long as 45 minutes per administration for the IV, whilst preparation time for the SC is not required. As such, and in the absence of a specific tariff for subcutaneous drug administration, Janssen consider the specialist nursing tariff for cancer treatment (N10AF) more appropriate and reflective of the service delivery costs actually incurred. Janssen note that this tariff was also recently accepted by NICE in the appraisal of daratumumab in combination for untreated multiple myeloma when stem cell transplant is suitable (TA763).

	To further investigate service delivery costs associated with the provision of SC daratumumab in clinical practice, Janssen conducted a micro-costing exercise in the UK, using a Discrete Event Simulation tool to model treatment delivery in the hospital setting. Inputs relating to hospital capacity, time for treatment, and patient characteristics were collected from a quantitative survey of treatment providers, including 60 health care professionals (20 haematologists or haemato-oncologists, 20 haemato-oncologist nurses, 10 hospital payers and 10 hospital pharmacists) in general hospitals, teaching / academic hospital and specialist treatment centres in the UK.[18] Simulations (10 repeats) were run using parameters for a typical NHS hospital over a 5-year timeframe, and 27 new patients were treated with daratumumab SC every year. Results showed that average administration cost of daratumumab SC in the hospital setting is £123 per dose. The micro-costing exercise broadly supports the HRG code N10AF used in the updated company base case results (see Appendix 1, Table 4). However, in line with the committee preferred assumptions, we include a scenario using an administration cost of £332 although, as noted above, Janssen considers that this significantly overestimates the actual associated cost to the NHS (refer to Appendix 1, Table 6). For information, we also provide a scenario using the average cost of £123 resulting from the micro-costing analysis (refer to Appendix 1, Table 7).

Insert extra rows as needed

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- Complete the disclosure about links with, or funding from, the tobacco industry.
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- Do not paste other tables into this table – type directly into the table.
- 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
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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.

Appendix 1 Revised economic base case results

Considering the preferences of the AC, alongside the issues covered in Points 1 – 7 above, Janssen present an updated economic base case in which the following changes have been implemented as compared with the economic model submitted at the Technical Engagement stage:

- PAS discount for daratumumab has been updated – see Summary section
- PR and NR haematologic response categories are modelled separately, by splitting out the combined PR/NR state in the decision tree model according to the ratios/separate response rates observed in the respective trials, and then followed up separately as part of the Markov model
- Haematologic response rates of UK-based patients from the EMN23 study have been recategorised as per the ANDROMEDA study – see response to Point 2, and Appendix 2.1 for methodological details
    - Following this re-categorisation, the base case extrapolation distributions for overall survival have been updated as presented in Table 3, based on combined criteria of worst survival at Year 1, visual fit, and statistical fit.
    - Base case reflects the AC's preferred assumption to assess haematologic response at 3-month and explore the 6-month decision-tree exit timepoint as a scenario analysis(ACD, page 22)

Table 3: Overall survival extrapolations implemented in the updated base case

Response category	Decision-tree exit timepoint	
	Three months (base case)	Six months (scenario)
CR	Log-normal	Log-normal
VGPR	Log-logistic	Log-logistic
PR	Log-normal	Log-normal
NR	Log-normal	Log-normal

Abbreviations: BCd: bortezomib, cyclophosphamide and dexamethasone; CR: complete response; DBCd: daratumumab SC in combination with bortezomib, cyclophosphamide and dexamethasone; NR: no response; PR: partial response; VGPR: very good partial response.

- Administration costs for chemotherapy (bortezomib and daratumumab) have not been updated, as per point 7. Results of scenario analysis using £123 average hospital cost for drug administration from the micro-costing tool, and for £332 drug administration cost as per AC's preferred assumption are shown in Table 6 and Table 7 respectively
- The approach to modelling subsequent therapy lines is based on estimates from the UK clinical advisory board, and include ASCT at second-line therapy, as per preferred AC's assumptions– see Appendix 2.2 for details
- In addition, as per point 4, increased relative survival benefit observed for DBCd versus BCd after 20.3 months median follow-up is reflected in the model via **1.044** multiplier in the base case results

Results for the revised deterministic RWE responses base case results are presented in Table 4 and for the 6-month scenario analysis in Table 5. Considering important factors such as the rarity of AL amyloidosis and approximately 20% of the eligible patient population being end-of-life, these results indicate DBCd represents a cost-effective use of NHS resources.

Table 4: Revised base case results (3-months assessment of haematologic response and RWE responses base case)

Treatment	Total			Incremental			ICER (£/QALY)
	Costs (£)	QALYs	LYs	Costs (£)	QALYs	LYs	
BCd	[redacted]	[redacted]	[redacted]				
DBCd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£30,327

Abbreviations: BCd: bortezomib, cyclophosphamide and dexamethasone; DBCd: daratumumab SC in combination with bortezomib, cyclophosphamide and dexamethasone; ICER: incremental cost-effectiveness ratio; QALYs: quality-adjusted life years.

Table 5: Scenario results (6-months decision tree exit)

Treatment	Total			Incremental			ICER (£/QALY)
	Costs (£)	QALYs	LYs	Costs (£)	QALYs	LYs	
BCd	[redacted]	[redacted]	[redacted]				
DBCd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£29,066

Abbreviations: BCd: bortezomib, cyclophosphamide and dexamethasone; DBCd: daratumumab SC in combination with bortezomib, cyclophosphamide and dexamethasone; ICER: incremental cost-effectiveness ratio; QALYs: quality-adjusted life years.

Table 6: Scenario results (SC administration costs informed by micro-costing tool)

Treatment	Total			Incremental			ICER (£/QALY)
	Costs (£)	QALYs	LYs	Costs (£)	QALYs	LYs	
BCd	[redacted]	[redacted]	[redacted]				
DBCd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£30,781

Abbreviations: BCd: bortezomib, cyclophosphamide and dexamethasone; DBCd: daratumumab SC in combination with bortezomib, cyclophosphamide and dexamethasone; ICER: incremental cost-effectiveness ratio; QALYs: quality-adjusted life years.

Table 7: Scenario results (SC administration costs as per Committee preference)

Treatment	Total			Incremental			ICER (£/QALY)
	Costs (£)	QALYs	LYs	Costs (£)	QALYs	LYs	
BCd	[redacted]	[redacted]	[redacted]				
DBCd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£34,788

Abbreviations: BCd: bortezomib, cyclophosphamide and dexamethasone; DBCd: daratumumab SC in combination with bortezomib, cyclophosphamide and dexamethasone; ICER: incremental cost-effectiveness ratio; QALYs: quality-adjusted life years.

Appendix 2 Updated model approaches and data inputs

Appendix 2.1 Re-categorisation of haematologic response data for UK-based patients in the EMN23 study to align with the ANDROMEDA trial

As described in the response to Point 2, the EMN23 UK cohort data was first adjusted to ensure that patients who switched treatment no longer confounded the analyses. The haematologic response data were then re-categorised to align with the response criteria per the ANDROMEDA trial.

Appendix 2.1.1 EMN23 UK cohort patient characteristics

A comparison of patient baseline characteristics at diagnosis from the EMN23 UK study cohort and ANDROMEDA are presented in Table 8.

Table 8: Comparison of patient characteristics between ANDROMEDA and EMN23 UK cohort

Characteristic	ANDROMEDA (N=388)	EMN23 UK cohort (N=1,166)
Age, years		
Median	[redacted]	[redacted]
Sex, n (%)		
Female	[redacted]	[redacted]
Male	[redacted]	[redacted]
Cardiac stage based on Mayo Clinic Cardiac Staging System, n (%)		
I	[redacted]	[redacted]
II	[redacted]	[redacted]
IIIa	[redacted]	[redacted]
IIIb	[redacted]	[redacted][a]
Not reported	[redacted]	[redacted]
Organ involvement, n (%)[b]		
Heart	[redacted]	[redacted]
Kidneys	[redacted]	[redacted]
Liver	[redacted]	[redacted]
Gastrointestinal tract	[redacted]	[redacted]
Lung	[redacted]	[redacted]
Nerve	[redacted]	[redacted]
Soft tissue	[redacted]	[redacted]
Number of organs involved, n (%)		
1 organ	[redacted]	[redacted]
2 organs	[redacted]	[redacted]
≥3 organs	[redacted]	[redacted]
Not reported	[redacted]	[redacted]

[a] As per the Mayo Clinic 2012 staging system, this is reported as Stage IV. The 2012 revision to the staging system incorporated serum immunoglobulin free-light chain (dFLC) as a prognostic factor, assigning patients to Stages I, II, III and IV based on the number of prognostic factors, NT-proBNP, cTnT and dFLC, found to be elevated above defined thresholds.[19] [b] Patients could have >1 involved organs.
Abbreviations: EMN: European Myeloma Network.
Source: Janssen ANDROMEDA CSR (14th February 2020 data cut-off);[20] Palladini *et al.* (2021).[21]

Appendix 2.1.2 Haematologic response definition criteria used in ANDROMEDA trial

As noted in Section B.2.3.2 (page 42) of the CS, CR in ANDROMEDA was assessed by the Independent Review Committee (IRC) and was originally defined as per the consensus guidelines criteria published in Comenzo *et al*., (2012).[22] These criteria included negative serum and urine immunofixation and normalisation of the FLC ratio (FLCr). However, this definition was later updated in line with subsequent publications that provided a broader understanding of the biological processes involved in AL amyloidosis.[12-14] As such, the definition of CR implemented during the ANDROMEDA trial was modified such that if the involved FLC (iFLC) was lower than the upper limit of normal, normalisation of uninvolved FLC (uFLC) level and FLCr were no longer required when determining haematologic CR. This modification was developed based on recommendations from the study steering committee and was agreed upon by the IRC. The clarification was recently published by Palladini *et al*., (2021), with contributions from clinicians at the UK-based NAC, and the original and updated definitions are presented in Table 9 below.[11]

Table 9: Validated haematologic response criteria for AL amyloidosis

Response categories	Original definition	Updated definitions
Complete	Negative serum and urine immunofixation and normal FLC ratio	Both criteria must be met: Absence of amyloidogenic light chains (either free and/or as part of a complete immunoglobulin) defined by negative immunofixation electrophoresis of both serum and urine Either a FLC ratio within the reference range or the uninvolved FLC concentration is greater than involved FLC concentration with or without an abnormal FLC ratio
Very good partial response	dFLC concentration < 40 mg/L	dFLC concentration < 40 mg/L
Partial response	dFLC decrease > 50% compared to baseline	dFLC decrease > 50% compared to baseline
No response	All other patients	All other patients

Abbreviations: dFLC: difference between amyloidogenic (involved) and non-amyloidogenic (uninvolved) free light chain concentrations; FLC: free light chain.
Source: Palladini *et al*., 2021.[11]

Appendix 2.1.3 Methodological details of process to re-categorise response data

Practical steps taken to obtain required EMN23 UK cohort data for re-categorisation of haematologic response

As noted in the response to Point 2, a number of steps were followed to gain access to the EMN23 UK data required to re-categorise haematologic responses in line with the ANDROMEDA trial.

Step 1:

- The EMN23 UK cohort was derived by extracting the UK-only population (N=1,165 in the post-2010 period) from the total EMN23 dataset (N=3,065 in the post-2010 period)

- Additional individual patient data (IPD) required to re-categorise haematologic responses at the 3- and 6-month timepoints to align with the response criteria used in ANDROMEDA were then identified (including the results of laboratory urine and serum tests)
- A request to the UK-based NAC was then submitted to facilitate the transfer of required data to the EMN23 study investigators

Step 2:

- The new EMN23 UK cohort dataset, containing all UK-based IPD and including the required results from laboratory urine and serum testing, was transferred from the UK NAC to the EMN23 study investigators on the 21st March 2022
- It was noted during this step that response assessments for patients in the UK were not based on the results of urine testing, as a result of challenges in postal transport of monthly urine samples

Step 3:

- The EMN23 investigators then performed the re-categorisation of haematologic responses at three and six months for the UK cohort, in order to align it with the criteria used in ANDROMEDA. A small number of modifications in the methodology were required to account for missing or unavailable data:
    - Due to unavailability of urine testing data, urine M-protein was not used in the haematologic response classification
    - Cases where response data were available in the original EMN23 UK database at three or six months, but the results of laboratory testing required for re-categorisation of response were missing in the new dataset, were excluded from the analysis
    - Cases where no response data were available in the original EMN23 UK database, but the results of laboratory testing required for re-categorisation of response were available in the new dataset, were included in the analysis (approximately 30 patients)
- Based on these modifications, 205 out of an initial 1155 patients were excluded from the three-month analysis, and 228 out of an initial 1052 patients were excluded from the six-month analysis.

Process taken by EMN23 study investigators to re-categorise EMN23 UK cohort haematologic response data

Calculation of haematologic responses at 3 months and 6 months was based on ANDROMEDA trial criteria. Some minor adaptations were performed on the criteria due to variable laboratory data availability in some instances (as is expected in the real-world environment). The adaptations were medically and clinically reviewed by the UK NAC principal investigator (PI) to ensure the scientific relevance of the results. The algorithm used for the re-categorisation of responses is presented in Table 10. Differences between ANDROMEDA criteria and the algorithm used were as follows:

- Urine M-protein was not available at any timepoint and was not taken into account for the calculations of VGPR, PR or progressive disease (PD); the evaluations were based on serum data.
- Urine immunofixation electrophoresis was not available at 3 months and was not taken into account for the calculations of CR at 3 months; the evaluations were based on serum data.

- The PD calculation was modified as follows:
    - For 3 months: Since there was no previous response−related laboratory data, patients were classified as PD focussing on the comparison of 3-month data to baseline. Furthermore, in addition to the criterion 'iFLC at 3 months has doubled compared to baseline' listed in the ANDROMEDA criteria, the following criterion was added as per PIs guidance: iFLC should also be >upper limit normal, to avoid false positive results for PDs.
    - For 6 months: In addition to the criterion 'iFLC at 6 months has doubled compared to 3 months' listed in the ANDROMEDA criteria, the following criterion was added as per PIs guidance: iFLC should also be >upper limit normal, to avoid false positive results for PDs.

The above adaptations to ANDROMEDA criteria were made based on the availability of laboratory data and after confirmation with the PI. Verbal confirmation from the NAC indicated that these results remain robust and reliable, despite not being able to match 100% of the ISA 2021 criteria.

Table 10: Adaptation of ANDROMEDA criteria used for the re-categorisation of haematologic response analysis

	Algorithm used for response re-categorisation
CR	**Patients are classified as CHR if they fall in one of the following 3 categories:** **Crit_1.** Negative serum IFE at XX months **AND** negative urine IFE (applicable only for 6 months) **AND** iFLC=Kappa AND Kappa at XX months ≤19.4 OR **Crit_2.** Negative serum IFE at XX months **AND** negative urine IFE (applicable only for 6 months) **AND** iFLC=Lambda AND Lambda at XX months ≤26.3 OR **Crit_3.** Negative serum IFE at XX months **AND** negative urine IFE (applicable only for 6 months) **AND** 0.26 ≤kappa/lambda at XX months ≤1.65 **AND** 3.3 ≤kappa FLC at XX months ≤19.4 **AND** 5.7 ≤Lambda at XX months ≤26.3
VGPR	Patients are classified as VGPR if they cannot be classified as CHR and the following holds: **Crit_1:** Baseline dFLC ≥50 AND dFLC at XX months<40
	Patients are classified as VGPR if they cannot be classified as CHR and the following holds: **Crit_2**: Baseline dFLC <50 AND ≥90% reduction in serum M−protein from baseline at XX months
PR	Patients are classified as PR if they cannot be classified as CHR/VGPR and the following holds: **Crit_1:** Baseline dFLC ≥50 AND >50% reduction in dFLC from baseline at XX months

	Patients are classified as PR if they cannot be classified as CHR/VGPR and the following holds: **Crit_2:** Baseline dFLC <50 AND ≥50% reduction in serum M−protein from baseline at XX months
PD	**For 3 months, patients were classified as PD if one of the following holds:** **Crit_1**: IF 0.26 ≤kappa/lambda at baseline ≤1.65 **AND** {kappa/lambda at 3 months <0.26 or kappa/lambda at 3 months >1.65} **AND** iFLC at 3 months has doubled compared to baseline **AND** iFLC at 3 months >Upper normal limit (i.e., >19.4 if iFLC= kappa and >26.3 if iFLC=lambda) Or **Crit_2**: If serum M-protein increase from baseline at 3 months ≥50% **AND** serum M-protein at 3 months >5 g/L Or **Crit_3**: If iFLC increase from baseline at 3 months ≥50% **AND** iFLC at 3 months is >100mg/L **For 6 months, patients were classified as PD if one of the following holds:** **Crit_1**: If response at 3 months was CHR **AND** (kappa/lambda at 6 months <0.26 or kappa/lambda at 6 months >1.65) **AND** iFLC at 6 months has doubled compared to 3 months **AND** iFLC at 6 months >Upper normal limit (i.e., >19.4 if iFLC= kappa and >26.3 if iFLC=lambda) Or **Crit_2**: If response at 3 months was (CHR, VGPR, PR) **AND** serum M-protein increase from 3 months at 6 months ≥50% **AND** serum M-protein at 6 months >5 g/L Or **Crit_3**: If iFLC increase from baseline or 3 months (whichever is lower) at 6 months ≥50% **AND** iFLC at 6 months is >100mg/L
NR	Cannot be classified as CHR/VGPR/PR/PD If all respective variables are present in order to be able to make an assessment

Abbreviations: CHR: complete haematologic response; dFLC: difference between iFLC and uninvolved free light chain; iFLC: involved free light chain; NR: no response; PD: progressive disease; PR: partial response; SD: stable disease; uIFE: urine immunofixation electrophoresis; VGPR: very good partial response.

Appendix 2.1.4 Clinical data following re-categorisation of response data

Haematologic response

In line with the approach described in the Janssen response to Technical Engagement, Key issue 7, a similar approach was used to calculate EMN23 UK cohort-based response rates for DBCd as was used in the ERG's model to calculate ALchemy-based response rates for DBCd. This involved the application of ANDROMEDA-based cycle-specific odds ratios (DBCd versus BCd) to response rates from EMN23 UK cohort. The conditioning order was again as preferred by the ERG (but also accounting for the now separated PR and NR states): alive, CR, VGPR, PR, NR. Patients in the PD and SD response categories of the EMN23 data set were considered NR when converting to categorisation of ANDROMEDA.

In order to derive the BCd response rates from the EMN23 UK cohort data, it was necessary to make an assumption regarding patients that were marked as 'NA' in the 3- and 6-month landmark response analyses, and that did not die before three or six months. It was assumed

that these patients were distributed among the response categories (CR, VGPR, PR and NR) in the same proportions as observed for the patients that were not marked as 'NA'.

Directly observed BCd response rates from EMN23 UK cohort data were only available for cycle 3 (3-month landmark analysis) and cycle 6 (6-month landmark analysis); corresponding response rates for earlier cycles (1–2 and 1–5, respectively) were calculated by applying the absolute difference for each response rate between the respective and last cycle as observed in the ANDROMEDA BCd arm.

Haematologic response rates by cycle derived from the EMN23 UK cohort study following re-categorisation of response data to align with ANDROMEDA are presented in Table 11 and Table 12.

Table 11: Haematologic response rates following re-categorisation of response data (3-month timepoint)

Cycle	Proportion of patients				
	CR	VGPR	PR	NR	Dead
DBCd					
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BCd					
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Presented figures are rounded to the nearest 1% and thus may not sum to 100%.
Abbreviations: BCd: bortezomib, cyclophosphamide and dexamethasone; CR: complete response; DBCd: daratumumab SC, bortezomib, cyclophosphamide and dexamethasone; NR: no response; PR: partial response; VGPR: very good partial response.

Table 12: Haematologic response rates following re-categorisation of response data (6-month timepoint)

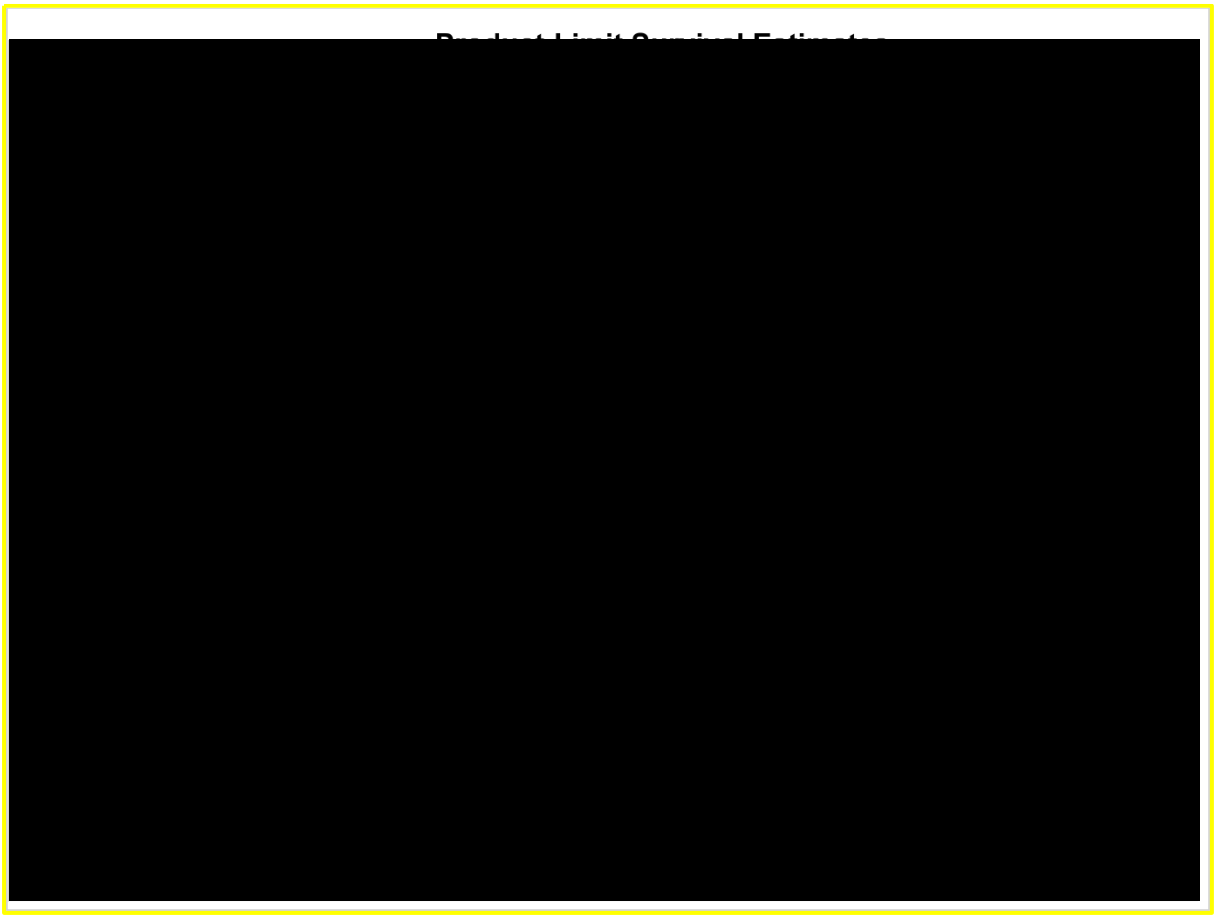
Cycle	Proportion of patients				
	CR	VGPR	PR	NR	Dead
DBCd					
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BCd					
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Presented figures are rounded to the nearest 1% and thus may not sum to 100%.
Abbreviations: BCd: bortezomib, cyclophosphamide and dexamethasone; CR: complete response; DBCd: daratumumab SC, bortezomib, cyclophosphamide and dexamethasone; NR: no response; PR: partial response; VGPR: very good partial response.

Updated survival data

KM curves of OS by haematologic response at 3 months and 6 months, following the re-categorisation of haematologic response aligned with ANDROMEDA response criteria, for patients in the UK who received first-line treatment in the post-2010 period are presented in Figure 1 and Figure 2 below.

Figure 1: Kaplan-Meier graph of overall survival by haematologic response at 3 months for patients in the UK who received first line treatment in 2011-2018



Abbreviations: CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease; VGPR, very good partial response.

Figure 2: Kaplan-Meier graph of overall survival by haematologic response at 6 months for patients in the UK who received first line treatment in 2011-2018

Abbreviations: CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease; VGPR, very good partial response.

Appendix 2.2 Updated model approaches to subsequent lines of therapy

Appendix 2.2.1 Costs for second- and third-line therapies updated to the UK clinical expert advisory board, with inclusion of ASCT

The types of treatment and related distributions of people having these treatments at second- and third-line in the treatment pathway have been updated to be derived from the UK clinical expert advisory board, as per the AC's preference (ACD, pages 18 and 19) and in alignment with the originally submitted approach (see Section B.3.5.2 of the CS).

Furthermore, in alignment with the AC's preference for ASCT to be included as a second-line therapy (ACD, page 18), the economic base case has been adjusted to include [redacted]% of patients modelled to receive ASCT at second-line in both the DBCd and BCd arms. This value was sourced from patients in the EMN23 study who initiated first-line treatment post-2010 as presented in Table 8 of the Janssen response to Part C of ERG Clarification Question B1. The cost of ASCT was modelled to be £15,065.25 (NHS Reference Costs 2019/2020, SA26A). Proportions of patients receiving other second-line regimens were re-scaled to account for ASCT as shown in Table 13, and the assumptions regarding deaths, dose reductions, discontinuation of treatment and proportions of patients receiving third-line treatment described in response to Issue 13 of the Technical Engagement response document were applied.

As previously indicated in response to Key Issue 12 of the Technical Engagement response document, daratumumab is expected to improve ASCT efficacy, and consequently long-term survival. An important limitation of this analysis is that the expected improved efficacy of ASCT following treatment with daratumumab is not reflected in the model results, and therefore these results are considered conservative.

Table 13: Second-line treatment regimen acquisition costs, updated base case

Second-line treatment regimen	Proportion of patients receiving regimen
Lenalidomide + dexamethasone (Rd)	[redacted]
Melphalan + dexamethasone (Md)	[redacted]
Carfilzomib + dexamethasone (Kd)	[redacted]
Bortezomib + cyclophosphamide + dexamethasone (BCd)	[redacted]
ASCT	[redacted]

Abbreviations: ASCT: autologous stem cell transplant; BCd: bortezomib, cyclophosphamide and dexamethasone; Kd: carfilzomib and dexamethasone; Md: melphalan and dexamethasone; Rd: lenalidomide and dexamethasone.

Appendix 2.3 Summary of expected upcoming data cuts from the ANDROMEDA trial

Further data cuts from the ANDROMEDA trial are expected, as previously indicated in response to Key issue 3 of the TE response document and Section A1 of the Clarification to questions response document:

- 200 MOD-PFS event driven data cut-off for the following pre-specified analyses: overall survival (OS), major organ deterioration progression-free survival (MOD-PFS), haematologic response, safety and organ response [redacted]
- Final OS event driven data cut-off: updated analyses have not yet been confirmed [redacted]

Appendix 3 Additional long-term data from the ANDROMEDA trial

Table 14: Sustained response in subsequent months observed in patients achieving CR at 3 months and 6 months per treatment arm. ANDROMEDA, May 2021 data cut-off (18-months landmark analysis)

CR at 3 months	M3	M4	M5	M6	M7	M8	M9	M10	M11	M12	M13	M14	M15	M16	M17	M18	M19	M20	M21	M22	M23	M24	%
DBCd																							
CR	[redacted]																						[redacted]
Total	[redacted]																						
BCd																							
CR	[redacted]																						[redacted]
Total	[redacted]																						
CR at 6 months	**M3**	**M4**	**M5**	**M6**	**M7**	**M8**	**M9**	**M10**	**M11**	**M12**	**M13**	**M14**	**M15**	**M16**	**M17**	**M18**	**M19**	**M20**	**M21**	**M22**	**M23**	**M24**	
DBCd																							
CR				[redacted]																			[redacted]
Total				[redacted]																			
BCd																							
CR				[redacted]																			[redacted]
Total				[redacted]																			

Abbreviations: CR: complete hematologic response; VGPR: very good partial response; PR: partial response; NR: no response; PD: progressive disease; M1–M24: Month 1 to Month 24; NE: not estimated.

Appendix 4 Multivariate analyses for the impact of baseline patient characteristics on overall survival in the ANDROMEDA trial

Figure 3: For all patients with CHR at 3 months multivariate analysis on the impact of baseline patient characteristics on overall survival at 11.4 months median follow up

Abbreviations: CHR: complete haematologic response; CI: confidence interval; CrCl: creatinine clearance; ECOG: Eastern Cooperative Oncology Group; FISH: fluorescent in situ hybridisation; HR: hazard ratio.

Figure 4: For DBCd patients with CHR at 3 months multivariate analysis on the impact of baseline patient characteristics on overall survival at 11.4 months median follow up

Abbreviations: CHR: complete haematologic response; CI: confidence interval; CrCl: creatinine clearance; ECOG: Eastern Cooperative Oncology Group; FISH: fluorescent in situ hybridisation; HR: hazard ratio.

Figure 5: For all patients with CHR at 6 months multivariate analysis on the impact of baseline patient characteristics on overall survival at 11.4 months median follow up

Abbreviations: CHR: complete haematologic response; CI: confidence interval; CrCl: creatinine clearance; ECOG: Eastern Cooperative Oncology Group; FISH: fluorescent in situ hybridisation; HR: hazard ratio.

Figure 6: For DBCd patients with CHR at 6 months multivariate analysis on the impact of baseline patient characteristics on overall survival at 11.4 months median follow up

Abbreviations: CHR: complete haematologic response; CI: confidence interval; CrCl: creatinine clearance; ECOG: Eastern Cooperative Oncology Group; FISH: fluorescent in situ hybridisation; HR: hazard ratio.

Daratumumab in combination for untreated systemic amyloid light-chain amyloidosis [ID3748]

Consultation on the appraisal consultation document – deadline for comments 5pm on 10 February 2022. Please submit via NICE Docs.

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Daratumumab in combination for untreated systemic amyloid light-chain amyloidosis [ID3748]

Consultation on the appraisal consultation document – deadline for comments 5pm on 10 February 2022. Please submit via NICE Docs.

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

Comment number	Comments

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Daratumumab in combination for untreated systemic amyloid light-chain amyloidosis [ID3748]

Consultation on the appraisal consultation document – deadline for comments 5pm on 10 February 2022. 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	We welcome that the committee have acknowledged that AL Amyloidosis is a serious, incurable condition, and that its mental and physical effects can be overwhelming. We also welcome that the committee has agreed that there is an unmet need for effective licensed treatments options for AL Amyloidosis and that Daratumumab in combination improves the haematological response for patients whilst having tolerable side effects. We are also pleased that NICE will consider daratumumab in combination within its full licensed population regardless of disease severity. We understand that there are several uncertainties to be resolved including on the data source for extrapolation of overall survival and the timeline for assessing haematological response. We are concerned that the first committee meeting did not include a clinical expert who was a haematologist. In NHS clinical practice a haematologist would be the lead consultant for patients with AL Amyloidosis. The clinical experts invited to the first committee meeting included cardiologists and nephrologists. The experts' contributions to the discussion were significant and important, including on the inclusion of patients with cardiac 3b disease severity in the full licensed indication. However, they would not normally be the lead consultants for patients with AL Amyloidosis. We feel that a haematologist would be better placed to answer committee questions on significant issues such as the generalisability of patient population data to UK NHS clinical practice and on the timelines for assessing haematological response. Both of which are key issues of uncertainty the committee highlighted in the appraisal consultation document. We would therefore request that both clinical and patient experts be invited to the second committee meeting. We would also request that at the second committee meeting a haematologist be invited as a clinical expert to help answer the committee's questions. We understand that the submitting company have nominated a clinical expert who is a haematologist and would welcome their invitation to the second committee meeting. Alternatively, the committee could reach out to the UK Myeloma Society for a clinical expert as many haematologists who specialise in myeloma also treat a significant number of patients with AL Amyloidosis. There are currently no licensed treatments for AL Amyloidosis available through the NHS and this is the first time a treatment for AL Amyloidosis that has come to NICE for HTA. We feel that by having a haematologist in the second meeting the committee will be better placed to answer key questions in this appraisal. If this were to be approved, then it would be the very first treatment for newly diagnosed AL Amyloidosis which would be a significant milestone for AL Amyloidosis patients and their families.
2	
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Daratumumab in combination for untreated systemic amyloid light-chain amyloidosis [ID3748]

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Insert extra rows as needed

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- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is 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.
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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.

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Comment on the appraisal consultation document by Dr Jennifer Pinney, consultant

Has all of the relevant evidence been taken into account?

yes

- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

  The cost effectiveness modelling is potentially flawed as there was no incorporation of costs related to progression to end stage renal failure. Dialysis is expensive with a range of costs estimated between £15,000 to £60,000 per year depending on frequency, modality and hospital admissions. The benefit from delay of disease progression to end stage renal failure or prevention of progression was not included in any of the modelling. This should be considered as part of the cost effectiveness modelling.

- Are the provisional recommendations sound and a suitable basis for guidance to the NHS?

  The recommendation is disappointing; it was surprising that a haematologist was not on the expert panel. Haematologists are the physicians who deliver the treatment and have most experience with the use of Daratumumab. I would strongly recommend involvement in future reviews.

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Evidence Review Group's Critique of the Company's Response to the Appraisal Consultation Document (ACD)

Daratumumab in combination for newly diagnosed systemic amyloid light-chain amyloidosis [ID3748]

Produced by	CRD and CHE Technology Assessment Group, University of York, Heslington, York, YO10 5DD
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Date completed	23/09/2022

Note on the text

All commercial-in-confidence (CIC) data have been highlighted in blue and underlined, all academic-in-confidence (AIC) data are highlighted in yellow and underlined.

Table of Contents

1 OVERVIEW OF THE COMPANY'S RESPONSE TO THE ACD

The company have provided seven points in response to the Appraisal Consultation Document (ACD). These relate to:

Point 1: Proportion of the eligible population being end-of-life and the existence of insufficiently captured benefits associated with daratumumab in combination with bortezomib, cyclophosphamide and dexamethasone (DBCd) treatment.

Point 2: Following re-categorisation and adjustment, data from the UK cohort of the EMN23 study represents the most robust source of real-world evidence to inform the economic model.

Point 3: Additional analysis investigating potential confounders in the association between haematologic response and overall survival reveal no evidence of confounding.

Point 4: Data from ANDROMEDA demonstrates higher levels of sustained response for DBCd versus BCd which has already translated to a survival benefit at 20.3 months median follow-up.

Point 5: DBCd represents an effective treatment for patients with end-stage cardiac disease.

Point 6: SF36v2 data from the ALchemy trial are unavailable, precluding their use to validate the utility dataset used in the economic model.

Point 7: The administration cost of £332 for daratumumab subcutaneous injection significantly overestimates the true cost.

The ERG provides a critical evaluation of the company's response to the ACD in relation to the seven points above and the company's revised base-case and scenario analyses following ACD. The ERG critique should be read in conjunction with the company's ACD response document, the ERG report, and the ERG critique of the company's response to technical engagement (TE).

2 CRITIQUE OF THE COMPANY'S RESPONSE TO THE ACD

2.1 Point 1: Proportion of the eligible population being end-of-life and the existence of insufficiently captured benefits associated with DBCd treatment.

Under point 1, the company first makes a case for additional consideration of the social value of treating a rare condition such as amyloid light-chain (AL) amyloidosis. The company provides no new additional analyses for this first point but refers to the updated NICE health technology evaluations manual [PMG36][1] to support the case for greater acceptance of the level of uncertainty surrounding

the incremental cost-effectiveness ratio (ICER) for an innovative treatment in a rare disease setting with a high unmet need. Because no new evidence or analyses are presented to support this point, the ERG have no additional comments and notes that this should be considered by the NICE Appraisal Committee.

The second point made by the company is that a significant proportion of the eligible patient population are at end-of-life. The company considers that patients with cardiac stage IIIb disease (suggested to be 18-20% of patients at the National Amyloidosis Centre (NAC)) meet NICE's end-of-life criteria on the grounds that they have a median survival of five months with bortezomib-based therapies based on the EMN23 study across Europe in the post-2010 period,[2] while evidence from an ongoing Phase 2 study evaluating the efficacy and safety of daratumumab monotherapy used off-label in newly diagnosed patients with stage IIIb disease has shown a median overall survival of 9 months.[3] The ERG notes that the median survival of five months for patients with stage IIIb disease and treated with bortezomib-based therapies is from the entire EMN23 study that includes 3,065 patients from 10 European countries and is not based on the UK subpopulation. Furthermore, we do not know what proportion of the European population had a median survival of five months in the post-2010 period; Palladini et al (2021) suggests that 15% of patients were at stage IIIb between 2004 and 2018, while Figure 1 of this study suggests that 342 patients were at risk for probability of survival at 3 months after first-line treatment initiation over the entire 2004-2018 period.[2] The NICE end-of-life criteria requires also evidence that the technology increases overall survival for at least an additional 3 months compared to current NHS treatments, in addition to patients having a short life expectancy. The company have not provided comparative effectiveness evidence of DBCd compared to BCd in the subpopulation with cardiac stage IIIb disease; only interim results showing a median overall survival estimate for off-label use of daratumumab monotherapy in patients with stage IIIb disease.[3] Therefore, it remains unclear whether the extension to life criterion with DBCd would be met for patients with cardiac stage IIIb disease. The company could overcome some of this concern by adapting the economic model to use data from the subgroup of patients with stage IIIb disease from the UK population of the EMN23 study (or ALchemy study) to inform overall survival by haematologic response at 3 months after first-line treatment initiation and reporting the estimates of overall survival with DBCd and BCd; however, this subgroup analysis would require the assumption that the relative effectiveness of DBCd versus BCd for the depth of haematologic response and the probability of progression as observed in the ANDROMEDA trial in patients with stages I-IIIa disease generalises to patients with stage IIIb disease.

Given current evidence, the true relative effectiveness of DBCd versus BCd in patients with stage IIIb disease remains highly uncertain. It is plausible that a proportion of patients with stage IIIb disease would not survive long enough to achieve complete haematologic response (see page10, section 2.1.4

of the ERG's Technical Engagement response). It is also worth noting that the company have not proposed that DBCd is limited exclusively to a subpopulation with stage IIIb disease. It is clear that the end-of-life criteria are not met in the full population because life expectancy with current clinical care (comprising BCd as first-line treatment) exceeds 24 months (see ERG report and NICE Appraisal Committee considerations in Section 3.18 of the ACD).

The third point made by the company under point 1 is the existence of health-related quality of life benefits associated with DBCd treatment that are not captured in the economic model. To support this point the company first highlights that feedback from clinical experts at the NAC indicates that health-related quality of life improvements in patients who achieve a complete or very good haematologic response are typically not observed before one year following the initiation of successful treatment [company data on file, ERG do not have access], while the utility values used in the model were derived from the ANDROMEDA trial with median follow-up time of 11.4 months, suggesting that the quality of life benefits had not reached maximum improvement. The ERG notes that the company have not provided any new health-related quality of life data to support this assertion. However, the ERG's clinical advisors had previously supported the view that improvements in health-related quality of life would be expected to peak at approximately nine to 12 months from the point of treatment initiation and continue to improve for a further 2-3 years, but at a much slower pace before stabilising. This may suggest that the early time point used in the ANDROMEDA trial is not sufficiently long to capture the impact of treatment on health-related quality of life. Therefore, the validity of the utility values applied in the model by depth of haematologic response is highly uncertain. This is further exacerbated by the fact that survival in the model is stratified by the distribution of haematologic response achieved at the response assessment time point and therefore the utility values derived from the ANDROMEDA trial by depth of haematologic response are extrapolated over the long-term (see Section 4.2.8 of the ERG report). The committee may want to take expert advice on this.

The company makes a few further points to support the existence of uncaptured benefits: (i) the introduction of DBCd into UK clinical practice may increase awareness of the rare disease with the potential to shorten diagnosis time and positively impact outcomes; (ii) the psychological benefit from increased peace of mind and hope with the availability of DBCd for newly diagnosed AL amyloidosis; (iii) increased benefit for patients with concomitant multiple myeloma; and (iv) improvement in outcomes associated with DBCd treatment post-autologous stem cell transplantation (ASCT). The ERG notes that no new evidence has been provided to support these claims.

In conclusion, no new evidence has been provided to resolve the uncertainty in health-related quality of life benefits, or to support the assertion that there are uncaptured quality of life benefits associated with DBCd treatment.

2.2 Point 2: Use of EMN23 UK study data following re-categorisation and adjustment.

In point 2 the company notes that the NICE Appraisal Committee expressed concern that the categorisation of haematologic response used in the analysis of the ANDROMEDA data was not consistent with that used in the ALchemy study due to the switching of treatment after 3 cycles, and subsequent concerns about linking of these data to estimate overall survival. This was predominantly a concern for response assessment at 6 months rather than 3 months because almost no one had switched treatment at 3 months in either study (see Section 3.11 of the ACD). The company indicates that following discussions with the UK NAC it was confirmed that haematologic response data from either the ALchemy study or the UK cohort of the EMN23 study would need to be re-categorised to ensure alignment with the ANDROMEDA trial, in terms of both:

a) The approach to the response categorisation of patients who had switched treatments, and
b) The criteria used to define each response category.

The discrepancy in the latter (i.e., the response criteria used to assess haematologic response) was only noted after the ACD was published.

The company did not have access to the patient-level data from ALchemy and therefore used the UK cohort of the EMN23 study to perform the re-categorisation and alignment with ANDROMEDA. The company justified the choice of the EMN23 UK study on the basis of access to the data and the substantial overlap (approximately 95%) between the UK-based patient population recruited to the EMN23 and ALchemy studies. Consequently, the EMN23 UK study cohort was used by the company in the revised economic model following the ACD as the preferred source of data that best reflects NHS clinical practice.

For the re-categorisation to avoid confounding by treatment switching, only a very small number of patients who had switched treatment at the three- [redacted] and six-month [redacted] time points were censored from the analyses. For the re-categorisation of the EMN23 UK study cohort data to align with the response criteria in ANDROMEDA, a number of steps were followed with the methodological details outlined in Appendix 2.1.3 of the company's response to the ACD.

The ERG considers the general approach taken by the company to be acceptable but the details and implications of the approach are discussed below.

Use of EMN23 UK study data to inform haematologic response rather than ALchemy data

As stated in the ERG report, the ERG had a strong preference for the use of ALchemy data to inform both (i) the baseline distribution of haematologic response for standard of care (BCd) and relative effectiveness from ANDROMEDA for DBCd; and (ii) extrapolation of overall survival by

haematologic response. This preference was supported by the NICE Appraisal Committee as ALchemy was considered the best source of data to represent NHS clinical practice rather than the entire EMN23 study (see Sections 3.11 and 3.21 of the ACD). However, following publication of the ACD, the company has revised its approach with a preference for the use of the UK-only population cohort of the EMN23 study. The ERG considers this cohort to be a suitable alternative to ALchemy because of the very high (~95%) level of overlap in participants between the two UK cohorts. This is also observed in the comparison of patient characteristics between the EMN23 UK cohort (Table 8 of the company's response to the ACD) and the ALchemy study (Table 7 of the ERG report). Therefore, the ERG would expect near equivalent outcomes for these two cohorts given that the ALchemy and the original unadjusted EMN23 UK cohort include essentially the same data from the same participants; however, the ERG cannot confirm that outcomes are near equivalent because the original unadjusted data for the UK-only EMN23 cohort were not presented by the company.

Re-categorisation of EMN23 UK cohort data to align with response criteria in ANDROMEDA

The approach to re-categorisation of data was originally intended to avoid confounding due to treatment switching after 3 cycles; however, as noted above, it emerged that the criteria used to assess haematologic response were not aligned between those used in the ANDROMEDA trial and either the EMN23 UK or ALchemy studies. This re-categorisation of data to define response category represents the largest change to the data. Censoring to avoid confounding due to treatment switching only affects a very small number of participants and the ERG expects this to have only minor implications on outcomes. However, the ERG cannot confirm this because the company have not presented data or outcomes with only the censoring for treatment switching implemented.

For the re-categorisation of data for the haematologic response analysis, additional individual participant data (IPD) from the UK cohort of the EMN23 study (including the results of laboratory urine and serum tests) were required to align with the response criteria used in ANDROMEDA. Whilst the ERG is satisfied with the general principles of the approach taken by the company, the ERG notes that the methodology and process of re-categorisation (outlined in Appendix 2.1.3 of the company's response to the ACD) has led to a substantial loss of participant data due to missing laboratory data; for example, for cases where response data were available in the original EMN23 UK database at three or six months, but the results of laboratory testing required for re-categorisation of response were missing in the new dataset, participants were excluded from the analysis. On the basis of missing laboratory data alone, 205 out of an initial 1,155 participants (18%) were excluded from the three-month haematologic response analysis, and 228 out of an initial 1,052 participants (22%) were excluded from the six-month response analysis. Adaptations to the criteria used to define each response category in ANDROMEDA were also required in the EMN23 UK dataset because of missing information such as the unavailability of urine M-protein at any time point, urine

immunofixation electrophoresis at 3 months, and no previous response-related laboratory data. The ERG cannot comment on the appropriateness of the criteria used for the re-categorisation, but the ERG's clinical advisor indicated that the reclassification of response is important as the older criteria used in the analysis of ALchemy were problematic. The ERG's clinical advisor also indicated that the missing data from the EMN23 UK cohort as a result of incomplete datasets, or lack of participant data at appropriate time points, is expected to be missing at random, although this cannot be formally checked.

Haematologic response following re-categorisation of EMN23 UK cohort data

The company presents updated haematologic response rates at the three- and six-month assessment time points for BCd from the EMN23 UK cohort following the re-categorisation of data associated with both the response criteria and censoring of treatment switching. In line with the approach used in the ERG report for the estimation of response rates for DBCd in the ALchemy population, the company applied the relative effectiveness of DBCd compared to BCd from the ANDROMEDA trial to the BCd response rates from the EMN23 UK cohort. The company also modelled the partial response (PR) and no response (NR) categories separately in line with the NICE Appraisal Committee's preferred assumptions (see Section 3.21 of the ACD). When converting to the categorisation of ANDROMEDA, the company classified patients in the progressive disease (PD) and stable disease (SD) categories as NR. The ERG considers the approach used by the company for the estimation of response rates following re-categorisation to be appropriate, and in line with the committee's preferred assumptions, with the ALchemy study replaced with the EMN23 UK cohort, as discussed above.

The ERG presents a comparison of the haematologic response rates for DBCd and BCd at the three- and six-month assessment time points for the EMN23 UK cohort following re-categorisation with ALchemy and ANDROMEDA. These are presented in Table 1 and 2 at the three- and six-month time points, respectively, with the corresponding difference in the depth of haematologic response between DBCd and BCd shown in XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX and **Error! Reference source not found.**. The ERG notes that at the three-month assessment time point there is a greater relative proportion of patients classified as PR and NR for BCd versus DBCd in the EMN23 UK cohort following re-categorisation compared to the ALchemy study, with approximately [redacted] relative treatment difference classified as a very good partial response (VGPR) in the EMN23 UK cohort (Table 1 and XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX). At the six-month

assessment time point, there is a greater relative proportion of patients classified as complete response (CR) for DBCd versus BCd in the EMN23 UK cohort following re-categorisation compared to the ALchemy study (approximately [redacted] more), while a greater relative proportion of patients are classified as PR and NR for BCd versus DBCd in the EMN23 UK cohort following re-categorisation (approximately [redacted] difference from VGPR and [redacted] from CR). Because the cohort of patients in EMN23 UK and ALchemy have very high overlap, the difference in haematologic response rates for DBCd versus BCd between the two cohorts are due to the re-categorisation and the missing participant data as a result of the re-categorisation.

Table 1: Distribution of patients by haematologic response for EMN23 UK, ALchemy and ANDROMEDA for DBCd and BCd after three treatment cycles.

	CR	VGPR	PR	NR	Dead
ANDROMEDA					
DBCd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BCd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EMN23 UK cohort					
DBCd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BCd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ALchemy study					
DBCd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BCd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change in haematologic response					
ANDROMEDA trial	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EMN23 UK cohort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ALchemy study	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BCd: bortezomib, cyclophosphamide and dexamethasone; CR: complete haematologic response; DBCd: daratumumab SC, bortezomib, cyclophosphamide and dexamethasone; NR: no response; PR: partial response; VGPR: very good partial response.

Table 2: Distribution of patients by haematologic response for EMN23 UK, ALchemy and ANDROMEDA for DBCd and BCd after six treatment cycles.

	CR	VGPR	PR	NR	Dead
ANDROMEDA					
DBCd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BCd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EMN23 UK cohort					
DBCd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BCd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ALchemy study					
DBCd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BCd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change in haematologic response					
ANDROMEDA trial	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EMN23 UK cohort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ALchemy study	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BCd: bortezomib, cyclophosphamide and dexamethasone; CR: complete haematologic response; DBCd: daratumumab SC, bortezomib, cyclophosphamide and dexamethasone; NR: no response; PR: partial response; VGPR: very good partial response.

[redacted]

[redacted]

[redacted]

Overall survival following re-categorisation of EMN23 UK cohort data

The company presents updated Kaplan-Meier (K-M) curves of overall survival by haematologic response at three- and six-months following the re-categorisation of the EMN23 UK cohort data (see Figures 1 and 2 of Appendix 2.1.4 of the company's response to the ACD). These K-M curves were subsequently extrapolated over the long-term for implementation in the economic model. The company indicates that the extrapolation distributions for overall survival (OS) by haematologic response category were based on the combined criteria of worst survival at year 1, visual fit and statistical fit; a log-normal distribution was selected for CR, PR and NR at both the three- and six-month assessment time points, while a log-logistic distribution was selected for VGPR at both time points.

The ERG shows the company's extrapolated OS curves by haematologic response after three treatment cycles following the re-categorisation of the EMN23 UK cohort data in **Error! Reference source not found.**(a) and the extrapolated curves from the ALchemy study in **Error! Reference source not found.**(b), while the corresponding curves after six treatment cycles are shown in **Error! Reference source not found.**(a) and (b). The reason for the ERG presenting both sets of extrapolations alongside each other is to show the implications of the re-categorisation and missing participant data on OS. The OS for CR is significantly higher in the re-categorised EMN23 UK cohort at the three-month assessment time point, while the relative difference in OS between CR and VGPR,

PR and NR is much greater in the re-categorised EMN23 UK cohort compared to ALchemy. It is also worth noting that the extrapolated OS for CR in EMN23 UK cohort data crosses the general population OS much sooner than the ALchemy data (an adjustment is made in the model to ensure that the survival curves are not greater than the general population mortality risk). The implications of the re-categorisation and missing participant data on OS for the cost-effectiveness results is shown in Section 3.2.

[redacted]

[redacted]

[redacted]

2.3 Point 3: Potential confounders in the association between haematologic response and overall survival.

Under point 3, the company quoted section 3.12, page 16 of the ACD: "The committee concluded that, because the company used haematological response as a surrogate for overall survival, the committee would prefer to see analyses that show whether the extrapolations are sensitive to potential confounders of the relationship between haematological response and death."

In Appendix 4 of the ACD response, the company presented multivariate analyses of 11.4 month median follow-up data from the ANDROMEDA trial to assess the impact of baseline patient characteristics on overall survival for patients who achieved a CR at three months and six months.

However, the plots presented by the company in Appendix 4 suggest a failure to adequately estimate the parameters of interest, so no conclusion can be made. Many of the HRs presented do not have appropriately estimated confidence intervals, almost all are estimated at 0, or extremely high (with values in the millions also presented). The ERG cannot comment on these results as they do not appear to be adequately estimated.

The company also cites clinical advice that any confounding between haematologic response and the overall survival predictions in ANDROMEDA would not be meaningfully impactful. Given the lack of reliable results from the statistical analysis, this is still an area of uncertainty.

2.4 Point 4: Data from ANDROMEDA demonstrates higher levels of sustained response for DBCd versus BCd.

For point 4 the company provides additional long-term data from ANDROMEDA of sustained response in subsequent months, up to month 24, in patients who achieved CR at three and six months in the DBCd and BCd treatment arms (see Table 14 of Appendix 3 of company's response to the ACD). It is worth noting that from cycle 7 onwards in ANDROMEDA, patients in the DBCd arm received daratumumab as monotherapy every four weeks for a maximum of 24 cycles, or until experiencing disease progression or starting a subsequent anti-plasma cell therapy. The data demonstrates that a higher proportion of patients in the DBCd arm ([redacted] and [redacted] at 3 months and 6 months respectively) sustained their response until month 24 as compared with patients in the BCd arm ([redacted] and [redacted] at 3 months and 6 months, respectively). These data, however, were not incorporated into the economic model because no other outcome data were available from the most recent 18-month data cut of ANDROMEDA. Instead, the company incorporated an expected survival benefit of daratumumab monotherapy in the model by comparing the survival of patients in the DBCd arm to the BCd arm at a median follow-up of 20.3 months from the 12.4-month landmark analysis and multiplying the per-cycle overall survival probability for each haematologic response group with a factor informed by the observed survival in the ANDROMEDA trial. The observed ratio of surviving patients in ANDROMEDA at a median follow-up of 20.3 months was 1.066 for DBCd versus BCd, while the equivalent ratio between treatment arms in the model (based on the re-categorised EMN23 UK cohort data) was 1.021. Consequently, the company uplifted the per-cycle survival probabilities for all response categories in the DBCd treatment arm from cycle 7 onwards by a factor of 1.044, indicating a 4.4% higher survival in patients treated with DBCd as compared with patients on BCd only. The implications for the cost-effectiveness results are shown in Section 3.2.

In the absence of mature OS data from ANDROMEDA, the ERG considers the company's general approach to be acceptable but there remains uncertainty surrounding the predicted treatment-specific OS over time. The ERG notes that the company's approach partly addresses the NICE Appraisal

Committee's concern that OS from ANDROMEDA had not been directly compared with the extrapolated curves from ALchemy and EMN23 (see section 3.12 of the ACD); however, the ERG notes that the comparison undertaken by the company is limited to overall life expectancy estimates and not conditioned by haematologic response. It also remains unclear to the ERG whether or not the observed ratio of surviving patients in ANDROMEDA at a median follow-up of 20.3 months includes participants who had switched treatment after three cycles (or whether these were censored from the analysis as per the response to point 2 above).

2.5 Point 5: DBCd for patients with end-stage cardiac disease.

The company seeks a recommendation for DBCd in newly diagnosed AL amyloidosis in the entire licensed population, including patients with Mayo Clinic Cardiac Stage IIIb disease, who have the most severe degree of cardiac involvement. However, patients with stage IIIb disease were excluded from the ANDROMEDA trial. Under point 5, the company highlights that these patients are included in the updated analysis using the EMN23 UK cohort for BCd and the company considers the assumption that the relative treatment benefit of DBCd versus BCd observed in the ANDROMEDA trial is generalisable to patients with cardiac stage IIIb disease. Furthermore, the company considers the latter assumption to be conservative because (i) subgroup data for patients in the ANDROMEDA trial stratified by cardiac disease stages I-IIIa demonstrate that the relative treatment effect of DBCd increases with increasing severity of cardiac disease according to the Mayo Clinic Cardiac Staging system; and (ii) an ongoing Phase 2 study evaluating the efficacy and safety of daratumumab monotherapy used off-label in newly diagnosed patients with stage IIIb disease has shown a median overall survival of 9 months.[3] However, as stated in section 2.1.4 of the ERG Technical engagement response, the assumption of a larger relative treatment effect amongst stage IIIb patients than the less severe patients observed in the ANDROMEDA trial may not be valid given the much poorer prognosis of patients with stage IIIb disease compared to other stages. It should also be noted that the cited ongoing phase 2 study does not evaluate the relative treatment effect of DBCd versus BCd – rather it observes the effect of off-label daratumumab monotherapy in 27 stage IIIb patients without any comparator group.

The ERG is satisfied that the cost-effectiveness of DBCd in the entire licensed population (including patients with Mayo Clinic Cardiac Stage IIIb and patients with less severe disease) is now presented under the critical assumptions that (i) the relative effectiveness of DBCd versus BCd for the depth of haematologic response, as observed in the ANDROMEDA trial, generalises to the entire licensed population; (ii) the health-related quality of life, safety and probability of progression observed in the ANDROMEDA trial also generalises to the entire licensed population; and (iii) the re-categorised EMN23 UK cohort data for overall survival stratified by depth of haematologic response for BCd provides the best available baseline data for NHS clinical practice. However, the ERG notes that no

new evidence on the relative effectiveness of DBCd compared to BCd in a subpopulation of patients with stage IIIb disease has been presented. Therefore, uncertainty about the cost-effectiveness of DBCd compared to BCd in a subgroup of patients with Mayo Clinic Cardiac Stage IIIb remains.

2.6 Point 6: SF36v2 data from the ALchemy trial.

For point 6 the company have been unable to access patient-level or unpublished SF36v2 data from the ALchemy study in order to validate the health-related quality of life utility values used in the model. This was in response to a request from the NICE Appraisal Committee (Section 3.13 of the ACD) and the uncertainties associated with the EQ-5D utility values from the ANDROMEDA trial highlighted in the ERG report. The company have emphasised that the utility values from the ANDROMEDA trial were based on a limited follow-up and as such are conservative because the improvements in health-related quality of life are typically not observed before the one-year time point. The ERG have commented on the latter point under the response to point 1, and therefore have no additional comments to add in response to point 6.

2.7 Point 7: The administration cost for daratumumab subcutaneous injection.

In the company's original model, the cost of subcutaneous (SC) administration of daratumumab and bortezomib was assumed to correspond to the cost of 5 minutes of a band 5 nurse at £3.08 and zero cost for cyclophosphamide and dexamethasone (oral administration). The ERG report highlighted that daratumumab and bortezomib require preparation in the pharmacy or in the ward, and that the first four administrations of daratumumab are expected to require the patient to stay for a few hours for monitoring. Furthermore, the NHS guidance for national cost collection specifies that, in recording the costs of chemotherapy, trusts should use the relevant healthcare resource group (HRG) codes for the procurement of chemotherapy and for the delivery of chemotherapy at £2,110 and £241-£332, respectively.[4] The ERG report presented a scenario (ERG Scenario 10) where HRG code SB12Z (Deliver Simple Parental Chemotherapy at First Attendance) was used for the first delivery of a cycle and HRG code SB15Z (Deliver Subsequent Elements of a Chemotherapy Cycle) was used for subsequent deliveries in the same cycle, for which the average cost weighted by activity is £241 and £332, respectively. In response to TE, the company increased its value for the administration cost of daratumumab and bortezomib to £99 based on specialist nursing costs for cancer treatment (N10AF) and in line with the NICE technology appraisal on daratumumab in combination for untreated multiple myeloma when stem cell transplant is suitable.[5] The Cancer Drugs Fund lead at the committee considered that £99 underestimated the true administration cost and considered it would likely be £332 based on HRG code SB15Z (Section 3.15 of the ACD).

In response to the ACD, the company have highlighted that the National Tariff Payment System does not distinguish between intravenous infusion (IV) or SC administration of cancer treatment, and that

HRG code SB15Z principally relates to infusional treatments that involve complex monitoring and extended chair time. Furthermore, the preparation time by a pharmacist for the SC administration is not required. Therefore, the company considers the specialist nursing tariff (N10AF) to be more appropriate and reflective of the service delivery costs incurred and was accepted in TA763. To further investigate service delivery costs associated with the provision of SC daratumumab in clinical practice, the company also conducted a micro-costing exercise in the UK, using a Discrete Event Simulation tool to model treatment delivery in the hospital setting. The company reported that the results showed that average administration cost of daratumumab SC in the hospital setting is £123 per dose. The ERG cannot comment on the micro-costing exercise because the tool or detailed information about it have not been presented in response to the ACD. However, the company have presented cost-effectiveness results for a base case using £99 for administration costs and alternative scenarios using the costs of £123 (micro-costing tool) and £332 (committee preferred assumption).

3 CRITIQUE OF THE COMPANY'S REVISED BASE-CASE AND SCENARIO ANALYSES FOLLOWING ACD

3.1 Company's revised base case and scenario analyses

The company presents results of a revised base-case and scenario analyses following the ACD. The assumptions in the company's revised base-case are summarised as follows:

- Inclusion of Patient Access Scheme (PAS) for daratumumab of [redacted] on the list price.
- Partial response and no response haematological categories are modelled separately.
- The distribution of haematologic response for BCd is based on the re-categorised EMN23 UK cohort data and relative effectiveness for DBCd informed by ANDROMEDA.
- Haematologic response is assessed at 3 months.
- Extrapolated overall survival by haematologic response is based on the re-categorised EMN23 UK cohort data.
- An increased relative survival benefit of 4.4% for DBCd compared to BCd has been applied by uplifting the per-cycle survival probabilities for all response categories in the DBCd treatment arm from cycle 7 onwards by a factor of 1.044.
- The administration costs for chemotherapy (daratumumab and bortezomib) of £99 are based on the specialist nursing tariff (N10AF).
- Estimates from the UK expert advisory board is used to inform second- and third-line therapies, and autologous stem cell transplant is included at second-line.

The company conducts three scenario analyses, where the base-case assumptions hold except for the following changes:

- Scenario 1: The haematologic response is assessed at 6 months rather than 3 months.
- Scenario 2: The administration costs for chemotherapy are £123 (informed by the micro-costing tool) rather than £99.
- Scenario 3: The administration costs for chemotherapy are £332 (committee preferred assumption) rather than £99.

The results of the company's revised base-case and scenario analyses are shown in Table 3 and Table 4, respectively.

Table 3: Company's revised base-case results following the ACD

Treatment	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
BCd	[redacted]	[redacted]			
DBCd	[redacted]	[redacted]	[redacted]	[redacted]	£ 30,327

Abbreviations: BCd: bortezomib, cyclophosphamide and dexamethasone. DBCd: daratumumab with bortezomib, cyclophosphamide and dexamethasone ICER: incremental cost-effectiveness ratio; QALYs: quality-adjusted life years.

Table 4: Results of the company's scenario analyses following the ACD

Treatment	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
Scenario 1: 6-month haematologic response assessment					
BCd	[redacted]	[redacted]			
DBCd	[redacted]	[redacted]	[redacted]	[redacted]	£ 29,066
Scenario 2: Administration costs changed from £99.30 (base case) to £123 (informed by micro-costing tool)					
BCd	[redacted]	[redacted]			
DBCd	[redacted]	[redacted]	[redacted]	[redacted]	£ 30,777
Scenario 3: Administration costs changed from £99.30 (base case) to £332 (AC preferred assumption)					
BCd	[redacted]	[redacted]			
DBCd	[redacted]	[redacted]	[redacted]	[redacted]	£ 34,741

Abbreviations: BCd: bortezomib, cyclophosphamide and dexamethasone. DBCd: daratumumab with bortezomib, cyclophosphamide and dexamethasone ICER: incremental cost-effectiveness ratio; QALYs: quality-adjusted life years; AC, Appraisal Committee.

Note that there is a minor discrepancy in the results of scenario 2 and 3 from those reported in the company's response to the ACD (see Table 6 and 7 of the company's response, respectively) because the company did not appear to update the SC administration costs of second-line therapies in the model (i.e., only first-line therapies were updated), which the ERG have corrected for the presentation of results in Table 4.

3.2 Critique of the company's revised base case and scenario analyses

It is worth firstly noting that the company states that the PAS discount for daratumumab has been updated increasing the simple discount to a [redacted] on the list price. The ERG notes that this

PAS discount had already been updated before the first Appraisal Committee Meeting and the committee had access to an ERG addendum with results that incorporated the new confidential price of daratumumab following communication between NICE and the ERG on the 3rd December 2021. Therefore, the ERG believes that the committee conclusions published in the ACD already reflect the revised PAS discount for daratumumab.

The ERG have compared the company's revised base-case assumptions with the committee's preferred assumptions (as outlined in Section 3.21 of the ACD) in Table 5 below.

Table 5: Comparison of committee and company preferred assumptions

Committee preferred assumption	Company's revised analyses	ERG comment
Model PR and NR groups separately	Yes	The company have revised the model structure by splitting out the combined PR/NR states and applying separate response rates for PR and NR.
Include people with end-stage cardiac and renal disease in the population	Yes	The primary source of data for standard care is now the EMN23 UK cohort which includes people with end-stage cardiac and renal disease.
Use data from ALchemy for the distribution of haematological response for standard care and use relative effectiveness from ANDROMEDA for the daratumumab in combination arm	Partially	The company have used the re-categorised EMN23 UK cohort data as an alternative to ALchemy because of the large overlap in the UK-based patient population and the need to re-categorise the data to ensure alignment with the ANDROMEDA trial.
Provide estimates of the association between haematological response and overall survival accounting for potential confounders	Partially	The company provide a response to point 3 indicating that additional analyses investigating potential confounders in the association between haematologic response and overall survival reveal no evidence of confounding. However, the ERG notes that the plots presented by the company in Appendix 4 of their response to the ACD suggest a failure to adequately estimate the parameters of interest. Therefore, the ERG does not consider that this preferred assumption has been adequately addressed.
Assess haematological response at 3 months in the base case but explore a scenario using 6 months, adjusting analyses to ensure consistency in response categorisation between the two data sources, ANDROMEDA and ALchemy	Yes	The company have assessed haematological response at 3 months in the base case and at 6 months in a scenario analysis. The EMN23 UK cohort data have been adjusted to align with ANDROMEDA in terms of the approach to the response categorisation of patients who had switched treatments and the criteria used to define each response category.
Use ALchemy to extrapolate overall survival, but explore fit compared with overall survival from ANDROMEDA	Partially	The company have used the re-categorised EMN23 UK cohort data as an alternative to ALchemy for the extrapolation of overall survival by haematologic response. The company have increased the relative survival benefit of DBCd versus BCd based on a comparison of the observed ratio of surviving patients in ANDROMEDA at a median follow-up of 20.3 months. The ERG notes that the comparison undertaken by the company is limited to overall life expectancy estimates and not conditioned by haematologic response.
Use SF36v2 data from ALchemy to validate the company's utility set.	No	The company were unable to access SF36v2 data from ALchemy to validate the company's utility values.

Apply a stopping rule for daratumumab monotherapy of a maximum of 24 cycles	Yes	Daratumumab is given for a maximum of 24 cycles.
Increase chemotherapy administration costs from £99 to £332	Partially	The company have increased the chemotherapy administration costs to £332 in a scenario analysis.
Include autologous stem cell transplant in the model	Yes	ASCT is included at second-line therapy.
Use estimates from the UK expert advisory board for second- and third-line treatments use	Yes	Included as per the company's original submission.

In order to understand the implications of the use of the re-categorised EMN23 UK cohort data, for informing both the baseline haematologic response distribution for BCd and the extrapolated overall survival by haematologic response, on the cost-effectiveness results, the ERG have conducted some additional analyses that reflect the committee's preferred assumption of using ALchemy. Although the ERG is aware that the committee may revise its preference in light of the availability of UK cohort data from the EMN23 study and the large overlap in the population between these two studies, the ERG considers it important to understand the implications of the re-categorisation of the data. Because the company have not presented results based on the EMN23 UK cohort data before and after the re-categorisation and adjustments made to the data, the closest comparison of cost-effectiveness results that show the implications of the adjustments is a comparison of the company's revised results with those based on the unadjusted ALchemy data.

Table 6 and Table 7 show the committee's preferred assumptions using the ALchemy data and resulting ICERs for 3-month and 6-month haematologic response assessment, respectively. The corresponding detailed cost-effectiveness results are presented in Table 9 and Table 10, respectively. The ICER results at the preferred 3-month assessment time point show that the re-categorisation, missing participant data, and extrapolation of overall survival for the EMN23 UK cohort has a combined effect of reducing the ICER from £43,908 to £30,327. This is predominantly the result of significantly higher OS for CR, a larger relative difference in OS between CR and VGPR, PR and NR, and, to a lesser extent, the approximate [redacted] relative treatment difference for DBCd versus BCd classified as VGPR rather than PR or NR in the re-categorised EMN23 UK cohort compared to ALchemy. The implications on the ICER at the 6-month assessment time point are similar but less substantial.

The chemotherapy administration costs are also a significant driver of the ICER results. The difference in costs between the company's preferred estimate (£99) and the committee's preferred estimate (£332) changes the ICER by £4,414 in the 3-month assessment analyses.

Table 6: Committee preferred assumptions and resulting ICERs for 3-month haematologic response assessment

Assumption number	Preferred assumption	ICER, /QALY	
		Individual (*)	Cumulative(*)
Company's revised base-case		£ 30,327	
1	ALchemy study is the source used to inform the baseline haematologic response distribution for BCd	£ 32,400	-
2	ALchemy study is the source used to inform overall survival, stratified by haematologic response (CR – Weibull distribution; VGPR - Weibull; PR – Weibull; NR - Weibull)	£ 39,594	£ 43,908
3	Administration costs of £332 in line with AC preferred assumption	£ 34,741	£ 50,445

(*) Individual ICER refers to the results when the alternative assumptions are applied individually; **Cumulative ICER** refers to the results when the alternative assumptions are applied cumulatively, in the order as indicated by the order in the table.
Abbreviations: BCd: bortezomib, cyclophosphamide and dexamethasone. DBCd: daratumumab with bortezomib, cyclophosphamide and dexamethasone; ERG: external assessment group; ICER: incremental cost-effectiveness ratio; AC, Appraisal Committee.

Table 7: Committee preferred assumptions and resulting ICERs for 6-month haematologic response assessment

Assumption number	Preferred assumption	ICER, /QALY	
		Individual (*)	Cumulative(*)
Company's revised base-case		£ 29,066	
1	ALchemy study is the source used to inform the baseline haematologic response distribution for BCd	£ 30,923	-
2	ALchemy study is the source used to inform overall survival, stratified by haematologic response (CR – Weibull distribution; VGPR - Weibull; PR – Weibull; NR - Weibull)	£ 32,552	£ 35,217
3	Administration costs of £332 in line with AC preferred assumption	£ 32,858	£ 39,881

(*) Individual ICER refers to the results when the alternative assumptions are applied individually; **Cumulative ICER** refers to the results when the alternative assumptions are applied cumulatively, in the order as indicated by the order in the table.
Abbreviations: BCd: bortezomib, cyclophosphamide and dexamethasone. DBCd: daratumumab with bortezomib, cyclophosphamide and dexamethasone; ERG: external assessment group; ICER: incremental cost-effectiveness ratio; AC, Appraisal Committee.

The ERG also conducted a scenario analysis to show the implications of the increased survival benefit for DBCd, whereby the company uplifted the per-cycle survival probabilities for all response categories in the DBCd treatment arm from cycle 7 onwards by a factor of 1.044 (i.e., a 4.4% higher survival in patients treated with DBCd as compared with patients on BCd), based on the survival benefit of daratumumab monotherapy in ANDROMEDA at a median follow-up of 20.3 months (see point 4 above). In the ERG scenario, no additional survival benefit for DBCd is incorporated, i.e., a factor of 1.0 is used where the treatment-specific overall survival is stratified by the depth of haematologic response at the assessment time point. The results of the ERG scenario are shown in Table 8. The results demonstrate that the company's revised ICER increases from £30,327 to £33,913

(with all other assumptions the same as the company's preferred approach), indicating that the increased survival benefit for DBCd is an important driver of the cost-effectiveness results.

Table 8: Results of ERG scenario analysis

Treatment	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
ERG scenario: No additional survival benefit with DBCd (i.e., factor of 1.044 set to 1.00)					
BCd	[redacted]	[redacted]			
DBCd	[redacted]	[redacted]	[redacted]	[redacted]	£ 33,913

Abbreviations: BCd: bortezomib, cyclophosphamide and dexamethasone. DBCd: daratumumab with bortezomib, cyclophosphamide and dexamethasone ICER: incremental cost-effectiveness ratio; QALYs: quality-adjusted life years.

Table 9: Detailed cost-effectiveness results for the committee's preferred assumptions for 3-month haematologic response assessment

Scenario	Option	Costs	QALYs	Inc. Costs	Inc. QALYs	ICER, £/QALY
Changes to the company revised model done individually						
Company's revised base-case (3-month haematologic response assessment)	BCd	[redacted]	[redacted]			
	DBCd	[redacted]	[redacted]	[redacted]	[redacted]	£ 30,327
ALchemy study is the source used to inform the baseline haematologic response distribution for BCd	BCd	[redacted]	[redacted]			
	DBCd	[redacted]	[redacted]	[redacted]	[redacted]	£ 32,400
ALchemy study is the source used to inform overall survival, stratified by haematologic response (CR – Weibull distribution; VGPR - Weibull; PR – Weibull; NR - Weibull)	BCd	[redacted]	[redacted]			
	DBCd	[redacted]	[redacted]	[redacted]	[redacted]	£ 39,594
Administration costs of £332 in line with AC preferred assumption	BCd	[redacted]	[redacted]			
	DBCd	[redacted]	[redacted]	[redacted]	[redacted]	£ 34,741
Changes to the company revised model done cumulatively						
ALchemy study is the source used to inform the baseline haematologic response distribution for BCd	BCd	[redacted]	[redacted]			
	DBCd	[redacted]	[redacted]	[redacted]	[redacted]	£ 32,400
ALchemy study is the source used to inform overall survival, stratified by haematologic response (CR – Weibull distribution; VGPR - Weibull; PR – Weibull; NR - Weibull)	BCd	[redacted]	[redacted]			
	DBCd	[redacted]	[redacted]	[redacted]	[redacted]	£ 43,908
Administration costs of £332 in line with AC preferred assumption	BCd	[redacted]	[redacted]			
	DBCd	[redacted]	[redacted]	[redacted]	[redacted]	£ 50,445

Abbreviations: BCd: bortezomib, cyclophosphamide and dexamethasone. CR: complete response. DBCd: daratumumab with bortezomib, cyclophosphamide and dexamethasone; ERG: external assessment group. ICER: incremental cost-effectiveness ratio. NR: No Response. PR: Partial Response. VGPR: very good partial response. AC, Appraisal Committee.

Table 10: Detailed cost-effectiveness results for the committee's preferred assumptions for 6-month haematologic response assessment

Scenario	Option	Costs	QALYs	Inc. Costs	Inc. QALYs	ICER, £/QALY
Changes to the company revised model done individually						
Company's revised scenario analysis with 6-month haematologic response assessment	BCd	[redacted]	[redacted]			
	DBCd	[redacted]	[redacted]	[redacted]	[redacted]	£ 29,066
ALchemy study is the source used to inform the baseline haematologic response distribution for BCd	BCd	[redacted]	[redacted]			
	DBCd	[redacted]	[redacted]	[redacted]	[redacted]	£ 30,923
ALchemy study is the source used to inform overall survival, stratified by haematologic response (CR – Weibull distribution; VGPR - Weibull; PR – Weibull; NR - Weibull)	BCd	[redacted]	[redacted]			
	DBCd	[redacted]	[redacted]	[redacted]	[redacted]	£ 32,552
Administration costs of £332 in line with AC preferred assumption	BCd	[redacted]	[redacted]			
	DBCd	[redacted]	[redacted]	[redacted]	[redacted]	£ 32,858
Changes to the company revised model done cumulatively						
ALchemy study is the source used to inform the baseline haematologic response distribution for BCd	BCd	[redacted]	[redacted]			
	DBCd	[redacted]	[redacted]	[redacted]	[redacted]	£ 30,923
ALchemy study is the source used to inform overall survival, stratified by haematologic response (CR – Weibull distribution; VGPR - Weibull; PR – Weibull; NR - Weibull)	BCd	[redacted]	[redacted]			
	DBCd	[redacted]	[redacted]	[redacted]	[redacted]	£ 35,217
Administration costs of £332 in line with AC preferred assumption	BCd	[redacted]	[redacted]			
	DBCd	[redacted]	[redacted]	[redacted]	[redacted]	£ 39,881

Abbreviations: BCd: bortezomib, cyclophosphamide and dexamethasone. CR: complete response. DBCd: daratumumab with bortezomib, cyclophosphamide and dexamethasone; ERG: external assessment group. ICER: incremental cost-effectiveness ratio. NR: No Response. PR: Partial Response. VGPR: very good partial response. AC, Appraisal Committee.

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