NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Daratumumab monotherapy for treating relapsed and refractory multiple myeloma [ID933]

The following documents are made available to the consultees and commentators:

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

2. **Consultee and commentator comments on the Appraisal Consultation Document** from:
   - Janssen
   - Myeloma UK
   - UK Myeloma Forum
   - Celgene

   Department of Health – had no comments

3. **Comments on the Appraisal Consultation Document from experts:**
   - Barry Neville – patient expert, nominated by Myeloma UK

4. **Evidence Review Group critique of the additional information submitted by the company**

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

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Single Technology Appraisal

Daratumumab monotherapy for treating relapsed and refractory multiple myeloma

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

Definitions:

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 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 determination (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, 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.

Comments received from consultees

Consultee	Comment [sic]	Response
Janssen	Janssen welcomes the opportunity to comment on the preliminary recommendation made by the Appraisal Committee (AC) detailed in the appraisal consultation document (ACD). We are extremely disappointed that the AC's preliminary decision is to not recommend daratumumab monotherapy (hereafter referred to as daratumumab) for patients with relapsed and refractory multiple myeloma (RRMM). We are, however, committed to working with the National Institute for Health and Care Excellence (NICE) to address the AC's key concerns, as outlined in the ACD, in order to gain access for patients to this innovative treatment.	Thank you for your response. The committee noted these issues with the evidence on whether daratumumab was more effective than current options in the NHS: • data limited to single-arm trials • small numbers of patients on the licensed dose of daratumumab • immature data on overall survival • mismatch between the populations in the 2 daratumumab trials, MMY2002 and GEN501 • poor generalisability of the trial results to people who would have daratumumab in the NHS because of differences in: o treatments taken before daratumumab o treatments taken after daratumumab, and their confounding effect o the fitness of patients • high degree of uncertainty in the relative effect estimates produced by the matching-
Janssen	Daratumumab in this indication is effectively being used as salvage therapy, as patients in these trials have relapsed multiple times and/or are highly refractory to all of their previous treatments. It is therefore important to distinguish between: 1) patients that received daratumumab, did not respond, and quickly died. 2) patients that initially responded to daratumumab, progressed and are now receiving subsequent treatment. 3) patients that responded to daratumumab and are still receiving daratumumab.	
Janssen	The Evidence Review Group (ERG) and AC are questioning whether the survival benefit observed with daratumumab is actually derived from daratumumab, or whether it is derived from subsequent treatment. Clearly, patients in Group 1 did not receive benefit from subsequent treatment as they died whilst still receiving daratumumab or shortly after progressing. For patients in Group 2, the mechanism of action (MoA) of daratumumab effectively 'reset' their disease and allowed them to receive benefit from treatments that they had previously failed on. For patients in Group 3, clearly these patients did not receive subsequent treatment as they are still receiving daratumumab. Either way, it is clear that the benefit in any of these groups of patients is derived from daratumumab.	

Consultee	Comment [sic]	Response
Janssen	Janssen wishes to comment on this and other key issues raised in both the AC meeting in February and thereafter in the ACD. These issues are consequential of accelerated regulatory assessment and early licensing, which are in turn a result of unprecedented clinical outcomes. The scarcity of comparative data and required modelling assumptions are inevitable in this case. Janssen emphasise that, in light of the single-agent efficacy observed in early phase trials, it would have been unethical to conduct a Phase III trial of daratumumab versus a comparator such as high-dose dexamethasone. However, understanding the importance of comparative effectiveness in health technology assessment (HTA), Janssen also invested in obtaining real world evidence (The International Myeloma Foundation [IMF] chart review) to determine the effectiveness of relevant comparators in a population of patients aligned to the daratumumab trials. Janssen is disappointed that, although included in the original submission, these data have not been assessed and, as such, does not consider that all of the relevant evidence for this appraisal has been taken into account. In addition, Janssen are exceedingly disappointed to see that daratumumab was not recognised as an innovative medicine and that end of life criteria were not considered applicable within the preliminary decision.	adjusted indirect comparison (MAIC) relating to: o the number of characteristics adjusted o the lack of cross validation of the MAIC estimates with other sources. The committee was concerned about the quality and validity of the available evidence, which meant that it could not fully interpret the clinical effectiveness of daratumumab from the available evidence. However, it acknowledged comments from clinical and patient experts on the possible benefits of daratumumab, and agreed that there was potential for daratumumab to be clinically effective compared with current treatment options. The committee agreed that the degree of uncertainty in the current evidence was too high for it to be able to identify a most plausible ICER for decision-making. The committee considered that the benefit of collecting further data would enhance the evidence for daratumumab while providing it to NHS patients until daratumumab's clinical and cost effectiveness could be reappraised based on new clinical evidence. The committee considered that if daratumumab was shown to have a level of clinical benefit comparable with the upper end of the range of estimates
Janssen	The clinical demand for daratumumab in this setting is high. The UK saw the fastest uptake of daratumumab across Europe when offered to clinicians and their patients through an Early Access Programme (EAP) and, since its launch in June 2017, an increasing number of patients (90 to date) are benefitting from daratumumab through private healthcare.	
Janssen	The key issues we wish to highlight are summarised below: Daratumumab has a new and unique MoA which sets it apart, in terms of both efficacy and tolerability, from the few treatment options currently available. Daratumumab is the first treatment since bortezomib to demonstrate single-agent activity in RRMM and, as a consequence, received breakthrough status by the Food and Drug Administration (FDA) and was granted a conditional license following accelerated assessment by the European Medicines Agency (EMA).	

Consultee	Comment [sic]	Response
Janssen	The benefit of daratumumab is three-fold: directly targeting the tumour, strengthening the patient's immune system and working synergistically with subsequent treatments, such as immunomodulatory drugs (IMiDs), by increasing the presence of cells upon which these treatments act. In patients who responded to daratumumab, a clear impact on progression free survival (PFS) and overall survival (OS) is observed (median PFS: 15 months, median OS not reached). Following treatment with daratumumab, 39% of patients responded to treatments which they were previously refractory to, clearly demonstrating the additional benefit daratumumab provides to patients who become refractory to currently available treatments.	presented, it has the potential to be cost effective compared with pomalidomide plus dexamethasone, and with panobinostat plus bortezomib and dexamethasone at its current price. The committee concluded that daratumumab met the criteria for inclusion in the Cancer Drugs Fund. It recommended daratumumab as an option for use within the Cancer Drugs Fund for adults with relapsed and refractory multiple myeloma, whose therapy included a proteasome inhibitor and an immunomodulator, and whose disease has progressed on the last therapy. For further details, see the Final Appraisal Determination (FAD).
Janssen	The EMA acknowledged the safety profile of daratumumab as both manageable and favourable in light of the current treatments available. Alongside efficacy, tolerability is of utmost importance to patients at this stage in the treatment pathway. As highlighted in the ACD, patient experts reinforced this and *"stressed the importance of quality of life after multiple lines of therapy because the adverse effects of treatment can build up over time, as the number of therapies a person receives increases"* [para 4.1].	
Janssen	The effectiveness of daratumumab has been evaluated in two single-arm trials where it was used as a salvage therapy. In these patients, who were more relapsed and refractory than eligible NHS patients, such that they had no further treatment options, daratumumab has demonstrated unprecedented single-agent efficacy (31% overall response rate [ORR] and 83% of patients achieving stabilisation of disease or better). Daratumumab presents a step-change in the treatment of patients with this incurable, orphan condition.	
Janssen	Daratumumab demonstrates a statistically significant survival benefit versus the key comparator pomalidomide plus dexamethasone (POM+DEX). Indeed, this benefit holds true under three different methodological approaches: • unadjusted cross-trial comparison: Hazard ratio [HR]=0.61 [0.46-0.81]; • revised base case with fully adjusted matched adjusted indirect comparison (MAIC): HR=0.56 [0.38-0.83]; • multivariate regression (MVR) with real world IMF data: HR=0.42 [0.30-0.60]. Moreover, assessment of the impact of the small number of missing variables from the MAIC demonstrates that any residual bias is likely to be against daratumumab.	

Consultee	Comment [sic]	Response
Janssen	Fully adjusted MAIC shows that patients treated with daratumumab can expect to live nine months longer than patients treated with POM+DEX. Given that the availability of subsequent treatment was the same across the daratumumab and pomalidomide trials, this additional benefit cannot reasonably be solely attributed to subsequent treatment. Rather it is the combination of daratumumab's ability to improve patients' health status and augment the benefit of subsequent treatment with regimens such as POM+DEX.	
Janssen	Even unadjusted cross-trial comparison suggests that patients receiving daratumumab can expect to live for an extra seven months and three months compared to patients receiving POM+DEX and PANO+BORT+DEX, respectively. As such daratumumab clearly meets the end of life criteria.	
Janssen	With the application of daratumumab's patient access scheme (PAS), which has now received Department of Health (DH) and Ministerial approval, daratumumab is highly cost-effective. The incremental cost-effectiveness ratio (ICER) of daratumumab versus POM+DEX is £15,772 and daratumumab dominates PANO+BORT+DEX (i.e., daratumumab is more effective and less costly). Probabilistic analyses demonstrate that with the PAS, daratumumab has a 99% probability of being cost-effective at a threshold of £50,000 versus both POM+DEX and PANO+BORT+DEX. The PAS not only substantially reduces treatment costs in all patients but also ensures that the NHS only pays for treatment in patients who benefit from daratumumab. By ensuring the NHS only pays for treatment in patients receiving benefit, Janssen is reducing the uncertainty associated with investing in daratumumab	
Janssen	Even in the highly unlikely worst-case scenario that daratumumab is of equal effectiveness to its comparators, daratumumab still represents good value for money. Assuming average treatment duration of 4 months, equal to 12 infusions, the average cost of daratumumab is £53,244, reducing to £31,059 with the PAS. Based upon information provided in the FAD for POM+DEX and the manufacturer's submission for PANO+BORT+DEX, the average cost of treatment is £44,420 and £79,528, respectively. Janssen understands that both pomalidomide and panobinostat have confidential simple discounts; however, for POM+DEX and PANO+BORT+DEX to have lower average treatment costs than daratumumab, treatment costs would need to decrease by at least [redacted] and [redacted] for POM+DEX and PANO+BORT+DEX, respectively.	

Consultee	Comment [sic]	Response
Janssen	Therefore, Janssen contends that daratumumab is cost-effective with a high degree of certainty against a threshold of £50,000/QALY in an EOL population and is thus a cost-effective use of NHS resources. **Please note:** the full consultation response from Janssen has not been reproduced, the full response can be found in the evaluation report.	

Consultee	Comment [sic]	Response
Myeloma UK	Myeloma UK welcomes the opportunity to comment on the NICE ACD on daratumumab monotherapy. Whilst we understand the difficult role that NICE has in assessing new medicines, and that NICE cannot approve all new medicines it appraises, we are extremely disappointed by the negative decision reached on daratumumab monotherapy for relapsed and refractory myeloma patients.	Thank you for your response. The committee concluded that they did not see evidence that daratumumab has demonstrable and distinctive benefits of a substantial nature other than those already captured in the quality-adjusted life year (QALY) measure. The committee noted these issues with the evidence on whether daratumumab was more effective than current options in the NHS: • data limited to single-arm trials • small numbers of patients on the licensed dose of daratumumab • immature data on overall survival • mismatch between the populations in the 2 daratumumab trials, MMY2002 and GEN501 • poor generalisability of the trial results to people who would have daratumumab in the NHS because of differences in: o treatments taken before daratumumab o treatments taken after daratumumab, and their confounding effect o the fitness of patients • high degree of uncertainty in the relative effect estimates produced by the matching-adjusted indirect comparison (MAIC) relating to: o the number of characteristics adjusted o the lack of cross validation of the MAIC estimates with other sources.
Myeloma UK	Daratumumab is an extremely innovative new drug and there is global clinical and patient expert consensus on its potential to significantly improve survival rates in myeloma. To assist NICE in taking forward this appraisal, and to reach a positive opinion on this important innovation, we provide comments on the ACD below.	
Myeloma UK	The central issue in the draft ACD relates to the early phase nature of the clinical trial data, particularly given small patient numbers involved and the lack of comparative data. As NICE is aware, the early phase nature of the relevant clinical trials is a result of the drug being granted conditional approval by the European Medicines Agency (EMA) due to the effectiveness of the drug as a single agent and the significant benefit this was likely to offer for heavily pre-treated patients. The conditional approval is set to be expanded to full marketing authorisation pending the European Commission ratification of the EMA CHMP recommendation of daratumumab combination treatments. Alongside the daratumumab monotherapy trials, the Phase III data of both the Pollux and Castor studies collectively make a compelling case for the efficacy and clinical effectiveness of daratumumab across all stages of relapse in myeloma.	
Myeloma UK	The inability of NICE to assess daratumumab monotherapy based on early phase data is to be expected, given the emphasis that health technology assessment (HTA) places on large Phase III randomised controlled trials. However, given this issue will increase in frequency due to regulatory and scientific changes, this appraisal has highlighted a need to further consider solutions and the disjoint between EMA regulatory and UK HTA data requirements. We understand the inability of NICE to tackle such systemic issues within the context of an ongoing appraisal. However, daratumumab monotherapy is an extremely important treatment for relapsed and refractory patients and we hope NICE will continue to work with the pharmaceutical company Janssen, Myeloma UK and the UK Myeloma Forum to provide a pragmatic solution to securing access.	
Myeloma UK	If a solution cannot be reached, the Cancer Drugs Fund would also be a logical place to try and widen access to daratumumab whilst collecting more data on the use of the drug in clinical practice, particularly as it is given as a monotherapy.	

Consultee	Comment [sic]	Response
Myeloma UK	However, the lack of ICERs contained within the ACD have made it difficult for stakeholders to consider this a way forward for accessing daratumumab. We hope this situation will be addressed as we move forward with the appraisal.	The committee was concerned about the quality and validity of the available evidence, which meant that it could not fully interpret the clinical effectiveness of daratumumab from the available evidence. However, it acknowledged comments from clinical and patient experts on the possible benefits of daratumumab, and agreed that there was potential for daratumumab to be clinically effective compared with current treatment options. The committee considered that the benefit of collecting further data would enhance the evidence for daratumumab while providing it to NHS patients until daratumumab's clinical and cost effectiveness could be reappraised based on new clinical evidence. The committee considered that if daratumumab was shown to have a level of clinical benefit comparable with the upper end of the range of estimates presented, it has the potential to be cost effective compared with pomalidomide plus dexamethasone, and with panobinostat plus bortezomib and dexamethasone at its current price. The committee concluded that daratumumab met the criteria for inclusion in the Cancer Drugs Fund. It recommended daratumumab as an option for use within the Cancer Drugs Fund for adults with relapsed and refractory multiple myeloma, whose therapy included a proteasome inhibitor and an immunomodulator, and whose disease has progressed on the last therapy. For further details, see the Final Appraisal Determination (FAD).
Myeloma UK	At the first NICE appraisal committee meeting, a strong case was made by the Janssen, alongside both clinicians and patient experts, on the importance of daratumumab monotherapy in the treatment of relapsed and refractory myeloma. Experience through clinical trials and use in clinical practice (through the Expanded Access Programme [EAP]) have highlighted that it is a very effective myeloma treatment and one that all relevant stakeholders would value access to in the NHS. The NICE ACD reflects the case that was made for the drug and that the committee accepts the majority of points made. To support the NICE committee in reaching a positive conclusion in this appraisal, we would like to emphasise the following information:	
Myeloma UK	As a first-in-class monoclonal antibody, targeting CD38 expressing tumour cells, daratumumab is a highly innovative new drug and is one of the only treatments in myeloma to demonstrate effectiveness as a single agent, which is particularly important in such a heavily pre-treated population. As daratumumab is one of the most innovative drugs to come along for myeloma patients, it is unthinkable that patients in the UK may not be able to access it in this setting or in combination with other drugs	
Myeloma UK	Collectively, the clinical trial data for daratumumab monotherapy through MMY2002 and GEN501, alongside the Phase III clinical trials and the EAP highlight that daratumumab has a strong anti-myeloma effect and improves both progression free and overall survival. This additional time means improved emotional wellbeing for patients, additional time to spend with their family and to do the things they enjoy.	
Myeloma UK	To support the above point, the clinical trial data provided by Janssen highlights that daratumumab extends survival to the extent it meets the criteria required to meet the NICE end-of-life guidance	
Myeloma UK	UK haematology clinicians are clearly keen to have access to daratumumab for their patients, evidenced by the UK daratumumab EAP recruiting extremely quickly. The real-world use through the EAP demonstrates that daratumumab works well in the setting being appraised by NICE and that there is a clinical need for it. At Myeloma UK we continue to regularly receive calls to our Myeloma Infoline on how to access daratumumab in the relapsed and refractory setting. Patients have expressed their worry and concern that they may not be able to access this effective treatment on the NHS	

Consultee	Comment [sic]	Response
Myeloma UK	Aligning with the NICE recognised need for effective and well-tolerated treatment options, daratumumab monotherapy is a safe and effective treatment. Patients who have received it through clinical trials and the EAP, report that it had a good anti-myeloma effect, very little negative impact on their quality of life and ability to complete normal daily-activities. Daratumumab can also improve patient quality of life due to the good anti-myeloma effect and positive impact on the immune system	
Myeloma UK	As daratumumab is given as a single agent in this setting, this also helps to minimise the negative impact on quality of life, particularly as most patients report dexamethasone is a treatment that is detrimental to their quality of life. This is particularly important given the heavily pre-treated nature of the patient population we are discussing in the context of this appraisal	
Myeloma UK	To provide a conditional license, on the basis of Phase II clinical trial data, the EMA were convinced that the safety and efficacy data in favour of daratumumab monotherapy were compelling to the extent of providing early access across Europe. Whilst this has an obvious, and well-known, impact on the level of data supplied to NICE in this appraisal – it does demonstrate that European regulators and clinical experts agree that it is an important treatment for relapsed and refractory myeloma patients	
Myeloma UK	The ACD highlights that patients on MMY2002 and GEN501 had so few or many treatments compared to NHS practice. Whilst the trials may not align exactly to NHS practice, they do reflect the heterogeneous nature of myeloma and patient treatment pathways. The trials show daratumumab works in patients at various stages of relapse and patients receiving the drug through the EAP in clinical practice have demonstrated that it fits well into existing NHS treatment pathways. If NICE remained unconvinced on the levels of uncertainty relating to daratumumab monotherapy, and if the option of the CDF were to be on the table in this appraisal, further data could be collected to demonstrate how it works in the real-world setting	
Myeloma UK	To support the above point, patients participating in the MM2002 and GEN501 trials were actually more heavily pre-treated than the setting being considered by the appraisal. Responses to daratumumab monotherapy in clinical practice may therefore be better than those observed in the trials	
Myeloma UK	Despite understanding the issues with demonstrating comparative cost-effectiveness in this appraisal and the level of uncertainty, we are nonetheless concerned that the lack of ICERs presented in the ACD leave the myeloma community with nowhere to go to continue to develop the case for approving daratumumab monotherapy on the NHS given the levels of uncertainty that NICE have highlighted	

Consultee	Comment [sic]	Response
Myeloma UK	From working with the company over a number of years, we understand and support their willingness to work with NICE, UK clinicians and Myeloma UK to support the approval of daratumumab monotherapy for relapsed and refractory myeloma patients and also in wider combination settings. We hope the additional information submitted by stakeholders on the ACD provides NICE with the additional information they require to reach a flexible and pragmatic decision on daratumumab monotherapy and to assist patients accessing it on the NHS	

Consultee	Comment [sic]	Response
UK Myeloma Forum	On behalf of the UK Myeloma Forum we thank you for the opportunity to comment on the ACD. We urge the Appraisal Committee (AC) to reconsider the ACD recommendation. This decision is flawed as a result of perceived uncertainties and will have a direct detrimental effect on the morbidity and mortality of myeloma patients with relapsed and refractory disease where end of life criteria clearly apply and where further treatment options are extremely limited.	Thank you for your response. The committee concluded that they did not see evidence that daratumumab has demonstrable and distinctive benefits of a substantial nature other than those already captured in the quality-adjusted life year (QALY) measure. The committee considered that it had not seen any empirical evidence to suggest that daratumumab improved response to subsequent therapy, and it heard from clinical experts that the synergistic, immune-mediated relationship between daratumumab and immunomodulators put forward by the company was unproven. The committee was concerned about the quality and validity of the available evidence, which meant that it could not fully interpret the clinical effectiveness of daratumumab from the available evidence. However, it acknowledged comments from clinical and patient experts on the possible benefits of daratumumab, and agreed that there was potential for daratumumab to be clinically effective compared with current treatment options. The committee considered that the benefit of collecting further data would enhance the evidence for daratumumab while providing it to NHS patients until daratumumab's clinical and cost effectiveness could be reappraised based on new clinical evidence. The committee considered that if daratumumab was shown to have a level of clinical benefit comparable with the upper end of the range of estimates presented, it has the potential to be cost effective compared with pomalidomide plus dexamethasone, and with panobinostat plus bortezomib and dexamethasone at its current price.
UK Myeloma Forum	We acknowledge that the trial data presented to the appraisal committee was earlier phase than would normally be considered as part of an appraisal however, this is purely a result of the drug gaining accelerated approvals and licensing (including EMA conditional marketing authorization and FDA approval) due to its unprecedented single agent activity in the relapsed / refractory setting. Despite a number of new agents becoming available over the last decade for myeloma such early authorization in such heavily pretreated patients is unprecedented and a direct consequence of its significant life lengthening activity.	
UK Myeloma Forum	The ACD questioned whether the patient trial data available was generalizable to the UK population. We would highlight that the trial patient groups are, on the whole more heavily pre treated (up to 14 previous lines with over 100 having received >3 lines) than the UK target patient group. We also highlight that the vast majority of patients treated had been previously treated and were refractory to immunomodulatory drugs (lenalidomide, thalidomide, pomalidomide) and proteasome inhibitors (mainly bortezomib). This reflects the treatments that UK patients are likely to have received prior to consideration of Daratumumab, As a result of the extremely heavily pretreated nature of the trial reported patients it is likely that the outcomes observed in a less heavily pre-treated UK population would be better resulting in a comparative bias against Daratumumab monotherapy in the presented data.	
UK Myeloma Forum	It is notable that the progression free survival (PFS) seen in patients responding to Daratumumab as single agent is similar to that of either Bortezomib/dexamethasone or Lenalidomide/Dexamethasone combinations which are used earlier in the treatment pathway, this is exceptional for any single agent in this setting.	
UK Myeloma Forum	The ACD felt that there would be potential confounding of any OS advantage demonstrated by Daratumumab due to subsequent treatments. There is no evidence available to support this assertion and it seems highly unlikely that such a close OS association with response category would be seen if the benefit is due to other unnamed and unknown therapies. We highlight that there is accumulating evidence that in addition to anti-myeloma activity that Daratumumab also has immunomodulatory activity which will have significant clinical benefit unrelated to changes in the myeloma protein levels.	

Consultee	Comment [sic]	Response
UK Myeloma Forum	The ACD has questioned the innovative nature of Daratumumab. The agent is a first in class monoclonal antibody binding to CD38, has been designated a breakthrough medicine and selected for accelerated assessment. It possesses both direct and immunomodulatory actions not usually seen in agents directly targeting tumours in this manner and this undoubtedly contributes to its significant single agent efficacy. Worldwide in clinical and patient circles this drug is considered as game changing in myeloma. There has never been a clinically effective monoclonal antibody for myeloma. Additionally it is extremely well tolerated. Within the myeloma field this drug is considered to be one of the most innovative drugs introduced for myeloma in the last 15 years.	The committee concluded that daratumumab met the criteria for inclusion in the Cancer Drugs Fund. It recommended daratumumab as an option for use within the Cancer Drugs Fund for adults with relapsed and refractory multiple myeloma, whose therapy included a proteasome inhibitor and an immunomodulator, and whose disease has progressed on the last therapy. For further details, see the Final Appraisal Determination (FAD).
UK Myeloma Forum	The ACD felt that the data did give sufficient certainty that Daratumumab would provide at least a three month increase in OS in a population of RRMM patients where the survival is accepted as less than two years. Over 60% of the patients treated with Daratumumab are alive after 31 months; this is unheard of in this setting. The degree of certainty regarding the relative benefit of Daratumumab is greater than that accepted in TA427 where Pomalidomide was assessed using EOL criteria.	
UK Myeloma Forum	Patient care and outcomes will suffer as a direct result of this negative ACD limiting the access to a novel, active and well tolerated therapy and will retard the significant progress that has been made on overall survival with this disease in the UK in the last 10 years.	
UK Myeloma Forum	Daratumumab monotherapy in this setting fully recruited in the UK extremely quickly demonstrating that there is a patient and clinician demand for access to what is the most exciting and innovative drug for myeloma in recent years.	
UK Myeloma Forum	The arguments made to reject this application are not sound and should be reconsidered. Daratumumab should be available for 4th line patients with relapsed and refractory multiple myeloma who have previously been treated with a proteasome inhibitor and an immunomodulatory agent and who have demonstrated disease progression on the last therapy. We urge the committee to reconsider this very poor decision which is likely to have an adverse impact on patient outcomes.	
UK Myeloma Forum	Thank you for the opportunity to respond to the ACD we hope that our comments are taken into consideration.	

Comments received from commentators

Commentator	Comment [sic]	Response
Celgene	Celgene welcomes the opportunity to comment on the Appraisal Consultation Document (ACD) for Daratumumab Monotherapy for Treating Relapsed and Refractory Multiple Myeloma [ID933]. Celgene agrees with the Committee's decision not to recommend Daratumumab Monotherapy for Treating Relapsed and Refractory Multiple Myeloma.	Thank you for your response. The committee heard from the clinical experts that bendamustine would be used as a last resort. Furthermore, it understood that bendamustine has a marketing authorisation for multiple myeloma only

Celgene	Celgene considers that bendamustine, available as a treatment option at 4th line through the Cancer Drugs Fund (CDF), should be included as a comparator to reflect routine NHS practice and ensure consistency with a recent NICE appraisal Daratumumab monotherapy was submitted at 4th line, bendamustine is available as a treatment option at 4th line through the Cancer Drugs Fund (CDF). NICE have requested the inclusion of bendamustine as a relevant comparator in a recent HTA positioned at fourth line, considering it to form routine NHS practice at this point in the pathway. Therefore, Celgene considers it is inappropriate and inconsistent to exclude bendamustine as a comparator for the current appraisal. At third relapse (fourth line) treatment would depend on previous treatments and response and toxicity to previous treatments. The available active therapies at fourth line currently are bendamustine based (via CDF)1, pomalidomide plus dexamethasone (TA427)2 and panobinostat plus bortezomib plus dexamethasone (TA380)3. In the ACD, the committee comment (Section 4.3): 'The committee concluded that, because daratumumab would be used after 3 previous treatments (see section 4.2), the appropriate comparators were pomalidomide plus dexamethasone, and panobinostat plus bortezomib plus dexamethasone'. Bendamustine with thalidomide and dexamethasone was included as a relevant comparator in the recent NICE TA4272 , for which Final Guidance was published in January 2017 and is available as a treatment option at 4th line through the CDF. The appraisal of pomalidomide plus dexamethasone (TA427)2 overlapped with the ongoing appraisal of daratumumab monotherapy and clinical practice would not have changed during this timeframe. As bendamustine was deemed to be a relevant comparator, Celgene had to invest significant resource in accessing real world evidence (RWE) for bendamustine. Celgene considers that, to ensure all relevant comparators are included, the submitting manufacturer should include bendamustine in a fully incremental analysis with the other identified comparators namely pomalidomide plus dexamethasone, and panobinostat plus bortezomib plus dexamethasone.	as a first-line treatment. Although available on the Cancer Drugs Fund for relapsed disease when all other treatments are contraindicated or inappropriate (off-label use), it was not routinely commissioned for this indication. The committee acknowledged that daratumumab is administered by intravenous infusion, whereas pomalidomide plus dexamethasone are taken orally. It heard that intravenous administration is associated with time spent in hospital and discomfort, which may not be captured by the model. For further details, see the Final Appraisal Determination (FAD).

Commentator	Comment [sic]	Response
Celgene	Celgene agrees with the Committee's decision that the treatments that patients in the trials had before Daratumumab Monotherapy was not reflective of routine NHS practice. A number of treatments that the patients in the trials had before Daratumumab Monotherapy was not reflective of UK practice. Carfilzomib is not available in the NHS at this stage of treatment, and so people in NHS clinical practice would not have had it. Carfilzomib use prior to daratumumab in MMY20024 was 50% and in the GEN5015 trial was 19%. Pomalidomide plus dexamethasone accounted for 63% of previous treatments in MMY20024 63% and 36% in GEN5015. In ACD, the committee comment (Section 4.6): 'NICE recommends pomalidomide plus low-dose dexamethasone, at third or subsequent relapse; that is, after at least 3 previous treatments including both lenalidomide and bortezomib. The committee agreed that, in clinical practice, people were unlikely to have had pomalidomide plus dexamethasone before daratumumab because both treatments were likely to be used after 3 previous treatments. The evidence review group (ERG) also stated (Section 4.6): 'pomalidomide plus dexamethasone is an alternative treatment option to daratumumab, it would be more appropriate to consider people who had not previously had pomalidomide plus dexamethasone as the relevant population'. The committee agreed that, because some of the treatments that patients had previously had in MMY20024 and GEN5015 differed from those used in clinical practice, the underlying survival trend of patients could also differ. Celgene agree with the committee's conclusion that the use of previous treatment that were not available in the NHS is a limitation of the evidence.	

Commentator	Comment [sic]	Response
Celgene	Celgene agrees with the Committee's decision that the subsequent treatments that patients in the trials had received was not reflective of routine NHS practice. The committee noted that in MMY20024 and GEN5015, treatments received after daratumumab monotherapy was not reflective of clinical practice. In the ACD, the committee comment (Section 4.13): 'dexamethasone, pomalidomide, cyclophosphamide, carfilzomib, bortezomib and lenalidomide, many of which were either not available in the NHS (for example, carfilzomib), or not available at this point in the treatment pathway (for example, lenalidomide and bortezomib)'. Celgene agrees that the treatments that patients had after daratumumab in MMY20024 and GEN5015 did not represent what would be offered in the NHS.	

Commentator	Comment [sic]	Response
Celgene	Celgene considers that a disutility should be applied for daratumumab monotherapy in the model to capture the impact of the IV route of administration versus oral alternatives The early phase trials presented by the company did not collect health-related quality of life data to estimate utility. In its absence, utility from the literature is used in the company base case. In the ACD, the committee comment (Section 4.22) 'The values chosen by the company to reflect the utility in the pre-progression and post-progression health states came from MM-003, which compared pomalidomide plus dexamethasone with dexamethasone only (Palumbo et al. 2013)'. The utility values used in the base case are based on the MM-0036 trial which compares oral treatment in both arms of the trial. Daratumumab monotherapy is administered through IV infusion, where as other fourth line options such as pomalidomide plus dexamethasone are via oral administration. NICE has recognised that IV administration of treatment has been shown to have an associated disutility2,7,8 which has not been applied to the utility estimates in the model for daratumumab, potentially overestimating the utility gain when compared to oral treatment options. The impact of applying a utility decrement for daratumumab in the model is not known and should be explored to assess the impact on cost-effectiveness.	

Consultee	Comment [sic]	Response
Patient expert	I was diagnosed with myeloma in January 2012. Since then, I have received two separate treatments on two different Trials. I am now relapsing and will soon start a third line of treatment, the precise nature of which has yet to be determined.	Thank you for your response. The committee was concerned about the quality and validity of the available evidence, which meant that it could not fully interpret the clinical effectiveness of daratumumab from the available evidence. However, it acknowledged comments from clinical and patient experts on the possible benefits of daratumumab, and agreed that there was potential for daratumumab to be clinically effective compared with current treatment options. The committee considered that the benefit of collecting further data would enhance the evidence for daratumumab while providing it to NHS patients until daratumumab's clinical and cost effectiveness could be reappraised based on new clinical evidence. The committee concluded that daratumumab met the criteria for inclusion in the Cancer Drugs Fund. It recommended daratumumab as an option for use within the Cancer Drugs Fund for adults with relapsed and refractory multiple myeloma, whose therapy included a proteasome inhibitor and an immunomodulator, and whose disease has progressed on the last therapy. For further details, see the Final Appraisal Determination (FAD).
Patient expert	In the 5¼ years since diagnosis, I have taken an interest in the many treatments available for patients. Like many other patients, I have been encouraged and excited by the possible availability of many new treatments, such as monoclonal antibodies and chimeric antigen receptors. As medical science has revealed greater and more complex knowledge and understanding about this enigmatic disease, the relevance of these new drugs, and the options available to clinicians for their patients, has increased. Daratumumab is one of these, and comes to England with a strong track record in the United States, where it has been accorded "breakthrough status" by the Food and Drugs Administration (USFDA). Additionally, the European Medical Agency (EMA) has given Daratumumab conditional approval as a single agent. Patients have been told by clinicians at Myeloma UK's Patient and Families InfoDays that Daratumumab is the closest that we have to a cure for myeloma.	
Patient expert	Against such positive backgrounds, it was with a mounting sense of disappointment and frustration that I read the draft ACD. I had attended the Committee meeting in February hoping that Daratumumab would receive further endorsement. As yet, it is not to be. This will be a strong disappointment to patients. It is hard for me to understand the deep, systemic issues that have led to the committee's decision. Patients generally may well feel stronger emotions.	
Patient expert	My initial reaction to the ACD was to make extensive comments on the systemic issues. These are, however, beyond NICE's sphere of current responsibilities. These systemic issues are admirably set out in Myeloma UK's (MUK) response to the ACD. I cannot better it. Rather than make those extensive comments, I will endorse MUK's response, subject to two additional comments below.	

Consultee	Comment [sic]	Response
Patient expert	An apt epithet for the process of drug approval is that it is catching tomorrow's train with yesterday's timetable. NICE and its appraisal committees are here constrained by NHS England pathways that no longer match the realities of current myeloma treatment. At least one – and arguably both – of my two treatments to date has been outside the NHS pathway. Some 4,400 patients took part in my first Trial, 300 in my second. Yet, as I read the ACD, I got the feeling that evidence coming from these two Trials would not be considered as relevant in drug assessments because the Trials did not feature in the pathway. This would be ludicrous. That would be yesterday's timetable. It would also beg the question of why people like me participate in Trials if they do not advance knowledge and future technologies.	
Patient expert	Whilst such a scenario continues to exist, patients will be largely confined to a pathway of drugs that, although effective in managing myeloma, are going to contribute to the build-up of toxicities in those patients. They are not a cure. Patients need to see, and to receive, a new generation of drugs that are closer to that cure and that minimize toxicities. We are in danger of seeing the paralysis of analysis that the pathway engenders. The pathway will remain a tail wagging the treatment dog.	
Patient expert	On the credit side, the ACD has set out a series of analyses that the committee would like to see before approval is given. This gives a clear steer to Janssen (and will also be helpful to other drug companies seeking approval of their products). Such a steer might have been more useful if Janssen had received it before submitting their evidence. There could even have been discussions relating to the merits or otherwise of evidence drawn for the analysis of Daratumumab's performance against drugs not considered to be in the NHSE pathway, yet tried and trusted within other reputable jurisdictions.	
Patient expert	With this steer in mind, I hope that Janssen will soon be able to bring forward fresh, more acceptable and sustainable evidence that substantiates the USFDA's awarding of "breakthrough status" to the drug, and EMA's conditional approval and that we patients will see it in clinic in England sooner rather than not at all.	
Patient expert	Above all, however, and on behalf of patients – and to ensure that this is a truly patient-centred process - it is crucial that the systemic issues highlighted in the MUK response are addressed urgently.	

Response to the Appraisal Consultation Document (ACD)

Daratumumab monotherapy for treating relapsed and refractory multiple myeloma [ID933]

April 7th 2017

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1. Overview

Janssen welcomes the opportunity to comment on the preliminary recommendation made by the Appraisal Committee (AC) detailed in the appraisal consultation document (ACD). We are extremely disappointed that the AC's preliminary decision is to not recommend daratumumab monotherapy (hereafter referred to as daratumumab) for patients with relapsed and refractory multiple myeloma (RRMM). We are, however, committed to working with the National Institute for Health and Care Excellence (NICE) to address the AC's key concerns, as outlined in the ACD, in order to gain access for patients to this innovative treatment.

Daratumumab in this indication is effectively being used as salvage therapy, as patients in these trials have relapsed multiple times and/or are highly refractory to all of their previous treatments. It is therefore important to distinguish between:

1) patients that received daratumumab, did not respond, and quickly died.
2) patients that initially responded to daratumumab, progressed and are now receiving subsequent treatment.
3) patients that responded to daratumumab and are still receiving daratumumab.

The Evidence Review Group (ERG) and AC are questioning whether the survival benefit observed with daratumumab is actually derived from daratumumab, or whether it is derived from subsequent treatment. Clearly, patients in Group 1 did not receive benefit from subsequent treatment as they died whilst still receiving daratumumab or shortly after progressing. For patients in Group 2, the mechanism of action (MoA) of daratumumab effectively 'reset' their disease and allowed them to receive benefit from treatments that they had previously failed on. For patients in Group 3, clearly these patients did not receive subsequent treatment as they are still receiving daratumumab. Either way, **it is clear that the benefit in any of these groups of patients is derived from daratumumab**.

Janssen wishes to comment on this and other key issues raised in both the AC meeting in February and thereafter in the ACD. These issues are consequential of accelerated regulatory assessment and early licensing, which are in turn a result of unprecedented clinical outcomes. The scarcity of comparative data and required modelling assumptions are inevitable in this case. Janssen emphasise that, **in light of the single-agent efficacy observed in early phase trials, it would have been unethical to conduct a Phase III trial of daratumumab versus a comparator such as high-dose dexamethasone**. However, understanding the importance of comparative effectiveness in health technology assessment (HTA), Janssen also invested in obtaining **real world evidence (The International Myeloma Foundation [IMF] chart review)** to determine the effectiveness of relevant comparators in a population of patients aligned to the daratumumab trials. Janssen is disappointed that, although included in the original submission, these data have not been assessed and, as such, does not consider that all of the relevant evidence for this appraisal has been taken into account. In addition, Janssen are exceedingly disappointed to see that daratumumab was not recognised as an innovative medicine and that end of life criteria were not considered applicable within the preliminary decision.

The **clinical demand** for daratumumab in this setting is **high**. The UK saw the fastest uptake of daratumumab across Europe when offered to clinicians and their patients through an Early Access Programme (EAP) and, since its launch in June 2017, an increasing number of patients (90 to date) are benefitting from daratumumab through private healthcare.

The key issues we wish to highlight are summarised below:

- Daratumumab has a new and unique MoA which sets it apart, in terms of both efficacy and tolerability, from the few treatment options currently available. Daratumumab is the **first treatment since bortezomib** to demonstrate **single-agent activity** in RRMM and, as a consequence, received breakthrough status by the Food and Drug Administration (FDA) and was granted a conditional license following accelerated assessment by the European Medicines Agency (EMA).
- **The benefit of daratumumab is three-fold**: directly targeting the tumour, strengthening the patient's immune system and working synergistically with subsequent treatments, such as immunomodulatory drugs (IMiDs), by increasing the presence of cells upon which these treatments act. **In patients who responded to daratumumab, a clear impact on progression free survival (PFS) and overall survival (OS) is observed** (median PFS: 15 months, median OS not reached). Following treatment with daratumumab, **39% of patients responded to treatments which they were previously refractory to**, clearly demonstrating the additional benefit daratumumab provides to patients who become refractory to currently available treatments.
- The EMA acknowledged the **safety** profile of daratumumab as both **manageable and favourable** in light of the current treatments available. Alongside efficacy, tolerability is of utmost importance to patients at this stage in the treatment pathway. As highlighted in the ACD, patient experts reinforced this and *"stressed the importance of quality of life after multiple lines of therapy because the adverse effects of treatment can build up over time, as the number of therapies a person receives increases"* [para 4.1].
- **The effectiveness of daratumumab** has been evaluated in two single-arm trials where it was used as a salvage therapy. In these patients, who were more relapsed and refractory than eligible NHS patients, such that they had no further treatment options, daratumumab has demonstrated unprecedented single-agent efficacy (31% overall response rate [ORR] and 83% of patients achieving stabilisation of disease or better). Daratumumab presents a **step-change** in the treatment of patients with this **incurable, orphan condition**.
- Daratumumab demonstrates a **statistically significant survival benefit versus the key comparator pomalidomide plus dexamethasone (POM+DEX). Indeed, this benefit holds true under three different methodological approaches**:
    - unadjusted cross-trial comparison: Hazard ratio [HR]=0.61 [0.46-0.81];
    - revised base case with fully adjusted matched adjusted indirect comparison (MAIC): HR=0.56 [0.38-0.83];
    - multivariate regression (MVR) with real world IMF data: HR=0.42 [0.30-0.60].

  Moreover, assessment of the impact of the small number of missing variables from the MAIC demonstrates that **any residual bias is likely to be against daratumumab**.

- Fully adjusted MAIC shows that patients treated with **daratumumab can expect to live nine months longer than patients treated with POM+DEX**. Given that the availability of subsequent treatment was the same across the daratumumab and pomalidomide trials, this additional benefit cannot reasonably be solely attributed to subsequent treatment. Rather it is the combination of daratumumab's ability to improve patients' health status and augment the benefit of subsequent treatment with regimens such as POM+DEX.
- Even unadjusted cross-trial comparison suggests that patients receiving daratumumab can expect to live for an extra seven months and three months compared to patients receiving

POM+DEX and PANO+BORT+DEX, respectively. As such **daratumumab clearly meets the end of life criteria**.

With the application of daratumumab's patient access scheme (PAS), which has now received Department of Health (DH) and Ministerial approval, daratumumab is **highly cost-effective**. The incremental cost-effectiveness ratio (**ICER) of daratumumab versus POM+DEX is £15,772 and daratumumab dominates PANO+BORT+DEX** (i.e., daratumumab is more effective and less costly). Probabilistic analyses demonstrate that with the PAS, daratumumab has a 99% probability of being cost-effective at a threshold of £50,000 versus both POM+DEX and PANO+BORT+DEX. **The PAS not only substantially reduces treatment costs in all patients but also ensures that the NHS only pays for treatment in patients who benefit from daratumumab**. By ensuring the NHS only pays for treatment in patients receiving benefit, Janssen is reducing the uncertainty associated with investing in daratumumab

Even in the highly unlikely worst-case scenario that daratumumab is of equal effectiveness to its comparators, daratumumab still represents good value for money. Assuming average treatment duration of 4 months, equal to 12 infusions, the average cost of daratumumab is £53,244, reducing to £31,059 with the PAS. Based upon information provided in the FAD for POM+DEX and the manufacturer's submission for PANO+BORT+DEX, the average cost of treatment is £44,420 and £79,528, respectively. Janssen understands that both pomalidomide and panobinostat have confidential simple discounts; however, for POM+DEX and PANO+BORT+DEX to have lower average treatment costs than daratumumab, treatment costs would need to decrease by at least [redacted] and [redacted] for POM+DEX and PANO+BORT+DEX, respectively.

Therefore, Janssen contends that daratumumab is cost-effective with a high degree of certainty against a threshold of £50,000/QALY in an EOL population and is thus a cost-effective use of NHS resources.

A detailed response to each of these key issues is provided on the following pages.

2. Innovation

"The committee understood that daratumumab was the first monoclonal antibody with a significant effect in people with multiple myeloma. The clinical experts considered it a major change in the management of the condition given its activity in a heavily pre-treated population, and favourable toxicity profile. They also noted that daratumumab is given as monotherapy without corticosteroids, which is a great benefit to people. The committee recognised that people whose disease progressed after 3 previous lines of therapy have a poor prognosis, limited treatment options, and a high clinical unmet need. Given the issues related to comparative effectiveness and estimates of utility, the committee could not assess whether daratumumab was innovative." [para 4.28]

Janssen strongly contests the AC's statement that it is not possible to assess whether daratumumab is innovative. **Daratumumab, with its novel and unique MoA, is undoubtedly an innovative medicine**. The fact that daratumumab was designated a breakthrough medicine and was selected for accelerated assessment is a result of the unprecedented single-agent efficacy observed in early phase trials. Daratumumab provides substantial short and long-term benefits over the few alternative treatments available in RRMM. As a consequence of its innovative nature, daratumumab is used as a single agent which provides highly sought after quality of life benefits. The details of daratumumab's multifaceted

MoA and the rationale of early licensing are presented below, with details on comparative effectiveness and quality of life provided in Section 5 and Section 3, respectively.

2.1 Dara MoA

Daratumumab is the first and only licenced human monoclonal antibody (mAb) that binds to CD38, an antigen expressed on multiple myeloma tumour cells. It works by targeting the myeloma cells directly, and uniquely modulates the immune system in a way that is not typically seen with targeted mAbs. **It is this combination of direct and immunomodulatory effects that explain the exceptional efficacy observed in monotherapy**. In addition, there is emerging evidence from Phase III trials and next generation mass cytometry studies that **daratumumab works synergistically with subsequent treatment**; particularly IMiDs.

Direct tumour action

Daratumumab specifically targets the elimination of tumour cells that express CD38 by directly inducing apoptosis (i.e., programmed cell death) both upon binding as well as by immune-mediated tumour cell lysis through various mechanisms; these include complement dependent cytotoxicity (CDC), antibody dependent cell mediated cytotoxicity (ADCC), and antibody dependent cellular phagocytosis (ADCP).[1-5] As recognised by the AC, these mechanisms have been described previously in therapeutic antibodies targeting cancers,[6] and in the case of daratumumab, this is also observed.

Immunomodulatory action

As a tumour-specific mAb, daratumumab is unique because it reduces the number of immune-suppressive cells (expressing CD38) and increases the number, activity and clonality of cytotoxic T-cells. These immunomodulatory effects, even observed in heavily pre-treated RRMM in MMY2002 and GEN501, indicate an improved adaptive immune response with daratumumab.[5] Interestingly, antibodies that solely promote this adaptive immune response such as those inhibiting CTLA-4 (promoting T-cell expansion) and PD-1 (enhancing T-cell activation), have shown efficacy in other haematological malignancies such as non-Hodgkins lymphoma (NHL) but have failed to show monotherapy effect in MM. This suggests that **both direct and immune-mediated mechanisms are required to maintain clinical responses in MM, which is exactly what daratumumab does**. Daratumumab is the only monotherapy in RRMM that is capable of demonstrating both these modes of action and it is this dual action that explains the high levels of effectiveness observed.

Synergy with subsequent treatment

In addition to the beneficial direct effects and the immunomodulatory action, the increased number of cytotoxic T cells observed in patients from MMY2002 and GEN501 may be utilised by subsequent treatments, particularly IMiDs such as pomalidomide. **IMiDs work by co-stimulating T-cells – the very cells daratumumab is known to increase.[7] Subsequent treatment effect may therefore be augmented by the activation of these cells**. Indeed, robust increases in T-cell fraction and clonality have been validated by a phase III combination trial with lenalidomide, confirming the synergistic immune-mediated relationship between daratumumab and IMiDs.[8] Subsequent evaluation using next-generation mass cytometry have confirmed that these changes were specific to daratumumab. Firstly, sustained depletion of immune-suppressive populations was observed in combination and monotherapy trials. Furthermore, in patient samples from MMY2002/GEN501 patients, the upregulation of immune cells was only seen in those who responded to daratumumab. Non-

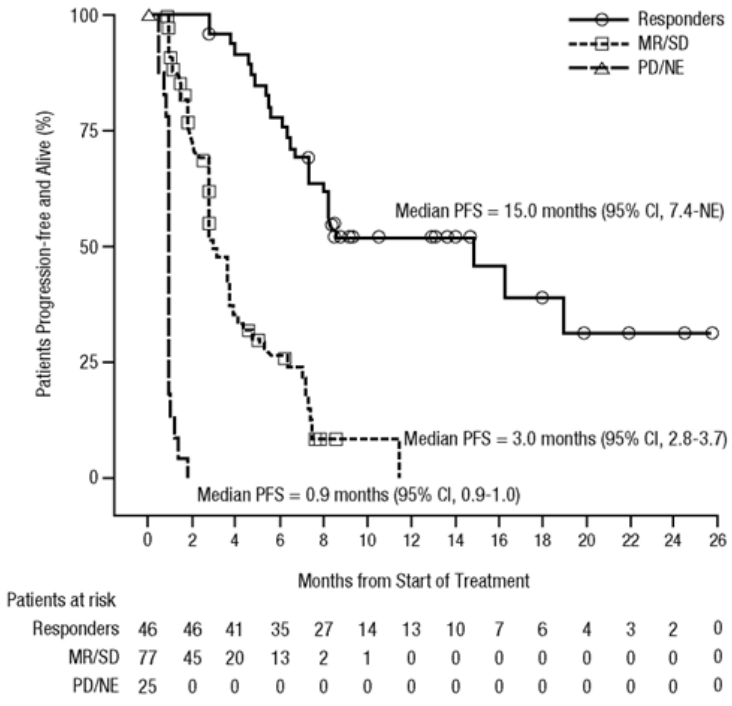
responders did not show these immunological changes.[9] This evidence, along with the OS benefit observed in patients achieving stabilisation of disease or better with daratumumab, suggests that the treatment effect of daratumumab extends beyond direct tumour action, to enhance the patients' immune system and sensitise the patient to subsequent treatment.

All the evidence above clearly demonstrates that **the extraordinary results seen in the highly refractory population of MMY2002/GEN501 can be attributed to the unique effectiveness of daratumumab**, which has simply not been demonstrated by any other single agent.

2.2 Accelerated Licensing

The absolute effectiveness of daratumumab has been demonstrated in patients who responded to treatment in MMY2002 and GEN501. In MMY2002/GEN501, median PFS in responding patients was 15 months (7.4-not evaluable [NE]), with median OS not reached (Figure 1, Figure 2).[10] The efficacy of daratumumab has since been confirmed in randomised, controlled Phase III trials conducted earlier in the treatment pathway. Median PFS of daratumumab used earlier in the treatment pathway in combination with lenalidomide and dexamethasone or bortezomib and dexamethasone has not been reached; whereas median PFS in patients treated with lenalidomide plus dexamethasone and bortezomib plus dexamethasone was 18.4 months and 7.2 months, respectively (Figure 3, Figure 4).[11,12] **The fact that median PFS in responding patients in MMY2002/GEN501 is similar to PFS in patients treated with either lenalidomide plus dexamethasone or bortezomib plus dexamethasone earlier in the treatment pathway is remarkable**.

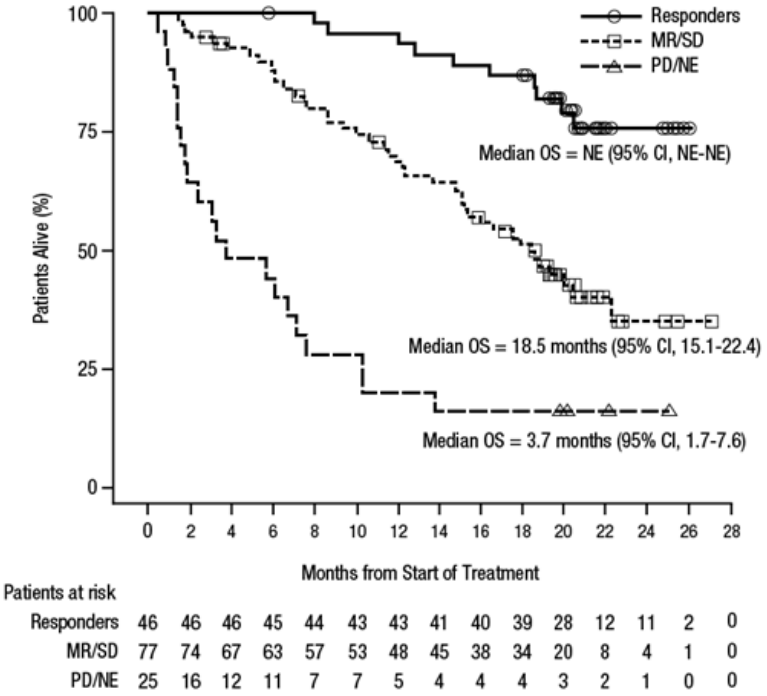
Figure 1. Progression free survival in MMY2002/GEN501, broken down by response



Key: CI, confidence interval; MR, minimal response; NE, not estimable; PD, progressive disease; PFS, progression-free survival; SD, stable disease.

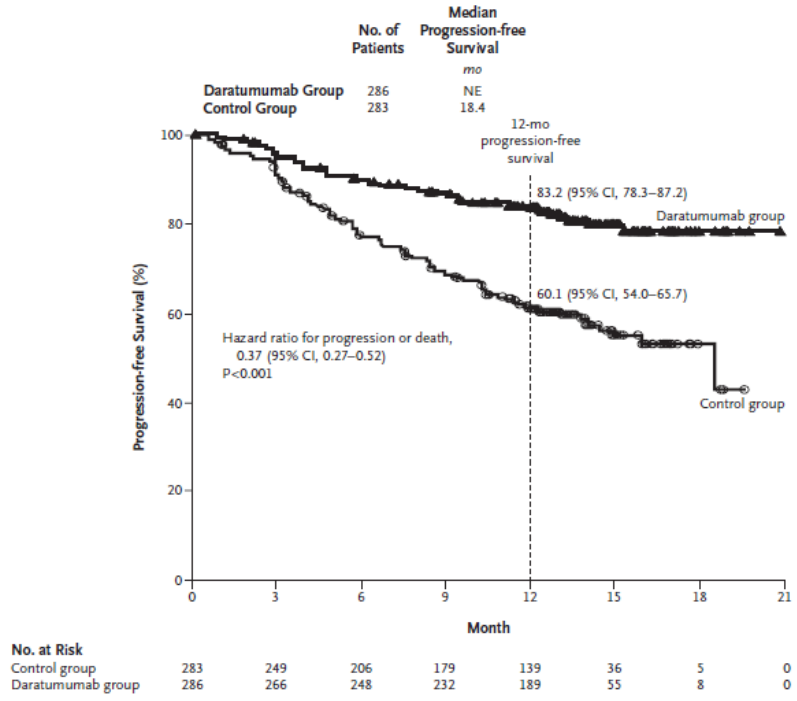
Notes: Circles, squares and triangles represent censoring; integrated analysis based on 9 January 2015 data cut-off for MMY2002, 31 December 2015 data cut-off for GEN501 Part 2.
Source: Usmani et al. 2016.[10]

Figure 2. Overall survival in MMY2002/GEN501, broken down by response



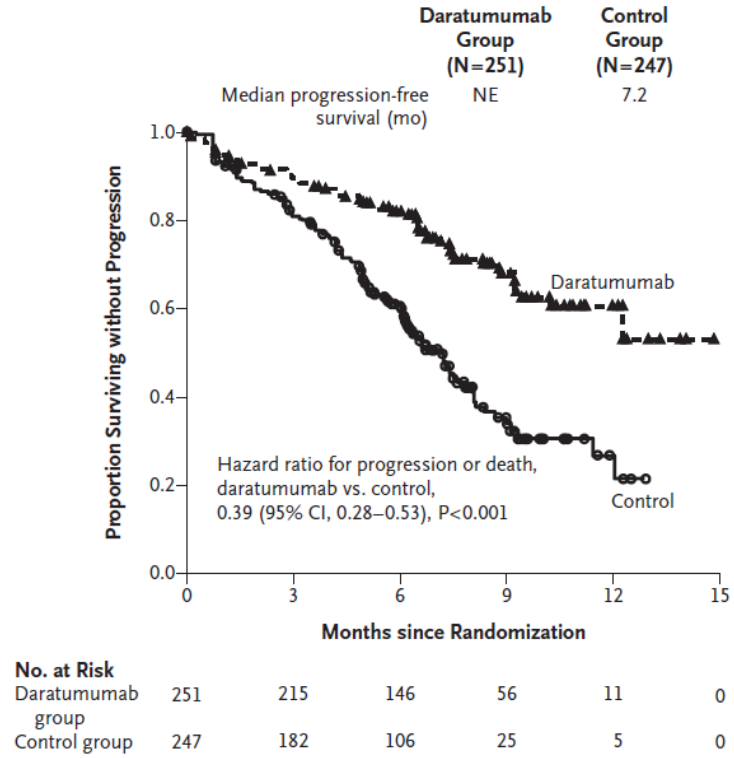
Key: CI, confidence interval; MR, minimal response; NE, not estimable; OS, overall survival; PD, progressive disease; SD, stable disease.
Notes: Circles, squares and triangles represent censoring.
Source: Usmani et al. 2016.[10]

Figure 3. Progression free survival in POLLUX, Daratumumab in combination with lenalidomide and dexamethasone versus lenalidomide plus dexamethasone



Key: CI, confidence interval.
Notes: Circles and triangles represent censoring.
Source: Dimopoulos 2016[11]

Figure 4. Progression free survival in CASTOR, Daratumumab in combination with bortezomib and dexamethasone versus bortezomib plus dexamethasone



Key: CI, confidence interval.
Notes: Circles and triangles represent censoring.
Source: Palumbo 2016[12]

Therapies that show promise in haemato-oncology are typically trialled as a single-agent in patient volunteers and RRMM is no exception. In GEN501, not only was safety demonstrated, but an extraordinary ORR was recorded [37%] in the 16mg/kg licenced dose. This is the highest ever observed in a monotherapy setting. To put this in context, other recently licenced therapies have been approved as combinations rather than as single agents, as the ORRs seen with these therapies, when used as monotherapies, did not come close to this figure. Elotuzumab, the only other licenced monoclonal antibody in MM, showed no objective response at all (ORR 0%) when studied as a single agent;[13] panobinostat showed only one partial response (PR), and pomalidomide showed an ORR of 18%.[14,15] In fact, in the very same trial, pomalidomide had to be combined with dexamethasone before an ORR approaching that observed with daratumumab monotherapy could be obtained.

It is for this reason that the EMA stipulated that both GEN501 and MMY2002 were suitable for registration within its monotherapy indication. Similarly, the FDA granted all four distinct expedited review designations available for serious diseases (Fast Track, Breakthrough Therapy, Accelerated Approval and Priority Review), which the FDA explicitly state do not, and cannot, replace the statutory standards for safety and effectiveness for regular approval, but aim to fulfil the unmet medical need in the treatment of a serious or life threatening condition.[16]

3. Quality of life

"The committee was aware that the early phase trials presented by the company did not collect health-related quality-of-life data to estimate utility. The values chosen by the company to reflect the utility in the pre-progression and post-progression health states came from MM-003, which compared

pomalidomide plus dexamethasone with dexamethasone only (Palumbo et al. 2013). The committee heard from the clinical experts that these utility values were lower than they would expect for people taking daratumumab because daratumumab is considered to be better tolerated. The patient experts highlighted the psychological benefit of daratumumab in reassuring people that an effective treatment is available at this stage, and that the favourable toxicity profile of this treatment might mean even more options down the treatment pathway. The committee concluded that the current utility values did not reflect daratumumab's additional benefits on quality of life perceived by the patient and clinical experts." [para 4.22]

Janssen agree with the AC that the **utility values used in the original submission did not reflect daratumumab's additional benefits on QoL**. As highlighted by clinical and patient experts, with its efficacy due to a novel MoA, the favourable safety profile and psychological benefits of daratumumab, ultimately benefits patients' health status. Recently available EQ-5D-5L data from the EAP demonstrates that daratumumab improves the QoL of patients on treatment (Table 1).

The EAP is a multi-centre, open-label, early access treatment protocol of daratumumab in subjects with multiple myeloma who have received at least three prior lines of therapy including a proteasome inhibitor (PI) and an IMiD or whose disease is double refractory to both a PI and an IMiD. As such, **patients in the EAP are reflective of those that would benefit from the recommendation of daratumumab for UK clinical practice**.[17]

A total of 90 UK patients have received treatment with daratumumab through the EAP; median age was 66.5 years, 60% of patients were male. Patients received a median of 3.69 months of therapy (range: 0.03 months, 10.58 months), median 11 infusions (range: 1, 21) and median total dose of 179.24 mg/kg (range: 15.9 mg/kg, 338.6 mg/kg).[18] A weighted average of the mean change from baseline, seen in the EAP, shows that **a utility increase of 0.04 can be expected with daratumumab**.

Table 1: EQ-5D-5L data from UK component of daratumumab EAP

	Utility			**Change from baseline**		
	n	**Mean**	**SD**	**n**	**Mean**	**SD**
Baseline	86	0.64	0.22	-	-	-
Cycle 2	57	0.68	0.20	57	0.04	0.18
Cycle 3	46	0.69	0.19	45	0.05	0.14
Cycle 6	23	0.67	0.19	22	0.02	0.17
Cycle 8	17	0.68	0.15	16	0.04	0.12
Cycle 10	6	0.69	0.13	6	-0.01	0.09
Cycle 12	2	0.77	0.10	2	0.02	0.09
Last assessment	69	0.64	0.22	67	0.00	0.18

Key: EAP, Early Access Programme; n, number; SD, standard deviation.
Source: Janssen 2017 (EAP)[18]

4. Clinical Effectiveness

A natural consequence of accelerated regulatory assessment and early licensing is a higher degree of uncertainty in the clinical evidence, to which there are several references within the ACD; these pertain to use of the integrated data from MMY2002 and GEN501 and the generalisability of the daratumumab trials to UK clinical practice. In the following sections, we provide a detailed response to each of the AC's points around these areas of uncertainty.

4.1 Integrated data

"The committee concluded that neither trial population fully reflected the place of daratumumab in clinical practice (after 3 previous treatments)" [para 4.6]

"The committee noted that the company pooled data from MMY2002 and GEN501, without adjusting for differences in the trial populations. The ERG did not consider that pooling data from the 2 trials was appropriate, because the 2 trial populations differed, most importantly, in the median number of lines of previous therapy, and the proportion of patients whose disease was refractory to the last treatment. Given the small sample size of the studies, and the limited data available, the committee agreed that it would be useful to use all available data. However, it concluded that pooling data was not appropriate because the populations in MMY2002 and GEN501 differed." [para 4.9]

The accelerated licensing of daratumumab means the evidence base available for HTA is limited when compared to what is normally available at time of marketing authorisation. As highlighted by the AC, it is important to make the best use of the available data. Integrating the data (by way of a simple pooling) from MMY2002 and GEN501 optimises use of the available evidence and is **appropriate for the assessment of absolute outcomes**. Janssen acknowledges that differences in patients' baseline characteristics should be considered carefully when pooling *relative* treatment effects across different comparative studies. However, in this case, where data are pooled for the assessment of absolute outcomes from single arm trials, **utilising both trials not only reduces uncertainty by increasing sample size, but increases the generalisability of trial outcomes to clinical practice**.

4.2 Generalisability

Janssen considers that the daratumumab trials are generalisable to UK clinical practice as patients in the daratumumab trials:

- are more relapsed and refractory than NHS patients;
- are of comparable fitness to NHS patients;
- have similar subsequent treatments available to that of NHS patients.

Each of the AC's points around the generalisability of the daratumumab trials are discussed below.

Marketing authorisation

"The committee discussed whether the trial populations reflected the marketing authorisation for daratumumab. It noted that, based on the marketing authorisation, a person's disease should not have responded to the last treatment for the person to be eligible to have daratumumab. This was seen in 97% of those in MMY2002 and 76% in GEN501. The committee agreed that MMY2002 matched the marketing authorisation more closely, and included more patients than GEN501, and therefore was a more appropriate source for decision-making" [para 4.5]

The licensed indication for daratumumab monotherapy is for "the treatment of adult patients with relapsed and refractory multiple myeloma whose prior therapy included a proteasome inhibitor and an immunomodulatory agent and who have demonstrated disease progression on the last therapy." Therefore, to be eligible for daratumumab, a person needs to be:

- relapsed and refractory;
- have received treatment with a PI and an IMID;
- demonstrated disease progression on the last therapy.

There is no specification within the license that a patient needs to be refractory to the last treatment received in order to be eligible for daratumumab. Consequently, given that 95% of patients in in the integrated trial data (99% in MMY2002 and 83% in GEN501) matched the marketing authorisation, Janssen contend that the integrated trial data are appropriate for decision making.[19]

Previous treatments

"…the committee noted that some patients had as few as 2 previous treatments, and some had as many as 14 previous treatments. It considered that patients who had so few or so many previous treatments did not reflect the place of daratumumab in clinical practice (after 3 previous treatments)" [para 4.6]

"The committee concluded that the use of previous treatments that were not available in the NHS was a limitation of the evidence, which introduced uncertainty about whether the effect of daratumumab from clinical trials could be generalised to clinical practice" [para 4.7]

The range in number of previous treatments in the daratumumab trials (2-14), is similar to that seen in the POM+DEX trial (MM-003, 2-17), and highlights the heterogeneity of RRMM. Of note, just 11 (7%) patients across MMY2002 and GEN501 had received only two previous treatments whilst 108 (73%) patients had received more than 3 previous treatments. Therefore, on average, patients in the daratumumab trials are more heavily pre-treated than UK patients. The fact that patients in MMY2002 and GEN501 received prior treatment with medicines not available in the NHS is due to the disparity in access to new medicines between the UK and the rest of Europe and the US. Since daratumumab is to be used at fourth line in the UK, patients will be less heavily pre-treated than those in the daratumumab trials, meaning real-world outcomes would only improve.

The impact of the number of previous treatments used in MMY2002/GEN501 can to a certain extent be demonstrated when comparing outcomes in the POM+DEX naïve subgroup to overall outcomes. These data are summarised in Table 2 and as expected, higher levels of ORR (33% vs 31%) are observed in the POM+DEX naïve patients. Importantly, **in this less relapsed and refractory population, duration of response (DOR) and OS are substantially higher (DOR: 18.7 months vs 8.0 months; OS, NE vs 20.1).**

Table 2: Clinical outcomes in the daratumumab trials, all patients and POM+DEX naïve patients (31 December 2015 data cut-off)

Effect	Integrated data, POM+DEX naïve patients (n=66)			Integrated data, all patients (n=148)		
	N	Median (95%CI)	%	n	Median (95% CI)	%
ORR*	22		33	46		31
Best ORR*						
sCR	2		3	3		2
CR	3		5	4		3
VGPR	4		6	13		9
PR	13		20	26		18
MR	3		5	9		6
SD	33		50	68		46
PD	5		8	18		12
NE	3		5	7		5
OS	**66**	**NE (22.4, NE)**		**148**	**20.1 (16.6, NE)**	
PFS	66	4.7 (2.8, 7.4)		148	4.0 (2.8, 5.6)	
TTR	66	NE (2.7, NE)		46	1.0 (range: 0.5 - 5.6)	
DoR	**22**	**18.7 (5.6, NE)**		**46**	**8.0 (6.5, 14.7)**	
TTD	66	4.1 (2.8, 5.9)		148	3.4 (2.8, 4.6)	

Key: CI, confidence interval; CR, complete response; DoR, duration of response; MR, minimal response; NE, not evaluable; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression free survival; PR, partial response; sCR, stringent complete response; SD, stable disease; TTD, time to treatment discontinuation; TTR, time to response; VGPR, very good partial response.

*Analysis based on 9 January 2015 data cut-off for MMY2002, 31 December 2015 data cut-off for GEN501 Part 2.

Fitness of patients

"The committee discussed the generalisability of the populations in MMY2002 and GEN501 to the NHS. The committee noted that 71% and 76% of patients in MMY2002 and GEN501 respectively switched to other treatments after daratumumab. It also noted that a high proportion of patients whose disease had not responded to both a proteasome inhibitor and an immunomodulatory agent (MMY2002 95%, GEN501 64%) went on to have a proteasome inhibitor and an immunomodulatory agent after daratumumab. The comments from NHS England suggested that this reflected a fit patient population. Conversely, the company suggested that it reflects daratumumab's favourable safety profile, which allows more people to have subsequent therapy than other less well-tolerated alternatives. The committee, however, did not see any evidence from the company to support this claim." [para 4.8]

In MMY2002/GEN501, 69% (n=52) of patients receiving subsequent treatment (n=75), received a treatment to which they were previously refractory. Of these, 60% received this treatment as their first subsequent treatment and achieved an ORR (PR or better) of 39%. When compared with the ORR of [redacted]% achieved in IMF patients receiving treatment to which they were previously refractory, this result is remarkable.[20] Moreover, this result is testament to the additional benefits afforded by

daratumumab's unique MoA. Furthermore, QoL data from the EAP demonstrates that daratumumab improves patients' health status compared to other treatments available (Section 3). Therefore, Janssen maintains that the high levels of subsequent treatment received by patients in the daratumumab trials is indeed a consequence of the combined effect of daratumumab's MoA and safety profile.

With respect to the fitness of patients, comparison of Eastern Cooperative Oncology Group (ECOG) performance status from the EAP and the daratumumab clinical trials suggests that **patients in the daratumumab trials are of comparable fitness to patients in UK clinical practice** (Table 3). As highlighted by the ERG, "The ECOG scale assesses how a person's disease is progressing and the level to which their condition impedes their day-to-day functioning. The ECOG performance scale can be applied in all oncological conditions and is typically used to assess whether a person is physically well enough to receive chemotherapy, and whether dose adjustment is necessary. Performance status is a key indicator of how a patient will tolerate treatment, as well as OS. Those with a higher ECOG score are less likely to be able to tolerate chemotherapy and thus have a poorer prognosis." (ERG report, pg 44).

Table 3: Baseline characteristics, EAP and MMY2002/GEN501

	EAP (n=90)	**MMY2002/GEN501 (n=148)**
Age, median (range)	66.5 (43-84)	64.0 (31-84)
Male, n (%)	60 (67)	78 (53)
ECOG score, n (%)	0: 30 (33) 1: 47 (52) 2: 13 (14)	0: 41 (28) 1: 97 (66) 2: 10 (7)
Key: EAP, Early Access Programme; ECOG, Eastern Cooperative Oncology Group. **Source**: Janssen 2017 (EAP)[18], Usmani 2016[10]		

Maturity of overall survival data

"[The committee] also noted that the data on overall survival were immature, with over 40% of patients alive at the end of the trials" [para 4.4]

More mature OS data are now available from MMY2002 and GEN501, with an additional 10 months of follow up, showing a further increase in median OS. Integrated analyses of these data, summarised in Table 4, Figure 5 and Figure 6, confirm the substantial OS benefit conferred in patients who respond to daratumumab and in patients whose disease is stabilised as a result of daratumumab (Individual results for MMY2002 and GEN501 are presented in Appendix 1).

At the latest data cut-off (18 November 2016), median follow-up of the integrated dataset was 31.31 months, with 42% of patients alive. Patients treated with daratumumab 16mg/kg demonstrated a median OS of 20.5 months (95% confidence interval [CI]: 16.6, 28.1) and a 2-year OS rate of 46.1%. – again, an unprecedented result in a highly refractory, end of life population.

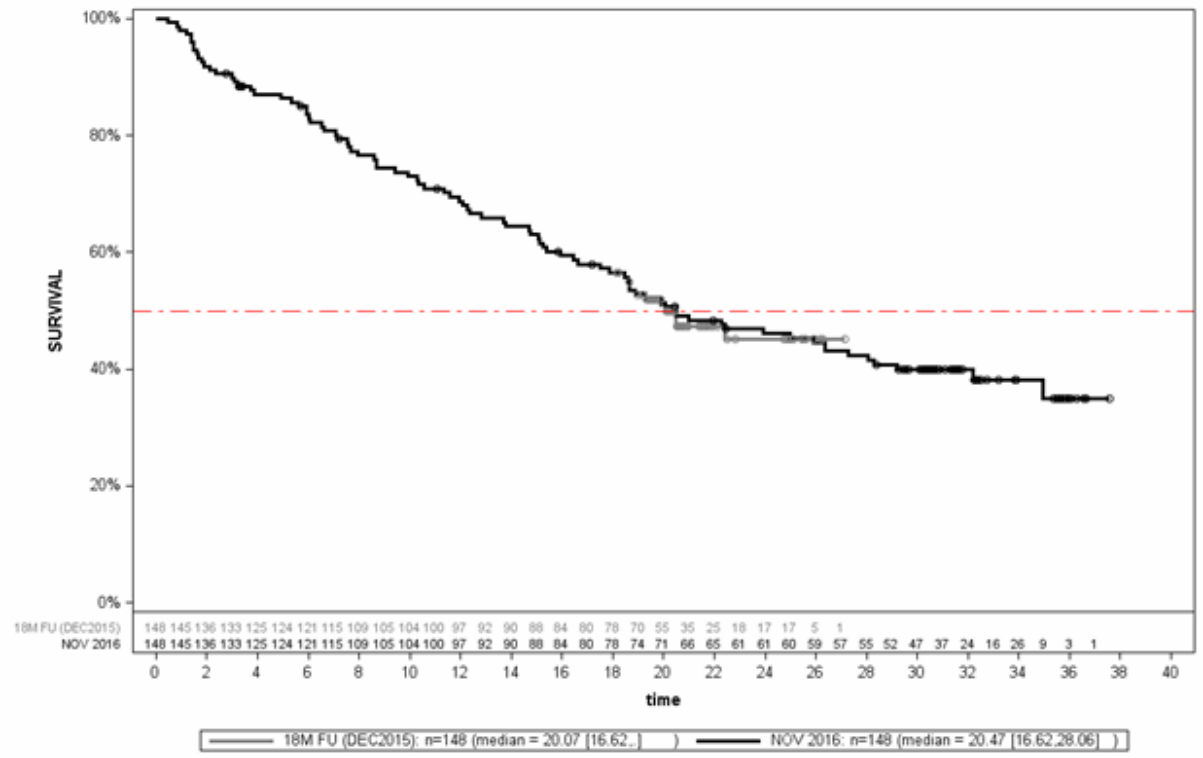
Table 4: Summary of updated overall survival, all treated patients (18 November 2016 data cut-off)

	Integrated analysis	**Responders**	**MR or SD**	**PD or NE**
	(n=148)	**(n=46)**	**(n=77)**	**(n=25)**
Median OS, months (95% CI)	20.47 (16.62, 28.06)	NE (29.21, NE)	18.46 (15.08, 22.41)	3.71 (1.68, 7.59)
Number of events, n (%)	86 (58.1%)	17 (33.3%)	48 (44.0%)	21 (58.3%)
6 month OS rate, % (95% CI)	83.6 (76.5, 88.7)	100.0 (100.0, 100.0)	86.6 (76.5, 92.6)	44.0 (24.5, 61.9)
12 month OS rate, % (95% CI)	68.7 (60.5, 75.6)	95.6 (83.4, 98.9)	68.4 (56.4, 77.8)	20.0 (7.3, 37.2)
18 month OS rate, % (95% CI)	56.5 (47.9, 64.2)	86.7 (72.7, 93.8)	51.1 (38.9, 62.0)	16.0 (5.0, 32.5)
24 month OS rate, % (95% CI)	46.1 (37.7, 54.1)	75.4 (60.0, 85.6)	37.5 (26.2, 48.7)	16.0 (5.0, 32.5)
30 month OS rate, % (95% CI)	40.0 (31.7, 48.0)	63.9 (48.0, 76.1)	32.6 (21.8, 43.8)	16.0 (5.0, 32.5)

Key: CI, confidence interval; MR, minimal response; NE, not evaluable; OS, overall survival; PD, progressive disease; SD, stable disease.

Source: Janssen 2017 (Updated OS)[21]

Figure 5. Kaplan–Meier plot for overall survival, all patients treated with daratumumab 16mg/kg, integrated analysis (18 November 2016 data cut- off)



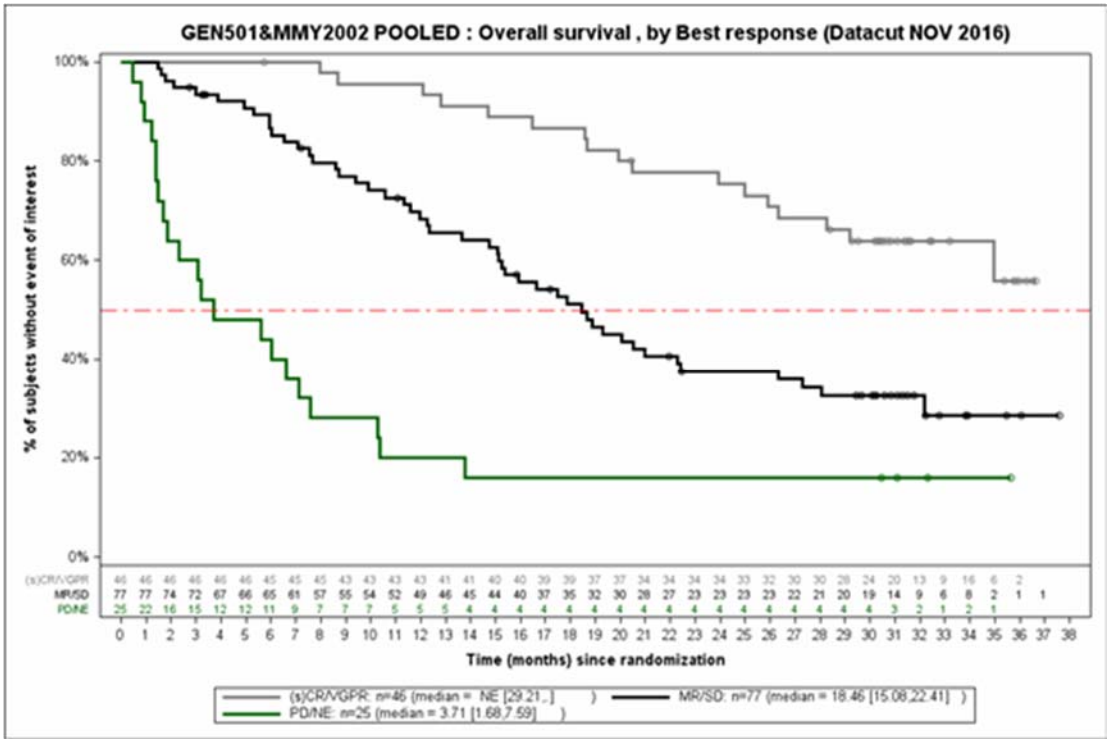
Notes: Circles represent censoring.
Source: Janssen 2017[21]

Patients with at least a PR to therapy demonstrate the greatest OS benefit with median OS yet to be reached and a 2-year OS rate of 75%. Indeed, **63% of responding patients (29/46) were alive after a median follow up of 31 months; this is extraordinary given that the life expectancy in this population is around one year.**[22-27]

A substantial OS benefit was also observed in patients with stabilisation of disease, with patients achieving stable disease (SD) or minimal response (MR) demonstrating a median OS of 18.5 months (95% CI: 15.1, 22.4) and a 2-year OS rate of 38%. Comparatively, patients with early progression (best optimal response of progressive disease [PD]) despite treatment with daratumumab demonstrated a median OS of only 3.7 months (95% CI: 1.7, 7.6) and a 2-year OS rate of 16%.

These results represent a major therapeutic advancement in the treatment of this end of life population.

Figure 6. Kaplan–Meier plot for overall survival, all patients treated with daratumumab 16mg/kg stratified by response, integrated analysis (18 November 2016 data cut-off)



Key: CR, complete response; MR, minimal response; NE, not evaluable; PD, progressive disease; SD, stable disease; VGPR, very good partial response.
Notes: Circles represent censoring.
Source: Janssen 2017[21]

Subsequent treatment

"The committee agreed that the treatments that patients had after daratumumab in MMY2002 and GEN501 did not represent what would be offered in the NHS." [para 4.13]

"The committee concluded that the absolute life expectancy seen in MMY2002 and GEN501 overestimated the overall survival benefit of daratumumab in patients who had treatment in the NHS." [para 4.14]

Comparison of the availability of subsequent treatment between the NHS and the daratumumab trials has been scrutinised by the AC with respect to generalisability of outcomes. In the daratumumab trials, patients received subsequent treatment with carfilzomib, lenalidomide and bortezomib (Table 5), which the AC contends are not available to NHS patients. Whilst carfilzomib is indeed not available to NHS patients, at this point in the treatment pathway the benefit of carfilzomib is expected to be negligible. When assessed as a single agent in heavily pre-treated rrMM patients, carfilzomib failed to show an OS benefit over low-dose dexamethasone with or without cyclophosphamide.[28] In addition, market share data in fact show that both lenalidomide and bortezomib are used in the NHS at this line of therapy, with market shares of lenalidomide at 10% and of bortezomib at 23% in 4th line plus patients (Table 6). The use of lenalidomide and bortezomib in the NHS is very similar to that in the daratumumab trials, with 15% and 24% of patients receiving lenalidomide and bortezomib, respectively. With these facts in mind and with the recent NICE recommendation of POM+DEX, it is clear that **the availability of effective treatments to NHS patients is similar to that of the daratumumab trials**.

Table 5: Subsequent therapies received in MMY2002/GEN501

Subsequent treatment	Proportion of MMY2002/GEN501 patients
Dexamethasone	58%
Pomalidomide	31%
Cyclophosphamide	32%
Carfilzomib	28%
Bortezomib	24%
Lenalidomide	15%
Melphalan	16%
Etoposide	10%
Bendamustine	14%
Thalidomide	7%
Source: Janssen 2016[19]	

Table 6: UK Market share data

Regimen	Percentage use in 3rd+ relapse/ 4th+ line (n=103)
Bortezomib regimen	[redacted]
Lenalidomide regimen	[redacted]
Pomalidomide regimen	[redacted]
Thalidomide regimen	[redacted]
Other	[redacted]

"The ERG looked at how long patients in the trials lived depending on which, if any, therapy they had after daratumumab. The committee interpreted this analysis as showing that treatment after daratumumab prolonged life, and that the impact of treatments on overall survival varied from one treatment to the other. It was unclear to the committee whether there were other important differences between the groups of patients who had the different therapies after daratumumab, which may have confounded the estimates of overall survival." [para 4.14]

With regards to the AC's interpretation of the post-hoc analysis of OS by subsequent treatment, the AC is correct to note that there may be important differences between the groups of **There is a high degree of bias in these analyses.** In particular, there is immortality bias since patients are required to live long enough to receive subsequent treatment. There is also selection bias, as patients are being indirectly selected on the outcome of treatment with daratumumab. Furthermore, there is much heterogeneity between the patients within each subsequent treatment subgroup. For example, in the subgroup of patients receiving bortezomib as a subsequent treatment, some patients will have received bortezomib directly after daratumumab, whereas others will have received bortezomib at a later stage. In addition, bortezomib may have been received as a monotherapy or as a combination therapy, as a fourth line treatment or as a seventh line treatment. Therefore, **no conclusions can be drawn from these analyses as to the impact of subsequent treatment.**

To better understand the impact of subsequent treatment and how this relates to daratumumab's new MoA, it is more reasonable to consider response to subsequent treatment. In MMY2002/GEN501, 31 (41%) patients received a treatment directly after daratumumab (i.e., their first subsequent treatment) to which they were previously refractory; ORR in these patients was 39% (Table 7).

Table 7: Response in patients receiving therapies to which they were refractory as their first subsequent treatment, in MMY2002 and GEN501

Patients receiving subsequent treatment with:	N (%)	ORR
Any	31 (41)	39%
Bortezomib, thalidomide or lenalidomide	21 (28)	38%
Key: ORR, overall response rate.		

In patients refractory to bortezomib, lenalidomide or thalidomide (n=21), ORR when treated with the same treatment to which they were refractory was 38%. As a comparison, ORR to bortezomib, lenalidomide or thalidomide in IMF patients who were refractory to a PI and an IMiD was [redacted]%.[20] This supports the hypothesis that daratumumab may enhance a patient's response to subsequent treatments.[10] Therefore, Janssen contends that the benefit of subsequent treatment is a result of treatment with daratumumab rather than a confounding factor in estimates of effectiveness. That is to say, the underlying patient condition is improved following therapy with daratumumab such that, on progression, they are in a more robust state of health to then receive further life-extending rather than palliative therapy.

In MMY2002/GEN501 daratumumab is effectively being used as salvage therapy, as patients in these trials have relapsed multiple times and/or are highly refractory to all of their previous treatments. It is therefore important to distinguish between:

1) patients that received daratumumab, did not respond, and quickly died.
2) patients that initially responded to daratumumab, progressed and are now receiving subsequent treatment.
3) patients that responded to daratumumab and are still receiving daratumumab.

Clearly, patients in Group 1 did not receive benefit from subsequent treatment as they died whilst still receiving daratumumab or shortly after progressing. For patients in Group 2, the MoA of daratumumab effectively 'reset' their disease and allowed them to receive benefit from treatments that they had previously failed on. For patients in Group 3, clearly these patients did not receive subsequent treatment as they are still receiving daratumumab. Either way, it is clear that the benefit in any of these groups of patients is derived from daratumumab. Along with the evidence presented throughout this document, this clearly refutes the biased analysis of separating out those patients that did and did not receive subsequent treatment (which the ERG requested) which falsely implies that any survival benefit is derived from subsequent treatment, as opposed to daratumumab.

5. Comparative effectiveness

"The committee concluded that the maximum number of characteristics possible should be adjusted. Nevertheless, it recognised that the survival estimates would remain biased because of unobserved differences that will not be accounted for" [para 4.11]

"Although the committee agreed that the ERG's exploratory analysis reflected its preferred approach to matching characteristics, it recognised that all the estimates were unreliable. To characterise the uncertainty, the committee considered that the company could validate the results of the MAIC with data from the International Myeloma Foundation chart review." [para 4.12]

Following publication of NICE's Decision Support Unit's (DSU) technical support document (TSD) on population adjusted indirect comparisons (TSD 18),[29] Janssen understands the requirement to adapt the methodology used in the original submission. At the time of submission, prior to publication of TSD 18, Janssen followed the precedents of MAIC used in the POM+DEX (TA427) and PANO+BORT+DEX appraisals (TA380), which sought to balance appropriate adjustment with effective sample size. However, as highlighted in TSD 18, in the case of an unanchored comparison (such as that seen in this appraisal and in the POM+DEX and PANO+BORT+DEX appraisals) it is best to adjust as fully as possible to minimise the potential for bias. Therefore, **Janssen provides a revised base case which uses fully adjusted MAIC. Importantly, daratumumab is estimated to provide greater relative benefit in the revised base case than in the original submission**; emphasising the conservative nature of Janssen's original submission.

As highlighted in Section 4.1, Janssen agrees with the AC that it is important to make full use of available data, particularly in relation to an HTA based on accelerated licensing where the evidence base is limited. Pooling data from MMY2002 and GEN501 makes full use of the available daratumumab data and serves to reduce uncertainty through the increased sample size and increased generalisability. In addition, utilising these integrated data increases the degree of similarity (or overlap) between datasets used to inform comparative effectiveness. **The greater the degree of overlap, the less uncertainty there is in estimates of comparative effectiveness**. This can be seen when comparing the effective sample sizes within the ERG's preferred approach which limits the data used to MMY2002 (daratumumab vs POM+DEX, neff=19; daratumumab vs PANO+BORT+DEX, neff=13), with Janssen's revised base case, which uses all available data (daratumumab vs POM+DEX, neff=55; daratumumab vs PANO+BORT+DEX, neff=46).

Janssen acknowledges that the few baseline characteristics missing from GEN501 means that not all characteristics available in MMY2002 can be adjusted for. As such, sensitivity analysis has been carried out to assess the impact of these missing characteristics on the comparison with POM+DEX. Similar to the methods recommended by the AC in the appraisal of abiraterone for treating metastatic hormone-relapsed prostate cancer before chemotherapy is indicated (TA387), this analysis imputed the missing data for GEN501 using the relationship between all available characteristics. Fully adjusted MAIC was then carried out using the imputed data for GEN501. The OS HR obtained from this sensitivity analysis (0.55 [0.38, 0.85]) is highly comparable to that of Janssen's revised base case (0.56 [0.38-0.83]). This indicates that **the impact of missing characteristics on the OS HR is minimal and likely to be biased against daratumumab** (full details of this analysis are presented in Appendix 2). Therefore, Janssen contends that **the integrated dataset is most appropriate for decision making**.

Using the integrated data, Janssen has assessed comparative effectiveness versus the key comparator POM+DEX with three different methodological approaches (Table 8). As a consequence of the low uptake of panobinostat, no real-world evidence is available on the effectiveness of PANO+BORT+DEX from the IMF and so comparative effectiveness has been assessed using two methodological approaches.

Table 8. Assessments of comparative effectiveness

Method	**OS HR (95% CI)**	
	Daratumumab vs POM+DEX	**Daratumumab vs PANO+BORT+DEX**
Unadjusted cross-trial comparison of MMY2002/GEN501 with MM-003	0.61 (0.46, 0.81)	0.82 (0.53, 1.26)
Fully adjusted MAIC of MMY2002/GEN501 to MM-003	0.56 (0.38, 0.83)	0.76 (0.44, 1.30)
MVR of IPD from MMY2002/GEN501 and from real-world evidence from the IMF	0.42 (0.30, 0.60)	NA
Janssen's original base case	*0.57 (0.41, 0.81)*	*0.84 (0.52, 1.37)*

Key: CI, confidence interval; HR, hazard ratio; IMF, International Myeloma Foundation; IPD, individual patient level data; MAIC, matched adjusted indirect comparison; MVR, multivariate regression; OS, overall survival; PANO+BORT+DEX, panobinostat plus bortezomib plus dexamethasone; POM+DEX, pomalidomide plus dexamethasone.

All three analyses of daratumumab versus POM+DEX generate comparable, statistically significant estimates of OS benefit that follow a logical flow with respect to face validity. That is, the OS HR decreases from the unadjusted cross-trial comparison to the fully adjusted MAIC and then further with MVR. An unadjusted cross-trial comparison is a reasonable approach to assessing comparative effectiveness in trials with similar baseline characteristics and assessment of outcomes. However, patients in the daratumumab trials were more relapsed and refractory than patients in the pomalidomide trial. Therefore, addressing this bias (by adjusting as fully as possible within an MAIC) serves to increase estimates of relative treatment effect. The IMF chart reflects the inclusion and exclusion criteria of the daratumumab trials. Since individual patient-level data (IPD) from a population aligned with the daratumumab eligible population were available from the IMF chart review, a more robust assessment (compared to MAIC) of comparative effectiveness is possible with these data. Furthermore, this MVR analysis serves to validate the MAIC estimates and indicates that **any residual bias within the MAIC is likely to be against daratumumab**.

The fact that the patient population of MMY2002/GEN501 were more relapsed and refractory than patients in MM-003 is a consequence of prior treatments available at the time and thus received within the trials. Of note, 55% of patients in MMY2002/GEN501 had previously received POM+DEX. In those patients who were naïve to POM+DEX (i.e., less refractory) estimates of comparative effectiveness improve (Table 9).

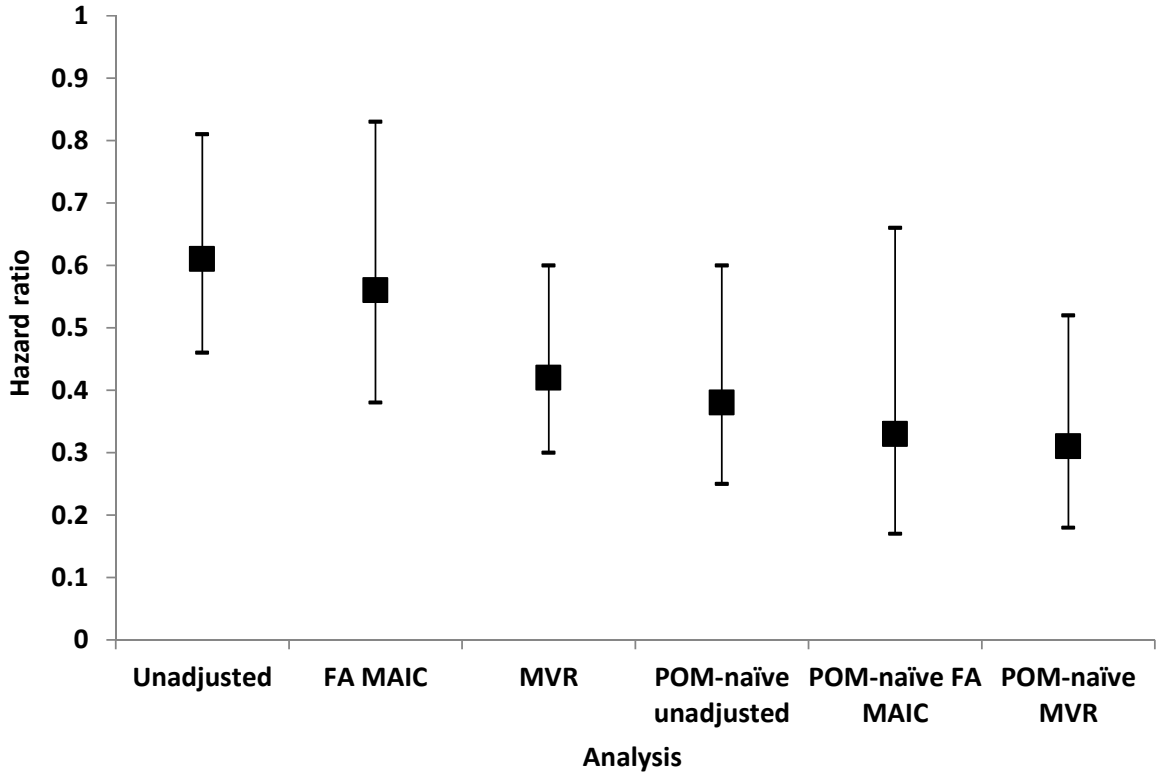
Table 9. Assessment of comparative effectiveness, daratumumab versus POM+DEX, POM-naïve patients

Method	OS HR (95% CI)
Unadjusted cross-trial comparison of MMY2002/GEN501 with MM-003	0.38 (0.25, 0.60)
Fully adjusted MAIC of MMY2002/GEN501 to MM-003	0.33 (0.17, 0.66)
MVR of IPD from MMY2002/GEN501 and from real-world evidence from the IMF	0.31 (0.18, 0.52)
Janssen's original base case	*0.40 (0.20, 0.80)*

Key: CI, confidence interval; HR, hazard ratio; IMF, International Myeloma Foundation; IPD, individual patient level data; MAIC, matched adjusted indirect comparison; MVR, multivariate regression; OS, overall survival; POM+DEX, pomalidomide plus dexamethasone.

Figure 7 summarises the comparative estimates of OS under the three different methods used for all patients and POM+DEX naïve patients, respectively. Figure 8 and Figure 9 contextualise these estimates against the available data sources.

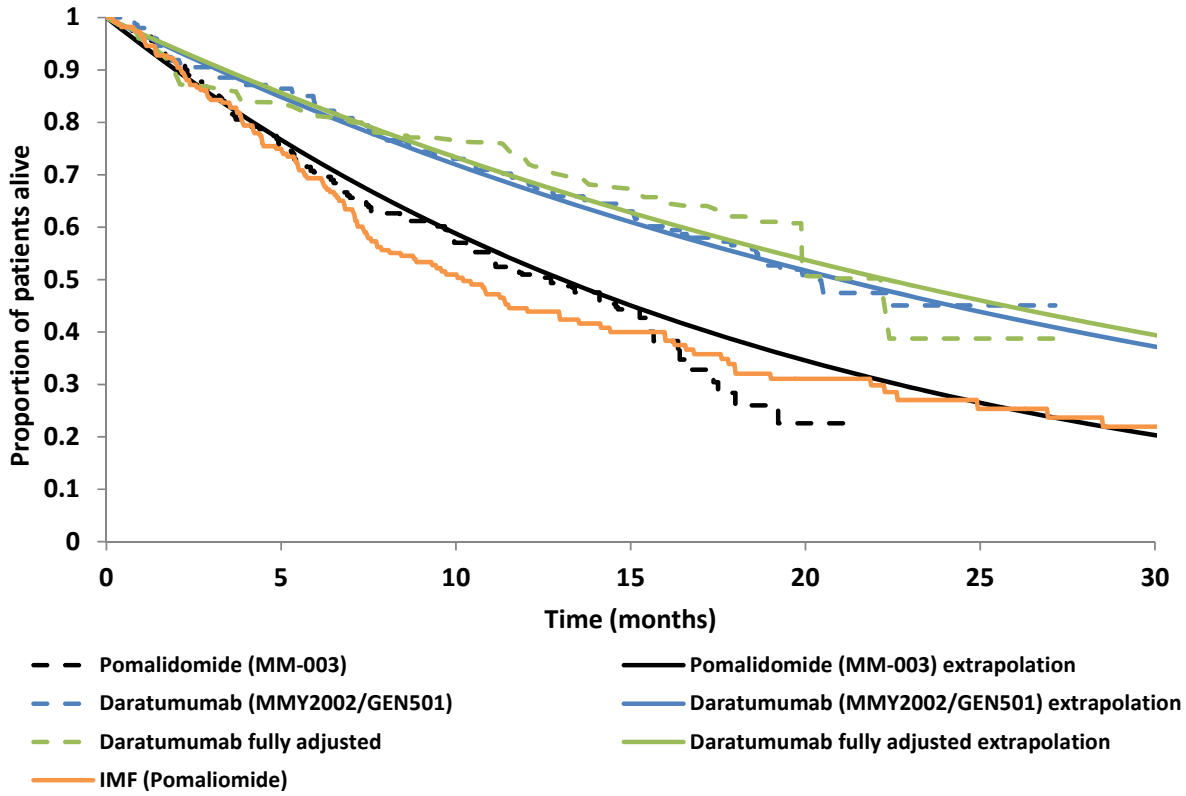
Figure 7. Summary of comparative estimates of overall survival, daratumumab versus POM+DEX



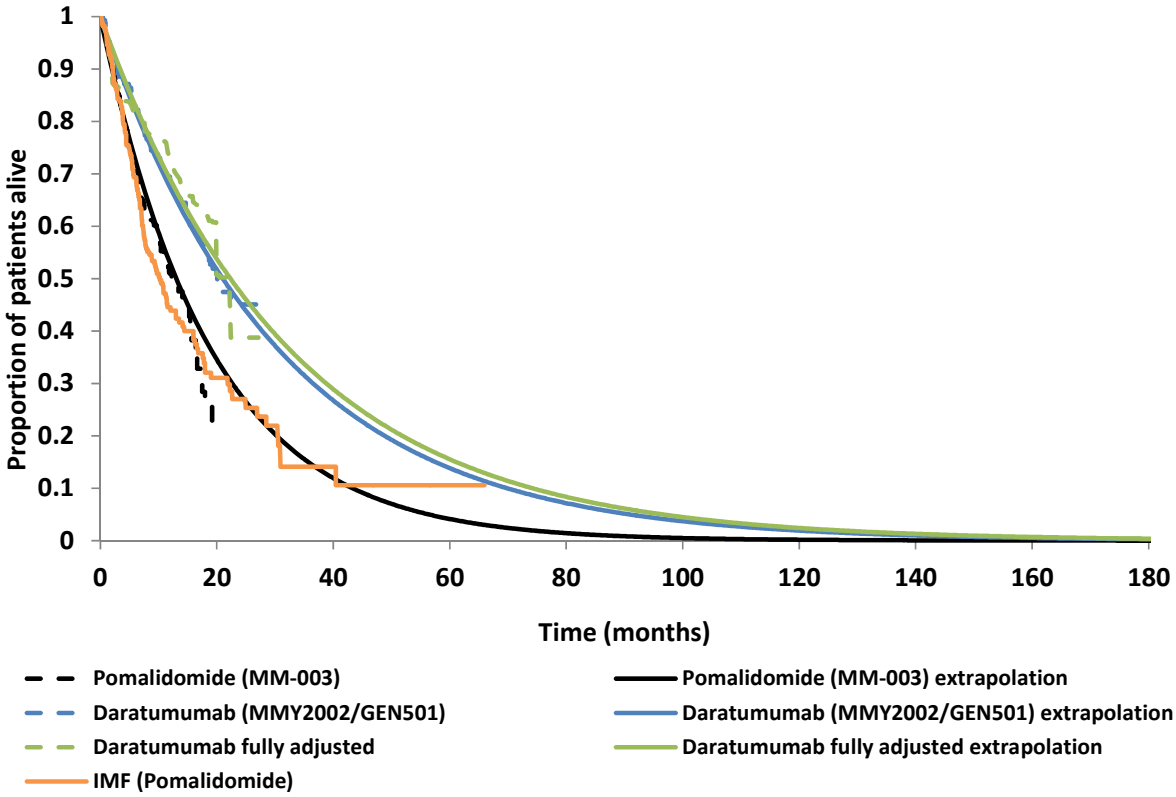
Key: FA, fully adjusted; MAIC, matched adjusted indirect comparison; MVR, multivariate regression; POM+DEX, pomalidomide plus dexamethasone.

It is clear from Figure 8 and Figure 9 that OS extrapolations for POM+DEX have overestimated OS for POM+DEX and as such **estimates of comparative effectiveness are conservative**. Furthermore, real-world outcomes for POM+DEX are comparable with outcomes observed in the MM-003 trial. Given that patients in the daratumumab trials were very similar to patients in the pomalidomide trial (Table 11) and that the availability of subsequent treatment across these trials was the same (Table 10), a similar effect could be anticipated for daratumumab.

Figure 8. Summary of overall survival (all patients)

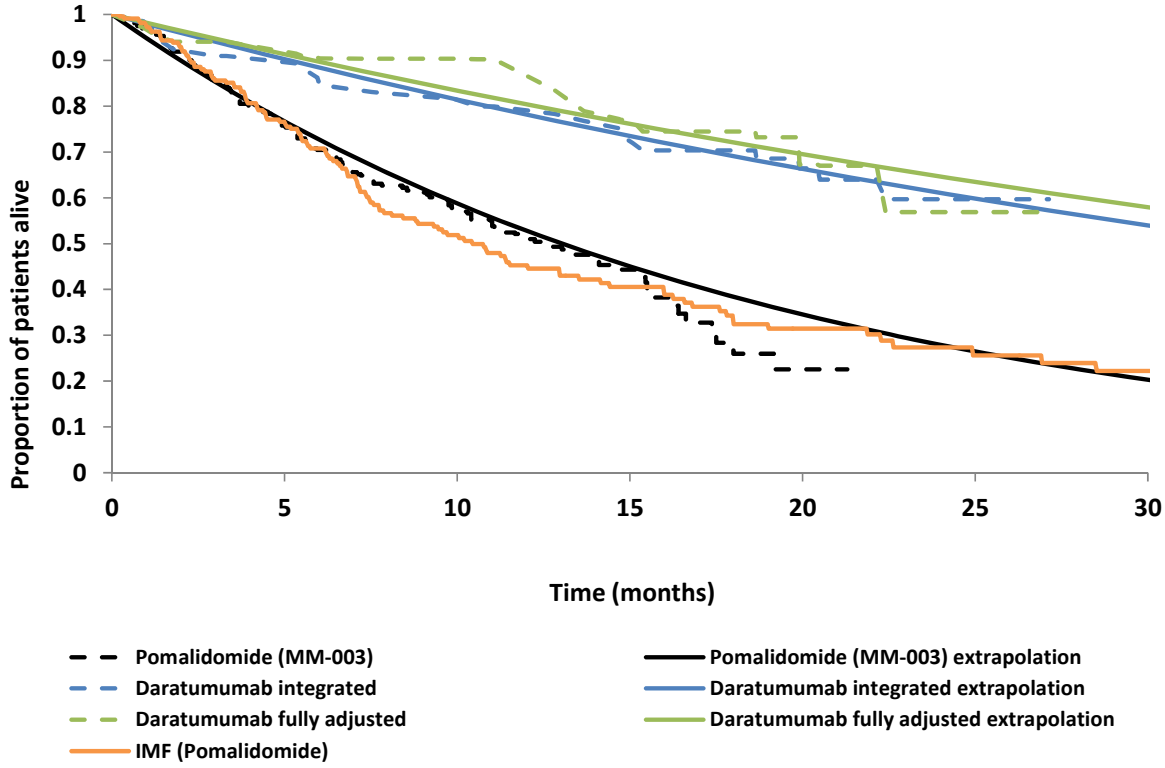


A:2.5 year time horizon

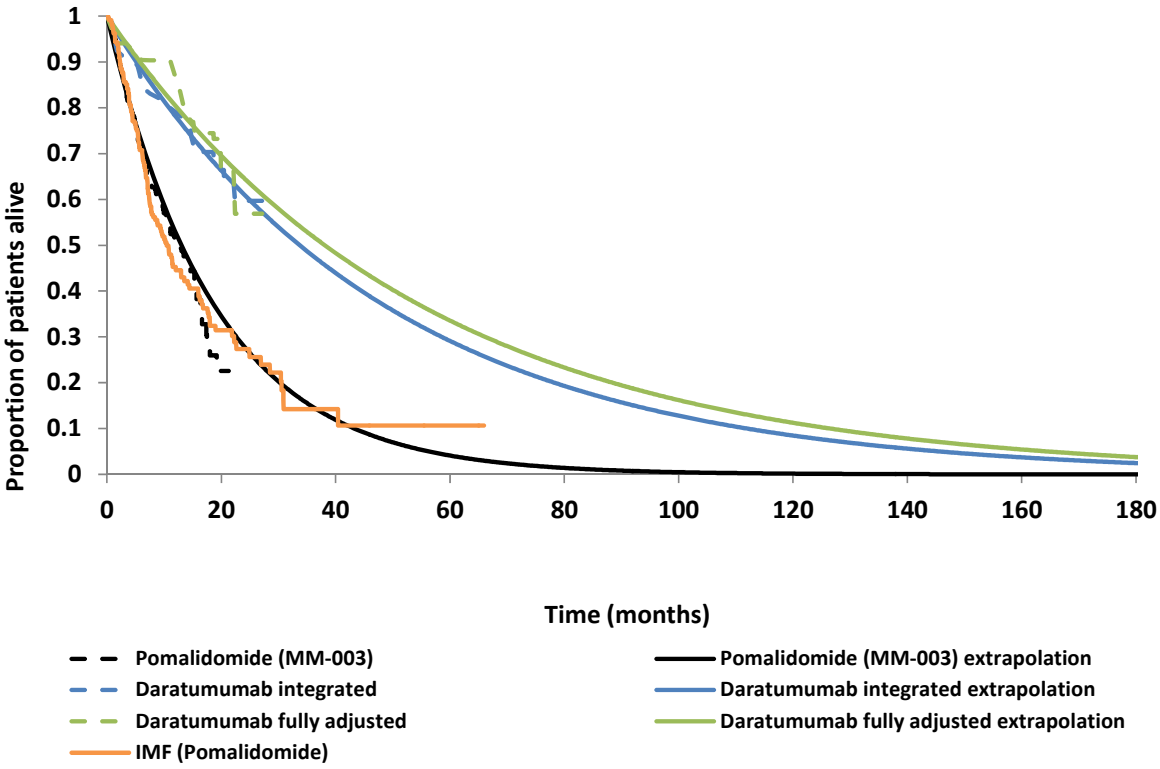


B:15 year time horizon

Figure 9. Summary of overall survival (pomalidomide naive patients)



A: 2.5 year time horizon



B: 15 year time horizon

As requested by the AC, Janssen explored methods to validate MAIC of time to event outcomes using data from the IMF with academic experts. Unfortunately, there are currently no established methods with which to undertake such a validation. Furthermore, Janssen considers it important to note that **similar issues around the uncertainty of MAIC were present in both the POM+DEX (TA427) and PANO+BORT+DEX (TA380) appraisals. Both of these treatments were approved by NICE, despite the absence of fully adjusted MAIC and without any assessment of residual bias**.

"The committee agreed that the estimate of overall survival for pomalidomide plus dexamethasone were likely to be less confounded than that for daratumumab because a smaller proportion of patients had therapies after pomalidomide plus dexamethasone (44%) in MM-003 than after daratumumab (72%) in MMY2002 and GEN501" [para 4.15]

Janssen strongly contests the AC's conclusion that estimates of OS for POM+DEX are likely to be less confounded than estimates for daratumumab. With the obvious exception of pomalidomide, the **availability of subsequent treatment in the daratumumab trials and in the pomalidomide trial was the same** (Table 10). That is, patients in MMY2002/GEN501 and MM-003 were able to receive subsequent treatment with bendamustine, bortezomib, carfilzomib, cyclophosphamide, dexamethasone, etoposide, lenalidomide, melphalan and thalidomide. The fact that, despite similar baseline characteristics and levels of fitness (Table 11), more patients in the daratumumab trials received more active subsequent treatment is testament to daratumumab's novel MoA and favourable safety profile. The improved health status of patients following daratumumab and its multifaceted MoA allow more patients to receive and to benefit from subsequent treatment (see Section 2.1 and Section 3).

Table 10: Subsequent treatment available in MMY2002/GEN501 and MM-003

Subsequent treatment	Proportion of MMY2002/GEN501 patients	Proportion of MM-003 patients
Dexamethasone	58%	29%
Pomalidomide	31%	0%
Cyclophosphamide	32%	21%
Carfilzomib	28%	2%
Bortezomib	24%	18%
Lenalidomide	15%	5%
Melphalan	16%	8%
Etoposide	10%	3%
Bendamustine	14%	11%
Thalidomide	7%	7%
Source: Janssen 2016[19], Federal Joint Committee 2016[30]		

Table 11: Baseline characteristics of patients in MMY2002/GEN501 and MM-003

Baseline characteristics	**POM+DEX** MM-003	**Daratumumab** MMY2002/GEN501
N	302	148
Refractory to lenalidomide (%) Refractory to bortezomib (%) Refractory to both (%)	95 79 75	84 84 77
Mean no. of prior regimens >2 prior regimens (%)	5.0 94	5.4 93
Creatinine clearance <30 (%) Creatinine clearance 30-60 (%) Creatinine clearance ≥60 (%)	1 31 68	3 36 60
ECOG 0 (%) ECOG 1 (%) ECOG 2 (%)	37 46 17	28 66 7
Median time since diagnosis (years)	6.2	6.3
Myeloma subtype, IgA (%) Myeloma subtype, IgG (%) Myeloma subtype, IgM (%) Myeloma subtype, IgD (%) Light chain Kappa (%) Light chain lambda (%)	26 62 0 1 8 3	18 49 1 3 15 11
White (%) Asian (%) Black (%)	96 2 2	85 3 12
Bone lesions (%)	68	75

Baseline characteristics	POM+DEX MM-003	Daratumumab MMY2002/GEN501
Prior ASCT (%)	71	78
Mean age (years) Age >65 years (%) Age >75 years (%)	63.6 45 8	63.2 41 9
Key: ASCT, autologous stem-cell transplantation; ECOG, Eastern Cooperative Oncology Group; Ig, immunoglobulin; POM+DEX, pomalidomide plus dexamethasone. **Source:** Janssen 2016[19], NICE Manufacturers submission[31]		

6. EOL

"The committee considered life expectancy for people with relapsed and refractory multiple myeloma and was satisfied that it was less than 24 months. The committee was unable to conclude whether the criterion of at least a 3-month life extension was met because of the many uncertainties in the relative effectiveness and survival modelling. The committee concluded that it could not make an informed decision as to whether daratumumab meets the end-of-life criteria." [para 4.32]

Daratumumab monotherapy is undoubtedly an end of life medicine for patients with RRMM. **The fact that 63% of patients responding to daratumumab are alive after a median follow up of 31 months is unparalleled in this indication where life expectancy is around one year**.[21,22-27] Moreover, when all available effectiveness data are used, daratumumab demonstrates a statistically significant survival benefit of greater than 3 months when compared with POM+DEX, regardless of the methods of indirect comparison employed. In comparison with PANO+BORT+DEX, daratumumab is anticipated to provide an additional 5.1 months of survival benefit, based upon medians obtained though modelling using fully adjusted MAIC and independent curve fits.

Indeed, **the degree of certainty with respect to the relative benefit of daratumumab is greater than previously seen in the appraisal of POM+DEX in this same setting and where end-of-life criteria were used** (TA427).[31]

7. Model assumptions

"The committee agreed that it would like to see analyses that:

- *used the MMY2002 trial population (see section 4.5)*
- *adjusted for all potential confounders in the MAIC (see section 4.11)*
- *cross validated the MAIC analysis with data from other sources (see section 4.12)*
- *explained the definition and calculations to estimate time to stopping treatment (see section 4.23)*
- *presenting scenarios reflecting different assumptions about the long-term effects of daratumumab (see section 4.18)*
- *included scenario analyses using dependently and independently fitted curves (see section 4.21)*
- *explored alternative utility values to reflect daratumumab's additional benefits on quality of life perceived by the patient and clinical experts (see section 4.22)*

- *carried out and documented further internal quality assurance (see section 4.25)*
- *present results as probabilistic ICERs within a fully incremental analysis."*

[Para 4.27]

For the original submission, Janssen conducted full cost-effectiveness analysis versus the appropriate comparators within the NHS, using the most appropriate data sources and most appropriate methods at the time of submission. Whilst numerous assumptions were necessary in the economic modelling, Janssen explored a range of methodologies in order to present a balanced case to NICE.

Following publication of NICE's Decision Support Unit's technical support document on population adjusted indirect comparisons (TSD 18).[29] Janssen understands the requirement to adapt the methodology used and have used fully adjusted MAIC in revised base case analyses.

Revised base case

Considering the AC's stated wishes, alongside the issues covered in Sections 1-6 of this document, Janssen provide a revised base case, differing from that originally submitted as follows:

1. MAICs adjusted for all potential confounders.
2. Independently fitted curves for OS and PFS (based on ERG preference).
3. Weibull model to extrapolate OS (based on ERG preference).
4. Utility benefit of 0.04 for daratumumab based on QoL data from the EAP (Section 3).
5. Implementation of model corrections from Section 6.1 of the ERG report.
6. Updates following further internal quality assurances (by the vendor who built the model, an external vendor and Janssen).

As noted earlier, Janssen contends that the **integrated data from the daratumumab trials is most appropriate for decision making** (see Section 4.1 and 5) and as such is used in Janssen's revised base case. However, the evidence base has been limited to MMY2002 in scenario analyses. In addition to this, the following scenario analyses have been explored alongside those of the original submission:

1. Dependent curve fits for OS and PFS.
2. Different assumptions about the long-term effects of daratumumab.
3. Alternative utility values.
4. Alternative costing assumptions with respect to resource use and subsequent treatment.

Since Janssen's original submission, more mature OS data from MMY2002 and GEN501 have become available. These data have been used to validate the OS extrapolations originally submitted to NICE. The **original OS extrapolations have been found to be conservative** (see Appendix 3).

As requested in the ACD, Janssen has also performed additional quality assurance on the economic model (see Appendix 4). With respect to time to treatment discontinuation (TTD), Janssen is not clear what additional information is required. TTD was a simple assessment of the difference in time between starting and stopping treatment with daratumumab and has been used to more accurately capture the cost of treatment. Importantly, the use of TTD rather than PFS decreases the cost of treatment with POM+DEX to a greater extent than that of daratumumab as more patients stopped treatment ahead of progression with POM+DEX than with daratumumab. Probabilistic estimates of cost-effectiveness are provided for the comparisons of daratumumab versus POM+DEX and versus PANO+BORT+DEX. However, as a consequence of using independently fitted curves (the ERG's preferred approach), a fully incremental probabilistic analysis is not possible.

Janssen's revised base case demonstrates that **daratumumab is cost-effective at list price** with incremental cost-effectiveness ratios (ICERs) of £44,988 and £21,910 versus POM+DEX and PANO+BORT+DEX, respectively. These estimates of cost-effectiveness have been shown to be **robust** across numerous sensitivity analyses, including one-way, probabilistic and scenario analyses. Probabilistic analyses demonstrate that daratumumab has a 64% and 76% chance of being cost-effective at a threshold of £50,000 per QALY versus POM+DEX and PANO+BORT+DEX, respectively.

The application of daratumumab's PAS, now formally approved by the DH and the Minister, shows that daratumumab is **highly cost-effective**; £15,772 versus POM+DEX and daratumumab dominating versus PANO+BORT+DEX. Probabilistic analyses show that with the PAS daratumumab has a **99% chance of being cost-effective** under end-of-life criteria, versus both POM+DEX and PANO+BORT+DEX. Furthermore, Janssen's PAS is such **that the cost of treatment in patients that do not respond to treatment is covered by Janssen rather than the NHS**. As discussed in Section 2.1, patients who do not respond to daratumumab do not accrue the benefits of immunological changes and as such receive no benefit from treatment. By ensuring the NHS only pays for treatment in patients receiving benefit, Janssen is reducing the uncertainty associated with investing in daratumumab.

As a worst case scenario, if one assumed that daratumumab is on average no more effective than POM+DEX or PANO+BORT+DEX but with a better safety profile. In this case, assuming average treatment duration of 4 months, equal to 12 infusions, the average cost of daratumumab is £53,244, reducing to £31,059 with the PAS. Based upon information provided in the FAD for POM+DEX and the manufacturer's submission for PANO+BORT+DEX, the average cost of treatment is £44,420 and £79,528, respectively. Janssen understands that both pomalidomide and panobinostat have confidential simple discounts; however, for POM+DEX and PANO+BORT+DEX to have lower average treatment costs than daratumumab, treatment costs would need to decrease by at least [redacted] and [redacted] for POM+DEX and PANO+BORT+DEX, respectively.

8. Revised economic analyses

This section presents results from the revised base case and scenario analyses described in Section 7.

8.1 Revised base case results

The revised base case results, with and without the PAS, versus POM+DEX and PANO+BORT+DEX are reported in Table 12 and Table 13, respectively. A breakdown of the costs and QALYs are provided in Appendix 5. The results show that daratumumab is a highly cost-effective option in RRMM.

Table 12: Revised base case results versus POM+DEX

	Total			Incremental			ICER
	Costs	QALYs	LYs	Costs	QALYs	LYs	
Without PAS							
POM+DEX	£52,396	0.75	1.49	£31,217	0.69	1.24	£44,988
Daratumumab	£83,613	1.44	2.74				
With PAS							
POM+DEX	£52,396	0.75	1.49	£10,909	0.69	1.24	£15,772
Daratumumab	£63,306	1.44	2.74				

Key: ICER, incremental cost-effectiveness ratio; LY, Life years; PAS, patient access scheme; POM+DEX, pomalidomide plus dexamethasone; QALY, quality-adjusted life years.

Table 13: Revised base case results versus PANO+BORT+DEX

	Total			Incremental			ICER
	Costs	QALYs	LYs	Costs	QALYs	LYs	
Without PAS							
PANO+BORT+DEX	£76,008	0.93	1.80	£6,646	0.30	0.48	£21,910
Daratumumab	£82,654	1.23	2.28				
With PAS							
PANO+BORT+DEX	£76,008	0.93	1.80	-£13,662	0.30	0.48	Daratumumab Dominates
Daratumumab	£62,346	1.23	2.28				
Key: ICER, incremental cost-effectiveness ratio; LY, Life years; PANO+BORT+DEX, panobinostat plus bortezomib plus dexamethasone; PAS, patient access scheme; QALY, quality-adjusted life years.							

8.2 Revised probabilistic results

The revised probabilistic results, with and without the PAS, versus POM+DEX and PANO+BORT+DEX are presented in Table 14 and Table 15, respectively. The probabilistic sensitivity analysis plots and cost-effectiveness acceptability curves are presented in Appendix 6. With the PAS, the chances of being cost-effective at a threshold of £20,000 versus POM+DEX and PANO+BORT+DEX are 72% and 99%, respectively.

Table 14: Revised Probabilistic Results versus POM+DEX

	Total			Incremental			ICER
	Costs	QALYs	LYs	Costs	QALYs	LYs	
Without PAS							
POM+DEX	£52,280	0.75	1.50	£30,442	0.71	1.28	£43,113
Daratumumab	£82,722	1.46	2.78				
With PAS							
POM+DEX	£52,279	0.75	1.50	£10,204	0.71	1.28	£14,464
Daratumumab	£62,483	1.46	2.78				
Key: ICER, incremental cost-effectiveness ratio; LY, Life years; PAS, patient access scheme; POM+DEX, pomalidomide plus dexamethasone; QALY, quality-adjusted life years.							

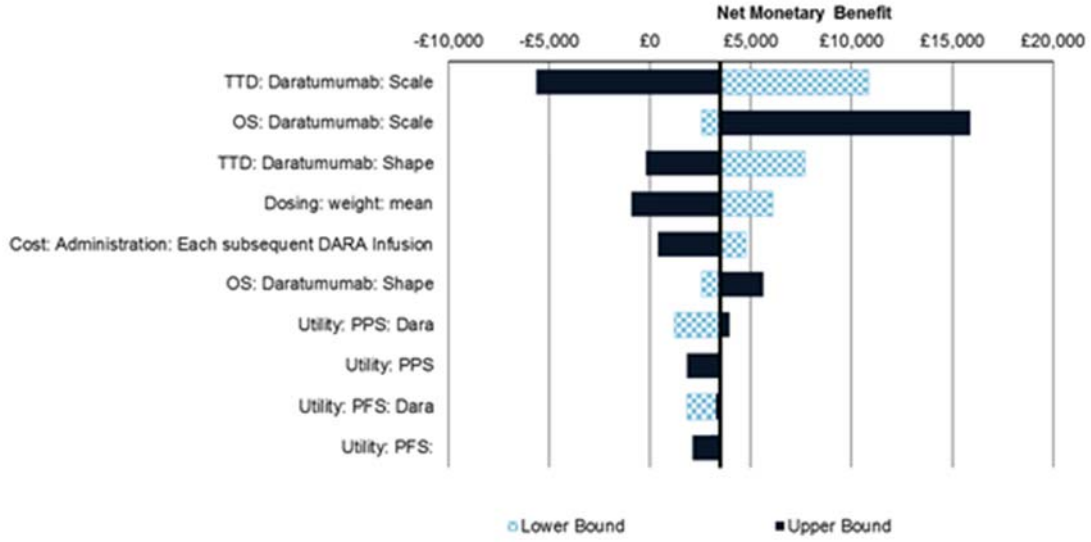
Table 15: Revised Probabilistic Results versus PANO+BORT+DEX

	Total			Incremental			ICER
	Costs	QALYs	LYs	Costs	QALYs	LYs	
Without PAS							
PANO+BORT+DEX	£75,868	0.95	1.84	£5,366	0.30	0.47	£18,102
Daratumumab	£81,235	1.24	2.30				
With PAS							
PANO+BORT+DEX	£75,948	0.95	1.84	-£14,896	0.29	0.46	Daratumumab Dominates
Daratumumab	£61,052	1.24	2.30				
Key: ICER, incremental cost-effectiveness ratio; LY, Life years; PANO+BORT+DEX, panobinostat plus bortezomib plus dexamethasone; PAS, patient access scheme; QALY, quality-adjusted life years.							

8.1 Revised one-way sensitivity analysis results

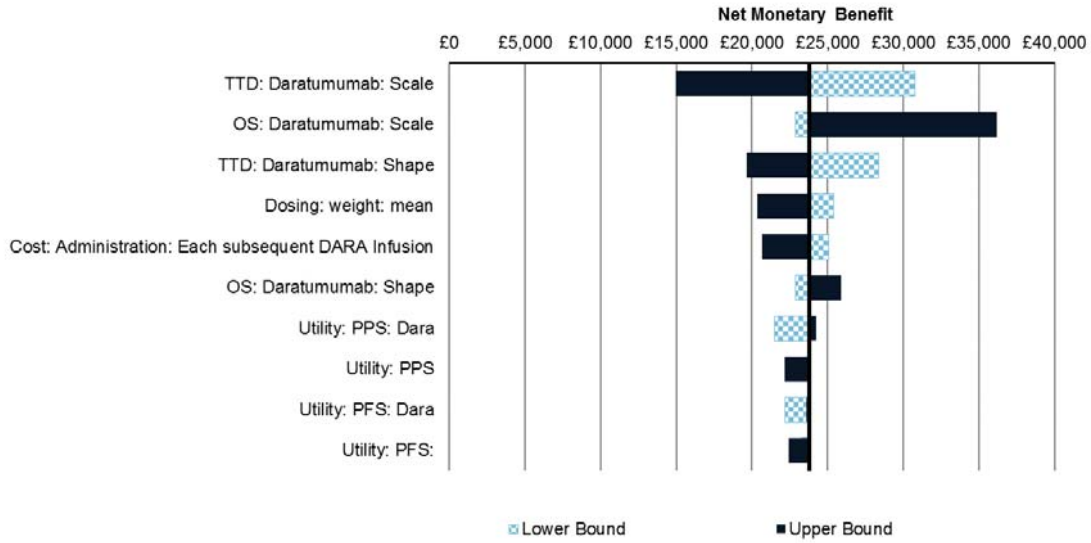
The results of the one-way sensitivity analysis are presented, with and without the PAS, versus POM+DEX and PANO+BORT+DEX in Figure 10 to Figure 13. Results are presented using net monetary benefit, rather than ICERs, with a higher net monetary benefit indicating better value for money with daratumumab versus the comparator.

Figure 10: Revised one-way sensitivity analysis results versus POM+DEX, without PAS



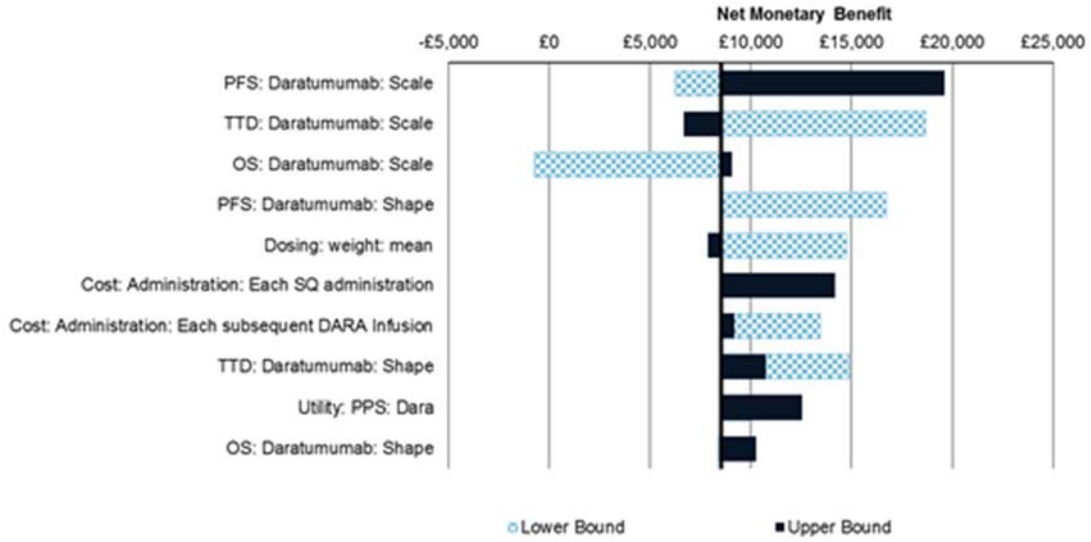
Key: Dara, daratumumab; OS, overall survival; PAS, patient access scheme; PFS, progression-free survival; POM+DEX, pomalidomide plus dexamethasone; PPS, post-progression survival; TTD, time to treatment discontinuation.

Figure 11: Revised one-way sensitivity analysis results versus POM+DEX, with PAS



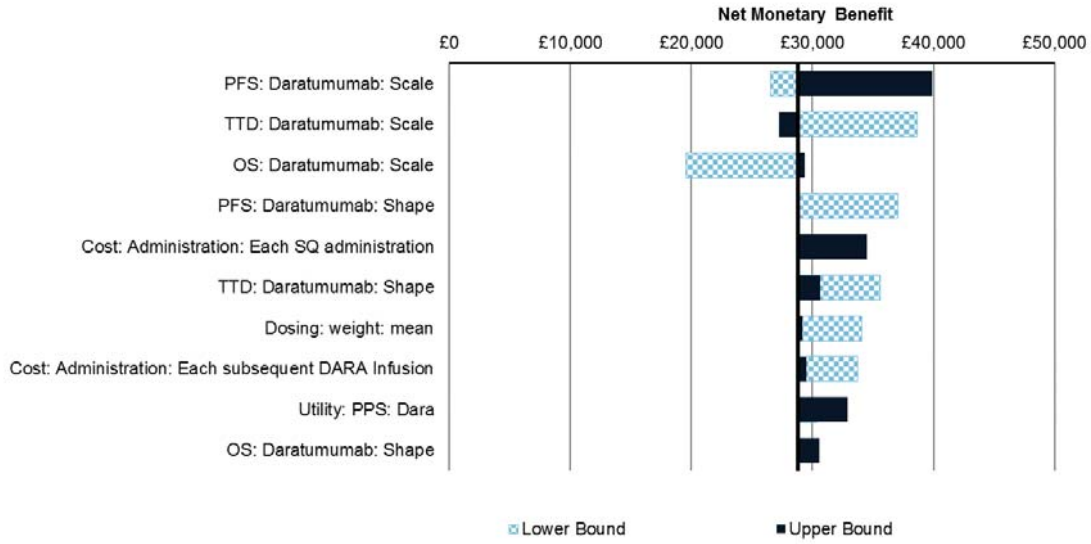
Key: Dara, daratumumab; OS, overall survival; PAS, patient access scheme; PFS, progression-free survival; POM+DEX, pomalidomide plus dexamethasone; PPS, post-progression survival; TTD, time to treatment discontinuation.

Figure 12: Revised one-way sensitivity analysis results versus PANO+BORT+DEX, without PAS



Key: Dara, daratumumab; OS, overall survival; PANO+BORT+DEX, panobinostat plus bortezomib plus dexamethasone; PAS, patient access scheme; PFS, progression-free survival; PPS, post-progression survival; TTD, time to treatment discontinuation.

Figure 13: Revised one-way sensitivity analysis results versus PANO+BORT+DEX, with PAS



Key: Dara, daratumumab; OS, overall survival; PANO+BORT+DEX, panobinostat plus bortezomib plus dexamethasone; PAS, patient access scheme; PFS, progression-free survival; PPS, post-progression survival; TTD, time to treatment discontinuation.

8.3 Revised scenario analysis results

The results of the scenario analyses, with and without the PAS, are shown in Table 16 and Table 17, respectively. These suggest that the economic value of daratumumab is robust to structural, data and methodological changes. In the comparison of daratumumab with POM+DEX, decreasing the time horizon, using dependent rather than independent curve fits, using trial subsequent treatment costs and assuming no benefit after the trial follow up all increase the ICER; however, with the PAS the ICER remains under £30,000. Limiting the data used to MMY2002 decreases the ICER as does more optimistic utility benefits. With the PAS, daratumumab remains dominant over PANO+BORT+DEX in all scenarios.

Table 16: Scenario Analyses Results, without PAS

	Base case	Scenario Analysis	ICER (DARA vs POM+DEX)	ICER (DARA vs PANO+BORT+DEX)
Base case			**£44,988**	**£21,910**
Time horizon	15 years	5 years	£56,468	£17,517
Time horizon	15 years	10 years	£45,985	£21,325
Discount rate (costs and QALYs)	3.50%	0%	£41,349	£24,198
Discount rate (costs and QALYs)	3.50%	6%	£47,773	£20,230
Utilities	Palumbo with 0.04 uplift for daratumumab: PFS (comparators) 0.61, PFS(DARA) 0.65, PPS 0.57	Utilities from Palumbo et al assuming no uplift for daratumumab (PFS 0.61, PPS 0.57)	£47,237	£24,336
Utilities	Palumbo with 0.04 uplift for daratumumab: PFS (comparators) 0.61, PFS(DARA) 0.65, PPS 0.57	Utilities from TA 380, utilities assumed the same for daratumumab and comparators (PFS 0.71, PPS 0.64)	£41,974	£21,688
Utilities	Palumbo with 0.04 uplift for daratumumab: PFS (comparators) 0.61, PFS(DARA) 0.65, PPS 0.57	utilities from TA338, utilities assumed the same for daratumumab and comparators (PFS 0.65, PPS 0.57)	£46,390	£23,855

	Base case	Scenario Analysis	ICER (DARA vs POM+DEX)	ICER (DARA vs PANO+BORT+DEX)
Utilities	Palumbo with 0.04 uplift for daratumumab: PFS (comparators) 0.61, PFS(DARA) 0.65, PPS 0.57	Palumbo with 0.04 uplift for daratumumab pre and post-progression: PFS (comparators) 0.61, PFS(DARA) 0.65, PPS(comparators) 0.57, PPS(DARA) 0.61	£41,039	£18,547
Daratumumab TTD curve fits	Log-logistic	Log-normal	£45,998	£26,256
Daratumumab TTD curve fits	Log-logistic	Exponential	£33,242	£75
Daratumumab TTD curve fits	Log-logistic	Weibull	£32,956	Daratumumab Dominates
Daratumumab PFS curve fits	Log-normal	Exponential	£39,515	£1,822
Daratumumab PFS curve fits	Log-normal	Log-logistic	£47,440	£24,790
Daratumumab PFS curve fits	Log-normal	Gamma	£49,556	£21,133
Daratumumab PFS curve fits	Log-normal	Weibull	£40,027	Daratumumab Dominates
Daratumumab OS curve fits	Weibull	Exponential	£49,436	£20,373
Daratumumab OS curve fits	Weibull	Log-logistic	£34,395	£17,709
Daratumumab OS curve fits	Weibull	Log-normal	£31,421	£13,643
Daratumumab PFS	IRC	INV	£45,090	£21,910

	Base case	Scenario Analysis	ICER (DARA vs POM+DEX)	ICER (DARA vs PANO+BORT+DEX)
MAIC	Daratumumab patient population used is integrated GEN501/MMY2002	Daratumumab patient population used is MMY2002	£25,744	Daratumumab Dominates
MAIC	Daratumumab patient population used is integrated GEN501/MMY2002	Daratumumab patient population used is integrated GEN501/MMY2002, POM-naïve patients	£46,543	NA
MAIC vs POM+DEX	Fully adjusted MAIC, independent curve fits	Cox proportion hazard model versus IMF data (applied as a hazard ratio vs daratumumab unadjusted)	£40,287	NA
MAIC	Fully adjusted MAIC, independent curve fits	Fully adjusted MAIC, dependent curve fits	£51,859	£32,407
Survival extrapolation	Extrapolation of daratumumab survival based on parametric curve fit	After trial, follows same trajectory as comparator survival, using conditional survival.	£60,011	Daratumumab Dominates
Subsequent Treatment	Based on those used in ERG Model	Based on those received in the trial (ERGs exploratory analysis)	£53,859	£44,532
Resource use	Based on original submission	Based on ERG estimated resource use	£46,362	£23,075

Key: DARA, daratumumab; DEX, dexamethasone; ERG, Evidence review group; IRC, independent review committee; IMF, international myeloma foundation; INV, investigator; MAIC, match adjusted indirect comparison; NA, not applicable; OS, overall survival; PFS, progression-free survival; POM, pomalidomide; PPS post-progression survival; QALY, quality adjusted life year; TA, technology appraisal; TTD, time to treatment discontinuation.

Table 17: Scenario Analysis Results, with PAS

Parameter	Base case	Scenario Analysis	ICER (DARA vs POM+DEX)	ICER (DARA vs PANO+BORT+DEX)
Base case			**£15,722**	**Daratumumab Dominates**

Parameter	Base case	Scenario Analysis	ICER (DARA vs POM+DEX)	ICER (DARA vs PANO+BORT+DEX)
Time horizon	15 years	5 years	£16,743	Daratumumab Dominates
Time horizon	15 years	10 years	£15,630	Daratumumab Dominates
Discount rate (costs and QALYs)	3.50%	0%	£15,767	Daratumumab Dominates
Discount rate (costs and QALYs)	3.50%	6%	£15,665	Daratumumab Dominates
Utilities	Palumbo with 0.04 uplift for daratumumab: PFS (comparators) 0.61, PFS(DARA) 0.65, PPS 0.57	Utilities from Palumbo et al assuming no uplift for daratumumab (PFS 0.61, PPS 0.57)	£16,508	Daratumumab Dominates
Utilities	Palumbo with 0.04 uplift for daratumumab: PFS (comparators) 0.61, PFS(DARA) 0.65, PPS 0.57	Utilities from TA 380, utilities assumed the same for daratumumab and comparators (PFS 0.71, PPS 0.64)	£14,668	Daratumumab Dominates
Utilities	Palumbo with 0.04 uplift for daratumumab: PFS (comparators) 0.61, PFS(DARA) 0.65, PPS 0.57	utilities from TA338, utilities assumed the same for daratumumab and comparators (PFS 0.65, PPS 0.57)	£16,212	Daratumumab Dominates
Utilities	Palumbo with 0.04 uplift for daratumumab: PFS (comparators) 0.61, PFS(DARA) 0.65, PPS 0.57	Palumbo with 0.04 uplift for daratumumab pre and post-progression: PFS (comparators) 0.61, PFS(DARA) 0.65, PPS(comparators) 0.57, PPS(DARA) 0.61	£14,342	Daratumumab Dominates
Daratumumab TTD curve fits	Log-logistic	Log-normal	£16,992	Daratumumab Dominates
Daratumumab TTD curve fits	Log-logistic	Exponential	£4,277	Daratumumab Dominates

Parameter	Base case	Scenario Analysis	ICER (DARA vs POM+DEX)	ICER (DARA vs PANO+BORT+DEX)
Daratumumab TTD curve fits	Log-logistic	Weibull	£4,457	Daratumumab Dominates
Daratumumab PFS curve fits	Log-normal	Exponential	£9,932	Daratumumab Dominates
Daratumumab PFS curve fits	Log-normal	Log-logistic	£18,286	Daratumumab Dominates
Daratumumab PFS curve fits	Log-normal	Gamma	£21,295	Daratumumab Dominates
Daratumumab PFS curve fits	Log-normal	Weibull	£10,460	Daratumumab Dominates
Daratumumab OS curve fits	Weibull	Exponential	£17,209	Daratumumab Dominates
Daratumumab OS curve fits	Exponential	Log-logistic	£12,204	Daratumumab Dominates
Daratumumab OS curve fits	Exponential	Log-normal	£11,226	Daratumumab Dominates
Daratumumab PFS	IRC	INV	£15,726	Daratumumab Dominates
MAIC	Daratumumab patient population used is integrated GEN501/MMY2002	Daratumumab patient population used is MMY2002	Daratumumab Dominates	Daratumumab Dominates
MAIC	Daratumumab patient population used is integrated GEN501/MMY2002	Daratumumab patient population used is integrated GEN501/MMY2002, POM-naïve patients	£29,526	Daratumumab Dominates
MAIC vs POM+DEX	Fully adjusted MAIC, independent curve fits	Cox proportion hazard model versus IMF data (applied as a hazard ratio vs daratumumab unadjusted)	£13,132	NA

Parameter	Base case	Scenario Analysis	ICER (DARA vs POM+DEX)	ICER (DARA vs PANO+BORT+DEX)
MAIC	Fully adjusted MAIC, independent curve fits	Fully adjusted MAIC, dependent curve fits	£16,784	Daratumumab Dominates
Survival extrapolation	Extrapolation of daratumumab survival based on parametric curve fit	After trial, follows same trajectory as comparator survival, using conditional survival.	£3,168	Daratumumab Dominates
Subsequent Treatment	Based on those used in ERG Model	Based on those received in the trial (ERGs exploratory analysis)	£24,592	Daratumumab Dominates
Resource use	Based on original submission	Based on ERG estimated resource use	£17,096	Daratumumab Dominates

Key: DARA, daratumumab; DEX, dexamethasone; ERG, Evidence review group; IRC, independent review committee; IMF, international myeloma foundation; INV, investigator; MAIC, match adjusted indirect comparison; NA, not applicable; OS, overall survival; PFS, progression-free survival; POM, pomalidomide; PPS post-progression survival; QALY, quality adjusted life year; TA, technology appraisal; TTD, time to treatment discontinuation.

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Appendix 1 Updated OS for MMY2002 and GEN501

At the latest data cut-off (18 November 2016), median follow-up of MMY2002 and GEN501 was 31.31 and 31.77 months, respectively. In MMY2002, patients treated with daratumumab 16mg/kg demonstrated a median OS of 18.6 months (95% CI: 13.7, 25.0) and a 2-year OS rate of 40.5%. In GEN501, median OS is not reached (95% CI: 19.8, NE), with 59.3% of patients alive at 2 years.

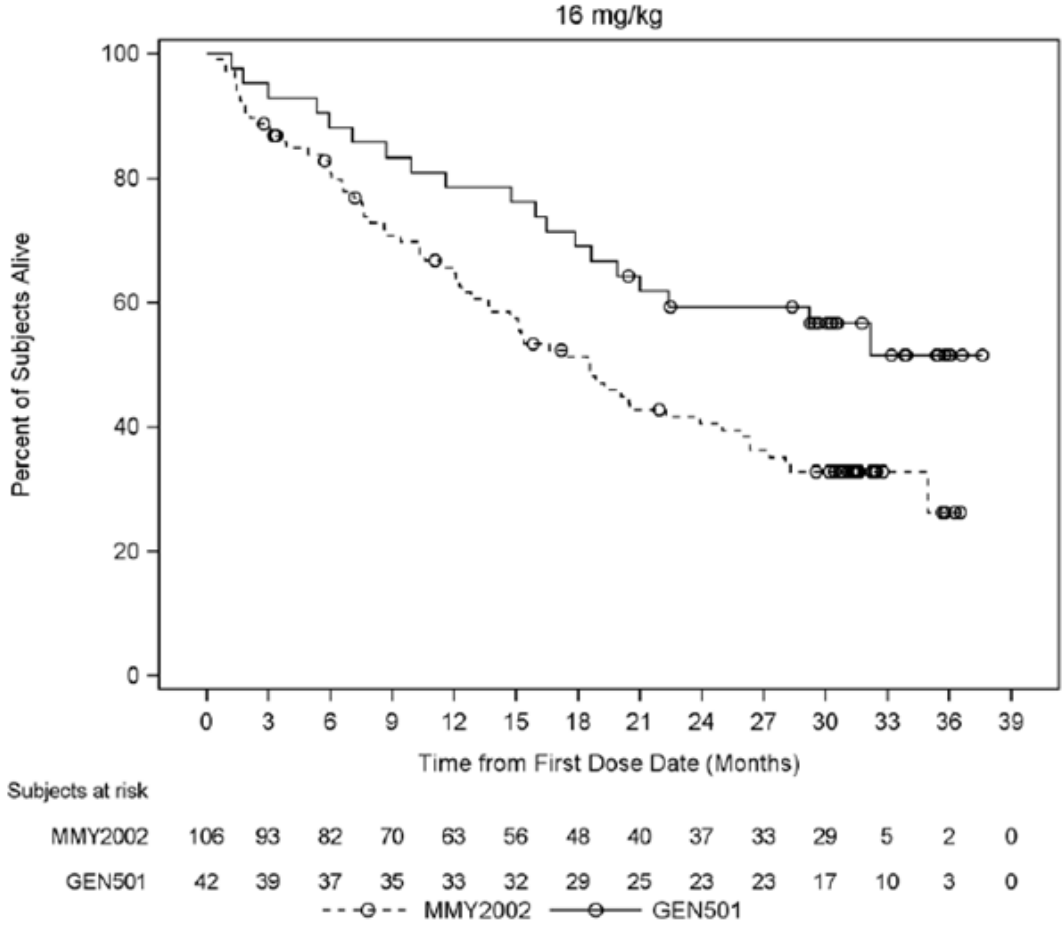
Table 18: Summary of updated overall survival, all treated patients (18 November 2016 data cut-off)

	MMY2002	GEN501	Total
	(n=106)	(n=42)	(n=148)
Median OS, months (95% CI)	18.60 (13.67, 25.00)	NE (19.91, NE)	20.47 (16.62, 28.06)
Number of events, n (%)	67 (63.2%)	19 (45.2%)	86 (58.1%)
6 month OS rate, % (95% CI)	81.8 (73.0, 88.0)	88.1 (73.7, 94.9)	83.6 (76.5, 88.7)
12 month OS rate, % (95% CI)	64.7 (54.5, 73.1)	78.6 (62.9, 88.2)	68.7 (60.5, 75.6)
18 month OS rate, % (95% CI)	51.3 (41.1, 60.6)	69.0 (52.7, 80.7)	56.5 (47.9, 64.2)
24 month OS rate, % (95% CI)	40.5 (30.7, 50.1)	59.3 (43.0, 72.4)	46.1 (37.7, 54.1)
30 month OS rate, % (95% CI)	32.9 (23.7, 42.3)	56.6 (40.3, 70.1)	40.0 (31.7, 48.0)

Key: CI, confidence interval; OS, overall survival.

Source: Janssen 2017 (Updated OS)[21]

Figure 14: Kaplan–Meier plot for overall survival, all patients treated with daratumumab 16mg/kg, integrated analysis (18 November 2016 data cut- off)



Notes: Circles represent censoring.
Source: Janssen 2017[21]

Appendix 2 MAIC sensitivity analyses

Introduction

When estimating relative effectiveness between trial arms across trials using the approach of unanchored MAIC, it is assumed that absolute outcomes can be predicted from the covariates, and all prognostic factors and effect modifiers are accounted for, in order to minimize potential confounding bias.[29]

The MAIC initially applied to the pooled data of the MMY2002 (N=106) and GEN501 (N=42) trial could not take into account ISS-stage and cytogenetic risk as prognostic factors in the MAIC algorithm, as both baseline characteristics were not available for in GEN501.

To investigate the impact of these variables on the MAIC outcome comparing the integrated daratumumab population to the POM+DEX arm of the MM-003 trial, multiple imputation was used in a first step to impute the missing values for the 42 GEN501 patients (out of 148 patients in the integrated data). In a second step, the full dataset including imputed values for these characteristics for the subset of GEN501 patients was used in the MAIC algorithm. This approach allowed use of all

available prognostic variables for all patients in the integrated dataset (N=148) which in the end is expected to minimizing residual confounding.

Method

Multiple imputation (MI) provides a useful strategy for dealing with data sets with missing values. Instead of filling in a single value for each missing value, Rubin's multiple imputation procedure replaces each missing value with a set of plausible values (typically 10 times) to represent the uncertainty of the imputed values.[32]

The MI process was used to generate 10 different imputed datasets to each of which the MAIC procedure was then applied. A single final analysis is obtained by pooling the separate analyses according to Rubin's principles.

All available baseline characteristics available in both trials were used in the imputation process to impute missing values for ISS Stage and cytogenetic risk. As baseline albumin (one of two parameters defining ISS stage), was available for GEN501, this information was also used to optimally inform the imputation process.

The results of MI-MAIC process were summarized by averaging the HRs across the 10 obtained values and calculating the confidence interval by taking the between-imputation variance properly into account.[33] The analysis was performed in SAS 9.4 using proc MI and MIANALYZE. As a sensitivity analysis, the MI was also carried out based on a Bayesian approach, using the AMELIA package in R.[34]

Results

Table 19 and Table 20 show the distributions of the imputed values for the baseline cytogenetic risk and ISS-stage, respectively. The percentage of cytogenetic risk predicted for GEN501 is identical to MMY2002; however, the proportion of stage 1 patients (based on imputed values) is somewhat higher in GEN501 (together with less stage 2/3-patients), representing a somewhat less advanced patient population compared to MMY2002.

Table 19: Distribution of observed baseline cytogenetic risk in MMY2002 (study 2) and for the imputed values for GEN501 (study 1)

Study	0		1		All	
	N	%	N	%	N	%
1	32	75	10	24	42	100
2	80	75	26	24	106	100
All	112	75	36	24	148	100

Table 20: Distribution of observed baseline ISS-stage in MMY2002 (study 2) and for the imputed values for GEN501 (study 1)

Study	1		2		3		All	
	N	%	N	%	N	%	N	%
1	15	36	13	31	13	31	42	100
2	26	24	40	37	40	37	106	100
All	42	28	53	36	53	36	148	100

The results of the imputation process presented in Table 21 show a minimal increase in the HR comparing daratumumab to POM+DEX (0.56 vs 0.57) compared to the original MAIC (which did not take the baseline cytogenetic risk and ISS-stage into account).

The sensitivity analysis using the AMELIA R- package gave similar results, with a HR slightly more in favour of daratumumab compared to the original MAIC.

Table 21: HR obtained for the original MAIC (no imputation) excluding the baseline cytogenetic risk and ISS-stage as matching variables and summary of the HR's obtained after applying MI (average, 95%CI, min and max HR obtained across the 10 imputations).

Method	N	HR (95% CI)	Min	Max
No imputation	136	0.56 (0.38, 0.83)		
MI (proc MI)	148	0.57 (0.38, 0.85)	0.55	0.59
MI (Amelia)	148	0.55 (0.37, 0.82)	0.53	0.56

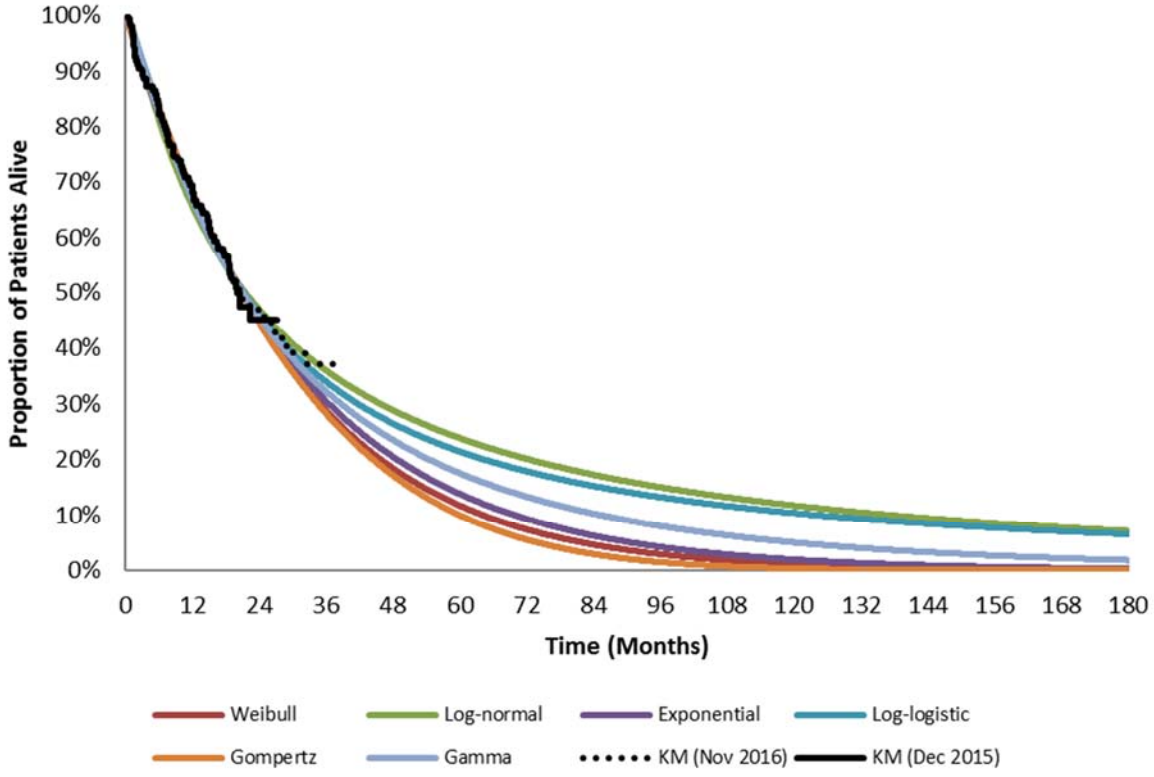
Discussion

By using MI to impute missing values for cytogenetic risk and ISS disease stage for the small subset of patients (42/148), we were able to demonstrate that the MAIC-results were stable regarding including or excluding these two characteristics, and that initial results based on a matching process without both variables were not confounded.

Appendix 3 OS Extrapolations

Since Janssen's original submission, more mature OS data from MMY2002 and GEN501 have become available. These data have been used to validate the OS extrapolations originally submitted to NICE. Figure 15 overlays the 18 November 2016 OS Kaplan-Meier (KM) data and the parametric survival curves used in the model, based on model fits to the 31 December 2015 data-lock for the integrated dataset. The 18 November 2016 KM curve suggests that both the exponential curve used in the original base case and the Weibull (ERG's preferred curve) are conservative estimates of the expected long-term survival of patients receiving daratumumab.

Figure 15: OS KM data (Dec 2015 and Nov 2016 datacuts) and extrapolations based on Dec2015 datacut



Appendix 4 Quality Assurance

The model was quality-assured using the internal processes of the vendor who built the model and by a vendor not involved in the original model build. In these processes, economists not involved in model build reviewed the model for coding errors, inconsistencies, and the plausibility of inputs. The model was also put through a checklist of known modelling errors, and questioning of the assumptions based upon the Phillips checklist.

In addition to the above, Janssen conducted a thorough validation of all parametric extrapolations. All parametric models were refitted using the same (monthly) time scale, to allow comparison of goodness-of-fit across all parametric models.

Table 22. Summary of parametric curve fits, integrated analysis

			Weibull	Log-normal	Exponential	Log-logistic	Gompertz	Gamma
Overall survival								
Daratumumab – integrated data	Unadjusted	AIC	647.8	648.2	**646.1**	648.1	648.0	649.3
		BIC	653.8	654.2	**649.1**	654.1	654.0	658.3
	Fully adjusted MAIC (versus POM+DEX	AIC	565.7	569.1	**563.7**	568.6	565.1	565.2
		BIC	571.5	574.9	**566.7**	574.5	570.9	573.9
	Fully adjusted MAIC (versus PANO+BORT+DEX	AIC	539.5	544.3	540.0	541.0	**539.4**	541.3
		BIC	545.2	550.0	542.8	546.6	**545.1**	549.8
Daratumumab – MMY2002	Unadjusted	AIC	488.0	488.4	**486.3**	488.3	488.2	489.6
		BIC	493.3	493.7	**488.9**	493.7	493.5	497.6
	Fully adjusted MAIC (versus POM+DEX)	AIC	347.0	339.4	358.8	343.1	338.4	**327.2**
		BIC	352.0	344.5	361.4	348.2	343.5	**334.8**
	Fully adjusted MAIC (versus PANO+BORT+DEX)	AIC	320.9	323.2	**320.1**	321.9	321.9	322.4
		BIC	325.8	328.1	**322.5**	326.8	326.8	329.7
Daratumumab – POM naïve integrated data	Fully adjusted MAIC (versus POM+DEX)	AIC	215.1	218.0	213.9	216.1	**213.7**	216.3
		BIC	219.5	222.4	216.1	220.4	**218.1**	222.9
Daratumumab – POM naïve MMY2002	Fully adjusted MAIC (versus POM+DEX)	AIC	129.9	127.0	133.9	128.6	126.9	**116.4**
		BIC	132.8	129.9	135.4	131.6	129.9	**120.8**
POM+DEX		AIC	1348.2	1347.6	1347.6	**1347.1**	1349.4	1347.2

		BIC	1355.7	1355.0	1351.3	**1354.5**	1356.8	1358.4
PANO+BORT+DEX		AIC	230.7	230.2	**230.0**	230.7	231.2	232.1
		BIC	234.7	234.2	**232.0**	234.7	235.2	238.2
Progression free survival								
Daratumumab – integrated data	Unadjusted	AIC	609.8	588.6	608.0	593.6	602.7	**582.8**
		BIC	615.8	594.6	611.0	599.6	608.7	**591.8**
	Fully adjusted MAIC (versus POM+DEX	AIC	595.2	578.2	593.2	581.4	591.2	**576.4**
		BIC	601.0	584.0	596.1	587.3	597.0	**585.1**
	Fully adjusted MAIC (versus PANO+BORT+DEX	AIC	539.4	523.3	537.5	525.8	534.1	**521.9**
		BIC	545.1	529.0	540.3	531.5	539.8	**530.4**
Daratumumab – MMY2002	Unadjusted	AIC	416.4	403.3	415.0	407.2	416.2	**400.8**
		BIC	421.7	408.6	417.7	412.5	421.5	**408.8**
	Fully adjusted MAIC (versus POM+DEX	AIC	323.6	314.6	321.8	318.0	323.1	**314.0**
		BIC	328.7	319.6	324.4	323.0	328.2	**321.6**
	Fully adjusted MAIC (versus PANO+BORT+DEX	AIC	363.2	**354.6**	361.7	355.1	356.5	355.4
		BIC	368.0	**359.4**	364.1	360.0	361.3	362.7
Daratumumab – POM naïve integrated data	Fully adjusted MAIC (versus POM+DEX	AIC	268.9	258.7	267.6	261.1	260.0	**252.4**
		BIC	273.3	263.1	269.7	265.4	264.4	**259.0**
Daratumumab – POM naïve MMY2002	Fully adjusted MAIC (versus POM+DEX	AIC	119.0	114.1	117.4	115.3	115.0	**111.2**
		BIC	121.9	117.0	118.8	118.3	117.9	**115.6**
POM+DEX		AIC	1307.5	1307.5	1312.3	1284.8	1314.3	**1272.3**

	BIC	1314.9	1314.9	1316.0	1292.2	1321.7	**1283.4**
PANO+BORT+DEX	AIC	230.6	**228.3**	232.5	229.7	233.0	230.3
	BIC	234.6	**232.3**	234.5	233.7	237.0	236.3

Key: AIC, Akaike information criteria; BIC, Bayesian information criteria; PANO+BORT+DEX, panobinostat plus bortezomib plus dexamethasone; POM+DEX, pomalidomide plus dexamethasone.

Notes: Best statistical fit in **bold.**

Appendix 5 Disaggregated Costs and QALYs

Table 23: Revised Cost Breakdown, without PAS

	Daratumumab		POM+DEX				PANO+BORT+DEX			
	DARA (vs PANO)	DARA (Vs POM)	POM+DEX	Incremental	Absolute Increment	% Increment	PANO+BORT+ DEX	Incremental	Absolute Increment	% Increment
Drug costs	£71,920	£72,593	£46,214	£26,379	£26,379	74%	£60,951	£10,969	£10,969	68%
Admin Costs	£5,919	£5,974	£192	£5,782	£5,782	16%	£7,530	-£1,611	£1,611	10%
Co-medication costs	£240	£240	£393	-£153	£153	0%	£272	-£33	£33	0%
Adverse Events	£941	£941	£2,334	-£1,392	£1,392	4%	£3,009	-£2,067	£2,067	13%
Pre-progression Monitoring	£1,307	£1,330	£769	£562	£562	2%	£1,230	£77	£77	0%

	Daratumumab		POM+DEX				PANO+BORT+DEX			
	DARA (vs PANO)	DARA (Vs POM)	POM+DEX	Incremental	Absolute Increment	% Increment	PANO+BORT+ DEX	Incremental	Absolute Increment	% Increment
costs on treatment										
Pre-progression Monitoring costs off treatment	£71	£113	£99	£14	£14	0%	£0	£71	£71	0%
Subsequent treatment costs	£183	£164	£499	-£334	£334	1%	£767	-£583	£583	4%
Subsequent treatment Admin costs	£241	£216	£405	-£189	£189	1%	£623	-£382	£382	2%
Post-progression Monitoring	£1,043	£1,265	£682	£584	£584	2%	£824	£218	£218	1%
Terminal Care	£789	£776	£811	-£35	£35	0%	£802	-£13	£13	0%
Total	**£82,654**	**£83,613**	**£52,396**	**£31,217**	**£31,217**	**100%**	**£76,008**	**£6,646**	**£6,646**	**100%**

Key: DARA, daratumumab; PANO+BORT+DEX, panobinostat plus bortezomib plus dexamethasone; PAS, patient access scheme; POM+DEX, pomalidomide plus dexamethasone.

Table 24: Revised Cost Breakdown, with PAS

	Daratumumab		POM+DEX				PANO+BORT+DEX			
	DARA (vs PANO)	DARA (Vs POM)	POM+DEX	Incremental	Absolute Increment	% Increment	PANO+BORT+ DEX	Incremental	Absolute Increment	% Increment
Drug costs	£51,052	£51,725	£46,214	£5,511	£5,511	36%	£60,951	-£9,899	£9,899	69%
Admin Costs	£6,479	£6,534	£192	£6,342	£6,342	42%	£7,530	-£1,051	£1,051	7%
Co-medication costs	£240	£240	£393	-£153	£153	1%	£272	-£33	£33	0%
Adverse Events	£941	£941	£2,334	-£1,392	£1,392	9%	£3,009	-£2,067	£2,067	14%
Pre-progression Monitoring costs on treatment	£1,307	£1,330	£769	£562	£562	4%	£1,230	£77	£77	1%
Pre-progression Monitoring costs off treatment	£71	£113	£99	£14	£14	0%	£0	£71	£71	0%
Subsequent treatment costs	£183	£164	£499	-£334	£334	2%	£767	-£583	£583	4%
Subsequent treatment Admin costs	£241	£216	£405	-£189	£189	1%	£623	-£382	£382	3%

	Daratumumab		POM+DEX				PANO+BORT+DEX			
	DARA (vs PANO)	DARA (Vs POM)	POM+DEX	Incremental	Absolute Increment	% Increment	PANO+BORT+ DEX	Incremental	Absolute Increment	% Increment
Post-progression Monitoring	£1,043	£1,265	£682	£584	£584	4%	£824	£218	£218	2%
Terminal Care	£789	£776	£811	-£35	£35	0%	£802	-£13	£13	0%
Total	**£62,346**	**£63,306**	**£52,396**	**£10,909**	**£10,909**	**100%**	**£76,008**	**-£13,662**	**£13,662**	**100%**
Key: DARA, daratumumab; PANO+BORT+DEX, panobinostat plus bortezomib plus dexamethasone; PAS, patient access scheme; POM+DEX, pomalidomide plus dexamethasone.										

Table 25: Revised cost breakdown by health state, without PAS

	Daratumumab		POM+DEX				PANO+BORT+DEX			
	DARA (vs PANO)	DARA (Vs POM)	POM+DEX	Incremental	Absolute Increment	% Increment	PANO+BORT+ DEX	Incremental	Absolute Increment	% Increment
Pre-Progression On Treatment	£80,327	£81,079	£49,901	£31,178	£31,178	100%	£72,992	£7,335	£7,335	90%
Pre-Progression Off Treatment	£71	£113	£99	£14	£14	0%	£0	£71	£71	1%
Post-Progression	£1,466	£1,646	£1,585	£61	£61	0%	£2,214	-£748	£748	9%
Terminal Costs	£789	£776	£811	-£35	£35	0%	£802	-£13	£13	0%
Total	**£82,654**	**£83,613**	**£52,396**	**£31,217**	**£31,287**	**100%**	**£61,438**	**£21,215**	**£21,215**	**100%**
Key: DARA, daratumumab; PANO+BORT+DEX, panobinostat plus bortezomib plus dexamethasone; PAS, patient access scheme; POM+DEX, pomalidomide plus dexamethasone.										

Table 26: Revised cost breakdown by health state, with PAS

	Daratumumab		POM+DEX				PANO+BORT+DEX			
	DARA (vs PANO)	DARA (Vs POM)	POM+DEX	Incremental	Absolute Increment	% Increment	PANO+BORT+ DEX	Incremental	Absolute Increment	% Increment
Pre-Progression On Treatment	£60,020	£60,771	£49,901	£10,870	£10,870	99%	£72,992	-£12,973	£12,973	94%
Pre-Progression Off Treatment	£71	£113	£99	£14	£14	0%	£0	£71	£71	1%
Post-Progression	£1,466	£1,646	£1,585	£61	£61	1%	£2,214	-£748	£748	5%
Terminal Costs	£789	£776	£811	-£35	£35	0%	£802	-£13	£13	0%
Total	**£62,346**	**£63,306**	**£52,396**	**£10,909**	**£10,979**	**100%**	**£61,438**	**£908**	**£908**	**100%**

Key: DARA, daratumumab; PANO+BORT+DEX, panobinostat plus bortezomib plus dexamethasone; PAS, patient access scheme; POM+DEX, pomalidomide plus dexamethasone.

Table 27: Revised QALY breakdown by health state

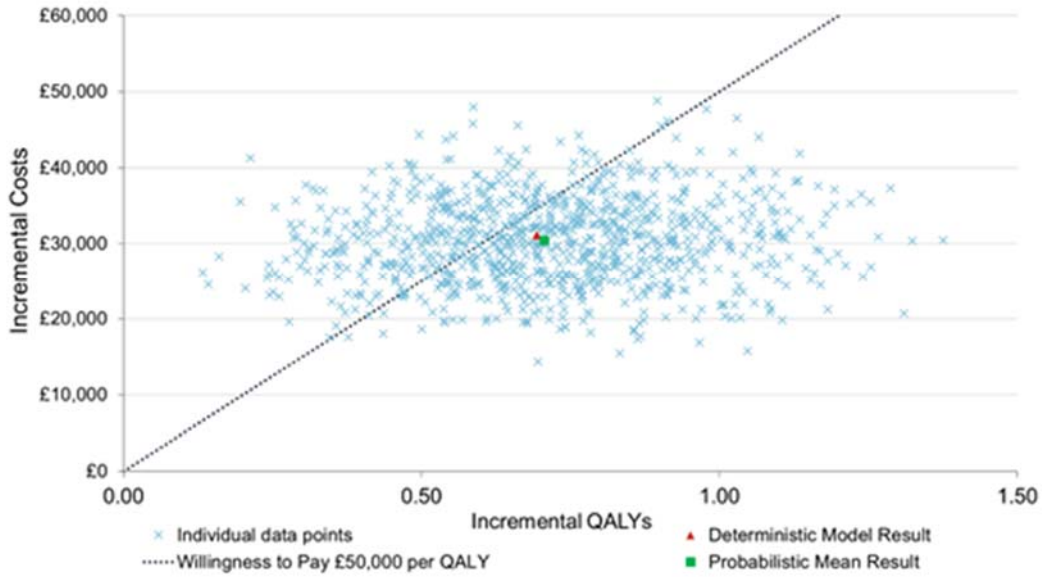
	Daratumumab		POM+DEX				PANO+BORT+DEX			
	DARA (vs PANO)	DARA (Vs POM)	POM+DEX	Incremental	Absolute Increment	% Increment	PANO+BORT+ DEX	Incremental	Absolute Increment	% Increment
Pre-Progression On Treatment	0.43	0.43	0.24	0.20	0.20	29%	0.38	0.05	0.05	16%

Pre-Progression Off Treatment	0.06	0.10	0.08	0.02	0.02	3%	0.00	0.06	0.06	21%
Post-Progression	0.78	0.95	0.51	0.44	0.44	63%	0.62	0.16	0.16	54%
AE	-0.04	-0.04	-0.08	0.04	0.04	5%	-0.07	0.03	0.03	8%
Total	**1.23**	**1.44**	**0.75**	**0.69**	**0.69**	**100%**	**0.93**	**0.30**	**0.30**	**100%**

Key: AE, adverse events; DARA, daratumumab; PANO+BORT+DEX, panobinostat plus bortezomib plus dexamethasone; PAS, patient access scheme; POM+DEX, pomalidomide plus dexamethasone; QALY, quality adjusted life year.

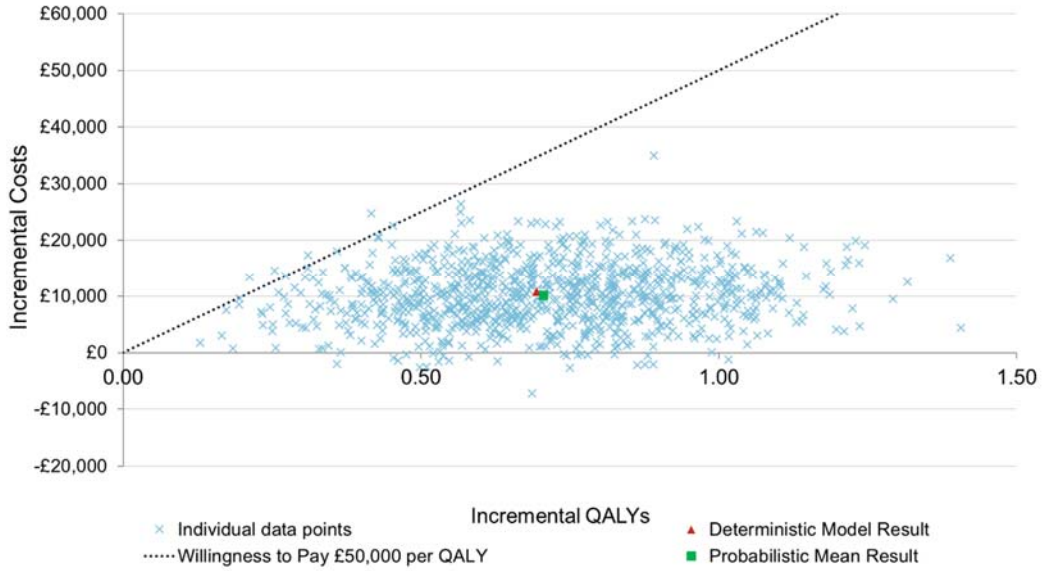
Appendix 6 PSA Scatter plots and CEACs

Figure 16: Revised PSA plot for daratumumab versus POM+DEX, without PAS



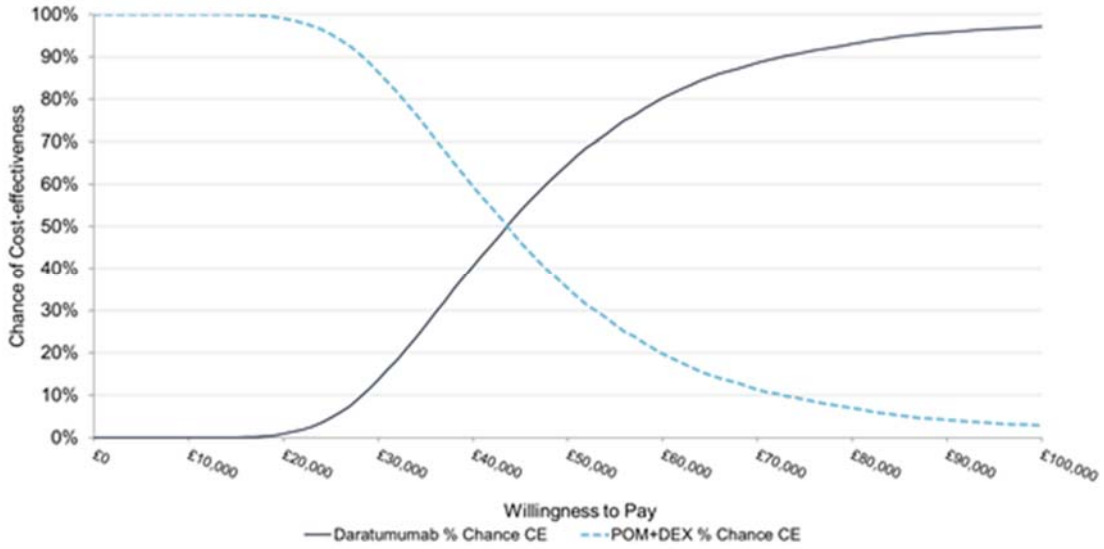
Key: PAS, patient access scheme; POM+DEX, pomalidomide plus dexamethasone; PSA, probabilistic sensitivity analysis; QALY, quality adjusted life year.

Figure 17: Revised PSA plot for daratumumab versus POM+DEX, with PAS



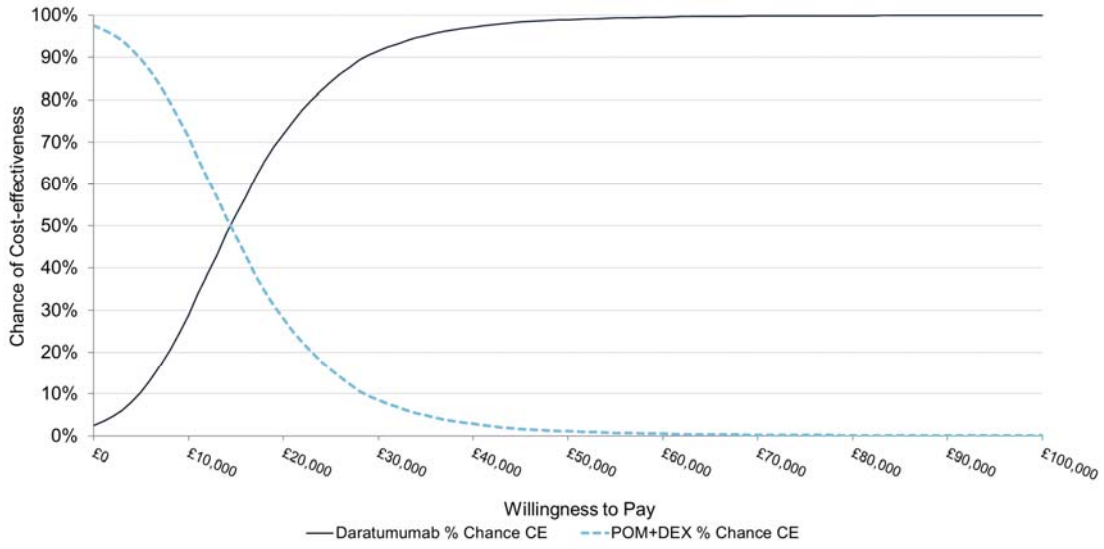
Key: PAS, patient access scheme; POM+DEX, pomalidomide plus dexamethasone; PSA, probabilistic sensitivity analysis; QALY, quality adjusted life year.

Figure 18: Revised CEAC for daratumumab versus POM+DEX, without PAS



Key: CE, cost-effective; CEAC, cost-effectiveness acceptability curve; PAS, patient access scheme; POM+DEX, pomalidomide plus dexamethasone; PSA, probabilistic sensitivity analysis.

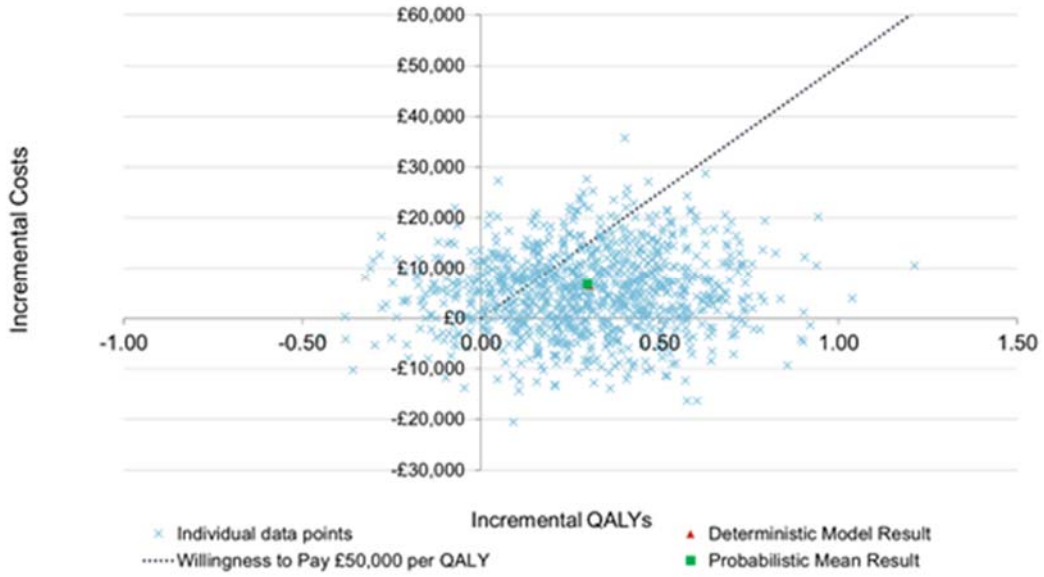
Figure 19: Revised CEAC for daratumumab versus POM+DEX, with PAS



Key: CE, cost-effective; CEAC, cost-effectiveness acceptability curve; DEX, dexamethasone; PAS, patient access scheme; POM, pomalidomide; PSA, probabilistic sensitivity analysis.

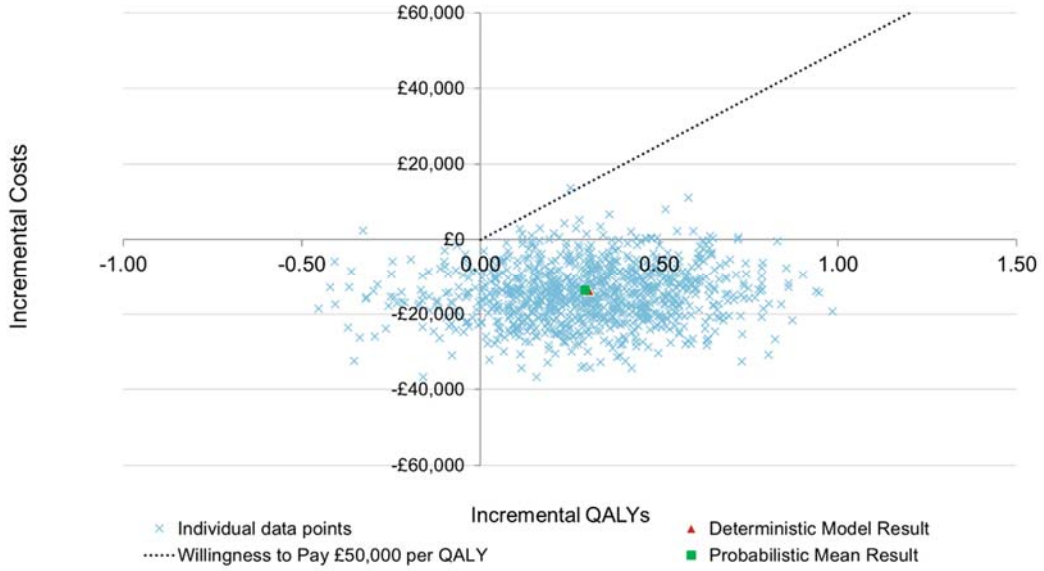
.

Figure 20: Revised PSA plot for daratumumab versus PANO+BORT+DEX, without PAS



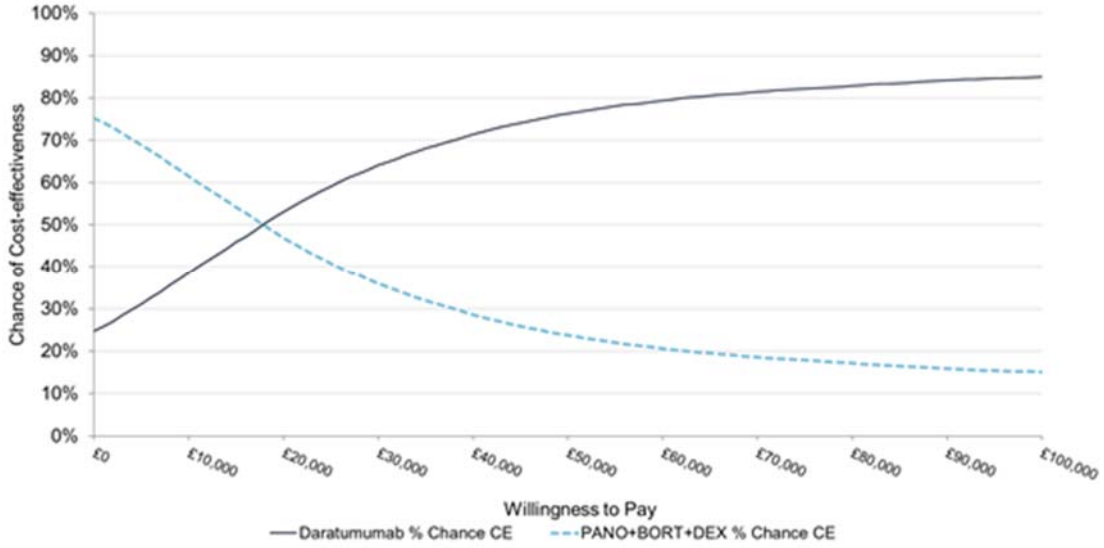
Key: PANO+BORT+DEX, panobinostat plus bortezomib plus dexamethasone; PAS, patient access scheme; PSA, probabilistic sensitivity analysis; QALY, quality adjusted life year.

Figure 21: Revised PSA plot for daratumumab versus PANO+BORT+DEX, with PAS



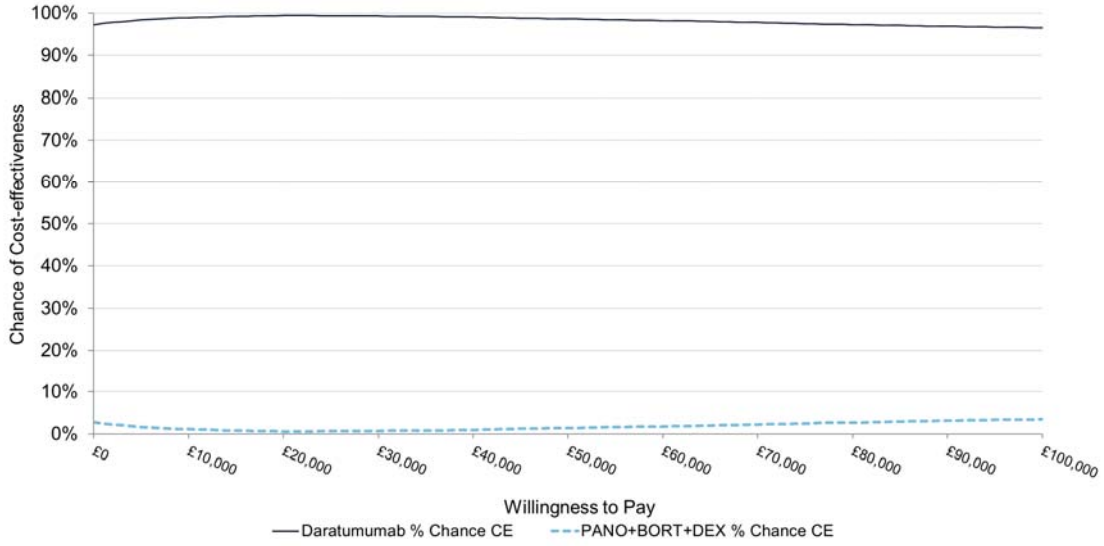
Key: PANO+BORT+DEX, panobinostat plus bortezomib plus dexamethasone; PAS, patient access scheme; PSA, probabilistic sensitivity analysis; QALY, quality adjusted life year.

Figure 22: Revised CEAC for daratumumab versus PANO+BORT+DEX, without PAS



Key: CE, cost-effective; CEAC, cost-effectiveness acceptability curve; PANO+BORT+DEX, panobinostat plus bortezomib plus dexamethasone; PAS, patient access scheme; PSA, probabilistic sensitivity analysis.

Figure 23: Revised CEAC for daratumumab versus PANO+BORT+DEX, including PAS



Key: CE, cost-effective; CEAC, cost-effectiveness acceptability curve; PANO+BORT+DEX, panobinostat plus bortezomib plus dexamethasone; PAS, patient access scheme; PSA, probabilistic sensitivity analysis.

Appendix 7 Factual Inaccuracies

One factual inaccuracy was found in the ACD and is highlighted in Table 28.

Table 28: Factual Inaccuracies

Description of problem	Description of proposed amendment	Justification for amendment
Page 9 of the ACD report states: "Thalidomide	This should be: "Thalidomide (MMY2002 44%, GEN501 45%)"	Factually inaccurate

(MMY2002 47%, GEN501 45%)”		

Myeloma UK response to NICE Appraisal Consultation Document (ACD) on daratumumab (Darzalex®) monotherapy – ID933

Introduction

Myeloma UK welcomes the opportunity to comment on the NICE ACD on daratumumab monotherapy. Whilst we understand the difficult role that NICE has in assessing new medicines, and that NICE cannot approve all new medicines it appraises, we are extremely disappointed by the negative decision reached on daratumumab monotherapy for relapsed and refractory myeloma patients.

Daratumumab is an extremely innovative new drug and there is global clinical and patient expert consensus on its potential to significantly improve survival rates in myeloma. To assist NICE in taking forward this appraisal, and to reach a positive opinion on this important innovation, we provide comments on the ACD below.

Systemic issues

The central issue in the draft ACD relates to the early phase nature of the clinical trial data, particularly given small patient numbers involved and the lack of comparative data. As NICE is aware, the early phase nature of the relevant clinical trials is a result of the drug being granted conditional approval by the European Medicines Agency (EMA) due to the effectiveness of the drug as a single agent and the significant benefit this was likely to offer for heavily pre-treated patients. The conditional approval is set to be expanded to full marketing authorisation pending the European Commission ratification of the EMA CHMP recommendation of daratumumab combination treatments. Alongside the daratumumab monotherapy trials, the Phase III data of both the Pollux and Castor studies collectively make a compelling case for the efficacy and clinical effectiveness of daratumumab across all stages of relapse in myeloma.

The inability of NICE to assess daratumumab monotherapy based on early phase data is to be expected, given the emphasis that health technology assessment (HTA) places on large Phase III randomised controlled trials. However, given this issue will increase in frequency due to regulatory and scientific changes, this appraisal has highlighted a need to further consider solutions and the disjoint between EMA regulatory and UK HTA data requirements. We understand the inability of NICE to tackle such systemic issues within the context of an ongoing appraisal. However, daratumumab monotherapy is an extremely important treatment for relapsed and refractory patients and we hope NICE will continue to work with the pharmaceutical company Janssen, Myeloma UK and the UK Myeloma Forum to provide a pragmatic solution to securing access.

If a solution cannot be reached, the Cancer Drugs Fund would also be a logical place to try and widen access to daratumumab whilst collecting more data on the use of the drug in clinical practice, particularly as it is given as a monotherapy. However, the lack of ICERs contained within the ACD have made it difficult for stakeholders to consider this a way forward for accessing daratumumab. We hope this situation will be addressed as we move forward with the appraisal.

Restating the clinical case for daratumumab

At the first NICE appraisal committee meeting, a strong case was made by the Janssen, alongside both clinicians and patient experts, on the importance of daratumumab monotherapy in the treatment of relapsed and refractory myeloma. Experience through clinical trials and use in

clinical practice (through the Expanded Access Programme [EAP]) have highlighted that it is a very effective myeloma treatment and one that all relevant stakeholders would value access to in the NHS. The NICE ACD reflects the case that was made for the drug and that the committee accepts the majority of points made. To support the NICE committee in reaching a positive conclusion in this appraisal, we would like to emphasise the following information:

- As a first-in-class monoclonal antibody, targeting CD38 expressing tumour cells, daratumumab is a highly innovative new drug and is one of the only treatments in myeloma to demonstrate effectiveness as a single agent, which is particularly important in such a heavily pre-treated population. As daratumumab is one of the most innovative drugs to come along for myeloma patients, it is unthinkable that patients in the UK may not be able to access it in this setting or in combination with other drugs

- Collectively, the clinical trial data for daratumumab monotherapy through MMY2002 and GEN501, alongside the Phase III clinical trials and the EAP highlight that daratumumab has a strong anti-myeloma effect and improves both progression free and overall survival. This additional time means improved emotional wellbeing for patients, additional time to spend with their family and to do the things they enjoy.

- To support the above point, the clinical trial data provided by Janssen highlights that daratumumab extends survival to the extent it meets the criteria required to meet the NICE end-of-life guidance

- UK haematology clinicians are clearly keen to have access to daratumumab for their patients, evidenced by the UK daratumumab EAP recruiting extremely quickly. The real-world use through the EAP demonstrates that daratumumab works well in the setting being appraised by NICE and that there is a clinical need for it. At Myeloma UK we continue to regularly receive calls to our Myeloma Infoline on how to access daratumumab in the relapsed and refractory setting. Patients have expressed their worry and concern that they may not be able to access this effective treatment on the NHS

- Aligning with the NICE recognised need for effective and well-tolerated treatment options, daratumumab monotherapy is a safe and effective treatment. Patients who have received it through clinical trials and the EAP, report that it had a good anti-myeloma effect, very little negative impact on their quality of life and ability to complete normal daily-activities. Daratumumab can also improve patient quality of life due to the good anti-myeloma effect and positive impact on the immune system

- As daratumumab is given as a single agent in this setting, this also helps to minimise the negative impact on quality of life, particularly as most patients report dexamethasone is a treatment that is detrimental to their quality of life. This is particularly important given the heavily pre-treated nature of the patient population we are discussing in the context of this appraisal

- To provide a conditional license, on the basis of Phase II clinical trial data, the EMA were convinced that the safety and efficacy data in favour of daratumumab monotherapy were compelling to the extent of providing early access across Europe. Whilst this has an obvious, and well-known, impact on the level of data supplied to NICE in this appraisal – it does demonstrate that European regulators and clinical experts agree that it is an important treatment for relapsed and refractory myeloma patients

- The ACD highlights that patients on MMY2002 and GEN501 had so few or many treatments compared to NHS practice. Whilst the trials may not align exactly to NHS practice, they do reflect the heterogeneous nature of myeloma and patient treatment pathways. The trials show daratumumab works in patients at various stages of relapse and patients receiving the drug through the EAP in clinical practice have demonstrated that it fits well into existing NHS treatment pathways. If NICE remained unconvinced on the levels of uncertainty relating to daratumumab monotherapy, and if the option of the CDF were to be on the table in this appraisal, further data could be collected to demonstrate how it works in the real-world setting

- To support the above point, patients participating in the MM2002 and GEN501 trials were actually more heavily pre-treated than the setting being considered by the appraisal. Responses to daratumumab monotherapy in clinical practice may therefore be better than those observed in the trials

Conclusions

- Despite understanding the issues with demonstrating comparative cost-effectiveness in this appraisal and the level of uncertainty, we are nonetheless concerned that the lack of ICERs presented in the ACD leave the myeloma community with nowhere to go to continue to develop the case for approving daratumumab monotherapy on the NHS given the levels of uncertainty that NICE have highlighted

- From working with the company over a number of years, we understand and support their willingness to work with NICE, UK clinicians and Myeloma UK to support the approval of daratumumab monotherapy for relapsed and refractory myeloma patients and also in wider combination settings. We hope the additional information submitted by stakeholders on the ACD provides NICE with the additional information they require to reach a flexible and pragmatic decision on daratumumab monotherapy and to assist patients accessing it on the NHS

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6th April 2017

To the Chair,

Regarding Daratumumab monotherapy for treating relapsed and refractory multiple myeloma [ID933]

On behalf of the UK Myeloma Forum we thank you for the opportunity to comment on the ACD. We urge the Appraisal Committee (AC) to reconsider the ACD recommendation. This decision is flawed as a result of perceived uncertainties and will have a direct detrimental effect on the morbidity and mortality of myeloma patients with relapsed and refractory disease where end of life criteria clearly apply and where further treatment options are extremely limited.

1. We acknowledge that the trial data presented to the appraisal committee was earlier phase than would normally be considered as part of an appraisal however, this is purely a result of the drug gaining accelerated approvals and licensing (including EMA conditional marketing authorization and FDA approval) due to its unprecedented single agent activity in the relapsed / refractory setting. Despite a number of new agents becoming available over the last decade for myeloma such early authorization in such heavily pretreated patients is unprecedented and a direct consequence of its significant life lengthening activity.
2. The ACD questioned whether the patient trial data available was generalizable to the UK population. We would highlight that the trial patient groups are, on the whole more heavily pre treated (up to 14 previous lines with over 100 having received >3 lines) than the UK target patient group. We also highlight that the vast majority of patients treated had been previously treated and were refractory to immunomodulatory drugs (lenalidomide, thalidomide, pomalidomide) and proteasome inhibitors (mainly bortezomib). This reflects the treatments that UK patients are likely to have received prior to consideration of Daratumumab, As a result of the extremely heavily pretreated nature of the trial reported patients it is likely that the outcomes observed in a less heavily pre-treated UK population would be better resulting in a comparative bias against Daratumumab monotherapy in the presented data.

3. It is notable that the progression free survival (PFS) seen in patients responding to Daratumumab as single agent is similar to that of either Bortezomib/dexamethasone or Lenalidomide/Dexamethasone combinations which are used earlier in the treatment pathway, this is exceptional for any single agent in this setting.
4. The ACD felt that there would be potential confounding of any OS advantage demonstrated by Daratumumab due to subsequent treatments. There is no evidence available to support this assertion and it seems highly unlikely that such a close OS association with response category would be seen if the benefit is due to other unnamed and unknown therapies. We highlight that there is accumulating evidence that in addition to anti-myeloma activity that Daratumumab also has immunomodulatory activity which will have significant clinical benefit unrelated to changes in the myeloma protein levels.
5. The ACD has questioned the innovative nature of Daratumumab. The agent is a first in class monoclonal antibody binding to CD38, has been designated a breakthrough medicine and selected for accelerated assessment. It possesses both direct and immunomodulatory actions not usually seen in agents directly targeting tumours in this manner and this undoubtedly contributes to its significant single agent efficacy. Worldwide in clinical and patient circles this drug is considered as game changing in myeloma. There has never been a clinically effective monoclonal antibody for myeloma. Additionally it is extremely well tolerated. Within the myeloma field this drug is considered to be one of the most innovative drugs introduced for myeloma in the last 15 years.
6. The ACD felt that the data did give sufficient certainty that Daratumumab would provide at least a three month increase in OS in a population of RRMM patients where the survival is accepted as less than two years. Over 60% of the patients treated with Daratumumab are alive after 31 months; this is unheard of in this setting. The degree of certainty regarding the relative benefit of Daratumumab is greater than that accepted in TA427 where Pomalidomide was assessed using EOL criteria.

Patient care and outcomes will suffer as a direct result of this negative ACD limiting the access to a novel, active and well tolerated therapy and will retard the significant progress that has been made on overall survival with this disease in the UK in the last 10 years.

We note that a recent Expanded Access Programme (MMY3010) study for Daratumumab monotherapy in this setting fully recruited in the UK extremely quickly demonstrating that there is a patient and clinician demand for access to what is the most exciting and innovative drug for myeloma in recent years.

The arguments made to reject this application are not sound and should be reconsidered. Daratumumab should be available for 4th line patients with relapsed and refractory multiple myeloma who have previously been treated with a proteasome inhibitor and an immunomodulatory agent and who have demonstrated disease progression on the last therapy. We urge the committee to reconsider this very poor decision which is likely to have an adverse impact on patient outcomes.

Thank you for the opportunity to respond to the ACD we hope that our comments are taken into consideration.

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Celgene Comments on the Appraisal Consultation Document (ACD) for Daratumumab Monotherapy for Treating Relapsed and Refractory Multiple Myeloma [ID933]

Celgene welcomes the opportunity to comment on the Appraisal Consultation Document (ACD) for Daratumumab Monotherapy for Treating Relapsed and Refractory Multiple Myeloma [ID933]. Celgene agrees with the Committee's decision not to recommend Daratumumab Monotherapy for Treating Relapsed and Refractory Multiple Myeloma.

Celgene has four areas of comment:

1. **Celgene considers that bendamustine, available as a treatment option at 4th line through the Cancer Drugs Fund (CDF), should be included as a comparator to reflect routine NHS practice and ensure consistency with a recent NICE appraisal**

Daratumumab monotherapy was submitted at 4th line, bendamustine is available as a treatment option at 4th line through the Cancer Drugs Fund (CDF). NICE have requested the inclusion of bendamustine as a relevant comparator in a recent HTA positioned at fourth line, considering it to form routine NHS practice at this point in the pathway. Therefore, Celgene considers it is inappropriate and inconsistent to exclude bendamustine as a comparator for the current appraisal.

At third relapse (fourth line) treatment would depend on previous treatments and response and toxicity to previous treatments. The available active therapies at fourth line currently are bendamustine based (via CDF)[1], pomalidomide plus dexamethasone (TA427)[2] and panobinostat plus bortezomib plus dexamethasone (TA380)[3].

In the ACD, the committee comment (Section 4.3):

'The committee concluded that, because daratumumab would be used after 3 previous treatments (see section 4.2), the appropriate comparators were pomalidomide plus dexamethasone, and panobinostat plus bortezomib plus dexamethasone'.

Bendamustine with thalidomide and dexamethasone was included as a relevant comparator in the recent NICE TA427[2] , for which Final Guidance was published in January 2017 and is available as a treatment option at 4th line through the CDF. The appraisal of pomalidomide plus dexamethasone (TA427)[2] overlapped with the ongoing appraisal of daratumumab monotherapy and clinical practice would not have changed during this timeframe. As bendamustine was deemed to be a relevant comparator, Celgene had to invest significant resource in accessing real world evidence (RWE) for bendamustine.

Celgene considers that, to ensure all relevant comparators are included, the submitting manufacturer should include bendamustine in a fully incremental analysis with the other identified comparators namely pomalidomide plus dexamethasone, and panobinostat plus bortezomib plus dexamethasone.

2. Celgene agrees with the Committee's decision that the treatments that patients in the trials had before Daratumumab Monotherapy was not reflective of routine NHS practice.

A number of treatments that the patients in the trials had before Daratumumab Monotherapy was not reflective of UK practice. Carfilzomib is not available in the NHS at this stage of treatment, and so people in NHS clinical practice would not have had it. Carfilzomib use prior to daratumumab in MMY2002[4] was 50% and in the GEN501[5] trial was 19%. Pomalidomide plus dexamethasone accounted for 63% of previous treatments in MMY2002[4] 63% and 36% in GEN501[5].

In ACD, the committee comment (Section 4.6):

'*NICE recommends pomalidomide plus low-dose dexamethasone, at third or subsequent relapse; that is, after at least 3 previous treatments including both lenalidomide and bortezomib. The committee agreed that, in clinical practice, people were unlikely to have had pomalidomide plus dexamethasone before daratumumab because both treatments were likely to be used after 3 previous treatments.*

The evidence review group (ERG) also stated (Section 4.6):

'pomalidomide plus dexamethasone is an alternative treatment option to daratumumab, it would be more appropriate to consider people who had not previously had pomalidomide plus dexamethasone as the relevant population'.

The committee agreed that, because some of the treatments that patients had previously had in MMY2002[4] and GEN501[5] differed from those used in clinical practice, the underlying survival trend of patients could also differ. Celgene agree with the committee's conclusion that the use of previous treatment that were not available in the NHS is a limitation of the evidence.

3. Celgene agrees with the Committee's decision that the subsequent treatments that patients in the trials had received was not reflective of routine NHS practice.

The committee noted that in MMY2002[4] and GEN501[5], treatments received after daratumumab monotherapy was not reflective of clinical practice.

In the ACD, the committee comment (Section 4.13):

'*dexamethasone, pomalidomide, cyclophosphamide, carfilzomib, bortezomib and lenalidomide, many of which were either not available in the NHS (for example, carfilzomib), or not available at this point in the treatment pathway (for example, lenalidomide and bortezomib)'*.

Celgene agrees that the treatments that patients had after daratumumab in MMY2002[4] and GEN501[5] did not represent what would be offered in the NHS.

4. Celgene considers that a disutility should be applied for daratumumab monotherapy in the model to capture the impact of the IV route of administration versus oral alternatives

The early phase trials presented by the company did not collect health-related quality of life data to estimate utility. In its absence, utility from the literature is used in the company base case.

In the ACD, the committee comment (Section 4.22)

'*The values chosen by the company to reflect the utility in the pre-progression and post-progression health states came from MM-003, which compared pomalidomide plus dexamethasone with dexamethasone only (Palumbo et al. 2013)*'.

The utility values used in the base case are based on the MM-003[6] trial which compares oral treatment in both arms of the trial. Daratumumab monotherapy is administered through IV infusion, where as other fourth line options such as pomalidomide plus dexamethasone are via oral administration. NICE has recognised that IV administration of treatment has been shown to have an associated disutility[2,7,8] which has not been applied to the utility estimates in the model for daratumumab, potentially overestimating the utility gain when compared to oral treatment options. The impact of applying a utility decrement for daratumumab in the model is not known and should be explored to assess the impact on cost-effectiveness.

Kind regards,

[redacted]

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Appraisal Consultation Document (ACD) - Draft

Daratumumab monotherapy for treating relapsed and refractory multiple myeloma

Comments from Barry Neville, Patient Expert at the Appraisal

1. I was diagnosed with myeloma in January 2012. Since then, I have received two separate treatments on two different Trials. I am now relapsing and will soon start a third line of treatment, the precise nature of which has yet to be determined.

2. In the 5¼ years since diagnosis, I have taken an interest in the many treatments available for patients. Like many other patients, I have been encouraged and excited by the possible availability of many new treatments, such as monoclonal antibodies and chimeric antigen receptors. As medical science has revealed greater and more complex knowledge and understanding about this enigmatic disease, the relevance of these new drugs, and the options available to clinicians for their patients, has increased. Daratumumab is one of these, and comes to England with a strong track record in the United States, where it has been accorded "breakthrough status" by the Food and Drugs Administration (USFDA). Additionally, the European Medical Agency (EMA) has given Daratumumab conditional approval as a single agent. Patients have been told by clinicians at Myeloma UK's Patient and Families InfoDays that Daratumumab is the closest that we have to a cure for myeloma.

3. Against such positive backgrounds, it was with a mounting sense of disappointment and frustration that I read the draft ACD. I had attended the Committee meeting in February hoping that Daratumumab would receive further endorsement. As yet, it is not to be. This will be a strong disappointment to patients. It is hard for me to understand the deep, systemic issues that have led to the committee's decision. Patients generally may well feel stronger emotions.

4. My initial reaction to the ACD was to make extensive comments on the systemic issues. These are, however, beyond NICE's sphere of current responsibilities. These systemic issues are admirably set out in Myeloma UK's (MUK) response to the ACD. I cannot better it. Rather than make those extensive comments, I will endorse MUK's response, subject to two additional comments below.

5. An apt epithet for the process of drug approval is that it is catching tomorrow's train with yesterday's timetable. NICE and its appraisal committees are here constrained by NHS England pathways that no longer match the realities of current myeloma treatment. At least one – and arguably both – of my two treatments to date has been outside the NHS pathway. Some 4,400 patients took part in my first Trial, 300 in my second. Yet, as I read the ACD, I got the feeling that evidence coming from these two Trials would not be considered as relevant in drug assessments because the Trials did not feature in the pathway. This would be ludicrous. That would be yesterday's timetable. It would also beg the question of why people like me participate in Trials if they do not advance knowledge and future technologies.

6. Whilst such a scenario continues to exist, patients will be largely confined to a pathway of drugs that, although effective in managing myeloma, are going to contribute to the build-up of toxicities in those patients. They are not a cure. Patients need to see, and to receive, a new generation of drugs that are closer to that cure and that minimize toxicities. We are in danger of seeing the paralysis of analysis that the pathway engenders. The pathway will remain a tail wagging the treatment dog.

7. On the credit side, the ACD has set out a series of analyses that the committee would like to see before approval is given. This gives a clear steer to Janssen (and will also be helpful to other drug companies seeking approval of their products). Such a steer might have been more useful if Janssen had received it before submitting their evidence. There could even have been discussions relating to the merits or otherwise of evidence drawn for the analysis of Daratumumab's performance against drugs not considered to be in the NHSE pathway, yet tried and trusted within other reputable jurisdictions.

8. With this steer in mind, I hope that Janssen will soon be able to bring forward fresh, more acceptable and sustainable evidence that substantiates the USFDA's awarding of "breakthrough status" to the drug, and EMA's conditional approval and that we patients will see it in clinic in England sooner rather than not at all.

9. Above all, however, and on behalf of patients – and to ensure that this is a truly patient-centred process - it is crucial that the systemic issues highlighted in the MUK response are addressed urgently.

Barry Neville
7th April 2017

Daratumumab for treating relapsed and refractory multiple myeloma [ID933]

ERG critique of the company's response to the Appraisal Consultation Document

This report was commissioned by the NIHR HTA Programme as project number 16/10/05

BMJ Technology Assessment Group

1 SUMMARY

This document critiques the company response to the Appraisal Consultation Document (ACD) for daratumumab monotherapy (hereafter referred to as daratumumab) for treating relapsed and refractory multiple myeloma (rrMM). The ERG had several theoretical and methodological concerns with the company's original submission. The subsections below list the ERG's original concerns with the company's analysis of clinical and cost-effectiveness of daratumumab compared with pomalidomide in combination with dexamethasone (pom+dex) and compared with panobinostat, bortezomib and dexamethasone (pano+bort+dex). Along with the list of the original issues raised by the ERG, a critique of the company's new analysis is presented, indicating if/to what extent the company's new analysis has mitigated the ERG's original concerns.

2 CLINICAL EFFECTIVENESS

2.1 Integrating data from MMY2002 and GEN501 Part 2

ERG's initial comment: The ERG acknowledged that MMY2002 and GEN501 Part 2 represent the best available evidence on daratumumab and also noted that the trials are associated with a high risk of bias that is inherent in observational studies. Considering the two studies separately, based on differences between the populations enrolled in the two studies, together with variation in study design, the ERG considered it inappropriate to simply combine the results from the two studies and subsequently chose to focus on results reported from MMY2002. Factors that led to the ERG's decision were:

- Comparison of baseline characteristics across MMY2002 and GEN501 Part 2 identified differences in characteristics associated with prognosis and outcome. Based on the median number of prior therapies (5.6 in MMY2002 vs 4.9 in GEN501 Part 2), and the proportion of people who were refractory to their last treatment (97.2% in MMY2002 and 76.2%), the ERG notes that people in MMY2002 are more heavily pre-treated and are more refractory to treatment than those in GEN501 Part 2.

- Information on ISS stage and cytogenetics, characteristics that are also associated with prognosis, were not recorded for GEN501 Part 2.

- Outcomes were captured at three time points in both MMY2002 and GEN501 Part 2. However, the same outcomes were not recorded at the same time points, with longer follow-up for ORR in GEN501 Part 2 compared with MMY2002.

- MMY2002 was designed and planned to record ORR, which GEN501 Part 2 was not (designed to evaluate safety).

The ERG recognised that with a median of 5.6 lines of prior therapy, the population in MMY2002 is likely to be more heavily pre-treated than those who would be eligible for treatment with daratumumab in the UK and the results are likely to be biased against daratumumab in that setting.

Company's response: The company comments that..."*The accelerated licensing of daratumumab means the evidence base available for HTA is limited when compared to what is normally available at time of marketing authorisation. As highlighted by the AC, it is important to make the best use of the available data. Integrating the data (by way of a simple pooling) from MMY2002 and GEN501 optimises use of the available evidence and is appropriate for the assessment of absolute outcomes. However, in this case, where data are pooled for the assessment of absolute outcomes from single arm trials, utilising both trials not only reduces uncertainty by increasing sample size, but increases the generalisability of trial outcomes to clinical practice*".

ERG's comment: The ERG agrees that increasing sample size and reducing uncertainty is favourable. However, the ERG considers that the principles of combining results from studies with more than one group for the purposes of a meta-analysis also applies to combining results for single-arm studies, in that, the studies must be sufficiently comparable in terms of patient populations to minimize bias and uncertainty associated with heterogeneity. The ERG considers that combining the results from MMY2002 and GEN501 Part 2 in this way compromises the generalisability of the results from the two individual studies rather than increasing the external validity of the results as a whole. Thus, the ERG maintains that the results from MMY2002 and GEN501 Part 2 should be considered separately as outlined in the ACD: "*Given the small sample size of the studies, and the limited data available, the committee agreed that it would be useful to use all available data. However, it concluded that pooling data was not appropriate because the populations in MMY2002 and GEN501 differed*".

2.2 Generalisability of populations in MMY2002 and GEN501

ERG's initial comment: The ERG considers that the patient population in neither MMY2002 nor GEN501 Part 2 fully reflects the population likely to be eligible for treatment with daratumumab in the UK.

Company response: The company commented that they consider..."*that the daratumumab trials are generalisable to UK clinical practice as patients in the daratumumab trials:*

- *are more relapsed and refractory than NHS patients;*
- *are of comparable fitness to NHS patients;*
- *have similar subsequent treatments available to that of NHS patients*".

ERG's comment: As noted in its original report, the ERG agrees with the company that, with a median of 5.6 and 4.9 lines of prior therapy, respectively, the population in MMY2002 and GEN501 Part 2 are likely to be more heavily pre-treated than those who would be eligible for treatment with daratumumab in the UK and the results are likely to be biased against daratumumab in that setting.

The ERG also raised concerns around the differences between MMY2002/GEN501 Part 2 and UK clinical practice in treatments received prior to enrolment and on disease progression. In terms of previous treatments, the ERG raised that people in MMY2002 and GEN501 Part 2 had received prior treatment with interventions to which people in the UK did not have access. The ERG also noted that, based on number and type of prior therapies received, the population of GEN501 Part 2 is more closely aligned with the population who would most likely be eligible for daratumumab therapy in the UK. The company comments in their response to the ACD..."*The fact that patients in MMY2002 and GEN501 received prior treatment with medicines not available in the NHS is due to the disparity in access to new medicines between the UK and the rest of Europe and the US*". The ERG acknowledges that differences in prior treatments, and treatments received post progression, have arisen because of site location and maintains that the impact of previous treatment on response to daratumumab in unclear. The same comment also applies to treatments received post disease progression. The issues around subsequent treatment are discussed in more detail in subsequent sections.

2.3 Results from MMY2002 and GEN501 Part 2

2.3.1 Overall response rate

In the response to the ACD, the company highlights the overall response rate (ORR) associated with the licensed dose of daratumumab achieved in GEN501 Part 2 of 37%. The ERG agrees that this is a high ORR for a monotherapy. The company goes on the comment that..."*To put this in context [the ORR], other recently licenced therapies have been approved as combinations rather than as single agents, as the ORRs seen with these therapies, when used as monotherapies, did not come close to this figure*". The ERG agrees that perhaps other monotherapies do not achieve this level of tumour response. However, the interventions of interest to the decision problem are combination regimens, and the ORRs reported for the combination treatments are similar to that of daratumumab in GEN501 Part 2 and higher than that for daratumumab in MMY2002 (29.2%). In PANORAMA 2, pano+bort+dex was associated with an ORR of 34.2% and pom+dex a response rate (partial response or better) of 31.4% in MM-003. In the context of ORR, the ERG reiterates guidance from the FDA that ORR is an indicator of anti-tumour activity and does not necessarily relate to disease stability or prognosis. The ERG emphasises that conclusions on comparative effectiveness cannot be drawn as data are derived from a single arm in each study.

2.3.2 Overall survival

ERG's initial comment: The ERG highlighted that it considered the overall survival (OS) estimate for daratumumab monotherapy to be confounded by treatments received post progression.

Company response: The company's view is that benefit in OS can be attributed to daratumumab and that it is important to distinguish between people receiving daratumumab who:

- did not respond, and quickly died;
- initially responded to daratumumab, progressed and are now receiving subsequent treatment;
- responded to daratumumab and are still receiving daratumumab.

ERG's comment: The variation in OS across the three subgroups described above was not the focus of the company's original submission. Although the ERG agrees with the company that these subgroups are of interest, it also considers that, to address the question of relevance to the decision problem, if data are available, it would be important to consider equivalent subgroups for the comparators of interest, pom+dex and pano+bort+dex. Due to time constraints, the ERG was unable to investigate whether data on similar subgroups are available for all interventions of interest to the decision problem.

The company goes on to state that..."*in light of the single-agent efficacy observed in early phase trials, it would have been unethical to conduct a Phase III trial of daratumumab versus a comparator such as high-dose dexamethasone*". The ERG disagrees with this statement. Given the clinical equipoise around the effectiveness of daratumumab monotherapy versus an active comparator, the ERG considers that a well-designed RCT would generate robust evidence on the clinical effectiveness of daratumumab as a monotherapy. The ERG agrees it would be unethical to use a comparator that has been supplanted by more effective treatments (i.e. high dose dexamethasone).

The ERG's response to the company's comments on treatments received on progression in MMY2002 and GEN501 Part 2 is given in Section 3.

2.3.3 More mature OS data

The ACD noted that..."*...the data on overall survival were immature, with over 40% of patients alive at the end of the trials"*. In the response to ACD, the company presents more mature OS data, with an additional 10 months of follow up (summarised in Table 1): median follow-up of the integrated dataset was 31.31 months.

The company draws attention to..."*the substantial OS benefit conferred in patients who respond to daratumumab and in patients whose disease is stabilised as a result of daratumumab*". The ERG agrees

that median OS in those responding to treatment or with minimal response or stable disease is longer than those with disease progression or not estimable. As noted earlier, for context of the decision problem, the ERG considers it important to compare the equivalent subgroups for the comparators of interest to this STA (pom+dex and pano+bort+dex).

The ERG notes that median OS has been reached in MMY2002 but not in GEN501 Part 2. Median follow-up in the two studies is similar (31.31 months for MMY2002 vs 31.77 months for GEN501 Part 2). Given the comparable length of follow-up for the two studies, the ERG considers the finding that the median OS in MMY2002 (18.60 months) is close to the lower limit of the confidence interval for median OS in GEN501 Part 2 (19.91 months) suggests that there are key differences between the two trial populations that is influencing response to daratumumab and supports the ERG's position that it is inappropriate to integrate the results from the two studies.

Table 1. OS as of November 2016

	MMY2002	GEN501	Integrated analysis	Responders	MR or SD	PD or NE
	(n=106)	(n=42)	(n=148)	(n=46)	(n=77)	(n=25)
Median OS, months (95% CI)	18.60 (13.67, 25.00)	NE (19.91, NE)	20.47 (16.62, 28.06)	NE (29.21, NE)	18.46 (15.08, 22.41)	3.71 (1.68, 7.59)
Number of events, n (%)	67 (63.2%)	19 (45.2%)	86 (58.1%)	17 (33.3%)	48 (44.0%)	21 (58.3%)
6 month OS rate, % (95% CI)	81.8 (73.0, 88.0)	88.1 (73.7, 94.9)	83.6 (76.5, 88.7)	100.0 (100.0, 100.0)	86.6 (76.5, 92.6)	44.0 (24.5, 61.9)
12 month OS rate, % (95% CI)	64.7 (54.5, 73.1)	78.6 (62.9, 88.2)	68.7 (60.5, 75.6)	95.6 (83.4, 98.9)	68.4 (56.4, 77.8)	20.0 (7.3, 37.2)
18 month OS rate, % (95% CI)	51.3 (41.1, 60.6)	69.0 (52.7, 80.7)	56.5 (47.9, 64.2)	86.7 (72.7, 93.8)	51.1 (38.9, 62.0)	16.0 (5.0, 32.5)
24 month OS rate, % (95% CI)	40.5 (30.7, 50.1)	59.3 (43.0, 72.4)	46.1 (37.7, 54.1)	75.4 (60.0, 85.6)	37.5 (26.2, 48.7)	16.0 (5.0, 32.5)
30 month OS rate, % (95% CI)	32.9 (23.7, 42.3)	56.6 (40.3, 70.1)	40.0 (31.7, 48.0)	63.9 (48.0, 76.1)	32.6 (21.8, 43.8)	16.0 (5.0, 32.5)

Key: CI, confidence interval; MR, minimal response; NE, not evaluable; OS, overall survival; PD, progressive disease; SD, stable disease.

Source: Janssen 2017 (Updated OS)[21]

2.4 Comparative effectiveness

2.4.1 Results from CASTOR and POLLUX

In their response to the ACD, the company reports results from two Phase III RCTs that are evaluating the clinical effectiveness of daratumumab in combination with lenalidomide and dexamethasone (len+dex; POLLUX) and with bortezomib plus dexamethasone (bort+dex; CASTOR). The company comments that..."*The absolute effectiveness of daratumumab has been demonstrated in patients who responded to treatment in MMY2002 and GEN501. In MMY2002/GEN501, median PFS in responding patients was 15 months (7.4-not evaluable [NE]), with median OS not reached [figures not presented*

in ERG response]." Here, the company has focused on the subgroup of responders. For completeness, the ERG notes median PFS for the full populations of the key studies (MMY2002 and GEN501 Part 2) and the key comparators relevant to the decision problem:

- 3.7 months for MMY2002;
- 6.2 months for GEN501 Part 2;
- 5.4 months for pano+bort+dex;
- 4.0 months for pom+dex.

The ERG emphasises that conclusions on comparative effectiveness cannot be drawn from PFS results as data are derived from a single arm in each study. In addition, the FDA advises that a single-arm study design is not appropriate to capture time to event outcomes.

CASTOR and POLLUX both enrolled people with rrMM who had received at least one prior line of treatment and, as highlighted by the company, the populations are less heavily pre-treated than would be eligible for treatment with daratumumab monotherapy in UK clinical practice. The company reports that..."*Median PFS of daratumumab used earlier in the treatment pathway in combination with lenalidomide and dexamethasone or bortezomib and dexamethasone has not been reached; whereas median PFS in patients treated with lenalidomide plus dexamethasone and bortezomib plus dexamethasone was 18.4 months and 7.2 months, respectively [figures not presented in ERG response]. The fact that median PFS in responding patients in MMY2002/GEN501 is similar to PFS in patients treated with either lenalidomide plus dexamethasone or bortezomib plus dexamethasone earlier in the treatment pathway is remarkable*". The ERG advises interpreting the results in the subgroup of responders from MMY2002/GEN501 Part 2 with caution as comparable information on responders in MM-003 (evaluated bort+dex) and PANORAMA 2 (evaluated pano+bort+dex) has not been assessed in the context of the decision problem.

2.4.2 Effect estimates from MAIC

ERG's initial comment: To address the lack of evidence from RCTs on comparative effectiveness of daratumumab, the company carried out a MAIC comparing daratumumab versus the identified relevant comparators of pom+dex and pano+bort+dex for PFS and OS. The company followed reported methods. The ERG's preferred dataset from the MAIC differs from that of the company. Based on guidance from the Decision Support Unit [DSU], the ERG considers the most adjusted dataset to be the most appropriate, which included adjustment for ISS and cytogenetics and was therefore based on MMY2002 alone as baseline information on ISS and cytogenetics was not collected in GEN501.

The ERG advised that the results of the MAIC be interpreted with caution. The most adjusted sets had small effective sample sizes, which indicates poor overlap between studies and that the estimates were likely to be unstable. In addition, there was considerable uncertainty around the results, as illustrated by the change in direction of effect within some MAIC with number of characteristics adjusted for and the wide 95% CIs.

Company comment: "*...Janssen agrees with the AC that it is important to make full use of available data, particularly in relation to an HTA based on accelerated licensing where the evidence base is limited. Pooling data from MMY2002 and GEN501 makes full use of the available daratumumab data and serves to reduce uncertainty through the increased sample size and increased generalisability. In addition, utilising these integrated data increases the degree of similarity (or overlap) between datasets used to inform comparative effectiveness. The greater the degree of overlap, the less uncertainty there is in estimates of comparative effectiveness*".

The company goes on to state... "*Janssen acknowledges that the few baseline characteristics missing from GEN501 means that not all characteristics available in MMY2002 can be adjusted for. As such, sensitivity analysis has been carried out to assess the impact of these missing characteristics on the comparison with POM+DEX. Similar to the methods recommended by the AC in the appraisal of abiraterone for treating metastatic hormone-relapsed prostate cancer before chemotherapy is indicated (TA387), this analysis imputed the missing data for GEN501 using the relationship between all available characteristics. Fully adjusted MAIC was then carried out using the imputed data for GEN501*".

ERG's comment: The ERG could not identify the methods recommended by the AC in abiraterone Technology Appraisal (TA: TA387) for imputing missing data. The ERG noted a comment by the ERG for the TA: "*The manufacturer argued that the ITT population could not be used for estimating prediction equations because for a number of patients baseline data were missing. However, this approach introduced bias in favour of AAP for both TTD and OS (as OS is dependent on TTD). The ERG would have preferred an approach in which the prediction equations are based on the total ITT population and imputing any missing baseline data or to use only treatment as a covariate*". The ERG did not identify guidance on the methods to be used.

The ERG acknowledges that the company has attempted to adjust for unknown characteristics but considers the adjustment to be flawed. The premise of the MAIC assumes that variables are independent from each other. Imputing missing data based on observed data introduces dependency into the analysis.

The company references Rubin's multiple imputation procedure as the method followed for generating missing values and provides details on the variables included in the imputation and the number of generated imputed datasets. However, the assumptions around the type of analysis are unclear, that is,

whether data were considered missing completely at random, missing at random, or missing not at random. The ERG has reservations around the robustness of the results of the MAIC including imputed data because of the similarity of the effect estimate generated to those of the company's original analyses, given the considerable variation in effect estimate with number of characteristics adjusted for in the original analysis, as reported in the ERG report. A publication reviewing multiple imputation recommends that results also be provided for analyses restricted to complete cases.[1] The ERG provides results from analysis of complete cases in Table 2.

Aside from the ERG's reservations around the MAIC adjusting for missing baseline characteristics, the ERG maintains that it is inappropriate to combine results from MMY2002 and GEN501 Part 2 and considers the results based on data from MMY2002 alone to be the most appropriate. The ERG summarises results from the ERG's preferred dataset, the company's original analyses, and the MAIC including imputed data in Table 2.

Table 2. Summary of OS and PFS from MAIC

	Pom+dex HR (95% CI)	**Pano+bort+dex HR (95% CI)**
ERG's preferred dataset		
PFS	1.14 (0.64 to 2.03)	0.85 (0.39 to 1.88)
OS	0.88 (0.44 to 1.77)	0.61 (0.25 to 1.45)
Company's preferred dataset (submission)		
PFS	0.84 (0.52 to 1.37)	1.09 (0.74 to 1.61)
OS	0.57 (0.41 to 0.81)	0.81 (0.60 to 1.09)
MAIC including imputed data		
OS	0.56 (0.38 to 0.83)	0.76 (0.44 to 1.30)
Abbreviations: CI, confidence interval; ERG, Evidence Review Group; HR, hazard ratio; MAIC, matching-adjusted indirect comparison; OS, overall survival; Pano+bort+dex, panobinostat plus bortezomib plus dexamethasone; PFS, progression-free survival; Pom+dex, pomalidomide plus dexamethasone.		

3 COST-EFFECTIVENESS

This section is structured to present the issues originally raised by the ERG about the company's cost-effectiveness analysis of daratumumab compared with pom+dex and pano+bort+dex, followed by a summary of the company's post-ACD analysis and finally a critique of the latter. Considering the very limited time period that the ERG had available to review the new evidence submitted by the company, and the substantial amount of new evidence submitted (a new economic model, with a new approach to the estimation of clinical effectiveness), the ERG had to prioritise its review. For the purpose of transparency, the ERG lists all the issues originally raised upon the company's original submission, and explicitly points to the ones that were either not addressed by the company, or those that the ERG did not have time to review during the review period.

3.1 Quality assurance of economic model

a) **ERG's initial issue:** The ERG had serious concerns with the robustness of the economic analysis undertaken by the company as it encountered several errors and discrepancies in the different versions of the economic model, CS and data forward by the company to the ERG after the clarification stage. It was the ERG's opinion that the company's model and data analysis needed further internal consistency checks and a thorough quality check before a robust ICER could be determined for daratumumab.

b) **Company's response:** In their response to the ACD, the company reports that the model was quality-assured using the internal processes of the vendor who built the model and by a vendor not involved in the original model build. It adds that the model was reviewed for coding errors, inconsistencies, and the plausibility of inputs and that all parametric models were refitted using the same (monthly) time scale, to allow comparison of goodness-of-fit across all parametric models.

c) **ERG's comment:** The ERG did not have time to quality-assure the company's new economic model in terms of formulae used and data implementation processes.

3.2 Pre-treatment with pomalidomide

a) **ERG's initial issue:** As part of the original request for clarification, the ERG requested the daratumumab adjusted and unadjusted OS, PFS and TTD KM data excluding pomalidomide pre-treated patients for the integrated data and for the MMY2002 and for the GEN501 trials separately. The ERG found inconstancies in the data provided by the company which meant that these data could not be guaranteed to reflect the pomalidomide naïve OS, PFS and TTD curves. Even though the ERG lacked confidence in the validity of the data sent through by the company at the clarification stage, analysis of the data trends suggested that there was no difference in PFS across pom-naïve and non-pom-naïve patients and that OS outcomes were better for pom-naïve patients than for the overall trial population. The ERG interpreted this trend in the data as a possible consequence of the effect of pomalidomide as a subsequent therapy. It hypothesised that given that pre-treatment with pomalidomide did not seem to influence PFS, the considerable difference in the OS curves across the pom-naïve and the overall trial population was due to the effect that pomalidomide would have as a subsequent treatment in the pom-naïve patients, compared to the effect that pomalidomide would have as a subsequent treatment in patients pre-treated with pomalidomide. Unfortunately the ERG could not validate this hypothesis given the uncertainty around the data and the fact that

company did not provide the OS KM curve for patients subsequently treated with pomalidomide, despite the ERG's request for such data.

b) **Company's response:** The company did not submit any new data to mitigate the original concerns raised by the ERG.

3.3 Subsequent treatments received in MMY2002/GEN501

a) **ERG's initial issue:** The ERG was concerned with the highly confounded OS estimates in the company analysis. The ERG considered that the evidence put forward by the company was not robust enough to determine the cost-effectiveness of daratumumab monotherapy alone and that the effectiveness of daratumumab needed adjusting for the impact of subsequent therapies currently not available in the UK. This issue is particularly important given the lack of RCT data for daratumumab. While in theory this confounding effect might also apply to the comparator treatments, as pom+dex and pano+bort+dex patients could receive subsequent therapies in MM-003 and PANORAMA2, respectively, the ERG's investigation showed that the risk of OS confounding for pom+dex patients was likely to be considerably smaller than for daratumumab patients. This is related with the fact that 72% of patients in MMY2002/GEN501 received subsequent therapies, while the corresponding estimate for MM-003 was 44%, but more importantly, the fact that in MM-003 patients received carfilzomib, lenalidomide and bortezomib in much smaller numbers than in MMY2002/GEN501 (2% vs 28% for carfilzomib; 5% vs 15% for lenalidomide and 18% vs 24% for bortezomib – Table 3). Daratumumab patients also received pomalidomide (31%) while pom+dex patients did not receive any pomalidomide (or daratumumab) after the main treatment in MM-003. As discussed in the ERG's original report, treatment with carfilzomib and retreatment with lenalidomide and bortezomib are not available in the UK and are likely to considerably increase overall survival as subsequent therapies for rrMM patients (Figure A).

Table 3. Subsequent treatments received in daratumumab trials and in MM-003

Subsequent treatment	Proportion of MMY2002/GEN501 patients	Proportion of MM-003 patients[85, 140]
Dexamethasone	58%	29%
Pomalidomide	31%	0%
Cyclophosphamide	32%	21%
Carfilzomib	28%	**2%**
Bortezomib	24%	18%
Lenalidomide	15%	**5%**
Melphalan	16%	**8%**
Etoposide	10%	**3%**
Bendamustine	14%	11%
Thalidomide	7%	**7%**

Values in bold are from a cut-off date of March 2013 while the other values are from a more up to date cut-off point of September 2013

b) **Company's response:** The company presented the following arguments, which the ERG briefly summarises below.

   i. Presentation of market share data on the use of subsequent rrMM therapies not reimbursed by the NHS in the UK;

   ii. The existence of an "immortality bias" in the ERG's requested analysis of OS by subsequent treatment as patients are required to live long enough to receive subsequent treatment. The company also refers to a selection bias, as patients are being indirectly selected on the outcome of treatment with daratumumab. The company also notes the heterogeneity between the patients within each subsequent treatment subgroup. For example, in the subgroup of patients receiving bortezomib as a subsequent treatment, some patients will have received bortezomib directly after daratumumab, whereas others will have received bortezomib at a later stage. In addition, bortezomib may have been received as a monotherapy or as a combination therapy, as a fourth line treatment or as a seventh line treatment. The company concludes that the OS analysis requested by the ERG (separating patients who received subsequent treatment from those who did not) falsely implied that any survival benefit is derived from subsequent treatments, as opposed to daratumumab;

   iii. The company reports that MMY2002/GEN501 patients refractory to bortezomib, lenalidomide or thalidomide (n=21) had an ORR, when treated with the same treatment to which they were refractory, of 38%. As a comparison, ORR to bortezomib, lenalidomide or thalidomide in IMF patients who were refractory to a PI and an IMiD was [redacted]. The company considered that this supports the hypothesis that daratumumab enhances patients' response to subsequent treatments and contends that the benefit of subsequent treatment is a result of treatment with daratumumab rather than a confounding factor in estimates of effectiveness;

   iv. The company considers that the fact that more patients received subsequent treatments in MMY2002/GEN501 than in MM-003 is evidence of daratumumab's novel MoA which allows more patients to receive and benefit from subsequent treatments compared to patients receiving pom+dex.

c) **ERG's comment:** The ERG considers that the company has not submitted any evidence capable of mitigating the original concerns related with a highly confounded OS estimate in the

analysis of daratumumab's survival benefit. Clinical expert opinion sought by the ERG indicates that while it seems plausible that daratumumab's favourable safety profile allows patients to be able to tolerate further treatment lines, thus resulting in more patients being able to receive subsequent treatments, there are no data proving or indicating that daratumumab, "increases the likelihood of patients benefiting from subsequent therapy". This means that while it would be plausible that daratumumab allows more patients to benefit from subsequent therapy (which in itself is a benefit) there is no evidence that it increases the effectiveness of the subsequent therapies given.

The fact that more patients received subsequent treatments in MMY2002/GEN501 than in MM-003 has no scientific substantiation to be considered as evidence of daratumumab's benefit. The company is hypothesising a causal relationship that has not been supported by any data or analysis indicative of such relationship. The ERG's consideration that OS in MM-003 is less likely to be confounded by the impact of subsequent therapies, relies on the factual observation that less patients (44%) received subsequent treatments in MM-003, which are not available in the NHS than in MMY2002/GEN501, where 72% of patients received subsequent therapies, the majority of which are not currently available through the NHS.

The ERG considers the substantial difference between the estimated large survival benefit associated with daratumumab and the small (if any) gain in progression-free survival of daratumumab is likely to be related to the impact of subsequent treatments received on patients' survival. While the ERG understands that the benefit of daratumumab might be that it allows more patients to receive subsequent therapies, if there are no treatment options left for patients at the point daratumumab is given in the clinical pathway reimbursed by the NHS, then the benefit of daratumumab remains an unrealised benefit. Positioning daratumumab as a fourth-line treatment option for rrMM patients means that, in the current NHS, patients would only have pom+dex, pano+bort+dex and BSC regimens (including bendamustine) left after treatment with daratumumab. To note is that pom+dex and pano+bort+dex are the relevant comparators in this STA, and that 67% of daratumumab patients were pre-treated with pom+dex and that 31% of patients also received pom+dex as a subsequent treatment after daratumumab in the MMY2002/GEN501 trials (Table 4).

Table 4. Type of susbsequent treatment reported by the company

Subsequent treatment	MMY2002 patients (n=106) (CS)	GEN501 patients (n=42) (CS)	Integrated (n=148) (CS)	Integrated (n=148) (Reply to ERG clarification question A6)
Patients undergoing subsequent treatment	75 (71%)	32 (76%)	107 (72%)	104 (70%)
Dexamethasone	60 (57%)	26 (62%)	86 (58%)	Not reported

Pomalidomide	34 (32%)	16 (38%)	50 (34%)	46 (31%)
Carfilzomib	31 (29%)	11 (26%)	42 (28%)	41 (28%)
Bortezomib	27 (26%)	9 (21%)	36 (24%)	36 (24%)
Lenalidomide	8 (8%)	15 (36%)	23 (16%)	22 (15%)

During the original clarification process, the ERG asked the company to provide OS estimates, together with KM data, for the different subgroups of patients receiving the following subsequent treatments:

- Bortezomib;
- Carfilzomib;
- Lenalidomide;
- Pomalidomide;
- No subsequent treatment at all.

The company replied with the OS estimates reported in Table 5. These compare with a median integrated OS for daratumumab of **20.1 months (CI; 16.6; not reached)**. To note is that the median OS for daratumumab includes the effect of patients receiving further treatment lines. The median OS for patients receiving no subsequent treatment and patients receiving any subsequent treatment in MMY2002 is [redacted] (with the caveat that there is no HR provided or analysis of statistical significance). Importantly, subsequent treatment could include other treatments such as autologous stem cell transplant. Figure A shows the KM curves produced by the ERG with the data provided by the company on OS for patients receiving subsequent treatments for rrMM after daratumumab. The company did not provide the KM data for patients subsequently treated with pomalidomide as requested by the ERG and did not provide such data upon reply to the ACD. Figure A suggests that patients receiving subsequent treatments do considerably better in terms of survival than patients receiving no subsequent treatments after daratumumab. It is difficult to predict where the pomalidomide curve would appear in the graph, but it is known that the median survival is [redacted] (showing all patients who received any subsequent treatment, which could include treatments beyond the ones portrayed here). Patients receiving carfilzomib and lenalidomide seem to do extremely well compared with other patients.

Of note, the only treatment combination that would be available for patients in the NHS (daratumumab followed by pom+dex), has the [redacted] median survival as the MMY2002/GEN501 overall population.

Table 5. Estimates of OS from post-hoc subgroup analysis

Dataset	Subgroup	Median OS (95% CI)	Sample size
Integrated	Bortezomib as a subsequent treatment	[redacted]	[redacted]
	Carfilzomib as a subsequent treatment	[redacted]	[redacted]
	Lenalidomide as a subsequent treatment	[redacted]	[redacted]
	Pomalidomide as a subsequent treatment.	[redacted]	[redacted]
	Overall population	20.1 (CI; 16.6; NE)	N=148
MMY2002	No subsequent treatment	[redacted]	[redacted]
	Any subsequent treatment.	[redacted]	[redacted]
GEN501	No subsequent treatment	[redacted]	[redacted]
	Any subsequent treatment.	[redacted]	[redacted]

Key: CI, confidence interval; NE, not evaluable; OS, overall survival.

[redacted]

[redacted]

3.4 Statistical approach undertaken by the company to model survival outcomes:

a) **ERG's initial issue:** The ERG had several concerns with the company's statistical approach to the economic analysis. The ERG disagreed with the company's assessment of proportional hazards (PH) for OS data and thus with the company's modelling approach. The ERG was also concerned with the validity of the curve fitting exercise undertaken by the company for OS data, as some of the OS extrapolated curves by the company differed considerably from the ones obtained by the ERG.

The ERG's preferred approach would have been to use the independently fitted curves, however using the MAIC fully adjusted daratumumab curves for OS and PFS compared with unadjusted pom+dex and pano+bort+dex curves. This would have entailed using the MMY2002 dataset. The company provided the ERG with these data (i.e. the fully MAIC-adjusted OS and PFS KM curves for daratumumab for MMY2002) at the clarification stage. Analysis of the fully adjusted KM curves led to important conclusions:

- The number of characteristics included in the MAIC adjustment drastically changed the positioning of the daratumumab OS adjusted KM curves in relation to pom+dex (and to a less but also important extent) in relation to pano+bort+dex. In fact the fully adjusted, 28-characteristic-adjusted OS curve for daratumumab showed a lower survival benefit with daratumumab compared with pom+dex before month 10, and a modest benefit after that point in time (Figure C). This was a major departure from the 11-characteristic-adjusted OS curve (used in the company's original base case to extrapolate survival curves for daratumumab), which crosses the pom+dex curve at month 4, to then show an impressive survival benefit compared with pom+dex (Figure C). This represented an even bigger departure from the dependent fit approach (company's base case) where the daratumumab OS curve was consistently above the pom+dex OS curve (Figure B). Conversely, the 5-characteristic-adjusted OS curve for daratumumab vs pano+bort+dex seemed to underestimate the survival benefit for daratumumab when compared with the fully adjusted, 16-characteristic-adjusted OS curve.

  The ERG was concerned with the crucial implications of this for the OS estimated curves and therefore the cost-effectiveness of daratumumab when compared with pom+dex and pano+bort+dex. The company's base case approach overestimated the survival benefit of daratumumab compared with pom+dex and was likely to underestimate the survival benefit compared with pano+bort+dex. Analysis of Figure B, Figure C and Figure D show that the dependent fit approach was unlikely to be appropriate for the estimation of cost-effectiveness for daratumumab.

Figure B. Company's base case OS curves for daratumumab, pom+dex and pano+bort+dex

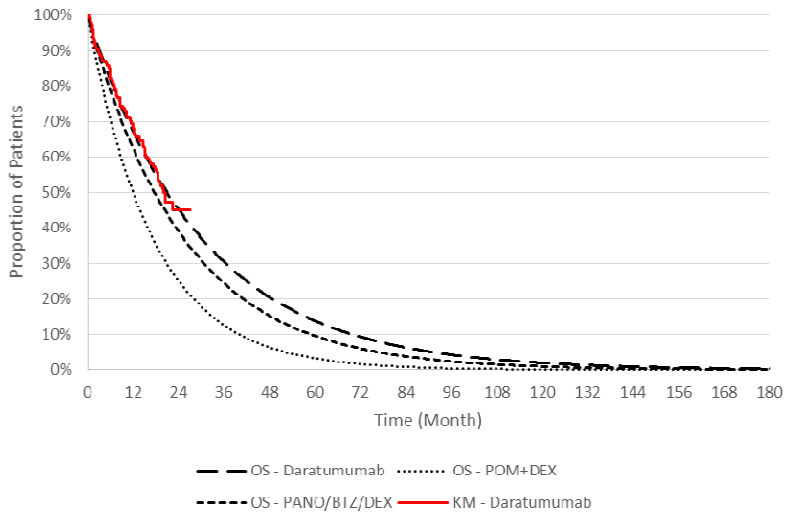


Figure C. Overall survival KM data for daratumumab (adjusted) vs pom+dex (unadjusted)

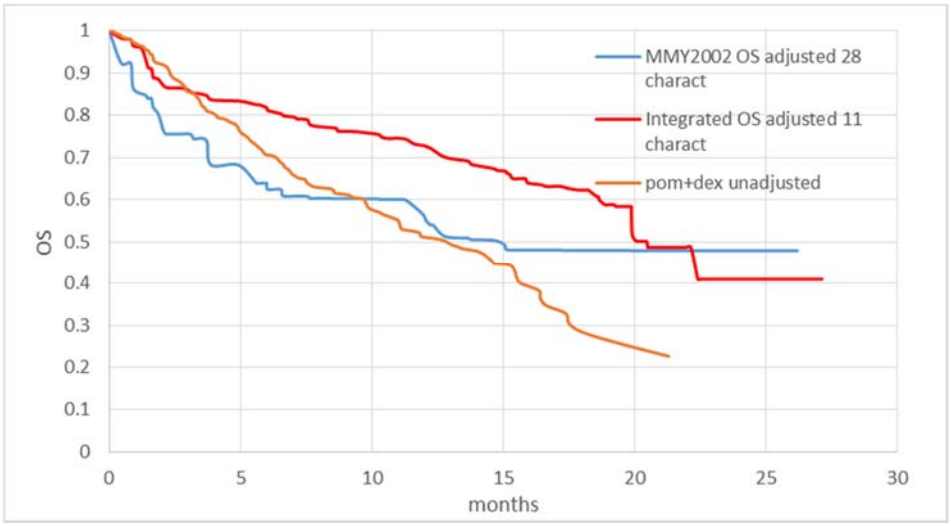
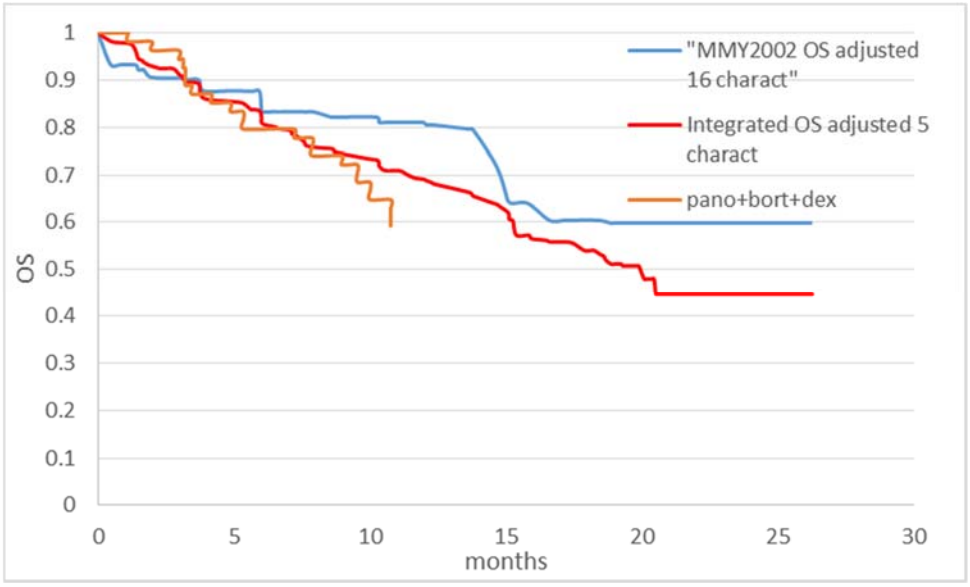


Figure D. Overall survival KM data for daratumumab (adjusted) vs pano+bort+dex (unadjusted)



- The number of characteristics included in the MAIC adjustment also changed the positioning of the daratumumab PFS adjusted KM curves in relation to pom+dex and in relation to pano+bort+dex, although to a less extent than observed for OS data. Regardless of this, given that PFS curves are key diver of treatment costs, the slightest shift in the curves was likely to have an impact on the cost-effectiveness analysis' results.

b) **Company's response:** The company reports that survival curves were checked for their internal validity, however there was no explanation as to why the curves estimated by the ERG were so different from the ones originally estimated by the company. The ERG did not have time to re-estimate survival curves therefore could not produce curves for validation of the new survival curves.

The company implemented an independent fit approach in the cost-effectiveness model. Nonetheless, instead of using the MMY2002 dataset together with the independent fit approach in the model (ERG's preferred option), it only included the options of using an independent fit approach using the integrated MMY2002/GEN501 dataset or using the MMY2002 dataset but with a dependent fit approach.

c) **ERG's comment:** As explained in Section 2 of the report, the ERG disagrees with the use of the integrated dataset for the purpose of estimating a measure of relative clinical effectiveness

for daratumumab. Therefore, the ERG considers that the company's new statistical approach to modelling cost-effectiveness is still unfit for purpose. Figure E below shows the company's new base case OS curves for daratumumab, pom+dex and pano+bort+dex. Comparing Figure E with Figure F and Figure G, it is noticeable that the ERG's original concerns with the overestimation and underestimation of daratumumab's effectiveness compared with pom+dex and compared with pano+bort+dex, respectively, remain unchanged.

The blue and the orange curves in Figure F reflect what the ERG considers the most appropriate representations of the OS estimates for daratumumab and pom+dex mortality, respectively. These show that pom+dex has a higher survival benefit than daratumumab up to around month 9, when daratumumab becomes more effective at delaying death (this analysis is caveated by the fact that no analysis of statistical significance was undertaken). This compares with Figure E, where daratumumab has a survival benefit compared with pom+dex from time 0 to month 160. The gap between observed and estimated survival curves is the same as it was when the company used its original dependent fit approach. In fact, the new KM curve (blue curve in Figure F) using the fully adjusted MMY2002/GEN501 data is very similar to the 11-characteristics-adjusted MMY2002/GEN501 data used in the company's original base case approach (Figure C).

Additionally the ERG questions the appropriateness of the curve fitting exercise undertaken by the company. Even if the red KM curve in Figure F was to be considered the best set of data to fit survival curves (instead of the blue curve as the ERG is suggesting), the fact that the daratumumab KM curve is overlapping or below the pom+dex curve up until approximately month 4 is completely disregarded in the fitting exercise of the survival curves, as shown by Figure E (and more detailed in Figure H). Considering that the company's new approach is in theory based on an independent fit (and does not rely on applying HRs to estimate survival curves), the ERG finds the disparity between the KM curves used by the company to fit data and the estimated survival curves concerning.

Finally the ERG notes that the issues originally raised for PFS and for OS for pano+bort+dex also remain the same, even though these are not explored in detail in this repost due to time constraints. Nonetheless, considering that the company's new approach has not been deemed to address any of ERG's concerns, these remain unchanged and can be found in detail in the ERG's original report.

Figure E. Company's base case OS curves for daratumumab, pom+dex and pano+bort+dex

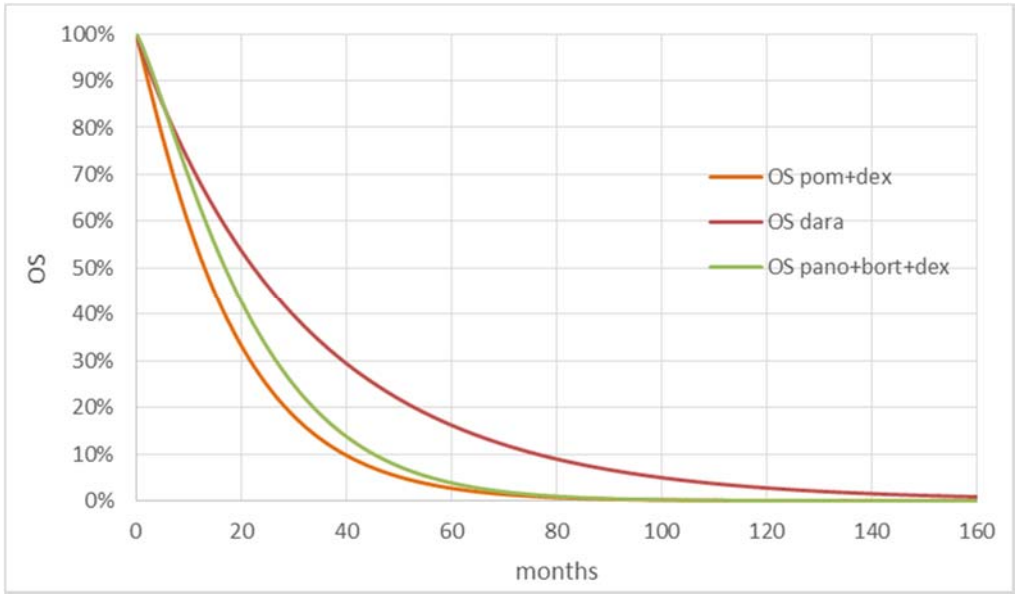


Figure F. Overall survival survival KM data for daratumumab (adjusted) vs pom+dex (unadjusted)

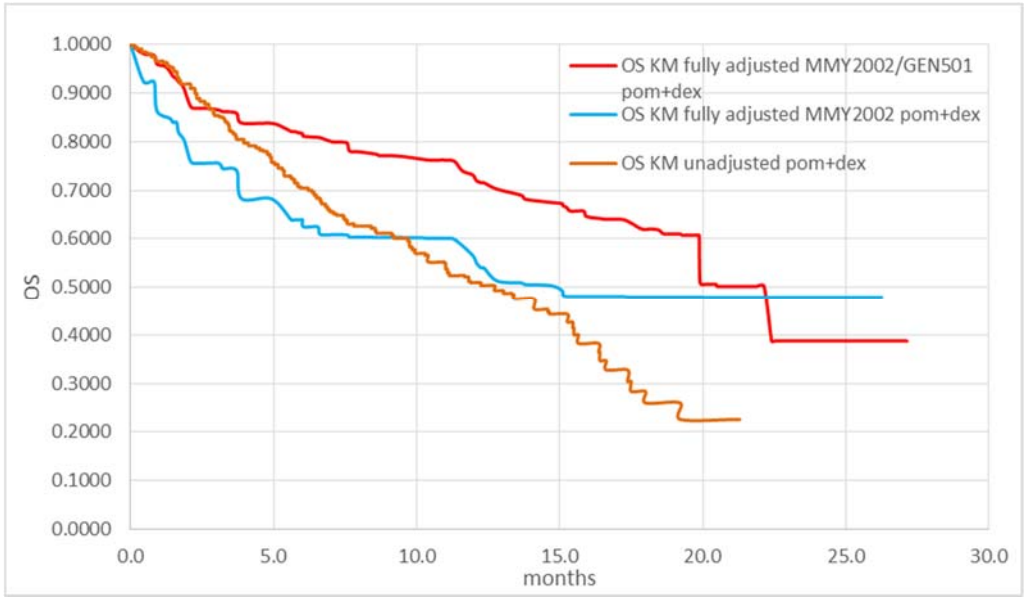


Figure G. Overall survival KM data for daratumumab (adjusted) vs pano+bort+dex (unadjusted)

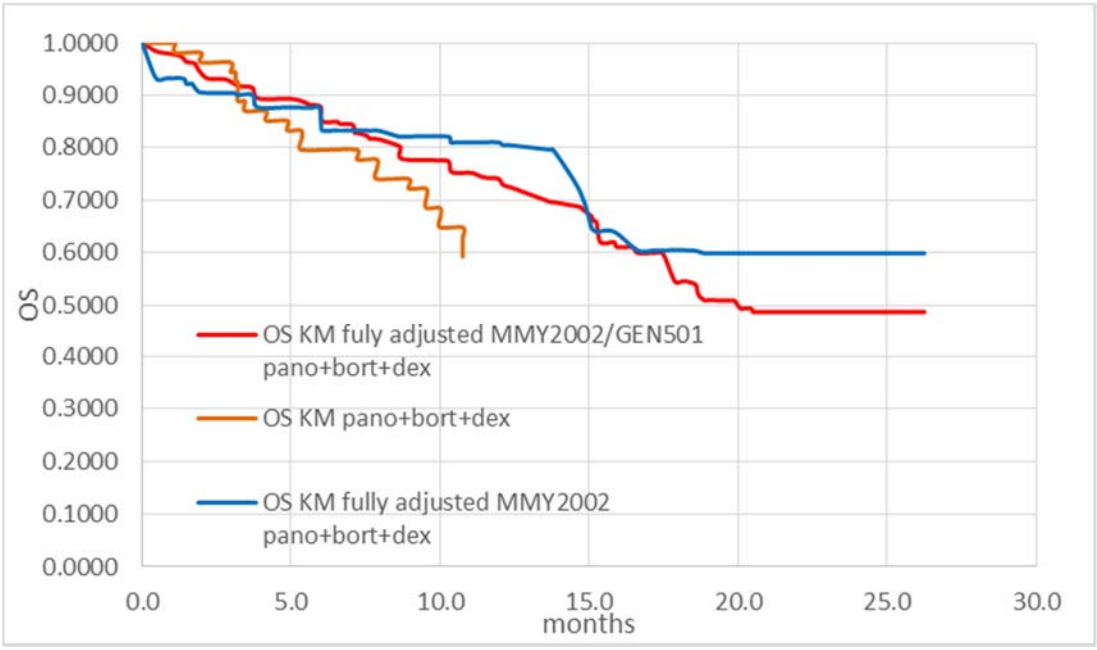
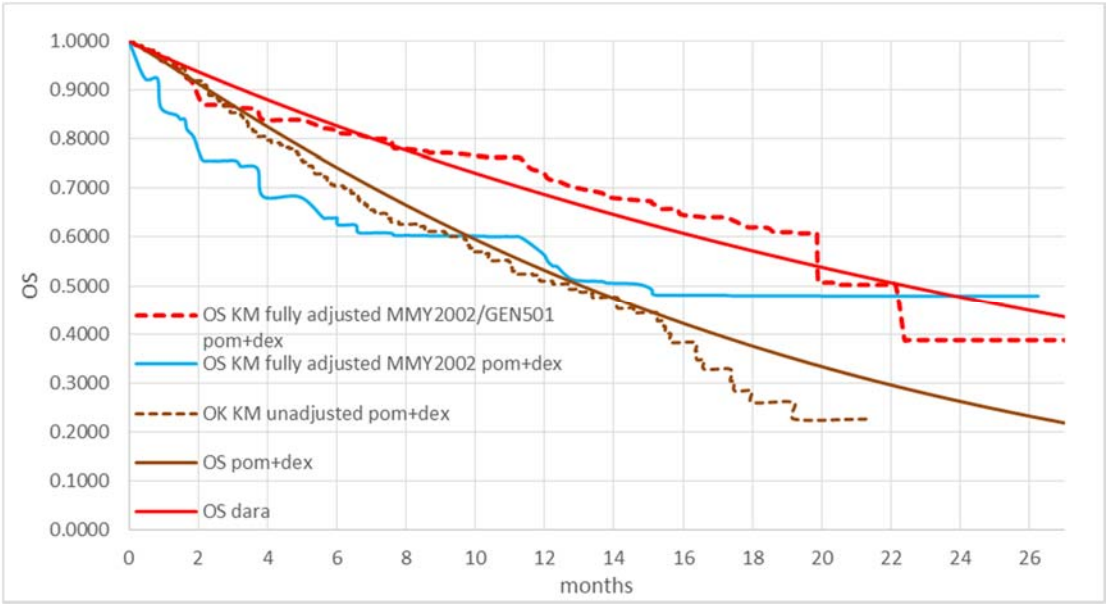


Figure H. Overall survival survival KM data for daratumumab (adjusted) vs pom+dex (unadjusted) 26 months



3.5 Time to treatment discontinuation data:

a) **ERG's initial issue:** The estimation of TTD curves in the company's analysis lacks transparency and clarity throughout the STA. Time to treatment discontinuation was not a pre-specified outcome in the MMY2002 and GEN501 trials but instead resulted from a *post-hoc* analysis of patient level data. Therefore the ERG has little to no information on this clinical

outcome. Secondly, the estimation of adjusted TTD curves for daratumumab through the "calibration approach" is a black box in the company's analysis. No further details were provided by the company other than the fact that, "*…the TTD curves for daratumumab were calibrated to match the observed mean and median from MM-003*". Considering the uncertainty around the TTD data, the ERG considers that using these data in the economic analysis carries a potentially high risk. While the PFS curves and data are also not without problems, PFS curves were used as an exploratory approach to derive treatment costs, implying that patients receive treatment until progression;

b) **Company's response:** The company reported that it is not clear what additional information was required.

c) **ERG's comment:** The ERG is still unclear what the "calibration exercise" of the curves consists of.

3.6 Estimation of utility and subsequent treatment costs:

a) **ERG's initial issue:** The ERG also had some concerns with the utility data used and with the application of disutility values to AEs. Similarly, the ERG found some issues in the company's estimation of subsequent treatment costs.

b) **Company's response:** The company reports implementing the model corrections suggested by the ERG in Section 6.1 of the original ERG report. The company has also reported new utility data for daratumumab from the Early Access Programme (EAP).

The EAP is a multi-centre, open-label, early access treatment protocol of daratumumab in subjects with multiple myeloma who have received at least three prior lines of therapy including a proteasome inhibitor (PI) and an IMiD or whose disease is double refractory to both a PI and an IMiD. A total of 90 UK patients have received treatment with daratumumab through the EAP; median age was 66.5 years, 60% of patients were male. Patients received a mean of 3.69 months of therapy (0.03 months to 10.58 months), mean 11 infusions (range 1 to 21) and a mean number of 4.6 cycles of treatment (range 1 to 10). The change from baseline in utility values is reported in Table 6 below.

The company took a weighted average of the mean change from baseline seen in the EAP dataset and estimated a utility increase of 0.04 for daratumumab patients. The values used in the company's updated economic model are presented in

Table 7. In the company's new analysis, progression-free patients are assumed to experience a higher utility while on daratumumab treatment compared with patients receiving pom+dex or pano+bort+dex.

Table 6. Utility data from EAP dataset

	Utility			Baseline	Change from baseline				ERG's analysis	
	n	Mean	SD	Mean	n	Mean	SD	SE	95% lower confidence interval	95% upper confidence interval
Baseline	86	0.64	0.22	-	-	-	-			
Cycle 2	57	0.68	0.20	0.64	57	0.04	0.18	0.02	-0.01	0.09
Cycle 3	46	0.69	0.19	0.64	45	0.05	0.14	0.02	0.01	0.09
Cycle 6	23	0.67	0.19	0.65	22	0.02	0.17	0.04	-0.05	0.09
Cycle 8	17	0.68	0.15	0.64	16	0.04	0.12	0.03	-0.02	0.10
Cycle 10	6	0.69	0.13	0.70	6	-0.01	0.09	0.04	-0.08	0.06
Cycle 12	2	0.77	0.10	0.74	2	0.02	0.09	0.06	-0.10	0.14
Last assessment	69	0.64	0.22	0.64	67	0.00	0.18	0.02	-0.04	0.04
Key: EAP, Early Access Programme; n, number; SD, standard deviation. **Source:** Janssen 2017 (EAP)[18]									**Source:** ERG analysis	

Table 7. Utility values used in the model

State	Utility value in original CS	Utility value used in updated model
Pre-progressive disease daratumumab	0.61	0.65
Pre-progressive disease comparators	0.61	0.61
Progressive disease	0.57	0.57

c) **ERG's comment:** The ERG did not have enough time to fully validate the implementation of all the ERG's suggested changes in the updated economic model, however some superficial validation was undertaken which seems to indicate that the company has correctly implemented the mentioned changes in the model.

Regarding the company's new analysis of utility data, the ERG has concerns about the robustness of the conclusions reached by the company. The utility data presented by the company in

Table 7 was not accompanied by any statistical analysis of significance, thus the weighted average mean change is a rather week measure. Especially when we consider the large variation demonstrated by the high standard deviation (SD) reported for all the mean changes from baseline. The ERG undertook a statistical analysis to derive 95% confidence intervals (CIs) around the mean changes from baseline, which are also reported in

Table 7. The CIs estimated by the ERG show that all changes from baseline, with the exception of the change in utility from baseline to cycle 3 are unlikely to be statistically significant (as the CIs cross 0). Additionally, it is difficult to understand if the improvement in patients' quality-of-life is due to daratumumab (alone) or due to improvement in disease status, i.e. patients on daratumumab will remain progression-free as a direct consequence of taking daratumumab, during which time their quality of life would improve. However, it could be argued that patients receiving pom+dex would also see their quality of life improve for a certain period of time while they remain progression-free.

Furthermore the company also applied utility decrements to AEs in the economic analysis. Considering that the company's new analysis of utility data tries to address the fact that daratumumab has a better safety profile than its comparators, applying utility decrements to AEs has a double counting effect. Not only patients on daratumumab have a higher utility value while on the progression-free state compared with patients receiving comparator treatments, but patients also experience a "smaller loss" in quality of life related with AEs while on daratumumab because of its advantageous safety profile.

As the company uses utility values derived from MM-003 to estimate quality of life in the PFS and PD sates, these values implicitly incorporate the impact of the AEs associated with pom+dex on patients' QoL in MM-003. Therefore, not only the company's approach double-counts the impact of chronic AEs related with pom+dex in the model (please see the ERG's original report for more details on this), but it also double-counts the benefit of daratumumab by applying the utility increment associated with daratumumab for patients in the PFS state and considering utility decrements for AEs.

3.7 Other issues

3.7.1 Using IMF data

The Committee requested that the company used the IMF data to validate results from the MAIC. The company undertook multivariate regression analysis to estimate a HR comparing the integrated daratumumab survival data with the patient-level pom+dex data.

The ERG notes that the company did not undertake an independent fit approach to estimate the relative effectiveness of daratumumab using IMF data, which would be the comparable method to the one used by the company in the base case analysis.

3.7.2 ERG's original alterations to company's model

The ERG notes that some of the alterations proposed by the ERG in the original report were not included by the company in their revised submission as scenario analysis. For inclusiveness purposes the ERG lists these below, but notes that these are only secondary to the fact that the estimation of clinical effectiveness in the model is not robust and to the highly confounded OS data used by the company in their analysis.

1. The ERG's clinical experts did not agree with the resource use included in the model, and suggested a different resource use regimen (Table 73, Section 5.5.9.2 of the ERG original report);

2. Use the distribution of subsequent therapies received in the daratumumab trials (Table 50, Section 5.5.9.3) and in the pom+dex trial as far as evidence allows in the economic model;

3. Remove the AE-related disutility estimates from the economic analysis to avoid double-counting and overestimating the impact of AEs on patients' QoL.

3.8 Probabilistic sensitivity analysis

The company has undertaken probabilistic sensitivity analysis (PSA) in their updated economic model. The company reports that as a consequence of using independently fitted curves (the ERG's preferred approach) a fully incremental probabilistic analysis was not possible.

The ERG is unclear to which limitation the company is referring too. The ERG does not see any impediments of running a fully incremental PSA when an independent fit approach is taken, as survival curves could have been sampled and included in the PSA. The ERG did not verify the PSA analysis ran by the company as the estimation of clinical effectiveness in the economic analysis is still deemed inappropriate, rendering the PSA results uninformative.

3.9 Results

The revised results presented by the company are reported in Table 8 and Table 9 below.

Table 8: Revised base case results versus POM+DEX

	Total			Incremental			ICER
	Costs	QALYs	LYs	Costs	QALYs	LYs	
Without PAS							
POM+DEX	£52,396	0.75	1.49	£31,217	0.69	1.24	£44,988
Daratumumab	£83,613	1.44	2.74				
With PAS							
POM+DEX	£52,396	0.75	1.49	£10,909	0.69	1.24	£15,772
Daratumumab	£63,306	1.44	2.74				
Key: ICER, incremental cost-effectiveness ratio; LY, Life years; PAS, patient access scheme; POM+DEX, pomalidomide plus dexamethasone; QALY, quality-adjusted life years.							

Table 9: Revised base case results versus PANO+BORT+DEX

	Total			Incremental			ICER
	Costs	QALYs	LYs	Costs	QALYs	LYs	
Without PAS							
PANO+BORT+ DEX	£76,008	0.93	1.80	£6,646	0.30	0.48	£21,910
Daratumumab	£82,654	1.23	2.28				
With PAS							
PANO+BORT+ DEX	£76,008	0.93	1.80	-£13,662	0.30	0.48	Daratumumab Dominates
Daratumumab	£62,346	1.23	2.28				
Key: ICER, incremental cost-effectiveness ratio; LY, Life years; PANO+BORT+DEX, panobinostat plus bortezomib plus dexamethasone; PAS, patient access scheme; QALY, quality-adjusted life years.							

3.10 End of life

In the ACD it reads that "*The Committee considered life expectancy for people with relapsed and refractory multiple myeloma and was satisfied that it was less than 24 months. The Committee was unable to conclude whether the criterion of at least a 3-month life extension was met because of the many uncertainties in the relative effectiveness and survival modelling. The Committee concluded that it could not make an informed decision as to whether daratumumab meets the end-of-life criteria.*"

The ERG considers that the uncertainty on the survival benefit of daratumumab has not been mitigated and that there are no new data to help inform this issue.

4 OVERALL CONCLUSIONS

Clinical

The ERG maintains that it is inappropriate to integrate results for clinical effectiveness from MMY2002 and GEN501 Part 2. Considering the revised MAIC, the ERG has reservations around the robustness of the analysis. The ERG advises interpreting all results from the MAIC with caution due to the small

effective sample sizes and wide confidence intervals. The ERG also has reservations around the multiple imputation method implemented to generate the updated MAIC.

Economic

The ERG remains seriously concerned with the robustness of the economic analysis undertaken by the company. The key issues surrounding the cost-effectiveness of daratumumab remain unchanged and are summarised below.

1. **Pre-treatment with pomalidomide**: Daratumumab data suggests that there is no difference in PFS across pom-naïve and non-pom-naïve patients and that OS outcomes are better for pom-naïve patients compared with the overall trial population. The ERG interpreted this trend in the data as a possible consequence of the effect of pomalidomide as a subsequent therapy. The ERG found inconstancies in the data originally provided by the company for pom-naïve patients. The company did not submit any new data to mitigate the original concerns raised by the ERG.

2. **Subsequent treatments received in MMY2002/GEN501**: The ERG is still concerned with the highly confounded OS estimates in the company analysis. The ERG considers that the evidence put forward by the company is not robust enough to determine the cost-effectiveness of daratumumab monotherapy alone as the effectiveness of daratumumab would need adjusting for the impact of subsequent therapies currently not available in the UK.

   The ERG considers the substantial difference between the estimated large survival benefit associated with daratumumab and the small (if any) gain in progression-free survival of daratumumab is likely to be related to the impact of subsequent treatments received on patients' survival. While the ERG understands that the benefit of daratumumab might be exactly the fact that it allows more patients to receive subsequent therapies, if there are no treatment options left for patients at the point daratumumab is given in the clinical pathway reimbursed by the NHS, then the benefit of daratumumab becomes a moot point. Positioning daratumumab as a fourth-line treatment option for rrMM patients means that, in the current NHS system, patients would only have pom+dex, pano+bort+dex and BSC regimens (including bendamustine) left after treatment with daratumumab.

3. **Statistical approach undertaken by the company to model survival outcomes:** The company implemented an independent fit approach in the cost-effectiveness model. Nonetheless, instead of using the MMY2002 dataset together with the independent fit approach in the model (ERG's preferred option), it only included the options of using an independent fit approach using the integrated MMY2002/GEN501 integrated dataset or using the MMY2002

dataset but with a dependent fit approach. As explained in Section 2 of the report, the ERG disagrees with the use of the integrated dataset for the purposes of estimating a measure of relative clinical effectiveness for daratumumab. Therefore, the ERG considers that the company's new statistical approach to modelling cost-effectiveness is still unfit for purpose. Figure E, Figure F and Figure G in this report, show that the ERG's original concerns with the overestimation of daratumumab's effectiveness compared with pom+dex and underestimation compared with pano+bort+dex remain unchanged.

4. **Time to treatment discontinuation data**: The company did not submit any evidence on the estimation of TTD outcomes in the model, therefore is still unclear what the "calibration exercise" of the curves consists on.

5. **Estimation of utility and costs in the model:** The company submitted new utility data, however the ERG is unclear on the statistical significance of the data considered by the company to be supportive of a utility increment attributable to daratumumab. Furthermore the company also applied utility decrements to AEs in the economic analysis. Considering that the company new analysis of utility data tries to address the fact that daratumumab has a better safety profile than its comparators, applying utility decrements to AEs has a double counting effect. Not only patients on daratumumab have a higher utility value while on the progression-free state compared with patients receiving comparator treatments, but patients also experience a "smaller loss" in quality of life while on daratumumab because of its advantageous safety profile.

5 REFERENCES

1. Sterne JAC, White IR, Carlin JB, et al. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. *BMJ* 2009;338:b2393