NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Carfilzomib with dexamethasone and lenalidomide for treating multiple myeloma after at least 1 previous therapy [ID1493]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Carfilzomib with dexamethasone and lenalidomide for treating multiple myeloma after at least 1 previous therapy [ID1493]

Contents:

The following documents are made available to consultees and commentators:

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

2. **Comments on the Appraisal Consultation Document from Amgen UK**
   a. Response form
   b. Addendum to ACD response

3. **Consultee and commentator comments on the Appraisal Consultation Document** from:
   a. Myeloma UK
   b. UK Myeloma Forum-British Society of Haematology-Royal College of Pathologists

   Comments on the Appraisal Consultation Document from experts:
   None

   Comments on the Appraisal Consultation Document received through the NICE website
   None

4. **Evidence Review Group critique of company comments on the ACD**

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

Carfilzomib with dexamethasone and lenalidomide for previously treated multiple myeloma

Single Technology Appraisal

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

Type of stakeholder:

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

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

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

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

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

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
1	Consultee	UK Myeloma Forum/British Society for Haematology/Royal College of Pathologists	We note that Carfilzomib lenalidomide and dexamethasone has not been approved on the basis that there is uncertainty about how long the benefit lasts after stopping treatment. Myeloma remains an incurable illness, combination therapies at relapse presents a significant step up in salvage options for patients who have an unstable myeloma genome. The responses obtained with combination therapies are deeper and sustained. This is reflected in improved remission periods and translates to improved overall survival.	Comments noted. The committee has recommended carfilzomib with lenalidomide and dexamethasone for treating multiple myeloma in adults, only if they have had 1 previous therapy which included bortezomib. See FAD sections 1.1 and 3.12
2	Consultee	UK Myeloma Forum/British Society for Haematology/Royal College of Pathologists	**Has all of the relevant evidence been taken into account**? Yes	Comments noted. No action required.
3	Consultee	UK Myeloma Forum/British Society for Haematology/Royal College of Pathologists	**Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** The appraisal consultation document reflects the discussion at the meeting, particularly around the advantages to myeloma patients of having Carfilzomib, Lenalidomide and dexamethasone combination as an option for treatment of relapsed myeloma. There was agreement on Lenalidomide and dexamethasone being a suitable comparator. During discussion around treatment pathway, there was agreement on 1st relapse or second line population being the relevant position for use of this combination. Posthoc subgroup: Posthoc sub group discussion particularly around prior lenalidomide use, the committee has concluded patients who have been exposed to prior Lenalidomide will be excluded. This presents a complete contradiction to current practice when patients who have received prior lenalidomide and not refractory are eligible for Ixazomib lenalidomide and dexamethasone combination therapy in the NHS. In addition, Myeloma XI academic trial which recruited over 4000 myeloma patients have been exposed to prior Lenalidomide and these patients would be disadvantaged if committee takes a stance to restrict use of this combination in Lenalidomide naïve patients. There are other currents trials in the UK which offer lenalidomide in upfront therapy. Therefore a suitable wording should be sought, which would be restricting this combination to lenalidomide sensitive patients. Clinical community struggles to understand the position taken by the appraisal committee on the grounds that there is uncertainty about how long the benefit lasts with the Carfilzomib Lenalidomide	Comments noted. Please see responses to individual issues below. <u>Subgroups</u> The company positioned the treatment for people who have had 1 previous bortezomib treatment (see FAD section 3.3). The committee agreed that this reflects the current treatment pathway in the NHS. Although the committee's preferred analyses were based on the ERG's post-hoc subgroup, it did not consider it needed to specify that people should not have previously had lenalidomide in the recommendation, to avoid excluding people who have lenalidomide and bortezomib as their first treatment (see section 3.9 of the FAD).

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			dexamethasone combination therapy. ASPIRE study is the only Phase III relapsed myeloma trial with long follow up every considered by NICE committee with over 6 years actual follow up. The trial demonstrates a clear improvement in overall survival which often remains immature when other combinations have been considered by NICE. In addition, the use of carfilzomib with ASPIRE trial is limited to 18 months fixed duration which brings to the table certainty duration and therefore costs of therapy. Overall survival: The study has most mature overall survival data presented in relapsed myeloma studies. Overall survival separate early between test and control arms. Carfilzomib frequency is reduced after 12 months and stopped after a fixed duration of 18 months. Visually examination of the overall survival curves do not show a drop in survival in the test arm, during these key timepoints. Therefore a significant proportion of patients stay benefitting from therapy induced response beyond 18 months period when carfilzomib is stopped. QoL data: Quality of life data from the trial was considered by the committee. There is a significant improvement in quality of life of patients treated with carfilzomib lenalidomide and dexamethasone combination. This is derived from improved and faster disease control. We request NICE to be consistent in application of utility values derived from Qol studies across all myeloma relapsed study technology appraisals. We are concerned about clinical evidence considered at NICE committee meetings. They are increasing artificial hypothetical discussions and do not reflect current clinical practice	Overall survival and treatment benefit The committee welcomed the mature trial data from ASPIRE. However, it concluded that it is uncertain about how long any treatment benefit with carfilzomib plus lenalidomide and dexamethasone lasts after stopping treatment, beyond the observed ASPIRE data. The committee considered that the treatment effect is likely to diminish over time in the extrapolated period. See FAD sections 3.5 and 3.9. Utility values The committee considered that it had not been presented with strong evidence to support the company's use of treatment-specific utility values. The committee concluded that it would consider both treatment-specific and using the same values for both treatments in its decision-making. It noted that applying either choice of utility values resulted in carfilzomib plus lenalidomide and dexamethasone being cost-effective. See FAD section 3.6. The committee has considered all the relevant clinical evidence presented to it during the appraisal process, in line with the Guide to the processes of technology appraisal.
4	Consultee	UK Myeloma Forum/British Society for	**Are the recommendations sound and a suitable basis for guidance to the NHS?** Based on the above comments committee should reconsider the recommendations	Comments noted. Based on the evidence presented to it and the revised commercial arrangement,

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		Haematology/Royal College of Pathologists		the committee has recommended carfilzomib plus lenalidomide and dexamethasone as an option for previously treated myeloma (see FAD sections 1.1 and 3.12).
5	Consultee	UK Myeloma Forum/British Society for Haematology/Royal College of Pathologists	**Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity**? No	Comments noted. No action required.
6	Consultee	Myeloma UK	Myeloma UK is disappointed that carfilzomib (Kyprolis®) in combination with lenalidomide (Revlimid®) and dexamethasone for multiple myeloma patients who have received one prior therapy has not been approved for routine commissioning.	Comments noted. No action required. Based on the evidence presented to it and the revised commercial arrangement, the committee has decided to recommend carfilzomib plus lenalidomide and dexamethasone as an option for previously treated myeloma. (see FAD sections 1.1 and 3.12).
7	Consultee	Myeloma UK	**Has all of the relevant evidence been taken into account?** Yes, the Committee's request to the company for further work to be undertaken on the analyses of prolonged treatment benefit notwithstanding. We welcome the following findings in the ACD based on the evidence presented: - that carfilzomib with lenalidomide and dexamethasone gives longer periods of remission and people live longer than with lenalidomide and dexamethasone - Agreement that second line (first relapse) is the relevant patient population, whether or not stem cell transplant is a suitable treatment option - That this combination would be a welcome addition to the treatment pathway for patients giving them increased options for treating their myeloma. We would go further and argue that it meets a clear need for further treatment options with different mechanisms of action, with a triplet combination representing a significant improvement on lenalidomide and dexamethasone alone - The maturity of the data from the ASPIRE trial showing overall survival benefit	Comments noted. No action required.
8	Consultee	Myeloma UK	**Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** Partially. Agreed areas of evidence are set out above. Areas where we disagree with interpretations of the evidence are set out below:	Comments noted. Please see responses to individual issues below. <u>Subgroups</u> The company positioned the

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			Post hoc subgroups – We disagree with the decision to exclude all patients who have previously received lenalidomide. There is clear precedent in relation to the use of ixazomib, lenalidomide and dexamethasone that patients who have been exposed but are not refractory to lenalidomide should be able to access subsequent combination treatments which include lenalidomide. *Utility values used in the economic model* – We disagree with the decision not to use the treatment specific utility values presented by the company. In the trial data, the EORTC QLQ-C30 GHS disease questionnaire was used to establish a clinically meaningful improvement in HRQOL. This is entirely consistent with improved quality of life being derived from improved and faster disease control. We believe strongly that this data collected directly from patients should stand; there is an important principle at stake about valuing quality of life evidence gathered from patients using a validated tool which is accepted under NICE methodology. We do not believe that a case has been made from deviating from this first hand patient reported evidence. *Extrapolation of overall survival and prolonged treatment benefit* – We note the Committee's request for further analyses of prolonged treatment benefit. Our understanding is that overall survival (OS) curves show that survival is maintained in the test arm at the points where carfilzomib frequency is first reduced (at 12 months) and then stopped (at 18 months). This supports the proposition that a significant proportion of patients continue to benefit after carfilzomib has been stopped. As the Committee is aware, the myeloma treatment pathway is continuously and rapidly evolving. This inevitably leads to additional challenges in meaningful extrapolation of overall survival over long time horizons. We support companies being required to present rigorous and complete modelling to capture long term OS benefit. However, alongside this, it is essential that HTA takes a proportionate approach to the uncertainty which arises from the welcome development of the myeloma treatment pathway. There must be a balance between methodological approaches to give us the best understanding of a possible future, and a recognition that such methodology has its limits in the context of scientific development and changing clinical practice. *Cancer Drugs Fund comparators* - We understand the need to avoid building a treatment pathway on the "conditional" foundation of CDF approved treatments which may ultimately not be routinely commissioned. However, we do not believe the current rules strike the right balance between recognising the conditional nature of CDF approval and reflecting real world clinical practice. We acknowledge that it is not possible for the Committee to resolve this issue directly as part of a single appraisal. However, we ask that the Committee takes this issue (particularly dominance of CDF funded daratumumab, bortezomib and dexamethasone at second line for eligible patients) into account when considering what flexibility can be applied in its decision making, in order to reach a decision which is reasonable and meaningful. *Combination treatments* - We note the ACD's reference to the challenge of achieving cost effectiveness for combination treatments and the extent to which this impacts many cancer appraisals. Clearly a key factor in determining cost effectiveness is the price of drugs and any associated patient access scheme which is commercial in confidence. However, we also note the calculation presented by the company which demonstrates the extent to which the cost of lenalidomide is driving the price of the combination - a factor which the makers of carfilzomib are not in a position to influence. Like	treatment for people who have had 1 previous bortezomib treatment (see FAD section 3.3). The committee agreed that this reflects the current treatment pathway in the NHS. Although the committee's preferred analyses were based on the ERG's post-hoc subgroup, it did not consider it needed to specify that people should not have previously had lenalidomide in the recommendation, to avoid excluding people who have lenalidomide and bortezomib as their first treatment (see section 3.9 of the FAD). <u>Overall survival and treatment benefit</u> The committee welcomed the mature trial data from ASPIRE. It concluded that it is uncertain about how long any treatment benefit with carfilzomib plus lenalidomide and dexamethasone lasts after stopping treatment, beyond the observed ASPIRE data. The committee considered that the treatment effect is likely to diminish over time in the extrapolated period. See FAD sections 3.5 and 3.9. <u>Utility values</u> The committee considered that it had not been presented with strong evidence to support the company's use of treatment-specific utility values. The committee concluded that it would consider both treatment-specific and using the same values for both treatments in its decision-making. It noted that applying either choice of utility

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			issues relating to CDF treatments we appreciate it is not within the gift of the Committee to resolve this issue in a single appraisal, but we believe it is important context.	values resulted in carfilzomib plus lenalidomide and dexamethasone being cost-effective. See FAD section 3.6. Cancer drugs fund comparators The committee understood that technologies recommended by NICE for use within the Cancer Drugs Fund cannot be considered established practice and therefore cannot be considered as comparators in new appraisals. See FAD section 3.2. Combination therapies The committee acknowledged that treatments that extend the use of other high-cost drugs (such as lenalidomide) can lead to additional cost associated with those other drugs. However, it concluded that because the NHS would incur these additional costs in practice, they should be included in the model. See FAD section 3.10.
9	Consultee	Myeloma UK	**Are the provisional recommendations sound and a suitable basis for guidance to the NHS?** No. For the reasons set out above we believe that the Committee should reconsider its decision not to approve this treatment for use on the NHS. Finally, we wish to record that we strongly disagree with approach that, due to uncertainty in relative treatment benefit, an acceptable ICER would be no higher than the middle of the range normally considered a cost-effective use of NHS resources (£20,000 to £30,000 per QALY gained). We note that the NICE guide to methodology in technical appraisals confirms that "the Committee will be more cautious about recommending a technology when they are less certain about the ICERs presented". This is understood. However, we are very concerned that this has been translated into effectively lowering what is normally seen as the cost-effectiveness threshold. We have never seen this approach before in our considerable engagement with myeloma technology appraisals. We believe that such an approach disadvantages a relapsing and recurring cancer like myeloma, where its complex treatment pathway inevitably leads to higher levels of uncertainty and the need for theoretical modelling.	Comments noted. The committee considered that the cost-effectiveness estimates may be optimistic because some waning of treatment benefit with carfilzomib plus lenalidomide and dexamethasone is likely to occur beyond the observed ASPIRE data. Based on the evidence presented to it and the revised commercial arrangement, the committee concluded that the most plausible ICERs are within the range that NICE normally considers an acceptable use of NHS resources.

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				Therefore, the committee has recommended carfilzomib plus lenalidomide and dexamethasone. See FAD sections 1.1, 3.11 and 3.12.
10	Consultee	Amgen	**Section 1 – Executive Summary** We have carefully reviewed the Committee's consideration of the evidence for the part review of single technology appraisal (STA) of *Carfilzomib with dexamethasone and lenalidomide [CRd] for previously treated multiple myeloma* [ID1493]. We are extremely disappointed by the conclusions reached and the resulting preliminary guidance not to recommend carfilzomib in this indication. We welcome the Committee's recognition of the clinical need for an effective second-line therapy and the maturity of data from ASPIRE which demonstrates clear and meaningful benefit in survival outcomes. However, the Committee considered there to be uncertainty in the cost-effectiveness evidence, and that likely cost-effectiveness estimates are higher than what NICE normally considers a cost-effective use of NHS resources. We remain committed to working with NICE to address all of the Committee's concerns and ensure patients can access this important combination medicine. This was also our commitment and approach in Scotland where the Scottish Medicines Consortium (SMC) has just published positive guidance for CRd (Monday 12th October). We are confident that the further analyses presented here will sufficiently address the uncertainties identified by the Committee. Furthermore, by considering key model assumptions that are consistent with both the extensive evidence base and prior NICE appraisals in this disease area, recognising the challenges associated with combination therapies, [redacted], we believe NICE can be confident in recognising CRd as cost-effective. Our response will focus on the following components, which when taken together, we believe can allow NICE to overturn the initial negative recommendation: **<u>Priority Issues</u>** • **The Committee-preferred overall survival (OS) assumptions used in the economic evaluation underestimates long-term survival and are inconsistent with accepted estimates considered clinically plausible in previous appraisals in this disease area [See Section 2]** *An exploratory analysis investigating the impact on the incremental cost-effectiveness ratio*	Comments noted. The committee considered the consultation response, new evidence and revised commercial offer from the company. Please see comment numbers 11-14 below for responses to each priority issue.

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			(ICER) of applying an OS extrapolation assumption consistent with previous appraisals in this disease area significantly reduces the Committee preferred ICER from £50,960 to £35,513 (using lenalidomide list price). • **Amgen consider that there is a clear case for a treatment-specific utility impact beyond progression-free survival (PFS) and OS gains to be captured in the economic evaluation. Such an approach is consistent with NICE preferred assumptions during the original TA457 appraisal and incorporation of this evidence-base is supported by strong clinical expert opinion. Health-related quality of life (HRQoL) data was also collected as part of the robust pivotal Ph3 ASPIRE trial and has been presented by Amgen. [See Section 3]** *The ACD states that the Amgen preferred assumptions are '*reasonable*' and that CRd '*would increase the effectiveness of controlling the disease, which in turn would improve quality of life'*. However, the Committee preferred approach is to exclude this benefit, citing that it had '*little effect on the ICER*'. Amgen believe that NICE should incorporate this evidence base into its decision-making as it is an essential component of the cost-effectiveness evaluation of this combination therapy and reflects patients' actual experience of disease control.* • **The ACD does not adequately reflect the mature evidence from the high-quality Ph3 ASPIRE RCT. A reduced decision-making threshold appears unfair and is unjustified in light of the long-term follow-up data presented. [See Section 4]** *Within the extensive trial data follow-up (>6 years), no trend supportive of a reduction in treatment effect was observed and we strongly believe that the Amgen and ERG preferred assumption of a consistent treatment effect remains valid. Furthermore, as reported in the ACD '*the clinical expert stated that this is the first multiple myeloma trial with a long follow-up period to provide clear evidence of improved progression-free survival and overall survival.*' Amgen strongly believes that a reduced decision-making threshold on the grounds of uncertainty places an unfair burden on gaining access for patients and does not recognise the maturity of the data set presented.* • **There are significant access challenges to combination therapies, whereby the new technology is penalised by increased costs of background therapy, that create additional barriers to gaining patient access to this important medicine. [See Section 5]** *Lenalidomide remains a major cost-driver in the acquisition of CRd (accounting for* [redacted] *of the acquisition cost at list price, Committee preferred base case) providing Amgen little opportunity to influence the decision making ICER with respect to the cost of carfilzomib - this issue is compounded by the fact that lenalidomide plus dexamethasone was recommended*	

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			despite not demonstrating cost-effecitveness in TA586. [redacted] ***We strongly urge the NICE Committee to take these considerations into account and apply appropriate flexibility to remove unjust barriers to access.*** **<u>Additional Considerations</u>** **Amgen believe there are several inconsistencies in the application of assumptions in this appraisal compared with other TAs (both within and outside the MM disease area) that place an unfair burden on demonstrating the cost-effectiveness of CRd.** *In addition to the clinically plausible OS extrapolation, preferred utilities and application of a reduced decision-making threshold in the prescence of mature Ph3 data, we believe there is precedent for NICE to consider flexibility of the EoL criteria. We are aware that NICE have previously applied flexibility and discretion in the application of end-of-life criteria to appraisals of treatments for metastatic cancer when:* ***1)*** *OS without the new drug exceeds 24 months;* ***2)*** *the new drug provides significant extension to life beyond 3 months;* ***3)*** *the new drug is combined with existing treatment, and* ***4)*** *both the existing treatment and the new drug are used until disease progression.* ***We maintain CRd meets these criteria and thus there is a case for additional flexibility to be applied during the decision-making process and a higher cost-effective threshold to be considered.*** • **Considerations by the Committee do not fully reflect clinical reality by failing to consider comparative analyses presented versus daratumumab in combination with bortezomib and dexamethasone (DVd).** *Although we recognise NICEs existing Position Statement on the consideration of products recommended for use in the Cancer Drugs Fund as comparators, it is our view that the conclusions of this analysis should be taken into account outside of the reference case. Clinical experts consulted by NICE suggested as many as 80% of patients receive DVd in England as a second-line treatment and conclusions of an indirect comparison exploring the relative efficacy of CRd versus DVd presented in our original submission* [redacted]*. Given the current use of DVd in the second line treatment of myeloma and the potential for CRd to offer increased benefit at a reduced cost, we believe this analysis is of* ***significant importance*** *to the decision problem and is reflective of current clinical reality.* • **Following the recent positive recommendation for CRd in Scotland (SMC2290, October**	

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			12th) Amgen are concerned that maintaining a negative decision would lead to an inequity in patient access to CRd across the UK and are committed to working with NICE to resolve this. *Although we recognise that NICE and the SMC approach decision making differently and independently, the ability of the SMC to consider DVd as a comparator and apply flexibility in decision making with respect to combination therapies enabled them to make a positive decision. We urge the NICE Committee to take external circumstances into account and apply appropriate flexibility in decision making.* [redacted]Following the 1st Appraisal Committee Meeting, Amgen engaged extensively with NICE and NHSE to find a solution that would enable patient access to CRd. [redacted]£50,960[redacted] **Conclusions** Given the external challenges with this appraisal, in particular relating to demonstrating cost-effectiveness for combination medicines, **Amgen genuinely believe we have done everything we can to ensure patients can access this important medicine.** We have shown in this response that by applying appropriate and consistent assumptions, considering wider but no less important context, [redacted] NICE can be confident in recognising CRd as cost-effective treatment option.	
11	Consultee	Amgen	**Section 2 – Overall Survival Extrapolation Assumptions** Amgen maintain that real world evidence sources incorporated in our submission dossier provide reliable and informative data to capture plausible long-term survival extrapolations; this is supported by evidence put forward during the technical engagement consultation that supports the fact that parametric extrapolation from the ASPIRE clinical trial may result in an underestimation of long-term survival and may not reflect reduction in mortality rates beyond the trial follow-up. Furthermore, as feedback from clinical experts suggests long-term survival with CRd is expected to be *at least* comparable with DVd, both the Amgen and ERG ICER estimates may reasonably be considered conservative when taking in to account clinically plausible long-term survival extrapolations accepted	Comments noted. The committee understood that clinically plausible extrapolations of overall survival could be estimated entirely from the mature ASPIRE data. It concluded that it preferred to estimate overall survival for both treatment arms based on the ASPIRE trial data only. See FAD section 3.7.

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<tr><td></td><td></td><td></td><td>in other MM appraisals.

In particular, we suggest it is informative to consider previously accepted estimates of long-term survival by NICE in the recent TA573 appraisal of DVd. In the TA573 FAD, it states that the Committee preferred the ERG's more conservative survival estimate for the daratumumab combination at 20 years of 11% (see Table 1). Feedback from clinical experts during an advisory board conducted to inform this appraisal concluded that long-term survival with CRd was expected to be at least comparable with DVd. This conclusion is supported in the matched-adjusted indirect treatment comparison of CRd vs. DVd presented in the company's submission. Given this, it can reasonably be concluded that Amgen's base case estimate of 20-year survival (6%) remains conservative. Furthermore, theERGs base case prediction of 4% is much lower than the 20-year survival that experts have previously deemed to be clinically valid.

Table 1: Comparison of 20-year survival rates
<table>
<tr><th></th><th>20-year survival</th></tr>
<tr><th></th><th>CRd</th></tr>
<tr><td>Amgen Base Case – RWE (MyelomaToul) informed long-term extrapolation</td><td>6%</td></tr>
<tr><td>ERG Base Case – parametric extrapolation from ASPIRE</td><td>4%</td></tr>
<tr><td>NICE Committee Preferred Assumptions for DVd (TA583) - 2L</td><td>DVd
11%</td></tr>
</table>

Exploratory Analysis
The ERG's preferred OS model, the Exponential model fitted to ASPIRE subgroup data, estimates survival proportions for CRd patients at 10, and 20 years to be 19% and 4%, respectively. These estimates are more conservative than those predicted for DVd and accepted by the ERG. In the FAD for the NICE appraisal of DVd, the 20-year survival probability was 11%. To estimate the impact of OS extrapolation using a similar approach as for DVd, we have performed an explarotary analysis where the proportion of CRd patients alive at 20 years was set to 11%.

For the purpose of this scenario, the NICE Committee's preferred assumptions were selected and then the CRd survival rate beyond the trial follow-up period (72 months) was calibrated using the goal seek function in excel such as 11% of CRd patients were alive at 20 years. The estimated survival probabilities at 10 and 20 years were 26% and 11% respectively. This exploratory analysis yielded a significantly lower ICER than the one estimated by the ERG (35,513 £/QALY vs 50,960 £/QALY).</td><td></td></tr>
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<tr><th>Comment number</th><th>Type of stakeholder</th><th>Organisation name</th><th>Stakeholder comment
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Table 2. Scenario analysis results for CRd vs Rd, 2L/prior bortezomib no prior lenalidomide subgroup assuming the proportion of patients alive at 20 years is similar to previously accepted

<table>
<tr><th>Technologies</th><th>Total costs (£)</th><th>Total LYG</th><th>Total QALYs</th><th>Incremental costs (£)</th><th>Incremental LYG</th><th>Incremental QALYs</th><th>ICER versus baseline (£/QALY)</th></tr>
<tr><td>Rd</td><td>[redacted]</td><td>3.97</td><td>2.40</td><td>-</td><td>-</td><td>-</td><td>-</td></tr>
<tr><td>CRd</td><td>[redacted]</td><td>7.75</td><td>4.05</td><td>58,642</td><td>3.78</td><td>1.65</td><td>35,513</td></tr>
<tr><td colspan="8">CRd: carfilzomib/lenalidomide/dexamethasone; Rd: lenalidomide/dexamethasone; ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years.</td></tr>
</table>

In conclusion, we believe there is strong evidence to suggest that extrapolation from the ASPIRE clinical trial may underestimate long-term survival and that the use of external clinical data is appropriate in the base case analysis. Indeed, both the Amgen and ERG ICER estimates may reasonably be considered conservative when taking into account clinically plausible long-term survival extrapolations.
</td><td></td></tr>
<tr><td>12</td><td>Consultee</td><td>Amgen</td><td>

Section 3 – Treatment Specific Utility Values

Multiple myeloma (MM) is a systemic, incurable disease and patients often have noticeable symptoms and decreased HRQoL. Physical symptoms include bone pain, fatigue, infections, and reduced physical function and mobility due to the uncontrolled growth of myeloma cells. As such, it is expected that by bringing the disease under control, through both the *depth* and duration of response to treatment, patient symptom burden can be meaningfully reduced and a resulting impact on quality of life observed.

The pivotal Ph3 clinical trial investigating CRd versus Rd reported that the overall response rate (ORR) was significantly higher in the CRd arm compared with the Rd arm (87.1% vs 66.7%; [redacted] $p < 0.0001$). Further, the proportion of patients who achieved a complete response (CR) or better was more than 3 times higher in the CRd arm than in the Rd arm (CRd 31.8%; Rd 9.3%). This includes 14.1% of patients in the CRd arm and 4.3% of patients in the Rd arm who achieved a stringent CR (sCR). In addition, CRd was shown to be fast acting, with a mean time to response of 1.6 months compared to 2.3 months, in the Rd arm. Feedback from clinical experts suggested that the difference in response profiles observed for CRd and Rd would likely result in treatment specific differences in quality of life. Furthermore, the of use of treatment specific utility
</td><td>Comments noted. The committee considered that it had not been presented with strong evidence to support the company's use of treatment-specific utility values. The committee concluded that it would consider both treatment-specific and using the same values for both treatments in its decision-making. It noted that applying either choice of utility values resulted in carfilzomib plus lenalidomide and dexamethasone being cost-effective. See FAD section 3.6.</td></tr>
</table>

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			values are also justified by the HRQoL data reported in the ASPIRE clinical trial. Overall, we believe that the compelling data reported in ASPIRE, combined with the clinical rationale for observing improved quality of life with greater disease control, provides sufficient justification for Amgen's approach used in the economic evaluation. This was also the conclusion reached during the original TA457 appraisal where the inclusion of treatment specific utility values was accepted and formed part of the NICE Committee's preferred assumption for carfilzomib. Although the NICE Committee consider the application of treatment specific utility values to be 'reasonable' and the ACD re-affirms the clinical expert view that the quality of life of patients treated with CRd is likely to be improved versus Rd, this is not captured in the NICE preferred assumptions. Although it is considered by NICE that the impact with be small, application of treatment specific utility values has the effect of reducing the NICE preferred ICER from £50,960 to £45,919 per QALY (lenalidomide at list price). Given the challenges in demonstrating cost-effectiveness for combination therapies and the importance of reflecting patients' actual experience of disease control Amgen believe NICE should incorporate this evidence base into its decision-making.	
13	Consultee	Amgen	**Section 4 - Uncertainty in long term treatment benefit** The ACD states that the '*committee agreed it was unclear how long the treatment benefit would last for carfilzomib with lenalidomide and dexamethasone*' and that '*additional analyses [would be required] before it can accept that a treatment benefit for carfilzomib with lenalidomide and dexamethasone would persist after treatment has stopped*.' Furthermore, it is stated that '*Because of uncertainty in the relative treatment benefit of carfilzomib with lenalidomide and dexamethasone beyond the observed ASPIRE data, the committee agreed that an acceptable ICER would be no higher than the middle of the range normally considered a cost-effective use of NHS resources (£20,000 to £30,000 per QALY gained)'.* Amgen believe that the concerns highlighted in the ACD relating to long term treatment benefit overstate the uncertainty in this appraisal and do not reflect the mature evidence from the high-quality Ph3 ASPIRE RCT. Following the 1st Appraisal Committee Meeting, Amgen submitted two addendums demonstrating that the evidence from the ASPIRE clinical trial, which includes follow-up >6-years, supports a consistent treatment effect over time across the populations relevant to decision making. **Given this, we believe that it is highly unlikely that a strong and sustained treatment effect observed over such a long duration would diminish after the trial follow-up period.** This evidence base was used to inform Amgen's Base Case analysis, and the approach utilised was	Comments noted. The committee agreed that the new evidence clearly showed that a treatment benefit is maintained for carfilzomib plus lenalidomide and dexamethasone after 18 cycles of carfilzomib treatment (28 days of treatment per cycle) and during the entire trial follow-up period (72 months). However, it was not convinced there was sufficient evidence or clinical rationale to support the assumption of a continued treatment benefit beyond the observed ASPIRE data. See FAD section 3.9. The committee considered that the cost-effectiveness estimates may be optimistic because some waning of treatment benefit with carfilzomib plus lenalidomide and dexamethasone is likely to occur beyond the observed ASPIRE data

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			supported by the ERG during the appraisal. **Amgen do not believe this additional evidence base has been considered during development of the ACD and have thus included both addendums as a part of our response (see Addendum 1 and Addendum 2).** Across all populations explored, no trend suggesting a reduction in the hazard ratio over time was observed within the >6-years of follow-up in these analyses. This is supported with conclusions drawn from KM plots, Schoenfeld residuals and cumulative hazard plots which all suggest that a consistent treatment effect beyond the observed timeframe in the clinical trial remains appropriate. Finally, the maturity of the clinical evidence base was welcomed by the Committee in the ACD which also reports the clinical expert stating '*that this is the first multiple myeloma trial with a long follow-up period to provide clear evidence of improved progression-free survival and overall survival.'* However, this position is inconsistent with the proposed application of a reduced decision-making threshold due to uncertainty in the evidence base. Indeed, from our own experience, it is rare to have such definitive and long-term data that is directly relevant to the decision problem at the time of NICE submission. **Amgen believe that considering a reduced upper threshold limit on the basis of uncertainty fails to reflect the maturity of the data available, and places an additional, unjust burden on patient access to an effective combination therapy.**	(see FAD section 3.9). Based on the evidence presented to it and the revised commercial arrangement, the committee concluded that the most plausible ICERs are within the range that NICE normally considers an acceptable use of NHS resources. There, the committee recommended carfilzomib plus lenalidomide and dexamethasone. See FAD sections 1.1, 3.11 and 3.12.
14	Consultee	Amgen	**Section 5 – Combination Therapies** We welcome the consideration of the challenges posed by combination therapies in the ACD and the reflection that when excluding the additional cost of the backbone therapy, the base case ICER is substantially reduced (£16,751 per QALY, lenalidomide list price). However, it is Amgen's view that this issue can create isurmountable barriers to demonstrating cost- effectiveness and further interrogation is required. As reported in our submission dossier and during the technical engagement consultation, only [redacted] of the acquisition cost of CRd was due to the carfilzomib cost (analysis conducted at lenalidomide list price). As a result, Amgen has little opportunity to influence this ICER with respect to the cost of carfilzomib, creating in some circumstance scenarios where CRd is not cost-effective when carfilzomib is provided free-of-charge. This clearly presents a circumstance where the HTA process requires additional flexibility to ensure appropriate decisions around access for new and effective treatment combinations are made. We recognise this issue is broader than the CRd appraisal, however, there are a few specific aspects we believe are pertinent for the Committee to consider:	Comments noted. The committee acknowledged that treatments that extend the use of other high-cost drugs (such as lenalidomide) can lead to additional cost associated with those other drugs. However, it concluded that because the NHS would incur these additional costs in practice, they should be included in the model. See FAD section 3.10.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			• Prior to TA586 Guidance, lenalidomide was available with a complex 26-cycle cap to the NHS which resulted in an ICER of £27,221 when applied in the Amgen base case analysis; this was replaced by an '*equivalent'* simple discount when the TA586 Guidance was published. Despite this simple discount, it was stated in the FAD that '*the most plausible cost-effectiveness estimate for lenalidomide plus dexamethasone may be above the range that NICE normally considers to be a cost-effective use of NHS resources*'. **The specific implication is that the cost-effectiveness of adding carfilzomib to Rd is penalised by the cost of the background therapy. As previously mentioned, the background therapy cost-effectiveness is amplified beyond what is typically accepted for other combination therapies.** • [redacted] ***Amgen strongly urge NICE to give greater consideration to these issues and apply appropriate flexibility to remove unjust barriers to access.***	

NICE National Institute for Health and Care Excellence

Carfilzomib with dexamethasone and lenalidomide for treating multiple myeloma after at least 1 previous therapy [ID1493]

Consultation on the appraisal consultation document – deadline for comments 5pm on Tuesday 13 October 2020 **Return to:** NICE DOCS

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

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.

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Carfilzomib with dexamethasone and lenalidomide for treating multiple myeloma after at least 1 previous therapy [ID1493]

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Section 1 - Executive Summary	We have carefully reviewed the Committee's consideration of the evidence for the part review of single technology appraisal (STA) of *Carfilzomib with dexamethasone and lenalidomide [CRd] for previously treated multiple myeloma* [ID1493]. We are extremely disappointed by the conclusions reached and the resulting preliminary guidance not to recommend carfilzomib in this indication. We welcome the Committee's recognition of the clinical need for an effective second-line therapy and the maturity of data from ASPIRE which demonstrates clear and meaningful benefit in survival outcomes. However, the Committee considered there to be uncertainty in the cost-effectiveness evidence, and that likely cost-effectiveness estimates are higher than what NICE normally considers a cost-effective use of NHS resources. We remain committed to working with NICE to address all of the Committee's concerns and ensure patients can access this important combination medicine. This was also our commitment and approach in Scotland where the Scottish Medicines Consortium (SMC) has just published positive guidance for CRd (Monday 12th October). We are confident that the further analyses presented here will sufficiently address the uncertainties identified by the Committee. Furthermore, by considering key model assumptions that are consistent with both the extensive evidence base and prior NICE appraisals in this disease area, recognising the challenges associated with combination therapies, [redacted], we believe NICE can be confident in recognising CRd as cost-effective. Our response will focus on the following components, which when taken together, we believe can allow NICE to overturn the initial negative recommendation: **<u>Priority Issues</u>** • **The Committee-preferred overall survival (OS) assumptions used in the economic evaluation underestimates long-term survival and are inconsistent with accepted estimates considered clinically plausible in previous appraisals in this disease area [See Section 2]** *An exploratory analysis investigating the impact on the incremental cost-effectiveness ratio (ICER) of applying an OS extrapolation assumption consistent with previous appraisals in this disease area significantly reduces the Committee preferred ICER from £50,960 to £35,513 (using lenalidomide list price).* • **Amgen consider that there is a clear case for a treatment-specific utility impact beyond progression-free survival (PFS) and OS gains to be captured in the economic evaluation. Such an approach is consistent with NICE preferred assumptions during the original TA457 appraisal and incorporation of this evidence-base is supported by strong clinical expert opinion. Health-related**

quality of life (HRQoL) data was also collected as part of the robust pivotal Ph3 ASPIRE trial and has been presented by Amgen. [See Section 3]
*The ACD states that the Amgen preferred assumptions are '*reasonable*' and that CRd* 'would increase the effectiveness of controlling the disease, which in turn would improve quality of life'*. However, the Committee preferred approach is to exclude this benefit, citing that it had '*little effect on the ICER*'. Amgen believe that NICE should incorporate this evidence base into its decision-making as it is an essential component of the cost-effectiveness evaluation of this combination therapy and reflects patients' actual experience of disease control.*

- **The ACD does not adequately reflect the mature evidence from the high-quality Ph3 ASPIRE RCT. A reduced decision-making threshold appears unfair and is unjustified in light of the long-term follow-up data presented. [See Section 4]**
Within the extensive trial data follow-up (>6 years), no trend supportive of a reduction in treatment effect was observed and we strongly believe that the Amgen and ERG preferred assumption of a consistent treatment effect remains valid. Furthermore, as reported in the ACD 'the clinical expert stated that this is the first multiple myeloma trial with a long follow-up period to provide clear evidence of improved progression-free survival and overall survival*.' Amgen strongly believes that a reduced decision-making threshold on the grounds of uncertainty places an unfair burden on gaining access for patients and does not recognise the maturity of the data set presented.*

- **There are significant access challenges to combination therapies, whereby the new technology is penalised by increased costs of background therapy, that create additional barriers to gaining patient access to this important medicine. [See Section 5]**
Lenalidomide remains a major cost-driver in the acquisition of CRd (accounting for [redacted] *of the acquisition cost at list price, Committee preferred base case) providing Amgen little opportunity to influence the decision making ICER with respect to the cost of carfilzomib - this issue is compounded by the fact that lenalidomide plus dexamethasone was recommended despite not demonstrating cost-effecitveness in TA586.* [redacted] ***We strongly urge the NICE Committee to take these considerations into account and apply appropriate flexibility to remove unjust barriers to access.***

<u>Additional Considerations</u>

- **Amgen believe there are several inconsistencies in the application of assumptions in this appraisal compared with other TAs (both within and outside the MM disease area) that place an unfair burden on demonstrating the cost-effectiveness of CRd.**

In addition to the clinically plausible OS extrapolation, preferred utilities and application of a reduced decision-making threshold in the prescence of mature Ph3 data, we believe there is precedent for NICE to consider flexibility of the EoL criteria. We are aware that NICE have previously applied flexibility and discretion in the application of end-of-life criteria to appraisals of treatments for metastatic cancer when: ***1)*** *OS without the new drug exceeds 24 months;* ***2)*** *the new drug provides significant extension to life beyond 3 months;* ***3)*** *the new drug is combined with existing treatment, and* ***4)*** *both the existing treatment and the new drug are used until disease progression.* ***We maintain CRd meets these criteria and thus there is a case for additional flexibility to be applied during the decision-making process and a higher cost-effective threshold to be considered.***

- **Considerations by the Committee do not fully reflect clinical reality by failing to consider comparative analyses presented versus daratumumab in combination with bortezomib and dexamethasone (DVd).**
  Although we recognise NICEs existing Position Statement on the consideration of products recommended for use in the Cancer Drugs Fund as comparators, it is our view that the conclusions of this analysis should be taken into account outside of the reference case. Clinical experts consulted by NICE suggested as many as 80% of patients receive DVd in England as a second-line treatment and conclusions of an indirect comparison exploring the relative efficacy of CRd versus DVd presented in our original submission [redacted].
  Given the current use of DVd in the second line treatment of myeloma and the potential for CRd to offer increased benefit at a reduced cost, we believe this analysis is of ***significant importance*** *to the decision problem and is reflective of current clinical reality.*

- **Following the recent positive recommendation for CRd in Scotland (SMC2290, October 12th) Amgen are concerned that maintaining a negative decision would lead to an inequity in patient access to CRd across the UK and are committed to working with NICE to resolve this**.
  Although we recognise that NICE and the SMC approach decision making differently and independently, the ability of the SMC to consider DVd as a comparator and apply flexibility in decision making with respect to combination therapies enabled them to make a positive decision. We urge the NICE Committee to take external circumstances into account and apply appropriate flexibility in decision making.

[redacted]

Carfilzomib with dexamethasone and lenalidomide for treating multiple myeloma after at least 1 previous therapy [ID1493]

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	[redacted] £50,960 [redacted] [redacted] **Conclusions** Given the external challenges with this appraisal, in particular relating to demonstrating cost-effectiveness for combination medicines, **Amgen genuinely believe we have done everything we can to ensure patients can access this important medicine.** We have shown in this response that by applying appropriate and consistent assumptions, considering wider but no less important context, [redacted] NICE can be confident in recognising CRd as cost-effective treatment option.
Section 2 – Overall Survival Extrapolation Assumptions	Amgen maintain that real world evidence sources incorporated in our submission dossier provide reliable and informative data to capture plausible long-term survival extrapolations; this is supported by evidence put forward during the technical engagement consultation that supports the fact that parametric extrapolation from the ASPIRE clinical trial may result in an underestimation of long-term survival and may not reflect reduction in mortality rates beyond the trial follow-up. Furthermore, as feedback from clinical experts suggests long-term survival with CRd is expected to be *at least* comparable with DVd, both the Amgen and ERG ICER estimates may reasonably be considered conservative when taking in to account clinically plausible long-term survival extrapolations accepted in other MM appraisals. In particular, we suggest it is informative to consider previously accepted estimates of long-term survival by NICE in the recent TA573 appraisal of DVd. In the TA573 FAD, it states that the Committee preferred the ERG's more conservative survival estimate for the daratumumab combination at 20 years of 11% (see Table 1). Feedback from clinical experts during an advisory board conducted to inform this appraisal concluded that long-term survival with CRd was expected to be at least comparable with DVd. This conclusion is supported in the matched-adjusted indirect treatment comparison of CRd vs. DVd presented in the company's submission. Given this, it can reasonably be concluded that Amgen's base case estimate of 20-year survival (6%) remains conservative. Furthermore, theERGs base case prediction of 4% is much lower than the 20-year survival that experts have previously deemed to be clinically valid.

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Table 1: Comparison of 20-year survival rates

	20-year survival
	CRd
Amgen Base Case – RWE (MyelomaToul) informed long-term extrapolation	**6%**
ERG Base Case – parametric extrapolation from ASPIRE	**4%**
NICE Committee Preferred Assumptions for DVd (TA583) - 2L	**DVd**
	11%

Exploratory Analysis

The ERG's preferred OS model, the Exponential model fitted to ASPIRE subgroup data, estimates survival proportions for CRd patients at 10, and 20 years to be 19% and 4%, respectively. These estimates are more conservative than those predicted for DVd and accepted by the ERG. In the FAD for the NICE appraisal of DVd, the 20-year survival probability was 11%. To estimate the impact of OS extrapolation using a similar approach as for DVd, we have performed an explarotary analysis where the proportion of CRd patients alive at 20 years was set to 11%.

For the purpose of this scenario, the NICE Committee's preferred assumptions were selected and then the CRd survival rate beyond the trial follow-up period (72 months) was calibrated using the goal seek function in excel such as 11% of CRd patients were alive at 20 years. The estimated survival probabilities at 10 and 20 years were 26% and 11% respectively. This explarotary analysis yielded a significantly lower ICER than the one estimated by the ERG (35,513 £/QALY vs 50,960 £/QALY).

Table 2. Scenario analysis results for CRd vs Rd, 2L/prior bortezomib no prior lenalidomide subgroup assuming the proportion of patients alive at 20 years is similar to previously accepted

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)
Rd	[redacted]	3.97	2.40	-	-	-	-
CRd	[redacted]	7.75	4.05	58,642	3.78	1.65	**35,513**

CRd: carfilzomib/lenalidomide/dexamethasone; Rd: lenalidomide/dexamethasone; ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years.

In conclusion, we believe there is strong evidence to suggest that extrapolation from the ASPIRE clinical trial may underestimate long-term survival and that the use of external clinical data is appropriate in the base case analysis. Indeed, both the Amgen and ERG ICER estimates may reasonably be considered conservative when taking into account clinically

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	plausible long-term survival extrapolations.
Section 3 – Treatment Specific Utility Values	Multiple myeloma (MM) is a systemic, incurable disease and patients often have noticeable symptoms and decreased HRQoL. Physical symptoms include bone pain, fatigue, infections, and reduced physical function and mobility due to the uncontrolled growth of myeloma cells. As such, it is expected that by bringing the disease under control, through both the *depth* and duration of response to treatment, patient symptom burden can be meaningfully reduced and a resulting impact on quality of life observed. The pivotal Ph3 clinical trial investigating CRd versus Rd reported that the overall response rate (ORR) was significantly higher in the CRd arm compared with the Rd arm (87.1% vs 66.7%; [redacted] $p < 0.0001$). Further, the proportion of patients who achieved a complete response (CR) or better was more than 3 times higher in the CRd arm than in the Rd arm (CRd 31.8%; Rd 9.3%). This includes 14.1% of patients in the CRd arm and 4.3% of patients in the Rd arm who achieved a stringent CR (sCR). In addition, CRd was shown to be fast acting, with a mean time to response of 1.6 months compared to 2.3 months, in the Rd arm. Feedback from clinical experts suggested that the difference in response profiles observed for CRd and Rd would likely result in treatment specific differences in quality of life. Furthermore, the of use of treatment specific utility values are also justified by the HRQoL data reported in the ASPIRE clinical trial. Overall, we believe that the compelling data reported in ASPIRE, combined with the clinical rationale for observing improved quality of life with greater disease control, provides sufficient justification for Amgen's approach used in the economic evaluation. This was also the conclusion reached during the original TA457 appraisal where the inclusion of treatment specific utility values was accepted and formed part of the NICE Committee's preferred assumption for carfilzomib. Although the NICE Committee consider the application of treatment specific utility values to be 'reasonable' and the ACD re-affirms the clinical expert view that the quality of life of patients treated with CRd is likely to be improved versus Rd, this is not captured in the NICE preferred assumptions. Although it is considered by NICE that the impact with be small, application of treatment specific utility values has the effect of reducing the NICE preferred ICER from £50,960 to £45,919 per QALY (lenalidomide at list price). Given the challenges in demonstrating cost-effectiveness for combination therapies and the importance of reflecting patients' actual experience of disease control Amgen believe NICE should incorporate this evidence base into its decision-making.

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Section 4 - Uncertainty in long term treatment benefit	The ACD states that the '*committee agreed it was unclear how long the treatment benefit would last for carfilzomib with lenalidomide and dexamethasone*' and that '*additional analyses [would be required] before it can accept that a treatment benefit for carfilzomib with lenalidomide and dexamethasone would persist after treatment has stopped*.' Furthermore, it is stated that '*Because of uncertainty in the relative treatment benefit of carfilzomib with lenalidomide and dexamethasone beyond the observed ASPIRE data, the committee agreed that an acceptable ICER would be no higher than the middle of the range normally considered a cost-effective use of NHS resources (£20,000 to £30,000 per QALY gained)'.* Amgen believe that the concerns highlighted in the ACD relating to long term treatment benefit overstate the uncertainty in this appraisal and do not reflect the mature evidence from the high-quality Ph3 ASPIRE RCT. Following the 1st Appraisal Committee Meeting, Amgen submitted two addendums demonstrating that the evidence from the ASPIRE clinical trial, which includes follow-up >6-years, supports a consistent treatment effect over time across the populations relevant to decision making. **Given this, we believe that it is highly unlikely that a strong and sustained treatment effect observed over such a long duration would diminish after the trial follow-up period.** This evidence base was used to inform Amgen's Base Case analysis, and the approach utilised was supported by the ERG during the appraisal. **Amgen do not believe this additional evidence base has been considered during development of the ACD and have thus included both addendums as a part of our response (see Addendum 1 and Addendum 2).** Across all populations explored, no trend suggesting a reduction in the hazard ratio over time was observed within the >6-years of follow-up in these analyses. This is supported with conclusions drawn from KM plots, Schoenfeld residuals and cumulative hazard plots which all suggest that a consistent treatment effect beyond the observed timeframe in the clinical trial remains appropriate. Finally, the maturity of the clinical evidence base was welcomed by the Committee in the ACD which also reports the clinical expert stating '*that this is the first multiple myeloma trial with a long follow-up period to provide clear evidence of improved progression-free survival and overall survival.'* However, this position is inconsistent with the proposed application of a reduced decision-making threshold due to uncertainty in the evidence base. Indeed, from our own experience, it is rare to have such definitive and long-term data that is directly relevant to the decision problem at the time of NICE submission. **Amgen believe that considering a reduced upper threshold limit on the basis of uncertainty fails to reflect the maturity of the data available, and places an additional, unjust burden on patient access to an effective combination therapy.**
Section 5 – Combination Therapies	We welcome the consideration of the challenges posed by combination therapies in the ACD and the reflection that when excluding the additional cost of the backbone therapy, the base case ICER is substantially reduced (£16,751 per QALY, lenalidomide list price). However, it is Amgen's view that this issue can create isurmountable barriers to demonstrating cost-

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	effectiveness and further interrogation is required. As reported in our submission dossier and during the technical engagement consultation, only [redacted] of the acquisition cost of CRd was due to the carfilzomib cost (analysis conducted at lenalidomide list price). As a result, Amgen has little opportunity to influence this ICER with respect to the cost of carfilzomib, creating in some circumstance scenarios where CRd is not cost-effective when carfilzomib is provided free-of-charge. This clearly presents a circumstance where the HTA process requires additional flexibility to ensure appropriate decisions around access for new and effective treatment combinations are made. We recognise this issue is broader than the CRd appraisal, however, there are a few specific aspects we believe are pertinent for the Committee to consider: • Prior to TA586 Guidance, lenalidomide was available with a complex 26-cycle cap to the NHS which resulted in an ICER of £27,221 when applied in the Amgen base case analysis; this was replaced by an '*equivalent*' simple discount when the TA586 Guidance was published. Despite this simple discount, it was stated in the FAD that '*the most plausible cost-effectiveness estimate for lenalidomide plus dexamethasone may be above the range that NICE normally considers to be a cost-effective use of NHS resources*'. **The specific implication is that the cost-effectiveness of adding carfilzomib to Rd is penalised by the cost of the background therapy. As previously mentioned, the background therapy cost-effectiveness is amplified beyond what is typically accepted for other combination therapies.** [redacted] ***Amgen strongly urge NICE to give greater consideration to these issues and apply appropriate flexibility to remove unjust barriers to access.***

Insert extra rows as needed

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the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more information.

- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the appraisal consultation document, please submit these separately.

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

Addendum 1 – consistency of treatment effect

During the 1st Committee Meeting for ID1493 there were concerns highlighted that treatment waning had not fully been accounted for in the economic model. This short addendum intends to demonstrate that the evidence from the ASPIRE clinical trial, which includes follow-up >6-years, supports a consistent treatment effect over time across the populations relevant to decision making. Given this, we believe that it is highly unlikely that a strong and sustained treatment effect for more than 72 months would diminish after the trial follow-up period. This approach, used in the Amgen Base Case analysis, was supported by the ERG during the appraisal.

Supporting Evidence

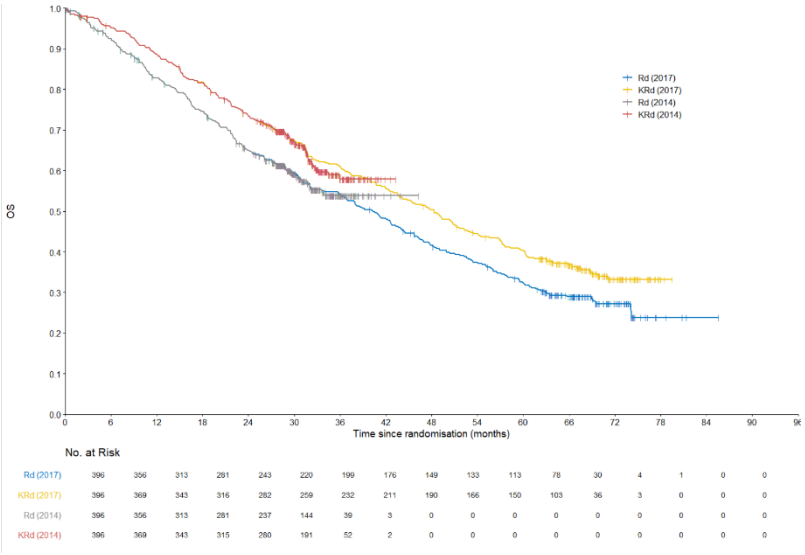
The strong evidence from the phase 3 ASPIRE RCT of a sustained treatment effect over the 72+ months of trial follow-up supports the assumption that the treatment effect is maintained beyond the study period. This can be demonstrated from direct observation of the overall survival (OS) Kapan-Meier curves and interrogation of the diagnostic plots (Schoenfeld residuals, cumulative hazards) which demonstrate that the proportional hazards assumption is satisfied. Data is presented for three populations of interest: 1) intent-to-treat (ITT); 2) 1pLoT with bortezomib; 3) 1pLoT with bortezomib and no prior lenalidomide.

ITT population

In the ITT population, it is clearly demonstrated that OS Kaplan-Meier curve for KRd did not converge towards the OS Kaplan-Meier curve for Rd (Figure 1). Further, the proportional hazards assumption was satisfied during the entire follow-up time of the trial (

Figure 2, Figure 3). It is important to note that at the time of the first interim analysis (June 2014) where the median follow-up time for KRd and Rd was 32.3 and 31.5 months, respectively, there was already a positive trend for KRd vs Rd (HR: 0.79; 95% CI, 0.63-0.99; P = 0.04). After more than two times longer follow-up at the final OS analysis (median follow-up time was 69.2 and 68.1 months for KRd and Rd, respectively), there was an observed 7.9-month increase in median OS with KRd vs. Rd and the OS benefit was statistically significant (HR: 0.79; 95% CI 0.67-0.94). Figure 1 presents OS in ASPIRE based on data at the first interim data cut and at the Final OS analysis and demonstrates a consistent continuation of treatment effect when longer-term data was available.

Figure 1. Overall Survival in ASPIRE, by Data Cut in the ITT population



Notes: Dates in the legend refer to data cut-off dates

Figure 2. Schoenfeld residuals plot in the ITT population

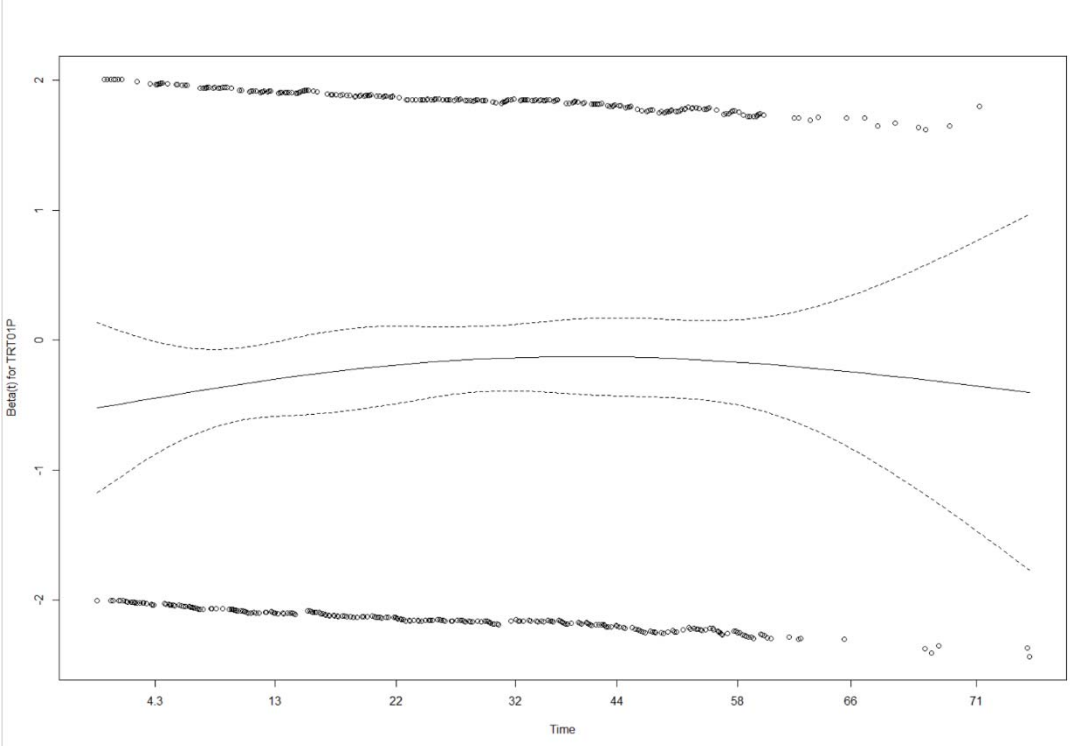
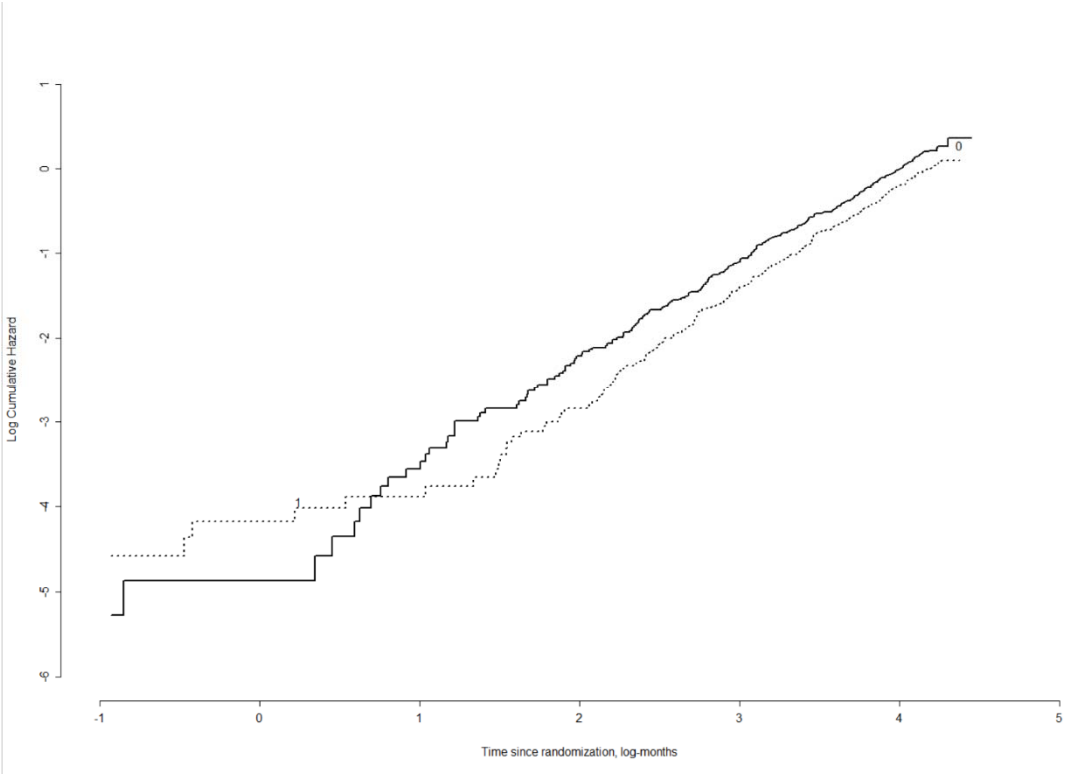


Figure 3. Cumulative hazard plot in the ITT population



1pLoT with bortezomib

The Amgen base case analysis explored the population with one prior line of therapy and who had received treatment with bortezomib. As with the ITT population, the treatment effect was observed consistently during the entire follow-up period, which is demonstrated by the (OS) Kapan-Meier curve and interrogation of the diagnostic plots (Figure 4,

Figure **5**,

Figure 6).

Given this, we think it is highly unlikely that the treatment effect sustained with no signs of waning for more than 72 months would disappear after the trial follow-up period and that the assumption of a consistent treatment effect is appropriate.

Figure 4. Overall Survival in ASPIRE in patients who have received 1pLoT with BTZ

[redacted]

Figure 5. Cumulative hazard plot in in patients who have received 1pLoT with BTZ

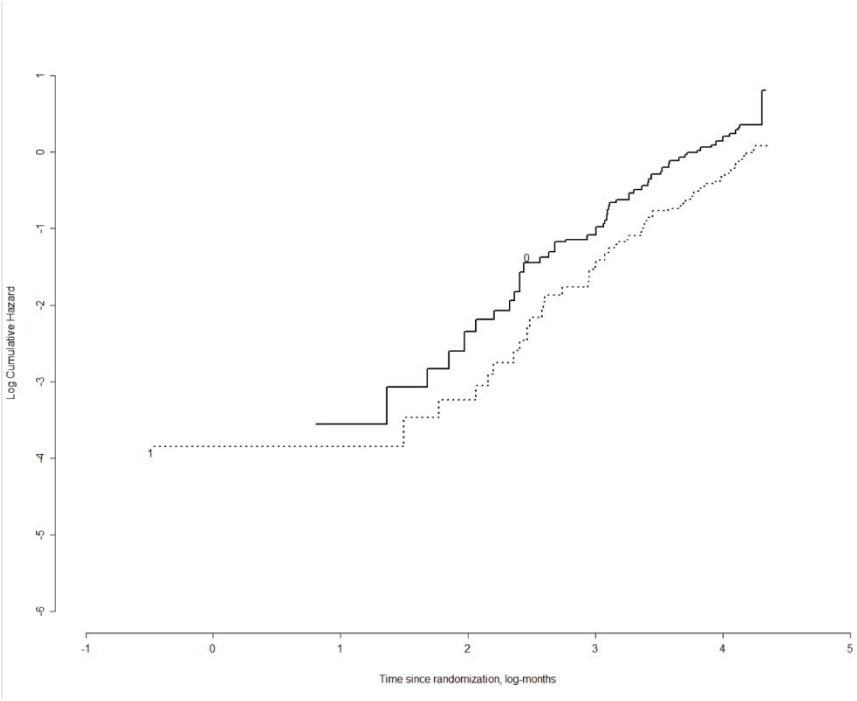
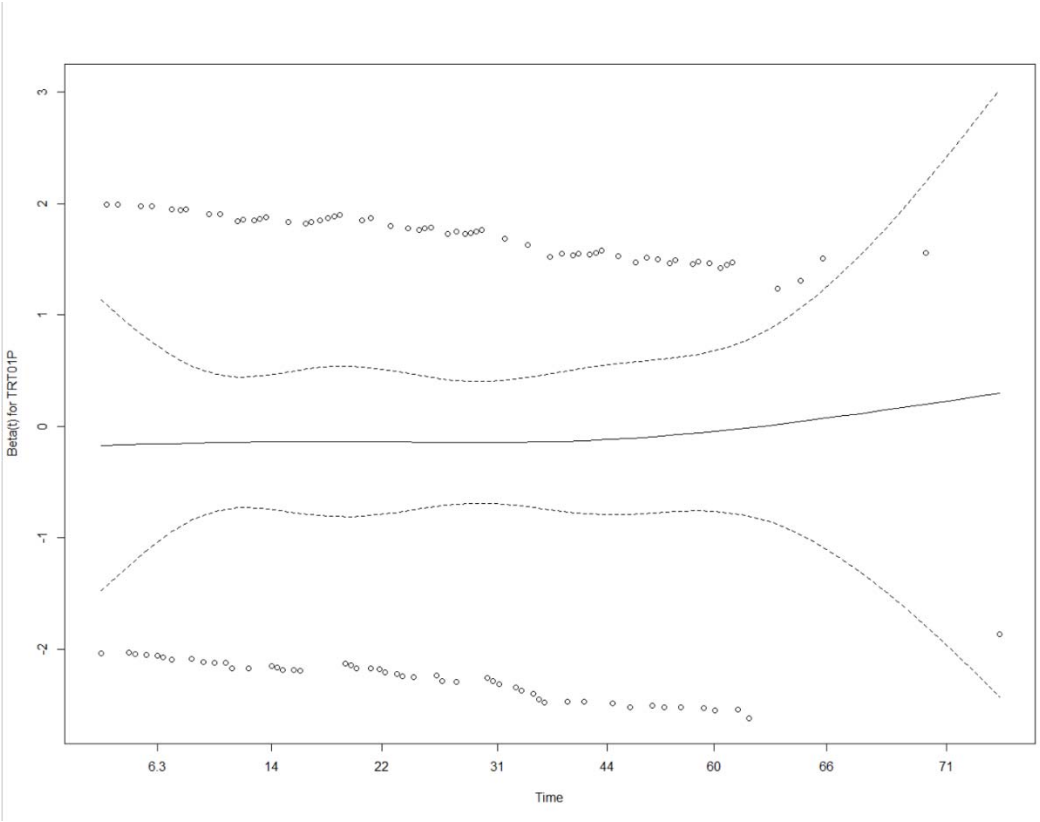


Figure 6. Schoenfeld residuals plot patients who have received 1pLoT with BTZ



1pLoT with bortezomib and no prior lenalidomide

The ERG preferred case analysis explored the population with one prior line of therapy and who had received treatment with bortezomib with no prior treatment with lenalidomide. As with the above analyses, the treatment effect was observed consistently during the entire follow-up period, which is demonstrated by the (OS) Kapan-Meier curve and interrogation of the diagnostic plots (Figure 7, Figure 8,

Figure 9).

Given this, we think it is highly unlikely that the treatment effect sustained with no signs of waning for more than 72 months would disappear after the trial follow-up period and that the assumption of a consistent treatment effect is appropriate.

Figure 7. Overall Survival in ASPIRE in patients who have received 1pLoT with BTZ no prior Len

Figure 8. Schoenfeld residuals plot patients who have received 1pLoT with BTZ no prior len

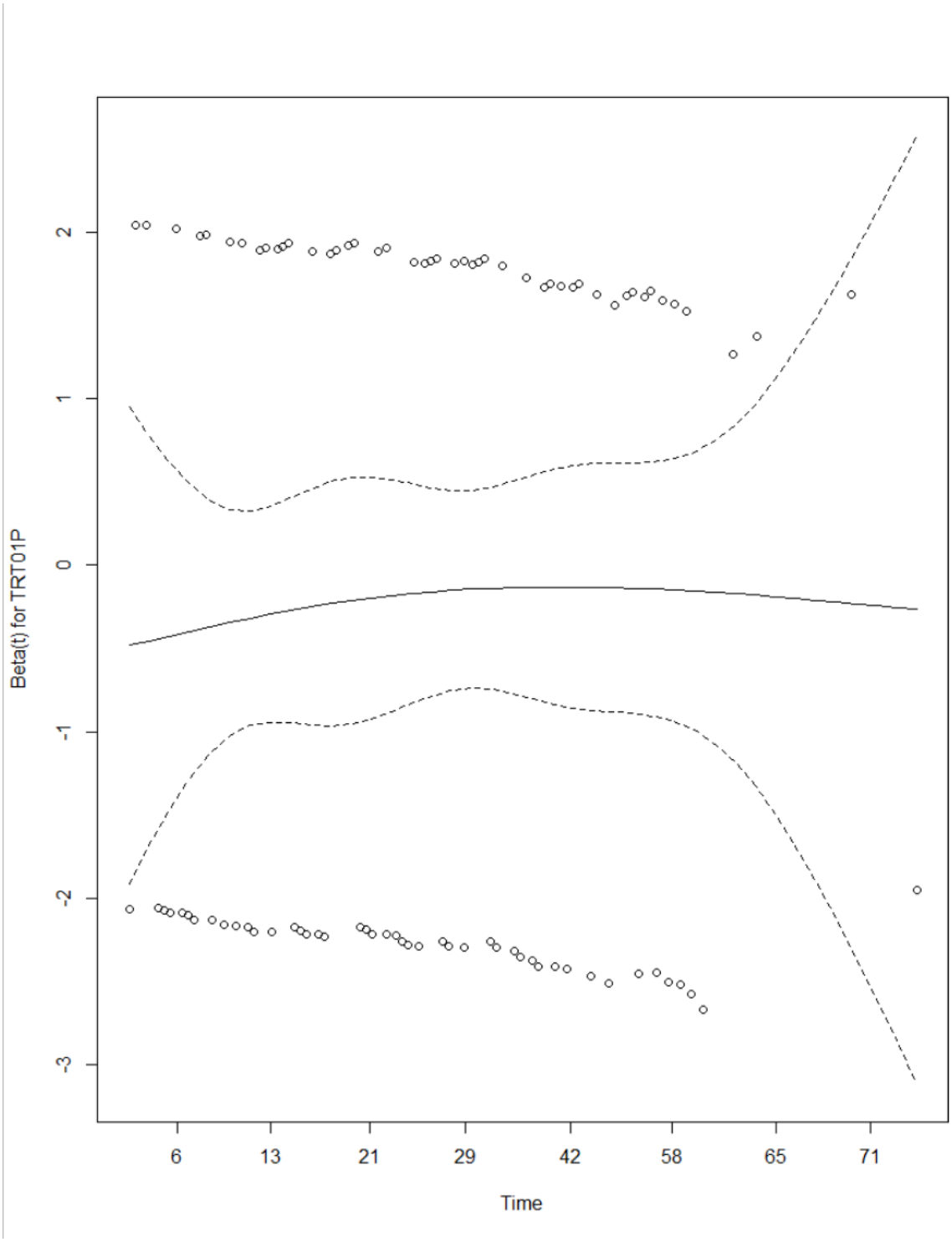
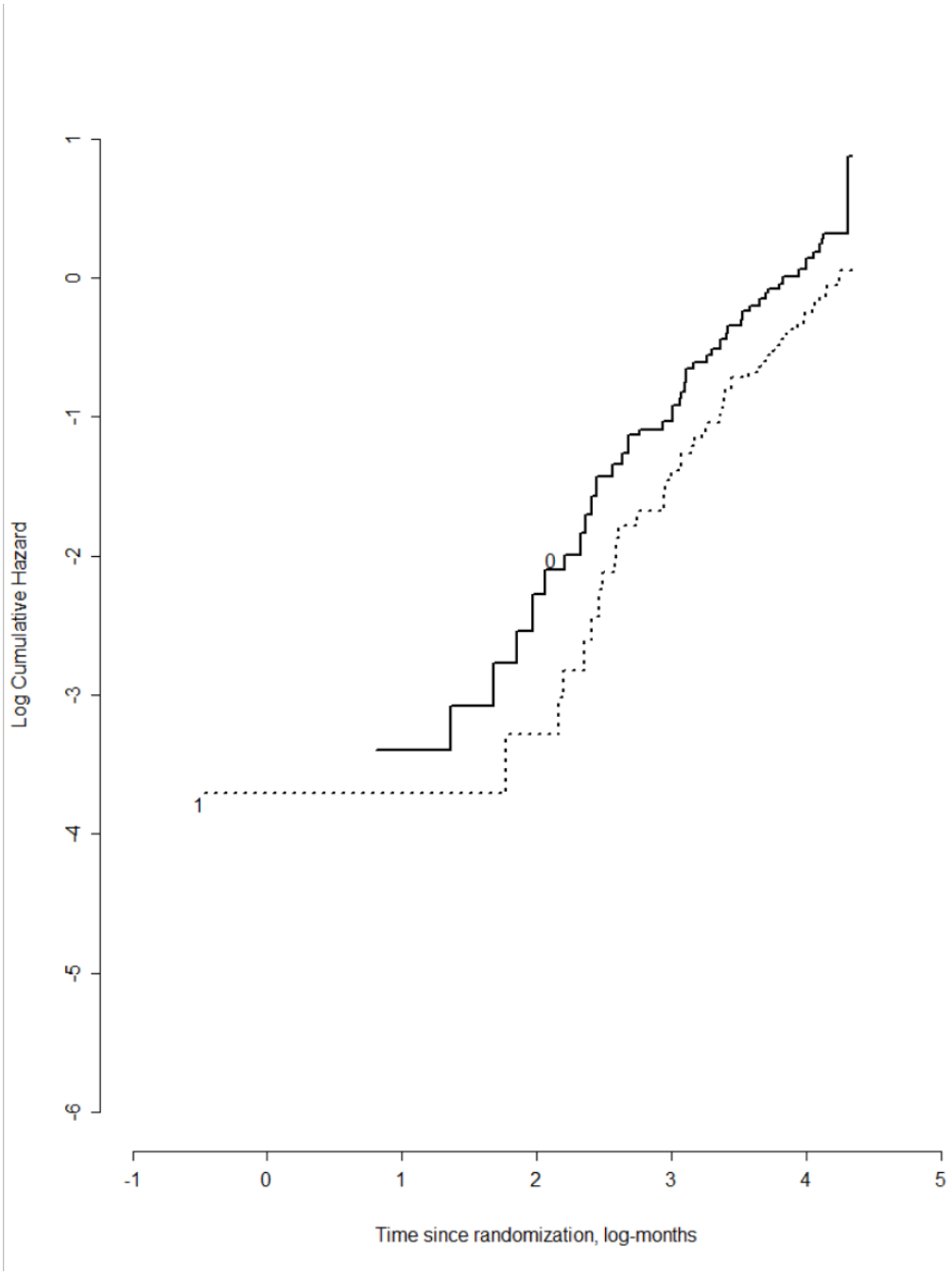


Figure 9. Cumulative hazard plot in in patients who have received 1pLoT with BTZ no prior Len;



Addendum 2– additional analyses on hazard function and hazard ratio

Methodological Note

Empirical death rates were estimated for each 6-month period; this time-period was chosen to capture potential changes in the rates over time and to smooth fluctuations that would have been seen with shorter selected time intervals.

Empirical death rates were calculated based on the Kaplan-Meier survival estimates as follows:

death rate = ln(S[t]) - ln(S[t+1])

where t denotes month 0, 6, 12, etc and S(t) denotes the Kaplan-Meier estimate

For each population of interest, two figures are provided:

- ***Figure 1. Empirical death rate by 6-month periods***

  Under the figure, the number of patients at risk is presented for the starting month of the 6-month period (e.g, 396 refers to the number of KRd patients at month 0 in the ITT population). In parenthesis the number of deaths during that period is presented.

- ***Figure 2. Estimated hazard ratio based on empirical death rates***

  In the figure, the HR and associated 95% confidence intervals estimated by a jointly fitted exponential model (ie, the preferred modeling approach by the ERG for the subgroups) is also provided.

Conclusions

Across all populations explored, no trend supportive of a treatment waning effect was observed within the >5-years of follow-up in these analyses. Given this, and in conjunction with the conclusions drawn from KM plots, Schoenfeld residuals and cumulative hazard plots presented in Addendum #1, we believe that the assumption of no waning effect beyond the observed timeframe remains appropriate.

1. **1pLoT with bortezomib (Amgen Base Case)**

Figure 1.1. Empirical death rate by 6-month periods

Figure 2.1. Estimated hazard ratio based on empirical death rates

2. 1pLoT with bortezomib and no prior lenalidomide (ERG Preferred Population)

Figure 1.2. Empirical death rate by 6-month periods

Figure 2.2. Estimated hazard ratio based on empirical death rates

3. **ITT population (for information)**

Figure 1.3. Empirical death rate by 6-month periods

Figure 2.3. Estimated hazard ratio based on empirical death rates

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Carfilzomib with dexamethasone and lenalidomide for treating multiple myeloma after at least 1 previous therapy [ID1493]

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Myeloma UK
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted]

Comment number	Comments

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	Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
	Myeloma UK Response to Carfilzomib, Lenalidomide and Dexamethasone Appraisal Consultation Document (ACD) Myeloma UK is disappointed that carfilzomib (Kyprolis®) in combination with lenalidomide (Revlimid®) and dexamethasone for multiple myeloma patients who have received one prior therapy has not been approved for routine commissioning.
1	**Has all of the relevant evidence been taken into account?** Yes, the Committee's request to the company for further work to be undertaken on the analyses of prolonged treatment benefit notwithstanding. We welcome the following findings in the ACD based on the evidence presented: - that carfilzomib with lenalidomide and dexamethasone gives longer periods of remission and people live longer than with lenalidomide and dexamethasone - Agreement that second line (first relapse) is the relevant patient population, whether or not stem cell transplant is a suitable treatment option - That this combination would be a welcome addition to the treatment pathway for patients giving them increased options for treating their myeloma. We would go further and argue that it meets a clear need for further treatment options with different mechanisms of action, with a triplet combination representing a significant improvement on lenalidomide and dexamethasone alone - The maturity of the data from the ASPIRE trial showing overall survival benefit
2	**Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** Partially. Agreed areas of evidence are set out above. Areas where we disagree with interpretations of the evidence are set out below: *Post hoc subgroups* – We disagree with the decision to exclude all patients who have previously received lenalidomide. There is clear precedent in relation to the use of ixazomib, lenalidomide and dexamethasone that patients who have been exposed but are not refractory to lenalidomide should be able to access subsequent combination treatments which include lenalidomide. *Utility values used in the economic model* – We disagree with the decision not to use the treatment specific utility values presented by the company. In the trial data, the EORTC QLQ-C30 GHS disease questionnaire was used to establish a clinically meaningful improvement in HRQOL. This is entirely consistent with improved quality of life being derived from improved and faster disease control. We believe strongly that this data collected directly from patients should stand; there is an important principle at stake about valuing quality of life evidence gathered from patients using a validated tool which is accepted under NICE methodology. We do not believe that a case has been made from deviating from this first hand patient reported evidence. *Extrapolation of overall survival and prolonged treatment benefit* – We note the Committee's request for further analyses of prolonged treatment benefit. Our understanding is that overall survival (OS) curves show that survival is maintained in the test arm at the points where carfilzomib frequency is first reduced (at 12 months) and then stopped (at 18 months). This supports the proposition that a significant proportion of patients continue to benefit after carfilzomib has been stopped. As the Committee is aware, the myeloma treatment pathway is continuously and rapidly evolving. This inevitably leads to additional challenges in meaningful extrapolation of overall survival over long

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	time horizons. We support companies being required to present rigorous and complete modelling to capture long term OS benefit. However, alongside this, it is essential that HTA takes a proportionate approach to the uncertainty which arises from the welcome development of the myeloma treatment pathway. There must be a balance between methodological approaches to give us the best understanding of a possible future, and a recognition that such methodology has its limits in the context of scientific development and changing clinical practice. *Cancer Drugs Fund comparators* - We understand the need to avoid building a treatment pathway on the "conditional" foundation of CDF approved treatments which may ultimately not be routinely commissioned. However, we do not believe the current rules strike the right balance between recognising the conditional nature of CDF approval and reflecting real world clinical practice. We acknowledge that it is not possible for the Committee to resolve this issue directly as part of a single appraisal. However, we ask that the Committee takes this issue (particularly dominance of CDF funded daratumumab, bortezomib and dexamethasone at second line for eligible patients) into account when considering what flexibility can be applied in its decision making, in order to reach a decision which is reasonable and meaningful. *Combination treatments* - We note the ACD's reference to the challenge of achieving cost effectiveness for combination treatments and the extent to which this impacts many cancer appraisals. Clearly a key factor in determining cost effectiveness is the price of drugs and any associated patient access scheme which is commercial in confidence. However, we also note the calculation presented by the company which demonstrates the extent to which the cost of lenalidomide is driving the price of the combination - a factor which the makers of carfilzomib are not in a position to influence. Like issues relating to CDF treatments we appreciate it is not within the gift of the Committee to resolve this issue in a single appraisal, but we believe it is important context.
3	**Are the provisional recommendations sound and a suitable basis for guidance to the NHS?** No. For the reasons set out above we believe that the Committee should reconsider its decision not to approve this treatment for use on the NHS. Finally, we wish to record that we strongly disagree with approach that, due to uncertainty in relative treatment benefit, an acceptable ICER would be no higher than the middle of the range normally considered a cost-effective use of NHS resources (£20,000 to £30,000 per QALY gained). We note that the NICE guide to methodology in technical appraisals confirms that "the Committee will be more cautious about recommending a technology when they are less certain about the ICERs presented". This is understood. However, we are very concerned that this has been translated into effectively lowering what is normally seen as the cost-effectiveness threshold. We have never seen this approach before in our considerable engagement with myeloma technology appraisals. We believe that such an approach disadvantages a relapsing and recurring cancer like myeloma, where its complex treatment pathway inevitably leads to higher levels of uncertainty and the need for theoretical modelling.
4	
5	
6	

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- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the appraisal consultation document, please submit these separately.

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

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

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	UKMF-BSH-RCPath
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted]

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1	We note that Carfilzomib lenalidomide and dexamethasone has not been approved on the basis that there is uncertainty about how long the benefit lasts after stopping treatment. Myeloma remains an incurable illness, combination therapies at relapse presents a significant step up in salvage options for patients who have an unstable myeloma genome. The responses obtained with combination therapies are deeper and sustained. This is reflected in improved remission periods and translates to improved overall survival.
2	Has all of the relevant evidence been taken into account? Yes
3	Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? The appraisal consultation document reflects the discussion at the meeting, particularly around the advantages to myeloma patients of having Carfilzomib, Lenalidomide and dexamethasone combination as an option for treatment of relapsed myeloma. There was agreement on Lenalidomide and dexamethasone being a suitable comparator. During discussion around treatment pathway, there was agreement on 1st relapse or second line population being the relevant position for use of this combination. Posthoc subgroup: Posthoc sub group discussion particularly around prior lenalidomide use, the committee has concluded patients who have been exposed to prior Lenalidomide will be excluded. This presents a complete contradiction to current practice when patients who have received prior lenalidomide and not refractory are eligible for Ixazomib lenalidomide and dexamethasone combination therapy in the NHS. In addition, Myeloma XI academic trial which recruited over 4000 myeloma patients have been exposed to prior Lenalidomide and these patients would be disadvantaged if committee takes a stance to restrict use of this combination in Lenalidomide naïve patients. There are other currents trials in the UK which offer lenalidomide in upfront therapy. Therefore a suitable wording should be sought, which would be restricting this combination to lenalidomide sensitive patients. Clinical community struggles to understand the position taken by the appraisal committee on the grounds that there is uncertainty about how long the benefit lasts with the Carfilzomib Lenalidomide dexamethasone combination therapy. ASPIRE study is the only Phase III relapsed myeloma trial with long follow up every considered by NICE committee with over 6 years actual follow up. The trial demonstrates a clear improvement in overall survival which often remains immature when other combinations have been considered by NICE. In addition, the use of carfilzomib with ASPIRE trial is limited to 18 months fixed duration which brings to the table certainty duration and therefore costs of therapy. Overall survival: The study has most mature overall survival data presented in relapsed myeloma studies. Overall survival separate early between test and control arms. Carfilzomib frequency is reduced after 12 months and stopped after a fixed duration of 18 months. Visually examination of the overall survival curves do not show a drop in survival in the test arm, during these key timepoints. Therefore a significant proportion of patients stay benefitting from therapy induced response beyond 18 months period when carfilzomib is stopped.

Carfilzomib with dexamethasone and lenalidomide for treating multiple myeloma after at least 1 previous therapy [ID1493]

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	QoL data: Quality of life data from the trial was considered by the committee. There is a significant improvement in quality of life of patients treated with carfilzomib lenalidomide and dexamethasone combination. This is derived from improved and faster disease control. We request NICE to be consistent in application of utility values derived from Qol studies across all myeloma relapsed study technology appraisals. We are concerned about clinical evidence considered at NICE committee meetings. They are increasing artificial hypothetical discussions and do not reflect current clinical practice.
3	Are the recommendations sound and a suitable basis for guidance to the NHS? Based on the above comments committee should reconsider the recommendations
4	Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity? No

Insert extra rows as needed

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Carfilzomib for previously treated multiple myeloma (part review of TA457) (ID1493)

ERG response to company comments on ACD

October 2020

Source of funding

This report was commissioned by the NIHR Evidence Synthesis Programme as project number 129575/T

1 Introduction

This document provides the Evidence Review Group (ERG) response to the company's comments on the appraisal consultation document (ACD) for carfilzomib in combination with lenalidomide and dexamethasone (hereafter referred to as CRd) for adult patients with multiple myeloma who have received only one prior therapy with bortezomib.

The company has not made any changes to their base case ICER of £43,952 but presented [redacted]. In addition, the company has provided a new scenario exploring improved overall survival (OS) for CRd based on survival estimates for daratumumab in combination with bortezomib and dexamethasone (hereafter referred to as DVd) from TA573 and addenda presenting additional evidence requested by the committee on the consistency of the treatment effect for CRd. The new OS scenario and consistency of treatment effect are explored further in Section 2 of this report.

The company also reaffirm their position on the appropriateness of treatment specific utility values and the issue of demonstrating cost effectiveness for combination therapies. With regards to the issue of treatment specific utility values, the company has provided no new evidence, but maintains that improved objective response rate (ORR) and consistency with previous committee decisions should overturn the committee's decision to use health-state specific utility values. However, the ERG's position on use of treatment specific utility values remains unchanged from the original ERG report. Furthermore, in the appraisal committee meeting, the committee discussed the issue of inclusion of lenalidomide and dexamethasone costs for CRd but deemed that it was relevant to include them because the NHS would incur those costs in practice. As such, the issues of treatment specific utilities and the cost-effectiveness of combination therapies are not discussed further in this report.

As the company has provided no new evidence in support of their submission, the ERG's position remains unchanged and so the ERG base case ICER remains £50,960.

2 ERG critique of additional company evidence

2.1 Overall survival

The issue of appropriate extrapolation of overall survival (OS) data was discussed by the committee during the appraisal committee meeting and in the appraisal committee document (ACD) it is stated that, "*The committee preferred the exponential model for estimating overall survival for both treatment arms because it used data entirely from the ASPIRE trial*". In response to the ACD, the company reaffirmed that survival estimates for DVd from TA573 are relevant for consideration when determining the most appropriate method to estimate OS for CRd.

Specifically, the company state that in the final appraisal document (FAD) for TA573, the committee preferred the ERG's OS estimate of 11% for DVd and that the company's clinical experts considered that long-term survival with CRd is likely to be comparable with DVd. As such, the company provided a scenario where OS is improved for CRd beyond the trial follow-up (72 months) by calibrating the model to ensure 11% of CRd patients were alive at 20 years, while the OS estimates for Rd remain unchanged. The updated estimated survival probabilities for CRd at 10 and 20 years were 26% and 11%, respectively. The ERG notes that the scenario survival estimates are higher than both the company base case and the ERG preferred analyses. Based on the exponential distribution, the ERG's preferred estimates for OS for CRd at 10 and 20 years were 19% and 4%, respectively and the company's base case estimates were 21% and 6%, respectively. Table 1 presents the results of the company's OS scenario applied to the ERG's preferred analysis with the company's patient access scheme (PAS) discount of [redacted] applied.

Table 1. OS Scenario analysis results - CRd vs Rd, 2L/prior bortezomib no prior lenalidomide subgroup

Interventions	Total Costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
ERG preferred analysis							
Rd	[redacted]	3.97	2.40	-	-	-	-
CRd	[redacted]	5.98	3.44	53,017	2.01	1.04	50,960
Company OS scenario							
Rd	[redacted]	3.97	2.40	-	-	-	-

CRd	[redacted]	7.75	4.05	58,642	3.78	1.65	35,513

Abbreviations: CRd, carfilzomib with lenalidomide and dexamethasone; ICER, incremental cost-effectiveness ratio; OS, overall survival; QALY, quality-adjusted life-year; Rd, lenalidomide and dexamethasone.

The ERG highlights that in the FAD for TA573 the committee, "*was aware of the substantial uncertainty in the extrapolation, which predicted survival up to 30 years based on a trial with a median follow-up of under 3 years, and in the relative treatment effect of daratumumab in the long term"*. As such, the OS estimate of 11% at 20 years for DVd was highly uncertain and the committee considered that it was hard to judge the plausibility of the estimate. The ERG considers it inappropriate to improve OS for CRd based on immature data for another combination treatment when mature trial data from ASPIRE, with a median follow-up for 67.1 months, are available. As such, the ERG view remains that inverse probability weighted (IPW) OS data from ASPIRE should be used for the base-case analysis as it is now mature, which was a considerable limitation in TA457 and thus a clinically plausible extrapolation of OS for CRd can be estimated entirely from trial data. Furthermore, data from ASPIRE are based on the subgroup of interest, the patient characteristics have been adjusted to limit bias and it maintains the observed treatment effect between the two trial arms (a key concern for the committee), increasing the robustness of the cost-effectiveness analysis. The ERG's preference for the exponential model also remains unchanged and the ERG reiterates that the company deemed the exponential distribution provides the most plausible long-term predictions of survival (response to ERG clarification question B7).

2.2 Consistency of treatment benefit

In the ACD, it was stated that the committee, "*were unclear how long the treatment benefit would last for carfilzomib with lenalidomide and dexamethasone. It considered that the application of a prolonged treatment benefit may potentially overestimate survival and be favourable to carfilzomib with lenalidomide and dexamethasone*". In response, the company provided supporting evidence of a sustained treatment effect for CRd, in the form of visual inspection of the Kaplan-Meier (KM) curves and interrogation of diagnostic plots (Schoenfeld residuals and cumulative hazards). Furthermore, the company provided plots of empirical death rates by six-month periods and estimated hazard ratios based on the empirical death rates by six-month periods. All plots were provided for the intention-to-treat population, the 2L prior bortezomib subgroup (company base case) and the 2L prior bortezomib/ no prior lenalidomide subgroup (ERG preferred subgroup).

Based on the diagnostic plots, the ERG agrees that the assumption of proportional hazards cannot be rejected, and the KM curves do not demonstrate a substantial convergence. Moreover, ASPIRE OS data are quite mature and so it is likely that treatment waning associated with CRd is captured in the data, especially as the treatment duration for CRd was a maximum of 18 cycles and median PFS and OS follow-up was 48.8 and 67.1 months, respectively. With regards to the company's analysis of death rates and resulting hazard ratios using six-month categories, the ERG considers that there isn't enough evidence to reject a consistent treatment benefit with CRd, but neither do the plots provided strongly support the assumption. As such, the ERG's view remains that including a treatment waning effect may not be appropriate.