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:

The **final scope** and **final stakeholder list** are available on the NICE website.

1. **Company submission** from **Amgen UK**

2. **Clarification questions and company responses**

3. **Patient group, professional group and NHS organisation submission** from:
   a. Myeloma UK
   b. Royal College of Pathologists-British Society of Haematology

4. **Expert personal perspectives** from:
   a. Dr Karthik Ramasamy – clinical expert, nominated by the Royal College of Pathologists
   b. Shelagh McKinlay – patient expert, nominated by Myeloma UK
   c. Franko Kowalczuk – patient expert, nominated by Myeloma UK
   d. Clinical expert discussion with Karthik Ramasamy prior to Technical engagement

5. **Evidence Review Group report** prepared by **BMJ Group**

6. **Evidence Review Group – factual accuracy check**

7. **Technical Report sent out for Technical Engagement**

8. **Technical engagement response** from **Amgen UK**

9. **Technical engagement responses from experts:**
   a. Karthik Ramasamy – clinical expert, nominated by the Royal College of Pathologists

10. **Technical engagement response from consultees and commentators:**
    a. Myeloma UK
    b. Janssen

11. **Evidence Review Group critique of company response to technical engagement** prepared by **BMJ Group**

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

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Carfilzomib for previously treated multiple myeloma ID1493

Document B

Company evidence submission

January 2020

File name	Version	Contains confidential information	Date
ID1493_Carfilzomib_RR_MM_Amgen Evidence Submission_Document B	2.0	Yes	03/04/2020

Contents

Tables and figures

B.1 Decision problem, description of the technology and clinical care pathway

B.1.1 *Decision problem*

Carfilzomib, in combination with dexamethasone (Cd) or with lenalidomide and dexamethasone (CRd) is indicated for the treatment of adult patients with multiple myeloma who have received at least one prior therapy. In NICE TA457 (2017), Cd was recommended as a 2nd line (2L) treatment option in patients who had not received prior bortezomib; however, CRd was appraised only as a 3rd line (3L) option as an ongoing review of lenalidomide in combination with dexamethasone (Rd) in the 2L setting (part-review of TA171) effectively prevented appropriate consideration of CRd in the 2L setting. CRd was perceived not to be cost effective in the 3L setting, in part due to uncertainty arising from immature overall survival (OS) data from the ASPIRE randomised controlled trial (RCT) of CRd versus Rd.

This submission is in response to a part-review of TA457 relating to CRd only. As NICE has recently completed its appraisal of Rd and recommends its use in the 2L setting (TA586), this now permits appropriate consideration of CRd in the 2L setting. In addition, mature OS data are now available from the ASPIRE RCT (median 5.5 years of survival follow-up, i.e., double the length of follow-up available at the time of our original submission for TA457), which removes the previous uncertainty in the significant and clinically meaningful reduction in the risk of death with CRd versus Rd (Section B.2.6) and supports this 2L positioning.

This submission focusses on the use of CRd as 2L treatment only, in patients who received prior bortezomib in the first line (1L) setting. This proposed patient population and positioning is narrower than the marketing authorisation for CRd permits, but is appropriate and justified as this reflects:

- the clear unmet need for triplet therapies that target multiple pathways and enable deeper and more durable responses, as well as improved survival outcomes, earlier in the pathway;[1, 2]
- feedback from clinical experts that CRd will offer the greatest benefit to patients in the 2L setting;[3]
    - In the pivotal ASPIRE trial, patients at 2L demonstrated improved clinical outcomes compared with later lines (post hoc subgroup analysis, see Section B.2.7), which supports the value of CRd being used early in the pathway.
- an alignment with the reimbursement criteria of the most relevant comparator (Rd) which is supported by a phase 3 randomised comparison;
- the subgroup where CRd offers the greatest economic value given the substantial clinical benefit observed in this population.

In addition, this subgroup population in particular faces the greatest unmet need in the multiple myeloma treatment pathway – extensive use of bortezomib in the 1L setting (in approximately [redacted] % of patients), results in an urgent need for improved access to effective non-bortezomib containing 2L treatment options, which are currently limited.[3]

The decision problem addressed in this submission is summarised in Table 1 below.

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with multiple myeloma who have received at least one prior therapy	Adults with multiple myeloma who have received only one prior therapy with bortezomib	CRd is not positioned for use in patients who have received more than one prior therapy as it is anticipated to be used earlier in the treatment pathway in clinical practice
Intervention	CRd	Per final scope	N/A
Comparator(s)	For people who have received one prior therapy: • carfilzomib plus dexamethasone (Cd) • lenalidomide plus dexamethasone (Rd) • bortezomib For people who have received two prior therapies: • lenalidomide plus dexamethasone (Rd) • panobinostat plus bortezomib and dexamethasone (FVd) For people who have received three prior therapies: • lenalidomide plus dexamethasone (Rd) • panobinostat plus bortezomib and dexamethasone (FVd) • pomalidomide plus dexamethasone (Pd)	For people who have received one prior therapy with bortezomib: • lenalidomide plus dexamethasone (Rd) An additional analysis is also presented versus daratumumab plus bortezomib and dexamethasone (DVd) which is currently recommended for use within the Cancer Drugs Fund as a treatment option for adults who have had one prior therapy.	People who have received one prior therapy: • Amgen proposes that CRd will be used primarily as an alternative treatment option to Rd in patients who have received one prior therapy with bortezomib. This positioning is aligned with clinical experts' opinion on appropriate use of CRd in UK clinical practice, the primary evidence base underlining this appraisal, the reimbursed population of the primary comparator, and where CRd is likely to derive the most benefit for patients. • In addition, Amgen proposes that a comparison versus DVd remains informative to the decision problem given the high expected uptake of DVd in clinical practice following the CDF recommendation • Amgen does not propose that CRd will be used as an alternative treatment to bortezomib re-challenge as it is anticipated that use bortezomib will be limited in this

			population, due to the availability of superior regimens with alternative mechanisms of action and the standard clinical practice of switching between drug classes with different mechanisms of action. This position is aligned with the recent conclusion of the NICE Committee during TA586 where treatment re-challenge with bortezomib was not considered to be an appropriate comparator to lenalidomide plus dexamethasone in the population under consideration. As such, bortezomib is not considered to be a relevant comparator within this appraisal. People who have received at least two prior therapies: • As outlined above, Amgen does not propose that CRd will be used in patients who have received at least two prior therapies. • CRd was previously appraised as a 3rd-line treatment option (NICE TA457) and was not recommended for use in this setting
Outcomes	• Progression-free survival • Overall survival • Response rates (e.g. complete response) • Time to next treatment • Adverse effects of treatment • Health-related quality of life	Per final scope	N/A
Economic analysis	• The reference case stipulates that	Per final scope	NA

	the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year • The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared • Costs will be considered from an NHS and Personal Social Services perspective • The availability of any patient access schemes for the intervention or comparator technologies will be taken into account		
Subgroups to be considered	• If the evidence allows, subgroup analyses based on type and number of lines of previous therapy will be considered.	• Patients who have received one prior therapy with bortezomib	• Amgen propose to consider a subgroup of the marketing authorisation as the primary population of interest in this appraisal • Specifically, patients who have received prior bortezomib are the most appropriate population for consideration given: o this positioning is aligned with clinical expert opinion on the optimal use of CRd in UK clinical practice; o the most relevant comparator, Rd, is recommended by NICE in this subgroup and a comparison is supported by robust head-to

			evidence; and o in this position CRd is likely to derive the most benefit for patients.
Special considerations including issues related to equity or equality	None included	None included	NA
Reference: NICE Carfilzomib Final Scope Cd, carfilzomib/dexamethasone; CDF, Cancer Drugs Fund; CRd, carfilzomib/lenalidomide/dexamethasone; DVd, daratumumab/bortezomib/dexamethasone; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; N/A, not applicable; Pd, pomalidomide/dexamethasone; FVd, panobinostat/bortezomib/dexamethasone; Rd, lenalidomide/dexamethasone; TA, technology appraisal; Vd, bortezomib/dexamethasone.			

B.1.2 *Description of the technology being appraised*

A brief overview of carfilzomib is provided in Table 2. The summary of product characteristics (SmPC) for carfilzomib is provided in the reference pack (more information is presented in Appendix C).

Table 2: Technology being appraised

UK approved name and brand name	Carfilzomib (KYPROLIS®)
Mechanism of action	Carfilzomib is a tetrapeptide epoxyketone–based proteasome inhibitor, which binds to the N-terminal threonine active sites of the proteasome, where degradation of proteins predominantly occurs. Proteasome inhibition affects a number of components in cell signalling pathways, leading to cell cycle arrest, and promotes apoptosis by stabilising proapoptotic proteins while reducing levels of some antiapoptotic proteins. Carfilzomib is the only irreversible proteasome inhibitor (the other two proteasome inhibitors, bortezomib and ixazomib, are reversible). Carfilzomib is a selective proteasome inhibitor, with lower levels of off-target proteasome inhibition, which may be responsible for the observed improvements in safety profile.
Marketing authorisation/CE mark status	Carfilzomib was granted orphan designation by the European Commission (EC) in 2008.[4] Marketing authorisation for carfilzomib in combination with lenalidomide and dexamethasone was granted by the EC on 19 November 2015. • A type II variation extending the marketing authorisation to include carfilzomib in combination with dexamethasone was approved on 29 June 2016. • A type II variation incorporating the updated ASPIRE overall survival and safety data in the label was approved on 24 April 2018.
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	Carfilzomib in combination with either lenalidomide and dexamethasone or dexamethasone alone is indicated for the treatment of adult patients with MM who have received at least one prior therapy.[5] For full details of the contraindications, warnings and precautions for use, see Appendix C.
Method of administration and dosage	• Carfilzomib is administered by intravenous infusion. In combination with lenalidomide and dexamethasone (CRd): • Carfilzomib is administered on 2 consecutive days each week for 3 weeks (Days 1, 2, 8, 9, 15, and 16), followed by a 12-day rest period (Days 17 to 28). From cycle 13, the day 8 and 9 doses of carfilzomib are omitted.[5] • Carfilzomib is administered at a starting dose of 20 mg/m^2 (maximum dose 44 mg) in Cycle 1 on Days 1 and 2. If tolerated, the dose should be increased to 27 mg/m^2 (maximum dose 60 mg)[a] from Day 8 of Cycle 1.[5] • Treatment with carfilzomib for longer than 18 cycles should be based on an individual benefit/risk assessment, as the data on the tolerability and toxicity of carfilzomib beyond 18 cycles are limited. In the ASPIRE phase 3 trial, carfilzomib was stopped after 18 cycles

Additional tests or investigations	No additional tests or investigations are required for treatment with carfilzomib.
List price and average cost of a course of treatment	The list price of carfilzomib is £1,056 per 60 mg vial / £528 per 30mg vial / £176 per 10 mg vial (£17.6 per mg).[6] In combination with lenalidomide and dexamethasone (CRd): • One course (cycle) of carfilzomib consists of one 28-day treatment period. Assuming a BSA of 1.79 m^2, the cost of carfilzomib for Cycle 1 (6 infusions totalling 264.92 mg) will be £4,663. • For Cycles 2 to 12 (6 infusions totalling 289.98 mg), the cost of carfilzomib per cycle will be £5,104. • From Cycle 13 onward (4 infusions totalling 193.32 mg), the cost of carfilzomib per cycle will be £3,402. The acquisition cost of lenalidomide is £4,368 per 21-tablet (25 mg) pack (£208 per tablet).[6] One course (cycle) of lenalidomide consists of one 28-day treatment period (21 tablets of 25 mg) at a cost of £4,368 per cycle. The acquisition cost of dexamethasone is £12.39 per 50-tablet (2 mg) pack (£0.25 per tablet).[7] One course (cycle) of dexamethasone consists of one 28-day treatment period (80 tablets of 2 mg) at a cost of £19.82 per cycle.
Patient access scheme (if applicable)	A simple discount PAS has been approved by the Department of Health. This provides a confidential discount of [redacted] % of the NHS list price for carfilzomib. The carfilzomib PAS price is £[redacted] per 60 mg vial / £[redacted] per 30 mg vial / £[redacted] per 10 mg vial (£[redacted] per mg). The cost of carfilzomib for Cycle 1 (six infusions totalling 264.92 mg) will be £[redacted]. For Cycles 2 to 12 (six infusions totalling 289.98 mg), the average cost of carfilzomib per cycle will be £[redacted]. From Cycle 13 onward (four infusions totalling 193.32 mg), the average cost of carfilzomib per cycle will be £[redacted]. The cost of carfilzomib for a patient that completes 18 cycles of treatment will be £[redacted]. Prior to the publication of TA586, lenalidomide was available to the NHS with a complex PAS (26-cycle cap) but this was replaced by a confidential commercial discount in June 2019. Analyses presented in this dossier reflect the list price of lenalidomide.

[a] Patients with a BSA > 2.2 m^2 should receive a dose based upon a BSA of 2.2 m^2.

BSA, body surface area; PAS, patient access scheme.

B.1.3 *Health condition and position of the technology in the treatment pathway*

Summary of Health Condition and Position of the Technology

- Multiple myeloma (MM) is a rare and incurable haematological cancer and represents a substantial burden to patients due to a range of disease- and treatment-related complications
- Despite recent advances in therapy, patients who respond to anti-myeloma agents will most likely develop resistance to their effects, with nearly all patients eventually relapsing or becoming refractory to treatment
- The current treatment pathway for MM is highly complex with multiple treatments approved at various lines of therapy, and treatment selection is highly individualised
- Carfilzomib is a highly selective proteasome inhibitor (PI). Despite being in the broad PI class, in contrast to bortezomib and ixazomib, it is an irreversible PI which has shown to offer increased efficacy and an improved safety profile compared to bortezomib.
- CRd is positioned as an alternative treatment option to Rd in patients who have received one prior therapy (2L) with bortezomib
- The proposed positioning is expected to maximise the value of CRd, due to:
    - the lack of effective, life-extending therapies at 2L and the clear unmet need for triplet regimens that enable deeper and more durable responses earlier in the pathway
    - improved clinical outcomes for prior-bortezomib patients receiving CRd at 2L, compared with later lines in the ASPIRE trial
    - an alignment with the reimbursement criteria of the most relevant comparator (Rd) which is supported by a phase 3 randomised comparison; and
    - the extensive use of bortezomib-containing regimens at 1L, resulting in a high need for non-bortezomib 2L treatment options
- CRd is also positioned and considered as a comparator versus DVd, which although currently reimbursed through the Cancer Drugs Fund, remains informative to the Decision Problem given the high expected uptake of DVd in clinical practice following the CDF recommendation

B.1.3.1 Disease overview

Multiple myeloma (MM) is a rare and complex haematological neoplastic disorder typified by uncontrolled proliferation of malignant plasma cells (myeloma cells) in the bone marrow.[8-10] Despite recent advances in therapy, MM remains incurable, with nearly all patients eventually relapsing or becoming refractory to treatment.[8] With each successive relapse, MM returns more aggressively in a shorter period of time. A patient's ability to achieve and sustain a meaningful response declines with each relapse due to acquired drug resistance and disease biology.[11-13] A recent study showed a decline in response rate from 58% in 2L to 45%, 30% and 15% in 3L, 4L, and 5L treatment, respectively.[14]

MM is an orphan disease, accounting for around 1% of all cancers in the United Kingdom (UK).[15] The median age at diagnosis of MM is 70 years, although approximately 40% of patients are <65 years of age at diagnosis.[10, 16] Although MM survival rates have improved over the past decade, in England and Wales only 33% of patients are estimated to survive for at least 10 years from diagnosis.[17] This is substantially lower than the target set by the England's Independent Cancer Taskforce of 57% by 2020.[18] UK registry data suggest that median survival is less than 2 years

from the start of second line (2L) therapy and around 1 year from the start of third line (3L) therapy.[19]

Whilst living with the disease, MM represents a substantial burden to patients as a result of a range of disease-and treatment related complications.[8, 20] Relapsed patients may have worsened health as a result of disease progression, comorbidities, and cumulative treatment-related toxicities.[20, 21] For example, 37% of relapsed patients may discontinue bortezomib due to adverse events (AEs) and peripheral neuropathy associated with bortezomib and thalidomide use.[16, 22-24] Furthermore, psychological distress due to MM can result in a burden to both patients and caregivers/family members;[25-27] In patients experiencing multiple relapses, a particularly heavy emotional burden with increasing distress and loss of hope has been observed as they realise that treatment options are running out.[27]

B.1.3.2 Carfilzomib

Carfilzomib, in addition to bortezomib and ixazomib, is one of the three proteasome inhibitors currently approved by the European Medicines Agency (EMA). Proteasome inhibition affects a number of components in cell signalling pathways,[28] leads to cell cycle arrest,[29] and promotes apoptosis through the stabilisation of pro-apoptotic proteins whilst reducing the levels of some anti-apoptotic proteins.

Whilst the proteasome is the target of carfilzomib, bortezomib and ixazomib, the chemical structure of carfilzomib results in critical mechanistic differences in the resulting effects on cell signalling pathways. Carfilzomib is a tetrapeptide epoxyketone-based, irreversible proteasome inhibitor which selectively inhibits the chymotrypsin-like subunit of the proteasome;[29, 30] in contrast, bortezomib and ixazomib are both dipeptide boronic acids and reversible proteasome inhibitors.[31]

B.1.3.3 Position of the technology in the treatment pathway

Aims of treatment

The primary treatment goals for MM are prolonging time to disease progression and survival. In addition, treatment goals include preventing damage to other organs of the body by controlling disease activity, preserving normal performance and HRQoL for as long as possible, providing lasting relief from pain and other disease symptoms, as well as managing side effects of treatment and managing remission.[9, 10, 32] Treatment selection is highly individualised,[8, 21] and, in choosing a therapeutic strategy, comorbidities and age are frequently taken into account.[16, 20] Treatment selection is also based on results of physical examinations and laboratory tests, disease stage, general health status, disease-related symptoms, prior myeloma treatment, and the patient's lifestyle and views on QoL.[32] As such, the treatment pathway for MM is complex and frequently changing.

Current treatment options

The standard 1L treatment for patients younger than 65 years or in good clinical condition is induction therapy, undertaken to reduce the number of myeloma cells in the bone marrow, followed by high-dose chemotherapy with stem cell transplant (SCT). In the UK, market research suggests that approximately [redacted] % of patients are treated with bortezomib at 1L as it is efficacious and well tolerated, allowing patients to rapidly achieve remission as a bridge to transplant.[3] However, many patients (around 65% in the UK based on clinical opinion) are not

suitable for SCT and will be treated with pharmacotherapy alone.[33, 34] A second SCT following relapse is uncommon, with pharmacotherapy considered the standard of care in these patients. Whilst multiple agents are licensed in the 2L+ setting (eg, bortezomib, lenalidomide, carfilzomib, elotuzumab, ixazomib, and daratumumab) there remains a significant unmet need for routinely commissioned treatments. Pharmacotherapies specifically indicated for use in MM consist of two-drug (doublet) combinations, three-drug (triplet) combinations, or single agents (monotherapy). There is a move towards the use of triplet regimens, which offer the advantage of targeting multiple pathways to overcome resistance or allow for improved outcomes in terms of the depth and duration of response.[35]

Clinical guidelines

NICE has previously published clinical guidelines titled 'Myeloma: diagnosis and management' (NICE guidance, NG35 2018).[36] However, beyond referencing relevant technology appraisal (TA) guidance these guidelines do not provide any additional guidance on use of specific chemotherapeutic regimens for treating MM, reflecting the requirement for treatment to be individualised to each patient.

The British Committee for Standards in Haematology (BCSH) has also published clinical guidelines for the diagnosis and management of MM (2014).[37] Although these guidelines do not provide recommendations on sequential treatment, thalidomide-, bortezomib-, and lenalidomide-based regimens are highlighted as having extensive clinical study data supporting use at first and subsequent relapses and, unless contraindicated, it is recommended that these agents are administered in combination with dexamethasone with or without chemotherapy to improve the response rate.

In addition to these guidelines, NHS England is developing a National Chemotherapy Algorithm for the management of MM, and published a draft version of its guidance in March 2015.[38] However, as highlighted in the NICE evidence review group (ERG) report for panobinostat, this guidance is still in draft form does not necessarily represent current clinical practice, and is based on an outdated assessment of patients' median survival from diagnosis meaning that clinicians following it may run out of treatment options quickly.[39] In summary, available clinical guidelines do not necessarily reflect current clinical practice therefore to obtain a relevant picture of the MM treatment pathway, individual TA guidance published by NICE and market research should be utilised.

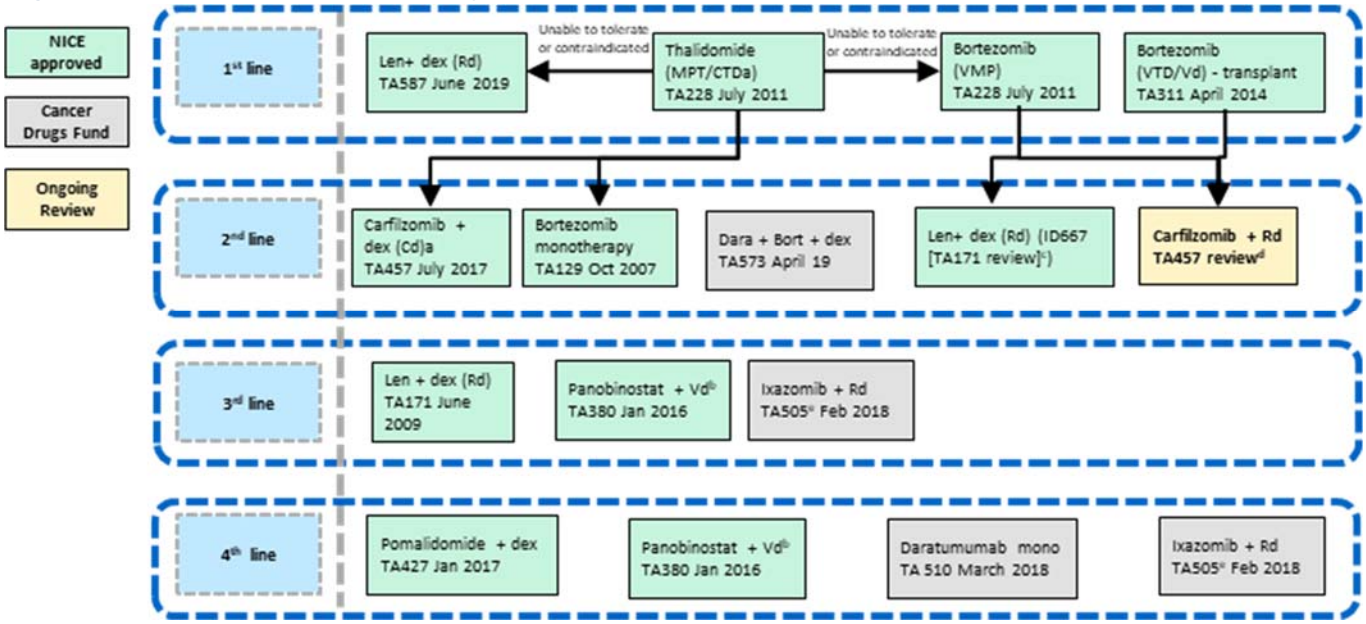
An overview of the current MM treatment pathway based on TA guidance published by NICE and relevant to the proposed positioning of CRd is provided in Figure 1. Until recently, there were no approved treatments for use in patients at 2L with prior bortezomib, with chemotherapy frequently used as a bypass to 3L treatment. Indeed, UK market research conducted in December 2018 indicated widespread use of Rd in the 2L prior-bortezomib setting in the absence of recommended funding, highlighting the lack of treatment options in this position.[3] These data demonstrate that the most frequent treatments used in clinical practice in this position are lenalidomide followed by chemotherapy, thalidomide, carfilzomib and daratumumab.[3]

However, since April 2019 the following relevant guidance has been released:

- **NICE TA573** recommending daratumumab plus bortezomib and dexamethasone for use within the Cancer Drugs Fund as a treatment option for adults who have had 1 previous therapy (April 2019)
- **NICE TA586** recommending lenalidomide plus dexamethasone as a treatment option for adults who had only 1 previous therapy which included bortezomib (June 2019)

The recent NICE TA586 guidance, alongside earlier market research data, underline the validity of including Rd as the primary comparator in this appraisal given its reflection of clinical practice in England and Wales today. However, it is Amgen's view that the recent CDF recommendation of DVd is also pertinent to the decision problem and should be considered by the Committee during this appraisal (see *Proposed CRd positioning below)*.

Figure 1. Current treatment pathway for MM and proposed position of CRd



[a] second line therapy, no prior bortezomib; [b] R/RMM, ≥ 2 prior therapies including bortezomib and an IMiD; [c] CRd second line prior bortezomib

CDF, Cancer Drugs Fund; CTDa, attenuated cyclophosphamide/thalidomide/dexamethasone; Dara, daratumumab: dex, dexamethasone; IMiD, immunomodulatory drug; Kd, carfilzomib/dexamethasone; KRd, carfilzomib/lenalidomide/dexamethasone; MM, multiple myeloma; MPT, melphalan/prednisone/thalidomide; NICE, National Institute for Health and Care Excellence; Rd, lenalidomide/dexamethasone; R/RMM, relapsed and/or refractory multiple myeloma; TA, technology appraisal; Vd, bortezomib/dexamethasone; VMP, bortezomib/melphalan/prednisone; VTD, bortezomib/thalidomide/dexamethasone.

Proposed CRd positioning

This submission addresses the use of CRd in patients who have received one prior therapy with bortezomib (2L with prior bortezomib), which is a narrower population than the marketing authorisation. This positioning reflects the clear unmet need for triplet therapies that enable deeper and more durable responses earlier in the pathway,[1, 2] and is based on clinical expert opinion that anticipates CRd will offer the greatest benefit to patients in the 2L setting.[3] This positioning is consistent with established use in clinical practice across Europe which has been reviewed within an ongoing single arm cohort study investigating the use of carfilzomib in routine clinical practice across Europe (Study 20150262).In this study, the majority of patients received CRd after 1 prior therapy and nearly all received frontline treatment with bortezomib.

There is a general move in clinical practice towards utilising triplet therapies earlier in the treatment pathway within multiple myeloma, as these offer the advantage of synergistic

mechanisms of action and target multiple pathways to allow for deeper and more durable responses.[1] Indeed, the pivotal ASPIRE clinical trial observed improved clinical outcomes when CRd was used at 2L compared with later lines (post hoc subgroup analysis, see Section B.2.7.2), which underlines the clinical value of using CRd early in the treatment pathway. Clinical expert opinion also suggests that patients in earlier settings better tolerate the more aggressive approach with triplet therapies than patients in later treatment lines, and a chart audit demonstrated that fewer patients are treated and responses are poorer in subsequent lines of treatment.[40] As a result, the use of CRd in the proposed 2L positioning is expected to maximise the value of CRd to patients and providers.

Importantly, the 2L prior bortezomib subgroup is also aligned with the NICE recommended population of the primary comparator considered in this submission, Rd (NICE TA586).[41, 42] Despite the recent approval of Rd in the 2L post-bortezomib setting, there remains a clear need for novel and effective therapies, with demonstrated superiority both in terms of the response and duration of progression-free survival achieved in multiple myeloma patients.[43] NICE has recently recommended the use of the triplet therapy DVd as a treatment option for adults who have had 1 previous therapy, although funding remains conditional through the CDF primarily due to uncertainties in its long-term survival benefit at the time of the appraisal. Consistent with the NICE Position Statement on the consideration of products recommended for use in the Cancer Drugs Fund as comparators, January 2019, DVd has not been included in the Final Scope of this appraisal. However, given the need for more effective treatments earlier in the pathway, clinical experts have informed Amgen that the uptake of DVd in the prior-bortezomib subgroup is expected to be significant, and this regimen realistically reflects the true standard of care in this setting. For this reason, Amgen considers this comparison to be pertinent to the decision problem and informative to the Committee. The clinical and cost-effectiveness of CRd versus DVd is therefore also explored within this submission.

Finally, the prior-bortezomib subgroup is also highly relevant for consideration as these patients arguably face the greatest unmet need – as bortezomib regimens are used in approximately [redacted]% of patients in the 1L setting, there is an urgent need for improved access to effective non-bortezomib 2L treatment options, which are currently limited.

B.1.4 *Equality considerations*

No equality issues relate to the use of carfilzomib for previously treated multiple myeloma.

B.2 Clinical effectiveness

Summary of Clinical Effectiveness

- A systematic literature review (SLR) was used to identify relevant RCT evidence with one RCT identified that evaluated the efficacy and safety of CRd (ASPIRE)
- ASPIRE is a robust high-quality randomised, open-label, phase 3 RCT of 792 patients with relapsed and/or refractory (R/RMM) who have received 1–3 prior therapies, comparing the efficacy and safety of CRd with Rd
    - The primary endpoint was PFS; secondary and exploratory endpoints included OS, overall response rate (ORR), and HRQoL
- In the ASPIRE study, CRd provided a statistically significant and clinically meaningful 9.5-month PFS improvement compared with Rd (26.1 months vs. 16.6 months; hazard ratio [HR] 0.66; 95% confidence interval [CI]: 0.55, 0.78; 1-sided p < 0.0001) in the overall study population (investigator assessed; median follow ≥ 48 months)
- Patients in the CRd arm had a statistically significant 21% reduction in the risk of death compared with those in the Rd arm (HR 0.79; 95% CI 0.67, 0.95; 1-sided p = 0.0045)
    - Importantly, results of the mature OS analysis demonstrated a consistent separation of Kaplan-Meier curves and sustained benefit with over 5.5 years follow-up
- Using methodologically robust analyses these PFS and OS benefits are demonstrated to be even more pronounced in the target subgroup of 2L patients following prior bortezomib therapy; in the IPW analyses median PFS was improved with CRd by [redacted] CRd versus [redacted] with Rd; HR [redacted] and median OS was improved by [redacted] with CRd versus [redacted] with Rd; HR [redacted]
- The vast majority of patients (87.1%) responded to CRd (Rd: 66.7%; odds ratio [redacted];1-sided p < 0.0001), and the proportion of patients who achieved a complete response (CR) or better was more than tripled with CRd relative to Rd (31.8% vs. 9.3%)
- CRd was generally well tolerated in ASPIRE with minimal additional toxicity compared with Rd, despite the longer overall duration of therapy ([redacted]) and the use of a three-drug versus two-drug combination

B.2.1 *Identification and selection of relevant studies*

See Appendix D for full details of the process and methods used to identify and select the clinical evidence relevant to the technology being appraised.

B.2.2 *List of relevant clinical effectiveness evidence*

The clinical efficacy/safety systematic literature review (SLR) identified one relevant Amgen-sponsored phase 3 trial assessing the efficacy and safety of CRd compared with lenalidomide and dexamethasone (Rd): ASPIRE. Details are provided in Appendix D.

Table 3: Clinical effectiveness evidence: ASPIRE

Study title	**ASPIRE**		
Study design	Randomised, controlled, open-label, multicentre, phase 3 study		
Population	Patients with R/RMM who have received 1 to 3 prior therapies		
Intervention(s)	CRd		
Comparator(s)	Rd		
Indicate if trial supports application for marketing authorisation	Yes	**Indicate if trial used in the economic model**	Yes
Rationale for use/non-use in the model	ASPIRE was used in the economic model as it provides RCT evidence on CRd and the comparator of interest, Rd		
Reported outcomes specified in the decision problem	• **Progression-free survival** • **Overall survival** • Response rates (ORR [defined as the proportion of patients who achieved a best response of sCR, CR, VGPR, or PR, according to the IMWG-URC]) • Time to next treatment • **Adverse effects of treatment** • **Health-related quality of life** (change over time in the EORTC QLQ-C30 and myeloma-specific QLQ-MY20 module)		
All other reported outcomes	N/A		

References: Stewart *et al*., 2015,[44] Stewart *et al.,* 2016,[45] and Siegel *et al*., 2018[46]

Note: Outcomes highlighted in bold indicate inclusion in the economic analysis.

CR, complete response; CRd, carfilzomib/lenalidomide/dexamethasone; IMWG-URC, International Myeloma Working Group Uniform Response Criteria; EORTC QLQ-C30 GHS/QoL, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; N/A, not applicable; PR, partial response; QLQ-MY20, Quality of Life Questionnaire Multiple Myeloma Module 20; R/RMM, relapsed or refractory multiple myeloma; sCR, stringent complete response; VGPR, very good partial response.

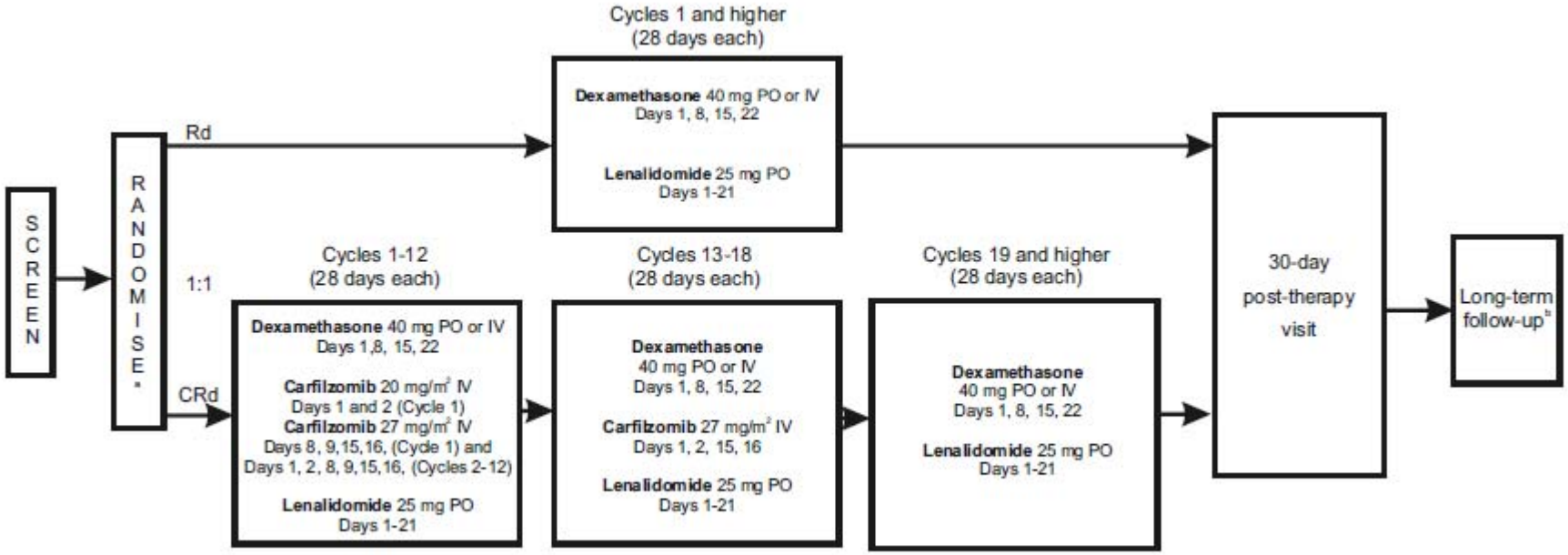
B.2.3 *Summary of methodology of the relevant clinical effectiveness evidence*

B.2.3.1 Summary of trial methodology

Trial design

ASPIRE is a randomised, controlled, open-label, multicentre, phase 3 study that enrolled adult patients with symptomatic R/RMM and measurable disease who had received one to three prior treatment regimens. Eligible patients were randomised to either CRd or Rd in a 1:1 ratio and randomisation was stratified according to β2-microglobulin levels (a marker highly correlated with total mass of myeloma cells; <2.5 mg per litre vs. ≥2.5 mg per litre), previous therapy with bortezomib (no vs. yes), and previous therapy with lenalidomide (no vs. yes). Patients received their randomised study regimen in 28-day cycles until disease progression or unacceptable toxicity. After discontinuation of study treatment, patients entered a long-term follow-up period. A schematic showing the design of ASPIRE is provided in Figure 2.

Figure 2. Study schema for ASPIRE



Reference: ASPIRE clinical study report (16 June 2014 data cut-off date).[47]

[a] Randomisation stratified by β2-microglobulin levels (< 2.5 mg/L vs. ≥ 2.5 mg/L), prior bortezomib therapy (no vs. yes), prior lenalidomide therapy (no vs. yes).
[b] Long-term follow-up every 3 months for 1 year from discontinuation of treatment and every 6 months thereafter.

CRd, carfilzomib/lenalidomide/dexamethasone; IV, intravenous; PO, oral; Rd, lenalidomide/dexamethasone.

Eligibility criteria

The inclusion and exclusion criteria for patients entering the ASPIRE study are listed in Table 4.

Table 4. Inclusion and exclusion criteria for patients in ASPIRE

Inclusion criteria	**Disease related** • Symptomatic multiple myeloma • Measurable disease[a] • Prior treatment with 1 to 3 multiple myeloma regimens • Documented relapsed or progressive disease on or after any regimen (patients refractory to the most recent line of therapy were eligible) • Achieved a response to ≥ 1 prior regimen[b] **Demographic** • Age ≥ 18 years • Life expectancy ≥ 3 months • ECOG performance status 0–2 **Laboratory** • Adequate hepatic function[c] • Absolute neutrophil count ≥ 1.0 × 10^9/L within 21 days prior to randomisation • Haemoglobin ≥ 80 g/L within 21 days prior to randomisation • Platelet count ≥ 50 × 10^9/L within 21 days prior to randomisation[d] • CrCl ≥ 50 mL/minute **Ethical/other** • Written informed consent in accordance with federal, local, and institutional guidelines • Women of childbearing potential must have agreed to ongoing pregnancy testing and to use contraception, and male patients must have agreed to use contraception
Exclusion criteria	**Disease related** • Progression during any previous treatment with bortezomib • Progression during the first 3 months of initiating previous treatment with Rd (or at any time if Rd was the most recent line of therapy) • Discontinued previous lenalidomide or dexamethasone due to intolerance • Prior carfilzomib treatment • POEMS syndrome; Waldenström macroglobulinaemia; IgM myeloma; or plasma cell leukaemia (> 2.0 × 10^9/L circulating plasma cells by standard differential) **Concurrent treatments** • Chemotherapy within 21 days prior to randomisation or antibody therapy within 42 days prior to randomisation • Radiotherapy to multiple sites or immunotherapy/antibody therapy within 28 days prior to randomisation; localised radiotherapy to a single site within 7 days prior to randomisation • Corticosteroid therapy at a dose equivalent to dexamethasone > 4 mg/day within 21 days prior to randomisation **Concurrent conditions** • Pregnancy or breast feeding • Major surgery within 21 days prior to randomisation • Acute active infection requiring treatment within 14 days prior to randomisation; known HIV infection; or active hepatitis B or C infection • MI within 4 months prior to randomisation, NYHA class III or IV heart failure,

	uncontrolled angina, history of severe CAD, severe uncontrolled ventricular arrhythmias, sick sinus syndrome, or electrocardiographic evidence of acute ischaemia or Grade 3 conduction system abnormalities, unless the patient had a pacemaker • Uncontrolled hypertension or uncontrolled diabetes within 14 days prior to randomisation • Other malignancy (including MDS) within the previous 3 years[e] • Significant neuropathy within 14 days prior to randomisation[f] • Known history of allergy to Captisol® (a cyclodextrin derivative used to solubilise carfilzomib) • Contraindication to any of the required concomitant drugs or supportive treatments[g] • Ongoing graft vs. host disease • Patients with pleural effusion requiring thoracentesis or ascites requiring paracentesis within 14 days prior to randomisation • Any other clinically significant medical disease or condition which, in the investigator's opinion, may have interfered with protocol adherence or a patient's ability to provide informed consent

References: Stewart *et al*., 2015,[44] and Stewart *et al*., 2015 supplementary material (ASPIRE protocol and SAP).[48]

[a] Defined by ≥ 1 of the following (assessed within 21 days prior to randomisation): serum M-protein ≥ 0.5 g/dL; urine Bence-Jones protein (M-protein) ≥ 200 mg/24 hours; for patients with IgA myeloma whose disease could only be reliably measured only by qIgA, qIgA was ≥ 0.75 g/dL.
[b] Defined as ≥ 25% decrease in M-protein (or total protein in countries in which electrophoresis was not routinely available).
[c] Serum ALT ≤ 3.5 times the ULN and serum direct bilirubin ≤ 2 mg/dL within 21 days prior to randomisation.
[d] Platelet count ≥ 30 × 10^9/L if myeloma involvement in the bone marrow was > 50%.
[e] With the exception of adequately treated basal cell carcinoma, squamous cell skin cancer or thyroid cancer; carcinoma in situ of the cervix or breast, prostate cancer of Gleason Score ≤ 6 with stable prostate-specific antigen levels; or cancer considered cured by surgical resection or unlikely to impact survival during the duration of the study, such as localised transitional cell carcinoma of the bladder or benign tumours of the adrenal or pancreas.
[f] Grades 3–4 or Grade 2 with pain.
[g] Including hypersensitivity to all anticoagulation and antiplatelet options, antiviral drugs, or intolerance to hydration.

ALT, alanine aminotransferase; CAD, coronary artery disease; CrCl, creatinine clearance; ECOG, Eastern Cooperative Oncology Group; HIV, human immunodeficiency virus; IgA, immunoglobulin A; IgM, immunoglobulin M; MDS, myelodysplastic syndrome; MI, myocardial infarction; M-protein, monoclonal protein; NYHA, New York Heart Association; POEMS, polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes; qIgA; serum quantitative immunoglobulin A; Rd, lenalidomide/dexamethasone; SAP, statistical analysis plan; ULN, upper limit of normal.

Settings and locations where the data were collected

ASPIRE was conducted in a secondary care (hospital) setting at 129 centres in 20 countries in Eastern and Western Europe, North America and Israel (Austria, Belgium, Bulgaria, Canada, Czech Republic, France, Germany, Greece, Hungary, Israel, Italy, Netherlands, Poland, Romania, Russia, Serbia, Spain, Sweden, the UK and the United States). Sixteen patients (2%) were enrolled in the UK.[47]

Trial drugs and concomitant medications

A detailed overview of ASPIRE study drugs and required, permitted and disallowed concomitant medications is provided in Table 5. Carfilzomib was administered on Days 1, 2, 8, 9, 15, and 16 of 28-day treatment cycles in the CRd arm. The dose of carfilzomib was 20 mg/m^2 (IV) on Days 1

and 2 of Cycle 1, stepped up to 27 mg/m^2 for subsequent doses. From Cycle 13, the Days 8 and 9 doses were omitted, and after Cycle 18 carfilzomib was discontinued. In both the CRd and Rd arms, lenalidomide was administered at a dose of 25 mg (oral) on Days 1 to 21 of each treatment cycle, and dexamethasone was administered at a dose of 40 mg (oral or IV) on Days 1, 8, 15, and 22 of each treatment cycle. Patients received their randomised study regimen until disease progression or unacceptable toxicity.

Table 5. Overview of ASPIRE study drugs and concomitant medications

Study drugs[a]	**CRd arm (28-day treatment cycles)** **Cycles 1 to 12:** • Carfilzomib 20 mg/m^2 IV on Days 1 and 2 of Cycle 1, escalating to 27 mg/m^2 on Days 8, 9, 15, and 16 of Cycle 1 and continuing on Days 1, 2, 8, 9, 15, and 16 of Cycle 2 to Cycle 12 • Lenalidomide 25 mg orally on Days 1 to 21 • Dexamethasone 40 mg oral or IV on Days 1, 8, 15, and 22 **Cycles 13 to 18:** • Carfilzomib 27 mg/m^2 IV on Days 1, 2, 15, and 16 • Lenalidomide 25 mg oral on Days 1 to 21 • Dexamethasone 40 mg oral or IV on Days 1, 8, 15, and 22 **Cycle 19 and higher:** • Lenalidomide 25 mg orally on Days 1 to 21 • Dexamethasone 40 mg oral or IV on Days 1, 8, 15, and 22 **Rd arm (28-day treatment cycles)** **Cycle 1 and higher:** • Lenalidomide 25 mg orally on Days 1 to 21 • Dexamethasone 40 mg orally or IV on Days 1, 8, 15, and 22
Required concomitant medications	**Started ≥ 24 hours prior to Cycle 1** • Ciprofloxacin through Cycle 1 only[b] • Valacyclovir continuing for the duration of treatment[c] • Lansoprazole continuing for the duration of treatment with dexamethasone[d] • Aspirin continuing for the duration of treatment with lenalidomide[e]
Permitted concomitant medications	• Allopurinol or other approved uric acid-lowering agents (patients at high risk for TLS) • Mycostatin or oral fluconazole • Antiemetics and antidiarrhoeal agents • Myeloid growth factors (reactive to onset of neutropenia only) • Red blood cell transfusions, erythropoietic stimulating agents, or platelet transfusions • Palliative radiation (pain management) • Bisphosphonates
Disallowed concomitant medications	• Concurrent therapy with an approved or investigational anticancer therapy or radiation to large marrow reserves for either a palliative or therapeutic intent • Corticosteroids for non-malignant conditions equivalent to a dexamethasone dose > 4.0 mg/day or equivalent • Other investigational agents

References: Stewart *et al*., 2015,[44] Stewart *et al*., 2015 supplementary material (ASPIRE protocol and SAP),[48] and ASPIRE clinical study report (16 June 2014 data cut-off date).[47]

[a] Patients received their randomised study regimen until disease progression or unacceptable toxicity.
[b] A similar prophylactic antibiotic such as a fluoroquinolone or amoxicillin could be used instead, at the investigator's discretion.
[c] Additional prophylaxis was at the investigator's discretion. For patients randomised to Rd who did not have a history of herpes zoster, valacyclovir prophylaxis was not required.
[d] Or other proton pump inhibitor.
[e] Patients with known thrombotic risk (e.g. prior thrombosis) should receive full anticoagulation at the investigator's discretion. Other antiplatelet or anticoagulation medications could be used in cases of intolerance to aspirin.

CRd, carfilzomib/lenalidomide/dexamethasone; IV, intravenous; Rd, lenalidomide/dexamethasone; SAP, statistical analysis plan; SC, subcutaneous; TLS, tumour lysis syndrome.

Outcomes used in the economic model or specified in the scope, including primary outcome

ASPIRE outcomes specified in the scope are provided in Table 6, with outcomes used in the cost effectiveness analyses highlighted in bold.

Table 6. ASPIRE outcomes specified in the scope[a]

	Outcome	Additional information
Primary outcome	• **PFS** (defined as the duration in months from randomisation to documented progressive disease or death due to any cause, whichever was earlier)	• Progression assessment was based upon the International Myeloma Working Group Uniform Response Criteria (IMWG-URC)[8, 49] and assessed by a blinded IRC (primary analysis) and the local investigators (supportive analysis)
Other outcomes specified in the scope	• **OS** (defined as the duration in months from randomisation to the date of death due to any cause) • Response rates (ORR, defined as the proportion of patients who achieved a best response of sCR, CR, VGPR, or PR, according to the IMWG-URC) • **Time to next treatment** (defined as the duration in months from randomisation to the initiation of subsequent anti-myeloma therapy) • **Adverse effects of treatment (**assessment of treatment-emergent AEs, laboratory values, vital signs, and ECGs) • **Health-related quality of life** (change over time in the EORTC QLQ-C30 and myeloma-specific QLQ-MY20 module)	• Five EORTC QLQ-C30 subscales were assessed: GHS/QoL, fatigue, nausea/vomiting, pain, physical functioning and role functioning • Two EORTC QLQ-MY20 subscales were assessed: disease symptoms and adverse effects of treatment

References: Stewart et al, 2015,[44] Stewart et al., 2015 supplementary material (supplementary appendix)[50] and Stewart et al 2016.[45]

[a] Additional ASPIRE secondary outcomes not specified in the scope or used in the economic analysis are duration of response, disease control, rate and duration of disease control.

Note: Outcomes highlighted in bold indicate inclusion in the economic analysis.

CR, complete response; CRd, carfilzomib/lenalidomide/dexamethasone; ECG, electrocardiogram; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; EORTC QLQ-MY20, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Multiple Myeloma Module 20;GHS/QoL, Global Health Status/Quality of Life; IMWG-URC, International Myeloma Working Group Uniform Response Criteria; IRC, Independent Review Committee; MM, multiple myeloma; PR, partial response; R/RMM, relapsed or refractory multiple myeloma; sCR, stringent complete response; VGPR, very good partial response.

B.2.3.2 Baseline characteristics

Baseline characteristics were similar across study arms in ASPIRE (Table 7). The overall median age was 64.0 years and most patients (90.5%) had an ECOG performance status of 0-1. Patients had received a median of two prior MM regimens; a total of 43.1% had received one prior MM regimen, [redacted] had received two, and [redacted] had received three. Almost [redacted] of patients ([redacted]) had previously received prior bortezomib, and [redacted] had previously received prior lenalidomide. Overall, a total of 28.9% of patients were refractory to their last regimen.

Table 7. Overview of baseline characteristics in ASPIRE (ITT population)

	CRd (N = 396)	Rd (N = 396)	Total (N = 792)
Age, years Median (min, max)	64.0 (38.0, 87.0)	65.0 (31.0, 91.0)	64.0 (31.0, 91.0)
Female, n (%)	181 (45.7)	164 (41.4)	345 (43.6)
Race, n (%) White Black Asian Native Hawaiian/Pacific Islander NR/other	 377 (95.2) 12 (3.0) 1 (0.3) [redacted] 6 (1.5)	 377 (95.2) 11 (2.8) 3 (0.8) [redacted] 4 (1.0)	 754 (95.2) 23 (2.9) 4 (0.5) [redacted] 10 (1.3)
Time since diagnosis, years Median (min, max)	N = 395 3.0 (0.4, 19.7)	N = 396 3.2 (0.5, 27.3)	N = 791 3.1 (0.4, 27.3)
Body surface area (m^2) Mean (SD)	[redacted]	[redacted]	[redacted]
ECOG PS, n (%) 0 1 2	 165 (41.7) 191 (48.2) 40 (10.1)	 175 (44.2) 186 (47.0) 35 (8.8)	 340 (42.9) 377 (47.6) 75 (9.5)
ISS stage at diagnosis, n (%) I II III Unknown	 64 (16.2) 99 (25.0) 185 (46.7) 48 (12.1)	 74 (18.7) 94 (23.7) 161 (40.7) 67 (16.9)	 138 (17.4) 193 (24.4) 3 (43.7) 115 (14.5)

	CRd (N = 396)	Rd (N = 396)	Total (N = 792)
Calculated ISS stage at baseline, n (%)[a]			
I	[redacted]	[redacted]	[redacted]
II	[redacted]	[redacted]	[redacted]
III	[redacted]	[redacted]	[redacted]
Unknown	[redacted]	[redacted]	[redacted]
Cytogenetic risk (%)[b]			
High	48 (12.1)	52 (13.1)	100 (12.6)
Standard	147 (37.1)	170 (42.9)	317 (40.0)
Unknown	201 (50.8)	174 (43.9)	375 (47.3)
Number of prior regimens			
Median (min, max)	2.0 (1, 4)	2.0 (1, 4)	2.0 (1, 4)
1, n (%)	184 (46.5)	157 (39.6)	341 (43.1)
2, n (%)	[redacted]	[redacted]	[redacted]
3, n (%)	[redacted]	[redacted]	[redacted]
4, n (%)	[redacted]	[redacted]	[redacted]
Prior therapy received, n (%)			
SCT	217 (54.8)	229 (57.8)	446 (56.3)
Bortezomib	261 (65.9)	260 (65.7)	521 (65.8)
Lenalidomide	79 (19.9)	78 (19.7)	157 (19.8)
Thalidomide	[redacted]	[redacted]	[redacted]
Pomalidomide	[redacted]	[redacted]	[redacted]
Any IMiD[c]	233 (58.8)	229 (57.8)	462 (58.3)
Bortezomib and IMiD	146 (36.9)	139 (35.1)	285 (36.0)
Corticosteroids	[redacted]	[redacted]	[redacted]
Anthracycline	[redacted]	[redacted]	[redacted]
Alkylators	[redacted]	[redacted]	[redacted]
Received in last regimen, n (%)			
Bortezomib	[redacted]	[redacted]	[redacted]
Lenalidomide	[redacted]	[redacted]	[redacted]
Refractory to last regimen, n (%)	110 (27.8)	119 (30.1)	229 (28.9)

References: Stewart *et al*., 2015,[44] Stewart *et al*., 2015 supplementary material (supplementary appendix),[50] and ASPIRE clinical study report (16 June 2014 data cut-off date).[47]

[a] ISS sponsor-derived using central laboratory data for β2-microglobulin and local laboratory data for serum albumin.
[b] The high-risk group consisted of patients with the genetic subtypes t(4; 14), t(14;16), or deletion 17p in ≥ 60% of plasma cells. The standard-risk group consisted of patients without t(4; 14), t(14;16), and < 60% of plasma cells with deletion 17p. The unknown risk group included patients with FISH results that could not be analysed or from whom samples were not collected.
[c] Lenalidomide, thalidomide, or pomalidomide.

CRd, carfilzomib/lenalidomide/dexamethasone; ECOG PS, Eastern Cooperative Oncology Group Performance Status; FISH, fluorescence in situ hybridisation; IMiD, immunomodulatory drug; ISS, International Staging System; ITT, intent-to-treat; max, maximum; min, minimum; NR, not reported; Rd, lenalidomide/dexamethasone; SCT, stem cell transplantation; SD, standard deviation.

B.2.4 *Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence*

The primary objective of ASPIRE was to compare PFS in patients with R/RMM who were receiving CRd versus PFS in patients receiving Rd alone. An interim analysis of PFS was planned to occur when approximately 420 (80%) of 526 planned PFS events had occurred.

The inferential tests for the primary outcome of PFS and the secondary outcomes, including OS, overall response rate (ORR), disease control rate (DCR), and QoL, were to be performed against a 1-sided family-wise type I error rate of 0.025 and in accordance with the following multiple testing procedure:

- The significance levels corresponding to the interim and final analyses of PFS were determined using an O'Brien-Fleming group sequential monitoring plan with Lan-DeMets alpha spending function to ensure a 1-sided type I error rate of 0.025.
- If the null hypothesis for the test of PFS was rejected at either the interim or the final analysis, then the secondary efficacy outcomes were to be tested sequentially in the following order: OS, ORR, DCR, QOL (as measured by EORTC QLQ-C30 GHS/QoL).
- The testing of these secondary outcomes was to continue provided the null hypothesis for the previously tested secondary outcome was rejected at the 1-sided significance level of 0.025; otherwise, no further testing was to be performed. The analysis of OS at the time of the primary analysis of PFS represents an interim analysis of the OS endpoint. As such, the significance levels corresponding to the interim and final analyses for OS were adjusted using the O'Brien-Fleming group sequential monitoring plan with Lan-DeMets alpha spending function.
- Formal inferential testing was not performed for other endpoints (e.g. time to next treatment and changes in other EORTC QLQ-C30 or QLQ-MY20 subscales). Instead, the analyses of these endpoints were descriptive only.

An overview of the statistical analyses methods, sample size and power calculations, and data management and patient withdrawals is provided in Table 8.

Table 8. Summary of statistical analyses in ASPIRE

Hypothesis objective	The primary objective of ASPIRE was to compare PFS in patients with R/RMM who were receiving CRd vs. PFS in patients receiving Rd alone
Statistical analysis	**Primary endpoint (PFS)** • The median and percentile durations of PFS were estimated using the K–M method. The associated 95% CIs were calculated using the method of Klein and Moeschberger with log-log transformation. In addition, PFS rates at selected time points and their corresponding 95% CIs were calculated using the method of Kalbfleisch and Prentice. Median follow-up for PFS was estimated using the reverse K–M method. The primary inferential comparison between study arms used the log-rank test stratified by randomisation stratification factors (β2-microglobulin levels < 2.5 mg/L vs. ≥ 2.5 mg/L, prior bortezomib treatment [no vs. yes], and prior lenalidomide treatment [no vs. yes]). The HR for the comparison of CRd treatment vs. Rd treatment and its 95% CI were estimated using a Cox proportional hazard model using the same randomisation stratification factors.

	Other endpoints in scope (OS, ORR, changes in EORTC QLQ-C30 and QLQ-MY20 subscales, time to next treatment) • OS was analysed in the same manner as PFS, as described above • The comparison between study arms for ORR was made using the Cochran–Mantel–Haenszel chi-square test, stratified by the aforementioned randomisation stratification factors. The ORR was calculated by study treatment arm and the associated 95% CI was estimated using the Clopper–Pearson method. The common OR and its 95% CI were calculated using the Mantel–Haenszel method • Time to next treatment was analysed using the K–M method and a Cox proportional hazards model, as described for PFS above. This analysis is descriptive • The EORTC QLQ-C30 GHS/QoL scores were compared between study arms using a restricted maximum likelihood-based MMRM under the assumption of missing at random. The dependent variable of this model was change over time in the EORTC QLQ-C30 GHS/QoL score measured at Day 1 of Cycle 3, 6, 12, and 18. The model included the fixed categorical effects of treatment, visit, and treatment-by-visit interaction, the fixed continuous covariates of baseline EORTC GHS/QoL score and baseline score-by-visit interaction, as well as the aforementioned randomisation stratification factors. The random subject effects were modelled as part of the within-subject error correlation structure. The p-value associated with the type III F test for fixed effects of treatment was used to determine the significance of this endpoint, and the LS mean differences were estimated for each visit • Other EORTC QLQ-C30 and QLQ-MY20 subscales were analysed in the same manner as the EORTC-C30 GHS/QoL subscale, as described above; these analyses are descriptive only.
Sample size, power calculation	• It was estimated that 526 progression events at the time of the final analysis of PFS would provide 90% power to detect a 33% increase in median PFS for the CRd treatment group compared with the Rd control group (14.9 months vs. 11.2 months, respectively) • The expected median PFS of 11.2 months for the Rd group was based on a phase 3 study of Rd.[a 51] A 33% increase in median PFS for the CRd group corresponds to a 25% decrease in risk of progression compared with control (i.e.HR 0.75) • The required number of PFS events assumed exponentially distributed PFS times and one interim analysis under a group sequential monitoring plan to ensure an overall 1-sided type I error rate of 0.025 • A total of 700 patients enrolled uniformly over an 18-month period and followed for an additional 18 months after the planned closure of enrolment was expected to result in the required 526 events within approximately 36 months of the first randomised patient. Based on recommendations from the IDMC following a first administrative interim analysis conducted in December 2011, the sample size was increased to approximately 780 patients in order to decrease the time to reach the required number of PFS events • The sample size calculation was based on Schoenfeld's formula using ADDPLAN software (version 4)
Data management, patient withdrawals	• Patients who withdrew from the study were not replaced • For time-to-event endpoints (e.g. PFS, OS), if the event of interest was not observed prior to the patient's withdrawal or loss to follow-up, the data were censored at the last disease assessment or last contact date as appropriate • For ORR, patients who were not evaluable for response were considered non-responders • For time to next treatment, data for patients who did not start subsequent

	anti-myeloma treatment were censored at the date when information was last available

References: Stewart *et al*., 2015,[44] Stewart *et al*., 2015 supplementary material (ASPIRE protocol and SAP),[48] and ASPIRE clinical study report (16 June 2014 data cut-off date).[47]

[a] High-dose dexamethasone.

CI, confidence interval; CRd, carfilzomib/lenalidomide/dexamethasone; EORTC QLQ-C30 GHS/QOL, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 Global Health Status/Quality of Life; HR, hazard ratio; IDMC, Independent Data Monitoring Committee; K–M, Kaplan–Meier; LS, least squares; MMRM, mixed model for repeated measures; OR, odds ratio; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; QLQ-MY20, Quality of Life Questionnaire Multiple Myeloma Module 20; Rd, lenalidomide/dexamethasone; RMM, relapsed multiple myeloma; RRMM, relapsed-and-refractory multiple myeloma; SAP, statistical analysis plan

Analysis of PFS, OS, ORR and time to next treatment was conducted using the ASPIRE intent-to-treat (ITT) population, which comprised all randomised patients.[44] Patients in the ITT population were analysed according to their randomised study treatment arm.[47]

Analysis of HRQoL outcomes (change over time in the EORTC QLQ-C30 and myeloma-specific QLQ-MY20 module) was based on those completing at least 1 post-baseline HRQoL assessment.[45]

Safety analyses were conducted using the safety population, which comprised all patients who had received at least one dose of study drug (carfilzomib, lenalidomide or dexamethasone).[44] Patients in the safety population were analysed according to the actual treatment received (e.g. if a patient received 1 or more doses of carfilzomib during the study treatment period, they were included in the CRd arm).[47]

Details of the participant flow for ASPIRE are presented in Appendix D.

B.2.5 *Quality assessment of the relevant clinical effectiveness evidence*

In order to assess the risk of bias and generalisability of the ASPIRE study, quality assessment was conducted using guidance from 'Systematic reviews: CRD's guidance for undertaking reviews in health care (University of York Centre for Reviews and Dissemination)'.[52] The quality assessment checklist is provided in Appendix D and shows that ASPIRE is a high quality RCT with an overall low risk of bias. Randomisation and concealment of treatment allocation was appropriately conducted via use of an interactive voice/web response system, all outcomes for which data were available at the time of data cut-off were reported, and the efficacy analyses employed an ITT approach. Moreover, the risk of bias from the open-label study design was mitigated by the fact that the data for the primary endpoint – PFS – and other response/progression outcomes (e.g. ORR) were reviewed and confirmed by a blinded Independent Review Committee (IRC).

The results of this trial are relevant to the current decision problem and are generalisable to England and Wales. Of the sites included in the study, six were in the UK. Furthermore, use of Rd as the comparator reflects the current clinical practice for patients with R/RMM at 2L in the UK.

B.2.6 *Clinical effectiveness results of the relevant trials*

Summary of Clinical Effectiveness Results

- In the ASPIRE study, CRd provided a statistically significant and clinically meaningful 9.5-month PFS improvement compared with Rd (26.1 months vs. 16.6 months; HR 0.66; 95% CI 0.55, 0.78; 1-sided p < 0.0001) in the overall study population (investigator assessed; median follow-up ≥ 48 months)
- Patients in the CRd arm had a statistically significant 21% reduction in the risk of death compared with those in the Rd arm (HR 0.79; 95% CI 0.67, 0.95; 1-sided p = 0.0045)
    - Importantly, results of the primary OS analysis demonstrated a consistent separation of Kaplan-Meier curves and sustained benefit with over 5.5 years follow-up
- The vast majority of patients (87.1%) responded to CRd (Rd: 66.7%; OR 3.472; 95% CI 2.411, 5.001;1-sided p < 0.0001), and the proportion of patients who achieved a CR or better was more than tripled with CRd relative to Rd (31.8% vs. 9.3%)
- CRd also improved HRQoL (EORTC QLQ-C30 GHS/QoL) relative to Rd over 18 cycles of treatment with clinically meaningful differences between groups reached at Cycle 12 and approached at Cycle 18 (1-sided descriptive p = 0.0001 for overall treatment effect)
- Time to next treatment was also consistently supportive of increased clinical benefit of CRd compared with Rd

B.2.6.1 Overview of ASPIRE data presentation

The ASPIRE study met its primary objective of demonstrating improved PFS for CRd compared with Rd based on results from the planned interim analysis (data cut off 16 June 2014). Data from this analysis were presented in our previous submission to NICE,[53] however OS data were immature at this time. Data from the pre-specified final analysis of OS (data cut-off 28 April 2017), which includes approximately 3 additional years of follow-up compared with the interim analysis, and updated analyses of PFS (investigator assessed) and time to next treatment are now available.

An overview of the data presented in this submission is provided in Table 9. In addition to ITT analyses, key outcomes (PFS, OS) are also presented for the 2L prior-bortezomib subgroup where CRd is positioned (see Section B.1.3.3) as these data inform the economic model.

Table 9. Overview of ASPIRE clinical effectiveness results presented in the submission

Outcome		Analysis (data cut-off date)	Population	Justification for presentation	Presented in previous NICE submission[53]	Used in economic model
PFS	Assessed by IRC	Interim analysis (16 June 2014)	ITT	Primary analysis of PFS	Yes	No
	Assessed by investigator	Interim analysis (16 June 2014)	ITT	Sensitivity analysis of PFS (showing concordance of assessment by investigator and IRC)	Yes	No

Outcome	Analysis (data cut-off date)	Population	Justification for presentation	Presented in previous NICE submission[53]	Used in economic model
	Primary OS analysis[c] (28 April 2017)	ITT and subgroups relevant to positioning	Pre-specified final analysis of PFS	No	No
	Updated analysis (5 December 2017)	ITT and subgroups relevant to positioning	Most recent analysis of PFS	No	Yes
OS	Primary OS analysis[c] (28 April 2017)	ITT and subgroups relevant to positioning	Pre-specified final analysis of OS	No	No
	Updated analysis (5 December 2017)	ITT and subgroups relevant to positioning	Most recent analysis of OS	No	Yes
ORR	Interim analysis (16 June 2014)	ITT	Primary analysis of ORR[a]	Yes	No
Time to next treatment	Primary OS analysis[c] (28 April 2017)	ITT	Most recent analysis of time to next treatment (descriptive)	No	No
HRQoL (EORTC QLQ-C30 and myeloma-specific QLQ-MY20 module)	Interim analysis (16 June 2014)	Patients completing at least 1 post-baseline HRQoL assessment	Primary analysis of HRQoL[b]	Yes	Yes

[a] Analysis of response by the IRC stopped once the study had demonstrated a PFS benefit at the interim analysis.
[b] HRQoL data were no longer collected once the study had demonstrated a PFS benefit at the interim analysis.
[c] Primary OS analysis refers to the pre-specified analysis undertaken following the final data cut-off (28 April 2017), and also includes updated PFS and time to next treatment.

EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; HRQoL, health-related quality of life; IRC, Independent Review Committee; NICE, National Institute for Health and Care Excellence; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; QLQ-MY20, Quality of Life Questionnaire Multiple Myeloma Module 20.

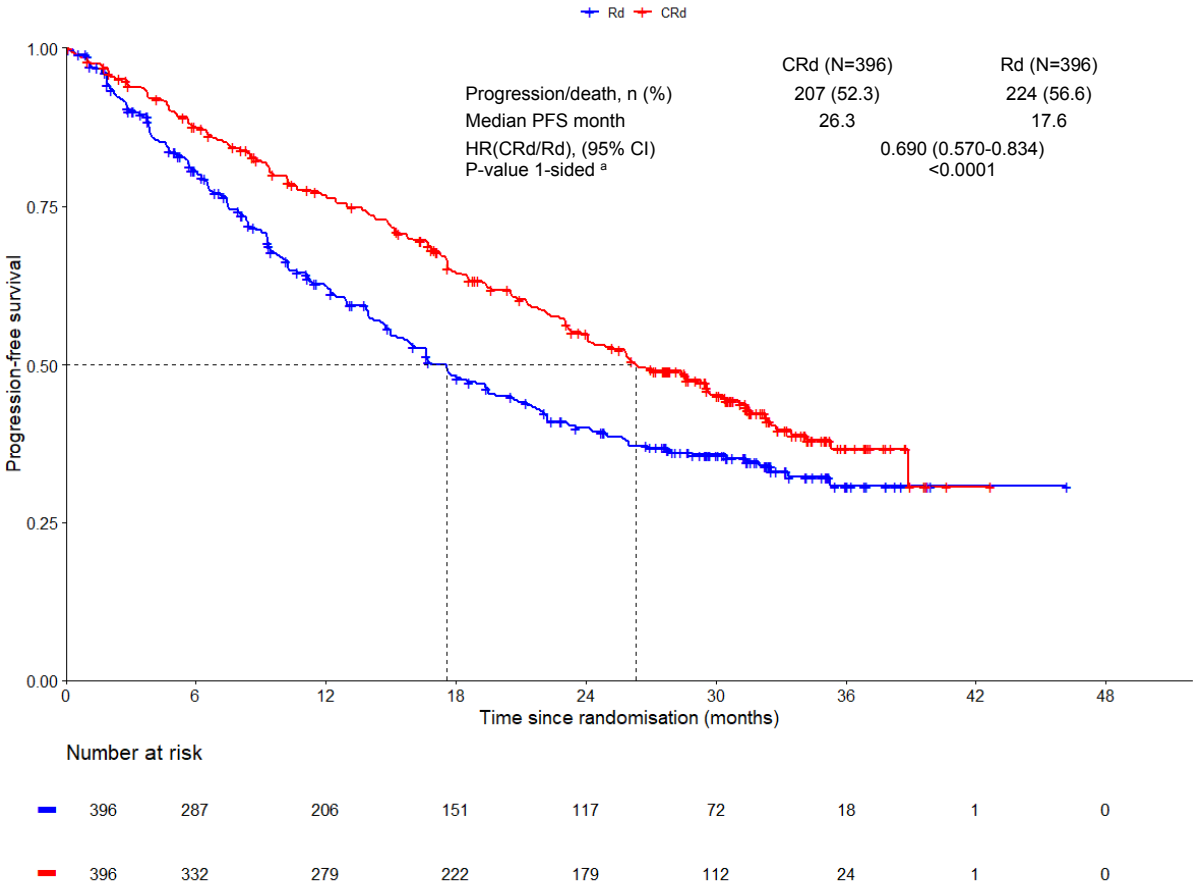
B.2.6.2 PFS

Interim analysis - primary analysis of PFS (PFS determined by the IRC)

ASPIRE demonstrated that the addition of carfilzomib to lenalidomide and dexamethasone improved PFS in patients with R/RMM (Figure 3 and Table 10). The median PFS significantly

increased from 17.6 months in the Rd arm to 26.3 months in the CRd arm, representing an 8.7-month improvement (HR = 0.69; 95% CI 0.57, 0.83; 1-sided p < 0.0001); this p-value passed the predetermined early stopping boundary for the interim analysis of PFS (1-sided p = 0.0127). The median follow-up for PFS was [redacted] in the CRd arm and [redacted] in the Rd arm.

Figure 3. Kaplan–Meier plot of PFS as determined by the IRC – interim analysis (ASPIRE, ITT population)



References: Stewart et al., 2015[44] and ASPIRE clinical study report (16 June 2014 data cut-off date) Figure 2.[47]

[a] P-value reported as a 2-sided p-value (p = 0.0001) in Stewart et al., 2015.[44]

CI, confidence interval; CRd, carfilzomib/lenalidomide/dexamethasone; HR, hazard ratio; IRC, Independent Review Committee; ITT, intent-to-treat; PFS, progression-free survival; Rd, lenalidomide/dexamethasone.

Table 10. PFS as determined by the IRC – interim analysis (ASPIRE, ITT population)[a]

	CRd (N = 396)	Rd (N = 396)
Total events, n (%) Progressed, n (%) Died without disease progression, n (%)	207 (52.3) [redacted] [redacted]	224 (56.6) [redacted] [redacted]
Censored, n (%)	[redacted]	[redacted]
PFS duration, median months (95% CI)	26.3 (23.3, 30.5)	17.6 (15.0, 20.6)

	CRd (N = 396)	Rd (N = 396)
Hazard ratio CRd:Rd, (95% CI)	0.690 (0.570, 0.834)	
p-value (1-sided)[a]	< 0.0001[b]	
Median follow-up for PFS, months (95% CI)	[redacted]	[redacted]

References: Stewart et al., 2015[44] and ASPIRE clinical study report (16 June 2014 data cut-off date)[47] Table 21.

[a] Unadjusted p-value from stratified log-rank test stratified with β2-microglobulin levels (< 2.5 mg/L vs. ≥ 2.5 mg/L), prior bortezomib (no vs. yes), and prior lenalidomide (no vs. yes) as stratification factors.
[b] Reported as a 2-sided p-value (p = 0.0001) in Stewart et al., 2015.

CI, confidence interval; CRd, carfilzomib/lenalidomide/dexamethasone; IRC, Independent Review Committee; ITT, intent-to-treat; PFS, progression-free survival; Rd, lenalidomide/dexamethasone.

Interim analysis - sensitivity analysis of PFS (PFS determined by the investigator)

Results of investigator-assessed PFS were consistent with those based on IRC assessments (

Figure 4 and Table 11). Patients in the CRd arm had a significantly longer PFS than those in the Rd arm [redacted] [47] The median PFS was [redacted] in the CRd arm versus [redacted] in the Rd arm, representing a 9.5-month improvement.

There was high concordance between the IRC and investigator assessments of progressive disease in the entire study population, with similar findings within each study arm (Figure 5) Overall, there was concordance on determination of progressive disease for [redacted] patients. Concordance on both determination of progressive disease and timing of progression occurred in [redacted] patients.[47]

Figure 4. Kaplan–Meier plot of PFS as determined by investigators – interim analysis (ASPIRE, ITT population)

References: ASPIRE clinical study report (16 June 2014 data cut-off date) Figure 3.[47]

CI, confidence interval; CRd, carfilzomib/lenalidomide/dexamethasone; HR, hazard ratio; ITT, intent-to-treat; PFS, progression-free survival; Rd, lenalidomide/dexamethasone.

Table 11. PFS as determined by investigators – interim analysis (ASPIRE, ITT population)

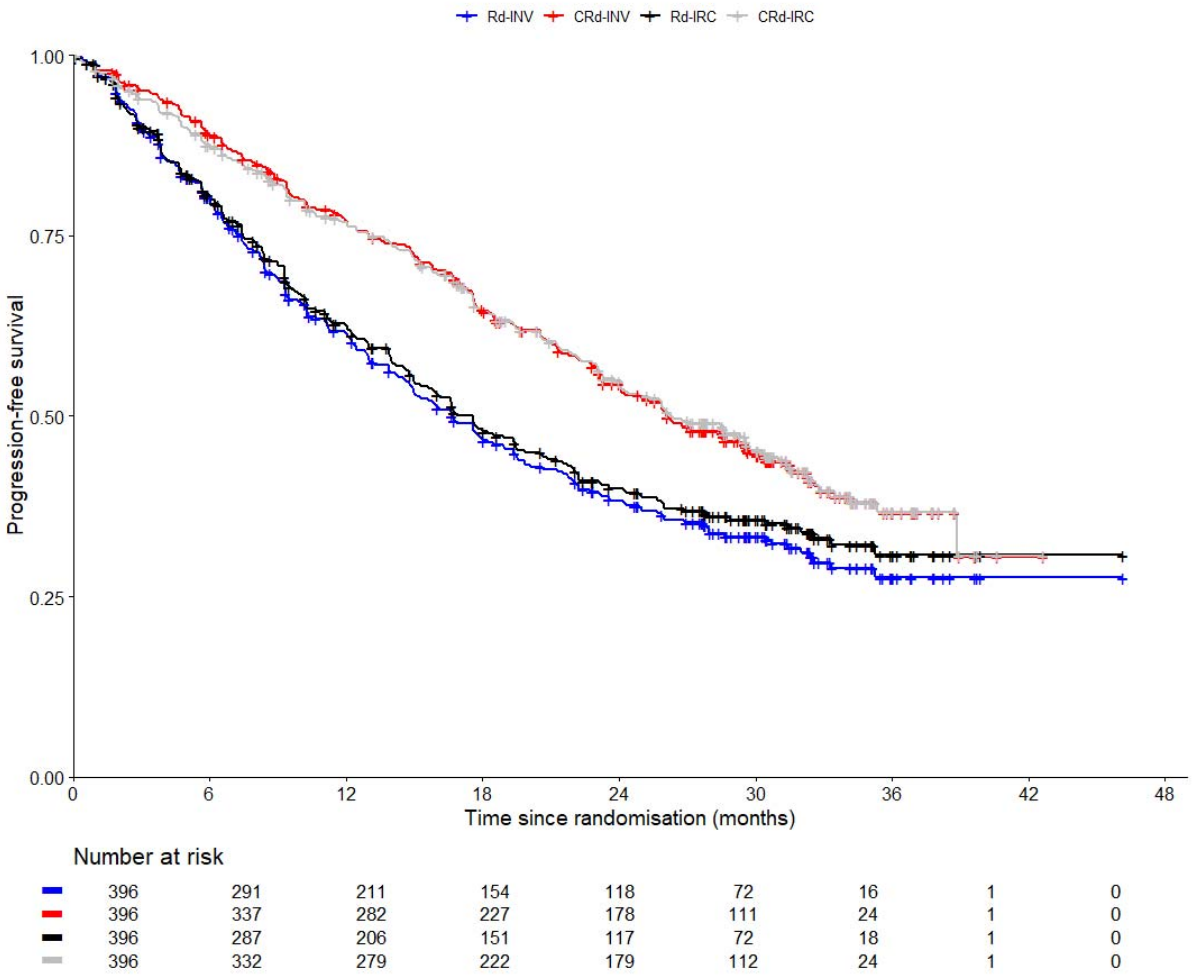
	CRd (N = 396)	Rd (N = 396)
Total events, n (%) Progressed, n (%) Died without disease progression, n (%)	209 (52.8) [redacted] [redacted]	240 (60.6) [redacted] [redacted]
Censored, n (%)	[redacted]	[redacted]
PFS duration, median months (95% CI)	26.1 [redacted]	16.6 [redacted]
Hazard ratio CRd:Rd, (95% CI)	0.651 (0.540, 0.785)	
p-value (1-sided)[a]	<0.0001	
Median follow-up for PFS, months (95% CI)	[redacted]	[redacted]

References: ASPIRE clinical study report (16 June 2014 data cut-off date)[47] Table 22.

[a] Unadjusted p-value from stratified log-rank test stratified with β2-microglobulin levels (< 2.5 mg/L vs. ≥ 2.5 mg/L), prior bortezomib (no vs. yes), and prior lenalidomide (no vs. yes) as stratification factors.

CI, confidence interval; CRd, carfilzomib/lenalidomide/dexamethasone; ITT, intent-to-treat; PFS, progression-free survival; Rd, lenalidomide/dexamethasone.

Figure 5. Concordance between PFS as assessed by the IRC and the investigator assessed PFS



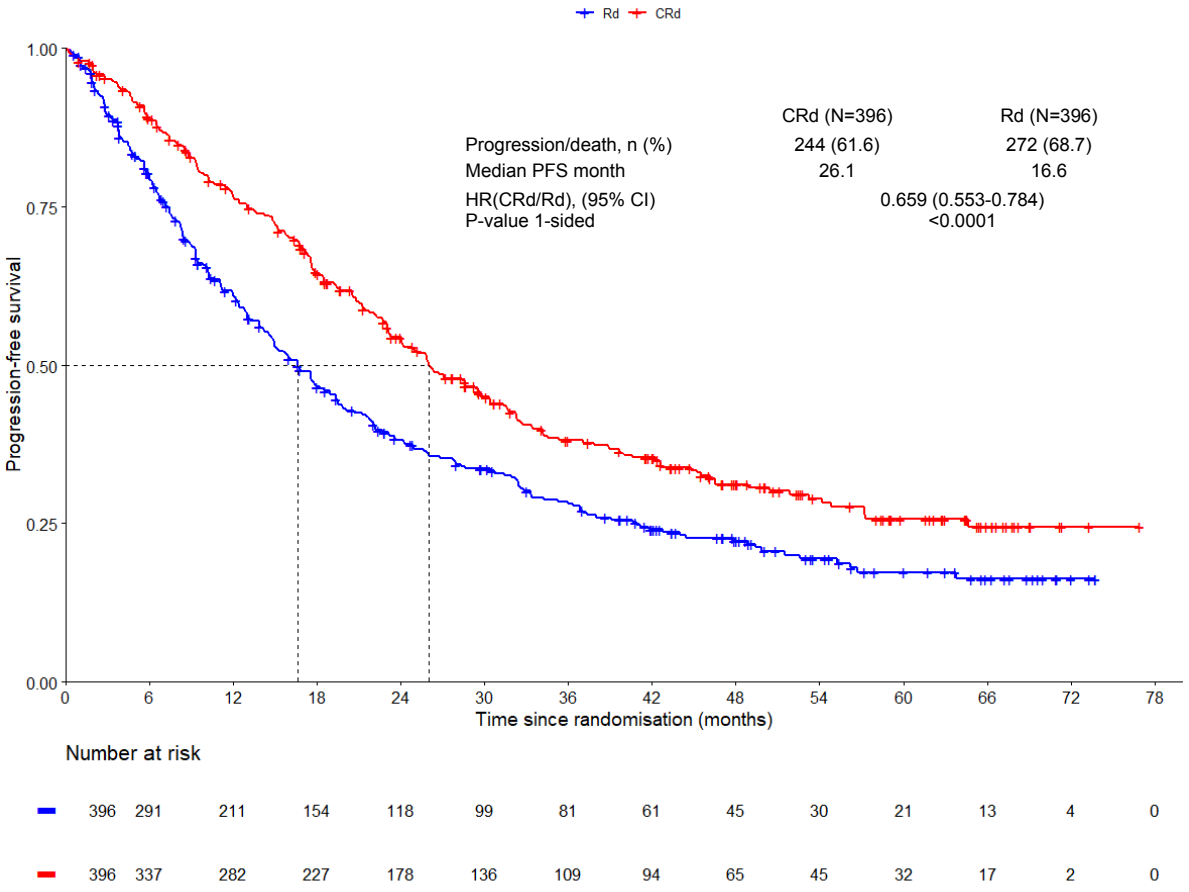
References: ASPIRE clinical study report (16 June 2014 data cut-off date) Figure 7.[47]

CRd, carfilzomib/lenalidomide/dexamethasone; INV, investigator; IRC, independent review committee; PFS, progression-free survival; Rd, lenalidomide/dexamethasone.

Primary OS analysis (PFS determined by the investigator)

A pre-specified updated analysis of PFS based on investigator assessment was performed at the time of the primary OS analysis (data cut-off of 28 April 2017). Median PFS was 16.6 months in the Rd arm versus 26.1 months in the CRd arm, representing a 9.5-month improvement (HR = 0.66; 95% CI 0.55, 0.78; descriptive 1-sided $p < 0.0001$) (Figure 6 and Table 12).[46] Importantly, in this analysis with substantially longer follow-up, the Kaplan–Meier curves remain separated over the duration of follow-up. Median follow-up for PFS was 48.8 months in the CRd arm and 48.0 months in the Rd arm. Three-year PFS rates were 38.2% (CRd) versus 28.4% (Rd) and 5-year rates were 25.6% (CRd) versus 17.3% (Rd).[46]

Figure 6. Kaplan–Meier plot of PFS as determined by investigator assessment – primary OS analysis (ASPIRE, ITT population)



Reference: Siegel et al, 2018[46] and ASPIRE clinical study report (28 April 2017 data cut-off date) Figure 7-3.[54]
CI, confidence interval; CRd, carfilzomib/lenalidomide/dexamethasone; HR, hazard ratio; ITT, intent-to-treat; OS, overall survival; Rd, lenalidomide/dexamethasone.

Table 12. PFS as determined by investigator assessment – primary OS analysis (ASPIRE, ITT population)[a]

	CRd (N = 396)	Rd (N = 396)
Total events, n (%) Progressed, n (%) Died without disease progression, n (%)	244 (61.6) [redacted] [redacted]	272 (68.7) [redacted] [redacted]
Censored, n (%)	[redacted]	[redacted]
PFS duration, median months (95% CI)	26.1 (23.2, 30.3)	16.6 (14.5, 19.4)
Hazard ratio CRd:Rd, (95% CI)	0.659 (0.553, 0.784)	
p-value (1-sided, descriptive)[a]	< 0.0001[b]	
Median follow-up for PFS, months (95% CI)	48.8 [redacted]	48.0 [redacted]

References: Siegel et al, 2018[46] and ASPIRE primary OS CSR Table 7-5.[54]

[a] Unadjusted p-value from stratified log-rank test stratified with β2-microglobulin levels (< 2.5 mg/L vs. ≥ 2.5 mg/L), prior bortezomib (no vs. yes), and prior lenalidomide (no vs. yes) as stratification factors.
[b] Reported as a 2-sided p-value (p = 0.0001) in Stewart et al., 2015.

	CRd (N = 396)	Rd (N = 396)
CI, confidence interval; CRd, carfilzomib/lenalidomide/dexamethasone; IMWG-URC, International Myeloma Working Group Uniform Response Criteria; IRC, Independent Review Committee; ITT, intent-to-treat; PFS, progression-free survival; Rd, lenalidomide/dexamethasone		

As noted in Section B.2.6.1, due to commitments in safety reporting, Amgen subsequently conducted an update of PFS (data cut-off 5 December 2017) which is used to inform the economic model given it provides the longest follow-up available. The results remain consistent with the primary OS analysis and further details are provided in Appendix M.

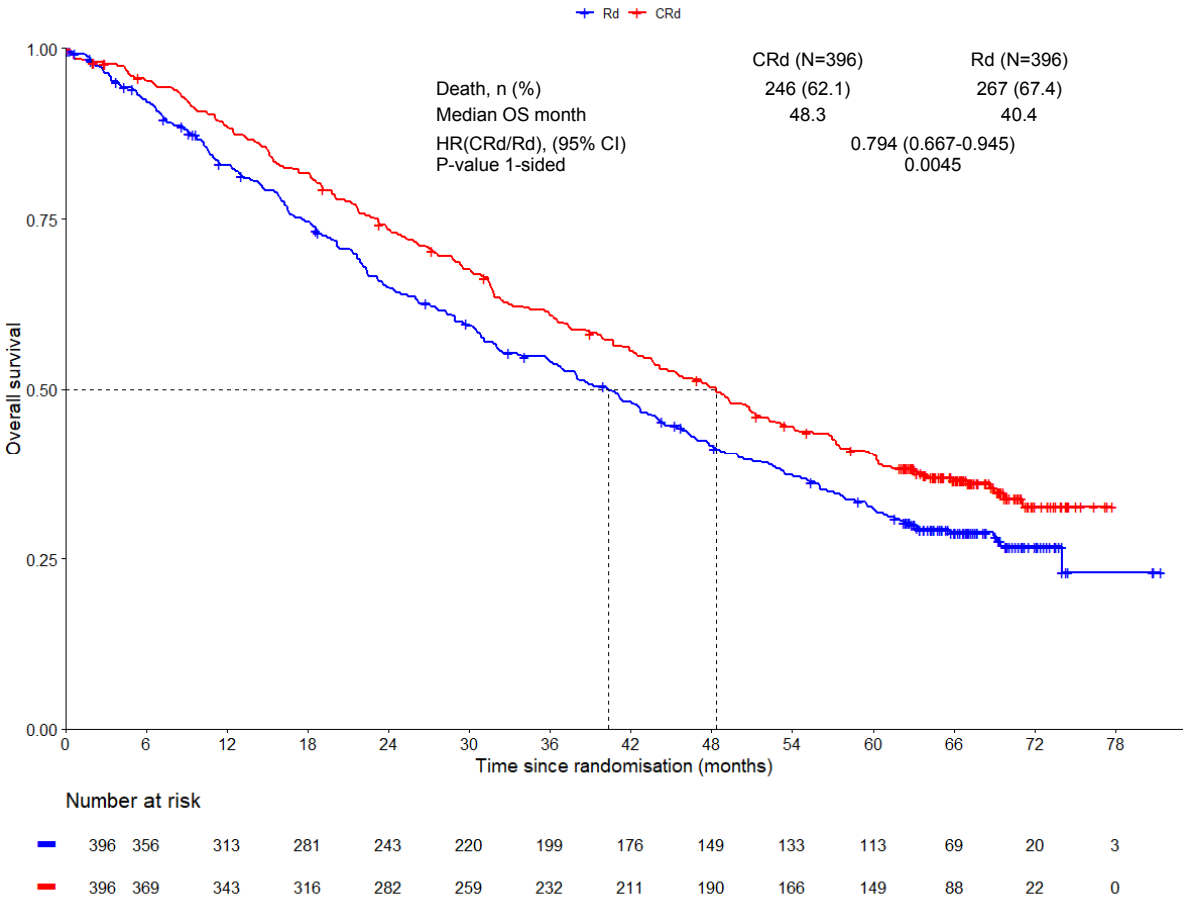
B.2.6.3 OS

Results from the interim analysis of OS (data cut-off 16 June 2014), based on a median follow up of 32 months per arm, were presented in our previous submission. At this time, 60% of the prespecified 510 events required for final analysis of OS had occurred. Although median OS was not reached in either arm, patients in the CRd arm had a nominally statistically significant reduction of 21% in the risk of death compared with those in the Rd arm (HR 0.79; 95% CI 0.63, 0.99); 1-sided p = 0.04).[44, 47] The stopping boundary for OS (0.0051) was not crossed at this interim analysis and the analysis was therefore repeated once the prespecified number of events for the primary OS analysis had occurred (510).[47] Results from this mature primary OS analysis (data cut-off 28 April 2017) are now available and are presented below.

Primary OS analysis

Patients in the CRd arm had a statistically significant reduction of 21% in the risk of death compared with patients in the Rd arm (HR = 0.79; 95% CI 0.67, 0.95; 1-sided p = 0.0045 [stopping boundary: 0.0231]). A total of 513 (64.8%) deaths were observed, 246 in the CRd arm and 267 in the Rd arm. CRd provided a median OS benefit of 7.9 months (48.3 months for CRd vs 40.4 months for Rd) with median follow-up 67.1 months for both arms.[46, 54] Importantly, in this analysis with substantially longer follow-up, the Kaplan–Meier curves remain separated over the duration of follow-up.

Figure 7. Kaplan–Meier plot of OS – primary OS analysis (ASPIRE, ITT population)



Reference: Siegel et al, 2018[46] and ASPIRE clinical study report (28 April 2017 data cut-off date) Figure 7-1

CI, confidence interval; CRd, carfilzomib/lenalidomide/dexamethasone; HR, hazard ratio; ITT, intent-to-treat; OS, overall survival; Rd, lenalidomide/dexamethasone

Table 13. OS – primary OS analysis (ASPIRE, ITT population)

	CRd (N = 396)	Rd (N = 396)
Died, n (%)	246 (62.1)	267 (67.4)
Censored, n (%)	[redacted]	[redacted]
OS duration, median months (95% CI)	48.3 (42.4, 52.8)	40.4 (33.6, 44.4)
Hazard ratio CRd:Rd (95% CI)	0.794 (0.667, 0.945)	
p-value (1-sided)[a]	0.0045	
Median follow-up for OS, months (95% CI)	67.1 [redacted]	67.1 [redacted]

References: Siegel et al, 2018[46] and ASPIRE clinical study report (28 April 2017 data cut-off date)[54] Table 7-1.

[a] Unadjusted p-value from stratified log-rank test stratified with β2-microglobulin levels (< 2.5 mg/L vs. ≥ 2.5 mg/L), prior bortezomib (no vs. yes), and prior lenalidomide (no vs. yes) as stratification factors.

CI, confidence interval; CRd, carfilzomib/lenalidomide/dexamethasone; ITT, intent-to-treat; OS, overall survival; Rd, lenalidomide/dexamethasone

Similar to the analysis of PFS (and as noted in Section B.2.6.1), Amgen subsequently conducted a further update of OS (data cut-off 5 December 2017) which is used to inform the economic model given it provides the longest follow-up available. The results remain consistent with the pre-specified analysis and further details are provided in Appendix M.

B.2.6.4 ORR

Results are presented from the interim analysis (16 June 2014), since analysis of response by the IRC stopped once the study had demonstrated a PFS benefit. The distribution of best overall responses and ORR, as determined by the IRC, is summarised in Table 14. The ORR was significantly higher in the CRd arm compared with the Rd arm (87.1% vs 66.7%; [redacted] p < 0.0001). 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). Furthermore, CRd was shown to be fast acting, with a median time to response of 1 month and mean of 1.6 months. The median and mean times to response in the Rd arm were 1 month and 2.3 months, respectively.

Table 14. Overall response rate as determined by the IRC – interim analysis (ASPIRE, ITT population)

	CRd (N = 396)	Rd (N = 396)
Best response, n (%)[a]		
Stringent complete response (sCR)	56 (14.1)	17 (4.3)
Complete response (CR)	70 (17.7)	20 (5.1)
⩾ CR	126 (31.8)	37 (9.3)
Very good partial response (VGPR)	[redacted]	[redacted]
⩾ VGPR	277 (69.9)	160 (40.4)
Partial response (PR)	[redacted]	[redacted]
Minimal response (MR)	[redacted]	[redacted]
Stable disease	[redacted]	[redacted]
Progressive disease (PD)	[redacted]	[redacted]
Not evaluable	[redacted]	[redacted]
ORR, n (%)[b]	345 (87.1)	264 (66.7)
95% CI of ORR	(83.4, 90.3)	(61.8, 71.3)
p-value (1-sided)[c]	< 0.0001[d,e]	
Odds ratio CRd:Rd (95% CI)	[redacted]	
Time to response[f]		
Mean, months (standard deviation)	1.6 (1.39)	2.3 (2.42)
Median, months	1	1

References: Stewart *et al*., 2015[44] and ASPIRE clinical study report (16 June 2014 data cut-off date) Table 27.[47]

[a] Best response was defined as a patient's best response during the study as determined by the IMWG-URC, with the exception of MR, which was determined by EBMT criteria.
[b] Defined as patients who had a best response of sCR, CR, VGPR, or PR.
[c] Unadjusted p-value from Cochran–Mantel–Haenszel chi-square test with β2-microglobulin levels (< 2.5 mg/L vs. ≥ 2.5 mg/L), prior bortezomib (no vs. yes), and prior lenalidomide (no vs. yes) as stratification factors.
[d] P-value is statistically significant (per hierarchical testing strategy described in Siegel et al 2018.[46]
[e] Reported as a 2-sided p-value (p < 0.0001) in Stewart *et al*., 2015.
[f] Time to response was defined as time from randomisation to the first evidence of a sCR, CR, VGPR, or PR.

	CRd (N = 396)	Rd (N = 396)
CI, confidence interval; CR, complete response; CRd, carfilzomib/lenalidomide/dexamethasone; EBMT, European Group for Blood and Marrow Transplantation; IRC, Independent Review Committee; IMWG-URC, International Myeloma Working Group Uniform Response Criteria; ITT, intent-to-treat; MR, minimal response; NE, not estimable; ORR, overall response rate; POMD, progressive disease; PR, partial response; Rd, lenalidomide/dexamethasone; sCR, stringent complete response; VGPR, very good partial response.		

B.2.6.5 Time to next treatment

Fewer patients in the CRd arm had started a new antimyeloma treatment by the time of the primary OS analysis data cut-off (28 April 2017) than in the Rd arm (46.0% vs 53.3%) (Table 15). In patients who received new antimyeloma treatment, the median time from randomisation to new treatment was substantially longer in the CRd arm than in the Rd arm ([redacted] months and [redacted] months, respectively). The Kaplan–Meier estimate of median time to next treatment among all randomised patients was also substantially longer in the CRd arm than in the Rd arm (39.0 months and 24.4 months, respectively; 1-sided descriptive p < 0.0001).

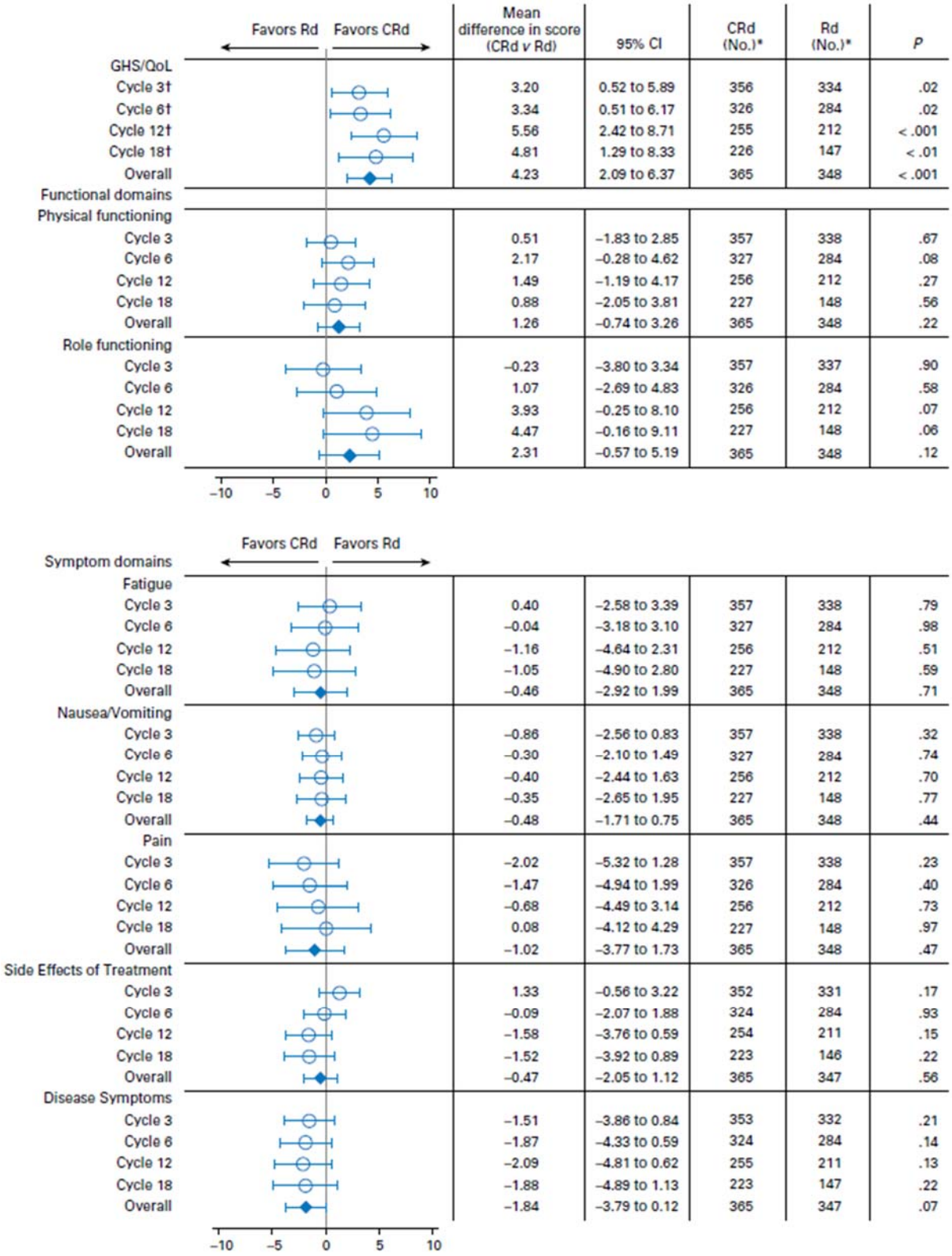
Table 15. Time to next treatment – primary OS analysis (ASPIRE, ITT population)

	CRd (N = 396)	Rd (N = 396)
Participants who started next treatment, n (%) Time to next treatment, median months (min, max)	182 (46.0) [redacted]	211 (53.3) [redacted]
K–M estimate of time to next treatment, median months (95% CI)	39.0 (31.8, 55.1)	24.4 (20.8, 28.4)
Hazard ratio CRd:Rd (95% CI)	0.65 (0.53, 0.79)	
Descriptive p-value (1-sided)	< 0.0001	
Median follow-up for time to next treatment, months (95% CI)	[redacted]	[redacted]
References: Siegel et al, 2018[46] and Amgen data on file, 2017[55] CI, confidence interval; CRd, carfilzomib/lenalidomide/dexamethasone; ITT, intent-to-treat; K–M, Kaplan–Meier; Rd, lenalidomide/dexamethasone.		

B.2.6.6 HRQoL outcomes

The EORTC QLQ-C30 questionnaire and the 20-item myeloma-specific QLQ-MY20 module were used to assess HRQoL in ASPIRE. These instruments are commonly used, and are valid and reliable in patients with MM.[46] Results are presented based on the interim analysis since HRQoL data were no longer collected once the study had demonstrated a PFS benefit. Among the 792 patients in the ITT population, 713 (90%) completed at least 1 post-baseline HRQoL assessment and were included in the analyses (CRd, n=365; Rd, n=348). Baseline QLQ-C30 and QLQ-MY20 subscale scores were similar between treatment groups. Treatment differences over time are shown in Figure 8.

Figure 8. Treatment difference in EORTC QLQ-C30 and myeloma-specific QLQ-MY20 module– interim analysis (ASPIRE, patients completing at least 1 post-baseline HRQoL assessment)



	Mean difference in score (CRd *v* Rd)	95% CI	CRd (No.)*	Rd (No.)*	*P*
GHS/QoL					
Cycle 3†	3.20	0.52 to 5.89	356	334	.02
Cycle 6†	3.34	0.51 to 6.17	326	284	.02
Cycle 12†	5.56	2.42 to 8.71	255	212	< .001
Cycle 18†	4.81	1.29 to 8.33	226	147	< .01
Overall	4.23	2.09 to 6.37	365	348	< .001
Functional domains					
Physical functioning					
Cycle 3	0.51	−1.83 to 2.85	357	338	.67
Cycle 6	2.17	−0.28 to 4.62	327	284	.08
Cycle 12	1.49	−1.19 to 4.17	256	212	.27
Cycle 18	0.88	−2.05 to 3.81	227	148	.56
Overall	1.26	−0.74 to 3.26	365	348	.22
Role functioning					
Cycle 3	−0.23	−3.80 to 3.34	357	337	.90
Cycle 6	1.07	−2.69 to 4.83	326	284	.58
Cycle 12	3.93	−0.25 to 8.10	256	212	.07
Cycle 18	4.47	−0.16 to 9.11	227	148	.06
Overall	2.31	−0.57 to 5.19	365	348	.12
Symptom domains					
Fatigue					
Cycle 3	0.40	−2.58 to 3.39	357	338	.79
Cycle 6	−0.04	−3.18 to 3.10	327	284	.98
Cycle 12	−1.16	−4.64 to 2.31	256	212	.51
Cycle 18	−1.05	−4.90 to 2.80	227	148	.59
Overall	−0.46	−2.92 to 1.99	365	348	.71
Nausea/Vomiting					
Cycle 3	−0.86	−2.56 to 0.83	357	338	.32
Cycle 6	−0.30	−2.10 to 1.49	327	284	.74
Cycle 12	−0.40	−2.44 to 1.63	256	212	.70
Cycle 18	−0.35	−2.65 to 1.95	227	148	.77
Overall	−0.48	−1.71 to 0.75	365	348	.44
Pain					
Cycle 3	−2.02	−5.32 to 1.28	357	338	.23
Cycle 6	−1.47	−4.94 to 1.99	326	284	.40
Cycle 12	−0.68	−4.49 to 3.14	256	212	.73
Cycle 18	0.08	−4.12 to 4.29	227	148	.97
Overall	−1.02	−3.77 to 1.73	365	348	.47
Side Effects of Treatment					
Cycle 3	1.33	−0.56 to 3.22	352	331	.17
Cycle 6	−0.09	−2.07 to 1.88	324	284	.93
Cycle 12	−1.58	−3.76 to 0.59	254	211	.15
Cycle 18	−1.52	−3.92 to 0.89	223	146	.22
Overall	−0.47	−2.05 to 1.12	365	347	.56
Disease Symptoms					
Cycle 3	−1.51	−3.86 to 0.84	353	332	.21
Cycle 6	−1.87	−4.33 to 0.59	324	284	.14
Cycle 12	−2.09	−4.81 to 0.62	255	211	.13
Cycle 18	−1.88	−4.89 to 1.13	223	147	.22
Overall	−1.84	−3.79 to 0.12	365	347	.07

Reference: Stewart et al., 2016.[45]

* number of patients with data at that timepoint. Overall timepoint includes patients with at least 1 post-baseline assessment.
ł Data also presented in Stewart et al, 2015.[44] Overall p-value (2-sided) for GHS/QoL is now statistically significant per hierarchical testing strategy described in Siegel et al 2018.[46]
Note: values shown are the adjusted least squares mean treatment difference in scores from a restricted maximum likelihood-based model for repeated measures under the assumption of missing at random. Scores are adjusted for baseline score, baseline score by visit interaction and the randomisation stratification factors (β2-microglobulin levels (< 2.5 mg/L vs. ≥ 2.5 mg/L), prior bortezomib (no vs. yes), and prior lenalidomide (no vs. yes).

CI, confidence interval; CRd, carfilzomib/lenalidomide/dexamethasone; Rd, lenalidomide/dexamethasone.

CRd improved global health status with significantly higher QLQ-C30 GHS/QoL scores compared to Rd over 18 cycles of treatment (2-sided p < 0.001). The minimal important difference (MID) for between-group differences on QLQ-C30 GHS/QoL is 5 points.[56-59] Based on this threshold, the MID between CRd and Rd was met at Cycle 12 (5.56) and approached at Cycle 18 (4.81). There were no differences between CRd and Rd on the other scales assessed, although point estimates tended to favour CRd.

B.2.7 *Subgroup analysis*

Summary of Subgroup Analysis Results

- Prespecified baseline covariate subgroup analyses for ASPIRE showed that PFS benefits were consistently observed in key subgroups, including subgroups for age, risk determined by cytogenetic testing, and treatment history (including number of lines of prior therapy, prior exposure to bortezomib, and prior exposure to lenalidomide); OS and ORR benefits were also consistently observed in the majority of subgroups.
- Post hoc subgroup analyses of ASPIRE were conducted, which provide more clinically relevant and appropriate estimates of the treatment effect for CRd versus Rd in the context of the proposed positioning than those observed in the overall study population
- Using methodologically robust analyses PFS and OS benefits are demonstrated to be even more pronounced in the target subgroup of 2L patients following prior bortezomib therapy; in the IPW analyses median PFS was improved with CRd by [redacted] with CRd versus [redacted] with Rd; HR [redacted] and median OS was improved by [redacted] with CRd versus [redacted] with Rd [redacted]

B.2.7.1 Prespecified subgroup analysis

Prespecified subgroup analyses defined by a range of baseline covariates were conducted for PFS, as well as for OS and ORR. An overview of the prespecified subgroups in ASPIRE is presented in Table 16. The analysis principles for the subgroup analyses were aligned with the primary analyses for the overall study population previously described in Section B.2.4. In addition, a stepwise Cox regression model (including treatment, each of the covariates, and the treatment-covariate interaction terms as predictor variables with a significance level of 0.20 for entering and 0.10 for removing) was fitted, separately for PFS and OS, to investigate the treatment–covariate interactions. Similarly, a stepwise logistic regression model was fitted for ORR.[47]

Table 16. Prespecified subgroups in ASPIRE[a]

Baseline demographics and characteristics	• Age (years; 18–64 vs. ≥ 65 and 18–74 vs. ≥ 75) • Sex (male vs. female) • Race (white vs. black vs. other) • Ethnicity (Hispanic or Latino vs. not Hispanic or Latino) • Geographic region (Europe vs. North America vs. rest of world)

	• Body surface area (m^2; ≤ 2.2 vs. > 2.2) • ECOG performance status (0 vs. 1 vs. ≥ 2) • Haemoglobin (g/L; < 105 vs. ≥ 105) • Absolute neutrophil count (10^9/L; < 1.5 vs. ≥ 1.5) • Platelet count (10^9/L; < 150 vs. ≥ 150) • Corrected calcium (mg/dL; ≤ 11.5 vs. > 11.5) • Sponsor-calculated CrCl by Cockroft–Gault (mL/min; 30 to < 50 vs. 50 to < 80 vs. ≥ 80) • Presence of neuropathy (no vs. yes, Grade 1 vs. ≥ Grade 2)
Baseline disease characteristics	• ISS disease stage at initial diagnosis (I vs. II vs. III vs. unknown) • Extent of plasma cell involvement (< 50% vs. ≥ 50% plasma cells vs. not done) • β2-microglobulin level per IVRS (mg/L; < 2.5 vs. ≥ 2.5)
Risk group as determined by FISH	• High risk, standard risk, and unknown risk o High-risk group consists of patients who have the genetic subtypes t(4; 14) or t(14;16), or have deletion 17p together with ≥ 60% of plasma cells o Standard-risk group consists of patients who do not have the genetic subtypes t(4;14), t(14;16), or deletion 17p, or have deletion 17p, but with < 60% of plasma cells o Unknown risk group consists of patients with FISH procedure not being done or with results that could not be analysed
Multiple myeloma treatment history	• Number of prior systemic therapies for multiple myeloma (1 vs. 2 vs. 3) • Prior haematopoietic SCT (yes vs. no) • Prior treatment with bortezomib (yes vs. no) • Prior treatment with lenalidomide (yes vs. no) • Bortezomib refractory in any prior line regimen (yes vs. no) • IMiD refractory in any prior line regimen (yes vs. no) • Double refractory to both bortezomib and IMiD in any prior regimen (yes vs. no); PFS and OS only[b] • Refractory to either bortezomib or IMiD in any prior line regimen (yes vs. no); ORR only[b]

References: Stewart *et al*., 2015,[44] Stewart *et al*., 2015 supplementary material (ASPIRE protocol and SAP),[48] and ASPIRE clinical study report (16 June 2014 data cut-off date).[47]

[a] Minor changes to the subgroup specification defined in the SAP (v4) were made prior to unblinding of study results. An additional subgroup for BSA was added; age was changed from 18–64 vs. 65–74 vs. ≥ 75 years to 18–64 vs. ≥ 65 years and 18-74 vs. ≥ 75 years; presence of neuropathy was changed from no vs. Grade 1 vs. Grade 2 to no vs. yes and Grade 1 vs. Grade 2; extent of plasma cell involvement was changed from < 50% vs. ≥ 50% to < 50% vs. ≥ 50% vs. not done; double refractory to both bortezomib and IMiD in any prior regimen (yes vs. no) was carried out only for PFS and OS; and refractory to either bortezomib or IMiD in any prior line regimen (yes vs. no) was carried out only for ORR.

BSA, body surface area; CrCl, creatinine clearance; CSR, clinical study report; ECOG, Eastern Cooperative Oncology Group; FISH, fluorescence in situ hybridisation; IMiD, immunomodulatory drug; ISS, International Staging System; IVRS, interactive voice response system; MRD, minimal residual disease; MR, minimal response; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; SAP, statistical analysis plan; SCT, stem cell transplantation.

A summary of results from the pre-specified subgroup analyses is provided in Appendix E.

The PFS benefit for CRd was consistently observed in key subgroups, including those defined by age, risk determined by cytogenetic testing (FISH), and treatment history (including number of lines of prior therapy, prior exposure to bortezomib, and prior exposure to lenalidomide).[44, 47] While differences in treatment effect were observed between certain subgroups, such variations were not unexpected given the large number of subgroup analyses conducted and small sample sizes in some subgroups.[47] Based on stepwise Cox regression modelling, there was a lack of evidence of treatment–covariate interactions for PFS suggesting an overall consistent treatment effect across the baseline covariate subgroups.[47] It should be noted that ASPIRE was not primarily designed to detect significant treatment effects within baseline covariate subgroups, and consequently lacked power to detect significant treatment-covariate interactions. In addition, there might be important differences in baseline characteristics across study arms in subgroups that confound the subgroup-specific treatment effect estimates, therefore unadjusted treatment effects estimated for subgroups should be interpreted with caution. Detailed results for all prespecified PFS subgroups are provided in Appendix E.

Of particular relevance to the decision problem, the treatment effect for PFS consistently favoured CRd over Rd irrespective of treatment history, which is one of the most important factors in determining treatment strategies for patients with R/RMM. The PFS benefit for CRd was consistently observed irrespective of the following factors:

- number of lines of prior systemic therapy, of which the one prior systemic therapy subgroup is more pertinent to the proposed 2L patient population for CRd in England and Wales than the three lines of prior therapy subgroup
- whether or not patients have received prior bortezomib and whether or not patients were refractory to prior bortezomib; this is relevant to the decision problem given that patients in the 2L proposed patient population for CRd in England and Wales will have received prior bortezomib based on the proposed place of CRd in the treatment pathway (Section B.1.3.3)
- whether or not patients have received a prior IMiD and whether or not patients were refractory to a prior IMiD; this is relevant to the decision problem as some patients in the 2L proposed patient population for CRd in England and Wales may have received a prior IMiD (specifically, thalidomide) based on the proposed place of CRd in the treatment pathway (Section B.1.3.3)
- whether or not patients have received prior lenalidomide, which is relevant to the decision problem as patients in the 2L proposed patient population for CRd in England and Wales are unlikely to receive lenalidomide in current clinical practice based on the proposed place of CRd in the treatment pathway (Section B.1.3.3)
- whether or not patients were double refractory to prior bortezomib and an IMiD; this is relevant to the decision problem as some patients in the 2L proposed patient population for CRd in England and Wales may have received both a prior IMiD (specifically, thalidomide) and bortezomib based on the proposed place of CRd in the treatment pathway (Section B.1.3.3).

Similarly to PFS, the OS and ORR benefits observed for the CRd arm in the overall study population were consistently observed in the majority of subgroups, and there was a lack of evidence of treatment–covariate interactions based on Cox regression modelling (OS) and

stepwise logistic regression modelling (ORR), suggesting an overall consistent treatment effect across the baseline covariate subgroups.[47]

B.2.7.2 Post hoc subgroup analysis relevant to the positioning of CRd

Rationale for post hoc subgroup analysis

CRd is primarily positioned as an alternative treatment option to Rd in patients who have received one prior therapy (2L) with bortezomib. This positioning reflects the location in the treatment pathway where clinicians anticipate CRd will offer the greatest benefit to patients,[3] addressing the unmet need for new triplet therapies in 2L, as previously discussed (Section B.1.3.3).

This target patient population for CRd reflects a subgroup of the full ASPIRE trial population. Therefore, aligned with the approach taken and accepted in the original TA457 submission, it was considered appropriate to conduct additional post-hoc subgroup analyses, beyond the prespecified covariate subgroup analyses presented in above, to evaluate the efficacy of CRd versus Rd in the subgroup of directly aligned with the target patient populations for CRd in England and Wales.

Furthermore, UK clinical experts confirmed that both the number and types of prior therapy (including bortezomib and lenalidomide) patients have received are important prognostic and predictive variables for both PFS and OS. This adds support to the rationale for conducting this post-hoc analysis given that the proposed patient population for CRd is defined based on both the number and types of prior therapy patients have received.

Methodology for post hoc subgroup analysis

Subgroup definition, covariates and Cox regression model

The subgroup was defined based on prespecified subgroup covariates in ASPIRE. These include prior bortezomib exposure (also a stratification factor, as this was considered when the trial was designed to be potentially important treatment effect modifiers), and number of lines of prior therapy.

For patients who have received one prior therapy with bortezomib, the ASPIRE post-hoc subgroup was defined as patients who:

- have received one prior therapy; AND
- have received prior bortezomib

To counter the limitations and uncertainties associated with the use of a subgroup that was not prespecified, imbalances in baseline characteristics were accounted for through adjustment of covariates which were prognostic of outcomes. Consistent with the methodology used in TA457, an approach informed by clinical expertise was considered preferable to a purely statistical approach based on automated variable selection procedures which does not take account of current knowledge and opinion regarding prognostic factors. With the large number of baseline variables recorded in ASPIRE, a purely statistical approach to variable selection may have resulted in inclusion of variables with no clinical relevance.[60] We therefore consulted two leading UK-based haemato-oncologists highly experienced in the treatment of MM and provided them with a list of baseline variables collected in ASPIRE. They were then asked to identify which variables they considered prognostic of outcomes in MM (no distinction was made between PFS

and OS). In addition to highlighting that the number of lines of prior therapy and prior exposure to either lenalidomide or bortezomib were predictive and prognostic factors for PFS and OS, the following additional covariates were considered:

- Age (< 65 vs ≥ 65 years)
- ECOG PS (0 vs. 1 or 2)
- Creatinine clearance (< 50, 50–80, or ≥ 80 mL/min)
- Time since diagnosis (continuous variable)
- Time since last relapse (continuous variable)
- International Staging System (ISS) stage (I vs. II or III)
- Prior SCT
- β2-microglobulin (< 3.5 vs ≥ 3.5 mg/L)
- Refractory to last prior treatment
- Cytogenetic risk status (high, standard, or unknown/missing).*

A stepwise approach to variable selection was then used, consistent with the analyses presented to, and preferred by the committee following the ACD in TA457. A Cox proportional hazards model was implemented, adjusting for treatment and those clinician-identified covariates retained based on a stepwise variable selection procedure. Variables were selected using a hybrid stepwise selection strategy that considers both forward and backward moves at each step and selects the "best" of the two. The variable selection strategy was implemented in R (stepAIC function from the MASS package) which uses the AIC criterion to weight the choices. At each step an add or drop was performed that minimised the AIC score. The stepwise variable selection model was used to identify which prognostic variables to adjust for.

Inverse probability weighted (IPW) treatment effect

Consistent with the preferred methodology of the ERG and Committee during the TA457 ACD, an inverse probability weighted (IPW) method was used to subsequently adjust the patient-level data for the covariates of interest. With the IPW approach, the treatment effect is estimated in two steps:

- In the first step, the covariate distribution is adjusted by reweighting patients using a logistic regression framework. In the logistic regression, the treatment indicator is defined as the dependent variable whereas the covariates identified in the stepwise selection Cox model are used as independent variables. With such a logistic regression model, the probability of receiving a particular treatment given the covariates the patient has can be estimated, and by taking the inverse of the estimated probabilities, the patient population is reweighted and imbalances in the included covariates are adjusted for.
- In the second step, semi-parametric and parametric survival models (e.g. Cox models or parametric survival models) are fitted on the reweighted patient level data without further adjustment.

The IPW approach is similar to matching-adjusted indirect comparison (MAIC) methodology, with the exception that patient-level data for baseline covariates are available for both treatment arms instead of just one. The main advantage of the IPW method is that after reweighting the patient

* Cytogenetic risk status was not included in the subgroup models because 375 (47.3%) patients in ASPIRE had unknown or missing risk group status, that is, FISH results were not collected or not analysed.

populations, there is no need for further adjustment, and so the methods for extrapolation beyond the trial data proposed in the DSU Technical Support guidance document 14[61] can be directly applied. Another major advantage of this method is that adjusting for imbalances takes place in the first step (logistic regression), so it is not necessary to explore the proportional hazards assumption for any covariate other than the treatment. In addition, the reweighted trial data (i.e. reweighted Kaplan-Meier curves) and the fitted parametric models can be directly assessed visually.

Results

A total of 166 patients (CRd 93, Rd 73) were included in the 2L post hoc subgroup; baseline characteristics are presented in detail in Appendix E. These suggest that there might be important differences in baseline characteristics across study arms within the subgroup and necessitate the use for further adjustment. Furthermore, the treatment HRs based on the Cox proportional hazards model before and after adjustment for covariates are provided in Table 17 and the difference between unadjusted and adjusted treatment HRs adds support to the need for covariate-adjustment to balance the groups on baseline characteristics. Detailed results for the Cox proportional hazard model are included in Appendix E.

Table 17. PFS and OS results within post hoc subgroup – 5 December 2017 data cut (ASPIRE)

	PFS (determined by investigator) HR (95% CI)		OS HR (95% CI)	
	Unadjusted[a]	Covariate-adjusted[b]	Unadjusted[a]	Covariate-adjusted[b]
ITT population	0.660 (0.555, 0.786)	N/A	0.794 (0.668, 0.944)	N/A
2L subgroup (one prior therapy with bortezomib)	[redacted]	[redacted]	[redacted]	[redacted]

References:, ASPIRE clinical study report (5 December 2017 data cut-off date)[54] and Amgen data on file, 2018[62]

[a] Adjusted for stratification variables
[b] Estimated using a stepwise selection Cox proportional hazards model based on clinician-identified covariates

CI, confidence interval; CRd, carfilzomib/lenalidomide/dexamethasone; HR, hazard ratio; N/A, not applicable; Rd, lenalidomide/dexamethasone

Re-weighted (or adjusted) Kaplan-Meier plots were generated using the IPW method described above and the covariates identified in the stepwise selection Cox model (Figure 9 and

Figure 10, respectively). The improvements in both PFS and OS observed for CRd versus Rd in the overall study population were consistently observed in the 2L prior bortezomib post hoc subgroup; median PFS was [redacted] months for CRd versus [redacted] for patients treated with Rd.[62] Similarly, OS [redacted]) and [redacted] in CRd and Rd treated patients, respectively.[62] The adjusted HRs, based on applying a Cox proportion hazards model to the IPW data, appear more favourable for CRd versus Rd in patients who have received 1 prior therapy, including bortezomib, than in the overall study population, which is consistent with the expectations of clinical experts who advised that both the number and types of prior therapy (including bortezomib and lenalidomide) patients have received are important prognostic and predictive variables for both PFS and OS. Furthermore, as described above, prior bortezomib exposure was a stratification factor in ASPIRE as it was acknowledged to be a potentially important treatment effect modifier. These data demonstrate that the proposed prior-bortezomib 2L positioning maximises the value of CRd for both patients and providers, offering an effective triplet therapy for patients who currently face limited treatment options and poor outcomes.

Figure 9. Kaplan–Meier plot of PFS in the 1 prior therapy, prior bortezomib subgroup (ASPIRE, weighted data, 5 December 2017 data cut)

CRd, Carfilzomib, lenalidomide, dexamethasone; Rd, Lenalidomide, dexamethasone; PFS, progression-free survival; CI, confidence interval; HR, hazard ratio.

Figure 10. Kaplan–Meier plot of OS in the 1 prior therapy, prior bortezomib subgroup (ASPIRE, weighted data, 5 December 2017 data cut)

CRd, Carfilzomib, lenalidomide, dexamethasone; Rd, Lenalidomide, dexamethasone; OS, overall survival; CI, confidence interval; HR, hazard ratio.

B.2.8 *Meta-analysis*

No meta-analyses were carried out as only one relevant RCT was identified by the SLR.

B.2.9 *Indirect and mixed treatment comparisons*

As discussed in Section B.1.3.3, the triplet therapy DVd is currently recommended as a treatment option for adults who have received 1 previous therapy with funding available through the CDF. Although DVd was not included in the Final Scope, given the need for more effective treatments earlier in the pathway, clinical experts have informed Amgen that the uptake of DVd in the prior-bortezomib subgroup is expected to be significant, and may realistically reflect the true standard of care in this setting. For this reason, Amgen considers this comparison to be pertinent to the decision problem and informative to the Committee, thus have explored this comparison in the dossier. This section pertains to the comparative clinical effectiveness of CRd vs. DVd in the population of interest.

As described in Section B.2.1, and detailed in Appendix D, a systematic literature review was conducted to identify relevant clinical evidence to inform this appraisal. Two randomised

controlled trials with CRd and DVd treatments listed as interventions were identified: ASPIRE (CRd vs Rd) and CASTOR (DVd vs Vd). As there is no direct evidence available to inform the comparative clinical effectiveness, indirect treatment comparison (ITC) methodologies were explored.

The compatibility of the data sources – and, hence, the feasibility and appropriateness of performing an indirect treatment comparison – was assessed through a review of the design, outcome definition, population profiles and availability of data reported such as Kaplan-Meier curves for OS and PFS. The next section summarises key information from this review and highlight discrepancies that present challenges or require specific assumptions in the analyses.

B.2.9.1 Summary of Trials and Network Diagram

In the absence of a head-to-head comparison between CRd and DVd, and a disconnected evidence network due to the absence of a common comparator, the relative effectiveness between CRd and DVd could not be assessed via an ITC or a network meta-analysis. Since individual patient level data (IPD) were available for ASPIRE, an unanchored matching adjusted indirect comparison (MAIC) was proposed [63]. For this analysis to be robust it is necessary to assess the comparability of the included trials as well as adjust for patients' characteristics that are likely to be effect modifiers and to adjust for prognostic factors [64].

B.2.9.2 Data Sources and Assessment of Compatibility for Comparison

Trial Design and Eligibility Criteria

Both trials identified in the SLR and relevant to this analysis (ASPIRE and CASTOR) were phase III, open-label RCTs that included adult patients with R/RMM who had received at least one prior line of therapy. The trial design and eligibility criteria for both trials are summarised in Table 18 below. Although the trials are largely similar there were a few differences that could potentially impact the results of an indirect analysis. Specifically, ASPIRE included patients who have received 1 to 3 prior lines whereas CASTOR included patients who have received at least 1 prior line (i.e. including >3 therapies). In addition, patients with an ongoing graft versus host disease were excluded from ASPIRE whereas CASTOR excluded patients who had an allogenic transplantation and the eligibility criteria were defined differently between the trials (ASPIRE inclusion CrCl>50 ml/min; CASTOR inclusion CrCl>20ml/min).

Nevertheless, clinical experts consulted by Amgen at a recent advisory board (n=6) considered ASPIRE and CASTOR to be reasonably similar in both their design and eligibility criteria with the minor differences identified unlikely to invalidate the comparison. Although the number of lines of prior therapy was considered to be a significant prognostic and predictive variable for PFS and OS, only a minority of patients in the ITT population received >3 prior therapies in CASTOR (N=50/498; 10%) and only (N=22/251; 8.8%) in the DVd arm.

Table 18. Key differences between the two trials

	ASPIRE	CASTOR
Comparators	CRd vs Rd	DVd vs Vd
Blinding	Open-label	Open-label
Eligibility criteria for participants	o Included patients who had received treatment with at least one, but no more than three, regimens for multiple myeloma o Included patients with a neutrophil count of 1000 per cubic millimetre or higher o Included patients with a haemoglobin level of 8 g per decilitre or higher within 14 days prior to randomization (subjects may be receiving red blood cell transfusions in accordance with institutional guidelines) o Included patients with a platelet count ≥ 50 × 10^9 /L (≥ 30 × 10^9 /L if myeloma involvement in the bone marrow is > 50%) o Included patients with a creatinine clearance of 50 ml or more per minute o Excluded patients previously treated with bortezomib (alone or in combination) who had a progression during treatment o Excluded patients with an ongoing graft-vs-host disease o Excluded patients who had radiotherapy to multiple sites or immunotherapy/antibody therapy within 28 days prior to randomization; localized radiotherapy to a single site within 7 days prior to randomisation o Included patients with an adequate hepatic function, with serum ALT ≤ 3.5 times the upper limit of normal and serum direct bilirubin ≤ 2 mg/dL (34 µmol/L) within 21 days prior to randomization	o Included patients who had received at least 1 prior line of therapy o Excluded patients with a neutrophil count of 1000 or less per cubic millimetre o Excluded patients with a haemoglobin level of 7.5 g or less per decilitre o Excluded patients with a platelet count of less than 75,000 per cubic millimetre o if <50% of bone marrow nucleated cells are plasma cells; otherwise platelet count <50 × 10^9/L o Excluded patients with a creatinine clearance of 20 ml or less per minute o Excluded patients refractory to bortezomib (i.e had progression of disease while receiving bortezomib therapy or within 60 days of ending bortezomib therapy) o Excluded patients with allogenic transplant o Excluded patients who have known meningeal involvement of multiple myeloma. o Excluded patients with Amyloidosis o Excluded patients with a potassium level <3.0 mEq/L; or a corrected serum calcium >14.0 mg/dL (3.5 mmol/L). o Excluded patients with an alanine aminotransferase level ≥2.5 times the upper limit of normal (ULN) o Total bilirubin level ≥2 × ULN, (except for Gilbert Syndrome: direct bilirubin 2 × ULN)
Reported outcomes of interest for indirect treatment comparisons	PFS and OS curves (Kaplan-Meier)	PFS and OS curves (Kaplan-Meier)
Patients characteristics	IPD available	Available for ITT and second line

CRd, Carfilzomib, lenalidomide, dexamethasone; Rd, Lenalidomide, dexamethasone; PFS, progression-free survival; OS, overall survival; ITT, intention to treat; IPD, individual patient level data; ALT, alanine aminotransferase; g, grams; L, liters; ml, millilitres; mg, milligrams; dL, decilitre; µmol, micromole; mEq, milliequivalent; mmol, millimole; ULN, upper limit of normal

Population(s) of Interest

As outlined in Section B.1.3.3, the target population of the submission is patients with one prior line of treatment with bortezomib. However, baseline patient characteristics data for DVd were not available for this specific subgroup in the CASTOR trial; baseline patient characteristics were published only for the broad second-line subgroup. As a result, the population that was used for the comparisons was the broader second line (1 prior line) population. Furthermore, available OS data for DVd from the CASTOR trial is immature with low number of events (n=82/251; 32.7%) for the ITT population and even lower (n=25/122; 20.5%) for the second line subpopulation.[65] The immaturity of the survival data, particularly in the 2nd-line setting, was a key component of NICEs decision to recommend DVd as a treatment option only within the CDF and presents a challenge to estimating robust outcomes in a MAIC analysis. Therefore, scenario analyses assessing the comparative effectiveness in the ITT population was also explored given the greater number of events observed for OS within the trial follow-up.

Patient Profile for The Second Line and Overall Population

A summary of baseline characteristics in the 2L and overall trial populations for both ASPIRE and CASTOR are presented in Table 19 below.

Within the 2L population, CRd patients included in ASPIRE were slightly older than DVd patients included in CASTOR and had a shorter average disease duration prior to enrolment on the trial. In addition, there were notable differences in ISS status, prior treatments including stem cell transplantation and the proportion of patients' refractory to the previous line of therapy. The ITT population was generally more balanced overall with similar characteristics for age, gender, ECOG status and ISS stage; however, there remained variations in potentially important predictive and prognostic factors (prior treatments, time since diagnosis and line of therapy) which may impact the validity of an indirect comparison.

Given the potentially important differences in the 2L and overall trial a MAIC was conducted to adjust the characteristics and ensure alignment between the trial populations.

Table 19: Summary of baseline Characteristics for ASPIRE and CASTOR – ITT and 2L populations

Baseline Characteristics	ITT population		Second line patients	
	CRd (N=396)	DVd (N=251)	CRd (N=184)	DVd (N=122)
Age N, (%)				
<65	211 (53.3)	132 (52.6)	86 (46.7)	67 (54.9)
≥65-<75	142 (35.9)	96 (38.2)	76 (41.3)	47 (38.5)
other	43 (10.9)	23 (9.2)	22 (12.0)	8 (6.6)
Gender N, (%)				
Male	215 (54.3)	137 (54.6)	109 (59.2)	74 (60.7)
ECOG status N, (%)				
ECOG 0	165 (41.7)	106 (42.4)	80 (43.5)	57 (46.7)
ECOG 1	191 (48.2)	131 (52.4)	83 (45.1)	58 (47.5)
ECOG 2	40 (10.1)	13 (5.2)	21 (11.4)	7 (5.7)
History of transplant N, (%)	217 (54.8)	156 (62.2)	88 (47.8)	76 (62.3)
Time since diagnosis, mean Years	3.76[a]	4.70	2.80[a]	3.62
Number of prior regimens N, (%)				
1	184 (46.5) [redacted]	122 (48.6)	184 (100.0)	122 (100.0)

2 3+	[redacted]	70 (27.9) 59 (23.5)	0 0	0 0
ISS status N, (%) I II III Unknown	 167 (42.2) 148 (37.4) 73 (18.4) 8 (2.0)	 98 (39.0) 94 (37.5) 59 (23.5)	 70 (38.0) 75 (40.8) 35 (19.0) 4 (2.2)	 57 (46.7) 42 (34.4) 23 (18.9)
Prior bortezomib N, (%)	261 (65.9)	162 (64.5)	93 (50.5)	62 (50.8)
Prior lenalidomide N, (%)	79 (20.0)	89 (35.5)	34 (18.5)	15 (12.3)
Refractory to last prior line N, (%)	110 (27.8)	76 (30.3)	36 (19.6)	18 (14.8)

References: ASPIRE clinical study report (16 June 2014 data cut-off date) Tables 14-17; DVD committee papers Tables 4 and 9; Palumbo et al. 2016; and Amgen data on file.
[a] Missing for 1 patient
ISS, International Staging System; ECOG, Eastern Cooperative Oncology Group; CRd, Carfilzomib, lenalidomide, dexamethasone; Rd, Lenalidomide, dexamethasone; DVd, daratumumab, bortezomib, dexamethasone

B.2.9.3 Methodology of Matched Adjusted Indirect Comparison

The following section describe the analytic process involved in the MAIC analyses. MAICs were applied to compare PFS and OS for CRd vs DVd adjusting for differences in patient characteristics across trials. Results are reported in terms of the hazard ratios and 95% confidence intervals.

The aim of MAIC analysis is to calculate an adjusted estimate of the outcome expected with the index treatment, CRd, in a population that matches the profile of the patient characteristics in which the comparator treatment was studied. Therefore, in the comparison between CRd and DVd, the relative effect of CRd versus DVd is estimated in the CASTOR population.

This is achieved by first applying the selection criteria of CASTOR to the patient population of ASPIRE and second by deriving and applying individual weights to the index population. The weights should be estimated such that, after weighting, all baseline characteristics included for adjustment in these analyses are equal across the populations. Predictive and prognostic factors used for the matching were identified by clinical experts as discussed above (see section B.2.7.2). These were the number of prior lines of therapy, prior bortezomib, prior lenalidomide, age (< 65 vs ≥ 65 years), ECOG PS (0 vs 1 or 2), creatinine clearance (< 50, 50–80, ≥ 80 mL/min), time since diagnosis (continuous variable), time since last relapse (continuous variable), ISS stage (I vs II or III), prior SCT, β2-microglobulin (< 3.5 vs ≥ 3.5 mg/L), refractory to last prior treatment, and cytogenetic risk status (high, standard, or unknown/missing). Adjusting for these prognostic and predictive variables in the MAICs requires the variables being available and defined in the same manner across the trials. β2-microglobulin, time from last relapse, and baseline creatinine clearance were not available from the CASTOR trial, therefore they had to be excluded from the comparison between CRd and DVd. Similarly, the MAIC could not adjust for cytogenetic risk status due to the limited available data on this characteristic.

Virtual patient level (VPL) data for the DVd arm were generated using digitised survival curves and the algorithm of Guyot.[66] The weighted CRd data and the VPL data created for DVd were used for the comparison of PFS and OS. Standard survival analyses were carried out, deriving relative efficacy measures and estimates of uncertainty. In particular, Cox proportional hazards models were fitted to the weighted CRd and the VPL DVd data to estimate hazard ratios for PFS and OS. MAIC analyses were performed in R-3.5.2 and use the R code published by NICE. [66]

PFS curve for DVd patients were digitized from a poster presented at the American Society for Hematology conference (median follow-up time 40.0 months, median PFS for 2L patients: 27.0 months, median PFS for ITT patients: 16.7 months) and OS curve was digitized from the NICE DVd appraisal document (median follow-up: 26.9 months, median OS for 2L and ITT patients: not reached) [65, 67].

B.2.9.4 Results

Matching of Second Line Patients in ASPIRE and CASTOR

The distribution of weights estimated by the MAIC algorithm is summarised in Table 20, which also shows the original sample sizes of the CRd population in the ASPIRE trial and the effective sample sizes after application of the weights. Sample size losses are expected in any matching and are an inevitable result of matching on variables that quantify population differences. In ASPIRE, 184 patients (i.e. approximately half of the trial participants) received CRd as a second line treatment. Of those, 24 patients were excluded after aligning for patient selection criteria between ASPIRE and CASTOR and a further 5 patients were excluded due to missing data on the matching variables (time from diagnosis and ISS). Overall, 155 patients were used for the MAIC. After applying the MAIC algorithm, the effective sample size was 124.

Table 20: Actual and effective sample sizes in MAIC analyses along with distribution of weights estimated by the matching algorithm for the second line population

Comparison	Sample Size (N), Total		Distribution of Weights[c]					
	Actual[a]	Effective[b]	Min	Q1	Median	Mean	Q3	Max
CRd vs DVd	155	124	0.353	0.690	0.847	1.000	1.209	4.244

[a] Number of patients after aligning for patients selection criteria between ASPIRE and CASTOR and for which complete data for the matching variables is available.
[b] Effective sample size calculated as the squared sum of weights divided by the sum of the squared weights
[c] Weighs were rescaled such that the sum of rescaled weights equalled the actual number of patients
Min, minimum; Q1, first quartile; Q3, third quartile; Max, maximum CRd, Carfilzomib, lenalidomide, dexamethasone; DVd, daratumumab, bortezomib, dexamethasone.

The matching was successful, reweighted baseline characteristics for CRd matched those for DVd for all included variables, as can be seen in Table 21.

Table 21: Effect of MAIC upon baseline characteristics of second line patients

Baseline Characteristics	CRd unmatched	CRd matched	DVd
Age>=65	0.531	0.451	0.451
Age < 65	0.469	0.549	0.549
ECOG 0	0.436	0.467	0.467
ECOG 1-2	0.564	0.533	0.533
Prior stem cell transplant	0.486	0.623	0.623
Time since diagnosis, years	2.8	3.62	3.62
ISS I	0.386	0.467	0.467
ISS II-III	0.615	0.533	0.533
Prior bortezomib use	0.503	0.508	0.508
Prior lenalidomide use	0.190	0.123	0.123
Refractory to last prior line	0.196	0.148	0.148

ISS, International Staging System; ECOG, Eastern Cooperative Oncology Group; CRd, Carfilzomib, lenalidomide, dexamethasone; DVd, daratumumab, bortezomib, dexamethasone

Survival Analyses for the Second-Line Population

PFS

The MAIC reweighting altered the CRd PFS curve for the second line population. The reweighting showed that CRd would have performed slightly better in the second line DVd population enrolled in CASTOR than in the ASPIRE population (Figure 11). In the second line population, there was [redacted]

Figure 11: Unmatched and matched (weighted) PFS for CRd versus PFS for DVd (second-line population)

[redacted]

The weighted CRd curve is presented using the weights estimated from the matching-adjusted indirect comparison
CRd, Carfilzomib, lenalidomide, dexamethasone; Rd, Lenalidomide, dexamethasone; DVd, daratumumab, bortezomib, dexamethasone

OS

Similarly to PFS, the weighting altered the OS for CRd in the second line population. The weighting showed that CRd would have performed better in the second line DVd population enrolled in CASTOR than in ASPIRE (Figure 12).

[redacted] However, there was considerable uncertainty in this analysis, indicated by the presence of very wide confidence intervals, driven by the low number of events observed in the CASTOR clinical trial at the time of the data-cut, in the

context of a subgroup of second-line patients that represents approximately half of the the ITT population. Of particular concern, the OS data appears inconsistent with the observed PFS results (based on more mature survival data).

Figure 12: Unmatched and matched (weighted) OS for CRd versus OS for DVd (second-line population)

The weighted CRd curve is presented using the weights estimated from the matching-adjusted indirect comparison
CRd, Carfilzomib, lenalidomide, dexamethasone; Rd, Lenalidomide, dexamethasone; DVd, daratumumab, bortezomib, dexamethasone

Matching of the ITT Population in ASPIRE and CASTOR

The distribution of weights derived from matching analyses in the MAIC as well as the original sample sizes of the CRd population in the ASPIRE trial and the effective sample sizes after application of the weights are summarised in Table 22. In ASPIRE 396 patients received CRd. Of those, 68 patients were excluded after aligning for patient selection criteria between ASPIRE and CASTOR and a further 8 patients were excluded due to missing data on the matching variables (time from diagnosis and ISS). Overall, 320 patients were used for the MAIC. After applying the MAIC algorithm, the effective sample size was 220 (i.e. almost double that of the second-line population discussed above).

Table 22: Actual and effective sample sizes in MAIC analyses along with distribution of weights derived from matching analyses for the overall population

Comparison	Sample Size (N)		Distribution of Weights[c]					
	Actual[a]	Effective[b]	Min	Q1	Median	Mean	Q3	Max
CRd vs DVd	320	220	0.287	0.579	0.758	1.000	1.255	4.151

[a] Number of patients after aligning for patients selection criteria between ASPIRE and CASTOR and for which complete data for the matching variables is available.
[b] Effective sample size calculated as the squared sum of weights divided by the sum of the squared weights
[c] Weighs were rescaled such that the sum of rescaled weights equalled the actual number of patients
Min: minimum; Q1: first quartile; Q3: third quartile; Max: maximum; CRd, Carfilzomib, lenalidomide, dexamethasone; DVd, daratumumab, bortezomib, dexamethasone

The matching was successful, reweighted baseline characteristics for CRd matched those for DVd for all included variables, as can be seen in Table 23.

Table 23: Effect of MAIC upon baseline characteristics in the overall population

Baseline Characteristics	CRd unmatched	CRd matched	DVd
Age>=65	0.470	0.474	0.474
Age < 65	0.530	0.526	0.526
ECOG 0	0.419	0.424	0.424
ECOG 1-2	0.581	0.576	0.576
Prior stem cell transplant	0.553	0.622	0.622
Time since diagnosis, years (mean)	3.77	4.70	4.70
Number of prior regimens (mean)	1.77	1.90	1.90
ISS I	0.429	0.390	0.390
ISS II-III	0.571	0.610	0.610
Prior bortezomib use	0.656	0.645	0.645
Prior lenalidomide use	0.199	0.355	0.355
Refractory to last prior line	0.279	0.303	0.303

ISS, International Staging System; ECOG, Eastern Cooperative Oncology Group

Survival Analyses for the ITT Population

PFS

The MAIC reweighting did not considerably alter the CRd PFS curve in the ITT population suggesting that CRd would have performed similarly in the overall DVd population enrolled in CASTOR as it did in ASPIRE (Figure 13). The MAIC results show that in the larger overall population, CRd had a statistically significant advantage over DVd in terms of PFS [redacted]

Figure 13: Unmatched and matched (weighted) PFS for CRd versus PFS for DVd (ITT population)

The weighted CRd curve is presented using the weights estimated from the matching-adjusted indirect comparison CRd, Carfilzomib, lenalidomide, dexamethasone; Rd, Lenalidomide, dexamethasone; DVd, daratumumab, bortezomib, dexamethasone

OS

Similarly to PFS, the MAIC reweighting did not considerably change CRd OS compared with in ASPIRE (

Figure 14). In the larger overall population [redacted]

Figure 14: Unmatched and matched (weighted) OS for CRd versus OS for DVd (ITT population)

The weighted CRd curve is presented using the weights estimated from the matching-adjusted indirect comparison CRd, Carfilzomib, lenalidomide, dexamethasone; Rd, Lenalidomide, dexamethasone; DVd, daratumumab, bortezomib, dexamethasone

B.2.9.5 Conclusion

After adjusting for observed differences in prognostic and/or predictive factors between ASPIRE and CASTOR, [redacted]. Although the analyses suggested no meaningful differences in CRd and DVd in terms of OS, this finding must be interpreted in the context of the known limitations of the MAIC approach and uncertainty arising from the lack of mature OS data for DVd.

A key limitation of the MAICs is that, as an unanchored comparison, it implicitly assumes that the prognostic and/or predictive factors considered for the matching adjust for all differences across the trial populations. Regrettably, these analyses are not capable of adjusting for any residual confounding that may exist across the comparator populations. Besides this, due to data limitations our MAIC could not adjust for certain covariates that were considered potentially important, such as β2-microglobulin (although it is part of the ISS level), cytogenic risk status, baseline creatinine clearance, and time from last relapse.

The lack of mature OS data for DVd to inform the comparisons presents particular challenges. Whilst both trials provided mature PFS data, and consequently the PFS comparisons have a high level of confidence. The OS data from the CASTOR trial were considerably less mature, i.e., only 20% of the second line patients and 33% of the ITT patients had died by the data cut-off [65]. Therefore, there is considerable uncertainty in the HRs for OS, especially in the second line population. As the second-line subgroup represented only approximately half of the ITT populations, this will have compounded the uncertainty in the OS results and adversely affected the ability of the MAIC to demonstrate statistically significant effects on PFS in the second line setting.

This is demonstrated by the comparison based on the ITT populations, for which more prognostic and/or predictive factors could be used for the matching, and for which the effective population sizes were larger and the DVd OS data weremore robust. In these ITT analyses, there was a statistically significant benefit for CRd over DVd with respect to PFS and a trend favouring CRd OS with considerably less uncertainty than in the second line population.

In summary, there are inherent uncertainties associated with the presented MAICs including the inability to adjust for all prognostic and/or predictive factors and lack of mature OS data for DVd. Despite this, based on clinical opinion sought at a recent advisory board, the results indicating longer PFS and at least comparable OS for CRd vs DVd appear reasonable in the absence of direct comparative data.

B.2.10 *Adverse reactions*

Summary of Adverse Reactions

- CRd was generally well tolerated in ASPIRE with minimal additional toxicity compared with Rd, despite the longer overall duration of therapy (88 weeks vs. 57 weeks) and the use of a three-drug versus two-drug combination
- The incidences of treatment discontinuations due to AEs (≥ 1 study drug discontinued; [redacted]) and incidence of deaths due to TEAEs (CRd, 11.5%; Rd, 10.8%) were similar across study arms
- Higher rates of some AEs of interest were noted in the CRd arm (including cardiac failure, ischaemic heart disease, venous thrombolic events, and dyspnoea); specific safety warnings and corresponding management recommendations are detailed in the carfilzomib SmPC

The safety and tolerability data presented below are derived from the relevant RCT (ASPIRE) identified in the clinical efficacy/safety SLR (Appendix D). ASPIRE data are presented from the most recent analysis (primary OS analysis, data cut-off 28 April 2017) which includes approximately 3 additional years of follow-up compared with the interim analysis presented in our previous submission (data cut-off 16 June 2014). There was no exposure to carfilzomib study treatment during this additional follow-up period, since all patients had completed carfilzomib treatment prior to the interim analysis.[54] However, patients could have received on-going study treatment with Rd in both treatment arms. As of the primary OS analysis data cut-off, [redacted] in the CRd arm and [redacted] in the Rd arm remained on study treatment ([redacted] of overall ITT population).[54]

A total of 392 patients in the CRd arm and 389 patients in the Rd arm received at least one dose of study drug and were included in the ASPIRE safety population.[46] Of relevance to the interpretation of safety data, patients were on study treatment (carfilzomib, lenalidomide or dexamethasone) longer in the CRd arm than the Rd arm, with median treatment duration of [redacted], respectively (primary OS analysis).[54] Patients in the CRd arm received carfilzomib for a median duration of 72 weeks. Median duration of lenalidomide was 85 weeks in the CRd arm and 57 weeks in the Rd arm.[46] Median duration of dexamethasone was 80 weeks in the CRd arm and 49 weeks in the Rd arm. The median number of treatment cycles initiated was [redacted] in the CRd arm and [redacted] in the Rd arm.[54]

B.2.10.1 Summary of AEs

A summary of the patient incidence of all AEs that occurred after the first dose of study drug and up to 30 days after the last dose of study drug (i.e. treatment-emergent AEs [TEAEs]) is provided in Table 24. A similar proportion of patients had at least 1 TEAE in each arm (CRd 98.0%; Rd 97.9%). The patient incidence of grade ≥ 3 AEs, serious AEs and AEs leading to discontinuation of study drug was slightly higher in the CRd arm compared with the Rd arm. When adjusted for person years of exposure to study drug, patient incidence rates for all-grade AEs, grade ≥ 3 AEs, serious AEs and fatal AEs were similar between study arms.

Table 24. Summary of patient incidence of treatment-emergent adverse events – primary OS analysis (ASPIRE, safety population)

	CRd (N = 392) n (%)	Rd (N = 389) n (%)	CRd (N = 392) Exposure-adjusted rate /100 PYs[b] (95% CI)	Rd (N = 389) Exposure-adjusted rate /100 PYs[b] (95% CI)
Any TEAE[a]	384 (98.0)	381 (97.9)	588.06 (532.08, 649.91)	575.53 (520.55, 636.32)
≥ Grade 3	341 (87.0)	324 (83.3)	115.67 (104.02, 128.62)	128.27 (115.03, 143.02)
Serious	256 (65.3)	221 (56.8)	48.18 (42.63, 54.46)	49.48 (43.37, 56.46)
Fatal	45 (11.5)	42 (10.8)	5.09 (3.80, 6.82)	6.23 (4.61, 8.43)
Leading to discontinuation of any study drug	[redacted]	[redacted]	-	-
Any treatment-related TEAE[b]	[redacted]	[redacted]	-	-
≥ Grade 3[a]	[redacted]	[redacted]	-	-

References: Siegel et al 2018,[46] and ASPIRE clinical study report (data cut-off 18 April 2017)[54] Table 8-2.

[a] Includes AEs that started or worsened during the period from the first dose of study drug until 30 days after the last dose of study drug.
[b] Exposure-adjusted rates are presented for categories of AEs reported in Siegel et al, 2018[46] and are adjusted for time on study treatment
[c] Considered related to ≥ 1 study drug by the investigator.

Note: AEs coded were using MedDRA version 20.0.

AE, adverse event; CRd, carfilzomib/lenalidomide/dexamethasone; N/A, not applicable; r, exposure-adjusted subject rate per 100 subject years (ratio of the total number of patients with events and the total person-time at risk in years multiplied by 100); Rd, lenalidomide/dexamethasone; SAE, serious adverse event; TEAE, treatment-emergent adverse event

B.2.10.2 All AEs

The incidence of the most frequently reported TEAEs (occurring in ≥ 20% of patients in either arm) is shown in Table 25. AEs with a ≥ 5% higher patient incidence in the CRd arm compared with the Rd arm were: diarrhoea, neutropenia, upper respiratory tract infection, pyrexia, cough, hypokalaemia, thrombocytopenia, muscle spasms, pneumonia, nausea, bronchitis, hypertension (CRd 15.8%; Rd 8.0%), hypophosphataemia (CRd 14.5%; Rd 8.5%) and headache (CRd 14.3%; Rd 8.2%) (Table 25 and ASPIRE CSR[54]). More detailed results on TEAEs occurring in ≥ 10% in either study arm can be seen in Appendix F.

Grade ≥ 3 AEs with a ≥ 2% higher patient incidence in the CRd arm compared with the Rd arm were neutropenia, thrombocytopaenia, pneumonia, hypokalaemia, hypophosphataemia (CRd 8.9%; Rd 5.1%) and hypertension (CRd 5.4%; Rd 2.3%) (Appendix F and ASPIRE CSR[54]).

Table 25. Summary of patient incidence of most frequently reported[a] treatment-emergent adverse events – primary OS analysis (ASPIRE, safety population)

Preferred Term	CRd (N = 392) n (%)		Rd (N = 389) n (%)	
	All Grades	Grade ⩾ 3	All Grades	Grade ⩾ 3
Diarrhoea	174 (44.4)	18 (4.6)	145 (37.3)	17 (4.4)
Anaemia	169 (43.1)	73 (18.6)	158 (40.6)	68 (17.5)
Neutropenia	157 (40.1)	122 (31.1)	136 (35.0)	107 (27.5)
Fatigue	131 (33.4)	32 (8.2)	124 (31.9)	26 (6.7)
Upper respiratory tract infection	118 (30.1)	9 (2.3)	81 (20.8)	4 (1.0)
Pyrexia	117 (29.8)	7 (1.8)	84 (21.6)	3 (0.8)
Cough	116 (29.6)	1 (0.3)	70 (18.0)	0 (0.0)
Hypokalaemia	116 (29.6)	41 (10.5)	58 (14.9)	23 (5.9)
Thrombocytopaenia	115 (29.3)	66 (16.8)	94 (24.2)	51 (13.1)
Muscle spasms	106 (27.0)	5 (1.3)	82 (21.1)	4 (1.0)
Pneumonia	91 (23.2)	63 (16.1)	66 (17.0)	47 (12.1)
Nausea	82 (20.9)	3 (0.8)	56 (14.4)	4 (1.0)
Constipation	81 (20.7)	1 (0.3)	70 (18.0)	2 (0.5)
Insomnia	81 (20.7)	12 (3.1)	65 (16.7)	11 (2.8)
Viral upper respiratory tract infection	80 (20.4)	1 (0.3)	68 (17.5)	0 (0.0)
Bronchitis	79 (20.2)	8 (2.0)	59 (15.2)	12 (3.1)
Back pain	73 (18.6)	6 (1.5)	83 (21.3)	12 (3.1)

References: Siegel at al, 2018,[46] ASPIRE clinical study report (18 April 2017 data cut-off date)[54] Table 8-3 and Table 14-3.2.2.

Preferred Term	CRd (N = 392) n (%)		Rd (N = 389) n (%)	
	All Grades	Grade ⩾ 3	All Grades	Grade ⩾ 3

Note: AEs were coded using MedDRA (Version 20.0).

[a] AEs (preferred terms) occurring in ≥ 20% of patients in either arm.

AE, adverse event; CRd, carfilzomib/lenalidomide/dexamethasone; MedDRA, Medical Dictionary for Regulatory Activities; Rd, lenalidomide/dexamethasone; TEAE treatment-emergent adverse event.

B.2.10.3 Serious AEs

Overall, there was a higher incidence of treatment-emergent SAEs in the CRd arm than in the Rd arm ([redacted]), however, when adjusted for duration of exposure to study drug, SAE rates were similar between arms ([redacted]) (Appendix F). The [redacted] SAEs that were reported with a ≥ 2% higher patient incidence in the CRd group compared with the Rd group were pneumonia ([redacted]) and respiratory tract infection ([redacted]). For more information, see Appendix F.

B.2.10.4 AEs leading to discontinuation of study drug

TEAEs leading to discontinuation of any study drug occurred in [redacted] of patients in the CRd arm compared with [redacted] in the Rd arm (Appendix F). The only AE leading to the discontinuation of any study drug with [redacted] [54] Further information on the AEs resulting in treatment discontinuation can be seen in Appendix F.

B.2.10.5 AEs leading to dose reductions

Dose reductions due to AEs were lower for carfilzomib in the CRd arm [redacted] than for lenalidomide in either study arm ([redacted]).[54]

B.2.10.6 Fatal AEs

The patient incidence of fatal TEAEs was similar in both arms (CRd 11.5% [5.09 per 100 PYs]; Rd 10.8% [6.23 per 100 PYs]). Fatal AEs events reported for ≥ 2 patients in the CRd group were pneumonia (CRd 1.5%; Rd 0.8%), sepsis (CRd 0.8%; Rd 0.8%), myocardial infarction (CRd 0.8%; Rd 0.5%), acute respiratory distress syndrome (CRd 0.8%; Rd 0.0%), death (CRd 0.5%; Rd 0.5%), and cardiac arrest (CRd 0.5%; Rd 0.3%). The only fatal AEs that occurred more frequently (≥ 2 patients) in the CRd group compared with the Rd group were pneumonia (CRd n=6 [1.5%]; Rd n=3 [0.8%]) and acute respiratory distress syndrome (CRd n=3 [0.8%]; Rd n=0 [0.0%]). The patient incidence of fatal cardiac disorders (based on system organ class) was 2.6% in the CRd arm and 2.3% in the Rd arm.[46, 54]

B.2.10.7 AEs of interest

Treatment-emergent adverse events of interest (AEIs) were prespecified based on their association with patients with advanced myeloma, protease inhibition, known side effects of bortezomib (first generation proteasome inhibitor) or lenalidomide, or results from prior

carfilzomib studies. An overview of results for the most clinically relevant AEIs is provided in Table 26, with results for all other AEIs available in the ASPIRE clinical study report.[54]

Cardiac failure ([redacted]) and ischaemic heart disease ([redacted]) AEIs occurred more frequently in the CRd arm than the Rd arm. A higher frequency of hypertension events ([redacted]), venous thromboembolic events ([redacted]) and dyspnoea events ([redacted]) was also observed in the CRd arm; however, most events were Grade 1 and 2 in severity. Acute renal failure events occurred in [redacted] of patients in the CRd arm compared with [redacted] in the Rd arm. Specific safety warnings and corresponding management recommendations are detailed in the carfilzomib SmPC (Appendix C).

Table 26. Selected treatment-emergent adverse events of interest – primary OS analysis (ASPIRE, safety population)

AEI	CRd (N = 392) n (%)	Rd (N = 389) n (%)
Cardiac failure (SMQN)	[redacted]	[redacted]
≥ Grade 3	[redacted]	[redacted]
Ischaemic heart disease (SMQN)	[redacted]	[redacted]
≥ Grade 3	[redacted]	[redacted]
Venous thromboembolic events (SMQN)	[redacted]	[redacted]
≥ Grade 3	[redacted]	[redacted]
Peripheral Neuropathy (SMQN)	[redacted]	[redacted]
≥ Grade 3	[redacted]	[redacted]
Dyspnoea (HLT)	[redacted]	[redacted]
≥ Grade 3	[redacted]	[redacted]
Interstitial lung disease (SMQN)	[redacted]	[redacted]
≥ Grade 3	[redacted]	[redacted]
Pulmonary hypertension (SMQN)	[redacted]	[redacted]
≥ Grade 3	[redacted]	[redacted]
Acute renal failure (SMQN)	[redacted]	[redacted]
≥ Grade 3	[redacted]	[redacted]
Haematopoietic thrombocytopenia (SMQN)	[redacted]	[redacted]
≥ Grade 3	[redacted]	[redacted]
Tumour lysis syndrome	[redacted]	[redacted]
≥ Grade 3	[redacted]	[redacted]
Hepatic failure, fibrosis, cirrhosis, and other liver damage-related conditions (SMQN)	[redacted]	[redacted]
≥ Grade 3	[redacted]	[redacted]
Hypertension (SMQN)	[redacted]	[redacted]
≥ Grade 3	[redacted]	[redacted]

References: Siegel at al, 2018[46] and ASPIRE clinical study report (18 April 2017 data cut-off date)[54] Table 8-9.

Note: AEs were coded using MedDRA (Version 20.0).

AEI, adverse event of interest; CRd, carfilzomib/lenalidomide/dexamethasone; HLT, high level term; MedDRA, Medical Dictionary for Regulatory Activities; Rd, lenalidomide/dexamethasone; SMQN, standardised MedDRA query, narrow scope

B.2.10.8 Summary of safety

Safety results from the ASPIRE primary OS analysis were consistent with those from the interim analysis presented in our previous submission and the known safety profile of carfilzomib. No new risks were identified.

CRd was generally well tolerated in ASPIRE with minimal additional toxicity compared with Rd, despite the longer overall duration of therapy (88 weeks vs. 57 weeks) and the use of a three-drug versus two-drug combination. Exposure-adjusted patient incidence rates for all-grade AEs, grade ≥ 3 AEs, serious AEs and fatal AEs were similar across study arms. Higher rates of some AEIs were noted in the CRd arm (including cardiac failure, acute renal failure, venous thrombolic events, dyspnoea and hypertension); specific safety warnings and corresponding management recommendations are detailed in the carfilzomib SmPC.

B.2.11 *Ongoing studies*

Additional studies of carfilzomib in multiple myeloma that are likely to report data within 12 months of this appraisal are described in Table 27.

Table 27. Carfilzomib studies in multiple myeloma likely to report data within 12 months of the appraisal

Study	Description	Number of patients	Primary outcome measure	Estimated completion date
NCT03158688 (CANDOR)	Phase 3, randomised, open-label study in in R/RMM Carfilzomib, dexamethasone, and daratumumab vs. carfilzomib + dexamethasone	450 (planned)	PFS	Primary analysis October 2019

CSR, clinical study report; MTD, maximum tolerated dose; ORR, overall response rate; PFS, progression-free survival; Q2, quarter 2.

B.2.12 *Innovation*

As an innovative triplet therapy available for 2L MM patients, CRd offers greater clinical benefit and flexibility in patients previously treated wth bortezomib.

There is a significant need for additional and more effective treatment options for patients with MM. It is widely acknowledged that there is no standard approach for MM management, and that treatment decisions are influenced by both disease- and patient-related factors.[68] Whilst some patients may be best suited to doublet regimens, triplet therapies have been shown to be superior in terms of both the response and duration of PFS achieved in MM patients, and in development of resistance, due to the enhanced synergies and targeting of multiple cellular pathways. Where clinically possible, triplet regimens are therefore preferred.

There is a lack of effective, triplet therapies available routinely for the treatment of MM patients who have been previously treated with bortezomib at 1L. As the first triplet therapy to be

approved at 2L in MM, and having demonstrated substantially improved clinical outcomes over the most relevant comparator in this setting, CRd would expand the treatment armamentarium with a more effective treatment option for these patients.

CRd is supported by mature, long-term OS data that demonstrate its sustained clinical benefit

The only other triplet therapy relevant to the proposed positioning of CRd in the clinical pathway (after first line treatment with bortezomib) is DVd. However, due to a lack of mature OS data and the uncertainty this creates in its long-term clinical and cost effectiveness, DVd was only recommended by NICE as an option for use in the CDF. In contrast to DVd, CRd is innovative in being a triplet regimen supported by mature OS data that demonstrate with little uncertainty its sustained clinical benefits over the long-term. At the primary OS analysis, over a mean follow-up of 67.1 months, CRd demonstrated a median OS benefit of 7.9 months compared with Rd (48.3 months in the CRd arm versus 40.4 months in the Rd arm), representing a statistically significant reduction of 21% in the risk of death (HR = 0.79; 95% CI 0.67, 0.99; p = 0.0045)). And in the subgroup of patients who have received one prior therapy with bortezomib – the proposed positioning of CRd – the OS gain with CRd was even more pronounced ([redacted] months with CRd versus [redacted] moths with Rd, representing a statistically significant reduction of [redacted] in the risk of death [redacted]). The availability of these mature OS data therefore provides confidence in the clinical benefit that CRd would afford MM patients, and improves certainty in analyses of its cost effectiveness.

B.2.13 *Interpretation of clinical effectiveness and safety evidence*

B.2.13.1 Summary of the principle findings of the clinical evidence base

Clinical evidence

CRd has demonstrated compelling efficacy versus Rd in the ASPIRE study. The 26.1 month median PFS observed at the 28 April 2019 data cut-off represents a meaningful 9.5 month improvement over the 16.6 month median PFS observed with Rd. In addition, although hierarchical statistical analyses preclude formal testing of additional endpoints, the vast majority of patients responded to CRd (ORR: CRd 87.1%; Rd 66.7%; 1-sided descriptive p < 0.0001), and more than 3 times as many patients achieved a CR or better in the CRd arm (CRd 31.8%; Rd 9.3%), including 14.1% in the CRd arm versus 4.3% in the Rd arm who achieved a sCR. Results from the primary OS analysis and the time to next treatment endpoint were also supportive of increased clinical benefit of CRd compared with Rd.

The PFS and OS benefit for CRd in ASPIRE was consistently observed in key prespecified subgroups including age, cytogenetic risk, and treatment history. Furthermore, improvements in PFS and OS were consistently observed in the post hoc subgroup analysis that was conducted in order to consider only the population relevant to the proposed positioning.

Health-related quality of life evidence

CRd was associated with significantly higher HRQoL (EORTC QLQ-C30 GHS/QoL) scores compared to Rd over 18 cycles of treatment (2-sided p < 0.001), with clinically meaningful differences observed between the two treatment arms. To date, carfilzomib is the only novel treatment in MM to demonstrate improvement in patient reported QoL metrics.

Safety evidence

CRd was generally well tolerated in ASPIRE with minimal additional toxicity compared with Rd, despite the longer overall duration of therapy ([redacted]) and the use of a three-drug rather than two-drug combination. The incidences of treatment discontinuations due to AEs (≥ 1 study drug discontinued; [redacted]) and deaths due to AEs (within 30 days of last dose of study drug; CRd 11.5%, Rd 10.8%) were slightly higher in the CRd arm compared with the Rd arm. However, when adjusted for person years of exposure to study drug these were similar between study arms. The overall incidences of ≥ Grade 3 AEs were also slightly higher in the CRd arm (CRd 87.0%, Rd 83.3%). Higher rates of some AEIs were noted in the CRd arm (including cardiac failure, ischaemic heart disease, hypertension events, venous thromboembolic events, and dyspnoea events); specific safety warnings and corresponding management recommendations are detailed in the carfilzomib SmPC (Appendix C).

Strengths of the clinical evidence base

The clinical evidence base for CRd versus Rd included in this submission includes data from a large, international, Phase 3 RCT (ASPIRE), the highest quality evidence for presenting and evaluating clinical efficacy. Quality assessment showed that the overall risk of bias was low in ASPIRE. This study is highly relevant to the decision problem, and included a broad spectrum of patients, including those with RMM and RRMM who have received multiple lines of prior therapy, with and without SCTs, and had been treated with a range of prior agents, including bortezomib and IMiDs (e.g. lenalidomide and thalidomide). The analyses of PFS were highly consistent irrespective of whether assessments were made by the blinded IRC (primary analysis) or investigators. Furthermore, PFS and OS benefits were consistently observed in key prespecified subgroups including subgroups for age, risk determined by cytogenetic testing, and treatment history. In addition, the post hoc subgroup analysis conducted provides more clinically relevant and appropriate estimates of the treatment effects for CRd versus Rd in the context of the proposed positioning than those observed in the overall study population.

The long duration of follow-up observed with the updated OS analysis allows for demonstration of the long-term clinical benefit offered by CRd versus Rd, with CRd continuing to demonstrate an improved PFS over Rd at 5 years of follow-up.

Weaknesses of the clinical evidence base

Whilst ASPIRE was a high quality RCT with an overall low risk of bias, it was open label and patients and investigators were aware of treatment allocation, potentially leading to bias. However, the IRC assessed response and disease progression outcomes centrally in a blinded manner in the primary analysis for these outcomes, which mitigates this risk. A limitation of the HRQoL analysis is that no data were collected beyond Cycle 18 (week 72) to assess the long-term impact of CRd treatment on HRQoL.

The use of post hoc subgroup analyses to provide more clinically relevant and appropriate estimates of the treatment effects for CRd versus Rd, in the context of the proposed positioning, may be considered a potential limitation. However, use of post hoc comparisons is common in MM due to the complex and sequential nature of the treatment pathway, and the population sizes in these post hoc analyses were of reasonable size. Furthermore, the use of more specific patient populations allows for increased confidence in the applicability of the cost-effectiveness analyses.

B.2.13.2 Relevance of the clinical evidence base to the decision problem

Patient population

The only relevant RCT included in this submission (ASPIRE) included a patient population that is broadly consistent with the overall patient population defined in the decision problem (patients with MM who have received at least one prior therapy). Whilst the target population for CRd is narrower than that of carfilzomib's marketing approval and the decision problem, prespecified subgroup analyses demonstrated that PFS, OS, and ORR results for CRd are generally consistent irrespective of the type and number of prior lines of therapy patients have received. Furthermore, post hoc subgroup analyses of patients more closely aligned with the proposed patient population CRd in England and Wales were conducted to provide PFS and OS data for subgroups aligned with these proposed patient populations.

A large proportion of patients in ASPIRE (65% of the ITT population) were enrolled in Europe, including at 6 sites in the UK. PFS, OS, and ORR outcomes were shown to be consistent irrespective of geographic region in subgroup analysis presented in Section B.2.7.

Intervention

CRd was directly evaluated as a treatment option for patients with relapsing multiple myeloma in a head to head comparison with a relevant comparator, Rd.

Comparators

The efficacy and safety of CRd was directly compared with that of Rd, a comparator highly relevant to the decision problem as the most relevant comparator in the patient populations for which CRd is being positioned in England and Wales.

An additional comparison was also provided versus DVD as Amgen believe this is pertinent to the decision problem (see SectionB.1.3.3).

Outcomes

The outcomes included in this submission, including PFS, OS, ORR, and HRQoL address all outcomes specified in the final scope for this appraisal, apart from time-to-next treatment which was a prespecified endpoint in ASPIRE. A particular strength of this submission is the availability of mature OS data, and a significant difference in OS between CRd and Rd was observed. This is notable as it is common for OS data to be immature at the time of regulatory approval for studies in R/RMM, and/or for a significant difference in OS between intervention and comparator to have not yet been observed.[69-71]

B.2.13.3 End-of-life criteria

In the proposed 2L positioning, CRd meets the extension to life criterion but does not meet the short life expectancy criterion. However, we were aware of a NICE clarification during the appraisal of pertuzumab for HER2 positive metastatic breast cancer [ID523][72] that committees can apply discretion in the application of end-of-life criteria to appraisals of treatments for metastatic cancer when:

- OS without the new drug exceeds 24 months, and;
- the new drug provides significant extension to life beyond 3 months, and;

- the new drug is combined with existing treatment, and;
- both the existing treatment and the new drug are used until disease progression.

CRd meets these criteria and, at the discretion of the committee, could therefore also be appraised as an end-of-life treatment especially given the minimal uncertainty of the proven OS benefit associated with CRd treatment.

Given the above and the significant therapeutic benefit offered by CRd, we believe that end-of-life considerations should apply to carfilzomib.

B.2.13.4 Conclusion

CRd is an innovative therapy that addresses an unmet need as an efficacious triplet therapy, for the 2L treatment of MM patients. CRd significantly improved PFS and OS compared to Rd, whilst being generally well tolerated with minimal additional toxicity compared with Rd. Furthermore, CRd has been shown to provide a clinically-effective alternative to DVd through MAIC analysis.

The quality of evidence provided by the ASPIRE trial is supported by a robust and well-reported methodology, and the trial results are directly relevant to the treatment of 2L MM patients in NHS clinical practice.

B.3 Cost effectiveness

B.3.1 *Published cost-effectiveness studies*

An SLR was performed to identify publications reporting cost-effectiveness studies for therapies used for the management of R/RMM, resource use and treatment costs for the management of R/RMM, and studies reporting HRQoL or utilities relevant for patients with R/RMM (see Appendix G for full details of the search strategies, inclusion/exclusion criteria, screening procedure, and quality assessment). Data from relevant studies were extracted as described in Appendix G.

No studies identified in the literature considered the cost-effectiveness of CRd relevant to the decision problem therefore a *de novo* economic evaluation was conducted. The de-novo analysis was largely informed by previous economic evlauations in the disease area which are summarised and discussed in the sections below (Table 28).

B.3.2 *Economic analysis*

Summary of economic analysis

- The cost-effectiveness of CRd was determined using a de novo three-state partitioned survival analysis (PartSA) model, developed in Microsoft® Excel, comprising three health states: '*progression-free*', '*progressed*', and '*death*'
- The clinical outcomes modelled were life-years and QALYs
- Based on the current treatment pathway for R/RMM in England and Wales and proposed positioning of CRd, our primary analysis compared CRd versus Rd and used the ASPIRE study to estimate the lifetime costs and outcomes of patients who have received one prior therapy (2L) with bortezomib (primary comparison) as high use of Rd is observed despite no active guidance available until the recent publication of guidance from TA586.
- Given the uncertainty in the treatment pathway for R/RMM due to the CDF recommendation for DVd, we also presented a secondary analysis comparing CRd versus DVd using an indirect comparison to estimate the lifetime costs and outcomes of patients who have received one prior therapy (2L) with bortezomib (secondary comparison) as a high uptake of DVd is anticipated despite the CDF recommendation.

B.3.2.1 Patient population

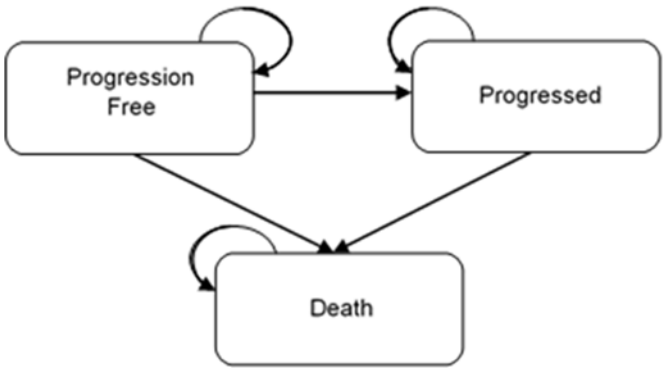
CRd received a MA for the treatment of adult patients with MM who have received at least one prior therapy on 19 November 2015 (Section B.1.2). ASPIRE, the pivotal phase 3 clinical trial used to inform this economic evaluation, included patients with R/RMM who received one to three prior therapies, which is consistent with the licensed indication for carfilzomib. Based on the current treatment pathway for R/RMM this evaluation considered patients who have received one prior therapy (2L) with bortezomib, which is a subset of the licensed population for CRd where we believe there is clear unmet need for triplet therapies that enable deeper and more durable responses earlier in the pathway and where CRd can provide the greatest clinical benefit to patients, based on clinical expert opinion.

B.3.2.2 Model structure

The cost-effectiveness model was developed in Microsoft® Excel using a three-state PartSA (or 'area under the curve') structure in both a deterministic and probabilistic (Monte Carlo simulation)

framework. This modelling approach has been deemed appropriate due to its common use in previous HTA oncology models and, specifically, models for MM have used variations on this structure.[73-77] The model diagram is presented in Figure 15.

Figure 15. Model structure



The model is based on three health states: 'progression-free', 'progressed disease', and 'death'. All patients begin the model in the progression-free health state and are at risk of progression. Death could occur from either the progression-free or progressed disease health states, and death is an 'absorbing state'. This model structure and the health states utilised represent the three most relevant health states from a patient, clinician, and NHS perspective.

- Progression-free: During this stage it is assumed that a patient's disease is in a stable or responding state, and not actively progressing. Patients in this state are assumed to incur costs associated with treatment, including drug acquisition costs, costs of drug administration, and costs associated with medical management of the condition and the management of Grade 3/4 AEs. Patients also experience a higher utility weighting compared with progressed disease. Patients receive their initial treatment while in this state, and may receive treatment until progression or until treatment discontinuation (modelled using time to treatment discontinuation [TTD] data derived from clinical trials). Therefore, patients may be in the progression-free health state and not receiving any treatment.
- Progressed disease: In this stage, a patient's disease is assumed to have returned or progressed, following which it is reasonable to assume that in clinical practice patients would still be eligible for active therapy, and therefore patients are assumed to move onto next-line treatment and eventually best supportive care before death. Subsequent lines of therapy following progression have been considered in this economic evaluation only in terms of their costs (Section B.3.5.4).
- Death: This is an absorbing health state; once patients experience death, they remain in this health state for the rest of the model time horizon.

A range of survival functions from the ASPIRE study, as well as from other oncology RCTs, indicates that the proportion of patients moving between health states is likely to vary over the course of the disease. The method used to model the proportion of patients in each health state over time allows for flexibility in the rate of change of the survival functions.

The analysis was conducted from an NHS perspective in England and Wales using 28-day model cycles, consistent with the treatment cycle length for carfilzomib. A lifetime time horizon

(40 years) was chosen, consistent with the NICE reference case[78] and in line with the median age at baseline in the ASPIRE study (64 years), given that cost-effectiveness outcomes remain unchanged when a longer time horizon is selected. A discount rate of 3.5% per annum was applied for costs and QALYs, in line with the NICE reference case[78]. A half cycle correction was applied.

An overview of the features of the economic models used for prior technology appraisals submitted to NICE and for the de novo analysis is provided in Table 28.

Table 28. Features of the economic models used for prior technology appraisals submitted to NICE and for the de novo analysis

	Previous appraisals								Current appraisal	
Factor	**TA171 (lenalidomide)**	**ID667 (lenalidomide post bortezomib)**	**TA129 (bortezomib)**	**TA457 (carfilzomib)**	**TA380 (panobinostat)**	**ID807 (ixazomib)**	**TA427 (pomalidomide)**	**TA510 (daratumumab)**	**Chosen values**	**Justification**
Model structure	Discrete event simulation utilising patient level information	Partitioned survival model, 3 health states	Semi-Markov state transition model.	Partitioned survival model, 3 health states	Direct comparison survival analysis with data from clinical trials	Partitioned survival model, 3 health states	Partitioned survival model, 3 health states	Partitioned survival model, 3 health states	Partitioned survival model, 3 health states	Best use of available data, minimal assumptions, captures key clinical outcomes measured in the ASPIRE study and those of most relevance to patients and clinicians and is consistent with the majority of previous appraisals in R/RMM allowing comparison of outcomes.
Time horizon	30 years	25 years	15 years	40 years	25 years	25 years	15 years	30 years	40 years (Lifetime)	This is consistent with the NICE reference case[78]. The mean age at baseline in the ASPIRE study was 64 years; therefore 40 years is an

										appropriate lifetime time horizon based on this mean age. Furthermore, cost-effectiveness results remain unchanged if a longer time horizon is selected.
Source of utilities	van Agthoven (2004)	van Agthoven (2004)	van Agthoven (2004)	Initial submission: Mapping analysis using change from baseline from clinical trial applied to van Agthoven (2004) Final analysis: Mapping analysis using change from baseline from clinical trial	Mapped utility values from trial Acaster et al. study	EQ-5D data from clinical trial	EQ-5D data from clinical trial	EQ-5D-5L data from trial, mapped to EQ-5D-3L; van Agthoven (2004) tested in scenario analysis	EORTC QLQ-C30 from ASPIRE mapped to EQ-5D	These data were preferred by the NICE appraisal committee in the previous appraisal of carfilzomib (TA457) as they use data collected directly in the ASPIRE trial.
Source of drug costs	British National Formulary (BNF 65)	British National Formulary (BNF 65), Department of Health Electronic Market	APEX trial	MIMS UK Drug Database, Department of Health Electronic Market Information Tool (eMIT)	BNF	N.R.	MIMS UK Drug Database	MIMS UK Drug Database	MIMS UK Drug Database, Department of Health Electronic Market Information Tool (eMIT)	These are standard sources of drug costs, are consistent with the NICE reference case and are

		Information Tool (eMIT)								the same sources accepted by NICE in the appraisal of Cd.[78]
Source of other costs	National Schedule of Reference Costs	NHS reference costs and ERG model (TA228)	OutPatient Mandatory Tariff 2005/6, Bruce et al (1999), expert interviews	National Schedule of Reference Costs	National Schedule of Reference Costs	N.R.	Admin cost driven from TA311, monitoring, concomitant medication and AE costs from questionnaire filled by clinicians.	National Schedule of Reference Costs	National Schedule of Reference Costs; PSSRU; literature	These are standard sources of costs and are consistent with the NICE reference case.[78]
Cycle length	Continuous time model	4 weeks	3 weeks	4 weeks	3 weeks	1 week	1 week	1 week	4 weeks (28 days)	This is in line with measurement points in the ASPIRE study and the treatment cycle length for CRd Any treatments with a different cycle length have been adjusted.
Health effects measure	QALYs	QALYs	LYs	QALYs	QALYs	QALYs	QALYs	QALYs	QALYs	This is in line with the NICE reference case.[78]
Discount rate for costs and effects	3.5% per annum	3.5% per annum	3.5% per annum	3.5% per annum	3.5% per annum	3.5% per annum	3.5% per annum	3.5% per annum	3.5% per annum	This is in line with the NICE reference case.[78]
Perspective	NHS & PSS	NHS & PSS	NHS	NHS	NHS & PSS	NHS & PSS	NHS	NHS	NHS & PSS	This is in line with the NICE

										reference case.[78]
Half cycle correction applied?	No	Yes	N.R.	Yes	Yes	Yes	Yes	Yes	Yes	The cycle length is sufficiently long that a half-cycle correction should be applied.
AE: adverse event; BNF: British National Formulary; eMIT: Electronic Market Information Tool; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; EQ-5D: EuroQol-5 dimension; ERG: Evidence Review Group; LY: life years; MIMS: Monthly Index of Medical Specialties; NHS: National Health Service; NICE: National Institute for Health and Care Excellence; N.R. Not reported; PSS: Personal Social Services; PSSRU: Personal Social Services Research Unit; QALY: quality-adjusted life year; R/RMM: relapsed/refractory multiple myeloma; UK: United Kingdom.										

B.3.2.3 Intervention technology and comparators

Intervention

CRd is implemented in the model as per the cycle dosing in the ASPIRE study and its MA; carfilzomib is administered as a 10-minute IV infusion on Days 1, 2, 8, 9, 15, and 16 of a 28-day treatment cycle during Cycles 1 to 12 (at a starting dose of 20 mg/m^2 on Days 1 and 2 of Cycle 1, and a target dose of 27 mg/m^2 thereafter) and on Days 1, 2, 15, and 16 during Cycles 13 to 18, after which carfilzomib is discontinued. Treatment duration for carfilzomib is implemented in the model as in the ASPIRE study (i.e. carfilzomib is capped at 18 cycles) Lenalidomide (25 mg per dose) is administered on Days 1–21 of a 28-day treatment cycle and dexamethasone (40 mg per dose) is administered on Days 1, 8, 15, and 22 of a 28-day treatment cycle. Both lenalidomide and dexamethasone are administered orally.

Comparators

Amgen proposes that CRd will be used primarily as an alternative treatment option to Rd in patients who have received one prior therapy with bortezomib as high use of Rd is observed despite no active guidance being available until the recent publication of guidance from TA586.[3, 79] The most relevant comparator for CRd is therefore Rd, and this was our primary comparison based on head to head data from the ASPIRE trial.

Amgen proposes that CRd will be used secondarily as an alternative treatment option to DVd as a high uptake of DVd is anticipated despite CDF recommendation. We therefore also present a secondary comparison versus DVd using an indirect comparison of the ASPIRE and CASTOR trials.

Both analyses are performed in the population of patients with MM who have received one prior therapy with bortezomib referred to as (2L prior bortezomib).

Rd

For Rd, lenalidomide and dexamethasone are dosed in the same way as in CRd, as described above. Although this dosing is not in line with the MA for lenalidomide, low-dose dexamethasone was chosen for ASPIRE and used in the model as clinical trial data suggest that lenalidomide plus low-dose dexamethasone is associated with better short-term OS and with lower toxicity than lenalidomide plus high-dose dexamethasone.[80] Furthermore, input from clinicians suggests that low-dose dexamethasone is preferred to high-dose dexamethasone in clinical practice in England and Wales. Treatment duration for Rd is implemented in the model per both the MA for lenalidomide and ASPIRE i.e. treatment until progression or unacceptable toxicity.

DVd

DVd is implemented in the model as per the cycle dosing in the CASTOR study; daratumumab 16 mg/kg is administered as an IV infusion on Days 1, 8, and 15 of a 21-day treatment cycle during Cycles 1 to 3, on Day 1 of a 21-day treatment cycle during Cycles 4 to 8 and on Day 1 of a 28-day treatment cycle during Cycles 9 onwards. Bortezomib 1.3 mg/m^2 is administered subcutaneously on Days 1, 4, 8 and 11 of a 21-day treatment cycle during Cycles 1-8 and then discontinued and dexamethasone (20 mg per dose) is administered orally on Days 1, 2, 4, 5, 8, 9, 11, and 12 of a 21-day treatment cycle during Cycles 1-8 and then discontinued.

B.3.3 *Clinical parameters and variables*

Summary of clinical parameters and variables

- Curves derived from the ASPIRE study using post-hoc subgroup data most relevant to the population of interest
- Post-hoc subgroup data were adjusted for baseline imbalances using the inverse probability weighting (IPW) method and stepwise variable selection based on a starting list of variables defined by clinical input
- Joint parametric curve fits were produced for CRd and Rd based on the weighted post-hoc subgroup data, and the most plausible curves were identified considering the visual and statistical fit to the observed data, and the plausibility of the long-term extrapolation
- A generalised gamma curve was selected for PFS of CRd and Rd
- A Weibull curve was selected for OS of CRd and Rd for the duration of ASPIRE
- Long-term OS extrapolations were informed by matched MM registry data
- Probabilities of being in each of the health states for DVd were calculated from PFS and OS curves derived by applying a HR to the CRd curve. In the base case, the OS for CRd and DVd were assumed equal and the PFS was derived by applying the HR estimated from MAIC analysis
- Time spent on treatment in the progression-free health state for CRd and Rd was modelled using time-to-treatment discontinuation curves derived from the best fitting parametric survival curves fit to post-hoc subgroup data for each treatment component in ASPIRE
- Time spent on treatment in the progression-free health state for DVd was modelled using a HR versus PFS derived from data available in the DVd submission to NICE.[81]

Data from the phase 3 ASPIRE RCT were used to estimate patients' demographic and baseline characteristics, the proportion of patients in each health state for CRd and Rd based on PFS and OS data, the proportion of patients experiencing treatment-related AEs for CRd and Rd, and time on treatment for CRd and Rd. ASPIRE provided a head-to-head comparison of CRd versus Rd. PFS and OS data from ASPIRE were based on the latest available 5 December 2017 data cut-off.

In ASPIRE, the primary outcome was PFS assessed by the IRC and this outcome was met at the time of the interim analysis (data cut-off 14 June 2014), hence no further updates of the primary outcome are available. OS data were however immature at that data cut-off (14 June 2014). At the primary analysis for OS (data cut-off 28 April 2017), the OS endpoint was met and updated results were published.[46] Since then, Amgen has performed an updated OS analysis (data cut-off 5 December 2017). This updated OS analysis provides the longest survival follow-up data for ASPIRE patients (median follow-up 68.7 months), with no further updates planned. For consistency, and to ensure the longest available follow-up data were used, PFS data used in the economic model are the investigator assessed PFS at the data cut-off of 5 December 2017; time to treatment discontinuation (TTD) data were also taken from this data cut-off. As discussed in Section B.2.6.2., there was high concordance between IRC and investigator assessed PFS in the ITT population, and therefore we have chosen to use the longer follow-up in preference to the primary outcome to reduce the uncertainty in the economic analysis. A summary of the data cuts used to inform all clinical parameters in the economic model is provided in Appendix M. Also presented in this appendix are data for OS and PFS in both the ITT (unadjusted) and 2L prior bortezomib (unadjusted and IPW-adjusted) populations, for the 28 April 2017 and 5 December 2017 data cuts, to illustrate the similarities between outcomes in these two data cuts.

To estimate the proportion of patients in each health state for DVd based on PFS and OS, a hazard ratio derived from MAICs for CRd in ASPIRE vs DVd in CASTOR as detailed in Section B.2.9 was applied to the CRd PFS curve. Based on clinical input, OS of DVd was assumed to be equal to the OS of CRd. Time on treatment for DVd was estimated through derivation of a hazard ratio versus DVd PFS, applied to the DVd PFS curve, and the proportion of DVd patients experiencing treatment-related AEs were taken from CASTOR.

Survival in the model is also capped by age-sex-matched general population mortality.

B.3.3.1 Extrapolation of data

CRd and Rd

For both PFS and OS, standard parametric curve fitting on post-hoc subgroup data from the ASPIRE study was conducted to estimate survival in the long term (beyond the end of the trial) for CRd and Rd. The post-hoc subgroup from ASPIRE is aligned with the proposed positioning of CRd in the treatment pathway, which is defined by important predictive and prognostic characteristics including numbers and types of prior therapy. Use of post-hoc subgroup data is therefore considered to provide more clinically-relevant and appropriate extrapolations in the context of the proposed positioning of CRd than those that could be derived from the overall study population. The post-hoc subgroup data were adjusted to account for imbalances in baseline characteristics as described in Section B.2.7.2. Survival curve fitting was conducted in line with the NICE Decision Support Unit (DSU) Technical Support Document (TSD) 14[61]. Conventional parametric models (i.e. exponential, Weibull, log-normal, log-logistic, Gompertz and generalized gamma) were assessed and the most plausible fits were selected by considering:

- Whether the proportional hazards assumption holds
- Visual inspection of fitted curves for CRd and Rd against 'Kaplan–Meier' estimates
- Comparisons of Akaike information criterion (AIC) and Bayesian information criterion (BIC) between the model types
- The clinical plausibility of long-term extrapolation

To inform the decision on whether to jointly or separately fit survival curves, proportional hazards assumption was tested using log-cumulative hazards versus log time plots. For this purpose, data were used for the 2L prior bortezomib subgroup and the broader ITT population.

DVd

To estimate the PFS of DVd, a hazard ratio derived from MAICs for CRd in ASPIRE vs DVd in CASTOR as detailed in Section B.2.9 was applied to the CRd PFS curve. Based on clinical input, OS of DVd was assumed to be equal to the OS of CRd.

B.3.3.2 Overall survival

CRd and Rd

In the 2L prior bortezomib subgroup long-term follow-up for IPW-adjusted OS data suggest that the treatment effect was maintained over the trial period (i.e., over 7 years, see Kaplan-Meier curves (KMs) for IPW-adjusted OS in Appendix M). Similarly, in the ITT population, the KMs for OS demonstrated consistency of treatment effect throughout the entirety of follow-up (Appendix M). The proportional hazards assumption for OS was assessed by inspecting the log cumulative

hazards versus log time plot which suggested that the proportional hazards assumption held for OS in both the ITT and 2L prior bortezomib population (Appendix M).

Since the constant treatment effect assumption was accepted based on the visual inspection of the curves, parametric survival models were jointly fitted to the CRd and Rd arms of the ASPIRE trial OS. In this case, jointly fitted survival models were considered the most appropriate since they can reduce uncertainty, due to the estimation of fewer parameters and the use of a larger data set.

In terms of statistical and visual fit to the observed data, all models performed similarly well, except for the log-normal distribution that had a worse fit. The fitted curves for CRd and Rd together with the AIC and BIC values of the estimated model are shown in Appendix M. Since most models had a similar fit to the ASPIRE data, assessment of the plausibility of the extrapolations based on clinical expert opinion and comparisons to long-term data were used to select the base case survival extrapolation approach.

Clinical Plausibility of OS Projections

Among the distributions that were considered to have similar fit, the log-logistic model provided the most optimistic predictions whereas the Gompertz model yielded the most pessimistic extrapolations (Appendix M). The statistically best-fitting Weibull model fitted to ASPIRE data estimates survival proportions for Rd patients at 10 and 20 years to be 5% and 0%, respectively. These estimates are significantly more conservative than those estimated by the manufacturer in TA586 (Lenalidomide for the treatment of multiple myeloma in people who have received at least one prior therapy).[73] In TA586, the company estimated survival at 25 years for patients starting on Rd to be substantially higher at 11%.[73] Although the ERG deemed this to be implausible for Rd on the basis that it was too high, no alternative values considered to be plausible were reported.

Recently, however, in the FAD for the NICE appraisal of DVd, clinical experts estimated that around 5-10% of *current* 2L patients would be expected to survive to 10 years (where current treatments in the appraisal were assumed to be bortezomib plus dexamethasone or carfilzomib plus dexamethasone).[82] The 10 years survival probability estimated by a Weibull model fitted exclusively to ASPIRE data is consistent with the lower bound of the range given by experts in the final appraisal of DVd. However, the estimate provided by experts during the final appraisal of DVd reflects the survival probability in clinical practice and it is reasonable to expect the survival probability of patients enrolled in clinical trials to be higher than in clinical practice. On this basis, the Weibull projection from ASPIRE was considered to provide overly pessimistic estimates of long-term survival. Based on additional clinical feedback sought by Amgen, alternative viable distributions (ie. log-normal, log-logistic) were could be considered plausible although were potentially optimistic due over the long-term – as such, additional real-world evidence sources were explored to guide the base case OS projections.

Real World Evidenc – MyelomaToul

MyelomaToul is a prospective, observational registry collecting data from patients on molecular and immunological information together with patient characteristics (including data on demographic, treatment, and clinical characteristics) and survival. Patients with a diagnosis of MM who have had a bone marrow sample in one of the 100 participating specialised centres for molecular and immunological explorations in France are included in the registry. The inclusion occurs when the initial bone marrow biopsy, which is done for a diagnosis and prognosis purpose, is taken. Included patients are then followed-up for response, administered treatments

until death or lost-to-follow-up. In the registry, patients were included retrospectively for the period between 1999 and 2016. Since 2016, patients are included prospectively. A summary report of the MyelomaToul registry was available to Amgen however access to the patient-level data was not feasible.[75]

Since MyelomaToul contains data from a very large number of patients (>12,000) with long-term follow-up (maximum follow-up > 10 years) and it allows assessing long-term OS for patients who received lenalidomide treatment as a second-line treatment, the use of the registry was considered as the most robust and reliable source currently available for long-term OS extrapolations for the economic model. Furthermore, combining shorter-term survival data from randomised trials with longer-term external data to aid extrapolation of the short-term data has been generally advocated in the economic evaluation literature.

The MyelomaToul registry data was utilised for the economic model as follows:

Step 1. OS curves for second line lenalidomide-treated patients (n=1,890) were digitized and virtual patient-level data were constructed using the algorithm of Guyot.[78]

Step 2. To capture the shape of the long-term OS in second line lenalidomide-treated patients observed in MyelomaToul, piecewise exponential parametric models were fitted to the virtual patient-level data. Three piecewise exponential models with cut-off dates defined at different time points were explored, i.e., cut off dates at 48 months, at 60 months, and at 72 months, and their fit to the MyelomaToul data in terms of AIC and visual assessment was compared. As all three models fitted the MyelomaToul data well (AIC was 7477.327, 7474.682, and 7473.325, respectively, see Figure 16), the one with the best statistical fit (i.e. 7473.325, lowest AIC value) was selected for use in the base case.

Figure 16 OS of second-line Rd treated patients in MyelomaToul Registry together with fitted piecewise exponential models.

Abbreviations: OS, overall survival; Rd, lenalidomide/dexamethasone; 2L, second line.

Step 3. In order to estimate the difference in mortality rate between the second-line lenalidomide-treated patients from the MyelomaToul registry and the IPW-adjusted 2L prior bortezomib patients from the ASPIRE trial, Cox models were fitted to the second line MyelomaToul data and 2L prior bortezomib Rd data from ASPIRE (see visual comparison of OS curves in Figure 17). Based on visual assessment, it was found that the OS curves overlapped during the first 10 months after which they started to diverge. As a consequence, two Cox models were explored, a Cox model that estimated time-dependent HRs, and a Cox model that estimated a constant HR. The Cox model with time-dependent HRs was selected for the base case analysis, which yielded a HR of 1.02 (95% CI 0.53-1.94) for the first 10 months and a HR of 2.04 (95% CI 1.52 – 2.73) for the period beyond 10 months. These HRs were used to match the mortality rate of second-line lenalidomide-treated patients in MyelomaToul to the weighted 2L prior bortezomib Rd-treated patients in ASPIRE (see **Error! Reference source not found.**).

Figure 17 OS of lenalidomide-treated patients in matched MyelomaToul Registry and ASPIRE

Abbreviations: OS, overall survival; 2L, second line; 2L prior bortezomib, second line prior bortezomib.

This matched MyelomaToul registry data was used for survival modelling in the economic model. That is, after 72 months, the Weibull distribution fitted to ASPIRE 2L prior bortezomib Rd arm was stopped, and the matched MyelomaToul mortality rates were used (i.e., the mortality rates in MyelomaToul adjusted for the HRs (1.02 during the first 10 months, 2.04 during the period afterwards) accounting for the differences between the data sources (**Error! Reference source not found.**).

Figure 18 Predicted OS for the Rd arm in the economic model

OS, overall survival; Rd, lenalidomide/dexamethasone; 2L, second line; 2L prior bortezomib, second line prior bortezomib.

Step 4. To estimate the OS profile of patients beyond 72 months for those who received CRd, the IPW-adjusted HR in 2L prior bortezomib patients for OS derived from ASPIRE based on the latest data (cut-off date 5 December 2017) was applied to the Rd curve ( ). Due to the availability of long-term follow-up OS data from ASPIRE, uncertainty associated with the treatment effect beyond the study period was considered to be limited.

Table 29 presents OS rates for Rd treated patients at 10 and 20 years based on the different approaches for the 2L prior bortezomib subgroup. Comparing the different OS model predictions to available data, using the matched MyelomaToul registry data for long-term survival extrapolations in the economic analysis is deemed to be justified.

Table 29 Comparison of Predicted OS for Rd-treated patients at 10 and 20 Years Across Different Models in 2L prior bortezomib subgroup

	At 10 years	At 20 years
MyelomaToul, matched data (based on Kaplan-Meier estimates)	8%	1% (18 years)
ASPIRE, Weibull	5%	0%
ASPIRE, log-logistic	12%	3%
ASPIRE, Weibull + matched MyelomaToul (Piecewise exponential, cut-off at 48 months)	7%	0%
ASPIRE, Weibull + matched MyelomaToul (Piecewise exponential, cut-off at 60 months)	8%	1%
ASPIRE, Weibull + matched MyelomaToul (Piecewise exponential, cut-off at 72 months) [a]	9%	1%

[a] Base case model
2L prior bortezomib, second line prior bortezomib

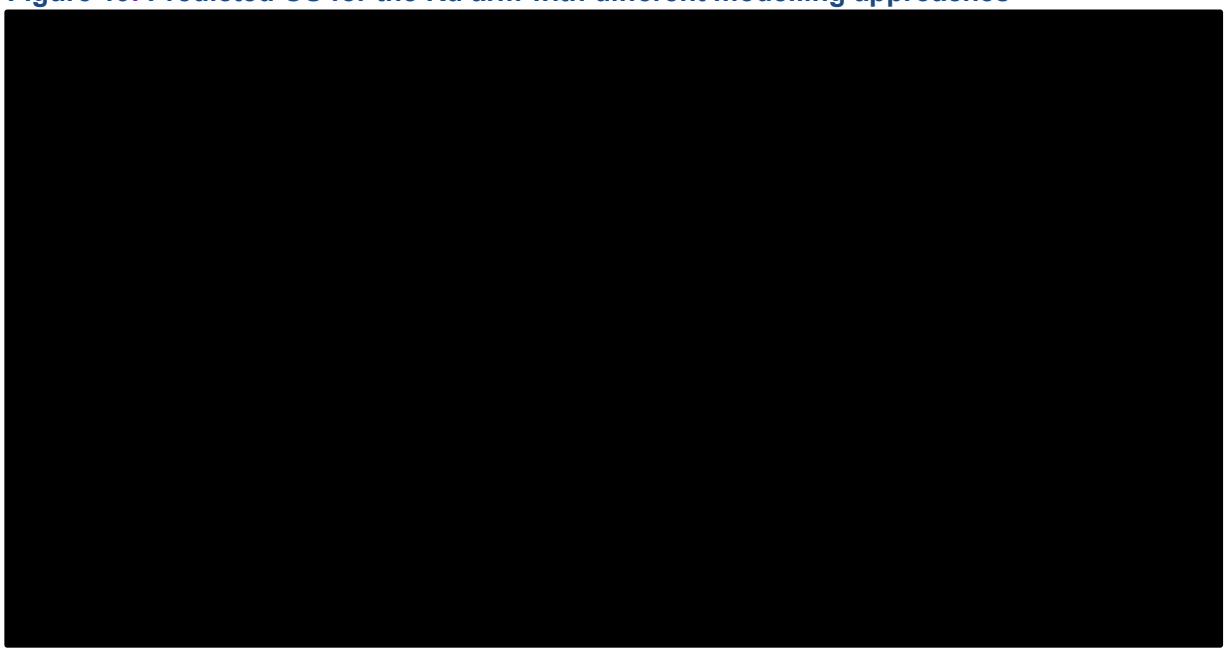
Applying a Weibull model during the trial follow-up period and using matched registry data beyond estimates survival proportions at 10, 20 and 30 years to be 9%, 1%, and 0%, respectively. These estimates are more conservative than that estimated by the manufacturer in TA586 and aligned with clinical expert opinion provided during TA510.

For patients starting on CRd, a Weibull model followed by external data predicts survival proportions at 10, 20 and 30 years to be 21%, 6% and 2% respectively. These estimates are based on more mature survival data than those available in the DVd appraisal (TA510) and estimate 10-year survival for patients starting on CRd of 21% which is more aligned with ERG preferred estimates for DVd survival in this appraisal (27%). As DVd and CRd are both triplet therapies for R/RMM, it may be reasonable to expect similar OS. [redacted]

Summary of OS Extrapolations

The predicted OS for Rd using both ASPIRE data only (Weibul, Log-logistic) are presented in Figure 19 below. Utilising external data from MyelomaToul, as described above, results in clinically valid projections and are consistent with previous clinical expert opinion recently provided to NICE for technology appriasals in this disease area. As as results, this approach is used in the base case analysis.

Figure 19. Predicted OS for the Rd arm with different modelling approaches

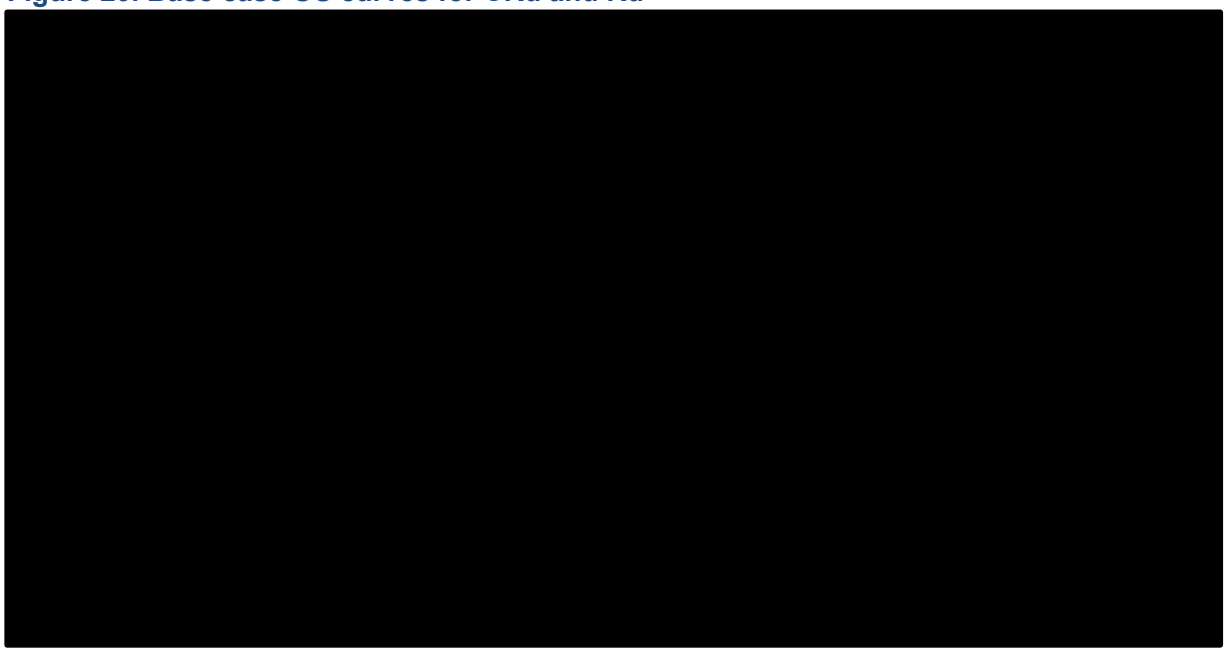


Abbreviations: KM, Kaplan-Meier, OS, overall survival; Rd, lenalidomide/dexamethasone.

The selected base case curves for CRd and Rd (jointly fitted Weibull curves, followed by external data) are presented in

Figure 20.

Figure 20. Base case OS curves for CRd and Rd



Alternative extrapolation assumptions are presented in scenario analyses including:

- Use of jointly fitted Weibull and lognormal curves without external data
- Exploratory analysis – alternative cut-off point for starting the use of external data
- Alternative cut-off points for piecewise exponential model (60 months and 48 months)
- Use of a constant HR for ASPIRE vs. MyelomaToul.

Results of these analysis are reported in Section B.3.8.

Exploratory analysis – multistate modelling

Additional analyses using a multistate modelling framework were also explored to assess the feasibility of the parametric models to inform long-term OS projections. This analysis, detailed in Appendix N, used a multistate modelling approach applied to data from all Rd patients in ASPIRE* to assess differences in long-term OS extrapolations versus the statistically best fitting Weibull model. The multistate model was developed in line with the methods guide described in the NICE DSU Technical Support Document 19.[74] .

There were two key conclusions drawn based on the multistate modelling approach. Firstly, later progression is associated with longer post-progression survival, which translates to non-increasing death risk in the overall population longer term. Secondly, OS predicted by the multistate model suggested longer estimates than those predicted by the Weibull model. A more detailed discussion is presented in the Appendix.

* Data from the Rd arm of the full ASPIRE trial population was used because to be able to estimate reliable parameters for the multistate model, a larger dataset is preferred (please see a discussion of the challenges associated with multistate modelling in the NICE DSU Technical Support Document 19).

However, in conclusion, both the comparison to external data and the exploratory multistate modelling in the ITT population support the conclusion that the best-fitting Weibull model yields overly pessimistic long-term OS extrapolations. In contrast, the log-logistic model fitted to ASPIRE data suggests overly optimistic estimates with 12% of patients starting Rd alive at 10 years and 5% alive at 20 years.

On balance, we therefore believe the approach taken in the base case analysis is justified, supported by the available data, and provides projections and aligned with clinical expectation.

DVd

The indirect comparison of CRd versus DVd gave an OS HR of 0.927 (95% CI 0.695, 1.235) based on the ITT population, as detailed in Section B.2.9 There is considerable uncertainty in the HR which is likely caused mostly by the immaturity of the OS data for DVd, and the MAIC suggests that OS for CRd and DVd are similar, although there is a trend in favour of CRd.

Given the high uncertainty in the estimated HR, and based on clinical opinion, the base case analysis assumes the OS of CRd and DVd are equal (HR=1), assuming no OS difference between the treatments on the cost-effectiveness of CRd compared with DVd. The HR obtained from the MAIC ITT analysis (HR = 0.927) is explored in scenario analysis.

B.3.3.3 Progression-free survival

In the 2L prior bortezomib subgroup survival data, the Kaplan-Meier curves for IPW-adjusted PFS demonstrated consistent treatment effect only up until the point where the number at risk became very small (N≤12 [≤15% of patients at risk] in both treatment arms), such that one event could cause a large change in the KM. After this point the KMs for PFS crossed. These KMs are presented in Appendix M. Following consultation with clinical experts in the UK, it was deemed clinically improbable that PFS between treatments would intersect while the treatment effect for OS remained consistent throughout follow-up. The reason this occurred is therefore ikely to have been the low number of patients at risk skewing the results, and it is likely that this would not have happened had there been more patients included within the subgroup. This is well demonstrated in the analysis of the ITT data, where the KMs for OS and PFS demonstrated consistency of treatment effect throughout the entirety of follow-up and was further supported by the log cumulative hazards versus log time plots (Appendix M). As these analyses were based on more patients, the consistency of treatment effect observed in the ITT data was considered more informative for the approach to fitting survival curves in the model.

Therefore, as per the approach taken for OS, PFS curves were jointly fitted in the base case analysis. Separately fitted curves were explored in scenario analysis and are detailed in Appendix M. The choice of PFS curve was also based on statistical fit and visual assessment, as no long-term data for PFS was identified. The fitted curves and their AIC and BIC for CRd and Rd are shown in Appendix M.

The models were indistinguishable in terms of their visual and statistical fit to the observed data, therefore the generalised gamma model was chosen as it provided a clinically plausible estimate of PFS. The model predicted PFS proportions for patients starting on Rd at 10, 20, and 30 years to be 2%, 0% and 0%, respectively. For CRd these proportions were 11%, 2%, and 1%.

The selected base case curves for CRd and Rd (jointly fitted generalised gamma curves) are presented in Figure 21. Alternative curves (Weibull [more conservative] and log-normal [more optimistic]) are presented in scenario analyses.

Figure 21. Base case PFS curves for CRd and Rd

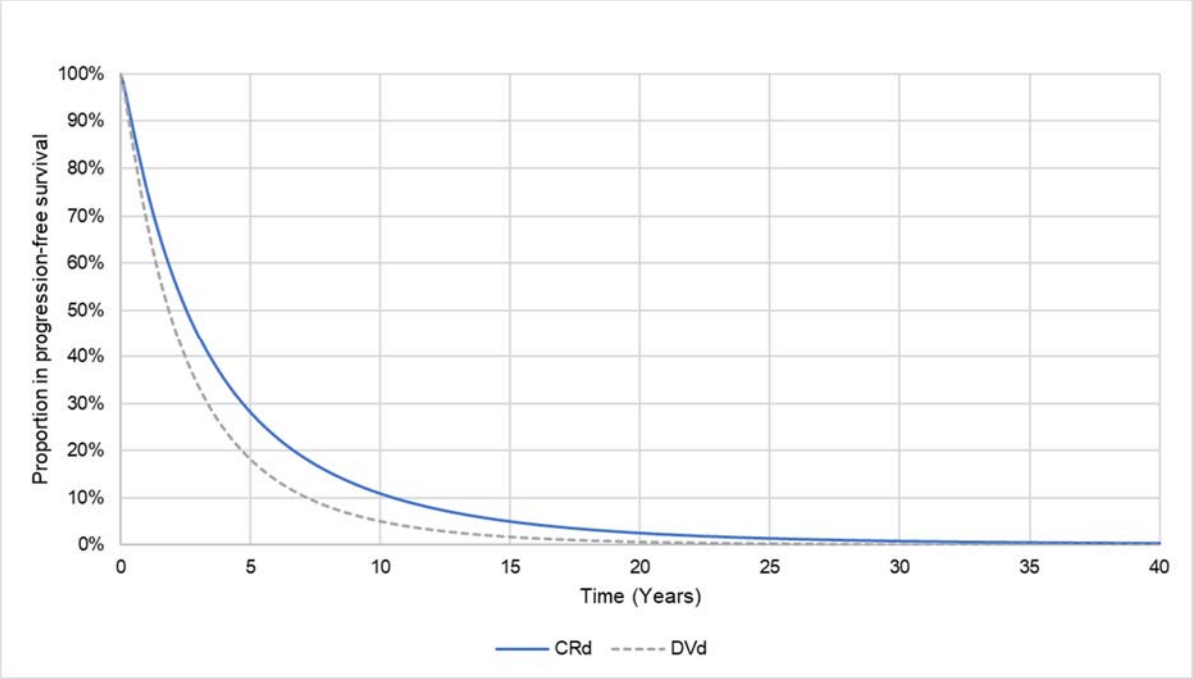
CRd, carfilzomib/lenalidomide/dexamethasone; KM, Kaplan-Meier; Rd, lenalidomide/dexamethasone.

DVd

The indirect comparison of CRd versus DVd gave a PFS HR of 0.745 (95% CI 0.542, 1.025) based on the 2L population, as detailed in Section B.2.9.

The base case curves for CRd and DVd are presented in Figure 22.

Figure 22. Base case PFS curves for CRd and DVd



CRd, carfilzomib/lenalidomide/dexamethasone; DVd, daratumumab/bortezomib/dexamethasone; KM, Kaplan-Meier.

B.3.3.4 Time to treatment discontinuation

CRd and Rd

Time-to-treatment discontinuation curves based on ASPIRE trial data were fitted in order to model time on treatment. Each component was modelled independently to reflect that, despite patients being assigned to a combination regimen, they may discontinue different components of the combination at different times. Curves were selected based on their statistical fit and plausibility of long-term extrapolation.

The curve fits for each component of CRd and Rd, and their associated AIC and BIC are presented in Appendix M. For the carfilzomib component of CRd, data were only available up to 18 cycles (~1.4 years) as treatment with carfilzomib was capped at 18 cycles in ASPIRE. All of the curve fits to the carfilzomib component data are indistinguishable during the observed period in terms of their statistical and visual fit to the data. As treatment with carfilzomib was discontinued after 18 cycles in the ASPIRE trial and assessment of the clinical plausibility of long-term extrapolations was not required, the best fitting curve (Gompertz) was selected based on the AIC and BIC for the carfilzomib component of CRd.

For the lenalidomide and dexamethasone components of CRd and Rd, the curves are all very similar both in terms of their visual and statistical fit to the observed data, and little difference in their extrapolations. Given this, we selected the best fitting curve based on the AIC and BIC (with preference for the BIC if these were different).

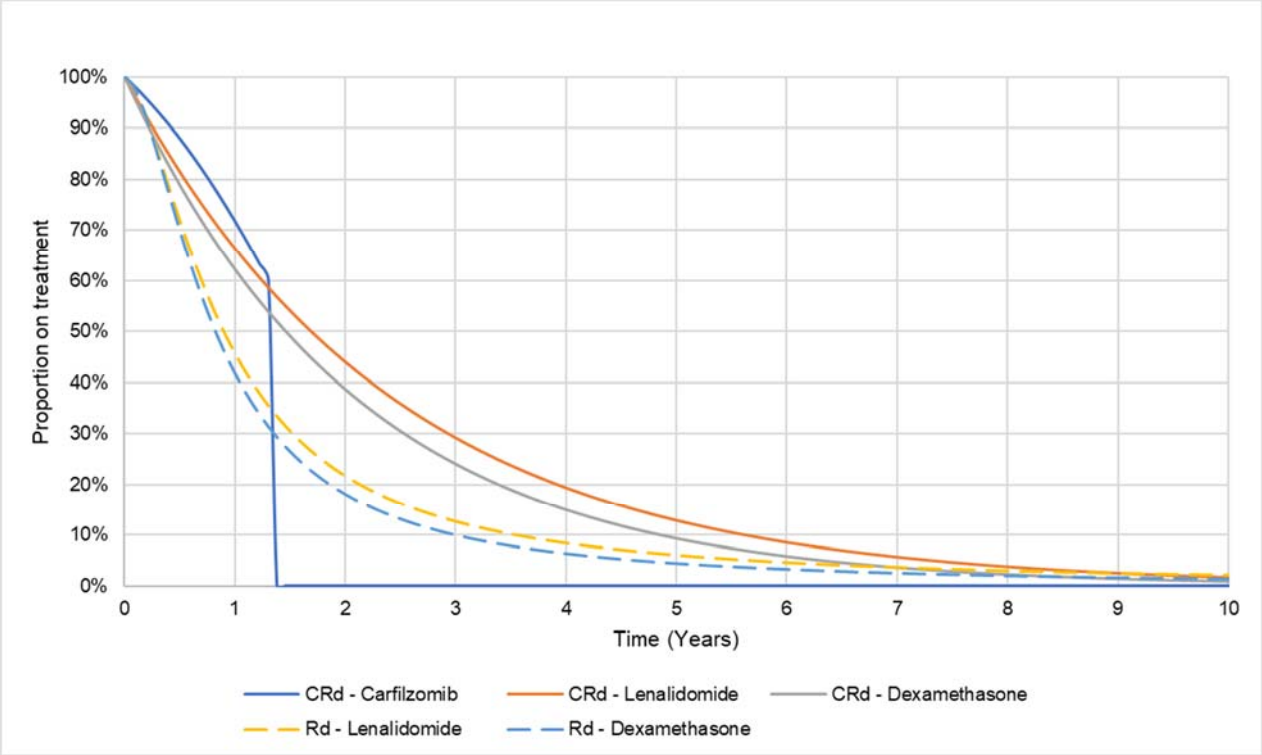
The curves selected for each component of CRd and Rd are summarised in Table 30 and presented in Figure 23.

Table 30: TTD curves selected for components of CRd and Rd

Component	Curve
CRd – carfilzomib	Gompertz
CRd – lenalidomide	Exponential
CRd – dexamethasone	Exponential
Rd – lenalidomide	Log-logistic
Rd – dexamethasone	Log-logistic

CRd: carfilzomib/lenalidomide/dexamethasone; Rd, lenalidomide/dexamethasone.

Figure 23. Base case TTD curves for components of CRd and Rd



CRd, carfilzomib/lenalidomide/dexamethasone; Rd: lenalidomide/dexamethasone.

In the model, all components of Rd in both the CRd and Rd arms are assumed to be continued until progression or unacceptable toxicity, subject to individual benefit–risk assessment, whereas carfilzomib is stopped after 18 cycles as in the ASPIRE trial (as discussed in Section B.3.2.3).

Given that the addition of carfilzomib to Rd significantly improves PFS compared with Rd alone, the TTD for the lenalidomide and dexamethasone components of the CRd and Rd arms are different and thus are modelled separately in the base case.

The NICE DSU report on assessing technologies that are not cost-effective at a zero price [83] discusses situations in which the intervention is a new drug combined with the current standard of care. The report details how this type of intervention can be penalised as, even though it

improves quality and length of life, it cannot be cost-effective even at a price of zero at the current price of the current standard of care. This is relevant for CRd – the increased time spent in PFS due to the increased efficacy of adding carfilzomib to Rd results in patients incurring incremental costs associated with additional Rd given until progression. A scenario analysis is therefore included whereby the TTD for the lenalidomide and dexamethasone components of the CRd treatment arm are assumed to be equal to those of the Rd treatment arm (i.e. the additional costs of Rd are excluded). This analysis is intended to explore the issue raised in the DSU report by presenting a scenario in which only the direct cost of the new intervention is considered, and which assumes that Rd is an indirect cost judged cost-effective by NICE in that setting and therefore excluded.

DVd

The time on treatment for DVd is modelled by applying a derived HR for TTD versus PFS to the modelled PFS curve for DVd. This approach was taken in the absence of sufficient publicly available data for TTD of DVd. TTD data for the latest available follow-up time as presented at ASH were not available. In the NICE DVd appraisal, K-M curves of TTD for the 2L setting were published but, since the number of patients at risk was not available, the TTD could not be estimated using these data. Therfore, to derive the HR for TTD versus PFS for DVd the following steps were taken:

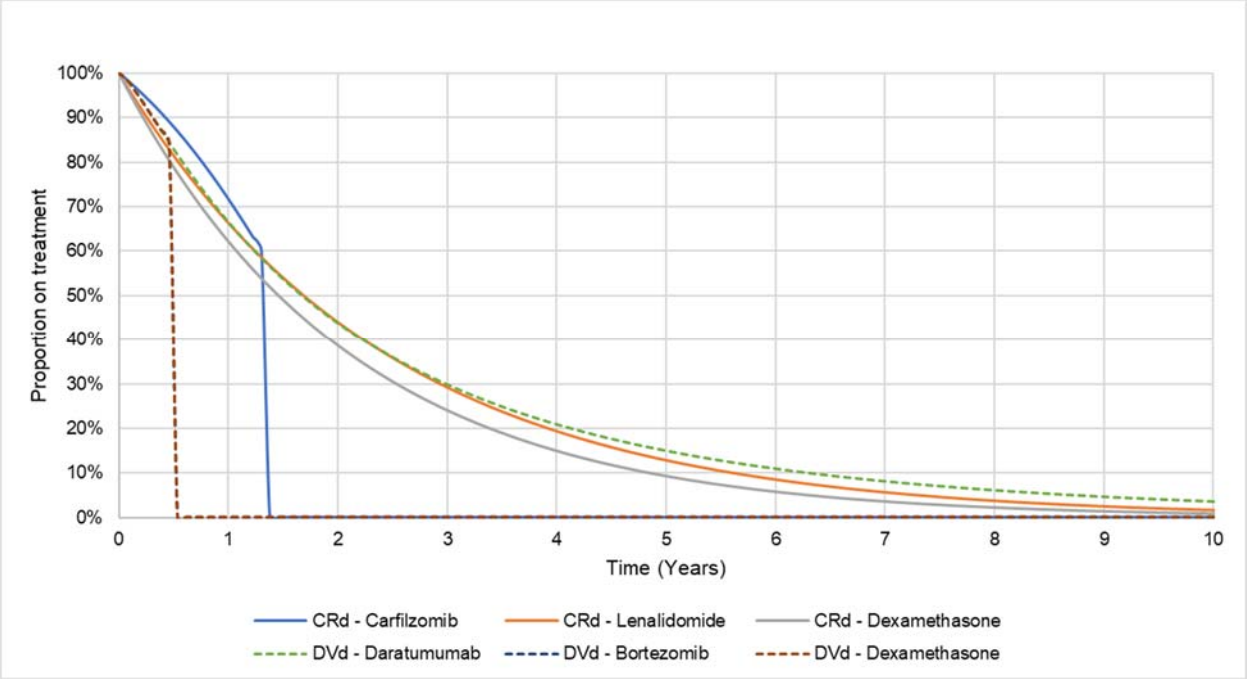
The 2L PFS curve for DVd from the CASTOR study as presented in a poster at the ASH conference (and consistent with the PFS data used in the MAIC analysis presented in Section B.2.9) was digitised and then a Gompertz curve was fitted to the reconstructed patient-level data to approximate the DVd PFS curve.[84] The median TTD in CASTOR (for the 2L population and follow-up time as presented at ASH) was estimated assuming that the difference between PFS and TTD in this data cut was equivalent to the difference between PFS and TTD reported in the DVd NICE appraisal.[81] A HR was then derived using the solver function in Excel which ensured that

$$(median\ PFS\ in\ CASTOR - median\ TTD\ in\ CASTOR) = (median\ modelled\ PFS - median\ modelled\ TTD)$$

The resulting estimated HR was 1.118, which was applied to the DVd PFS curve to estimate the TTD for all components of DVd assuming that this relationship holds in the 2L prior bortezomib subgroup.

The modelled TTD curves for all components of CRd and DVd are presented in Figure 24.

Figure 24. Base case TTD curves for components of CRd and DVd



CRd, carfilzomib/lenalidomide/dexamethasone; DVd: daratumumab/bortezomib/dexamethasone

B.3.3.5 Summary of base case assumptions

A summary of the key assumptions around OS, PFS and TTD are described in Table 31.

Table 31: List of clinical parameter assumptions

Assumptions	Assumption description	Justification
Use of post-hoc subgroup data from ASPIRE	Post-hoc subgroup data were used.	Post-hoc subgroup data were used to ensure alignment with the proposed positioning of CRd in the treatment pathway.
Adjustment of baseline characteristics in the post-hoc subgroup of ASPIRE	The IPW approach was used to adjust for covariates of interest. Potential covariates were identified through consultation with clinicians and then selected using a stepwise approach.	These methods were used and accepted in the previous appraisal of carfilzomib (TA457).[60] Imbalances were adjusted for given that the subgroup data were post-hoc. Use of the IPW method adjusts the underlying data, allowing parametric survival models to be applied using the methods proposed in DSU TSD 14 directly.[61, 85]
OS – CRd and Rd	OS for CRd and Rd was estimated using a Weibull distribution fit to ASPIRE and external data.	The statistical and visual fit to the observed data were similar for all curves except lognormal. However, long-term extrapolations of OS using exclusively the ASPIRE trial data yielded overly pessimistic estimates comparing with survival data

Assumptions	Assumption description	Justification
		available from external sources. The use of external data to inform OS extrapolation yielded more realistic estimates. The use of external data to inform OS extrapolation was further supported by the multistate modelling approach.
PFS – CRd and Rd	PFS for CRd and Rd was estimated using a generalised gamma distribution.	The statistical and visual fit to the observed data. In the absence of long-term PFS data for comparison, we selected the generalised gamma as this gave a middle estimate of PFS.
PFS – DVd	The PFS of DVd is estimated by applying the MAIC HR estimated from the 2L population to the CRd PFS curve	The MAIC HR was used as this is based on covariates which clinical experts deemed to be of prognostic importance
OS – DVd	For the purpose of the model, the OS of DVd is assumed to be equal to that of CRd	Based on clinical expert opinion, the OS for CRd and DVd is expected to be similar.
Proportional hazards	Proportional hazards was assumed for PFS and OS through the use of jointly fitted curve distributions for CRd and Rd, and the application of a HR for DVd	In the 2L prior bortezomib subgroup the OS curves retained good separation for the duration of follow-up. The PFS curves crossed only when the number of patients at risk were very low (N ≤ 12 in both arms) and it was deemed clinically improbable that PFS would intersect but OS would not. In the ITT population, the curves for PFS and OS remained separated for the duration of follow up. The proportional hazards assumption held in the ITT population based on log-log plots of cumulative hazards. Joint curve fitting can reduce uncertainty due to estimation of fewer parameters using a larger data set, as discussed in the literature. [42] [42] Given the lack of head to head data for CRd or Rd and DVd, the efficacy of DVd was estimated using a HR.
TTD – CRd and Rd	TTD for CRd and Rd was estimated with the best fitting curve for each treatment component	All curves were indistinguishable in terms of statistical and visual fit in the observed period for the Rd components in both arms. As carfilzomib is capped at 18 cycles per the ASPIRE trial evidence, long-term extrapolation is not required.
TTD – DVd	TTD for DVd was estimated through a HR versus PFS	In the absence of publicly available K-M data with the number of patients at risk for TTD of DVd in the subgroup of interest, this was deemed the most accurate approach

Assumptions	Assumption description	Justification
		to derive the TTD of DVd using the available information.

2L: second line; CRd, carfilzomib/lenalidomide/dexamethasone; CRUK: Cancer Research UK; DSU: decision support unit; DVd: daratumumab/bortezomib/dexamethasone; ERG: Evidence Review Group; HR: hazard ratio; IPW: inverse probability weighted; ITT: intent-to-treat; K-M, Kaplan-Meier; MAIC: matching adjusted indirect comparison; NICE: National Institute for Health and Care Excellence; OS, overall survival; PFS, progression-free survival; Rd, lenalidomide/dexamethasone; TSD: technical support document; TTD, time to treatment discontinuation

B.3.4 *Measurement and valuation of health effects*

Summary of measurement and validation of health effects

- Treatment-dependent pre-progression utilities and post-progression utilities during and following subsequent treatments were estimated using HRQoL data from ASPIRE mapped to EQ-5D for CRd and Rd
- Utilities for DVd were assumed equal to those for CRd
- Utility decrements due to AEs were included

As described in Section B.1.3.1., 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[86, 87]. Patients with relapse may have worsened health as a result of disease progression, comorbidities, and treatment-related toxicities[20, 88]. A patient's ability to achieve and sustain a meaningful response declines with each relapse due to acquired drug resistance and disease biology[11-13].

B.3.4.1 Health-related quality-of-life data from clinical trials

The ASPIRE study did not contain a generic, preference-based utility measure; however, it did contain two disease-specific HRQoL measures: the EORTC QLQ-C30, a questionnaire developed to assess HRQoL in cancer patients, and the EORTC QLQ-MY20, a questionnaire developed to assess HRQoL in MM patients. These disease-specific measures cannot be used directly in the economic evaluation of carfilzomib as they do not provide a single preference-based index of HRQoL.

There are two ways of dealing with the lack of general utility data; one is to map disease-specific HRQoL data to generic, preference-based utility data, and another is the use of literature-based utilities. For the CRd cost-effectiveness model, mapped utility estimates (from EORTC QLQ-C30 to EQ-5D) were used.

In the ASPIRE study, patient-reported outcomes (EORTC QLQ-C30 and QLQ-MY20) were given to patients prior to the administration of study treatments on Day 1 of Cycles 1, 3, 6, 12, and 18, and at the end of treatment visit. Assessment of the effect of CRd versus Rd on the change over time in the EORTC QLQ-C30 GHS/QoL subscale was one of the prespecified secondary objectives of the ASPIRE trial.

At baseline, compliance with completing the QLQ-C30 was high, with 94.1% of randomised patients completing the QLQ-C30. Questionnaire completion at baseline was very similar between the study arms, with 94.9% of patients in the CRd arm versus 93.2% in the Rd arm completing the questionnaires. As a proportion of the randomised study population, just under half of patients completed the QLQ-C30 (47.3%) at Cycle 18. A higher proportion of patients randomised to CRd completed the QLQ-C30 at each cycle compared with those randomised to Rd; this difference was largest at Cycle 18, with 57.3% completing the questionnaire in the CRd arm versus 37.4% in the Rd arm. Given that more patients progressed in the Rd group, the difference in QLQ-C30 completion rates was to be expected.

Table 32 presents the proportion of subjects with completed QLQ-C30 questionnaires out of the expected subjects, i.e. randomised patients who were still alive and had not discontinued study treatment at the visit. Compliance rates were generally high for both treatment arms.

Table 32: Proportion of subjects with EORTC QLQ-C30 questionnaire completed out of the number of expected subjects[a]

	CRd (N = 396)	Rd (N = 396)
Cycle 1 Day 1	95.4%	93.7%
Cycle 3 Day 1	93.5%	90.9%
Cycle 6 Day 1	90.1%	83.3%
Cycle 12 Day 1	83.9%	80.6%
Cycle 18 Day 1	86.6%	79.6%
End of treatment	69.0%	63.4%

[a] Participants expected at a visit included randomised patients who were still alive and had not discontinued study treatment at the visit.

CRd: carfilzomib/lenalidomide/dexamethasone; EORTC QLC-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; Rd: lenalidomide/dexamethasone

B.3.4.2 Mapping

In preparation of the original TA457 appraisal, an additional SLR of published literature was conducted in 2014 to identify algorithms for mapping EORTC QLQ-C30 scores to EQ-5D scores, the measure preferred by NICE as outlined in the reference case[78]. Algorithms identified in this review were considered and the most suitable algorithm was then applied to data from the ASPIRE study. Further detail on the literature review and resulting mapping exercise is provided in Appendix O. Although this review was conducted in 2014, a more recent focussed literature search using the University of Oxford Health Economic Research Centre database (April 2016) identified only one additional potentially relevant study, which was not considered further as it used data from a study in patients with newly-diagnosed MM (MYELOMA-IX).[89]

The cost-effectiveness model incorporates treatment-specific utilities. These utilities were mapped from patient-reported EORTC QLQ-C30 outcomes from the ASPIRE trial (as described in Section B.3.4.1) to EQ-5D utilities using the Proskorovsky *et al.* 2014 ordinary least squares mapping algorithm model[90]. This mapping algorithm was considered the most appropriate for this appraisal given that it is based on data from UK MM patients (i.e. a population similar to the population under consideration in this appraisal), and was considered to be an appropriate

mapping algorithm in the NICE TA for panobinostat and carfilzomib in combination with dexamethasone.[74]

Descriptives of mapped utility estimates

Descriptive statistics in terms of the mean and number of observations on the mapped EQ-5D utility index scores for the ASPIRE trial are presented in Table 33. The baseline utility estimate derived for the CRd and Rd arms were 0.694 and 0.696. The corresponding figures were 0.712 (CRd) and 0.718 (Rd) for patients in the ASPIRE trial who have received one prior therapy (2L) with bortezomib.

Table 33: Utility weights derived from mapping exercise

Cycle	CRd arm (full trial population)		Rd arm (full trial population)	
Time	**Mean**	**N**	**Mean**	**N**
Cycle 1 Day 1	0.694	375	0.696	367
Cycle 3 Day 1	0.711	356	0.700	334
Cycle 6 Day 1	0.735	326	0.714	284
Cycle 12 Day 1	0.735	255	0.711	212
Cycle 18 Day 1	0.750	226	0.730	147
End of treatment	0.675	187	0.651	192
Cycle	**CRd arm (subgroup[a])**		**Rd arm (subgroup[a])**	
Time	**Mean**	**N**	**Mean**	**N**
Cycle 1 Day 1	0.712	85	0.718	61
Cycle 3 Day 1	0.768	81	0.735	60
Cycle 6 Day 1	0.793	73	0.718	51
Cycle 12 Day 1	0.799	54	0.701	34
Cycle 18 Day 1	0.830	44	0.735	23
End of treatment	0.719	41	0.676	41

Note: Mapping was performed using the algorithm published in Proskorovsky *et al*., 2014[90], EORTC QLQ-C30 regression model

[a] Patients who have received one prior therapy (2L) with bortezomib

CRd: carfilzomib/lenalidomide/dexamethasone; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; Rd: lenalidomide/dexamethasone

Analyses of mapped utility estimates

Since differences in baseline patient characteristics and baseline utilities were observed between the treatment arms, mapped EQ-5D utility index scores were analysed using a linear regression model for repeated measurements. Specifically, repeated-measures mixed-effects models with random intercepts were used to assess treatment differences in utility measures over time. The outcome was chosen to be the change from baseline utility to control for the baseline imbalances. Fixed effects included treatment, baseline characteristics, and time-dependent

progression. Random effects included subject-level intercepts to account for repeated measures.*

In the post-hoc analysis of subgroup-specific clinical efficacy data, clinical expert opinion could guide the inclusion of relevant covariates into the Cox proportional hazards models (Section B.2.7.2); however, for the analyses of utility data this was not feasible. Instead, mixed effects utility regression models were built in two steps. In the first step, each potential predictor was assessed in a univariate model to determine whether it was associated with the outcome (p value < 0.2). In the second step, significant univariate predictors were combined into a multivariate model that underwent stepwise backward selection to remove variables that became non-significant (p value < 0.1). All available baseline characteristics were evaluated in the analysis, including baseline utility, time of utility measurement, time-treatment interaction, baseline demographics, organ function indicators and comorbid conditions, disease characteristics, and treatment history. The regression coefficients of the final utility models are presented in Table 34

Table 34: Change in mapped utility over time – regression model results

Covariate	Value	SE	p-value
(Intercept)	0.467	0.042	0.000
CRd (vs. Rd)	0.016	0.009	0.075
Progression	-0.047	0.008	0.000
Baseline utility	-0.403	0.025	0.000
Age	-0.001	0.001	0.010
ECOG PS 1	-0.032	0.010	0.001
ECOG PS 2	-0.044	0.019	0.020
Absolute neutrophil count $\geqslant 1.5 \times 10^9$/L	-0.033	0.016	0.036
Measurable disease category: SPEP only	-0.025	0.013	0.050
Measurable disease category: UPEP only	0.009	0.020	0.637
Number of prior therapies: $\geqslant 2$	-0.031	0.009	0.001

CRd, carfilzomib/lenalidomide/dexamethasone; ECOG PS, Eastern Cooperative Oncology Group performance status; Rd, lenalidomide/dexamethasone; SE, standard error; SPEP, serum protein electrophoresis; UPEP, urine protein electrophoresis

Mean predicted change for CRd patients (full trial population): 0.0145 (SE: 0.0259)
Mean predicted change for CRd patients (one prior therapy with bortezomib): 0.047 (SE: 0.0068)

Patients who received carfilzomib treatment had a statistically significantly larger average increase in utility than patients who received the control treatment, after adjusting for baseline imbalances (p-value for the treatment covariate was < 0.1). Besides the treatment, utility at baseline, ECOG PS at baseline, progression over time, age, neutrophil count, measurable disease category, and number of prior therapies were significant predictors of the average change in utility. No evidence of statistically significant continuous change over time was observed (i.e. the time of the utility measurement and the treatment-time interaction terms were

* Mixed effects repeated measurement models provide an appropriate framework for accounting for the correlations between and within patients over time.

not significant and were removed from the final models); utilities appeared to remain approximately stable over time following an initial increase after treatment initiation.

The mean predicted change from baseline for all patients / patients who have received one prior line of therapy (2L) with bortezomib was 0.0145 (SE: 0.0259) / 0.047 (SE: 0.0068).

B.3.4.3 Health-related quality of life studies

As described in Section B.3.1, an SLR was performed to identify publications reporting: cost-effectiveness studies for therapies used for the management of R/RMM, resource use and treatment costs for management of R/RMM, and studies reporting HRQoL or utilities relevant for patients with R/RMM. Searches were devised to identify relevant studies and were used to search Medline, EMBASE, MEDLINE In-Process, and the Cochrane library. Full details of the search strategies, inclusion/exclusion criteria, screening procedure, and quality assessment, and data extraction are described in Appendix G.

Most of publications identified in the review reported treatment-specific QoL/utility values based on clinical trial data, including (for carfilzomib) the primary ASPIRE study publication[44] and a study mapping EORTC QLQ-C30 scores from ASPIRE to EORTC-8D scores[91]. The findings of the publications reporting studies of HRQoL or utilities relevant for patients with R/RMM are provided in Appendix G.

It is important to note that, due to the restriction in the search strategies for indication (i.e. R/RMM), some QoL studies that were used as model inputs by some NICE technical appraisals (e.g. Acaster *et al.* 2013[92] and Agthoven *et al.* 2004[93]) were not captured by the search.

B.3.4.4 Adverse reactions

The impact of AEs on HRQoL has been considered as part of this evaluation. A utility decrement associated with an AE and the average duration of this AE were identified. The utility values for the AEs that were included in the model (treatment related AEs that occurred in at least 5% of patients treated with CRd or Rd in ASPIRE or DVd in CASTOR) are shown in Table 35. The utility decrement and duration of an AE were used to generate duration-adjusted utility decrements by dividing the expected disutility for each AE by its duration in days multiplied by the number of days in a year (365.25).

Table 35: Adverse events – utility values used in the economic models

State	Disutility	Duration (days)	Duration-adjusted utility decrement (decrement per event)
Neutropenia[a]	0.145	13.20	0.005
Anaemia[a]	0.310	10.70	0.009
Thrombocytopenia[a]	0.310	14.10	0.012
Cataract[b]	0.140	182.63	0.070
Hyperglycaemia[c]	0.060	4.02	0.001
Lymphopenia[a]	0.065	15.50	0.003

State	Disutility	Duration (days)	Duration-adjusted utility decrement (decrement per event)
Hypertension[a]	0.000	0.00	0.000
Fatigue[a]	0.115	14.60	0.005
Hypokalaemia[d]	0.200	0.02	0.000
Hypophosphataemia[e]	0.000	0.00	0.000
Pneumonia[a]	0.190	12.00	0.006

[a]Consistent with DVd NICE submission[81] Table 41
[b]Consistent with assumption made in NICE TA297 manufacturer's submisison[94]
[c]Disutility from Wehler *et al*. (2018); Duration estimated as weighted average length of stay from NHS reference costs 2017/18; Non-elective inpatients long stay: Fluid or Electrolyte Disorders, with Interventions, KC05G to KC05N
[d]Consistent with assumption made in NICE TA510 manufacturer's submission[95]
[e]Assumed 0 as usually asymptomatic

CRd, carfilzomib/lenalidomide/dexamethasone; ERG, evidence review group; NICE, National Institute for Health and Care Excellence; Rd, lenalidomide/dexamethasone; TA, technology appraisal

The disutility per model cycle for each AE for each treatment was obtained by multiplying the disutility per event of the AE by its per-cycle probability of occurrence (Grade 3+ frequencies). The per-cycle probability of AEs is presented in Section B.3.5.3. The total disutilities per model cycle for each treatment were obtained by summing the disutilities per event for all of the AEs. The resulting disutilities per cycle due to AEs were 0.00038 for CRd, 0.00041 for Rd and 0.00041 for DVd.

As a simplifying assumption, AEs of subsequent treatments have not been considered as AEs are not a key driver of results.

B.3.4.5 Health-related quality-of-life data used in the cost-effectiveness analysis

Using the mixed model results of the mapped utilities (as described in Section B.3.4.2), it was assumed that patients receiving second-line treatment with prior bortezomib have a baseline (i.e. first two cycles) utility equal to the baseline utility in ASPIRE patients with one prior treatment with bortezomib. Then, to estimate the treatment-specific pre-progression utilities in later cycles the mean predicted difference between CRd and Rd derived using the mixed effect model was utilised. The utility during the post-progression subsequent treatment phase was estimated as the pre-progression utility in later cycles for Rd minus the disutility associated with progression following Rd. The utility during the best supportive care (BSC) phase was assumed to be equal to the post-progression utility during the subsequent treatment phase, mirroring the assumption accepted by NICE in the appraisal of Cd.[96]

The calculations and assumptions corresponding to each utility estimate applied in the models are provided in Table 36.

Table 36: Utility values applied in the model – 1 prior treatment with bortezomib

Health state	CRd	Rd	Calculations/assumptions
Pre-progression (Cycles 1–2)	0.714	0.714	Baseline utility in ASPIRE patients with one prior treatments with bortezomib
Pre-progression (later cycles)	0.761	0.745	• CRd: baseline utility + average increase in utility from baseline (+ 0.047) • Rd: baseline utility + average increase in utility from baseline (+ 0.047) minus the utility difference between Rd and CRd (0.016) Utilities for off-treatment were assumed to be the same to on-treatment utilities because the impact of adverse events associated with treatments were taken into account separately
Post-progression, subsequent treatment phase	0.698	0.698	Pre-progression utility in later cycles for Rd (0.745) minus the disutility associated with progression following Rd (0.047)
Post-progression, best supportive care phase	0.698	0.698	Assumed equal to the utility in post-progression for the subsequent treatment phase
CRd, carfilzomib/lenalidomide/dexamethasone; Rd, lenalidomide/dexamethasone			

In the base case, utilities are not age-adjusted; however, an age-adjustment has been included in a scenario analysis using the values from Kind *et al.,* 1999[97]; as the average age of patients increases (up to the 75+ years age band), a utility decrement of 0.005 (from the age of 63 to 75 years) is applied per year to reflect the natural decrease in utility associated with increasing age. This decrement was calculated based on the starting age of patients in the ASPIRE trial.

B.3.5 *Cost and healthcare resource use identification, measurement and valuation*

Summary of Cost and healthcare resource use identification, measurement and valuation

- Cost outcomes included the costs of treatment acquisition and administration for initial and subsequent therapies, costs of medical resource use, and costs of management of AEs.

In line with recent NICE TAs and the published literature, the following range of cost inputs were considered in the modelling undertaken:

- drug acquisition costs for carfilzomib and comparator treatments as well as post-progression treatments
- administration costs
- NHS resource use associated with routine medical management
- NHS resource use associated with the treatment of AEs
- monitoring costs.

All costs are further described below.

B.3.5.1 Intervention and comparators' costs and resource use

Acquisition costs for generic treatments were taken from drugs and pharmaceutical electronic market information tool (eMIT).[98] For branded treatments, the Monthly Index of Medical Specialities (MIMS) was used.[99]

The current patient access scheme (PAS) for carfilzomib of a [redacted] discount to the list price, was considered in the analysis results. A scenario analysis is included assuming a price of £0 for carfilzomib, to illustrate the problems faced by interventions that are a new drug combined with the current standard of care whereby despite increased length and quality of life it is challenging for these interventions to be cost-effective at the current price of current standard of care.

Lenalidomide has a simple PAS discount which was agreed during technology appraisals TA586 and TA587.[79, 100] Daratumumab has a Commercial Access Agreement (CAA) which was agreed during technology appraisal TA510. The details of these agreements are confidential and so we base our analyses on the list prices for lenalidomide and daratumumab.

The patent on bortezomib is due to expire in 2019 and therefore the cost of bortezomib is likely to reduce in the future as generic alternatives become available at a lower list price. The exact timing and impact on the price of bortezomib of generics becoming available is highly uncertain at the time of this submission, therefore we present our base case analysis using the list price for bortezomib. A scenario analysis is presented assuming that the availability of generic bortezomib will reduce the price by 50%.

Treatment administration costs were sourced from the NHS reference costs[101] and the Unit Costs of Health and Social Care.[102]

Relative dose intensity (RDI) was applied to the treatment acquisition costs to reflect the impact of dose reductions and interruptions on the costs of treatment acquisition. The RDI for each component of each treatment arm is provided in Table 37, for the subgroup most relevant to the primary positioning of CRd in England and Wales. Values are reported for lenalidomide, however to accurately model the acquisition cost of lenalidomide, ASPIRE post-hoc subgroup data on lenalidomide doses received in both treatment arms was used to calculate a weighted average cost for lenalidomide in CRd and in Rd (Table 38).

Table 37: Relative dose intensity

Treatment arm	Component	RDI[a]	Reference
CRd	Carfilzomib	90.72%	ASPIRE study; patients who have received one prior therapy (2L) with bortezomib
	Lenalidomide	80.27%	

Treatment arm	Component	RDI[a]	Reference
	Dexamethasone	79.93%	
Rd	Lenalidomide	79.46%	
	Dexamethasone	82.90%	
DVd	Daratumumab	93.8%	DVd NICE appraisal Manufacturer's submission Table 44 (2L population in CASTOR)[81]
	Bortezomib	81.7%	
	Dexamethasone	87.3%	

[a] RDI (%) calculated as: actual dose intensity/planned dose intensity × 100. Actual (planned) dose intensity is actual (planned) cumulative dose (mg/m^2) divided by actual (planned) treatment duration (weeks).

CRd, carfilzomib/lenalidomide/dexamethasone; Rd, lenalidomide/dexamethasone; RDI, relative dose intensity; DVd, Daratumumab/bortezomib/dexamethasone.

Table 38: Dosing data for lenalidomide

Dose received	% doses lenalidomide in CRd	% doses lenalidomide in Rd
0 mg (missed dose)	3%	3%
5 mg	5%	6%
10 mg	14%	13%
15 mg	16%	18%
20 mg	0%	0%
25 mg	62%	60%

[a] RDI (%) calculated as: actual dose intensity/planned dose intensity × 100. Actual (planned) dose intensity is actual (planned) cumulative dose (mg/m^2) divided by actual (planned) treatment duration (weeks).

CRd, carfilzomib/lenalidomide/dexamethasone; Rd, lenalidomide/dexamethasone; RDI, relative dose intensity; DVd, Daratumumab/bortezomib/dexamethasone.

The proportions of missed doses were applied to the treatment administration costs to reflect the impact of missed doses on the costs of treatment administration. The proportion of missed doses for each component requiring an intravenous or subcutaneous administration is provided in Table 39, for the subgroup most relevant to the primary positioning of CRd in England and Wales. No data on missed doses were identified for DVd. As such, no missed doses were assumed for DVd in the model base case. A scenario analysis is included assuming daratumumab has missed doses equivalent to carfilzomib. It is important to note that no administration costs were assumed for Rd in the base case, therefore missed dose inputs for Rd had no impact on total cost in the base case analysis.

Table 39: Missed doses

Treatment arm	Component	Missed doses[a]	Reference
CRd	Carfilzomib	3.44%	ASPIRE study; patients who have received one prior therapy (2L) with bortezomib
DVd	Daratumumab	0%	Assumption, DVd involves only one dose of daratumumab every 4 weeks from 24 weeks which had a high dose intensity in TA573 (93.8%). TTD was also close to PFS in the trial.
	Bortezomib	0%	

[a] Missed doses (%) calculated as: % missed doses = 100 x (number of missed doses / [total doses administered + number of missed doses]).

CRd, carfilzomib/lenalidomide/dexamethasone; PFS, progression-free survival, RDI, relative dose intensity; TTD, time to treatment discontinuation.

Dosing for carfilzomib is based on body surface area, which is assumed to be 1.79 m^2 based on a study by Sacco *et al*.[103], which estimated the average body surface area of adult cancer patients in the UK[103]. Dosing for Rd is based on its SmPC.[104] Dosing for Rd in combination with carfilzomib (CRd) is in line with the ASPIRE study and is equivalent to the Rd arm. Dosing for DVd is in line with the CASTOR study and is based on weight, which is assumed to be 77.9 kg based on the mean weight used in the appraisal of DVd.[81]

Carfilzomib drug wastage is expected to be minimal, given that 10 mg dose steps are possible. Moreover, in the real world, doses slightly exceeding the content of a full vial may be rounded down, considering that dose adjustments do not need to be made for weight changes of 20% or less (SmPC for carfilzomib, Appendix C). For these reasons, in the base case analyses presented, wastage is excluded and the cost per mg is used, as this may be more likely to reflect the use of carfilzomib in practice. This is considered conservative in the secondary comparison with DVd as the impact of wastage is larger in the DVd treatment arm. A scenario analysis including wastage is presented to demonstrate the impact of this assumption on the results.

Acquisition costs are summarised in Table 40. In addition to acquisition costs, the costs of administration were included where appropriate (Table 41). Carfilzomib is expected to be administered via IV infusion, incurring the cost of a simple parenteral chemotherapy at first attendance (outpatient; £174.40).[101] As lenalidomide and dexamethasone are administered orally, they were assumed to incur no administration costs. The first dose of daratumumab was assumed to incur the cost of complex chemotherapy, including prolonged infusional treatment, at first attendance (day case; £374.52), plus a blood test (£2.51) consistent with the DVd appraisal.[81, 101] Subsequent doses of daratumumab incurred the cost of subsequent elements of a chemotherapy cycle (outpatient; £233.23) in line with the cost assumed in the DVd appraisal.[101] Bortezomib was assumed to be administered by a specialist nurse (outpatient; £89.16), in line with the cost assumed in the previous submission of Cd.[32, 101, 105] When the administrations of daratumumab and bortezomib coincide, it is assumed that only the cost of subsequent elements of a chemotherapy cycle is incurred.

After adjusting cycle lengths for consistency, the per-cycle acquisition and administration costs of each regimen is summarised in Table 42.

Table 40: Unit costs of intervention and comparator treatment components

Treatment	Dose	Pack size	Reference	Unit cost	Dose per cycle (treatment cycle length)	Cost per treatment cycle[a] cost without wastage (with PAS)	Cost per treatment cycle with wastage (with PAS) [a,b]
Carfilzomib	10 mg	1	MIMS[99]	£176.00	**Cycle 1:** 20 mg/m2 on Days 1 and 2, 27 mg/m2 on Days 8, 9, 15, and 16 (28-day cycle) **Cycles 2–12:** 27 mg/m2 on Days 1, 2, 8, 9, 15, and 16 (28-day cycles) **Cycles 13-18:** 27 mg/m2 on Days 1, 2, 15, and 16 (28-day cycles)	**Cycle 1:** £4,229.90 [redacted] **Cycle 2-12:** £4,630.03 [redacted] **Cycles 13-18:** £3,086.69 [redacted]	**Cycle 1:** £4,470.68 [redacted] **Cycle 2-12:** £4,790.02 [redacted] **Cycles 13-18:** £3,193.34 [redacted]
	30 mg	1	MIMS[99]	£528.00			
	60 mg	1	MIMS[99]	£1,056.00			
Lenalidomide	5 mg	21	MIMS[99]	£3,570.00	25 mg on Days 1–21 (28-day cycles)	CRd[c]: £4,049.58 Rd[c]: £4058.14	CRd[c]: £4,049.58 Rd[c]: £4058.14
	10 mg	21	MIMS[99]	£3,780.00			
	15 mg	21	MIMS[99]	£3,969.00			
	20 mg	21	MIMS[99]	£4,168.50			
	25 mg	21	MIMS[99]	£4,368.00			
Dexamethasone	2 mg	50	eMIT[98]	£12.39	CRd and Rd: 40 mg orally once daily on days 1, 8, 15 and 22 (28-day cycles) DVd:	CRd: £15.85 Rd: £16.43 DVd: £23.08	CRd: £15.85 Rd: £16.43 DVd: £23.08
	2 mg	100	eMIT[98]	£33.71			

					20 mg orally once daily on days 1, 2, 4, 5, 8, 9, 11 and 12 of cycles 1 through 8 (21-day cycles). Then no longer taken.		
Daratumumab	100 mg	1	MIMS[99]	£360.00	**Cycle 1-3:** 16mg/kg on days 1, 8 and 15 (21-day cycles) **Cycle 4-8:** 16mg/kg on day 1 (21-day cycles) **Cycle 9+:** 16mg/kg on day 1 (28-day cycles)	(28-day cycles) **Cycle 1-2:** £16,835.37 **Cycle 3:** £8,417.69 **Cycle 4-6:** £5,611.79 **Cycle 7+:** £4,208.84	(28-day cycles) **Cycle 1-2:** £17,559.36 **Cycle 3:** £8,779.68 **Cycle 4-6:** £5,853.12 **Cycle 7+:** £4,389.84
	400 mg	1	MIMS[99]	£1,440.00			
Bortezomib	3.5 mg	1	MIMS[99]	£762.38	(21-day cycles) 1.3mg/m^2 on days 1, 4, 8 and 11. Up to 8 cycles.	(28-day cycles) **Cycle 1-6:** £2,208.62	(28-day cycles) **Cycle 1-6:** £3,321.94

[a] Calculated accounting for relative dose intensity.
[b] Based on optimum combination of different vial sizes.
[c] Accounting for the cost of actual dose received, weighted average of dose received, and cost calculated from ASPIRE post-hoc subgroup data
Key: eMIT, electronic market information tool; MIMS, Monthly Index of Medical Specialities

Table 41: Administration costs for intervention and comparator treatment components

Treatment	Setting	Cost code	Description	Unit cost[101]
Carfilzomib	Outpatient	SB12Z	Deliver simple parenteral chemotherapy at first attendance	£174.40
Lenalidomide	Outpatient	N/A	No cost	£0
Dexamethasone	Outpatient	N/A	No cost	£0
Daratumumab	Day case	SB14Z	Deliver Complex Chemotherapy, including Prolonged Infusional Treatment, at First Attendance	£374.52
		DAPS05[a]	Blood test (directly accessed pathology services: haematology)	£2.51
	Outpatient	SB15Z	Deliver subsequent elements of a chemotherapy cycle	£233.23
Bortezomib	Outpatient	N10AF	Specialist Nursing, Cancer Related, Adult, Face to face	£89.16

N/A, not applicable
[a] Blood test was assumed to be done before the first administration for all patients receiving daratumumab to determine blood type

Table 42: Unit costs associated with the technology in the economic model (base case without wastage)

Items	CRd (cost with PAS)	Rd	DVd	Reference in submission
Technology cost per 28-day model cycle	Cycle 1: £8,295 [redacted] Cycles 2–12: £8,695 [redacted] Cycles 13+: £7,152 [redacted]	£4,075	Cycle 1: £19,067 Cycle 2: £19,067 Cycle 3: £10,649 Cycle 4: £7,843 Cycle 5: £7,843 Cycle 6: £7,843 Cycle 7+: £4,209	Table 40
Administration cost per 28-day model cycle	Cycle 1: £1,010 Cycles 2–12: £1,010 Cycles 13+: £674	£0	Cycle 1: £1,314 Cycle 2: £1,171 Cycle 3: £793 Cycle 4: £668 Cycle 5: £668 Cycle 6: £668 Cycle 7+: £233	Table 41
Monitoring cost	N/A – monitoring is expected to be based on health state rather than treatment			
Total cost per model cycle	Cycle 1: £9,306 [redacted] Cycles 2–12: £9,706 [redacted] Cycles 13+: £7,826 [redacted]	£4,075	Cycle 1: £20,382 Cycle 2: £20,238 Cycle 3: £11,443 Cycle 4: £8,511 Cycle 5: £8,511 Cycle 6: £8,511 Cycle 7+: £4,442	N/A

CI, confidence interval; CRd, carfilzomib/lenalidomide/dexamethasone; N/A, not applicable; Rd, lenalidomide/dexamethasone
Costs per treatment cycle account for relative dose intensity and missed doses

The cost of concomitant medications was also included for all treatments, based on the requirements in the ASPIRE study. These are applied as an average cost per model cycle for the duration of treatment in the progression-free health state.

Concomitant medications included are:

- valacyclovir 500 mg daily for duration of treatment
- lansoprazole 15 mg daily for duration of treatment with dexamethasone
- aspirin enteric coated at standard prophylactic dose (75 mg) daily for duration of treatment with lenalidomide.

The cost of concomitant medications for CRd and Rd are shown in Table 43. These are assumed to be taken as one tablet per day. The cost of concomitant medications for DVd are shown in Table 44, based on the DVd submission to NICE.[81] Consistent with the assumptions in the NICE appraisals for DVd, these are assumed to be taken once with each administration of DVd by 100% of patients receiving the dose.

Table 43: Concomitant medications – CRd and Rd

Treatment	Dose	Pack size	Unit cost (eMIT)[98]	Cost per tablet	Total cost per 28-day cycle	% receiving CRd (ASPIRE CSR Table 20)	% receiving Rd (ASPIRE CSR Table 20)
Valacyclovir	500 mg	42	£10.00	£0.24	£5.77	95%	67%
Lansoprazole	15 mg	28	£0.31	£0.01	£0.31	96%	95%
Aspirin	75 mg	56	£0.25	< £0.01	£0.13	96%	97%
Total cost of concomitant medications per 28-day cycle						**£5.88**	**£4.27**

CRd, carfilzomib/lenalidomide/dexamethasone; CSR, clinical study report; Rd, lenalidomide/dexamethasone

Table 44: Concomitant medications - DVd

Treatment	Dose	Pack size	Unit cost (eMIT)[98]	Unit cost (MIMS)[99]	Cost per tablet/vial
Methylprednisolone IV	125 mg	1	£4.75		£4.75
Prednisolone oral	5 mg	28	£0.26		£0.01
Paracetamol (acetaminophen)	500 mg	100	£0.38		< £0.01
Diphenydramine	50 mg	20		£4.07	£0.20
Total cost of concomitant medications per administration of DVd					**£4.97**

DVd: daratumumab/bortezomib/dexamethasone

B.3.5.2 Health-state unit costs and resource use

Resource utilisation assumptions were derived from a recent non-interventional, observational chart review study using retrospective data collected from medical records of symptomatic MM patients.[106, 107]

For the chart review study, oncologists and haematologists in the UK (N = 56) were asked to complete electronic case report forms and to provide retrospective data on patient characteristics, treatment patterns, treatment response, costs and health care resource use. To maximise the generalisability of the results in the relapsed setting, physicians were asked to provide costs and health care resource use data on 2L lenalidomide or bortezomib, 3L lenalidomide, 4L lenalidomide, pomalidomide or bendamustine treatment regimens, any regimen administered as 5L or later, and BSC only. Data were provided separately for the active treatment and treatment-free intervals.

For the purpose of the health economic model, monitoring costs associated with outpatient consultations, lab tests, scans and other procedures were considered. Since the average cost associated with these cost items were very similar across the different treatment regimens, the average of the considered costs items across all treatment regimens were used for the pre-

progression (on treatment [n=387] and off treatment (n=372), separately) and post-progression subsequent treatment phases. Best supportive care costs (i.e. costs associated with the post-progression phase after subsequent treatments) were informed by the chart review study as well. In particular, the weighted average of costs associated with end of treatment until progression (n=17) and end of treatment until death without progression (n=15). Although costs associated with progression until death were also available (n=13), the maximum follow-up time for these patients was two months, which indicated that these costs are likely to be associated specifically with end-of-life care, and subsequently were considered not to be appropriate for use in the health economic model as BSC costs. The costs are summarised in Table 45.

Table 45: Costs of monitoring

Health state	Monitoring cost per 4-week cycle (2016 price year)	Monitoring cost per 4-week cycle (2018 price year)[a]	Notes
Progression-free (on treatment)	£91.57	£94.51	Includes outpatient consultations, labs, scans and other procedures
Progression-free (off treatment)	£62.32	£64.32	Includes outpatient consultations, labs, scans and other procedures
Post-progression (on subsequent treatment)	£91.57	£94.51	Includes outpatient consultations, labs, scans and other procedures
Post-progression (BSC)	£188.72	£194.78	Includes outpatient consultations, labs, scans, other procedures and hospitalisations

[a] Uplifted using The hospital & community health services pay and prices index[102]

References: Amgen data on file, 2015[106]

BSC, best supportive care

It is assumed that all patients are assigned a standard cost for palliative care before death. This is assumed to cover hospital care in the 90 days before dying, based on Georghiou and Bardsley, 2014.[108] The costs of palliative care included services such as district nurse, nursing and residential care, hospice care, and Marie Curie nursing. This cost was applied as a one-off cost at the point of death. The total cost is estimated to be £7,652.92. The costs reported by Georghiou and Bardsley 2014[108] were uplifted to 2018 prices using the hospital and community health services pay and prices index.[102]

Table 46: Costs of palliative care

Costs	Unit cost reported (cost year)	Unit cost, 2018 prices	Reference
District nurse	£278 (2010/11)	£307.97	Georghiou and Bardsley, 2014[108]
Nursing and residential care	£1,000 (2009/10)	£1,141.22	

Costs	Unit cost reported (cost year)	Unit cost, 2018 prices	Reference
Hospice care – in-patient	£550 (2010/11)	£609.30	
Hospice care – final 3 months of life	£4,500 (2010/11)	£4,985.16	
Marie Curie nursing service	£550 (2010/11)	£609.30	
Total	**£6,878**	**£7,652.95**	

B.3.5.3 Adverse reaction unit costs and resource use

Treatment emergent AEs were included in the model if they were Grade 3 or higher with an incidence greater than 5% in either study arm ASPIRE or the DVd arm of CASTOR (ITT population).

The conversion to a 4-weekly probability of experiencing an AE has been calculated from the frequencies of occurrence of AEs during the trial and from the mean time on treatment, using the following formulae: 4-weekly probability of AE = 1 – EXP(((LN(1 – frequency of AE during trial))/(duration of trial in 4-week cycles)).

AE frequencies for CRd and Rd were taken from the ASPIRE study clinical study report (5 December 2017 data cut-off date). AE frequencies for DVd were taken from the CASTOR trial, as presented in Table 26 the manufacturer's submission for the appraisal of DVd.[81]

Frequency data are presented in Table 47. AE rates are assumed to be constant irrespective of the number and types of prior therapies received, i.e. it was implicitly assumed that the risk of experiencing an AE was the same in the full trial population as in post-hoc subgroups considered most relevant to the decision problem.

The proportion of patients treated for AEs in each different treatment setting (Table 48) was estimated. Costs for the AEs were taken from the NHS reference costs and the Unit Costs of Health and Social Care (Table 49).[101, 102] These sources were chosen as they presented the most robust costing of AEs of previous NICE submissions for treatments of MM. For inpatient costs, the weighted cost of a long and short inpatient stay is assumed.

Table 47: List of Grade ≥ 3 adverse events for CRd, Rd (ASPIRE, safety population) and DVd (CASTOR)

Adverse event	Total adverse events, % patients experiencing event			Adverse event rate per cycle, % patients experiencing event		
	CRd	Rd	DVd	CRd	Rd	DVd
Neutropenia	31.12	27.51	13.58	1.24	1.39	0.56
Anaemia	18.62	17.48	15.23	0.69	0.83	0.63
Thrombocytopenia	16.84	13.11	45.68	0.61	0.61	2.32
Cataract	5.10	4.37	0.00	0.17	0.19	0.00

Adverse event	Total adverse events, % patients experiencing event			Adverse event rate per cycle, % patients experiencing event		
	CRd	Rd	DVd	CRd	Rd	DVd
Hyperglycaemia	5.36	4.63	0.00	0.18	0.21	0.00
Lymphopenia	2.81	2.06	9.88	0.09	0.09	0.40
Hypokalaemia	10.46	5.91	2.47	0.37	0.26	0.10
Fatigue	8.16	6.68	4.94	0.28	0.30	0.19
Hypertension	5.36	2.31	0.00	0.18	0.10	0.00
Hypophosphataemia	8.93	5.14	0.00	0.31	0.23	0.00
Pneumonia	16.07	12.08	10.29	0.58	0.56	0.42

References: ASPIRE clinical study report (28 April 2017 data cut-off date) Table 14-3.4.1.2; DVd manufacturer's submission, Table 26, CASTOR trial[81]

CRd, carfilzomib/lenalidomide/dexamethasone; DVd: daratumumab/bortezomib/dexamethasone; Rd, lenalidomide/dexamethasone

Table 48: Proportion of patients treated in each treatment setting

Adverse event	Inpatient, %	Outpatient, %	Day case, %	General practice, %
Neutropenia[a]	100	0	0	0
Anaemia[a]	100	0	0	0
Thrombocytopenia[a]	100	0	0	0
Cataract[b]	0	0	100	0
Hyperglycaemia[c]	100	0	0	0
Lymphopenia[a]	100	0	0	0
Hypokalaemia[c]	100	0	0	0
Fatigue[d]	0	0	0	100
Hypertension[e]	0	0	0	100
Hypophosphataemia[d]	50	50	0	0
Pneumonia[a]	100	0	0	0

[a]Assumption, in line with DVd manufacturer's submission.[81]
[b]Assumption, in line with TA297[94]
[c]Assumption
[d]Assumption, in line with TA457[109]
[e]Assumed 100% will require treatment with a GP visit, as this is usually managed with diet, exercise or medication.

ERG, evidence review group; GP, general practitioner; NICE, National Institute for Health and Care Excellence; TA, technology appraisal

Table 49: Summary of adverse event costs in the economic model

Adverse event	Inpatient costs (weighted long and short stay)[101]	Outpatient costs[101]	Day costs[101]	General practice costs[102]	Weighted average	Total adverse event costs per patient per cycle		
						CRd	Rd	DVd
Neutropenia	£1,367.10[a]	£159.65[b]	£382.38[c]	£31.43[v]	£1,367.10	£16.91	£18.99	£7.66
Anaemia	£1,112.32[d]	£159.65[b]	£296.19[e]	£31.43[v]	£1,112.32	£7.63	£9.25	£7.05
Thrombocytopenia	£1,500.05[f]	£159.65[b]	£280.28[g]	£31.43[v]	£1,500.05	£9.21	£9.14	£34.82
Cataract	£1,192.78[h]	£136.26[i]	£847.08[j]	£31.43[v]	£847.08	£1.48	£1.64	£0.00
Hyperglycaemia	£959.04[k]	£159.65[b]	£383.48[l]	£31.43[v]	£959.04	£1.76	£1.97	£0.00
Lymphopenia	£1,367.10[a]	£159.65[b]	£382.38[c]	£31.43[v]	£1,367.10	£1.30	£1.23	£5.46
Hypokalaemia	£1,207.07[m]	£159.65[b]	£339.40[n]	£31.43[v]	£1,207.07	£4.44	£3.19	£1.16
Fatigue	£0.00[o]	£0.00[o]	£0.00[o]	£31.43[v]	£31.43	£0.09	£0.09	£0.06
Hypertension	£545.72[p]	£159.65[b]	£495.78[q]	£31.43[v]	£31.43	£0.06	£0.03	£0.00
Hypophosphataemia	£1,088.56[r]	£159.65[b]	£545.60[s]	£31.43[v]	£624.10	£1.95	£1.43	£0.00
Pneumonia	£1,642.61[t]	£159.65[b]	£375.34[u]	£31.43[v]	£1,642.61	£9.58	£9.17	£6.85
Total cost of adverse events per cycle						**£54.40**	**£56.15**	**£63.07**

[a]Non-elective inpatients, Combined stay (weighted): Other Haematological or Splenic Disorders, weighted average of SA08G to SA08J
[b]Total outpatient: Clinical Haematology: 303
[c]Day case: Other Haematological or Splenic Disorders, weighted average of SA08G to SA08J
[d]Non-elective inpatients, Combined stay (weighted): Iron Deficiency Anaemia, weighted average of SA04G to SA04L
[e]Day case: Iron Deficiency Anaemia, weighted average of SA04G to SA04L
[f]Non-elective inpatients, Combined stay (weighted): Thrombocytopenia, weighted average of SA12G to SA12K
[g]Day case: Thrombocytopenia, weighted average of SA12G to SA12K
[h]Non-elective inpatients, Combined stay (weighted): Cataract or Lens Procedures, weighted average of BZ30A - BZ33Z
[i]Outpatient 130 Ophthalmology; Weighted average of BZ03B to BZ34C
[j]Day case: Cataract or Lens Procedures, weighted average of BZ03A to BZ33Z

Adverse event	Inpatient costs (weighted long and short stay)[101]	Outpatient costs[101]	Day costs[101]	General practice costs[102]	Weighted average	Total adverse event costs per patient per cycle		
						CRd	Rd	DVd

[k]Non-elective inpatients, Combined stay (weighted): Diabetes with Hyperglycaemic Disorders, weighted average of KB02G to KB02K
[l]Day case: Diabetes with Hyperglycaemic Disorders, weighted average of KB02G to KB02K
[m]Non-elective inpatients, Combined stay (weighted): Fluid or Electrolyte Disorders, with Interventions, weighted average of KC05G to KC05N
[n]Day case: Fluid or Electrolyte Disorders, with Interventions, weighted average of KC05H to KC05N
[o]Assumption
[p]Non-elective inpatients, Combined stay (weighted): Hypertension, EB04Z
[q]Day case: Hypertension, EB04Z
[r]Non-elective inpatients, Combined stay (weighted): Other Endocrine Disorders, weighted average of KA08A to KA08C
[s]Day case: Other Endocrine Disorders, weighted average of KA08A to KA08C
[t]Non-elective inpatients, Combined stay (weighted): Lobar, Atypical or Viral Pneumonia, with Multiple Interventions, weighted average of DZ11K to DZ11V
[u]Day case: Lobar, Atypical or Viral Pneumonia, with Multiple Interventions, weighted average of DZ11K to DZ11V
[v]GP, 9.22 minute appointment at surgery including direct care staff costs and excluding qualification costs

CRd, carfilzomib/lenalidomide/dexamethasone; ERG, evidence review group; NICE, National Institute for Health and Care Excellence; Rd, lenalidomide/dexamethasone; TA, technology appraisal

B.3.5.4 Miscellaneous unit costs and resource use

Following progression, it is reasonable to assume that, in clinical practice, patients would still be treated. Subsequent treatment is included within the model only in terms of cost and it is therefore assumed that the impact of subsequent treatment on OS is consistent with the OS modelled.

Prior to receiving subsequent treatments, it is assumed that patients experience a 'treatment-free interval' during which no treatment costs are applied. The treatment-free interval was estimated from ASPIRE study data as the time between progression and start of subsequent treatment line, and is assumed to be the same irrespective of number of prior lines of therapy. This was estimated to be three model cycles for CRd, Rd and DVd.

Following treatment with CRd or Rd, the next line of treatment is assumed to be FVd followed by Pd, based on the current treatment pathway in England and Wales and the proposed positioning of CRd (Section B.1.3.3).

Following treatment with DVd, the next line of treatment is assumed to be Rd followed by Pd, based on the current treatment pathway in England and Wales.

The costs of FVd and Pd are provided in Table 50. The per-cycle cost of Rd is assumed to be equal to that presented in Table 40. It was estimated from a patient chart audit that 80% of 2L patients would go on to receive active 3L treatment, with the remaining 20% of patients receiving no further treatment.

The overall duration of subsequent therapy with FVd was estimated from the PANORAMA-1 study to be 5.0 months, which is approximately equal to 5 model cycles. The duration of subsequent therapy with Pd was estimated from the pomalidomide NICE appraisal[76] to be 3.91 months, which is approximately equal to 4 model cycles.[106] Therefore, the cost per cycle of subsequent therapy was applied within the model for up to 9 model cycles following CRd or Rd.

The duration of subsequent therapy with Rd was estimated from the DVd NICE appraisal to be 9.0 months, which is approximately equal to 10 model cycles. Therefore, the cost per cycle of subsequent therapy was applied within the model for up to 14 model cycles following DVd.

This gave a total cost of £7,295 per cycle for subsequent treatment following either CRd or Rd, for up to 9 cycles* and a total cost of £4,582 per cycle for subsequent treatment following DVd for up to 14 cycles.†

Administration of SC bortezomib is assumed to cost £89.16. Panobinostat, lenalidomide, pomalidomide and dexamethasone are oral therapies and are therefore assumed to incur no administration costs. The total cost of administration is £264.18 per cycle for subsequent treatment following either CRd or Rd.‡

* Calculated as (5 cycles * £8,432.46 + 4 cycles * £8,899.85 * 66%) / (5 + 4 cycles)
† Calculated as (10 cycles * £4,065.43 + 4 cycles * £8,899.85 * 66%) / (10 + 4 cycles)
‡ Calculated as (5 cycles * £89.16 x 4 x (28/21)) / (5 + 4 cycles)

Table 50: Subsequent treatment unit costs

Treatment (cycle length)	Unit	Unit cost	Reference	Dose	Frequency per treatment cycle	Cost per model cycle (28 days)
Panobinostat (21 days)	20 mg tablet × 6	£4656.00	MIMS[99]	20 mg	6	£6,208.00
Bortezomib (21 days)	3.5 mg vial	£762.38	MIMS[99]	1.3 mg/m^2	4	£2,208.62
Dexamethasone (21 days)	2 mg tablet × 50/100	£12.39/ £33.71	eMIT[98]	20 mg	8	£15.85
Total cost for FVd per 28-day cycle						**£8,432.46**
Pomalidomide	4mg x 21	£8884.00	MIMS[99]	4 mg	21	£8,884.00
Dexamethasone	2 mg tablet × 50/100	£12.39/ £33.71	eMIT[98]	20 mg	8	£15.85
Total cost for Pd per 28-day cycle						**£8.899.85**

eMIT, electronic market information tool; MIMS, Monthly Index of Medical Specialities

A scenario analysis is included whereby no cost of subsequent treatment is assumed, to test the impact of these costs on the results of the analysis.

B.3.6 *Summary of base-case analysis inputs and assumptions*

B.3.6.1 Summary of base-case analysis inputs

Key model inputs are described in Table 51. A full table of model parameters is provided in Appendix K.

Table 51: Summary of variables applied in the economic model

Parameter	Value	Measurement of uncertainty and distribution (95% CI)	Reference in submission
Settings			
Time horizon	40	None	Section B.3.2.2
Cycle length	28 days	None	
Discount rate costs	3.50%	None	
Discount rate LYs	0.00%	None	
Discount rate QALYs	3.50%	None	
Patient characteristics			

Body surface area (m^2)	1.79	Normal (1.78, 1.80)	Section B.3.5.1
Mean weight (kg)	77.9	Normal (62.63, 93.17)	
Mean age (years)	63.9	None	Section B.3.2.2
Patient access schemes			
PAS carfilzomib	[redacted]	None	Section B.3.5.1
Efficacy			
PFS curve CRd and Rd – generalised gamma – mu	[redacted]	Multivariate normal	Section B.3.3.3
PFS curve CRd and Rd – generalised gamma – sigma	[redacted]	Multivariate normal	
PFS curve CRd and Rd – generalised gamma – Q	[redacted]	Multivariate normal	
PFS curve CRd and Rd – generalised gamma – treatment effect	[redacted]	Multivariate normal	
OS curve CRd and Rd – Weibull – Shape	[redacted]	Multivariate normal	Section B.3.3.2
OS curve CRd and Rd – Weibull –Scale	[redacted]	Multivariate normal	
OS curve CRd and Rd – Weibull – treatment effect	[redacted]	Multivariate normal	
OS curve Rd MyelomaToul piecewise exponential rate	[redacted]	Multivariate normal	
OS curve Rd MyelomaToul piecewise exponential – period	[redacted]	Multivariate normal	
HR for OS, CRd vs Rd	[redacted]	Log-normal (0.438, 0.931)	
OS HR for ASPIRE vs MyelomaToul before 10 months	1.012	Log-normal (0.527, 1.942)	
OS HR for ASPIRE vs MyelomaToul after 10 months	2.041	Log-normal (1.525, 2.732)	
HR for PFS, CRd vs. DVd	0.745	Log-normal (0.542, 1.25)	
HR for OS, CRd vs. DVd	1.000	None	
Time to treatment discontinuation			
TTD - CRd carfilzomib curve – Gompertz – shape	[redacted]	Multinormal	Section B.3.3.4
TTD - CRd carfilzomib curve – Gompertz – rate	[redacted]	Multinormal	
TTD - CRd lenalidomide curve – exponential – rate	[redacted]	Multinormal	
TTD - Rd lenalidomide curve – log-logistic – shape	[redacted]	Multinormal	

TTD - Rd lenalidomide curve – log-logistic – scale	[redacted]	Multinormal	
TTD - DVd HR vs. PFS	1.118	Log-normal (0.899, 1.225)	
Drug costs			
Unit cost Carfilzomib 10 mg 1 pack – MIMs	£176.00	None	Section B.3.5.1
Unit cost Carfilzomib 30 mg 1 pack – MIMs	£528.00	None	
Unit cost Carfilzomib 60 mg 1 pack – MIMs	£1,056.00	None	
Unit cost Lenalidomide 5 mg 21 pack – MIMs	£3,570.00	None	
Unit cost Lenalidomide 10 mg 21 pack – MIMs	£3,780.00	None	
Unit cost Lenalidomide 15 mg 21 pack – MIMs	£3,969.00	None	
Unit cost Lenalidomide 20 mg 21 pack – MIMs	£4,168.50	None	
Unit cost Lenalidomide 25 mg 21 pack – MIMs	£4,368.00	None	
Unit cost Daratumumab 100 mg 1 pack – MIMs	£360.00	None	
Unit cost Daratumumab 400 mg 1 pack – MIMs	£1,440.00	None	
Unit cost Bortezomib 3.5 mg 1 pack – MIMs	£762.38	None	
Administration costs			
Unit cost - outpatient - Deliver simple Parenteral Chemotherapy at first attendance	£174.40	Gamma (£141.90, £210.21)	Section B.3.5.1
Unit cost - outpatient - Deliver subsequent elements of a chemotherapy cycle	£233.23	Gamma (£189.77, £281.11)	
Unit cost - outpatient - Specialist Nursing, Cancer Related, Adult, Face to face	£89.16	Gamma (£72.54, £107.46)	
Unit cost - day case - Deliver more complex Parenteral Chemotherapy at first attendance	£228.56	Gamma (£185.97, £275.49)	
Monitoring costs			
Unit cost - monitoring on an active treatment	£91.57	Gamma (£74.51, £110.37)	Section B.3.5.2
Unit cost - monitoring off treatment, progression-free	£62.32	Gamma (£50.71, £75.11)	
Unit cost - monitoring BSC	£188.72	Gamma (£153.55, £227.46)	

Utilities			
Utility - ASPIRE - baseline - 1 prior line of therapy	0.714	Beta (0.705, 0.722)	Section B.3.4.5
Utility - ASPIRE - average increase - 1 prior line of therapy	0.046	Beta (0.034, 0.060)	
Utility - ASPIRE - Rd progression	-0.047	Beta (-0.032, -0.063)	
Utility - ASPIRE - Difference between CRd and Rd	0.016	Beta (0.013, 0.019)	
BSC: best supportive care; CI confidence interval; CRd: carfilzomib/lenalidomide/dexamethasone; DVd: daratumumab/bortezomib/dexamethasone; HR: hazard ratio; LY: life year; MIMS: Monthly Index of Medical Specialties; OS: overall survival; PAS: patient access scheme; PFS: progression free survival; QALY: quality-adjusted life year; Rd: lenalidomide/dexamethasone TTD: time to treatment discontinuation.			

B.3.6.2 Assumptions

Key model assumptions are described in Table 52.

Table 52: List of assumptions

Assumptions	Assumption description	Justification
Model structure	The model is a 3-state PartSA model	Best use of available data, uses minimal assumptions, captures the key clinical outcomes measured in the ASPIRE study and those of most relevance to patients and clinicians and is consistent with the majority of previous appraisals in R/RMM allowing comparison of outcomes.
Time horizon	The time horizon is assumed to be 40 years (lifetime) in the base case	The mean age at baseline in the ASPIRE study was 65 years; therefore 40 years is an appropriate lifetime horizon based on this mean age and is therefore consistent with the reference case. Furthermore, cost-effectiveness results remain unchanged if a longer time horizon is selected
Cycle length	28 days	This is in line with measurement points in the ASPIRE study and the treatment cycle length for CRd Any treatments with a different cycle length have been adjusted
Use of post-hoc subgroup data from ASPIRE	Post-hoc subgroup data were used.	Post-hoc subgroup data were used to ensure alignment with the proposed positioning of CRd in the treatment pathway.
Adjustment of baseline characteristics in the post-hoc subgroup of ASPIRE	The IPW approach was used to adjust for covariates of interest. Potential covariates were identified through consultation with clinicians and then selected using a stepwise approach.	These methods were used and accepted in the previous appraisal of carfilzomib (TA457).[109] Imbalances were adjusted for given that the subgroup data were post-hoc.

Assumptions	Assumption description	Justification
		Use of the IPW method adjusts the underlying data, allowing parametric survival models to be applied using the methods proposed in DSU TSD 14 directly.[61]
OS – CRd and Rd	OS for CRd and Rd was estimated using a Weibull distribution and external data.	The statistical and visual fit to the observed data were similar for all curves except log-normal. However, long-term extrapolations of OS using exclusively the ASPIRE trial data yielded overly pessimistic estimates comparing with survival data available from external sources. The use of external data to inform OS extrapolation yielded more realistic estimates. The use of external data to inform OS extrapolation was further supported by the multistate modeling approach.
PFS – CRd and Rd	PFS for CRd and Rd was estimated using a generalised gamma distribution.	The statistical and visual fit to the observed data. In the absence of long-term PFS data for comparison, we selected the generalised gamma as this gave a plausible estimate of PFS.
PFS – DVd	The PFS of DVd is estimated by applying the MAIC HR estimated from the 2L population to the CRd PFS curve	The MAIC HR was used as this is based on covariates which clinical experts deemed to be of prognostic importance
OS – DVd	The OS of DVd is assumed to be equal to that of CRd	Based on clinical expert opinion, the OS for CRd and DVd is expected to be similar.
Proportional hazards	Proportional hazards was assumed for PFS and OS through the use of jointly fitted curve distributions for CRd and Rd, and the application of a HR for DVd	In the 2L prior bortezomib subgroup the OS curves retained good separation for the duration of follow-up. The PFS curves crossed only when the number of patients at risk were very low (N ≤ 12 in both arms) and it was deemed clinically improbable that PFS would intersect but OS would not. In the ITT population, the curves for PFS and OS remained separated for the duration of follow up. The proportional hazards assumption held in the ITT population based on log-log plots of cumulative hazards. Joint curve fitting can reduce uncertainty due to estimation of fewer parameters using a larger data set, as discussed in the literature. [42 42] Given the lack of head to head data for CRd or Rd and DVd, the efficacy of DVd was estimated using a HR.
TTD – CRd and Rd	TTD for CRd and Rd was estimated with the best fitting	All curves were indistinguishable in terms of statistical and visual fit in the observed period and there was little

Assumptions	Assumption description	Justification
	curve for each component treatment	difference for Rd components, in the extrapolation period.
TTD – DVd	TTD for DVd was estimated through a HR versus PFS	In the absence of sufficient publicly available data for TTD of DVd, this was deemed a sensible approach to derive the TTD of DVd using the available information. K-M data were available, however number of patients at risk were not reported and so robust reconstruction of patient-level data was not feasible.
Lenalidomide and dexamethasone TTDs differ by treatment arm	The lenalidomide and dexamethasone components of CRd and Rd are modelled separately	The modelled time to discontinuation was observed to be different by treatment arm
Carfilzomib treatment duration in CRd	Treatment with carfilzomib when given in combination with lenalidomide and dexamethasone is assumed to cease after 18 cycles	This is in line with the ASPIRE clinical trial from which efficacy data for CRd were estimated
Utilities	Utilities were assumed to be time- and treatment-dependent in the progression-free health state and are based on ASPIRE data mapped from EORTC QLQ-C30 to EQ-5D	Health-related quality of life data from the ASPIRE study suggested differences in pre-progression utilities between treatments that varied over time Trial based mapped utilities were preferred by the appraisal committee in the previous appraisal of carfilzomib in R/RMM (TA457)
Adverse events	The cost and disutility of treatment emergent adverse events occurring in at least 5% of patients in either arm of ASPIRE or the DVd arm of CASTOR were included. ITT data were used for adverse events; AE data were assumed consistent irrespective of population.	These inclusion criteria are consistent with those used in the DVd appraisal.[81] AE data were assumed consistent irrespective of population to provide a larger cohort of patients for whom safety data were available.
Source of drug costs	MIMs for branded drugs and eMIT for generic drugs	These are standard sources of drug costs and are consistent with the NICE reference case.
Source of other costs	National Schedule of Reference Costs; PSSRU; literature	These are standard sources of costs and are consistent with the NICE reference case.
Lenalidomide price	Lenalidomide list price is used in the base case	Lenalidomide has a simple PAS discount which was agreed during technology appraisals TA586 and TA587. The details of this are confidential and so we base our analysis of CRd versus Rd on the list price for lenalidomide.
Bortezomib price	Bortezomib list price is used in the base case	The patent on bortezomib is due to expire in 2019 and therefore the cost of

Assumptions	Assumption description	Justification
		bortezomib is likely to reduce in the future as generic alternatives become available at a lower list price. The exact timing and impact on the price of bortezomib of generics becoming available is highly uncertain at the time of this submission, therefore we present our base case analysis using the list price for bortezomib. A scenario analysis is presented assuming that the availability of generic bortezomib will reduce the price by 50%.
Daratumumab price	Daratumumab list price is used in the base case	Daratumumab has a Commercial Access Agreement (CAA) which was agreed during technology appraisal TA510. The details of this agreement are confidential and so we base our analysis of CRd versus DVd on the list price for daratumumab.
Drug wastage	Drug wastage was not included	Carfilzomib drug wastage is expected to be minimal, given that 10 mg dose steps are possible. Moreover, in the real world, doses slightly exceeding the content of a full vial may be rounded down, considering that dose adjustments do not need to be made for weight changes of 20% or less (SmPC for carfilzomib, Appendix C). For these reasons, in the base case analyses presented, wastage is excluded and the cost per mg is used, as this may be more likely to reflect the use of carfilzomib in practice.
Subsequent treatments	Following CRd or Rd at 2L the next treatments are FVd followed by Pd Following DVd at 2L the next treatments are Rd followed by Pd	This is based on the current clinical pathway for patients with MM in England and Wales

2L: second line; AE: adverse event; CRd, carfilzomib/lenalidomide/dexamethasone; CRUK: Cancer Research UK; DSU: Decision Support Unit; DVd: daratumumab/bortezomib/dexamethasone; eMIT: pharmaceutical electronic market information tool; ERG: Evidence Review Group; HR, hazard ratio; IPW: inverse probability weight; ITT, intent-to-treat; MAIC: matching adjusted indirect comparison; MIMs: Monthly Index of Medical Specialties; MM, multiple myeloma; NHS: National Health Service; OS, overall survival; PartSA: Partitioned survival analysis; PAS: patient access scheme; PFS, progression-free survival; Pd: pomalidomide/dexamethasone; PSSRU: Personal Social Services Research Unit; FVd, panobinostat/bortezomib/dexamethasone; Rd, lenalidomide/dexamethasone; R/RMM: relapsed/refractory multiple myeloma; SmPC: Summary of Product Characteristics; TSD: Technical Support Document; TTD, time to treatment discontinuation

B.3.7 *Base-case results*

Summary of Base case results

- Using list price for lenalidomide, in the primary analysis CRd was estimated to provide additional 2.54 life-years and 1.38 QALYs versus Rd at an additional cost of £60,467, resulting in an ICER of £43,952 per QALY gained.
- In the secondary analysis, CRd was estimated to provide no additional life-years, to provide 0.06 additional QALYs vs DVd at a cost saving of £55,317, resulting in CRd to dominate DVd.
- Sensitivity analyses were conducted to assess parameter and structural uncertainty within the model; these indicated that the model results were most sensitive to changes in the OS HR of CRd vs Rd, the hazard ratio applied to match the MyeloamToul registry to ASPIRE; the relative dose intensity of carfilzomib in patients treated with CRd, and the unit cost of administration of carfilzomib.

B.3.7.1 Base-case incremental cost-effectiveness analysis results – primary comparison CRd versus Rd

Using the list price for lenalidomide, the base case analysis results indicated a difference of £60,467 in total cost per patient for CRd (£[redacted]) versus Rd (£[redacted]) over the modelled time horizon. Patients treated with CRd were estimated to spend 4.39 years in pre-progression health state and 2.22 in the post-progression health state, resulting in a mean LY estimate of 6.62. Patients treated with Rd were estimated to spend 2.12 years in the pre-progression health state and 1.96 years in the post-progression health state for a total mean LYs of 4.08. CRd was predicted to provide an increase in 1.38 QALYs versus Rd; total QALYs were estimated to be 3.96 for CRd and 2.58 for Rd. In the base case, the ICER was estimated to be 43,952 £/QALY. Results are summarized in Table 53.

Table 53: Base-case results for CRd versus Rd

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)
Rd	[redacted]	4.08	2.58	-	-	-	-
CRd	[redacted]	6.62	3.96	60,467	2.54	1.38	43,952

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

B.3.7.2 Base-case incremental cost-effectiveness analysis results – secondary comparison CRd versus DVd

Using the list price for lenalidomide, the base case analysis results indicated a saving of £55,317 in total cost per patient for CRd (£[redacted]) versus DVd (£[redacted]). Patients treated with CRd were estimated to spend 4.39 years in pre-progression health state and 2.22 in the post-progression health state, resulting in a mean LY estimate of 6.62. Patients treated with DVd were estimated

to spend 3.09 years in the pre-progression health state and 3.53 years in the post-progression health state for a total mean LYs of 6.62. CRd was predicted to provide an increase in 0.06 QALYs versus DVd; total QALYs were estimated to be 3.96 for CRd and 3.90 for DVd. This resulted in CRd dominating DVd as treatment with CRd resulted in a cost saving and a QALY gain. Results are summarized in Table 54.

Table 54: Base case result for CRd vs. DVd

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)
DVd	[redacted]	6.62	3.90	-	-	-	-
CRd	[redacted]	6.62	3.96	-55,317	0.00	0.06	**Dominant**

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

B.3.8 *Sensitivity analyses*

The sensitivity analyses for the primary comparison (CRd versus Rd) are presented in Sections B.3.8.1 to B.3.8.4. Sensitivity analyses for the secondary comparison (CRd versus DVd) are presented in Sections B.3.8.5 to B.3.8.8.

B.3.8.1 Probabilistic sensitivity analysis – primary comparison CRd versus Rd

Probabilistic results have been calculated from an analysis with 2,000 simulations, using the mean costs and QALYs from the 2,000 simulations for each treatment.

To determine the number of simulations required to obtain approximately stable results from the probabilistic analysis 10,000 simulations were run five times. For each set of 10,000 simulations the total costs and QALYs for CRd and Rd were recorded and averaged over an increasing number of simulations. These results were then plotted (Appendix L) and based on these, the required number of simulations to produce approximately stable and reproducible results from each probabilistic analysis was determined to be 2,000.

The mean results from the probabilistic analysis are presented in Table 55. The results are very similar to the deterministic base case results as presented in Table 53 (ICER £44,988 vs. £43,952).

Table 55: Mean probabilistic results (CRd versus Rd; 2,000 iterations)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)
Rd	[redacted]	4.09	2.59	-	-	-	
CRd	[redacted]	6.79	4.01	63,955	2.69	1.42	44,988

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

Figure 25 shows the scatter plot of incremental cost and QALYs for CRd versus Rd.

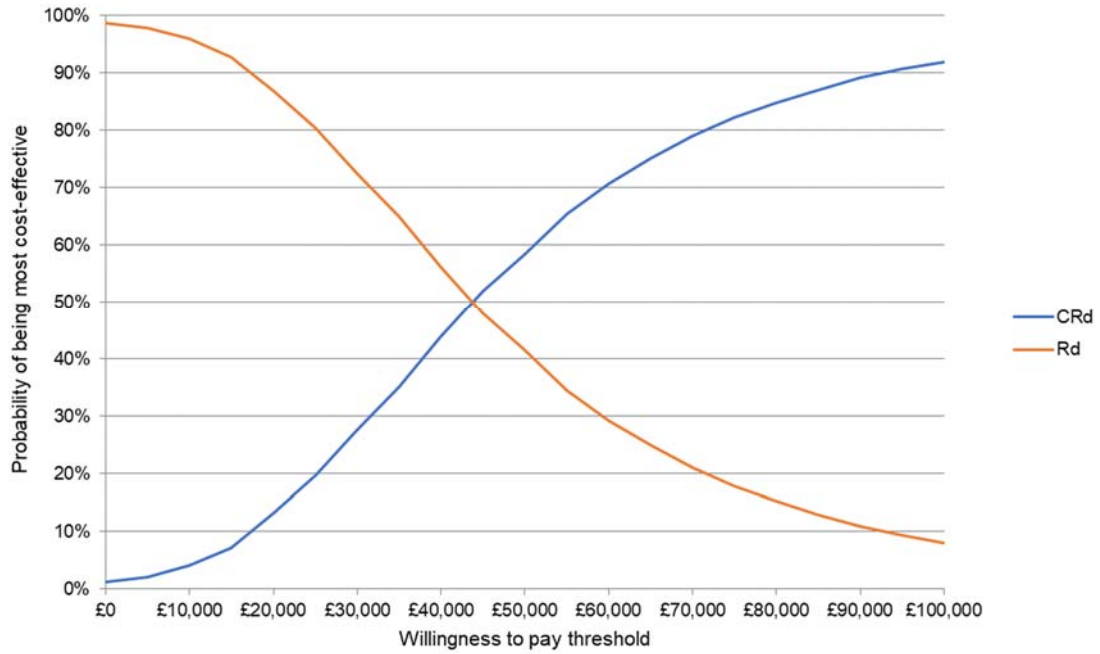
Figure 25: Scatter plot of incremental cost and QALYs (CRd vs. Rd)

CRd: carfilzomib/lenalidomide/dexamethasone; ICER: incremental cost-effectiveness ratio; PSA: probabilistic sensitivity analysis; QALY: quality-adjusted life-year; Rd: lenalidomide/dexamethasone

The cost-effectiveness acceptability curve is shown in

Figure 26 for CRd against Rd and projects probabilities that CRd will be most cost-effective at a willingness-to-pay thresholds of £30,000 and £50,000 of 28% and 58%.

Figure 26: Cost-effectiveness acceptability curve (CRd vs. Rd)



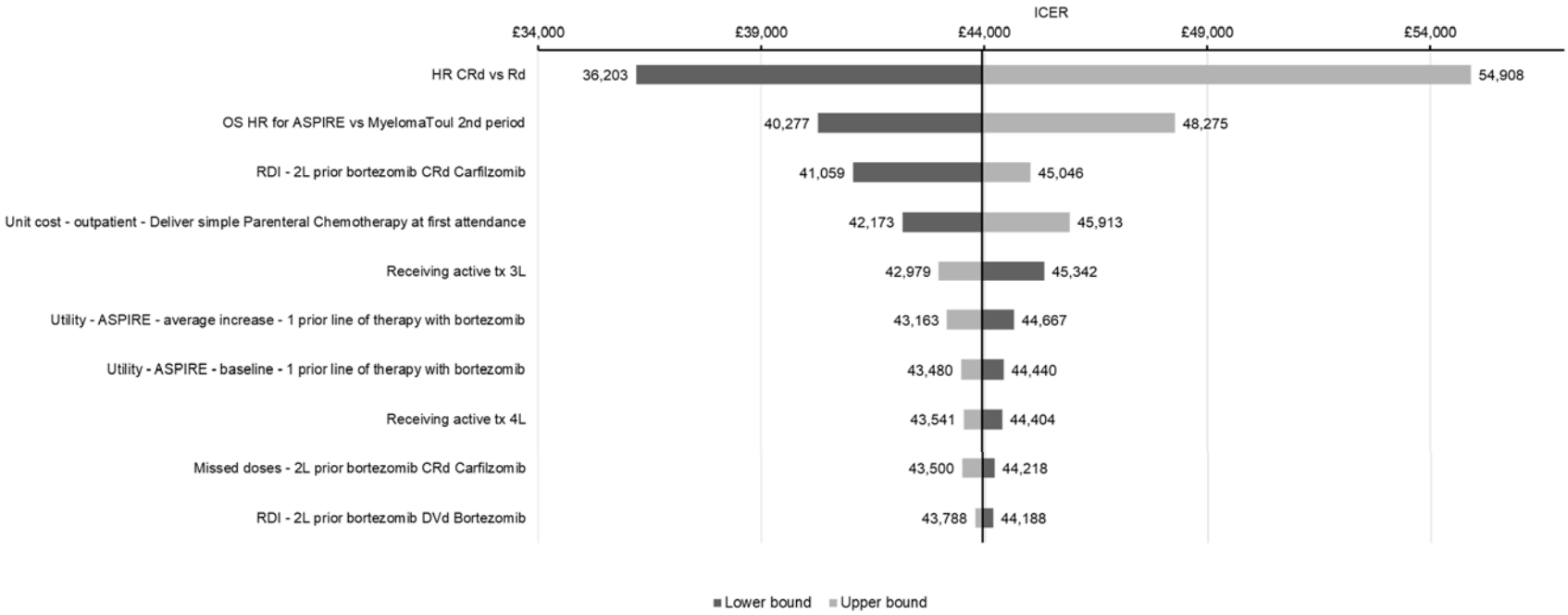
CRd: carfilzomib/lenalidomide/dexamethasone; Rd: lenalidomide/dexamethasone

B.3.8.2 Deterministic sensitivity analysis – primary comparison CRd versus Rd

Figure 27 shows the tornado diagram of ICERs produced as a result of one-way sensitivity analyses (OWSA) for CRd versus Rd.

The parameters that had the greatest impact on the ICER were the HR for OS, the hazard ratio applied to match the MyeloamToul registry to ASPIRE; the relative dose intensity of carfilzomib in patients treated with CRd, the cost of administration of carfilzomib, and the percentage of patients who receive subsequent third-line treatment. Other parameters had a smaller impact on the ICER can also be seen in Figure 27.

Figure 27: Tornado diagram (one-way sensitivity analysis – CRd vs. Rd)



2L: second line; 3L: third line; 4L: fourth line; CRd: carfilzomib/lenalidomide/dexamethasone; DVd: daratumumab/bortezomib/dexamethasone; Rd: lenalidomide/dexamethasone; RDI: relative dose intensity; tx: treatment; HR: hazard ratio; OS: overall survival.
Note: The RDI of bortezomib in DVd is used to calculate the cost of bortezomib as a component of subsequent treatment (FVd); the per cycle cost of bortezomib is assumed to be consistent in these two regimens for simplicity.

B.3.8.3 Scenario analysis – primary comparison CRd versus Rd

The assumptions tested in scenario analyses are detailed in Table 56. The results of the scenarios are summarised in order of influence in Figure 28 and are presented in full in Table 57. Excluding the additional cost of Rd in the CRd arm resulted in a highly cost-effective ICER of £16,751. Assuming the latest publicly available price point for lenalidomide (where the cost to the NHS was capped at 26 cycles) resulted in an ICER of £27,221. Other scenarios that significantly reduced the ICER included setting the price of carfilzomib to zero and assuming a 0% discount rate for both costs and benefits. More conservative assumptions around PFS and OS had the most detrimental impact on the ICER, as expected.

Table 56: Scenarios undertaken (CRd vs. Rd)

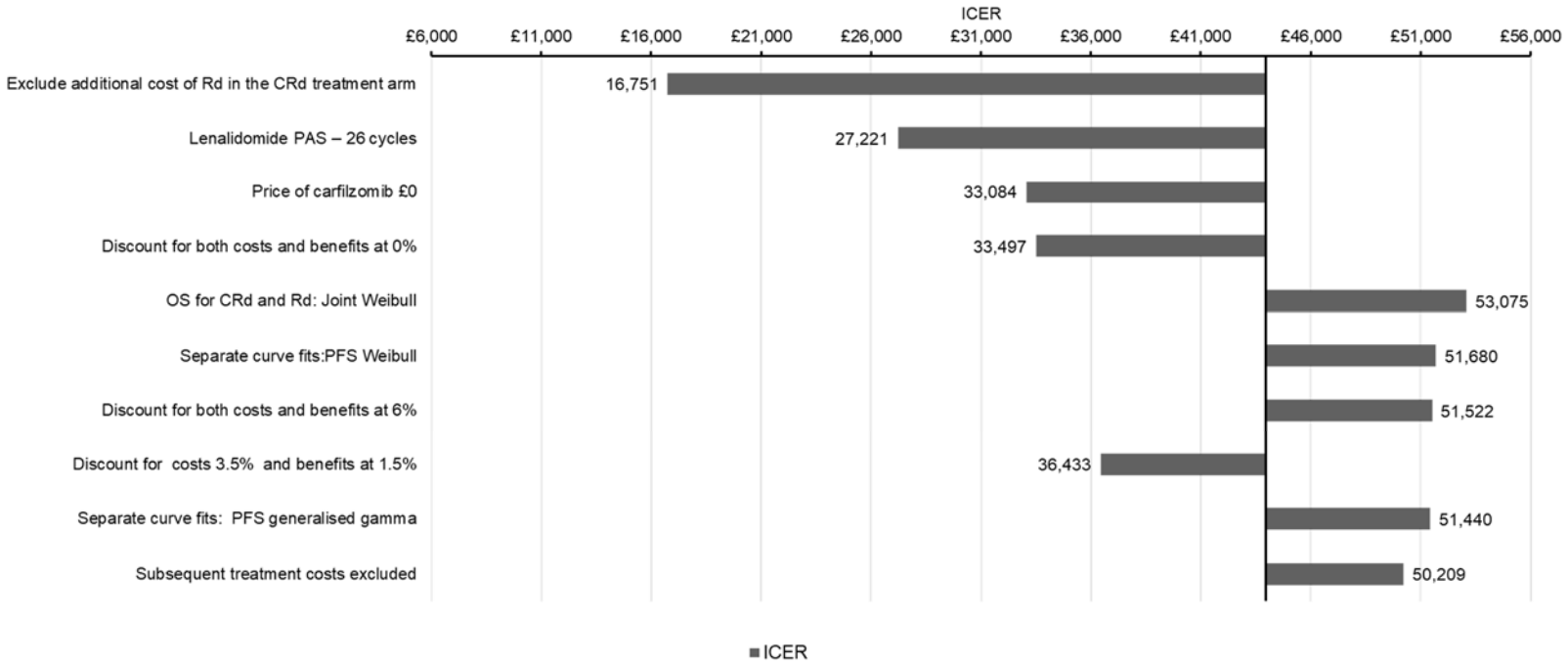
	Description	Base case setting	Scenario setting	Justification
1	Time horizon 30 years	Time horizon 40 years	Time horizon 30 years	Exploration of a shorter time horizon
2	Time horizon 50 years	Time horizon 40 years	Time horizon 50 years	Exploration of a longer time horizon
3	OS for CRd and Rd: Weibull	Weibull plus external data	Weibull OS curves	This scenario explores the use of curves fit to ASPIRE data only.
4	OS for CRd and Rd: log-normal	Weibull plus external data	Log-normal OS curves	This scenario explores the use of curves fit to ASPIRE data only.
5	PFS for CRd and Rd: Weibull (conservative)	Generalised gamma PFS curves	Weibull PFS curves	This scenario presents a more conservative PFS extrapolation for CRd and Rd
6	PFS for CRd and Rd: log-normal (optimistic)	Generalised gamma PFS curves	Log-normal PFS curves	This scenario presents a more optimistic PFS extrapolation for CRd and Rd
7	Separate curve fits for PFS: generalised gamma	Joint curve fits for PFS: generalised gamma	Separate curve fits for PFS: generalised gamma	Exploring the impact of using separate curve fits for PFS
8	Separate curve fits for PFS: Weibull		Separate curve fits for PFS: Weibull	

	Description	Base case setting	Scenario setting	Justification
9	Separate curve fits for PFS: log-normal		Separate curve fits for PFS: log-normal	
10	Exclude additional cost of Rd in the CRd treatment arm	Time to treatment discontinuation is modelled separately for each component of each treatment arm	Time to treatment discontinuation for the lenalidomide and dexamethasone components of CRd and Rd are assumed equal	This scenario is intended to explore the issue raised in the DSU report on technologies that are not cost effective at zero price by presenting the extreme scenario in which no additional cost of Rd is assumed to be incurred due to the improved efficacy of CRd; further discussion of this issue and scenario is provided in Section B.3.8.4.
11	Age adjusted utility	Utilities are not age adjusted	Utilities are age adjusted	This scenario explores the impact of adjusting utility for the ageing population in the model.
12	Lenalidomide cost capped at 26 cycles	No capping cost of lenalidomide	NHS pays for 26 cycles of treatment	The PAS for lenalidomide is now a simple discount and as such is confidential. Previously, a complex PAS capping scheme was in place for lenalidomide which capped the cost to the NHS at 26 cycles. As this is the last known price point for lenalidomide, we explore the cost-effectiveness of CRd vs. Rd using this price point.
13	Drug wastage included	Wastage excluded	Wastage included	To demonstrate the impact of this assumption on the results of the analysis.
14	Subsequent treatment costs excluded	Included	Excluded	To illustrate the impact of subsequent treatment cost assumptions on the results of the analysis.
15	Generic bortezomib	Bortezomib at list price (£762.38 per vial)	Bortezomib price 50% of list price (£381.19 per vial)	The patent on bortezomib is due to expire in 2019. The exact timing and impact on price of the availability of generic bortezomib is uncertain, the scenario illustrates the impact of a potential decrease of 50% to the price of bortezomib to the NHS.

	Description	Base case setting	Scenario setting	Justification
16	Exponential TTD for Rd components	Best fitting curves selected	Exponential curves	To explore the impact of alternative TTD assumptions on cost-effectiveness.
17	Exponential TTD curves for all treatment components	Best fitting curves selected	Exponential selected for all curves	
18	Use of external OS data from Month 63	External data used from Month 72	External data used from Month 63	To explore the impact of time-point from which external data are used.
19	Alternative Piecewise exponential cut-off for external OS data	Piecewise exponential cut-off for external OS data 72 months	Piecewise exponential for external OS data cut-off 60 months	To explore the impact of different cut-offs to the external OS extrapolation.
20			Piecewise exponential for external OS data cut-off 48 months	
21	Use of a constant HR for ASPIRE vs. external data	Use of piecewise HR	Use of constant HR	To explore the impact of the choice of HR.
22	Alternative discount rates	Discount for both costs and benefits 3.5%	Discount for both costs and benefits 0%	To explore the impact of alternative discount rates.
23			Discount for both costs and benefits 6%	
24			Discount for costs 3.5% and benefits 1.5%	
25	Price of carfilzomib £0	Price of carfilzomib list price with PAS applied	Price of carfilzomib £0	This scenario is intended to explore the issue raised in the DSU report on technologies that are not cost effective at zero price by presenting the extreme scenario in which the price of carfilzomib is set to £0

CRd, carfilzomib/lenalidomide/dexamethasone; DSU: Decision Support Unit; HR, hazard ratio; NHS: National Health Service; OS: overall survival; PAS: Patient Access Scheme; PFS: progression-free survival; Rd: lenalidomide/dexamethasone; TTD: time to treatment discontinuation.

Figure 28: Most influential scenarios (CRd vs. Rd)



CRd, carfilzomib/lenalidomide/dexamethasone; HR: hazard ratio; ICER: incremental cost effectiveness ratio; OS: overall survival; PAS: Patient Access Scheme; PFS: progression-free survival; Rd: lenalidomide/dexamethasone.

Table 57: Scenario analysis results (CRd vs. Rd)

	Scenario	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
N/A	*Base case*	*60,467*	*1.38*	*43,952*
1	Time horizon 30 years	60,426	1.36	44,582
2	Time horizon 50 years	60,480	1.38	43,825
3	OS for CRd and Rd: Weibull	58,709	1.11	53,075
4	OS for CRd and Rd: log-normal	61,935	1.32	46,828
5	PFS for CRd and Rd: Weibull (conservative)	67,024	1.36	49,440
6	PFS for CRd and Rd: log-normal (optimistic)	58,027	1.40	41,570
7	Separate curve fits for PFS: generalised gamma	68,225	1.33	51,440
8	Separate curve fits for PFS: Weibull	69,175	1.34	51,680
9	Separate curve fits for PFS: log-normal	59,445	1.39	42,857
10	Exclude additional cost of Rd in the CRd treatment arm	23,090	1.38	16,751
11	Age adjusted utility	60,467	1.31	46,054
12	Lenalidomide cost capped at 26 cycles	37,449	1.38	27,221
13	Drug wastage included	60,286	1.38	43,820
14	Subsequent treatment costs excluded	69,101	1.38	50,209
15	Generic bortezomib	61,183	1.38	44,473
16	Exponential TTD curves for Rd treatment components	67,180	1.37	48,858
17	Exponential TTD curves for all treatment components	65,838	1.38	47,871
18	Use of external OS data from month 63	60,491	1.38	43,923
19	Alternative Piecewise exponential cut-off for external OS data – 60 months	59,646	1.29	46,100
20	Alternative Piecewise exponential cut-off for external OS data – 48 months	58,964	1.22	48,348
21	Use of a constant HR for ASPIRE vs. external data	61,299	1.46	41,900
22	Alternative discount rates – cost and benefits 0%	65,075	1.94	33,497
23	Alternative discount rates – cost and benefits 6%	57,737	1.12	51,522
24	Alternative discount rates – cost 3.5% and benefits 1.5%	60,467	1.66	36,433
25	Price of carfilzomib £0	[redacted]	1.38	[redacted]

	Scenario	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
CRd, carfilzomib/lenalidomide/dexamethasone; DSU: Decision Support Unit; HR, hazard ratio; Overall survival; PAS: Patient Access Scheme; PFS: progression-free survival; QALY, quality-adjusted life year; Rd: lenalidomide/dexamethasone; TTD: time to treatment discontinuation.				

B.3.8.4 Summary of sensitivity and scenario analyses results – primary comparison CRd versus Rd

Using the list price for lenalidomide, the ICER was below £50,000 per QALY gained in the majority of scenarios. The highest ICER was estimated in the scenario where the Weibull model was used exclusively to predict OS for both CRd and Rd. However, this scenario should be interpreted with caution as it was suggested that the use of external data to extrapolate OS beyond the study period is more appropriate.

Most of the scenarios resulted in ICERs below £50,000 and some resulted in significantly reduced ICERs. It should be noted that adopting the full list price in these analysis for lenalidomide, which is a component of both the CRd and the Rd regimens, effectively biases the ICER against CRd. **Adoption of a more realistic price for lenalidomide significantly reduces the ICER for CRd versus Rd to less than £30,000 per QALY (Scenario 12)**.

Furthermore, if the additional costs of Rd are excluded from the CRd arm, the ICER was as low as £16,751. In one-way sensitivity analyses, the ICER increased above £50,000 per QALY where the upper boundary of the HR for OS (0.931, ICER £54,908) was used. Probabilistic sensitivity analysis results were comparable with the base case deterministic results.

Scenario to address specific issues relating to combination therapies

An issue commonly being faced by new combination therapies which improve the length of time patients spend progression free as well as extending survival is that this increased time spent in the progression-free state results in prolonged use of expensive background therapies which are required to be given until progression. The new technology is therefore penalised by the increased costs of background therapy. This is relevant for CRd – the increased time spent in PFS due to the increased efficacy of adding carfilzomib to Rd results in patients incurring incremental costs associated with additional Rd which is given until progression

In some extreme cases, this issue can lead to new combination therapies being unable to demonstrate cost-effectiveness even at zero price, as the prolonged use of the background therapy is not considered cost-effective at usual willingness to pay thresholds. This is relevant for CRd since according to the Guidance published on the 26th of June 2019, "*the most plausible cost-effectiveness estimate for lenalidomide plus dexamethasone in patients who have received 1 prior line with bortezomib, may be above the range that NICE normally considers to be a cost-effective use of NHS resources*".

The NICE DSU report on assessing technologies that are not cost-effective at a zero price[83] discusses potential alternative approaches to appraising treatments which face these issues. One of these alternative approaches is to exclude costs from the ICER that are unrelated to the

technology being appraised (i.e. excluding the costs of background therapy if these are not impacted by the technology under assessment other than through its impact on survival).

We have therefore presented a scenario whereby the TTD for the lenalidomide and dexamethasone components of the CRd treatment arm are assumed to be equal to those of the Rd treatment arm (i.e. the additional costs of Rd as a result of prolonged survival due to the introduction of carfilzomib are excluded from the ICER). In this scenario the ICER is £16,751, which is significantly lower than the current NICE willingness to pay threshold of £30,000 per QALY gained and demonstrates that CRd is a cost-effective treatment option which is penalised by the high cost of underlying Rd therapy. Indeed, the acquisition cost of carfilzomib represents only [redacted] of the total acquisition cost of CRd (Figure 29). Furthermore, additional Rd cost accounts for [redacted] of the incremental drug acquisition cost.

Figure 29. Acquisition cost of carfilzomib as a component of CRd regimen

CRd, carfilzomib/lenalidomide/dexamethasone; C, carfilzomib; Rd: lenalidomide/dexamethasone.

Furthermore, the NICE DSU report on assessing technologies that are not cost-effective at a zero price[83] states that "*In some cases, a new technology may only be cost-effective at a positive price if discounts are offered on other technologies which are given alongside the new technology*". This is relevant to CRd as scenarios exist in the economic evaluation where even if carfilzomib is priced at £0, with lenalidomide at list price, CRd is [redacted] at a willingness to pay threshold of £30,000 per QALY gained, despite significant gains in LYs and QALYs.

B.3.8.5 Probabilistic sensitivity analysis – secondary comparison CRd versus DVd

As with the comparison to Rd, an appropriate number of simulations was determined to be 2,000 following an assessment of results stability over the course of 10,000 simulations.

The mean results from the probabilistic analysis are presented in Table 58. The results are very similar to the deterministic base case results as presented in Table 54 (in both analyses CRd is dominant).

Table 58: Mean probabilistic results (CRd versus DVd; 2,000 simulations)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)
DVd	[redacted]	6.786	3.95	-	-	-	-
CRd	[redacted]	6.786	4.01	-55,544	0.000	0.06	Dominant

CRd, carfilzomib/lenalidomide/dexamethasone; DVd, daratumumab/bortezomib/dexamethasone; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

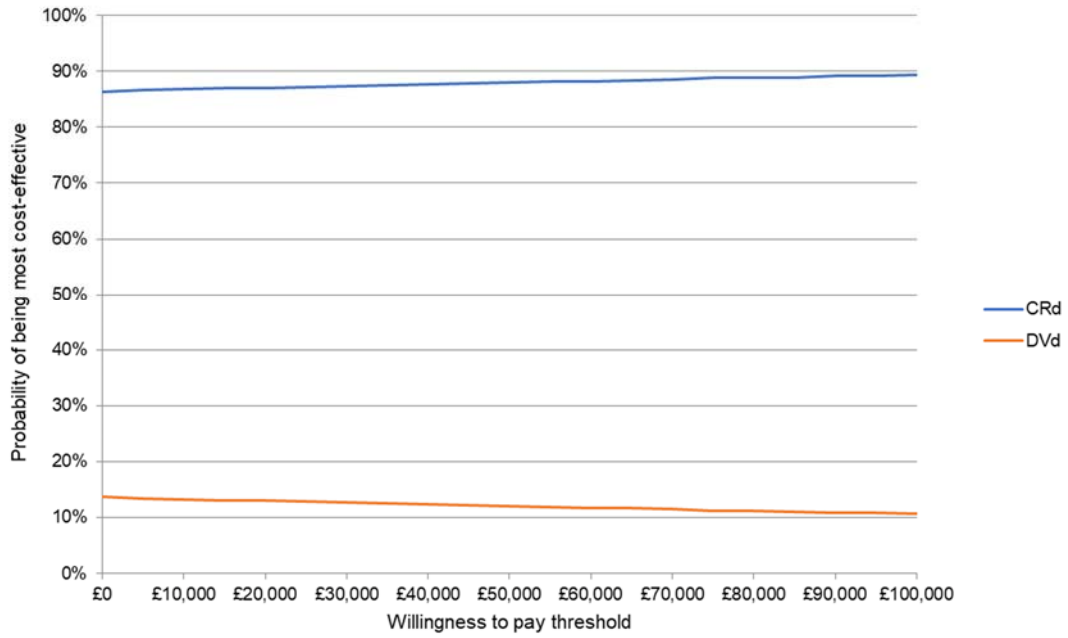
Figure 30 shows the scatter plot of incremental cost and QALYs for CRd versus DVd.

Figure 30: Scatter plot of incremental cost and QALYs (CRd vs. DVd)

CRd: carfilzomib/lenalidomide/dexamethasone; DVd: daratumumab/bortezomib/dexamethasone; ICER: incremental cost-effectiveness ratio; PSA: probabilistic sensitivity analysis; QALY: quality-adjusted life-yea

The probability that CRd will be cost-effective at a willingness-to-pay thresholds of £30,000 and £50,000 is 87% and 88%%. The CEAC is presented in

Figure 31: CEAC (CRd vs. DVd)



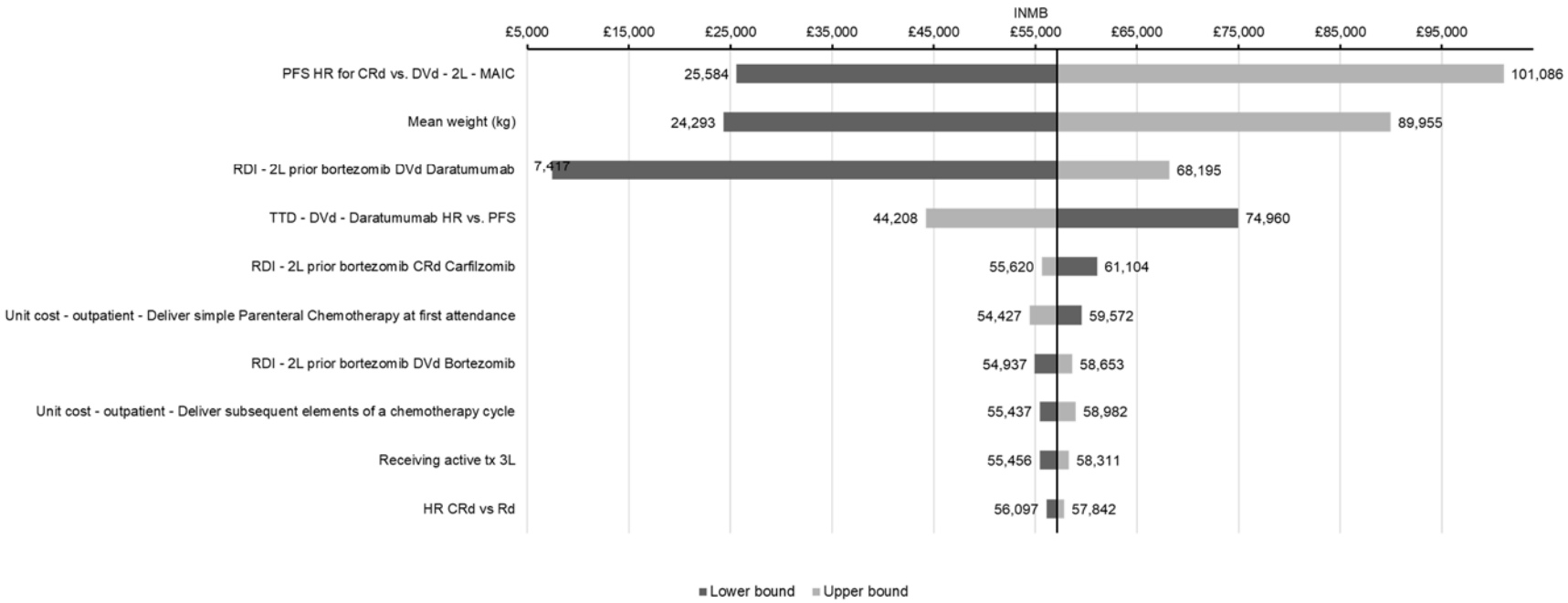
CRd: carfilzomib/lenalidomide/dexamethasone; DVd: daratumumab/bortezomib/dexamethasone.

B.3.8.6 Deterministic sensitivity analysis – secondary comparison CRd versus DVd

Due to the small positive difference in QALYs and negative difference in costs between CRd and DVd, in some cases the ICER was very large or the ICER moved between quadrants of the cost-effectiveness plane, making them difficult to interpret in isolation. Therefore, incremental net monetary benefit (INMB) with a willingness-to-pay threshold of £30,000 per QALY gained is presented to aid with interpretation. If the INMB is positive, this indicates that CRd is cost-effective at £30,000 per QALY gained.

Figure 32 shows the tornado diagram of INMB produced as a result of one-way sensitivity analysis (OWSA) for CRd versus DVd. All OWSA output suggested that CRd is a cost-effective alternative to DVd at a willingness to pay threshold of £30,000 per QALY (the INMB is positive in all cases). Most influential parameters were those relating to the treatment effect between CRd and DVd (HR for OS) and those relating to the cost of treatment with daratumumab.

Figure 32: Tornado diagram (one-way sensitivity analysis – CRd vs. DVd): INMB



Key: 2L: second line; 3L: third line; BSC: best supportive care; CRd: carfilzomib/lenalidomide/dexamethasone; DVd: daratumumab/bortezomib/dexamethasone; PFS: progression-free survival; RDI: relative dosage intensity; TTD: time to treatment discontinuation; HR: hazard ratio.

B.3.8.7 Scenario analysis – secondary comparison CRd versus DVd

The assumptions assessed in scenario analyses are presented in Table 59. The results of the scenarios are summarised in order of influence in Figure 33 and are presented in full in Table 60. In all explored scenarios CRd remained dominant compared with DVd.

Table 59: Scenarios undertaken (CRd vs. DVd)

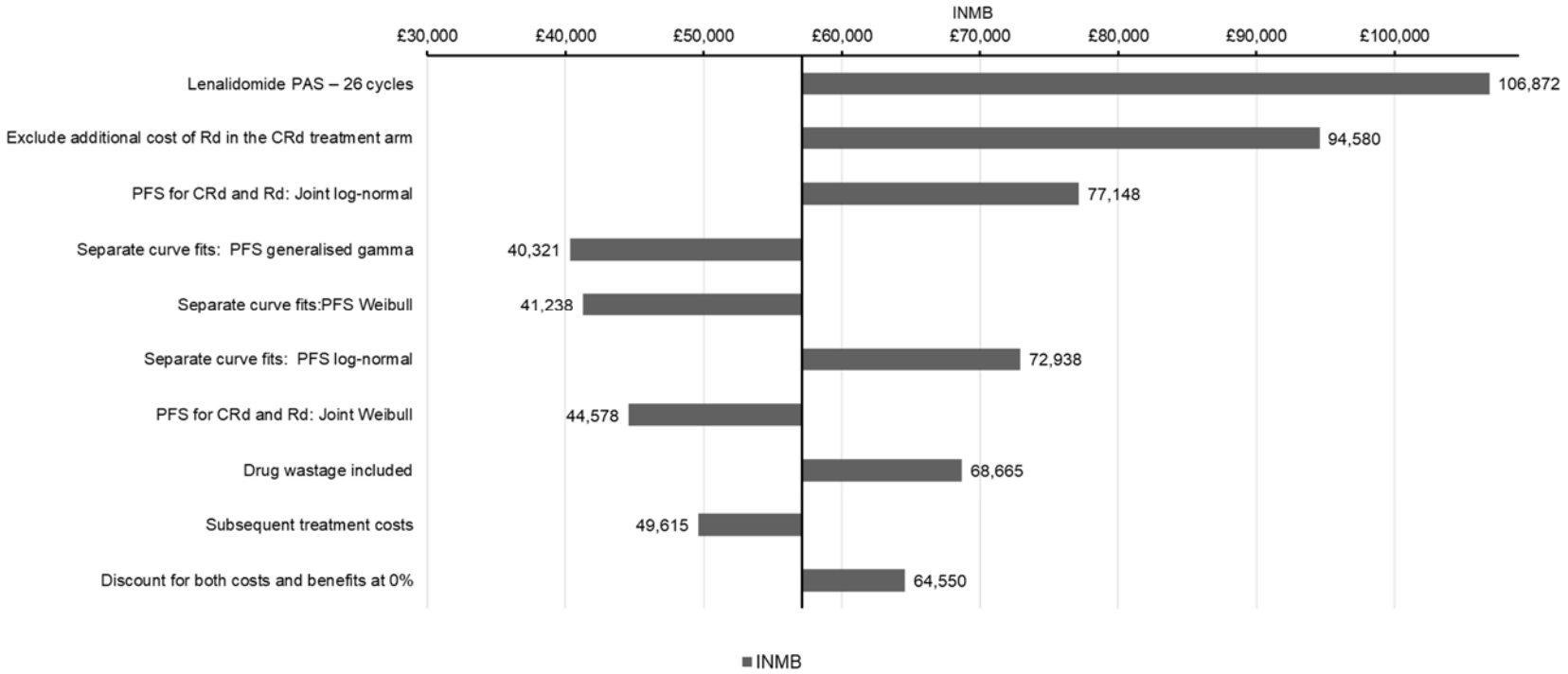
	Description	Base case setting	Scenario setting	Justification
1	Time horizon 30 years	Time horizon 40 years	Time horizon 30 years	Exploration of a shorter time horizon
2	Time horizon 50 years	Time horizon 40 years	Time horizon 50 years	Exploration of a longer time horizon
3	OS for CRd: Weibull	Weibull plus external data	Weibull OS curves	This scenario explores the use of curves fit to ASPIRE data only.
4	OS for CRd: log-normal	Weibull plus external data	Log-normal OS curves	This scenario explores the use of curves fit to ASPIRE data only.
5	PFS for CRd: Weibull (conservative)	Generalised gamma PFS curves	Weibull PFS curves	This scenario presents a more conservative PFS extrapolation for CRd
6	PFS for CRd: log-normal (optimistic)	Generalised gamma PFS curves	Log-normal PFS curves	This scenario presents a more optimistic PFS extrapolation for CRd
7	PFS curve for CRd: generalised gamma	Joint curve fits for PFS (CRd and Rd): generalised gamma	Separate curve fits for PFS: generalised gamma	Exploring the impact of using separate curve fits for PFS
8	Separate curve fits for PFS: Weibull		Separate curve fits for PFS: Weibull	
9	Separate curve fits for PFS: log-normal		Separate curve fits for PFS: log-normal	
10	Exclude additional cost of Rd in	Time to treatment discontinuation is modelled	Time to treatment discontinuation for the lenalidomide and	This scenario is intended to explore the issue raised in the DSU report on technologies that are not cost effective at

	Description	Base case setting	Scenario setting	Justification
	the CRd treatment arm	separately for each component of each treatment arm	dexamethasone components of CRd and Rd are assumed equal	zero price by presenting the extreme scenario in which no additional cost of Rd is assumed to be incurred due to the improved efficacy of CRd; further discussion of this issue and scenario is provided in Section B.3.8.4.
11	Age adjusted utility	Utilities are not age adjusted	Utilities are age adjusted	This scenario explores the impact of adjusting utility for the ageing population in the model.
12	Lenalidomide cost capped at 26 cycles	No capping cost of lenalidomide	NHS pays for 26 cycles of treatment	The PAS for lenalidomide is now a simple discount and as such is confidential. Previously, a complex PAS capping scheme was in place for lenalidomide which capped the cost to the NHS at 26 cycles. As this is the last known price point for lenalidomide, we explore the cost-effectiveness of CRd vs. DVd using this price point.
13	Drug wastage included	Wastage excluded	Wastage included	To demonstrate the impact of this assumption on the results of the analysis.
14	Subsequent treatment costs excluded	Included	Excluded	To illustrate the impact of subsequent treatment cost assumptions on the results of the analysis.
15	Generic bortezomib	Bortezomib at list price (£762.38 per vial)	Bortezomib price 50% of list price (£381.19 per vial)	The patent on bortezomib is due to expire in 2019. The exact timing and impact on price of the availability of generic bortezomib is uncertain, the scenario illustrates the impact of a potential decrease of 50% to the price of bortezomib to the NHS.
16	DVd OS HR from MAIC	DVd OS HR = 1	DVd OS HR from MAIC (0.927)	The MAIC demonstrated a numerical OS benefit for CRd vs DVd therefore the base case assumption can be considered conservative
17	Daratumumab missed doses equal to	Daratumumab missed doses = 0%	Daratumumab missed doses equal to carfilzomib	Assessing an alternative assumption in the absence of published evidence for missed doses for daratumumab

	Description	Base case setting	Scenario setting	Justification
	carfilzomib missed doses		missed doses (3.44%)	
18	Exponential TTD for Rd components	Best fitting curves selected	Exponential curves	To assess the impact of alternative TTD assumptions on cost-effectiveness
19	Exponential TTD curves for all CRd and Rd treatment components	Best fitting curves selected	Exponential selected for all curves	
20	Use of external OS data from Month 63	External data used from Month 72	External data used from Month 63	To explore the impact of time-point from which external data are used.
21	Alternative Piecewise exponential cut-off for external OS data	Piecewise exponential cut-off for external OS data 72 months	Piecewise exponential for external OS data cut-off 60 months	To explore the impact of different cut-offs to the external OS extrapolation.
22			Piecewise exponential for external OS data cut-off 48 months	
23	Use of a constant HR for ASPIRE vs. external data	Use of piecewise HR	Use of constant HR	To explore the impact of the choice of HR.
24	Alternative discount rates	Discount for both costs and benefits 3.5%	Discount for both costs and benefits 0%	To explore the impact of alternative discount rates.
25			Discount for both costs and benefits 6%	
26			Discount for costs 3.5% and benefits 1.5%	

AEs: adverse events; CRd, carfilzomib/lenalidomide/dexamethasone; DSU: Decision Support Unit; HR, hazard ratio; MAIC, matching-adjusted indirect comparison; NHS: National Health Service; OS: overall survival; PAS: Patient Access Scheme; PFS: progression-free survival; Rd: lenalidomide/dexamethasone; TTD: time to treatment discontinuation.

Figure 33: Most influential scenarios (CRd vs. DVd) - INMB



CRd, carfilzomib/lenalidomide/dexamethasone; DVd: daratumumab/bortezomib/dexamethasone; HR: hazard ratio; MAIC: matching adjusted indirect comparison; OS: overall survival; PAS: Patient Access Scheme; PFS: progression-free survival

Table 60: Scenario analysis results (CRd vs. DVd)

	Scenario	Incremental costs (£)	Incremental QALYs	INMB
N/A	*Base case*	*-55,317*	*0.06*	*CRd is dominant*
1	Time horizon 30 years	-55,236	0.06	57,021
2	Time horizon 50 years	-55,330	0.06	57,142
3	OS for CRd: Weibull	-55,693	0.06	57,376
4	OS for CRd: log-normal	-53,794	0.06	55,611
5	PFS for CRd: Weibull (conservative)	-43,115	0.05	44,578
6	PFS for CRd: log-normal (optimistic)	-74,924	0.07	77,148
7	Separate curve fits for PFS: generalised gamma	-39,166	0.04	40,321
8	Separate curve fits for PFS: Weibull	-40,040	0.04	41,238
9	Separate curve fits for PFS: log-normal	-70,742	0.07	72,938
10	Exclude additional cost of Rd in the CRd treatment arm	-92,695	0.06	94,580
11	Age adjusted utility	-55,317	0.06	57,124
12	Lenalidomide cost capped at 26 cycles	-105,065	0.06	106,872
13	Drug wastage included	-66,859	0.06	68,665
14	Subsequent treatment costs excluded	-47,747	0.06	49,615
15	Generic bortezomib	-50,478	0.06	52,285
16	DVd OS HR from MAIC	-52,948	0.30	61,862
17	Daratumumab missed doses equal to carfilzomib missed doses	-54,993	0.06	56,800
18	Exponential TTD curves for Rd treatment components	-55,317	0.06	57,124
19	Exponential TTD curves for all CRd and Rd treatment components	-56,659	0.06	58,475
20	Use of external OS data from Month 63	-55,291	0.06	57,098
21	Alternative Piecewise exponential cut-off for external OS data – 60 months	-55,761	0.06	57,565
22	Alternative Piecewise exponential cut-off for external OS data – 48 months	-56,050	0.06	57,842
23	Use of a constant HR for ASPIRE vs. external data	-54,851	0.06	56,661

	Scenario	Incremental costs (£)	Incremental QALYs	INMB
24	Alternative discount rates – cost and benefits 0%	-62,099	0.08	64,550
25	Alternative discount rates – cost and benefits 6%	-51,884	0.05	53,392
26	Alternative discount rates – cost 3.5% and benefits 1.5%	-55,317	0.07	57,449

CRd, carfilzomib/lenalidomide/dexamethasone; DSU: Decision Support Unit; HR, hazard ratio; MAIC, matching adjusted indirect comparison; OS: overall survival; PAS: Patient Access Scheme; PFS: progression-free survival; QALYs, quality-adjusted life years; Rd: lenalidomide/dexamethasone; TTD: time to treatment discontinuation.

B.3.8.8 Summary of sensitivity and scenario analyses results – secondary comparison CRd versus DVd

CRd remained dominant in all assessed scenarios. Scenarios having the largest positive influence on the INMB were those assuming the last known price point for lenalidomide (based on capping the cost at 26 cycles) and excluding the additional cost of Rd in the CRd treatment arm.

No scenarios assessing the impact of taking extreme values of parameters resulted in negative INMB confirming that CRd is cost-effective versus DVd. The probabilistic results were comparable with the base case deterministic results. These results suggest that the results of this analysis are robust.

B.3.9 *Subgroup analysis*

The economic analyses are focussed on the specific population of interest. No further subgroup analysis is presented.

B.3.10 *Validation*

B.3.10.1 Validation of cost-effectiveness analysis

Consistency with trial and literature

As summarised in Appendix H, modelled median PFS and OS are similar to the reported medians in the ASPIRE trial for CRd and Rd; the median PFS was slightly over-estimated for Rd and slightly underestimated for CRd, and median OS was slightly over-estimated for Rd but slightly underestimated for CRd. Modelled median PFS for DVd is similar to the reported median PFS in the CASTOR trial 2L prior bortezomib subgroup, however median OS was not reached in this group so a comparison of median OS for DVd is not possible at the time of this submission.

As discussed in Section B.3.3.2, the modelled proportions of patients alive at 10, 20 and 30 years for Rd (9%, 1% and 0%) have been compared with available long-term data. These estimates are lower than those estimated by CRUK[110] for the survival of patients with MM which is expected as these data are not reported by line of treatment, and patients who are at 2L can

be expected to have worse prognosis than the average patient at diagnosis. Recent clinical expert opinion in the DVd NICE appraisal process suggests that around 5-10% of *current* 2L patients (would be expected to survive to 10 years; where current treatments in the appraisal were assumed to be bortezomib plus dexamethasone or carfilzomib plus dexamethasone).[79] We expect survival in clinical trials to be slightly higher than in clinical practice. We estimate approximately 9% of patients receiving Rd will be alive at 10 years in our base case analysis which is consistent with this expectation and in-line with the estimated survival probability in second-line Rd treated patients in the French registry (MyelomaToul). These conclusions were further supported by clinical experts at an advisory board meeting held by Amgen.[73]

For CRd there are no long-term data available to compare against. In the technology appraisal of DVd, the company submission estimated that 40% of DVd patients would be alive at 10 years.[81] This estimate was adjusted by the ERG to 27% which they deemed more plausible. Our estimates of long-term survival for CRd are based on more mature data than are available from the CASTOR study for DVd and we estimated 21% of CRd patients to be alive at 10 years. We believe this to be aligned with the ERG's preferences in the DVd appraisal, and that as DVd and CRd are both triplet therapies, we might expect to see similar OS between the two treatment arms. This is consistent with the OS assumption made in the base case of our secondary analysis comparing CRd with DVd.

B.3.10.2 Quality control

The economic model was checked through internal processes at the company that built the economic model. A health economist who was not involved in the model construction reviewed the model for coding errors or inconsistencies and the plausibility of inputs.

B.3.11 *Interpretation and conclusions of economic evidence*

Summary of interpretation and conclusions of economic evidence

- CRd is a clinically effective option for R/RMM, which significantly improves life-years and QALYs compared with Rd, and which likely improves life-years and QALYs compared with DVd
- The primary analyses are based on randomised head-to-head RCT evidence and are therefore considered the most robust comparison available
- The most clinically plausible extrapolations of PFS and OS data were selected for the base case analyses and scenario analyses were presented which reflect more optimistic and pessimistic selections with only a small impact to the results of the analyses
- The base case modelling approach, including structure, costs included, and utility values applied, is consistent with those accepted in previous TAs for treatments of multiple myeloma, hence allowing consistency and comparability across evaluations
- In the primary comparison base case analysis, using the full list price for lenalidomide, the ICER for CRd versus Rd in 2L patients who have received prior therapy with bortezomib was £43,952 per QALY gained
- Adopting a more realistic, discounted NHS lenalidomide price the ICER is significantly reduced to £27,221 per QALY, indicating that CRd is likely to be cost effective at the commonly accepted cost-effectiveness threshold of £30,000 per QALY.
- We believe CRd presents an exception to NICE's usual end-of-life policy criteria based on its exceptional proportional gain in survival in people with a relatively modest life expectancy and significant unmet needs

B.3.11.1 Comparison with published economic literature

To our knowledge this is the first economic evaluation comparing CRd versus Rd or CRd versus DVd in patients with MM who have received one prior treatment with bortezomib; therefore, a comparison of cost-effectiveness results with published literature is not possible.

B.3.11.2 Relevance of the economic evaluation to all patients who could potentially use the technology as identified in the decision problem

The primary analysis presented a comparison of CRd with Rd and the secondary analysis presented a comparison of CRd with DVd, both in the population of patients with R/RMM who have received one prior treatment with bortezomib.

The primary comparison is based on randomised head-to-head RCT evidence for CRd versus Rd and is therefore considered the most robust comparison available. The secondary comparison is presented given the uncertainty in the future treatment pathway for R/RMM due to the CDF recommendation for DVd.[111] We believe that these analyses constitute the relevant comparisons in this patient population based on current NICE guidance for the treatment of patients with R/RMM.

B.3.11.3 Generalisability of the analysis

The analysis is relevant and generalisable to clinical practice in England. Where possible data are based on patients in the ASPIRE study, which included a total of 792 patients in North America, Europe, and the Middle East, most of whom were enrolled in Europe including six sites in the UK. Furthermore, the comparator of the ASPIRE trial (Rd) reflects the main treatment used in current clinical practice for patients with R/RMM at 2L following bortezomib. The results of this trial are therefore expected to be generalisable to England and Wales.

The model was developed using cost sources most relevant to the NHS in England,[98, 99, 101, 102] and trial based utility values that have been previously preferred by NICE have been used in the base case analysis.

B.3.11.4 Strengths of the economic evaluation

A key strength of the economic evaluation is that the primary analysis has been developed to use patient-level data from the pivotal phase 3 ASPIRE RCT extensively. The trial compared CRd versus Rd, the most relevant comparator based on the proposed positioning of CRd in the treatment pathway in England and Wales.

Given the uncertainty in the future treatment pathway for R/RMM at 2L due to the CDF recommendation for DVd in this setting,[82] we have also presented a secondary analysis comparing CRd with DVd in the same patient population using publicly available evidence for DVd at 2L.

The most clinically plausible extrapolations of PFS and OS data were selected for the base case analyses and scenario analyses were presented to test alternative curves. Where possible, modelled OS outcomes were compared with available literature and expert opinion to ensure the modelled estimates were plausible.

The base case modelling approach, including structure, costs included, and utility values applied, is consistent with those accepted in previous TAs for treatments of multiple myeloma including the previous appraisal of carfilzomib (TA457) and of DVd (TA573), hence allowing consistency and comparability across evaluations.

B.3.11.5 Limitations of the economic evaluation

A key limitation of the analysis is that OS data had to be extrapolated as data were incomplete (i.e. not all patients had experienced the corresponding event) at the time of this submission. Despite this, by extrapolating OS based on external data, the best available evidence has been considered. Efforts were made to account for the uncertainty arising from the incomplete data observed in the clinical trials using clinical input. The most clinically plausible extrapolations of OS data were selected for the base case analyses and scenario analyses were presented which reflect more optimistic and more pessimistic estimates of OS for the baseline curves.

A further limitation of the analysis is that due to the use of post-hoc subgroup analyses to derive estimates of clinical effectiveness for CRd and Rd in a population aligned with the proposed positioning of CRd, randomisation was broken. These data were, however, deemed to be the most clinically-relevant and appropriate data to use, as the populations of interest are defined by important predictive and prognostic factors and weighting analyses were performed to ensure that baseline characteristics were as balanced as possible between the two treatment arms.

Data on utilities were not directly available from the ASPIRE studies. Two disease-specific HRQoL measures, the EORTC QLQ-C30 and EORTC QLQ-MY20, can be mapped to EQ 5D and were collected in the studies. The mapped data were used to estimate utilities within the model and are considered the best available evidence for utilities of patients receiving CRd and Rd in population of patients with one prior treatment with bortezomib.

B.3.11.6 Conclusions

CRd, which has demonstrated compelling efficacy in the ASPIRE study, represents a valuable treatment option for patients with R/RMM. Our modelling reflects the NICE reference case, is based on conservative plausible assumptions, and is consistent with previous evaluations in MM.

The primary comparator for CRd in this evaluation is Rd. Rd was the comparator in the ASPIRE study for CRd. Therefore, our economic evaluation is based on robust head-to-head RCT data. A secondary comparison with DVd was also presented using publicly available data for DVd, reflecting the current uncertainty in the R/RMM treatment pathway due to the CDF recommendation for DVd.

The cost-effectiveness analyses presented in this submission are based on the PAS price of carfilzomib which has been agreed previously with PASLU and offers the NHS [redacted]. Amgen believes that carfilzomib is not a suitable candidate for the new CDF given that there is already compelling efficacy data from a robust phase 3, head-to-head RCT versus the most relevant comparator (ASPIRE).

The base case ICER for CRd versus Rd is £43,952 per QALY in the population of patients who have received one prior therapy with bortezomib. This is most sensitive to use of alternative curve fit assumptions, the exclusion of the additional costs of Rd on the CRd arm and the price

point for lenalidomide. Scenarios testing separate curve fits for PFS should be interpreted with care and represent extreme scenarios that are likely to overestimate the ICER.

In the base case, CRd is dominant compared with DVd as it is both cost saving and more efficacious in the population of patients who have received one prior therapy with bortezomib. This is sensitive to the choice of curve extrapolation for CRd, however under all scenarios CRd could still be considered the dominant treatment option. This does not account for the CAA which is currently in place for DVd as the details of this are confidential.

CRd is a clinically effective treatment options for R/RMM, which significantly improve life-years and QALYs compared with the most relevant comparator treatments used in clinical practice in England and Wales.

References

1. Balijevic M, Holstein S. Evidence-Based Support for Triplet Therapies in Multiple Myeloma. The ASCO Post 2017.
2. National Institute for Health and Care Excellence. Appraisal consultation document – Daratumumab with bortezomib for previously treated multiple myeloma. Available from: https://www.nice.org.uk/guidance/gid-ta10174/documents/appraisal-consultation-document (Accessed 7 February 2019) 2018.
3. Cello Health Insight. Kyprolis Customer Insight Program. 2018.
4. European Medicines Agency. Public summary of opinion on orphan designation: carfilzomib for the treatment of multiple myeloma. Available from http://www.ema.europa.eu/docs/en_GB/document_library/Orphan_designation/2009/10/WC500005936.pdf (accessed Jan 2018). 2008.
5. Amgen Europe. Kyprolis (carfilzomib) 10 mg, 30 mg and 60 mg powder for solution for infusion. Summary of Product Characteristics. 2018. Available from: http://www.medicines.org.uk/emc/medicine/31222 (Accessed September 2018).
6. Monthly Index of Medical Specialities (MIMS). 2017. Available from: http://www.mims.co.uk/ (Accessed December 2017).
7. Department of Health. Drugs and pharmaceutical electronic market information (eMit). 2018 Available from: http://www.gov.uk/government/publications/drugs-and-pharmaceutical-electronic-market-information-emit. (Accessed January 2018).
8. Durie BGM. Multiple Myeloma. Concise Review of the Disease and Treatment Options. North Holly wood, CA: International Myeloma Foundation; 2011.
9. Multiple Myeloma Research Foundation. Multiple Myeloma Disease Overview, 2012. Norwalk, CT: 2012. Available from: www.themmrf.org/assets/mmrf-disease-overview.pdf (Accessed June 2014).
10. Palumbo A, Anderson K. Multiple myeloma. N Engl J Med 2011;364:1046-60.
11. Durie BG, Moreau P, Sonneveld P. Regional differences in the treatment approaches for relapsed multiple myeloma: An IMF study. J Clin Oncol 2012;30:Abstr 8095.
12. Kumar SK, Therneau TM, Gertz MA, et al. Clinical course of patients with relapsed multiple myeloma. Mayo Clin Proc 2004;79:867-74.
13. Orlowski R. Novel agents for multiple myeloma to overcome resistance in phase III clinical trials. Semin Oncol 2013;40:634-51.
14. Durie BGM, Moreau P, Sonneveld P. Regional differences in the treatment approaches for relapsed multiple myeloma: An IMF study. J Clin Oncol 2012:suppl; abstr 8095.
15. Cancer Research UK. Myeloma incidence by sex and UK region. 2014 Available from: http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/myeloma/incidence#ref-0 (Accessed May 2016).
16. Palumbo A, Mateos MV, Bringhen S, et al. Practical management of adverse events in multiple myeloma: can therapy be attenuated in older patients? Blood Rev 2011;25:181-91.
17. Cancer Research UK. Myeloma incidence by age. 2014. Available from: http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/myeloma/incidence#ref-1. (Accessed September 2015).
18. Independent Cancer Taskforce. Achieving World-Class Cancer Outcomes: A Strategy for England 2015-2020. 2015. Available from: http://www.cancerresearchuk.org/sites/default/files/achieving_world-class_cancer_outcomes_-_a_strategy_for_england_2015-2020.pdf (Accessed June 2016).
19. Amgen data on file. Haematological Malignancy Research Network (HMRN) clinical management and outcomes in multiple myeloma. 2016.
20. Gay F, Palumbo A. Management of disease- and treatment-related complications in patients with multiple myeloma. Med Oncol 2010;27 Suppl 1:S43-52.
21. Jakubowiak A. Novel therapies for relapsed/refractory multiple myeloma: how can we improve on "salvage" therapy? Semin Hematol 2012;49 Suppl 1:S1-2.
22. Jakubowiak A. Novel therapies for relapsed/refractory multiple myeloma: how can we improve on "salvage" therapy? Semin Hema 2012;49.
23. Richardson PG, Sonneveld P, Schuster MW, et al. Bortezomib or high-dose dexamethasone for relapsed multiple myeloma. N Engl J Med 2005;352:2487-98.

24. Martin TG, Panjabi S, Kerr J. Association of treatment induced peripheral neuropathy (TIPN) with treatment patterns and outcomes in patients (pts) with newly diagnosed multiple myeloma (NDMM). Blood 2013;122:21.
25. Molassiotis A, Wilson B, Blair S, et al. Unmet supportive care needs, psychological well-being and quality of life in patients living with multiple myeloma and their partners. Psychooncology 2011;20:88-97.
26. Jordan K, Proskorovsky I, Lewis P, et al. Effect of general symptom level, specific adverse events, treatment patterns, and patient characteristics on health-related quality of life in patients with multiple myeloma: results of a European, multicenter cohort study. Support Care Cancer 2014;22:417-26.
27. Hulin C, Hansen T, Laurenson S, et al. A European study of the emotional and physical impact of relapse on patients with multiple myeloma. Haematologica 2014;99:Abstr P635.
28. Shah JJ, Orlowski RZ. Proteasome inhibitors in the treatment of multiple myeloma. Leukemia 2009;23:1964-79.
29. Orlowski RZ, Kuhn DJ. Proteasome inhibitors in cancer therapy: lessons from the first decade. Clin Cancer Res 2008;14:1649-57.
30. Bennett MK, Kirk CJ. Development of proteasome inhibitors in oncology and autoimmune diseases. Curr Opin Drug Discov Devel 2008;11:616-25.
31. Janssen Cilag Ltd. Velcade (bortezomib) 3.5 mg powder for solution for injection. Summary of Product Characteristics. 2013. Available from: http://www.medicines.org.uk/emc/medicine/17109 (Accessed October 2015).
32. Multiple Myeloma Research Foundation. Patients starting treatment: treatment options. Norwalk, CT: 2014. Available from: http://mmrf.pub30.convio.net/living-with-multiple-myeloma/patients-starting-treatment/treatment-options/ (Accessed May 2016).
33. Moreau P, San Miguel J, Ludwig H, et al. Multiple myeloma: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 2013;24 Suppl 6:vi133-7.
34. National Institute for Health and Care Excellence (NICE). Bortezomib and thalidomide for the first-line treatment of multiple myeloma (TA228). 2011. Available from: http://www.nice.org.uk/guidance/ta228 (Accessed September 2015).
35. Nooka A, Lonial S. Sequential or combination therapy for multiple myeloma. Expert Rev Hematol 2012;5:533-45.
36. National Institute for Health and Care Excellence (NICE). Myeloma: diagnosis and management. February 2016. Available from: http://www.nice.org.uk/guidance/ng35/resources/myeloma-diagnosis-and-management-1837394042821 (Accessed February 2016).
37. Bird JM, Owen RG, D'Sa S, et al. Guidelines for the diagnosis and management of multiple myeloma. 2014. Available from: http://www.bcshguidelines.com/documents/MYELOMA_GUIDELINE_Feb_2014_for_BCSH.pdf (Accessed September 2015).
38. NHS England. Multiple Myeloma National Chemotherapy Algorithm (draft for public consultation). 2015. Available from: https://www.engage.england.nhs.uk/consultation/specialised-services-consultation/user_uploads/chemothrpy-algrthms-mltpl-myeloma.pdf. (Accessed September 2015).
39. Durand A, Rtveladze K, Pritchard C, et al. The clinical and cost-effectiveness of panobinostat for treating multiple myeloma in people received at least one prior therapy. Single Technology Appraisal NIHR HTA Programme, Optimity Advisors and Peninsula Technology Assessment Group. 2015. Available from: http://www.nice.org.uk/guidance/indevelopment/gid-tag477/documents (Accessed October 2015).
40. Yong K, Delforge M, Driessen C, et al. Multiple myeloma: patient outcomes in real-world practice. Br J Haematol 2016;175:252-264.
41. National Institute for Health and Care Excellence (NICE). Lenalidomide for the treatment of multiple myeloma in people who have received one prior therapy with bortezomib (part rev TA171) [ID667]. Appraisal Consultation 3. Committee Papers. Available from: https://www.nice.org.uk/guidance/GID-TAG452/documents/committee-papers (Accessed 25 November 2016).
42. National Institute for Health and Care Excellence. ID974 Appraisal Consultation Document. 2018.

43. Offidani M, Corvatta L, Gentili S. Triplet vs. doublet drug regimens for managing multiple myeloma. Expert opinion on pharmacotherapy 2018;19:137-149.
44. Stewart AK, Rajkumar SV, Dimopoulos MA, et al. Carfilzomib, lenalidomide, and dexamethasone for relapsed multiple myeloma. N Engl J Med 2015;372:142-52.
45. Stewart AK, Dimopoulos MA, Masszi T, et al. Health-Related Quality of Life Results From the Open-Label, Randomized, Phase III ASPIRE Trial Evaluating Carfilzomib, Lenalidomide, and Dexamethasone Versus Lenalidomide and Dexamethasone in Patients With Relapsed Multiple Myeloma. J Clin Oncol 2016.
46. Siegel DS, Dimopoulos MA, Ludwig H, et al. Improvement in Overall Survival With Carfilzomib, Lenalidomide, and Dexamethasone in Patients With Relapsed or Refractory Multiple Myeloma. J Clin Oncol 2018:JCO2017765032.
47. Onyx. PX-171-009-A1 (ASPIRE) Clinical Study Report. 2014. (Data cutoff date 16-June 2014).
48. Stewart AK, Rajkumar SV, Dimopoulos MA, et al. Carfilzomib, lenalidomide, and dexamethasone for relapsed multiple myeloma (Supplementary material: protocol and statistical analysis plan). N Engl J Med 2015;372:142-52.
49. Rajkumar SV, Harousseau JL, Durie B, et al. Consensus recommendations for the uniform reporting of clinical trials: report of the International Myeloma Workshop Consensus Panel 1. Blood 2011;117:4691-5.
50. Stewart AK, Rajkumar SV, Dimopoulos MA, et al. Carfilzomib, lenalidomide, and dexamethasone for relapsed multiple myeloma (Supplementary appendix). N Engl J Med 2015;372:142-52.
51. Weber D, Chen C, Niesvizky R, et al. Lenalidomide plus dexamethasone for relapsed multiple myeloma in North America. N Engl J Med 2007;357:2133-42.
52. Center for Reviews and Dissemination (CRD). CRD's guidance for undertaking reviews in health care. 2008. Available from: https://www.york.ac.uk/media/crd/Systematic_Reviews.pdf (Accessed January 2018).
53. Amgen. Company evidence submission to NICE. Carfilzomib for treating multiple myeloma in people who have received at least one prior therapy {ID934]. 12 July 2016. 2016.
54. Amgen. 20130395 (Onyx Study No. PX-171-009) ASPIRE Clinical Study Report. 2017. (Data cutoff date 28-April 2017). 2017.
55. Amgen data on file. ASPIRE time to next treatment analysis (final OS data cut-off). 2017.
56. Cocks K, King M, Velikova G. Evidence based guidelines for determination of sample size and interpretation of the European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30. J Clin Oncol 2011;29:89-96.
57. Delforge M, Dhawan R, Robinson D, et al. Health-related quality of life in elderly, newly diagnosed multiple myeloma patients treated with VMP vs. MP: results from the VISTA trial. Eur J Haematol 2012;89:16-27.
58. Kvam A, Fayers P, Wisloff F. What changes in health-related quality of life matter to multiple myeloma patients? A prospective study. Eur J Haematol 2010;84:345-53.
59. Kvam A, Fayers P, Wisloff F. Responsive and minimal important score differences in quality-of-life questionnaires: a comparison of the EORTC QLQ-C30 cancer specific questionnaire to the generic utility questionnaires EQ-5D and 15D in patients with multiple myeloma. Eur J Haematol. 2011;87:330-7.
60. National Institute for Health and Care Excellence. Carfilzomib for previously treated multiple myeloma. Technology Appraisal Guidance TA457, 2017.
61. Latimer N. NICE DSU Technical Support Document 14: Undertaking survival analysis for economic evaluations alongside clinical trials - extrapolation with patient-level data., 2011.
62. Amgen data on file. 2018.
63. Signorovitch JE, Wu EQ, Yu AP, et al. Comparative effectiveness without head-to-head trials: a method for matching-adjusted indirect comparisons applied to psoriasis treatment with adalimumab or etanercept. Pharmacoeconomics 2010;28:935-45.
64. Phillippo DM, Ades AE, Dias S, et al. NICE DSU technical support document 18: Methods for population-adjusted indirect. Comparisons in submissions to nice. 2016.
65. NICE. Daratumumab in combination with bortezomib for treating relapsed or refractory multiple myeloma [ID974]. 2018.
66. Guyot P, Ades AE, Ouwens MJ, et al. Enhanced secondary analysis of survival data: reconstructing the data from published Kaplan-Meier survival curves. BMC Med Res Methodol 2012;12:9.

67. Mateos Mv, Sonneveld P, Hungria V. Efficacy and Safety of Daratumumab, Bortezomib, and Dexamethasone (D-Vd) Versus Bortezomib and Dexamethasone (Vd) in First Relapse Patients With Multiple Myeloma (MM): Update of CASTOR. ASH 2018.
68. Jakubowiak A. Management strategies for relapsed/refractory multiple myeloma: current clinical perspectives. Semin Hema 2012;49 (Suppl 1):S16-S32.
69. European Medicines Agency. Farydak: EPAR public assessment report. 2015. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/003725/WC500193300.pdf (Accessed February 2016).
70. European Medicines Agency. Velcade: EPAR public assessment report. 2004. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Scientific_Discussion/human/000539/WC500048467.pdf (Accessed February 2016).
71. European Medicines Agency. Revlimid: EPAR public assessment report. 2007. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Scientific_Discussion/human/000717/WC500056022.pdf (Accessed February 2016).
72. National Institute for Health and Care Excellence (NICE). Pertuzumab (with trastuzumab and docetaxel) for HER2 positive metastatic breast cancer [ID523]. Committee meeting 4 slides. 8 May 2017.
73. National Institute for Health and Care Excellence. Multiple myeloma - lenalidomide (post bortezomib) (part rev TA171) [ID667]: Committee Papers (Appraisal consultation: 3), 2014.
74. National institute for Health and Care Excellence. Panobinostat for treating multiple myeloma after at least 2 previous treatments. Technology appraisal guidance TA380. Committee Papers: Appraisal Consultation, 2015.
75. National institute for Health and Care Excellence. Lenalidomide for the treatment of multiple myeloma in people who have received at least one prior therapy. Technology appraisal guidance TA171, 2009.
76. National institute for Health and Care Excellence. Pomalidomide for treating relapsed and refractory multiple myeloma previously treated with both lenalidomide and bortezomib. Technology Appraisal Guidance TA388. Comittee Papers., 2015.
77. National institute for Health and Care Excellence. Bortezomib and thalidomide for the first-line treatment of multiple myeloma Technology appraisal guidance TA228, 2011.
78. National Institute for Health and Care Excellence (NICE). Guide to the methods of technology appraisal. , 2013.
79. National Institute for Health and Care Excellence (NICE). Lenalidomide plus dexamethasone for multiple myeloma after 1 treatment with bortezomib. Technology appraisal guidance TA586, 2019.
80. Rajkumar S, Jacobus S, Callander NS, et al. Lenalidomide plus high-dose dexamethasone versus lenalidomide plus low-dose dexamethasone as initial therapy for newly diagnosed multiple myeloma: an open-label randomised controlled trial. Lancet Oncol 2010;11:29-37.
81. National Institute for Health and Care Excellence. Daratumumab with bortezomib for treating relapsed or refractory multiple myeloma [ID974] Committee Papers (ACD), 2018.
82. National Institute for Health and Care Excellence. Daratumumab with bortezomib for treating relapsed or refractory multiple myeloma [ID974] Final Appraisal Determination, 2019.
83. Davis S. Assessing technologies that are not cost-effective at a zero price., 2014.
84. Spencer A, Hungria V, Mateos MV, et al. Daratumumab, Bortezomib, and Dexamethasone (DVd) Verus Bortezomib and Dexamethasone (Vd) in Relapsed or Refractory Multiple Myeloma (RRMM): Updated Efficacy and Safety Analysis of CASTOR. 59th American Society of Hematology (ASH) Annual Meeting and Exposition. Atlanta: United States of America, 2017.
85. Majer I, Castaigne J, Palmer S, et al. Modeling Covariate-Adjusted Survival for Economic Evaluations in Oncology. Pharmacoeconomics 2019;5:727-737.
86. Gulbrandsen N, Hjermstad MJ, Wisloff F, et al. Interpretation of quality of life scores in multiple myeloma by comparison with a reference population and assessment of the clinical importance of score differences. Eur J Haematol 2004;72:172-80.
87. Osborne TR, Ramsenthaler C, Siegert RJ, et al. What issues matter most to people with multiple myeloma and how well are we measuring them? A systematic review of quality of life tools. Eur J Haematol 2012;89:437-57.
88. Jakubowiak A. Management strategies for relapsed/refractory multiple myeloma: current clinical perspectives. Semin Hematol 2012;49 Suppl 1:S16-32.

89. Kharroubi SA, Edlin R, Meads D, et al. Use of Bayesian Markov chain Monte Carlo methods to estimate EQ-5D utility scores from EORTC QLQ data in myeloma for use in cost-effectiveness analysis. Med Decis Making 2015;35:351-60.
90. Proskorovsky I, Lewis P, Williams CD, et al. Mapping EORTC QLQ-C30 and QLQ-MY20 to EQ-5D in patients with multiple myeloma. Health Qual Life Outcomes 2014;12:35.
91. Ashaye AO, Altincatal A, Bender RH, et al. Estimating EORTC-8D health state utility values from EORTC Qlq-C30 scores in relapsed multiple myeloma. Value Health 2015;18:A468.
92. Acaster S, Gaugris S, Velikova G, et al. Impact of the treatment-free interval on health-related quality of life in patients with multiple myeloma: a UK cross-sectional survey. Support Care Cancer 2013;21:599-607.
93. Van Agthoven M, Segeren CM, Buijt I, et al. A cost-utility analysis comparing intensive chemotherapy alone to intensive chemotherapy followed by myeloablative chemotherapy with autologous stem-cell rescue in newly diagnosed patients with stage II/III multiple myeloma; a prospective randomised phase III study. Eur J Cancer 2004;40:1159-69.
94. National Institute for Health and Care Excellence. Ocriplasmin for treating vitreomacular traction. Technology appraisal guidance [TA297] committee papers, 2013.
95. National Institute for Health and Care Excellence. Daratumumab monotherapy for treating relapsed and refractory multiple myeloma. Technology appraisal guidance [TA510] committee papers, 2018.
96. National Institute for Health and Care Excellence (NICE). Carfilzomib for treated multiple myeloma in people who have received at least one prior therapy (ID 934). Evidence Review Group report. Available from: https://www.nice.org.uk/guidance/GID-TA10005/documents/committee-papers (Accessed November 2015).
97. Kind P, Hardman G, Macran S. UK Population Norms for EQ-5D. The University of York Centre for Health Economics. , 1999.
98. Department of Health. Drugs and pharmaceutical electronic market information (eMit). 2019.
99. Monthly Index of Medical Specialities (MIMS). 2019.
100. National Institute for Health and Care Excellence (NICE). Lenalidomide plus dexamethasone for previously untreated multiple myeloma. Technology appraisal guidance TA587, 2019.
101. Department of Health. NHS Reference costs 2017-18, 2018.
102. Curtis L. Unit costs of health and social care. Personal Social Services Research Unit 2017 (PSSRU). 2018.
103. Sacco JJ, Botten J, Macbeth F, et al. The average body surface area of adult cancer patients in the UK: a multicentre retrospective study. PLoS One 2010;5:e8933.
104. Celgene Europe Ltd. Revlimid (lenalidomide) 2.5 mg hard capsules. Summary of Product Characteristics., 2018.
105. National Institute for Health and Care Excellence (NICE). Single technology appraisal (STA) ID663: Panobinostat for treating multiple myeloma in people who have received at least one prior therapy. Appraisal Consultation Document. 2015. Available from: https://www.nice.org.uk/guidance/GID-TAG477/documents/multiple-myeloma-panobinostat-post-1-prior-therapy-id663-appraisal-consultation-document2 (Accessed November 2015).
106. Amgen data on file. Multiple myeloma medical resource use study. 2015.
107. Gonzalez-McQuire S, Yong K, Flinois A, et al. Retrospective Chart Review Study to Evaluate the Cost of Care of Patients with Symptomatic Multiple Myeloma in the UK. Poster presented at the ISPOR 21st Annual Meeting; May 21-25, 2016; Washington DC, United States. 2016.
108. Georghiou T, Bardsley M. Exploring the cost of care at the end of life., 2015.
109. National Institute for Health and Care Excellence. Carfilzomib for previously treated multiple myeloma (TA457). Technology appraisal guidance 29 July 2017. Available from: https://www.nice.org.uk/guidance/ta457/resources/carfilzomib-for-previously-treated-multiple-myeloma-pdf-82604850129349 (Accessed December 2017). 2017.
110. Cancer Research UK. Myeloma survival statistics, 2014.
111. National Institute for Health and Care Excellence (NICE). Daratumumab with bortezomib and dexamethasone for previously treated multiple myeloma. Technology appraisal guidance TA573, 2019.

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]

Clarification questions

February 2020

File name	Version	Contains confidential information	Date
ID1493 carfilzomib clarification letter to PM	2.0	Yes	6th April 2020

Notes for company

Highlighting in the template

Square brackets and grey highlighting are used in this template to indicate text that should be replaced with your own text or deleted. These are set up as form fields, so to replace the prompt text in [grey highlighting] with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

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Section A: Clarification on effectiveness data

In their submission, the company proposes that carfilzomib (C) in combination with lenalidomide (R) and dexamethasone (d) is most appropriately placed as a second line (2L) treatment after prior bortezomib in the management of multiple myeloma (MM). The final scope for this appraisal issued by the National Institute for Health and Care Excellence (NICE) specified the population of interest to be adults with MM, who have had at least 1 prior therapy. Based on the company submission (CS), NICE pathways, and feedback from the Evidence Review Group's (ERG's) clinical experts, the ERG considers the population proposed for consideration in this appraisal to be adults with MM who have received only 1 prior bortezomib-based treatment.

Population

A1. Priority question: Based on current NICE guidance for bortezomib-based regimens as first line (1L) treatments, the ERG considers that people receiving bortezomib-based therapy at 1L would not have received lenalidomide as part of that regimen. The baseline characteristics provided in Appendix E (Table 19, page 41) for the *post hoc* subgroup from which evidence is derived on clinical effectiveness of CRd compared with Rd indicate that:

a. **not all participants in the subgroup received bortezomib in their last regimen (proportion of people reported to receive bortezomib in their last regimen: [redacted] in CRd versus [redacted] in Rd);**

b. **a percentage of people received lenalidomide as part of their last regimen (proportion of people reported to receive lenalidomide in their last regimen: [redacted] in CRd versus [redacted] in Rd).**

Please clarify whether the ERG's interpretation of the baseline characteristics is correct. If so, in reference to the population outlined in A1, the ERG considers that the subgroup data presented by the company do not reflect the subgroup of

people who would most likely receive CRd at 2L after prior bortezomib. If the ERG's interpretation is correct, please:

c. **generate a new subgroup from the ASPIRE intention-to-treat (ITT) population comprising those who received only 1 prior regimen that was based on bortezomib and did not include lenalidomide (CRd 2L after prior bortezomib);**

d. **provide baseline characteristics for the subgroup by treatment arm as reported in Appendix E, Table 19. Please provide both the mean with accompanying standard deviation (SD) and the median with accompanying minimum and maximum values, where appropriate for individual baseline characteristics;**

e. **re-analyse data for clinical outcomes as described in B.2.7.2 (page 47) of the company submission (CS) based on the new subgroup.**

The ERG considers it important to carry out the analyses to ensure that the data and estimates of relative treatment effect are based on the subgroup that most closely reflects the patient population likely to receive CRd at 2L.

The ERG are correct in their interpretation that a small proportion of patients received prior lenalidomide in the post-hoc subgroup used to inform the submission and the decision problem. However, it is important to highlight that this subgroup was defined by two variables (ie. no. prior regimen = 1 and prior bortezomib =1) which explicitly captures the population under consideration in the decision problem – that is, patients who have received 1-prior treatment with bortezomib. The appropriateness of this population to inform the decision problem is confirmed in the baseline characteristics reported in Appendix E (Table 19, page 41) which state that [redacted] patients had both 1 prior line of treatment and were previously treated with bortezomib. A different variable is used in the CSR to define the specific 'last regimen' received which is the source of the discrepancy highlighted by the ERG.

We would maintain that the definitions used in our submission to create the post-hoc subgroup remain both relevant to the specific positioning of CRd and the similar restricted population in which the primary comparator is reimbursed. Furthermore, it is plausible in the UK pathway that a minority of patients could be exposed to prior lenalidomide whilst meeting the criteria defined in our subgroup – for example, the combination of bortezomib, lenalidomide and dexamethasone (VRd) was approved by the EMA in Q2 2019 for newly diagnosed multiple myeloma. At an advisory board meeting conducted to inform this appraisal all clinicians indicated this would be an attractive regimen to offer patients if it was available locally. Furthermore, there is an ongoing UK clinical trial, OPTIMUM, which is investigating a quintuplet regimen, which includes bortezomib and lenalidomide, in

patients with newly diagnosed high risk disease. If successful, this regimen may be used more extensively. Finally, data from the HMRN report available to us from 2016 indicated that about [redacted] of patients that received first-line therapy for MM received lenalidomide.[a]

Therefore, we envisage there being a small proportion of patients receiving bortezomib and lenalidomide in the first line setting.

Nevertheless, we have generated the requested subgroup and report the clinical and economic outcomes in the response to the following questions.

A total of 140 patients (CRd 74, Rd 66) were included in the 2L prior bortezomib and no prior lenalidomide (2L/prior bortezomib/no prior lenalidomide) subgroup in contrast to the 166 patients (CRd 93, Rd 74) that were included in the 2L prior bortezomib (2L/prior bortezomib) subgroup. The treatment HRs based on the Cox proportional hazards model before and after adjustment for covariates are provided Table 1. As can be seen in reference to Table 17 of the company submission, the unadjusted and covariate-adjusted HRs remain largely consistent with our original base case subgroup population.

Table 1: PFS and OS results within ERG requested post hoc subgroup – 5 December 2017 data cut (ASPIRE)

Population	PFS (determined by investigator) HR (95% CI)		OS HR (95% CI)	
	Unadjusted	Covariate-adjusted[a]	Unadjusted	Covariate-adjusted[a]
2L/prior bortezomib/no prior lenalidomide	[redacted]	[redacted]	[redacted]	[redacted]

References:, ASPIRE clinical study report (5 December 2017 data cut-off date)[1] and Amgen data on file, 2018[2]
[a] Estimated using a stepwise selection Cox proportional hazards model based on clinician-identified covariates
CI, confidence interval

An overview of results for the Cox proportional hazard model are included in Table 2. More detailed results such as median PFS/OS and IPW-adjusted HRs are described in Amgen's answer to questions A3 & A4.

Table 2: Detailed results for the Cox proportional hazards model within ERG requested post hoc subgroup – 5 December 2017 data cut (ASPIRE)

Covariate	CRd vs Rd, 2L/prior bortezomib/no prior lenalidomide	
	PFS HR (95% CI)	OS HR (95% CI)
Treatment (CRd vs Rd)	[redacted]	[redacted]
Prior stem cell transplantation (yes vs no)	[redacted]	[redacted]
Age (≥65 vs <65)	[redacted]	[redacted]
ECOG status (1-2 vs 0)	[redacted]	[redacted]
Creatinine clearance (≥50 - <80 vs other)	[redacted]	[redacted]
Creatinine clearance (≥80 vs other)	[redacted]	[redacted]
Time from diagnosis	[redacted]	[redacted]
Time from last relapse	[redacted]	[redacted]
ISS stage (II-III vs I)	[redacted]	[redacted]
B2-microglobulin (≥3.5 vs <3.5 mg/L)	[redacted]	[redacted]

[a] For 128 of the 1,580 HMRN patients that received first-line therapy, treatment was lenalidomide-based

Covariate	CRd vs Rd, 2L/prior bortezomib/no prior lenalidomide	
	PFS HR (95% CI)	OS HR (95% CI)
Refractory to last prior treatment (yes vs no)	[redacted]	[redacted]
CI, confidence interval; CRd, carfilzomib, lenalidomide/dexamethasone; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; ISS, International Staging System; PFS, progression-free survival; OS, overall survival; Rd, lenalidomide/dexamethasone.		

A summary of the baseline characteristics have also been presented for the ERG requested subgroup in Table 3, below. Overall, there were differences in important prognostic/predictive factors across the treatment arms, e.g., more CRd patients were refractory to prior bortezomib and had no prior SCT while more Rd patients were older. Therefore, statistical adjustment for the imbalances was considered to be warranted.

Table 3: Baseline characteristics: Patients who have received one prior therapy with bortezomib and have not received prior lenalidomide (ASPIRE)

Characteristic	Treatment Arm	
	Rd (N = 66)	CRd (N = 74)
	Summary n (%) or value as Indicated	Summary n (%) or value as Indicated
Age group, n (%)		
<65	[redacted]	[redacted]
65-74	[redacted]	[redacted]
≥ 75	[redacted]	[redacted]
ECOG performance status, n (%)		
0	[redacted]	[redacted]
1	[redacted]	[redacted]
2	[redacted]	[redacted]
Baseline creatinine clearance, n (%)		
30-<50 mL/min	[redacted]	[redacted]
50-<80 mL/min	[redacted]	[redacted]
≥ 80 mL/min	[redacted]	[redacted]
Time (months) since initial diagnosis		
Mean (SD)	[redacted]	[redacted]
Time (months) since last relapse		
Mean (SD)	[redacted]	[redacted]
Baseline ISS Stage, n (%)		
Stage I	[redacted]	[redacted]
Stage II	[redacted]	[redacted]
Stage III	[redacted]	[redacted]
Baseline β2 microglobulin, n (%)		
<3.5 mg/L	[redacted]	[redacted]
≥ 3.5mg/L	[redacted]	[redacted]
Number of prior regimens, n (%)		
1	[redacted]	[redacted]
Prior SCT, n (%)		
Yes	[redacted]	[redacted]
No	[redacted]	[redacted]
Prior therapy, n (%)		
Bortezomib	[redacted]	[redacted]
Lenalidomide	[redacted]	[redacted]
Refractory to last prior therapy, n (%)		
Bortezomib	[redacted]	[redacted]

Characteristic	Treatment Arm	
	Rd (N = 66)	CRd (N = 74)
	Summary n (%) or value as Indicated	Summary n (%) or value as Indicated
References: Amgen data on file, 2016[3]		
CRd, carfilzomib/lenalidomide/dexamethasone; ECOG, Eastern Cooperative Oncology Group; ISS, International Staging System; Rd, lenalidomide/dexamethasone; SCT, stem cell transplant; SD, standard deviation		

A2. Please clarify the discrepancy in the number of people reported to form the 2L prior bortezomib subgroup based on the ASPIRE RCT between the CS for NICE technology appraisal 457 (TA457) and the part review that is the focus of this appraisal:

a. TA457: CRd = 74, Rd = 66;

b. Part review: CRd = 93, Rd = 73.

The discrepancy in the number of patients in each subgroup is explained by the precise definitions of the population – in TA457, an additional variable to remove lenalidomide treatment was added (as requested in Q A1 by the ERG). However, in order to maximise the available data and given the rationale provided above, this additional variable was not utilised in the current part-review.

Progression-free and overall survival in post hoc subgroup

A3. Priority question: Based on the company's response to question A1, for progression-free survival (PFS) for the subgroup preferred by the ERG as detailed in question A1, please provide the items listed below for results based on assessment by the Independent Review Committee and Investigator assessment at the "primary overall survival (OS) analysis" cut-off (5 December 2017):

a. **Number of events in each treatment arm (broken down by progressed and died without disease progression);**

b. **Median PFS in each treatment arm, with accompanying 95% confidence interval (CI);**

c. **Mean PFS in each treatment arm, with accompanying SD;**

d. **Hazard ratio with accompanying 95% CI and p value for both the unadjusted (without adjustment for stratification factors) and adjusted estimate;**

e. **Median and mean follow-up for PFS, with accompanying measure of uncertainty;**

f. **Unadjusted Kaplan-Meier (KM) plot;**

g. **Adjusted KM plot.**

In ASPIRE, the primary outcome was PFS assessed by the independent review committee (IRC) and this outcome was met at the time of the interim analysis (data cut-off 14 June 2014), hence no further updates of the primary outcome are available. Therefore, to address the ERGs question, we present both unadjusted and IPW-adjusted PFS for the IRC June 2014 cut-off and the investigator assessed PFS December 2017 data cut-off.

The data requested by the ERG is presented below for both the original subgroup in our submission dossier (2L/prior bortezomib) and the new subgroup requested by the ERG (2L/prior bortezomib/no prior lenalidomide).

The unadjusted PFS data as assessed by investigators at the December 2017 data cut-off is summarised in Table 4 and the unadjusted KM curves for the 2L/prior bortezomib/no prior lenalidomide is presented in Figure 1, below.

Table 4: Data for the unadjusted PFS as determined by investigators (data cut-off December 2017)

	2L/prior bortezomib/no prior lenalidomide		2L/prior bortezomib	
	CRd (N=74)	*Rd (N=66)*	*CRd (N=93)*	*Rd (N=73)*
Total number of events, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Progression	[redacted]	[redacted]	[redacted]	[redacted]
Death	[redacted]	[redacted]	[redacted]	[redacted]
Median PFS (95%CI)	[redacted]	[redacted]	[redacted]	[redacted]
Restricted mean PFS time (95%CI) [SE]	[redacted]	[redacted]	[redacted]	[redacted]
Median follow-up (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
Mean follow-up (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
HR; CRd vs Rd (95% CI) Unadjusted	[redacted]		[redacted]	
HR; CRd vs Rd (95% CI) adjusted for stratification variables	[redacted]		[redacted]	

The following stratification factors were used in ASPIRE: β2-microglobulin level (<2.5 mg per liter vs. ≥2.5 mg per liter), previous therapy with bortezomib (no vs. yes), and previous therapy with lenalidomide (no vs. yes).
The truncation time for the restricted mean survival time was defined as the maximum observed event/censored time in the arm with the shortest follow-up.

Figure 1: Unadjusted KM for the investigator assessed PFS, 2L/prior bortezomib/no prior lenalidomide (data cut-off: December 2017)

The IPW-adjusted investigator assessed PFS for the December 2017 data cut are presented in Table 5 and Figure 2.

Table 5: Data for the IPW-adjusted PFS as determined by investigators (data cut-off December 2017)

	2L/prior bortezomib/no prior lenalidomide		2L/prior bortezomib	
	CRd (N=68)	Rd (N=69)	CRd (N=82)	Rd (N=81)
Total Events	[redacted]	[redacted]	[redacted]	[redacted]
Median PFS (95%CI)	[redacted]	[redacted]	[redacted]	[redacted]
Median follow-up (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
HR; CRd vs Rd (95% CI) IPW-adjusted (stepwise selection within Cox model)	[redacted]		[redacted]	
HR; CRd vs Rd (95% CI) IPW-adjusted (stepwise selection within logit model) *[QA10 response]*	[redacted]		[redacted]	

Clarification questions

Figure 2: IPW-adjusted KM for the investigator assessed PFS, 2L/prior bortezomib/no prior lenalidomide (data cut-off: December 2017)

For completeness, the unadjusted and adjusted IRC assessed PFS results have also been reported with data available from the June 2014 data cut-off. Table 6 and Table 7 summarise the unadjusted and adjusted IRC PFS, respectively, and

Figure **3** and

Figure **4** report the KM plots for the unadjusted and adjusted PFS outputs in the ERG requested subgroup.

Table 6: Data for the unadjusted PFS as determined by the IRC (data cut-off June 2014)

	2L/prior bortezomib/no prior lenalidomide		**2L/prior bortezomib**	
	CRd (N=74)	***Rd (N=66)***	***CRd (N=93)***	***Rd (N=73)***
Total number of events, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Progression	[redacted]	[redacted]	[redacted]	[redacted]
Death	[redacted]	[redacted]	[redacted]	[redacted]
Median PFS (95%CI)	[redacted]	[redacted]	[redacted]	[redacted]
Restricted mean PFS time (95%CI) [SE]	[redacted]	[redacted]	[redacted]	[redacted]
Median follow-up (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
Mean follow-up (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
HR; CRd vs Rd (95% CI) Unadjusted	[redacted]		[redacted]	
HR; CRd vs Rd (95% CI) adjusted for stratification variables	[redacted]		[redacted]	

The following stratification factors were used in ASPIRE: β2-microglobulin level (<2.5 mg per liter vs. ≥2.5 mg per liter), previous therapy with bortezomib (no vs. yes), and previous therapy with lenalidomide (no vs. yes).

The truncation time for the restricted mean survival time was defined as the maximum observed event/censored time in the arm with the shortest follow-up.

Figure 3: Unadjusted KM for the IRC assessed PFS, 2L/prior bortezomib/no prior lenalidomide (data cut-off June 2014)

Table 7: Data for the IPW-adjusted PFS as determined by the IRC (data cut-off June 2014)

	2L/prior bortezomib/no prior lenalidomide		2L/prior bortezomib	
	CRd (N=69)	Rd (N=68)	CRd (N=82)	Rd (N=81)
Total Events				
Median PFS (95%CI)				
Median follow-up (95% CI)				
HR; CRd vs Rd (95% CI) IPW-adjusted (stepwise selection within Cox model)				

Figure 4: IPW adjusted KM for the IRC assessed PFS, 2L/prior bortezomib/no prior lenalidomide (data cut-off June 2014)

A4. Priority question: Based on the company's response to question A1, for OS for the subgroup preferred by the ERG as detailed in question A1, please provide the items listed below for results based on the "updated analysis" cut-off (5 December 2017):

a. **Number of events in each treatment arm;**

b. **Median OS in each treatment arm, with accompanying 95% confidence interval (CI);**

c. **Mean OS in each treatment arm, with accompanying SD;**

d. **Hazard ratio with accompanying 95% CI and p value for both the unadjusted (without adjustment for stratification factors) and adjusted estimate;**

e. **Median and mean follow-up for OS, with accompanying measure of uncertainty;**

f. **Unadjusted KM plot;**

g. **Adjusted KM plot.**

The data requested by the ERG is presented below for both the original subgroup in the company submission dossier (2L/prior bortezomib) and the new subgroup (2L/prior bortezomib/no prior lenalidomide).

Unadjusted OS data are summarised in Table 8 and unadjusted KM for the 2L/prior bortezomib/no prior lenalidomide subgroup are presented in Figure 5. The IPW-adjusted OS for the December 2017 data cut are presented in Table 9 and Figure 6, respectively.

Table 8: Data for the unadjusted OS (December 2017)

	2L/prior bortezomib/no prior lenalidomide		2L/prior bortezomib	
	CRd (N=74)	*Rd (N=66)*	*CRd (N=93)*	*Rd (N=73)*
Total number of events, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Median OS (95%CI)	[redacted]	[redacted]	[redacted]	[redacted]
Restricted mean OS time (95%CI) [SE]	[redacted]	[redacted]	[redacted]	[redacted]
Median follow-up (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
Mean follow-up (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
HR; CRd vs Rd (95% CI) Unadjusted	[redacted]		[redacted]	
HR; CRd vs Rd (95% CI) adjusted for stratification variables	[redacted]		[redacted]	

The following stratification factors were used in ASPIRE: β2-microglobulin level (<2.5 mg per liter vs. ≥2.5 mg per liter), previous therapy with bortezomib (no vs. yes), and previous therapy with lenalidomide (no vs. yes).
The truncation time for the restricted mean survival time was defined as the maximum observed event/censored time in the arm with the shortest follow-up.

Figure 5: Unadjusted KM for OS, 2L/prior bortezomib/no prior lenalidomide (data cut-off December 2017)

[redacted]

Table 9: IPW-adjusted data for OS (data cut-off December 2017)

	2L/prior bortezomib/no prior lenalidomide		2L/prior bortezomib	
	CRd (N=69)	*Rd (N=68)*	*CRd (N=82)*	*Rd (N=81)*
Total Events	[redacted]	[redacted]	[redacted]	[redacted]
Median OS (95%CI)	[redacted]	[redacted]	[redacted]	[redacted]
Median follow-up (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
HR; CRd vs Rd (95% CI) IPW-adjusted (stepwise selection within Cox model)	[redacted]		[redacted]	
HR; CRd vs Rd (95% CI) IPW-adjusted (stepwise selection within logit model) *[QA10 response]*	[redacted]		[redacted]	

Figure 6: IPW-adjusted KM for OS, 2L/prior bortezomib/no prior lenalidomide (data cut-off December 2017)

[redacted]

A5. In Table 17 of the CS (page 49), please clarify why the reported hazard ratios (HRs) for the "unadjusted" results have been adjusted for stratification variables.

Apologies for the confusion here – the use of the term 'unadjusted' was used to clearly distinguish from the HRs estimated for the ITT population based on the ASPIRE protocol versus a fully covariate-adjusted approach used to inform the relevant post-hoc subgroup analyses. For completeness, both unadjusted and stratification-adjusted HRs for both PFS and OS outcomes have been reported in our response to questions above.

A6. For the adjusted PFS of CRd versus Rd in those receiving treatment 2L after bortezomib, the ERG notes that different HRs and accompanying 95% CIs are presented in Table 17 (page 49; HR [redacted]) and Figure 9 (page 50; HR [redacted]) of the CS and in Figure 32 of Appendix M (HR [redacted]). Please confirm the correct HR and 95% CI for adjusted PFS.

The difference in HRs presented in the submission dossier for the PFS endpoint is a result of the first HR ([redacted]) reflecting the overall treatment effect derived from a multiple Cox regression model, whereas as the second HR ([redacted]) is derived by applying a Cox regression model to the IPW-adjusted patient-level data (see Section B.2.7.2 of CS). Please note that none of these HRs is directly used to inform the economic model; instead, a jointly fitted parametric model is fitted to the IPW-adjusted data.

A7. For the adjusted OS of CRd versus Rd in those receiving treatment 2L after bortezomib, the ERG notes that different HRs and accompanying 95% CIs are reported in the evidence submission summary ([redacted] in text versus [redacted] in Table 5), in the CS ([redacted] in Table 17 versus [redacted] in Figure 10), and in the appendices (Appendix M, Figure 24; HR [redacted]). Please confirm the correct HR and 95% CI for adjusted OS.

As above – however, there is unfortunately a typo in the evidence submission. The HR for OS using IPW-adjustment is HR [redacted] (not HR [redacted]). Please note that only the IPW adjusted HR is used in the economic model.

A8. In Figures 9 and 10 of the CS, please clarify why the number of events reported in the analysis of OS is greater than the number of PFS events for the cut-off (5 December 2017). If reported event rates are incorrect, please provide the correct number of events in each treatment group for each outcome.

The reported number of events are correct – the difference here is due to the fact that for OS the number of censored patients were lower than that for PFS. Please note that PFS captures progression and pre-progression death events whereas OS captures death events (either before or after progression) – therefore, it can transpire that some

patients are censored for PFS but are followed for OS and have documented death event.

Inverse probability weighting analysis and regression analysis

A9. Priority question: In the descriptions of the selection of variables for adjustment of effect estimate, 2 different approaches and thresholds are described:

a. **P values applied for addition or removal of a variable (prespecified subgroup analysis; page 44 of the CS);**

b. **Optimisation of the AIC for the model fit (post hoc subgroup analysis; page 47 of the CS).**

Please clarify why 2 different approaches were followed for variable selection.

The approaches used for variable selection differ as one relates to the pre-specified analyses that was defined in the ASPIRE clinical trial study protocol and statistical analysis plan whilst the other relates to the specific analysis of the relevant post-hoc subgroup used to inform the decision problem.

With respect to the latter approach (ie. optimisation based on the AIC model fit), this methodology was utilised based on feedback received from Health Economics experts during TA457, and is consistent with the approach previously accepted by NICE and the ERG during the original appraisal.

A10. Priority question: Based on the CS, the ERG understands that the covariates applied in the inverse probability weighted (IPW) analyses were selected after a stepwise regression in a Cox model, and those evaluated in the Cox model were those highlighted as being important by clinical experts. The ERG considers that it would be more appropriate to apply the selection procedure for the covariates listed in the CS (Section B.2.6.2, page 48) for the logistic regression within the IPW analysis, independent from a Cox model. The ERG's preferred analysis is the logistic regression.

a. **Please present adjusted PFS and OS for the population of interest in this appraisal.**

b. **Please provide a list of covariates included in the adjusted analysis, together with the estimate of comparative treatment effectiveness for CRd**

versus Rd after adjustment for individual covariates and an overall estimate of comparative treatment effectiveness.

c. **Please provide coefficients and p values for treatment-covariate interaction at each step of the variable selection procedure and statistics for overall model fit (AIC for logistic regression).**

d. **Please provide the R code for the analysis.**

During the clarification call with the ERG and NICE on the 10th of February, it was discussed that in the response to the ERG's questions, Amgen should specifically describe the variable selection approach and the rationale why such an approach was followed. Please see a summary of this below:

The approach used in our base case analysis to perform the IPW analyses is consistent with the previous approach used and accepted by NICE during the TA457 appraisal and is also advocated for in the peer reviewed literature.[4] The IPW analysis was performed in four steps:

1) Variables that were considered to be predictive and prognostic factors by UK clinical experts in relapsed/refractory multiple myeloma were identified as discussed in the CS. Clinicians identified 13 risk factors, of which two were used to define the subgroup of interest (number of prior treatments, prior bortezomib exposure) and one (cytogenetic risk status) was not included due to the high proportion of missing data.

2) The treatment indicator and the clinician-identified covariates were considered in a Cox proportional hazards model, and an automated stepwise variable selection procedure was performed using the stepAIC function, which minimises the AIC. Treatment-covariate interactions were not tested due to constraints related to sample size.

3) A logistic regression model was subsequently conducted in which the treatment indicator was defined as the dependent variable and the covariates identified in the stepwise selection Cox model were used as independent variables. The logistic regression model allows for the estimation of the probability of receiving a particular treatment given the covariates of the patient - by taking the inverse of the estimated probabilities, the patient population is reweighted and imbalances in the included covariates are adjusted for. The retained variables for PFS and OS are summarised in Table 10.

4) Survival analyses were conducted on the weighted dataset (see also the provided R code).

Other than the fact that the above-described method has been accepted by NICE in a similar context, it is important to mention that covariate selection within the logistic regression model can be interpreted as an approach where one searches and adjusts for covariates that are strongly related to the treatment received. However, the subgroup

data is coming from a well-conducted randomised clinical trial where patients were randomly assigned to treatments. Therefore, in our view a more appropriate approach is to identify which covariates are strongly related to the outcome and adjust for imbalances in these covariates.

Nevertheless, given the ERG's specific question, we have conducted an exploratory analysis in which the stepwise selection was performed within the logistic model itself. We would like to note that treatment-covariate interactions cannot be tested within the logistic framework due to the fact that the treatment indicator is the dependent variable. The results of this analysis, included the adjusted hazard ratios and the retained variables were presented in Table 5 and Table 9 above in this response document.

The resulting AIC for the model based on the stepwise selection within the logistic model were higher than those obtained when applying the stepwise selection within the Cox proportional hazard model, suggesting that the approach used in our base case analysis may provide a better representation of the data. Furthermore, given the estimated hazard ratios obtained with the ERGs preferred analysis indicate an improved treatment effect compared to what was estimated in our base case analysis, the original approach used may be described as conservative.

A11. Priority question: For the results presented in Table 20 in Appendix E, please clarify the subgroup and reference groups for the effect estimates presented for PFS and OS. Are the estimates for the covariate assessed irrespective of allocated treatment group, other than the covariate of "Treatment"? For example, in relation to the HR and 95% CI for prior stem cell transplantation (SCT), are PFS and OS based on having (subgroup) or not having (reference group) undergone SCT? Or is the estimate CRd versus Rd after adjustment for having undergone SCT? In either case, please expand on a clinical rationale for the [redacted]

We can confirm that the estimate presented is for CRd versus Rd after adjustment for having undergone SCT.

Reception or not of SCT was included as a covariate in the analyses of the relevant post-hoc subgroup analysis as it was highlighted by clinical experts to be potentially prognostic/predictive of clinical outcomes and thus should be balanced between treatment groups. [redacted]

Regardless, we believe our approach to addressing imbalances in baseline characteristics through adjustment of covariates identified to be prognostic of outcomes is a robust and appropriate way to assess the clinical effectiveness within the population relevant to the decision problem.

Clarification questions

A12. Priority question: Please provide a list of variables for which the PFS and OS reported in Table 17 of the CS have been adjusted, and the order in which the variables have been applied, together with the AIC of the final model.

The list of variables for which the aforementioned PFS and OS HRs were adjusted for are provided in Table 20 (Appendix E) of the CS dossier. To identify these variables, a Cox proportional hazards model was implemented, adjusting for treatment and clinician-identified covariates. The approach used was described in detail on page 47 (Section B.2.7.2) of the CS.

A stepwise variable selection procedure was implemented to identify which prognostic variables to adjust for, and was performed using a hybrid stepwise selection strategy that considers both forward and backward moves at each step and selects the "best" of the two. The variable selection strategy was implemented in R (stepAIC function from the MASS package) which uses the AIC criterion to weight the choices. At each step an add or drop was performed that minimised the AIC score. The final AIC of the selected model was 881.20 and 958.17 for PFS and OS, respectively.

Table 10 below summarises the list of variables retained and used to adjust the PFS and OS HRs.

Table 10: List of variables for which the HR for PFS and OS was adjusted for

Covariate	CRd vs Rd - patients with 1 prior therapy and prior bortezomib exposure (ASPIRE)	
	PFS Variable adjusted for	OS Variable adjusted for
Treatment (CRd vs Rd)	[redacted]	[redacted]
Prior lenalidomide (yes vs no)	[redacted]	[redacted]
Prior stem cell transplantation (yes vs no)	[redacted]	[redacted]
Age (≥65 vs <65)	[redacted]	[redacted]
ECOG status (1-2 vs 0)	[redacted]	[redacted]
Creatinine clearance (≥50 - <80 vs other)	[redacted]	[redacted]
Creatinine clearance (≥80 vs other)	[redacted]	[redacted]
Time from diagnosis	[redacted]	[redacted]
Time from last relapse	[redacted]	[redacted]
ISS stage (II-III vs I)	[redacted]	[redacted]
B2-microglobulin (≥3.5 vs <3.5 mg/L)	[redacted]	[redacted]
Refractory to last prior treatment (yes vs no)	[redacted]	[redacted]

CRd, carfilzomib, lenalidomide/dexamethasone; ECOG, Eastern Cooperative Oncology Group; ISS, International Staging System; PFS, progression-free survival; OS, overall survival; Rd, lenalidomide/dexamethasone.

A13. In stepwise regression analysis, the ERG considers that the cut-off probability for adding variables should be less than the cut-off probability for removing variables. In the

CS on page 44, it is stated that “a stepwise Cox regression model (including treatment, each of the covariates, and the treatment-covariate interaction terms as predictor variables with a significance level of 0.20 for entering and 0.10 for removing) was fitted”.

a. Please clarify how the significance levels have been applied in the stepwise Cox regression model for adding or removing a variable in the prespecified subgroup analysis for the ITT population of ASPIRE (discussed in Section B.2.7.1 of the CS). The ERG considers that the stepwise regression analyses for PFS and OS should be run applying a cut-off of <0.10 to add a variable and >0.20 to remove a variable. If this is not the case in the reported analyses, please re-run applying these cut-offs.

Pre-specified subgroup analyses were conducted for the ASPIRE study to evaluate consistency of the observed treatment effect on progression-free survival (PFS), overall survival (OS), and overall response rate (ORR) in subgroups defined by a range of baseline covariates.

A stepwise Cox regression model (including treatment, each of the covariates, and the treatment-covariate interaction terms as predictor variables with significance level of 0.20 for entering and 0.10 for removing) was fitted, separately for PFS and OS, to investigate the treatment-covariate interactions. Similarly, a stepwise logistic regression model was fitted for ORR.

Full results of the prespecified subgroup analyses have been provided in response to QA14.

ITT population from ASPIRE

A14. Please provide results for comparative treatment effectiveness of CRd versus Rd in the prespecified subgroup analyses for PFS and OS for the full population of ASPIRE referred to on page 46 of the CS (unadjusted analyses). The ERG could not locate the analyses in Appendix E.

We apologise for this omission. We have enclosed an addendum to Appendix E containing full results of the ASPIRE prespecified subgroup analyses in the Reference Pack submitted alongside this response.

A15. Please provide HR and accompanying 95% CI for adjusted PFS and adjusted OS, as per the methodology described in Section B.2.7.1 of the CS.

The analysis principles for the prespecified subgroup analyses were aligned with the primary analyses for the overall study population and conducted in accordance to the

statistical analysis plan of ASPIRE. In ASPIRE, adjusted PFS and OS analyses for the prespecified subgroups were not available. Indeed, only unadjusted analyses were conducted for the prespecified subgroups. However, further analyses were performed to investigate the treatment–covariate interactions. For this reason, a stepwise Cox regression model (including treatment, each of the covariates, and the treatment-covariate interaction terms as predictor variables with a significance level of 0.20 for entering and 0.10 for removing) was fitted, separately for PFS and OS.

Section B: Clarification on cost-effectiveness data

For any scenarios requested in Section B, please ensure these are implemented as user selectable options in the economic model. Furthermore, if the company chooses to update its base case results, please ensure that cost-effectiveness results, sensitivity and scenario analyses incorporating the revised base case assumptions are provided with the response.

B1. Priority question: If responses to questions in the clinical section (e.g., questions A1, A3 and A4) result in reanalyses of PFS and OS for the 2L prior bortezomib subgroup, please implement these new results in the economic model and provide updated cost-effectiveness results.

Further to our response to QA1, A3 and A4, we have implemented the clinical results in to the economic model and presented the top-line results and methodology below. In addition to this, we will provide an updated executable economic model alongside this response template.

Results of the requested analysis are presented in Table 11 and demonstrate that the analysis in the requested subgroup is highly consistent with the base case analysis presented in our submission dossier.

Table 11: Scenario analysis results for CRd vs Rd, 2L/prior bortezomib/no prior lenalidomide subgroup

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)
Rd	[redacted]	4.12	2.58				
CRd	[redacted]	6.65	3.94	54,626	2.53	1.35	**40,335**

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

An overall summary of the main assumptions together with the input parameters that were updated to reflect the requested subgroup analysis is reported in the following sections. The modelling approach and input data derivation performed to inform the cost-effectiveness analysis for CRd vs. Rd in patients who have received 1 prior line of therapy with bortezomib but without lenalidomide is consistent with our approach for the base case subgroup (2L/prior bortezomib).

Clarification questions

Table **12** summarises the key assumptions and

Table 13 summarises the main parameters that were updated in the model to reflect this specific subgroup.

A summary of the applied survival analysis methods is also described.

Table 12: Key model features, 2L/prior bortezomib/no prior lenalidomide subgroup

Model input and cross reference	Source/assumption	Justification
Adjustment for imbalances in prognostic / predictive factors	The IPW approach was used to adjust for imbalances in prognostic/predictive factors. Potential covariates were identified through consultation with clinicians and then selected using a stepwise approach.	These methods were used and accepted in the previous appraisal of carfilzomib (TA457). Potential imbalances in baseline characteristics were adjusted for given that post-hoc subgroup data were used to inform the decision problem.[5] Use of the IPW method adjusts the underlying data, allowing parametric survival models to be applied using the methods proposed in DSU TSD 14 directly.[6]
OS – CRd and Rd	OS for CRd and Rd was estimated using a Weibull distribution fit to ASPIRE and external data matched to this specific subgroup.	The statistical fit to the observed data were similar for all curves except for the log-normal. Visual assessment of the fit suggest that the Weibull model fits the KM data best; however, long-term extrapolations of OS using exclusively the ASPIRE trial data yielded unrealistic survival estimates when comparing with survival data available from external sources. The use of external data to inform OS extrapolation yielded more realistic estimates.
PFS – CRd and Rd	PFS for CRd and Rd was estimated using a generalised gamma distribution.	The statistical and visual fit to the observed data, were similar for all curves. In the absence of long-term PFS data for comparison, we selected the generalised gamma as this gave a plausible estimate of PFS.
Proportional hazards – CRd and Rd	Proportional hazards was assumed for PFS and OS through the use of jointly fitted curve distributions for CRd and Rd.	In the 2L/prior bortezomib/no prior lenalidomide subgroup, OS curves demonstrated a positive and sustained treatment effect that began at treatment initiation (Figure **7**). Although the PFS curves did cross, this only occurred when the number of patients at risk were extremely low (N ≤ 12 in both arms) (see Figure 2). As we reported in the CS, clinical experts consulted by Amgen consistently supported the fact that it is clinically improbable that PFS would intersect but OS would not. Moreover, as discussed in the CS, PFS and OS remained clearly separated and the proportional hazards assumption held in the ITT population based on log-log plots of cumulative hazards.

		Finally, joint curve fitting can reduce uncertainty due to estimation of fewer parameters using a larger data set, as discussed in the literature.
Lenalidomide and dexamethasone TTDs differ by treatment arm	The lenalidomide and dexamethasone components of CRd and Rd are modelled separately. Best fitting curves were selected. Hence, the exponential distribution was selected for both lenalidomide and dexamethasone in CRd and loglogistic in Rd	The modelled time to discontinuation was observed to be different by treatment arm
Carfilzomib treatment duration in CRd	Treatment with carfilzomib when given in combination with lenalidomide and dexamethasone is assumed to cease after 18 cycles. Time on treatment with carfilzomib was modelled with the best fitting exponential distribution.	This is in line with the ASPIRE clinical trial from which efficacy data for CRd were estimated.
Utilities	Utilities were assumed to be time- and treatment-dependent in the progression-free health state and were based on ASPIRE data mapped from EORTC QLQ-C30 to EQ-5D. Baseline utility and mean change from baseline were updated to reflect the utilities in the 2L/prior bortezomib/no prior lenalidomide subgroup.	Health-related quality of life data from the ASPIRE study suggested differences in pre-progression utilities between treatments that varied over time. Trial-based mapped utilities were preferred by the appraisal committee in the previous appraisal of carfilzomib in R/RMM (TA457).
Subsequent treatments	Following CRd or Rd at 2L, the next treatments are: FVd followed by Pd	This is based on the current clinical pathway for patients with MM in England and Wales.
Acquisition costs	PAS discount applied to Carfilzomib. List price assumed for lenalidomide. Relative dose intensities were updated to reflect the 2L prior bortezomib and no prior lenalidomide subgroup	Although the manufacturers of lenalidomide have agreed discounted prices, the level of discount is commercially confidential. Base case ICERs are therefore based on their list prices.
Administration costs	Proportion of missed doses of carfilzomib was updated to reflect the 2L prior bortezomib and no prior lenalidomide subgroup	Align administration costs with specific population of interest.

Abbreviations: FVd: panobinostat, bortezomib, dexamethasone; Pd: pomalidomide, dexamethasone

Table 13: Summary of the main inputs that were updated to reflect the second line prior bortezomib no prior lenalidomide subgroup

Input Parameter	Updated value
IPW adjusted HR for OS (CRd vs. Rd)	[redacted]
HR to adjust MyelomaToul to the 2L/prior bortezomib/no prior lenalidomide subgroup	
Baseline utility	[redacted]
Average increase in utility	
Missed doses for carfilzomib	
RDI-CRd carfilzomib	
RDI-CRd lenalidomide	
RDI-CRd dexamethasone	
RDI-Rd lenalidomide	
RDI-Rd dexamethasone	
Weighted average cost of a 25mg lenalidomide tablet based on the SKU use in ASPIRE	

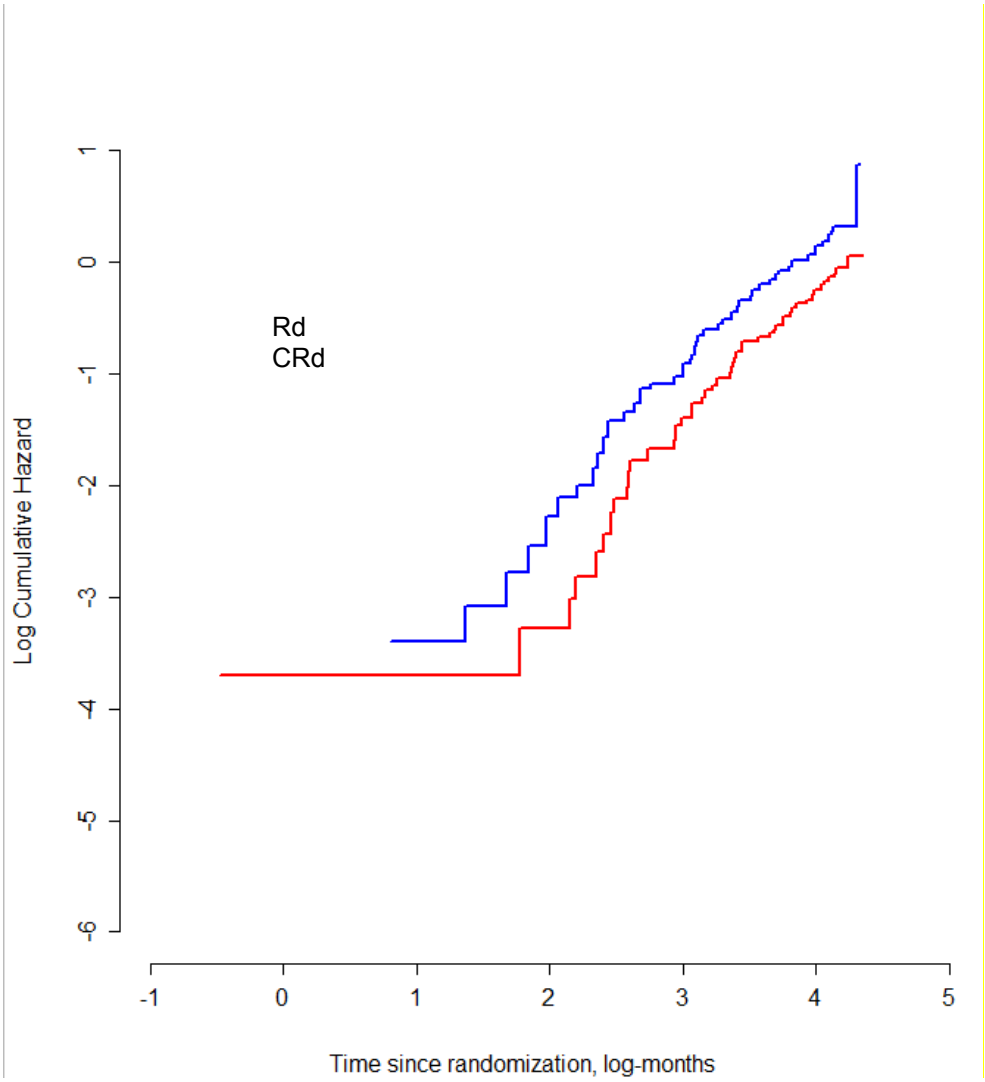
Summary of the applied survival analysis methods for the 2/prior bortezomib/no prior lenalidomide into the model

The survival modelling approach performed for this subgroup was based on the approach presented in the company submission for the 2L/prior bortezomib subgroup.

Overall survival

Similarly to the 2L/prior bortezomib subgroup that was presented in the base case, OS data in the 2L/prior bortezomib/no prior lenalidomide subgroup suggest that the treatment effect was maintained over the trial period (i.e., over 7 years). This is well demonstrated in Figure 6 in our response to question A4 and the log cumulative hazards versus log time plot presented below (
Figure **7**).

Figure 7: Log cumulative hazards versus log time plot for OS in the 2L/prior bortezomib/no prior lenalidomide



Based on the visual inspection of the curves, the constant treatment effect assumption was accepted, and parametric survival models were jointly fitted to the CRd and Rd arms of the IPW-adjusted subgroup OS data from the ASPIRE trial.

Clarification questions

In terms of statistical and visual fit to the IPW-adjusted data, all models performed similarly well, except for the log-normal distribution that had notably worse fit. The jointly fitted OS curves for CRd and Rd and their respective AIC and BIC are presented within the economic model (Tab "OS"). Since most models had a similar statistical fit to the ASPIRE data, assessment of the visual fit and the plausibility of the extrapolations based on clinical expert opinion and comparisons to long-term data were used to select the survival extrapolation approach. The exponential model had the lowest AIC and BIC. However, the Weibull distribution presented the best visual fit to the KM data. As highlighted in the company submission and in our response to question B4, the Weibull distribution fitted to ASPIRE data provides pessimistic estimates of long-term survival (proportions of Rd patients alive at 10 and 20 years to be 5% and 0%, respectively).

Therefore, MyelomaToul registry data matched to the 2L/prior bortezomib/no prior lenalidomide was used for the OS extrapolation. That is, after 72 months, the Weibull distribution jointly fitted to ASPIRE 2L/prior bortezomib/no prior lenalidomide Rd arm was stopped, and the matched MyelomaToul mortality rates were used (i.e., the mortality rates in MyelomaToul adjusted for the HRs ([redacted] during the first 10 months, [redacted] during the period afterwards) accounting for the differences between the data sources. To derive the CRd curve beyond 72 months the IPW adjusted HR of [redacted] was applied to the modelled Rd curve.

Figure 8: Overall Survival selected in the model for the 2L/prior bortezomib/no prior lenalidomide subgroup

Progression-free survival

The Kaplan-Meier curves of the IPW-adjusted PFS data demonstrated consistent treatment effect up until the point where the number at risk became extremely small (N≤12 of patients at risk in both treatment arms), such that one event could cause a large change in the Kaplan-Meier curve – after this point the Kaplan-Meier curves for PFS crossed. These Kaplan-Meier curves are presented in Figure 2 in our response to question A3. As stated in the company submission, clinical experts in the UK deemed it clinically improbable that PFS between treatments would intersect while the treatment effect for OS remained consistent throughout follow-up. As per the approach taken for the 2L/prior

bortezomib subgroup, the consistency of treatment effect observed in the ITT data was considered more informative for the approach to fitting survival curves in the model (Figures 26 and 40 in Appendix of the CS).

Based on this rationale, and consistent with our base case analyses presented in the company submission, PFS curves were jointly fitted to the two arms. The fitted curves and their AIC and BIC for CRd and Rd are reported in the model (Tab "PFS"). The models were very similar in terms of their visual and statistical fit to the observed data, therefore the generalised gamma model was chosen as it provided a clinically plausible estimate of PFS. The model predicted PFS proportions for patients starting on Rd at 10, 20, and 30 years to be 3%, 0% and 0%, respectively. For CRd these proportions were 12%, 3%, and 0%, respectively.

The selected curves for CRd and Rd (jointly fitted generalised gamma curves) are presented in Figure 9.

Figure 9: Selected PFS curves for the 2L/prior bortezomib/no prior lenalidomide subgroup

Time to treatment discontinuation

Time to treatment discontinuation curves were fitted to IPW-adjusted ASPIRE data to model the proportion of patients on treatment in each cycle. Each component was modelled independently, and curves were selected based on their statistical fit and plausibility of long-term extrapolation. As treatment with carfilzomib was discontinued after 18 cycles in the ASPIRE trial and assessment of the clinical plausibility of long-term extrapolations was not required, the best fitting curve (Exponential) was selected based on the AIC and BIC for the carfilzomib component of CRd.

For the lenalidomide and dexamethasone components of CRd and Rd, the curves were all similar in terms of both visual and statistical fit to the observed data, and there was little apparent difference in the long-term extrapolations. Given this, we selected the best fitting curve based on the AIC and BIC (with preference for the BIC if these were different).

The curves selected for each component of CRd and Rd are summarised in

Table **14** and presented in Figure 10. The curve fits for each component of CRd and Rd, and their associated AIC and BIC are presented in

Figure **20**, Figure 21,

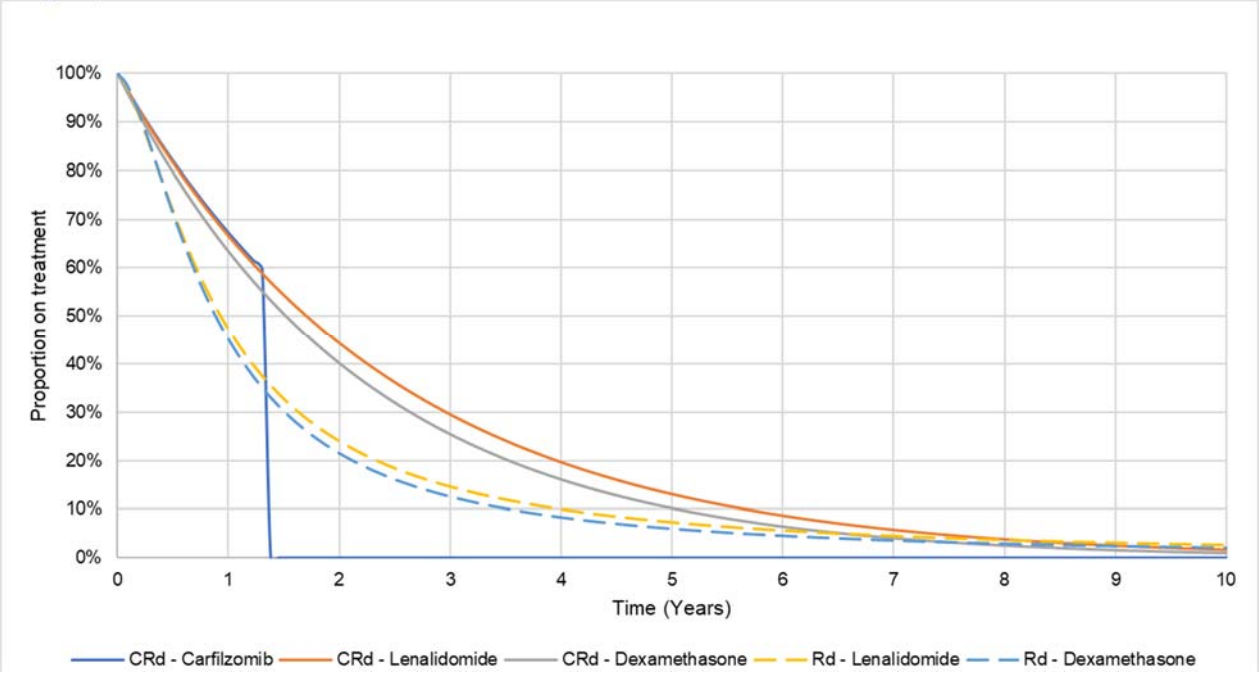
Figure **22**, Figure 23,

Figure **24**, Table 21, and Table 22 provided in our response to question B9.

Table 14: TTD curves selected for components of CRd and Rd

Component	Curve
CRd – carfilzomib	Exponential
CRd – lenalidomide	Exponential
CRd – dexamethasone	Exponential
Rd – lenalidomide	Log-logistic
Rd – dexamethasone	Log-logistic
CRd: carfilzomib/lenalidomide/dexamethasone; Rd, lenalidomide/dexamethasone.	

Figure 10: TTD curves for components of CRd and Rd in the 2L/prior bortezomib/ no prior lenalidomide subgroup



CRd, carfilzomib/lenalidomide/dexamethasone; Rd: lenalidomide/dexamethasone.

B2. Priority question: In the CS on page 46, the company states that, "based on stepwise Cox regression modelling, there was a lack of evidence of treatment-

covariate interactions for PFS suggesting an overall consistent treatment effect across the baseline covariate subgroups". Given this statement, the ERG considers that the HR ratios derived from the ITT population are relevant for consideration. Therefore, please conduct a scenario using the HRs obtained for the ITT population for PFS and OS and apply these to the baseline Rd PFS and OS extrapolations.

In the company submission, we indeed mentioned that there was a lack of evidence for treatment-covariate interaction for PFS within the prespecified subgroup analyses suggesting an overall consistent treatment effect across baseline covariate subgroups. However, in the company submission, we also noted that ASPIRE was not primarily designed to detect significant treatment effects within subgroups, and consequently lacked power to detect significant treatment-covariates interactions. In addition, we also noted that there may be important differences in baseline characteristics across study arms in subgroups (particularly if the subgroup is constructed by multiple covariates such as for the current assessment) that confound the subgroup-specific treatment effect estimates.

In TA457, carfilzomib/dexamethasone (Cd) was assessed versus bortezomib/ dexamethasone (Vd) based on a subgroup of the ENDEAVOR trial. That subgroup was defined as patients who received 1 prior line of therapy not including bortezomib. The ERG and the committee accepted the use of subgroup data because clinical experts confirmed that the number of prior therapies and prior bortezomib treatment could be predictive factors for PFS and OS. In ENDEAVOR, the number of prior therapies and previous proteasome inhibitor therapy were both stratification factors. For the current evaluation, the subgroup is defined by the same factors as for TA457 and in ASPIRE – previous therapy with bortezomib and previous therapy with lenalidomide were both stratification factors. Therefore, we strongly believe that the efficacy results for the ITT population are not relevant for the current analysis.

Overall survival (OS)

B3. Priority question: In the economic model, data in tab 'OS' column F145:F718 are not the same as the data presented in tab 'OS Registry' column R108:R618. For example, in model cycle 170, tab 'OS registry' R199 the value is 0.143, in tab 'OS' F236 it is 0.145. Please clarify why there is a difference, as the company states in the CS that after month 72, the extrapolation of the curve switches to the HR adjusted OS registry curve for CRd?

a. **Please run a scenario, where data in tab 'OS' column F145:F718 and tab 'OS Registry' column R108:R618 are equal.**

The difference between the values presented on the 'OS' tab, column F145:F718, and the 'OS Registry' tab, column R108:R618, is due to the way OS estimates for CRd are stored.

On the "OS" tab, OS estimates for CRd present the modelling approach described in the company submission:

- Between 1-72 months: a Weibull survival model fitted jointly to the CRd and Rd arms of the IPW-adjusted subgroup ASPIRE OS data is applied. The treatment effect parameter of the Weibull model represents an implicit HR [redacted]
- After 72 months: OS estimates for the Rd arm are based on the matched MyelomaToul registry data. OS estimates for the CRd arm are anchored to the modelled OS estimates for Rd by applying the HR of [redacted], which was separately estimated by a Cox proportional hazards model using IPW-adjusted ASPIRE subgroup OS data [redacted]

In contrast, on the "OS registry" tab, the OS for CRd was derived by applying the HR of [redacted] to the survival probabilities estimated for Rd throughout the entire model horizon. Consequently, the proportion of patients alive estimated by these two approaches are slightly different, which leads to the observed differences between the two tabs noted by the ERG. We must note however, that the second is not active in the model.

Nevertheless, we have implemented a scenario analysis where the HR from the Cox proportional model was applied to the separately fitted Rd curve throughout the entire model horizon.

Results of this scenario analysis are presented for the 2L prior bortezomib and 2 prior bortezomib no prior lenalidomide in Table 15 and Table 16, respectively.

Table 15. Scenario analysis results, 2L/prior bortezomib subgroup

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)
Rd	[redacted]	4.09	2.58	-	-	-	-
CRd	[redacted]	6.59	3.94	60,339	2.51	1.36	44,420

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

Table 16. Scenario analysis results, 2L/prior bortezomib and no prior lenalidomide subgroup

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)
Rd	[redacted]	4.13	2.59	-	-	-	-
CRd	[redacted]	6.50	3.86	53,812	2.37	1.28	42,085

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

B4. The ERG considers that OS extrapolations in the model should solely be based on data from ASPIRE as it provides mature, long-term, trial-based, head to head data for the population of interest. However, in TA457 and mentioned in the current submission (reference 19), UK registry data from the Haematological Malignancy Research Network (HMRN) is available. In TA457, the data from HMRN were used in a scenario analysis for the Rd arm. Please clarify why data from MyelomaToul, a French registry, was preferred over HMRN, a UK registry?

Within our response, we would like to take the opportunity to comment on the ERG's position regarding the most suitable long-term OS modelling approach for the economic model. We also provide clarity as to why the Myeloma Toul data was used rather than UK data from the HMRN registry.

Modelling long-term OS in the economic model

There are several pieces of published evidence that make Amgen believe that extrapolating survival solely based on data from the ASPIRE trial with the statistically best-fitting Weibull model gives overly pessimistic long-term survival estimates. Please see a summary of these below (part of which has already been presented in the company submission):

- The best-fitting Weibull model fitted to ASPIRE subgroup data estimates survival proportions for Rd patients at 10, and 20 years to be 5% and 0%, respectively (see Table 29 in the company submission). These estimates are more conservative than those predicted by the manufacturer in the technology appraisal submitted to NICE for Rd in relapsed/refractory multiple myeloma (TA586, Lenalidomide for the treatment of multiple myeloma in people who have received at least one prior therapy). In TA586, the company estimated survival at 25 years for patients starting on Rd to be 11%.[7] Although the ERG assessing the submission deemed this to be too high, an alternative more plausible value was not reported.

- In the recent FAD for the NICE appraisal of DVd, clinical experts in the UK estimated that around 5-10% of current second-line patients would be expected to survive to 10 years.[8] The 10-year survival probability estimated by a Weibull model fitted exclusively to ASPIRE data is notably at the lower end of this range. We feel is important to note that the estimate provided by experts during the final appraisal of DVd reflects the survival probability in clinical practice and the survival probability of patients enrolled in clinical trials are generally higher than in routine clinical practice.

- In 2016, Amgen submitted carfilzomib/dexamethasone (Cd) to NICE as a part of appraisal TA457 to assess the cost-effectiveness of Cd versus bortezomib/dexamethasone (Vd) using subgroup data from the phase 3 ENDEAVOR randomised controlled trial. In the submission, reference was made to the DOXIL-MMY-3001 study, which was highlighted as the study with the longest follow-up for OS with bortezomib-treated relapsed/refractory multiple myeloma patients.[9] The DOXIL-MMY-3001 study was an open-label trial comparing bortezomib monotherapy with bortezomib in combination with pegylated liposomal doxorubicin (n=646) in patients who had received at least one prior regimen. At the time of the data cut-off for the most recent analysis (May 2014), 80% of the patients in the bortezomib monotherapy arm had died and the median follow-up was 8.6 years.[10] Therefore, the study was considered to represent a rich external data source from which clinical plausibility of the OS extrapolation for Vd could be meaningfully assessed. Specifically, in the bortezomib monotherapy arm of the DOXIL-MMY-3001 study, the proportion of patients alive after 9 years was estimated to be about 13% and the shape of the survival curve started to display a flattening shape after about 4-5 years. While the patient population of the DOXIL-MMY-3001 study is not directly comparable to the current subgroup of interest of ASPIRE, there are a few important points to emphasise:
    - **1)** since there is no reason to expect that OS for lenalidomide-treated patients is considerably different from that for bortezomib-treated patients, long-term OS for bortezomib-treated patients can be considered as a reference point for the OS predictions of Rd for the current evaluation;
    - **2)** the flattening shape of the survival curve is a pattern which is not captured by the Weibull model fitted to the trial data and is displayed by other long-term data specific to Rd-treated patients with relapsed/refractory multiple myeloma
    - **3)**The study recruited patients from December 2004 to March 2006 and 66% of patients who received bortezomib monotherapy had received 2 prior lines of treatment. This population would have a lower OS than those considered in this study as the population is 2nd line only and have many more medicines/combinations available to manage the disease after almost 15 years since this study completed recruitment. Hence our OS estimates are plausible.

- Finally, long-term OS data with more than 8 years of follow-up for Rd-treated patients was recently published for a Czech/Slovakian registry cohort (Registry of monoclonal Gammopathies; RMG).[11] RMG was founded by the Czech Myeloma group in 2007 and is intended for collecting data concerning the diagnosis and treatment results of patients in Czech Republic and Slovakia. In the published analysis, OS data were presented based on patients who received 1-3 prior therapies and were treated outside of clinical trials. Altogether, data from 880 patients treated with Rd in the Czech Republic and Slovakia, who had documented follow-up time, were analysed for OS. Table 17 presents a summary of available patient characteristics in the RMG registry and in the ASPIRE trial.

Table 17 Baseline patient characteristics of Rd-treated patients, RMG vs ASPIRE

	RMG (N=880)	ASPIRE (N=396)
ECOG Performance score: 0	82 (10.4%)	175 (44.2%)

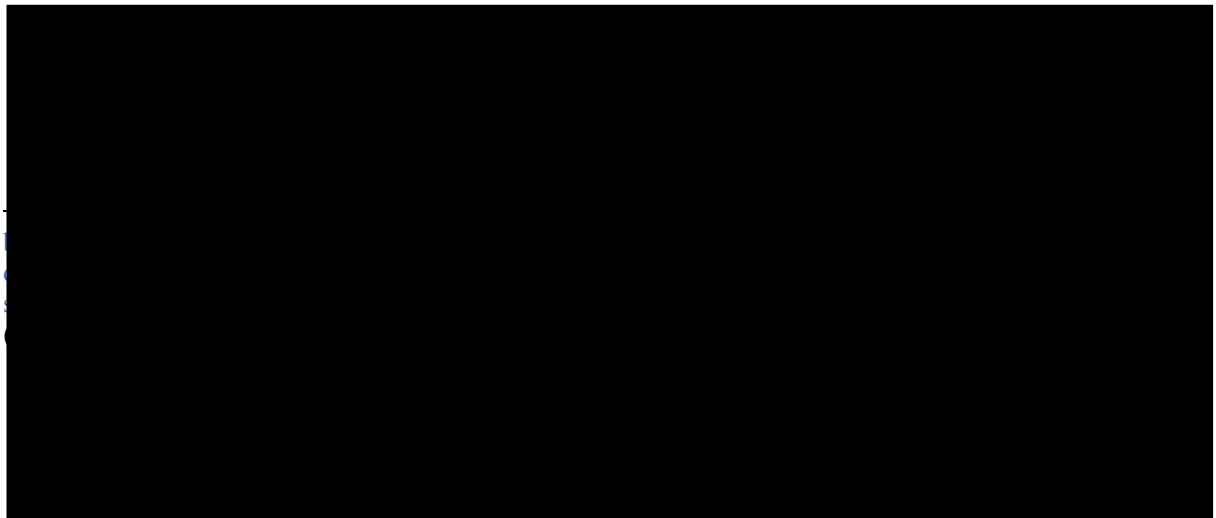
ECOG Performance score: ≥1	708 (89.5%)	221 (55.8%)
ISS: I	298 (43.4%)	154 (38.9%)
ISS: II-III	391 (56.7%)	235 (59.3%)
Number of prior lines: 1	444 (49.8%)	157 (39.6%)
Number of prior lines: 2	308 (34.5%)	139 (35.1%)
Number of prior lines: 3	140 (15.7%)	99 (25.0%)

Similarly, to what was performed using the MyelomaToul registry for Rd in ASPIRE, the RMG registry data was matched to ASPIRE Rd patients and used for OS extrapolation. Specifically, the following steps were made:

1. Published RMG registry data was digitised and virtual patient-level data was simulated using the Guyot algorithm[12]
2. Standard parametric models and piecewise exponential models were fitted to the virtual patient-level data. The models were compared based on statistical fit (AIC/BIC) and visual assessment. The generalized gamma and the piecewise exponential model with a cut-off date at 35 cycles had the best fit and provided plausible OS estimates (please see Figure 11 for the OS predictions and the corresponding AIC values below the figure)[b]
3. To adjust for differences between the RMG and ASPIRE patient populations, a Cox proportional hazards model was fitted to the virtual patient-level RMG data and the Rd arm of the ASPIRE data. The resulting HR was [redacted] (95% CI: [redacted]) indicating that Rd patients in ASPIRE had lower risk of death than Rd patients in the RMG registry.
4. Applying this HR, the RMG-based predictions with the generalized gamma and piecewise exponential models were adjusted (matched) to the Rd patients in ASPIRE. Subsequently, these adjusted survival models were used for OS extrapolations. That is, during the first 72 months, the Weibull model fitted to the ASPIRE trial data was applied to obtain OS estimates whereas beyond 72 months, the adjusted RMG-based mortality rates were applied to obtain long-term OS extrapolations for Rd.
5. The predicted OS at 10 and 20 years with the adjusted RMG data approach were 15.4% (generalized gamma)/13.7% (piecewise exponential) and 5.7% (generalized gamma)/2.9% (piecewise exponential), respectively.

Regrettably, RMG data for second-line patients was not available in RMG, however the analysis described above suggested that in the full ASPIRE trial population the OS estimates predicted for Rd based on matched MyelomaToul data and the matched RMG data were very similar, and that the trial-based extrapolations with a Weibull model were pessimistic (see
Figure *12*).

Figure 11: Fitted models to the RMG OS data



Notes: the following AIC/BIC values were obtained for the various models: exponential: 4195.5/4200.3, Weibull: 4196.6/4206.2, Lognormal: 4196.2/4205.8, Log-logistic: 4192.8/4202.4, Gompertz: 4193.2/4202.7, Generalized Gamma: 4189.6/4204.0, Piecewise exponential: 4189.2/4199.1

Figure 12: Survival predictions for Rd patients with different survival models, full trial population

Considering the totality of this evidence, we strongly believe that despite the relatively long follow-up time in ASPIRE, the matched MyelomaToul registry data provides more plausible and relevant survival estimates for Rd than those based on the best-fitting Weibull model from the trial. Besides statistical considerations, from a clinical perspective, the longer predicted OS estimates based on matched MyelomaToul registry data (or based on the RMG registry data in the broader full trial population) may be explained by the fact that multiple myeloma is a genetically, biologically, and immunologically diverse disease. Therefore, it is expected that some patients will achieve long-term durable response to treatment and will have a long survival despite not being cured from the disease.

Use of HMRN data

Clarification questions

In TA457, data from the UK HMRN registry were available for the OS and TTD of patients receiving lenalidomide as a third-line therapy.[13] These data were used in sensitivity analyses for CRd vs Rd to estimate the OS and TTD of Rd in patients with two prior therapies and no prior lenalidomide.

Unfortunately, reliable and robust data from HMRN were not available for second-line patients treated with lenalidomide, possibly because lenalidomide was not routinely available and funded within the NHSE until recently and it was not considered a standard treatment in this setting at the time of the HMRN data Amgen had access to.[c]

Table 18 presents the number and proportion of patients recorded in HMRN for second-line setting by treatment and shows that only 2.2% of patients received second-line lenalidomide treatment.

Table 18: Second-line therapies in HMRN

	N	%
Total	[redacted]	[redacted]
Bortezomib	[redacted]	[redacted]
Thalidomide	[redacted]	[redacted]
Cyclophosphamide	[redacted]	[redacted]
Melphalan	[redacted]	[redacted]
Lenalidomide	[redacted]	[redacted]
Idarubicin	[redacted]	[redacted]
Carfilzomib	[redacted]	[redacted]
Vincristine	[redacted]	[redacted]
Clinical trial	[redacted]	[redacted]

B5. Please explain how a piecewise exponential model was chosen to extrapolate the MyelomaToul data?

a. Please clarify whether or not standard parametric models were also assessed for the extrapolation of the MyelomaToul data?

Standard parametric models together with piecewise exponential models were fitted to the MyelomaToul data. A number of piecewise exponential models were explored with alternative cut-off dates. The models with the different cut-off dates were systematically compared and the most suitable model based on considerations for visual assessment, statistical fit, and clinical plausibility of predictions was selected for use. Please see further details below.

b. If standard parametric models were assessed, please provide the curve fits and AIC/BIC statistics for the MyelomaToul KM data.

The AIC/BIC values and the curve fits of the different models for the MyelomaToul Kaplan-Meier data are presented in Table 19 and

c Amgen had access to the HMRN data that contained adult patients diagnosed between September 2004 and August 2013.

Figure **13**, respectively. While the generalized gamma, lognormal, loglogistic functions fitted the Kaplan-Meier curve well, these provided overly optimistic long-term projections. In contrast, the Weibull and exponential functions did not capture the flattening shape of the OS Kaplan-Meier curve and predicted overly pessimistic extrapolations. Of the Gompertz and piecewise exponential models, which provided similarly good fit and long-term predictions, the AIC/BIC values were lower for the piecewise exponential model which was ultimately selected for use.

The cut-off date for the piecewise exponential model was defined at 78 cycles (~72 months or 6 years). While there were a few other cut-off dates around 78 cycles with which the piecewise exponential model had slightly lower AIC/BIC values (the lowest AIC/BIC values were obtained with the model where the cut-off date was specified at 70 cycles), these made virtually no difference in terms of OS predictions. For example, the predicted proportion of patients alive at 10 and 20 years with the models where the cut-off date was defined at 70/78 cycles were 29%/28% and 11%/11%, respectively. In our original submission dossier, we also explored sensitivity analyses around this parameter with OS predictions defined at 60 months and 48 months presented.

Table 19: AIC and BIC values of the different parametric survival functions fitted to the MyelomaToul registry data

	AIC	**BIC**
Weibull	7477.273	7488.362
Exponential	7476.600	7482.144
Gompertz	7476.524	7487.612
Generalized Gamma	7442.980	7459.613
Loglogistic	7456.574	7467.663
Lognormal	7441.476	7452.564
Piecewise exponential	7473.325	7484.566

Figure 13: Parametric survival models fitted to the MyelomaToul registry data, second-line patients treated with lenalidomide

B6. Please clarify if the cut-off points used for the MyelomaToul extrapolations (Figure 19 of the CS) relate to the cut-off point for each piece of the exponential extrapolation (e.g., for the 72-month cut-off, months 0-71 defines the time period for one exponential extrapolation and months 72 onwards defines the time period for the next exponential extrapolation)?

Piecewise exponential models were fitted to the virtual patient-level data that was generated to replicate the MyelomaToul Kaplan-Meier curve. For the piecewise exponential models, a single cut-off date was specified. In the base case model, this cut-off date was defined at 78 cycles (~72 months). This means that for the first 78 cycles (first 72 months) and the period beyond 78 cycles (beyond 72 months), the piecewise exponential model predicted MyelomaToul OS based on the constant rate that was estimated for these periods, respectively.

However, in the economic model, these rates were not used directly. Instead, they were first adjusted (or matched, see further explanations below) to the scale of the ASPIRE subgroup OS. These adjusted (or matched) mortality rates were used for the economic model beyond 72 months. Please note that during the first 72 months, the OS estimates

based on the Weibull model fitted to ASPIRE 2L prior bortezomib Rd arm was used. Adjusted (or matched) MyelomaToul registry was applied beyond 72 months only.

B7. Figures 17 and 18 of the CS present the "matched" MyelomaToul OS to the ASPIRE KM data for Rd and shows a decline to 0 at 12 years. The ERG notes that the data is not matched using IPW or matching adjusted indirect comparison (MAIC) analysis, as the company state they did not have access to the individual patient level data, but adjusted the MyelomaToul data using a HR. Please explain why the adjusted MyelomaToul curve was not considered as an external validation of the ASPIRE OS extrapolation for Rd?

Overall, based on the arguments described in B4, we believe that none of the parametric curves estimated solely based on the ASPIRE trial data provided as clinically plausible extrapolations for OS as those based on the matched MyelomaToul registry. While using the exponential distribution yields similar long-term OS estimates to the one based on the matched registry data, it did not fit the Kaplan-Meier curve as well as the Weibull model. We do acknowledge that the MyelomaToul registry could have been used to validate ASPIRE OS extrapolation predictions, and reasonably conclude that the exponential model provides the most plausible long-term predictions, however, given the statistical fit of this distribution to the observed ASPIRE data, we considered our base case approach to be more appropriate.

Further to this, with respect to validation of our approach, we would highlight the conclusions of the matched RMG data (presented in response to B4) and the multi-state modeling analyses presented in the CS – taken together, these analyses underline the validity of using the MyelomaToul registry data to inform our base case analysis and our conclusions that extrapolations with a Weibull distribution lead to overly pessimistic estimates of long-term survival.

Time to treatment discontinuation (TTD)

B8. Priority question: Please provide the percentage of patients who discontinued lenalidomide and dexamethasone before disease progression in the 2L prior bortezomib subgroup for:

a. **CRd;**

Table 20 presents an overview of the number and proportion of patients who discontinued lenalidomide and dexamethasone, as well as the median TTD and PFS estimated in the 2L/prior bortezomib and the in the 2L/prior bortezomib/no prior lenalidomide subgroups.

We would like to emphasise that both PFS and TTD are time-to-event variables, and as some patients were censored for PFS and TTD, the proportion of patients discontinuing

treatment before progression may not provide an unbiased picture of the true relationship between TTD and PFS. Therefore, besides the number of treatment discontinuations, the median TTD and PFS estimates are also provided. Given that the median TTD is consistently shorter than the median PFS, especially in the CRd arm, it can be concluded that on average patients discontinue treatment earlier than they experience progression.

In addition, in our answer to question B9, the Kaplan-Meier curves for TTD and PFS are plotted and the difference between these outcomes over time for CRd and Rd are visualised.

Table 20: Discontinuation of lenalidomide and dexamethasone by subgroup

		CRd		Rd	
		Lenalidomide	**Dexamethasone**	**Lenalidomide**	**Dexamethasone**
2L/ prior bortezomib	Safety population, N*	91	91	71	71
	Discontinuations, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
	Median TTD, months (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
	Median PFS, months (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
2L/ prior bortezomib/ no prior lenalidomide	Safety population, N*	73	73	64	64
	Discontinuations, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
	Median TTD, months (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
	Median PFS, months (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]

* Safety population: patients who received at least one dose of study drug
Notes: for simplicity, unadjusted data are presented in the table

B9. Priority question: Please clarify if TTD data for carfilzomib, lenalidomide and dexamethasone in the CRd arm and lenalidomide and dexamethasone in the Rd arm is based on the ITT population or the subgroup of interest, 2L prior bortezomib?

a. **If TTD in the model is not based on the 2L prior bortezomib subgroup from ASPIRE, please provide the following for the subgroup:**

   i. **KM TTD data for carfilzomib, lenalidomide and dexamethasone in the CRd arm and lenalidomide and dexamethasone in the Rd arm;**

   ii. **Extrapolations of the KM data requested in B9 a) i), including AIC/BIC statistics;**

   iii. **Graphical plot of:**

      a) **PFS for CRd vs TTD curves for carfilzomib, lenalidomide and dexamethasone in the CRd arm;**

      b) **PFS for Rd vs TTD curves for lenalidomide and dexamethasone in the Rd arm.**

   iv. **A scenario implementing the best fitting TTD curves for carfilzomib, lenalidomide and dexamethasone in the CRd arm and lenalidomide and dexamethasone in the Rd arm.**

We confirm that the TTD data in the model are implemented for the 2L/prior bortezomib subgroup. Although not explicitly requested here, we have also added TTD input data for the 2L/prior bortezomib/no prior lenalidomide subgroup. Please find below an overview of the IPW-adjusted TTD data for the 2L/prior bortezomib subgroup and for the 2L/prior bortezomib/no prior lenalidomide subgroup.

Post-hoc subgroup TTD data were adjusted for imbalances in important prognostic/predictive factors using the IPW method. Similarly, to the analyses performed for PFS and OS, in the first step, a Cox proportional hazards model was implemented with time to treatment discontinuation of lenalidomide as the dependent variable and the clinician-identified covariates described in the company submission as independent variables. Subsequently, a stepwise variable selection model that minimises AIC was used to identify which prognostic variables to adjust for. In the third step, imbalances in the covariate distribution was adjusted for by reweighting patients using a logistic regression framework. In the logistic regression, the treatment indicator was defined as the dependent variable whereas the covariates identified in the stepwise selection Cox

model were used as independent variables. With such a logistic regression model, the probability of receiving a particular treatment given the covariates the patients had could be estimated, and by taking the inverse of the estimated probabilities, the patient population was reweighted such that imbalances in the included covariates were adjusted for.

2L/prior bortezomib subgroup

Figure 14 presents the Kaplan-Meier estimates of the proportion of patients on treatment for carfilzomib, lenalidomide, and dexamethasone as well as the proportion of patients alive and progression-free for CRd. Figure 15 presents the same information for Rd.

Figure 14: Kaplan-Meier estimates of IPW-adjusted TTD for carfilzomib, lenalidomide and dexamethasone and PFS for CRd, 2L/prior bortezomib subgroup

Figure 15: Kaplan-Meier estimates of IPW-adjusted TTD for lenalidomide and dexamethasone and PFS for Rd, 2L/prior bortezomib subgroup

For the 2L/prior bortezomib subgroup, extrapolations with each parametric model and the corresponding AIC/BIC values can be found in Appendix M of the company submission and in the submitted economic model.

2L/prior bortezomib/no prior lenalidomide subgroup

Figure 16 presents the Kaplan-Meier estimates of the proportion of patients on treatment for carfilzomib, lenalidomide, and dexamethasone as well as the proportion of patients in progression-free in CRd.

Figure **17** presents the same information for Rd.

Figure 16: Kaplan-Meier estimates of IPW-adjusted TTD for carfilzomib, lenalidomide and dexamethasone and PFS for CRd, 2L/prior bortezomib/no prior lenalidomide subgroup

Figure 17: Kaplan-Meier estimates of IPW-adjusted TTD for lenalidomide and dexamethasone and PFS for Rd, 2L/prior bortezomib/no prior lenalidomide subgroup

Figure 18 and

Figure **19** presents the modelled TTD curves in the 2L/prior bortezomib/no prior lenalidomide subgroup for CRd and Rd, respectively.

Figure 18: Modelled TTD for CRd, 2L/ prior bortezomib/no prior lenalidomide subgroup

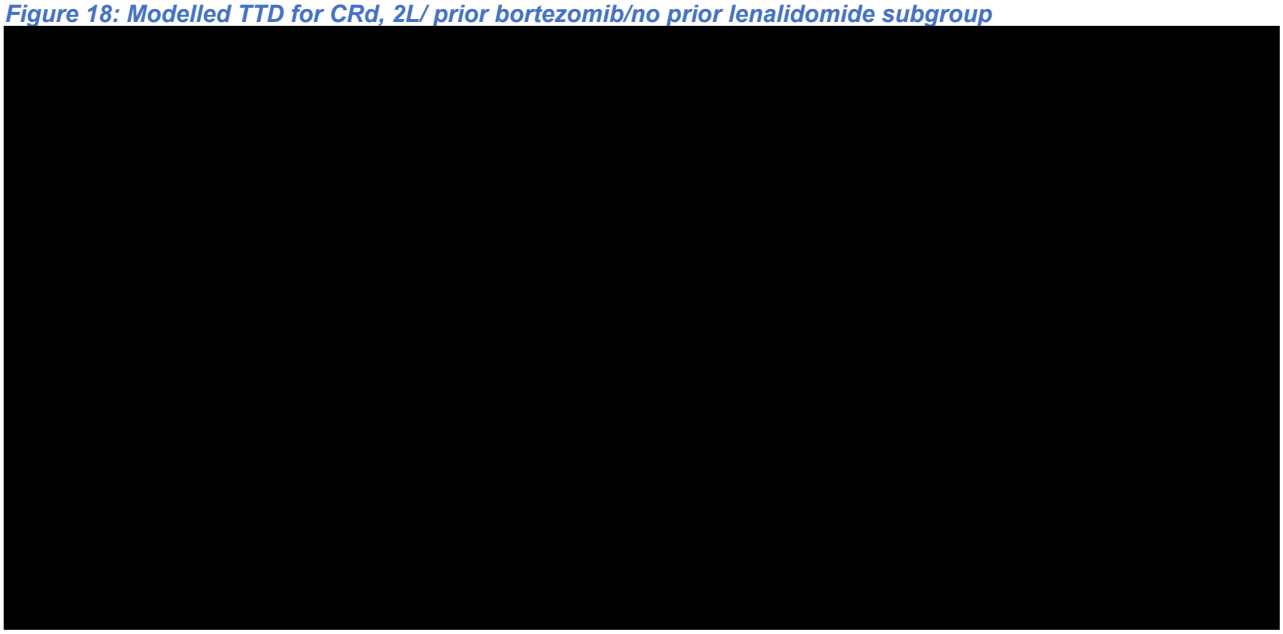


Figure 19: Modelled TTD for Rd, 2L/ prior bortezomib/no prior lenalidomide subgroup

For the 2L/prior bortezomib/no prior lenalidomide subgroup, AIC and BIC values of the parametric models fitted to the IPW-adjusted TTD data are summarised in Table 21 and Table 22. Extrapolations with each of the parametric models are presented in

Figure **20**–

Figure **24**.

Table 21: AIC and BIC values for parametric models fitted to IPW-adjusted TTD data, CRd

	Carfilzomib		Lenalidomide		Dexamethasone	
	AIC	BIC	AIC	BIC	AIC	BIC
Exponential	268.2	270.5	557.2	559.5	542.6	544.9
Gen. gamma	267.9	274.8	557.7	564.6	542.6	549.5
Gompertz	266.4	271.0	558.4	563.0	543.9	548.4
Log-logistic	266.6	271.2	557.3	561.9	541.8	546.3
Log-normal	268.3	272.8	559.4	564.0	546.2	550.8
Weibull	266.1	270.7	556.7	561.3	541.7	546.3

Table 22: AIC and BIC values for parametric models fitted to IPW-adjusted TTD data, Rd

	Lenalidomide		Dexamethasone	
	AIC	BIC	AIC	BIC
Exponential	498.6	500.8	493.4	495.5
Gen. gamma	499.5	505.9	490.7	497.1
Gompertz	496.6	500.8	491.3	495.5
Log-logistic	494.5	498.8	485.5	489.7
Log-normal	502.1	506.3	489.4	493.7
Weibull	500.2	504.5	495.2	499.5

Figure 20: Time on treatment (CRd, carfilzomib)

Note: in the model, patients stopped carfilzomib treatment after 18 cycles

Figure 21: Time on treatment curves (CRd, lenalidomide)

Figure 22: Time on treatment curves (CRd, Dexamethasone)

Figure 23: Time on treatment curves (Rd, lenalidomide)

Figure 24: Time on treatment curves (Rd, Dexamethasone)

B10. Priority question: Please include a scenario in the model where TTD is equal to PFS for the CRd vs Rd comparison.

The results of the requested scenario have been provided in Table 23 and Table **24** for the original subgroup presented in our submission and the ERG's requested subgroup, respectively. The requested scenario presents results assuming TTD is equal to PFS; however, since carfilzomib in ASPIRE was stopped after 18 cycles, the scenario assumed that patients will discontinue carfilzomib after 18 cycles and continue treatment with lenalidomide and dexamethasone until progression.

For both subgroups, this scenario results in an ICER above £50,000/ QALY. However, the requested scenario should be seen as an extreme case scenario which does not reflect the treatment discontinuation patterns, nor the exposure-efficacy relationship observed in ASPIRE, nor the expected utilisation of CRd in clinical practice. Indeed, evidence from ASPIRE consistently showed that on average treatment duration is notably shorter than PFS – this is well demonstrated in our response to questions B8 and B9, where the TTD was shorter than PFS in both subgroups (please see the median TTD and PFS estimates as well as the Kaplan-Meier curves). We would therefore suggest caution when interpreting the conclusions of these analyses.

Table 23: Scenario analysis results for CRd vs Rd, 2L/prior bortezomib subgroup

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)
Rd	[redacted]	4.08	2.58	-	-	-	-
CRd	[redacted]	6.62	3.95	117,192	2.54	1.37	85,470

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

Table 24: Scenario analysis results for CRd vs Rd, 2L/prior bortezomib/no prior lenalidomide subgroup

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)
Rd	[redacted]	4.12	2.58				
CRd	[redacted]	6.65	3.93	114,756	2.53	1.36	85,056

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

Adverse events

B11. Priority question: Please clarify why the adverse events of interest ≥Grade 3 presented in Table 26 of the CS were not included in the model?

a. **The ERG's clinical experts have advised that cardiac failure is an omission from the model. Therefore, please run a scenario using an incidence threshold of ≥2% for Grade 3 adverse events, including adverse events of interest presented in Table 26 of the CS.**

As discussed with the ERG during the clarification call with NICE, we have provided a pragmatic response to this question given the time constraints and the joint understanding that costs associated with AEs is not a driver of model results and thus unlikely to meaningfully alter conclusions.

We present below the results of two exploratory analyses: **1)** inclusion of costs associated specifically with cardiac failure; **2)** sensitivity analyses increasing AE costs by 50%.

Table 25 and Table 26 summarise the results for the scenarios including cardiac failure as an adverse event. The costs of cardiac failure were sourced from the NHS National Schedule of Reference Costs (2017/2018) and pertain to HRG codes EB03A–E(*Heart failure or shock)*.

Table 25: **Scenario analysis including cardiac failure as adverse event, 2L/prior bortezomib subgroup**

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)
Rd	[redacted]	4.08	2.58	-	-	-	-
CRd	[redacted]	6.62	3.96	60,517	2.54	1.38	43,989

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

Table 26: Scenario analysis including cardiac failure as adverse event, 2L/prior bortezomib/no prior lenalidomide subgroup

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)
Rd	[redacted]	4.12	2.58	-	-	-	-
CRd	[redacted]	6.65	3.94	54,672	2.53	1.35	40,369

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

To further explore the impact of AE costs, one way sensitivity analysis varying the AE costs by +50% was performed and the results are presented in Table 27 and Table 28 for both subgroups of interest.

Table 27 Scenario analysis increasing AE costs with 50%, 2L/ prior bortezomib

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)
Rd	[redacted]	4.08	2.58	-	-	-	-
CRd	[redacted]	6.62	3.96	60,735	2.54	1.38	44,147

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

Table 28 Scenario analysis increasing AE costs with 50%, 2L/ prior bortezomib/ no prior lenalidomide

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)
Rd	[redacted]	4.12	2.58	-	-	-	-
CRd	[redacted]	6.65	3.94	54,834	2.53	1.35	40,488

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

As anticipated, across all sensitivity analyses conducted on the costings associated with AE, the ICER remains stable and consistent with the base case analysis.

Utilities

B12. Priority question: For the analysis of mapped utility values, please provide:

a. **The regression results for the first step of the process to identify which variables had a p-value <0.2 in the univariate analyses;**

The following covariates were assessed in univariate models in terms of their impact on utilities.

Clarification questions

Table 29 presents an overview by P value (ie. whether the P value was below or above 0.20). Covariates with multiple categories were retained for inclusion in the full model if at least for one of the categories the P value was lower than 0.2.

Table 29: Covariates assessed in univariate utility models with P value lower vs higher than 0.2

Covariates with P value <0.2	P value	Covariate with P value ≥0.2	P value
Progression	<0.001	Previous hospitalization	0.0048
Best response to prior therapy		GCSF use	0.9233
PR	0.6921	Blood transfusion	0.7067
VGPR or better	0.0333	Previous surgery	0.3508
Age	0.0560	Prior radiotherapy	0.9731
Region		Race	
North America	0.3422	Asian	0.4466
Rest of the world	0.1389	Black / African American	0.6727
ECOG status		Other	0.5380
ECOG=1	0.6100	White	0.5003
ECOG=2	0.0163	Sex	0.539
Haemoglobin level	0.0330	BMI	0.8331
Absolute neutrophil count	0.0131	Platelet count	0.7504
Albumin level	0.1992	Corrected calcium	0.3054
Time from diagnosis	0.0662	Time from last relapse	0.964
ISS at baseline		Light chain	
ISS 2	0.7561	Lambda	0.6803
ISS 3	0.0246	Not detected	0.6831
Disease category		Time from last treatment	
SPEP only	0.0185	Prior SCT	0.7347
UPEP only	0.6213	Prior bortezomib	0.8168
Heavy chain		Refractory to bortezomib	0.5684
IgD	0.4903	Refractory to lenalidomide	0.4469
IgE	0.7561	History of neuropathy	0.2425
IgG	0.6129		
IgG IgA	0.1075		
Not detected	0.0799		
Plasma cell count	0.0162		
β2-microglobulin	0.0881		
Plasmacytoma	0.0942		
Bone lesion	0.0039		
Risk group			
Standard	0.9777		
Unknown	0.1483		
Prior surgery for MM	0.1150		
Number of prior regimens	0.0051		
Prior lenalidomide	0.1284		
Prior thalidomide	0.1644		

Abbreviations: PR: partial response; VGPR: very good partial response; SPEP: serum protein electrophoresis; UPEP: urine protein electrophoresis; MM: multiple myeloma; ECOG: Eastern Cooperative Oncology Group; ISS: International Staging System

b. **The coefficients and model fit statistics for each stage of the selection procedure process, including the final model.**

We have provided the output of the variable selection procedure as an accompanying reference to our response.

We would like to note that the variable selection procedure as well as the estimation of the utility models were performed by an external agency in 2016. For the current submission, the final utility model was re-estimated by Amgen; however, likely due to differences in the applied optimisation algorithm, there are some *very* minor differences in the estimated regression coefficients (ie. slight differences at 3 dp). Nevertheless, the impact of these differences is negligible and no meaningfully alter conclusions.

B13. Priority question: Please clarify why the final statistical model results reported in Table 34 on page 98 of the CS includes a variable with a p-value well above 0.2. If the model fit did not improve with this variable removed, please report the results of the statistical model with this variable removed.

The variable selection strategy considered categorical covariates with multiple categories as a single variable. For inclusion, if for at least one of the categories the P value was lower than 0.2, the variable was included. For exclusion, if for none of the categories the P value was less than 0.1, the variable was excluded.

In the company submission in Table 38, the P value for disease category UPEP was indeed above 0.2 however the P value for disease category SPEP was 0.05. As a result of the described methodology, the entire variable was therefore retained.

Unit costs

B14. Please justify why the following healthcare resource group (HRG) cost was not applied to subsequent administrations of carfilzomib within each treatment cycle:

"SB15Z: Deliver subsequent elements of a chemotherapy cycle"

a. Please provide a scenario where SB15Z is used after the first administration of carfilzomib.

Consistent with the accepted assumption in the original TA457, carfilzomib was assumed to incur an administration cost of a simple parental chemotherapy at first attendance for both the first and subsequent administrations. Carfilzomib in CRd is administered at 27mg/m^2 dose, for which the IV infusion lasts for approximately 10 minutes in all cycles. Therefore, the administration cost would not be expected to be higher for subsequent

administration and is well encapsulated by the HRG code used in both the original TA457 submission and our current base case. Furthermore, the description of the preferred HRG code states "*Overall time of 30 minutes nurse time and 30 to 60 minutes chair time for the delivery of a complete cycle*" which falls well within the administration requirements of carfilzomib.

As a result, we consider the scenario analyses reported in Table 30 and Table 31 to overestimate the associated drug administration costs.

Table 30: Scenario analysis results for CRd vs Rd, 2L/prior bortezomib

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)
Rd	[redacted]	4.08	2.58	-	-	-	-
CRd	[redacted]	6.62	3.96	64,843	2.54	1.38	47,133

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

Table 31: Scenario analysis results for CRd vs Rd, 2L/prior bortezomib/no prior lenalidomide subgroup

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)
Rd	[redacted]	4.12	2.58	-	-	-	-
CRd	[redacted]	6.65	3.94	58,789	2.53	1.35	43,409

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

Subsequent therapies

B15. Priority question: Please provide the following details of the subsequent treatments received by patients in the ASPIRE trial for both CRd and Rd arms in both the ITT population and the 2L prior bortezomib subgroup:

a. **Name of drug;**

b. **Proportion of patients received by;**

c. **Average duration of administration.**

Table 32 presents an overview of subsequent treatments based on the latest available ASPIRE trial data (data cut: December 5, 2017).[d]

The overview demonstrates that the most frequently administered subsequent antineoplastic agent was bortezomib, followed by cyclophosphamide. Only a few patients received immunomodulatory agents and investigational drugs. Daratumumab subsequent therapy was received by 2 CRd patients in the full trial population and none in either of the specific subgroups explored in this response.

d In ASPIRE, subsequent treatments were recorded as agents.

Table 32: Subsequent antimyeloma therapies reported for ≥2% of patients in any treatment arm of the intent-to-treat population

	Population								
	Intent-to-treat			2L / prior bortezomib			2L / prior bortezomib / no prior lenalidomide		
	CRd (N=396) n (%)	Rd (N=396) n (%)	Mean DOT¶	CRd (N=93) n (%)	Rd (N=73) n (%)	Mean DOT	CRd (N=74) n (%)	Rd (N=66) n (%)	Mean DOT
Nr of patients experienced progression	[redacted]								
Nr. of patients treated with ≥1 antimyeloma therapy	[redacted]								
Antineoplastic agents	[redacted]								
Bortezomib	[redacted]								
Cyclophosphamide	[redacted]								
Doxorubicin	[redacted]								
Melphalan	[redacted]								
Pomalidomide	[redacted]								
Bendamustine	[redacted]								
Carfilzomib	[redacted]								
Etoposide	[redacted]								
Cisplatin	[redacted]								
Immunosuppressants	[redacted]								
Lenalidomide	[redacted]								
Thalidomide	[redacted]								
Corticosteroids	[redacted]								
Dexamethasone	[redacted]								
Prednisone	[redacted]								
All other therapeutic products	[redacted]								
Investigational drug‡	[redacted]								
Blood substitutes and perfusion solutions	[redacted]								

Blood and related products	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

¶ Duration of treatment was calculated as the difference between the documented end and start date of the administration of the agent. If for a patient the end date was not documented, for that patient the duration of subsequent therapy was excluded from the calculations. Mean duration of treatment is reported here in 28-day cycles.
* No treatment end date was recorded for any of the patients in the case report forms
‡ There were separate categories for daratumumab and for monoclonal antibodies; 2 KRd patients were recorded to have received subsequent daratumumab therapy

Notes: World Health Organization Drug Dictionary versions September 2012 and December 2016 were used for coding medications. Subjects were counted only once for each class and preferred term.
Abbreviations: ATC: Anatomic Therapeutic Chemical; DOT: Duration of treatment; Nr: number

B16. Priority question: Please provide an option in the economic model to apply subsequent treatment costs based on the usage derived from the 2L prior bortezomib group of ASPIRE.

We have implemented the option of capturing subsequent treatments as observed in ASPIRE (see response to previous question) in the model and described the assumptions used in more detail below. Results are presented for both the original base case subgroup population and the ERGs requested population.

In this analysis, prior to receiving subsequent treatment it was assumed that patients experience a 'treatment-free interval' during which no treatment costs are applied. This approach is consistent with the base case analysis. The treatment-free interval was derived from the ASPIRE study data as the time between progression and start of subsequent treatment line and was estimated to be three model cycles for CRd and Rd.

In order to implement this scenario in the model, after progression with CRd or Rd, all patients were assumed to receive a basket of treatment including Vd, Pd and Rd as these were amongst the most used and, given the relative costs, the most likely to have an impact on the model conclusions (see Table 32). We acknowledge that this is a implying assumption but feel it is appropriate to reflect any uncertainty associated with these parameters.

To specifically implement subsequent treatments in the model, a weighted average cost per cycle based on the observed treatment usage in ASPIRE for each arm was estimated and applied over the mean observed treatment duration. The results of this are reported in Table 33.

Table 33 Data on subsequent treatment from ASPIRE

	Acquisition cost per cycle (£)	Administration cost per cycle (£)	% use in patients progressed, CRd	% use in patients progressed, Rd	Mean DOT in cycles, CRd	Mean DOT in cycles, Rd
Vd	2,224.46	475.52	31%	48%	3	4
Pom-d	8,899.85	0.00	12%	4%	2	5
Rd	4,065.43	0.00	14%	9%	5	8

Vd: bortezomib/dexamethasone; Pom-d: pomalidomide/dexamethasone; Rd: lenalidomide/dexamethasone

Given this, the total cost was estimated to be £2,497 per cycle for subsequent treatment following CRd for up to 10 cycles and £2,032 following Rd for up to 17 cycles, including administration (Table 34).

Table 34 Subsequent treatment costs by arm

	CRd	Rd
Weighted average acquisition cost per cycle	£2,352	£1,804
Weighted average administration cost per cycle	£146	£227
Mean treatment duration (cycles)	10	17

Clarification questions

The results of implementing this scenario are presented in Table 35 and Table 36 for the original base case population and ERG requested subgroup, respectively. AS can be seen from these results, the ICERs remain stable and consistent with the base case analysis when implementing subsequent treatments based on ASPIRE.

Table 35: Scenario analysis results for CRd vs Rd, 2L/prior bortezomib

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)
Rd	[redacted]	4.08	2.58	-	-	-	-
CRd	[redacted]	6.62	3.96	62,415	2.54	1.38	45,372

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

Table 36: Scenario analysis results for CRd vs Rd, 2L/prior bortezomib/no prior lenalidomide subgroup

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)
Rd	[redacted]	4.12	2.58	-	-	-	-
CRd	[redacted]	6.65	3.94	56,044	2.53	1.35	41,384

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

Probabilistic sensitivity analysis (PSA)

B17. The ERG re-ran the PSA in the economic model and produced the cost-effectiveness plane presented in Figure 1 for each treatment. For Rd, Figure 1 shows an apparent split of samples relating to total costs with a clear gap between them. Please explain why the split of samples occurred?

Figure 1. Cost-effectiveness plane by treatment taken from the economic model

Thank you for noticing that there was a split in the samples relating to the costs of Rd in the cost-effectiveness plane. Indeed, the cost data for the Rd series in the figure was referring to the lenalidomide acquisition costs in the 'PSA' tab (column K) instead of the total costs (column J) which has now been rectified.

Furthermore, we would like to note that we also identified and corrected a minor error in the model on the 'OS registry parameters' tab. We noticed that the HR used to adjust MyelomaToul to ASPIRE was not being varied in the PSA. We have corrected this and re-ran the PSA.

Please note that results remained consistent with what was previously reported in the company submission. Please see

Figure 25 and Table 37 for the updated results in the 2L/prior bortezomib subgroup.

Clarification questions

Figure 25: Cost-effectiveness plane by treatment, 2L/prior bortezomib subgroup

Table 37: PSA results for the 2L/prior bortezomib subgroup

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)
Rd	[redacted]	4.08	2.58	-	-	-	-
CRd	[redacted]	6.78	4.00	63,873	2.70	1.42	44,902

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

Section C: Textual clarification and additional points

C1. Please provide the following missing reference:

“106. Amgen data on file. Multiple myeloma medical resource use study. 2015.”

This reference refers to a Chart Review Study (described in our submission dossier) to evaluate the Healthcare Resource Use of Symptomatic Multiple Myeloma across France, Italy and the UK. Unfortunately, we are unable to provide the full dataset here as the scope is beyond that required in this appraisal, including data from countries outside the UK. However, the conclusions of this Chart Review have been published with the citation included in our reference pack (*Gonzalez-McQuire S, Yong K, Flinois A, et al. Retrospective Chart Review Study to Evaluate the Cost of Care of Patients with Symptomatic Multiple Myeloma in the UK. Poster presented at the ISPOR 21st Annual Meeting; May 21-25, 2016; Washington DC, United States. 2016*).

To note, the specific parameters that are sourced from this Chart Review and inform the economic model relate to the costs of monitoring patients within each modelled health state. These are reported in Table 45 of the CS.

C2. Please provide the data on fatal adverse effects referred to in Section B.2.10.6. The text directs the reader to Table 26, which presents selected treatment emergent adverse events of interest.

Apologies for the error: the table intended to be reported in the CS was a summary of the incidence of treatment-emergent adverse events in which an overview of fatal AEs are captured. This has now been incorporated in Table 38, below.

Table 38. Summary of patient incidence of treatment-emergent adverse events – final OS analysis (ASPIRE, safety population)

	CRd (N = 392) n (%)	Rd (N = 389) n (%)	CRd (N = 392) Exposure-adjusted rate /100 PYs[b] (95% CI)	Rd (N = 389) Exposure-adjusted rate /100 PYs[b] (95% CI)
Any TEAE[a]	384 (98.0)	381 (97.9)	588.06 (532.08, 649.91)	575.53 (520.55, 636.32)
≥ Grade 3	341 (87.0)	324 (83.3)	115.67 (104.02, 128.62)	128.27 (115.03, 143.02)
Serious	256 (65.3)	221 (56.8)	48.18 (42.63, 54.46)	49.48 (43.37, 56.46)
Fatal	45 (11.5)	42 (10.8)	5.09 (3.80, 6.82)	6.23 (4.61, 8.43)
Leading to discontinuation of any study drug	131 (33.4)	97 (30.3)		
Any treatment-related TEAE[b]	337 (86.0)	331 (85.1)		
≥ Grade 3a	273 (69.6)	241 (62.0)		

References: Siegel et al 2018,[14] and ASPIRE clinical study report (data cut-off 18 April 2017)[1] Table 8-2.

[a] Includes AEs that started or worsened during the period from the first dose of study drug until 30 days after the last dose of study drug.
[b] Exposure-adjusted rates are presented for categories of AEs reported in Siegel et al, 2018[14] and are adjusted for time on study treatment
[c] Considered related to ≥ 1 study drug by the investigator.

Note: AEs coded were using MedDRA version 20.0.

AE, adverse event; CRd, carfilzomib/lenalidomide/dexamethasone; N/A, not applicable; r, exposure-adjusted subject rate per 100 subject years (ratio of the total number of patients with events and the total person-time at risk in years multiplied by 100); Rd, lenalidomide/dexamethasone; SAE, serious adverse event; TEAE, treatment-emergent adverse event

References

1. Amgen. 20130395 (Onyx Study No. PX-171-009) ASPIRE Clinical Study Report. 2017. (Data cutoff date 28-April 2017). 2017.
2. Amgen data on file. 2018.
3. Amgen data on file. 2016.
4. Majer I, Castaigne J, Palmer S, et al. Modeling Covariate-Adjusted Survival for Economic Evaluations in Oncology. Pharmacoeconomics 2019;5:727-737.
5. National Institute for Health and Care Excellence. Carfilzomib for previously treated multiple myeloma. Technology Appraisal Guidance TA457, 2017.
6. Latimer N. NICE DSU Technical Support Document 14: Undertaking survival analysis for economic evaluations alongside clinical trials - extrapolation with patient-level data., 2011.
7. National Institute for Health and Care Excellence (NICE). Lenalidomide plus dexamethasone for multiple myeloma after 1 treatment with bortezomib. Technology appraisal guidance TA586, 2019.
8. National Institute for Health and Care Excellence. Daratumumab with bortezomib for treating relapsed or refractory multiple myeloma [ID974] Final Appraisal Determination, 2019.
9. Orlowski RZ, Nagler A, Sonneveld P, et al. Randomized phase III study of pegylated liposomal doxorubicin plus bortezomib compared with bortezomib alone in relapsed or refractory multiple myeloma: combination therapy improves time to progression. Journal of Clinical Oncology 2007;25:3892-3901.
10. Orlowski RZ, Nagler A, Sonneveld P, et al. Final overall survival results of a randomized trial comparing bortezomib plus pegylated liposomal doxorubicin with bortezomib alone in patients with relapsed or refractory multiple myeloma. Cancer 2016;122:2050-2056.
11. Maisnar V, Stefanikova Z, Spicka I, et al. Lenalidomide and dexamethasone in treatment of patients with relapsed and refractory multiple myeloma—analysis of data from the Czech Myeloma Group Registry of Monoclonal Gammopathies. Neoplasma 2019;66:499-505.
12. Guyot P, Ades AE, Ouwens MJ, et al. Enhanced secondary analysis of survival data: reconstructing the data from published Kaplan-Meier survival curves. BMC Med Res Methodol 2012;12:9.
13. Amgen data on file. Haematological Malignancy Research Network (HMRN) clinical management and outcomes in multiple myeloma. 2016.
14. Siegel DS, Dimopoulos MA, Ludwig H, et al. Improvement in Overall Survival With Carfilzomib, Lenalidomide, and Dexamethasone in Patients With Relapsed or Refractory Multiple Myeloma. J Clin Oncol 2018:JCO2017765032.

NICE National Institute for Health and Care Excellence

Patient organisation submission

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

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]

2. Name of organisation	Myeloma UK
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Myeloma UK is the only organisation in the UK dealing exclusively with myeloma. Our broad and innovative range of services cover every aspect of myeloma from providing information and support, to improving standards of treatment and care through research and campaigning. We receive no government funding and rely almost entirely on the fundraising efforts of our supporters. We also receive some unrestricted educational grants and restricted project funding from a range of pharmaceutical companies. We are not a membership organisation.
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] If so, please state the name of manufacturer, amount, and purpose of funding.	The table below shows the audited 2018 income from the relevant manufacturer. Funding is either for defined project specific work or a gift, honoraria or sponsorship.

Name of company	Project Specific Funding	Gifts, Honoraria and Sponsorship	Total
Amgen Ltd	80,000	204	80,204
Amgen Europe	1,233	14,935	16,168
Celgene	110,000	12,691	122,691
Takeda	75,000	28,317	103,317
GMA Research (Takeda Oncology) (MUK8)	191,624	-	191,624
Takeda Pharmaceuticals International AG	-	1,500	1,500
Total	**457,857**	**57,648**	**515,505**

4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	The information included in this submission has been gathered from the myeloma patients and carers we engage with through our research and services programmes, including: • Telephone interviews with myeloma patients about their expectations of treatment, and their thoughts on the myeloma treatment pathway. • A Myeloma UK patient experience survey of over 1,000 patients, conducted alongside the myeloma results of the National Cancer Patient Experience Survey. • A multi-criteria decision analysis study of 560 myeloma patients. The study, funded by Myeloma UK and run by the European Medicines Agency (EMA) and University of Groningen, explored patient preferences for different benefit and risk outcomes in myeloma treatment. It has also been informed by analysis of the experiences and views of patients, family members and carers gathered via our Myeloma Infoline, Patient and Family Myeloma Infodays and posts to our online Discussion Forum.
Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	**What is it like to live with myeloma?** *"Myeloma creeps up on you, engulfs you and, if you win the battle, leaves you wondering when it will come back." - Patient testimony* Myeloma is a highly individual and complex cancer originating from abnormal plasma cells in the bone marrow. There is currently no cure, but treatment can halt its progress and improve quality of life. Myeloma is also a relapsing and remitting cancer which evolves over time and becomes resistant to

	treatment. That is why a range of different treatment options with different mechanisms of action is so vital for myeloma patients. The complications of myeloma can be significant, debilitating and painful and include: severe bone pain, bone destruction, kidney damage, fatigue and a depleted immune system which can lead to increased infections. Myeloma patients are more likely to be diagnosed late and often present in secondary care with bone lesions, fractures and, in the worst cases, collapsed vertebrae. This compounds the distress of their diagnosis and impacts negatively on pain levels, mobility and their ability to complete everyday tasks. Treatment side-effects and frequent hospital visits have a social and practical impact on patients' lives, including significant financial implications. Reduction in mobility over time and a perceived increase in reliance on carers and family members, also impacts on patients' sense of control. However, many myeloma patients can have durable responses to treatment and good quality of life – but only if they have access to effective and innovative treatments. Most patients can be successfully retreated at relapse; however, as patients multiply relapse their remission is usually associated with diminishing duration and depth of response over time. At first relapse the median time to next treatment is 13 months with only 58% of patients achieving a complete response/ very good partial response (CR/ VGPR) compared to 74% at diagnosis. At second relapse the time to next treatment reduces even further to 7 months with CR/ VGPR being achieved in less than half of patients.[1] Relapsed and multiple relapsed patients, the population covered in this appraisal, often experience an even more significant disease burden. They not only face a worse prognosis but also a greater

[1] Bird and Boyd (2019) Multiple Myeloma: An Overview of Management Palliative Care and Social Practice 13:1-13 & Yong et.al (2016) Multiple Myeloma: Patient Outcomes in Real-World Practice Br J Heamatology 175:252-265

	symptomatic burden, due to the progressive nature of the disease and the cumulative effects of treatment which can result in reduced quality of life.[2] **What do carers experience?** *"I feel angry that I'm not going to get the future I wanted, but the hardest thing to feel is how my life at the moment is in limbo"* A recent Myeloma UK study[3] into the experiences of carers and family members found that looking after someone with myeloma has a significant emotional, social and practical impact: 25% of those in work had been unable to work or had to retire early to care for the person with myeloma; 84% always put the needs of their relative or friend with myeloma before their own; and 42% of carers were not given enough information at diagnosis about how myeloma may affect them. Living with myeloma is therefore often extremely challenging physically and emotionally for patients, carers and family members.
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	Myeloma is a relapsing and remitting cancer which evolves over time and becomes resistant to treatment; a range of treatment options with different mechanisms of action at each stage of the pathway is therefore vital for myeloma patients. Patients and carers appreciate the wider range of effective treatments that are now available for treating

[2] Ramsenthaler, C., Osbourne, T.R. et al (2016) The impact of disease related symptoms and palliative care concerns on health related quality of life in multiple myeloma: a multi-centre study. BMC cancer 16:1 P.427

[3] The study, "A Life in Limbo" conducted between May and June 2016, was designed with the input of carers and involved a survey of 374 carers and a second stage of interviews to explore issues in more depth.

relapsed myeloma which has delivered significant improvements in survival in myeloma over the past decade. However, myeloma remains a challenging cancer to treat, often particularly so for relapsed patients.

The different types of treatment benefit that are most valued by patients are set out below. Each of these benefits will be delivered to a greater or lesser extent by individual treatments currently available on the NHS. The treatments most valued by patients will be those that score most highly on these attributes – particularly the delivery of longer, deeper remissions and, where known, improved survival.

- Survival - The lived experience of myeloma patients is to stay in remission as long as possible; ***maximising remission at each treatment opportunity is of the utmost importance***. A study conducted jointly by Myeloma UK, the EMA and the University of Groningen showed that, achieving a lasting remission from treatment was the most important factor for most (75%) participants. This was true across all patient groups regardless of demographic and clinical characteristics. The data indicated that patients would accept severe side effects if the treatment had a superior efficacy suggesting that efficacy is the strongest driver of treatment choice.[4]

- Response – High response rates are important to patients because it increases the chance of a treatment working when they need it. As it stands if patients fail to respond to a treatment they miss a vital opportunity to prolong their life. A higher probability of a response delivers valued higher levels of confidence about the possibility of achieving meaningful remissions.

- Side effects - Patients value treatments with fewer side-effects with low severity ratings which stop when treatment ends However, in practice patients will accept varying levels of toxicity in a treatment if it delivers good survival benefit and depending on the stage of their myeloma.

- Innovation – Since myeloma becomes resistant to treatment, access to new and different mechanisms of action are very important to patients. Access to innovative treatment also delivers psychological benefits for patients who are encouraged and reassured that they are accessing

	optimum treatment. • Treatment administration - Some patients place a high value on oral regimens which give them more control over their day to day lives. However, views on the importance of how a treatment is administered will vary depending on patients' individual circumstances (e.g. if travel to hospital is difficult due to distance or frailty, or if patients work or look after dependents.) The issue of treatment administration is also inextricably linked to survival benefit. Patients view the inconvenience of hospital visits as a small price to pay when treatments deliver good remission.
8. Is there an unmet need for patients with this condition?	The relapsing and remitting nature of myeloma, along with its heterogeneity and resistance to treatment means that a range of different treatment options at each point in the pathway is especially vital in myeloma. There have been welcome recent approvals at second line in the myeloma treatment pathway which has addressed to some extent what was a chronic unmet need. However, the need for an effective triplet combination, combining a proteasome inhibitor and an immunomodulatory drug remains. This is especially true for patients who may have become refractory to Velcade. This gap means that some patients must undergo sub-optimal treatment at a critical time in their disease pathway. There is now considerable research evidence to show that longer and deeper remissions are gained in earlier relapses. Patients therefore deserve access to the widest possible range of effective treatments at the point in their myeloma where it has the greatest chance of delivering the best possible response. Further to this there is also a shortage of options for patients at third line of treatment. This combination will give patients a greater choice of options at this line of treatment. Approval for the use of carfilzomib, lenalidomide and dexamethasone within its marketing authorisation from second line provides an additional treatment option that is well tolerated and has shown superior results to currently approved treatments.[5]

[4] Galinsky et al (2017) Myeloma Paitent Value Mapping: A Discrete Choice Experiment Haematologica 102:600-614

[5] Siegel et.al. (2018) Improvement in Overall Survival With Carfilzomib, Lenalidomide, and Dexamethasone in Patients With Relapsed or Refractory Multiple Myeloma Journal of Clinical Oncology 2018 36:8, 728-734 & Dimopoulos et. al. (2017) Carfilzomib or bortezomib in relapsed or refractory multiple myeloma (ENDEAVOR): an interim overall survival analysis of an open-label, randomised, phase 3 trial The Lancent Oncology 18:10 P. 1327-1337

	Overall there is a need for a wide range of options at each stage of the treatment pathway given the hetergenous and evolving nature of myeloma.
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	The individual and heterogeneous nature of myeloma means that some patients may tolerate a treatment well and others may not. In addition, myeloma evolves and becomes resistant to treatment. It is therefore essential to have a range of treatment options throughout the myeloma pathway. This new treatment would bring greater options to patients at second or third lines of treatment. With evidence showing that that longer and deeper remissions are gained in earlier relapses, this triplet combination therapy can deliver longer progression free survival (PFS) compared to other therapies at second or third lines of treatment. • Survival – The Carfilzomib lenalidomide and dexamethasone (KRd) combination significantly improved progression-free survival (PFS) vs lenalidomide dexamethasone (Rd) by a median of 26.3 months vs 17.6 months. This subgroup analysis of the ASPIRE Clinical Trial evaluated KRd vs Rd by number of previous lines of therapy and previous exposure to bortezomib, thalidomide or lenalidomide. Treatment with KRd led to a 12-month improvement in median PFS vs Rd after first relapse and a 9-month improvement after ⩾2 previous lines of therapy. Treatment with KRd led to an approximate 8-month improvement vs Rd in median PFS in bortezomib-exposed patients, a 15-month improvement in thalidomide-exposed patients and a 5-month improvement in lenalidomide exposed patients. • Response – The Overall response rate (ORR) at both second and third line of treatment was higher for KRd patient's vs Rd patients. (Second line KRd 87% ORR vs Rd 70.1% ORR and third line KRd 87.3% ORR vs 64.4% ORR.) • Innovation - while carfilzomib lenalidomide and dexamethasone could not perhaps be described in and of itself as a step change in the treatment of myeloma, the availability of a triplet combination including a proteasome inhibitor and an immunomodulatory drug is a "first" for patients at second line of their myeloma, where there is significant unmet need

	• Well tolerated – the ASPIRE trial documents showed that patients who received this triplet combination consistently reported superior health related quality of life relative to those in the Rd group during the treatment.[6] These benefits also apply to carers and family members, for example: • Improved psychological and emotional wellbeing knowing that the patient has effective treatment options. • Alleviation of symptoms and prevention of complications enables patients to be more independent and reduces day-to-day reliance on carers. • A good side-effect profile improves quality of life and improves patients' ability to live a fuller life.
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	Giving the treatment by IV infusion does mean taking time out of the day to attend hospital. For some patients there are cost/capability issues associated with this and it can place an additional burden on carers who have to accompany the patient to hospital. Oral treatments are often valued by patients, particularly those who are working and have dependents. That said, our patient engagement has shown that there are also patients who welcome their treatment being delivered in the safety of a hospital environment and the opportunity to interact with clinical staff and other patients. Overwhelmingly, clinical efficacy and the opportunity of a good remission outweighs any disadvantages in the method of administration. *"Going to the hospital for an infusion is not a problem for me. I'm used to it and my husband is able to drive me." Patient Testimony*

[6] M Dimopoulos et al (2017) Carfilzomib–lenalidomide–dexamethasone vs lenalidomide– dexamethasone in relapsed multiple myeloma by previous treatment Blood Cancer Journal 7:e554

	"I have a business to run and that's very disruptive. That said, when you need to be treated and the only treatment available is delivered in the hospital you just get on with it; getting your treatment becomes your job, your purpose." Patient Testimony
Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	We strongly disagree with the patient population being restricted to patients who were not previously treated with lenalidomide. In our comments on the review of this appraisal we argued that the scope should be in line with the marketing authorisation for the treatment. We continue to believe that this is the case. Excluding patients who have had previous lenalidomide is also not consistent with existing practice and decisions, e.g. the NHS England Cancer Drugs Fund list does not stipulate that patients must be lenalidomide naïve to receive treatment with ixazomib, lenalidomide and dexamethasone – only that they must not be refractory. Patients who have been exposed to lenalidomide are clearly eligible. This is the correct approach. The decision on whether a lenalidomide exposed patient may benefit from retreatment with lenalidomide as part of a treatment combination should be one for physicians to make. Patients and their families feel strongly that the treatment pathway should not unfairly restrict treatment options that their physician may feel has clinical benefit.

Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	
Other issues	
13. Are there any other issues that you would like the committee to consider?	
Key messages	

14. In up to 5 bullet points, please summarise the key messages of your submission:

- Approval for the use of carfilzomib, lenalidomide and dexamethasone within its marketing authorisation from second line provides an additional treatment option that is well tolerated and has shown superior results to currently approved treatments.
- Overall there is a need for a wide range of options at each stage of the treatment pathway given the heterogenous and evolving nature of myeloma.
- Carfilzomib lenalidomide and dexamethasone delivers a progression free survival gain which is highly valued by patients and their families and carers and it should be made available as a treatment option. The higher response rate is also important to patients and

delivers benefits in terms of certainty. Evidence shows that positioning this at second and third line will give patients the greatest chance of achieving a longer progression free survival.

- Patients value the efficacy of the treatment above any possible inconvenience in the method of administration and consider the side effect profile to be tolerable.
- Patients and their families feel strongly that the treatment pathway should not unfairly restrict treatment options that their physician may feel has clinical benefit.

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Professional organisation submission

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

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

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- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	**UKMF/ BSH/ Royal College of pathology**

3. Job title or position	**Consultant Haematologist**
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with this condition? ☒ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	**UKMF – professional organisation for myeloma physicians**
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.]	**No**

If so, please state the name of manufacturer, amount, and purpose of funding.	
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	**No**
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	Prevent disease progression and improve overall survival
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by	Improved PFS Improved Overall response rate Improved OS

x cm, or a reduction in disease activity by a certain amount.)	
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes myeloma remains incurable
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	1st Relapse – Treatment options: Lenalidomide and dexamethasone (if received Bortezomib in first line, Daratumumab, Bortezomib, dexamethasone (if received Bortezomib in first line and non refractory), Carfilzomib and dexamethasone (If received Lenalidomide or Thalidomide in first line therapy) 2nd Relapse – Treatment options: Ixazomib/ Lenalidomide/ Dexamethasone (If Bortezomib and Lenalidomide non refractory),
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	NICE Guidelines NG35
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals	Pathway defined by treatment choices which are NICE approved

across the NHS? (Please state if your experience is from outside England.)	
• What impact would the technology have on the current pathway of care?	Improve treatment options for patients with relapsed myeloma
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes
• How does healthcare resource use differ between the technology and current care?	Not significantly different
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Secondary care
• What investment is needed to introduce the technology? (For	No additional resource required

example, for facilities, equipment, or training.)	
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes
• Do you expect the technology to increase length of life more than current care?	Yes
• Do you expect the technology to increase health-related quality of life more than current care?	Yes in responding patients
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	No

The use of the technology	
13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	Both IV and oral options are currently available for patients. So this technology places no additional clinical requirements
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Blood testing done 4 weekly or scans indicated by symptoms

15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	No
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Yes particularly for high risk Myeloma patients
• Is the technology a 'step-change' in the management of the condition?	
• Does the use of the technology address any	Combination therapy for High risk MM patients in first relapse

particular unmet need of the patient population?	
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Cardiac side effects can affect patients quality of life, this occurs in upto 10% of patients
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes
• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes, and were they measured in the trials?	PFS and OS
• If surrogate outcome measures were used, do they adequately predict	

long-term clinical outcomes?	
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TAXXX]? [delete if there is no NICE guidance for the comparator(s) and renumber subsequent sections]	No

21. How do data on real-world experience compare with the trial data?	We have not used this combination in real world
Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	No
22b. Consider whether these issues are different from issues with current care and why.	No
Key messages	

23. In up to 5 bullet points, please summarise the key messages of your submission.

- Improved PFS
- Improved OS
- HRQoL in trial has shown improvement
- Carfilzomib with dexamethasone is used in the NHS, and we have learnt to optimise therapy for routine care
-

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

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NICE National Institute for Health and Care Excellence

Clinical expert statement

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

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

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- Your response should not be longer than 13 pages.

About you	
1. Your name	**Dr Karthik Ramasamy**
2. Name of organisation	**Oxford University Hospitals NHS FT**

3. Job title or position	**Consultant Haematologist**
4. Are you (please tick all that apply):	☒ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with this condition? ☒ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☒ yes

The aim of treatment for this condition	
7. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	
8. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	
9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	
What is the expected place of the technology in current practice?	

10. How is the condition currently treated in the NHS?	
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	
• What impact would the technology have on the current pathway of care?	
11. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	

• How does healthcare resource use differ between the technology and current care?	
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	
12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	
• Do you expect the technology to increase length of life more than current care?	

• Do you expect the technology to increase health-related quality of life more than current care?	
13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	
The use of the technology	
14. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors	

affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	
16. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	
17. Do you consider the technology to be innovative in its potential to make a significant and substantial	

impact on health-related benefits and how might it improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	
• Does the use of the technology address any particular unmet need of the patient population?	
18. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	
Sources of evidence	

19. Do the clinical trials on the technology reflect current UK clinical practice?	
• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes, and were they measured in the trials?	
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	
20. Are you aware of any relevant evidence that might	

not be found by a systematic review of the trial evidence?	
21. Are you aware of any new evidence for the comparator treatments since the publication of NICE technology appraisal guidance: • TA457 • TA586 • TA129 • TA171 • TA380 • TA427	
22. How do data on real-world experience compare with the trial data?	
Equality	

23a. Are there any potential equality issues that should be taken into account when considering this treatment?	
23b. Consider whether these issues are different from issues with current care and why.	
Topic-specific questions	
24. Is carfilzomib plus lenalidomide and dexamethasone likely to be used for treating multiple myeloma after 1, 2 or 3 previous therapies in clinical practice?	
25. Is re-treatment with lenalidomide an option in people who have received	

lenalidomide earlier in therapy?	

Key messages

27. In up to 5 bullet points, please summarise the key messages of your statement.

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-
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Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

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NICE National Institute for Health and Care Excellence

Patient expert statement

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

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

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- Your response should not be longer than 10 pages.

About you	
1.Your name	**Shelagh McKinlay**

2. Are you (please tick all that apply):	☐ a patient with the condition? ☐ a carer of a patient with the condition? x☐ a patient organisation employee or volunteer? ☐ other (please specify):
3. Name of your nominating organisation	Myeloma UK
4. Did your nominating organisation submit a submission?	**x**☐ yes, they did ☐ no, they didn't ☐ I don't know
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	**x**☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)

6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	x☐ yes
7. How did you gather the information included in your statement? (please tick all that apply)	☐ I have personal experience of the condition ☐ I have personal experience of the technology being appraised ☐ I have other relevant personal experience. Please specify what other experience: x☐ I am drawing on others' experiences. Please specify how this information was gathered: • Telephone interviews with myeloma patients about their expectations of treatment, and their thoughts on the myeloma treatment pathway. • A Myeloma UK patient experience survey of over 1,000 patients, conducted alongside the myeloma results of the National Cancer Patient Experience Survey. • A multi-criteria decision analysis study of 560 myeloma patients. The study, funded by Myeloma UK and run by the European Medicines Agency (EMA) and University of Groningen, explored patient preferences for different benefit and risk outcomes in myeloma treatment. • It has also been informed by analysis of the experiences and views of patients, family members and carers gathered via our Myeloma Infoline, Patient and Family Myeloma Infodays and posts to our online Discussion Forum.

Living with the condition	
8. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	
Current treatment of the condition in the NHS	
9. What do patients or carers think of current treatments and care available on the NHS?	
10. Is there an unmet need for patients with this condition?	
Advantages of the technology	
11. What do patients or carers think are the advantages of the technology?	

Disadvantages of the technology	
12. What do patients or carers think are the disadvantages of the technology?	
Patient population	
13. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	
Equality	
14. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	

Other issues	
15. Are there any other issues that you would like the committee to consider?	

Key messages

16. In up to 5 bullet points, please summarise the key messages of your statement:

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Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

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Patient expert statement

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

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- Your response should not be longer than 10 pages.

About you	
1.Your name	**Franko Kowalczuk**

2. Are you (please tick all that apply):	☒ a patient with the condition? ☐ a carer of a patient with the condition? ☐ a patient organisation employee or volunteer? ☐ other (please specify):
3. Name of your nominating organisation	Myeloma UK
4. Did your nominating organisation submit a submission?	☒ yes, they did ☐ no, they didn't ☐ I don't know
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)

6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes
7. How did you gather the information included in your statement? (please tick all that apply)	☒ I have personal experience of the condition ☐ I have personal experience of the technology being appraised ☐ I have other relevant personal experience. Please specify what other experience: ☐ I am drawing on others' experiences. Please specify how this information was gathered:
Living with the condition	
8. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Myeloma is not a typical cancer and is largely invisible. There are no lumps to cut out and no visible physical signs. My condition was only diagnosed because it caused a fracture (L2 compression) in my spine. For several weeks whilst I was in pain, it remained undiagnosed and I was encouraged to undertake physiotherapy. Without scans ad x-rays it is undetectable and initially my local hospital were reluctant to do this. In terms of day to day living on a personal level, I found dealing with mobility issues that resulted from the Myeloma far tougher than the Myeloma itself. Radiotherapy helped a great deal to stabilise my back and I learned to walk again within a couple of months. The chemotherapy using Velcade, Thalidomide and Dexametazone didn't present me with too many side effects other tan bone pain which I suffered from very badly. Thalidomide made me sleepy in the evenings and Dexamethazone had the opposite effect. I took this once a week and often couldn't sleep on the day that I had taken it. I didn't suffer from classic

	chemotherapy side effects such as hair loss or nausea. Once I had improved my mobility, I returned to work and got on with my life and undertook the remainder of my chemotherapy as an outpatient whilst continuing to work. The biggest effect of Myeloma for me has been psychological, coming to terms with having a terminal condition and missing out on living whilst undergoing treatment. My mother also died during the course of my chemotherapy so I had this and sorting out her affairs to deal with as well as the disease. Two other members of my immediate family were also suffering from different cancers at the same time. Having to shield during the Coronavirus pandemic has been a big blow as I had made lots of plans for the year on the basis that this might be my only treatment free year until the Myeloma returned.
Current treatment of the condition in the NHS	
9. What do patients or carers think of current treatments and care available on the NHS?	In so far as I obtained a period of remission, the treatment I received was efficient but I am fearful of undergoing the same treatment on relapse as it's unlikely to be as efficient the second time around. I was grateful that Velcade was administered as an injection rather than an infusion as it meant less time waiting around hospitals (although I still had to wait for blood test results). I was grateful that the other drugs were administered as tablets or capsules that I could take myself.
10. Is there an unmet need for patients with this condition?	I found medical staff mainly clinical and lacking in empathy. I had to turn to charities and other support networks for emotional and mental support.
Advantages of the technology	
11. What do patients or carers think are the advantages of the technology?	Anything that could extend the remission period and ultimately the length and quality of life would be very welcome. I want to live as much of my life in normality as possible for as long as possible. The condition has focussed my mind on my priorities in life and anything that would help me achieve this would make a great difference.

Disadvantages of the technology	
12. What do patients or carers think are the disadvantages of the technology?	I haven't really come into contact with any disadvantages but perhaps this will happen after further treatments.
Patient population	
13. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	I'm not sure I'd really like to make that kind of judgement. Everybody has their own reasons for wanting to extend their life span. In my case I am still of working age but others will have families and lovced ones who need them.
Equality	
14. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	People with disabilities being adversely affected by having to travel to hospital regularly. People like myself living alone who do not have anyone to call upon on a day today basis if help is needed.

Other issues	
15. Are there any other issues that you would like the committee to consider?	

Key messages

16. In up to 5 bullet points, please summarise the key messages of your statement:

- New treatments that can extend remission and life span will make a huge difference to many.
- Treatments that avoid lengthy infusions make life easier for patients.
- Transport and carer issues should be considered for anyone undergoing treatment.
- Effects are psychological as well as physical and medical teams don't often consider this.
-

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Questions for clinical expert

Carfilzomib with dexamethasone and lenalidomide for treating multiple myeloma after at least 1 previous therapy (part review TA457)

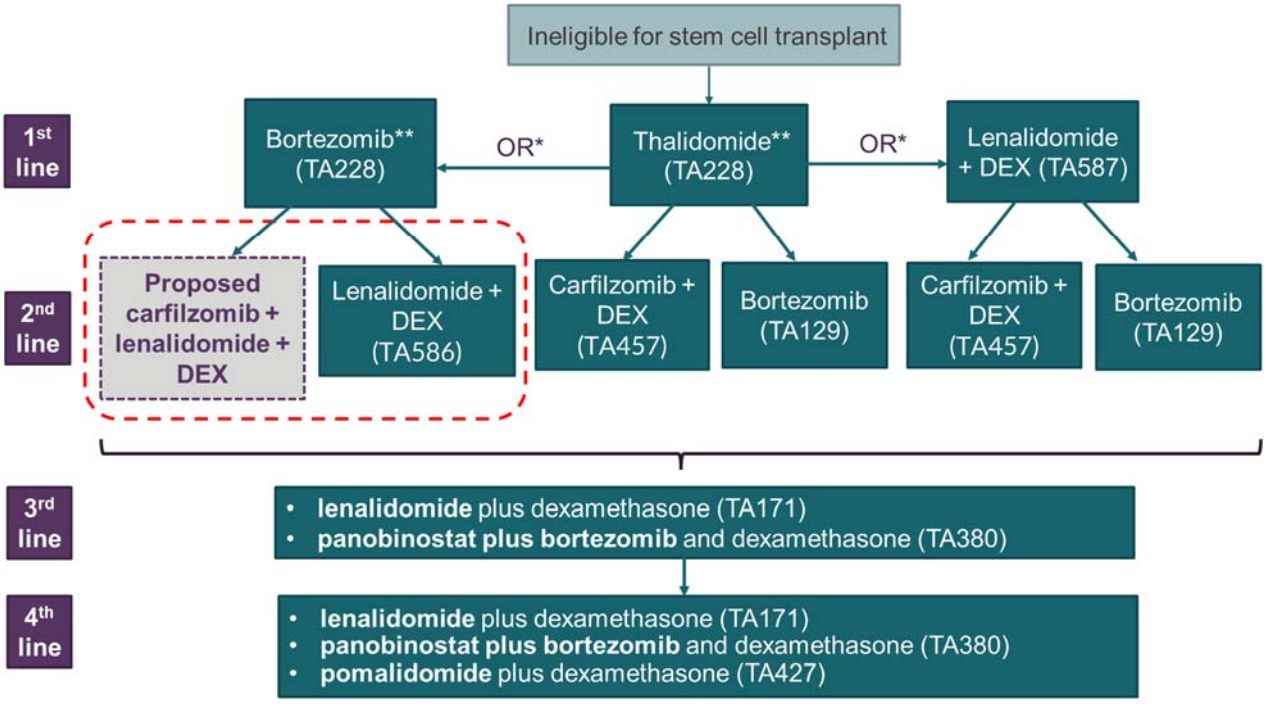
1. Treatment pathway and comparators

1.1 The company is positioning carfilzomib (C) in combination with lenalidomide (R) and dexamethasone (d) as a second-line treatment for people who have received only 1 prior therapy with bortezomib, irrespective of eligibility for stem cell transplant (SCT). This population is narrower than defined in the marketing authorisation for carfilzomib and is a subgroup of those enrolled in the key ASPIRE trial.

Would you agree with the company positioning of CRd and is the proposed positioning in the treatment pathways clear (see Figure 1 and 2 below)?

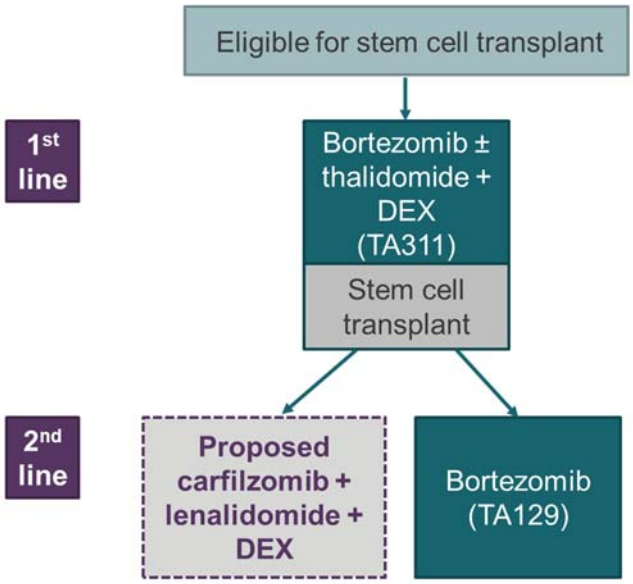
Yes

Figure 1: Treatment pathway for those ineligible for stem cell transplant



NICE guidance recommendations are dependent on a person's previous treatment.
Pathway based on comparators in final NICE scope and does not include technologies recommended for use within the Cancer Drugs Fund.
Red dashed line includes intervention and comparator included in the company's economic model
*OR if thalidomide is contraindicated or cannot be tolerated
**Taken in combination with alkylating agent + corticosteroid
DEX = dexamethasone

Figure 2: Treatment pathway for those eligible for stem cell transplant



NICE guidance recommendations are dependent on a person's previous treatment.
Pathway based on comparators in final NICE scope and does not include technologies recommended for use within the Cancer Drugs Fund
DEX = dexamethasone

1.2 In relation to the treatment pathways shown in Figures 1 and 2, would people receiving bortezomib at first line be re-challenged with a subsequent bortezomib based therapy in clinical practice?

Yes, but the preferred combination is Daratumumab Bortezomib dexamethasone which is currently on the CDF

1.3 The company submission includes lenalidomide (R) in combination with dexamethasone (d) as the only comparator, based on the restricted population defined by the company for CRd. Would you agree that this is the only relevant comparator?

Yes, unless DVD which on CDF can be compared. With over 80 % of second line patients in England getting DVD it is only fair if CdD is compared with DVD

2. Clinical effectiveness

2.1 Would carfilzomib (in combination with Rd) provide additional treatment-specific benefits to patients, other than progression-free survival, compared to treatment with Rd?

Yes overall survival benefit

2.2 The company conducted an inverse probability weighted analysis to produce effect estimates of progression free survival and overall survival for CRd versus Rd, in order to account for imbalances in baseline characteristics from the use of data derived from a post hoc subgroup.

The company adjusted for several covariates which may influence treatment prognosis, including prior SCT (yes vs no) and β2-microglobulin level (≥3.5 vs <3.5 mg/L). The adjusted results suggest that there was an [redacted]

Is there a clinically plausible reason why the risk of progression or death would be [redacted]?

There are no clinically plausible reasons

3. Generalisability of the ASPIRE trial

3.1 Please refer to Table 1 below on the baseline characteristics for the full trial population of ASPIRE. Are the baseline characteristics in the table reflective of those likely to be eligible for treatment with carfilzomib in the UK?

In the UK median age for patients is likely to be higher at 2nd line and more ECOG PS 2 patients

Table 1: ASPIRE RCT baseline characteristics

Characteristic	CRd (N = 396)	Rd (N = 396)	Total (N = 792)
Age, years, median (min, max)	64.0 (38.0, 87.0)	65.0 (31.0, 91.0)	64.0 (31.0, 91.0)
Female, n (%)	181 (45.7)	164 (41.4)	345 (43.6)
Race, n (%)			
• White	377 (95.2)	377 (95.2)	754 (95.2)
• Black	12 (3.0)	11 (2.8)	23 (2.9)
• Asian	1 (0.3)	3 (0.8)	4 (0.5)
• Native Hawaiian/Pacific Islander	[redacted]	[redacted]	[redacted]
• NR/other	6 (1.5)	4 (1.0)	10 (1.3)
Time since diagnosis, years, median (min, max)	3.0 (0.4, 19.7)[a]	3.2 (0.5, 27.3)	3.1 (0.4, 27.3)
Body surface area (m^2), mean (SD)	[redacted]	[redacted]	[redacted]
ECOG PS, n (%)			
• 0	165 (41.7)	175 (44.2)	340 (42.9)
• 1	191 (48.2)	186 (47.0)	377 (47.6)
• 2	40 (10.1)	35 (8.8)	75 (9.5)
ISS stage at diagnosis, n (%)			
• I	64 (16.2)	74 (18.7)	138 (17.4)
• II	99 (25.0)	94 (23.7)	193 (24.4)
• III	185 (46.7)	161 (40.7)	3 (43.7)
• Unknown	48 (12.1)	67 (16.9)	115 (14.5)
Calculated ISS stage at baseline, n (%)[b]			
• I	[redacted]	[redacted]	[redacted]
• II	[redacted]	[redacted]	[redacted]
• III	[redacted]	[redacted]	[redacted]
• Unknown	[redacted]	[redacted]	[redacted]

Cytogenetic risk (%)[c]			
• High	48 (12.1)	52 (13.1)	100 (12.6)
• Standard	147 (37.1)	170 (42.9)	317 (40.0)
• Unknown	201 (50.8)	174 (43.9)	375 (47.3)
Number of prior regimens			
• Median (min, max)	2.0 (1, 4)	2.0 (1, 4)	2.0 (1, 4)
• 1, n (%)	184 (46.5)	157 (39.6)	341 (43.1)
• 2, n (%)	[redacted]	[redacted]	[redacted]
• 3, n (%)	[redacted]	[redacted]	[redacted]
• 4, n (%)	[redacted]	[redacted]	[redacted]
Prior therapy received, n (%)			
• SCT	217 (54.8)	229 (57.8)	446 (56.3)
• Bortezomib	261 (65.9)	260 (65.7)	521 (65.8)
• Lenalidomide	79 (19.9)	78 (19.7)	157 (19.8)
• Thalidomide	[redacted]	[redacted]	[redacted]
• Pomalidomide	[redacted]	[redacted]	[redacted]
• Any IMiD[d]	233 (58.8)	229 (57.8)	462 (58.3)
• Bortezomib and IMiD	146 (36.9)	139 (35.1)	285 (36.0)
• Corticosteroids	[redacted]	[redacted]	[redacted]
• Anthracycline	[redacted]	[redacted]	[redacted]
• Alkylators	[redacted]	[redacted]	[redacted]
Received in last regimen, n (%)			
• Bortezomib	[redacted]	[redacted]	[redacted]
• Lenalidomide	[redacted]	[redacted]	[redacted]
Refractory to last regimen, n (%)	110 (27.8)	119 (30.1)	229 (28.9)

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

Single Technology Assessment Report

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Contribution of authors:

Steve Edwards	Critical appraisal of the company's submission; validated the statistical analyses; provided feedback on all versions of the report. Guarantor of the report
Samantha Barton	Critical appraisal of the company's submission; critical appraisal of the clinical evidence; cross checking of company's search strategies; and drafted the summary, and clinical results sections
Charlotta Karner	Critical appraisal of the company's submission; critical appraisal of the clinical evidence; cross checking of company's search strategies; and assisted with drafting the background and clinical results sections
Tracey Jhita	Critical appraisal of the company's submission; critical appraisal of the economic model; cross checking of company's search strategies; critical appraisal of the economic evidence; carried out the economic analyses; and drafted the economic sections
Peter Cain	Critical appraisal of the company's submission; critical appraisal of the economic model; cross checking of company's search strategies; critical appraisal of the economic evidence; carried out the economic analyses; and drafted the economic sections

All authors read and commented on draft versions of the ERG report.

Table of Contents

List of Tables

List of Figures

List of Abbreviations

2L	Second line
AE	Adverse event
AIC	Akaike Information Criterion
BSC	Best supportive care
C	Carfilzomib
CDF	Cancer Drugs Fund
CI	Confidence interval
CRd	Carfilzomib in combination with lenalidomide and dexamethasone
CS	Company's submission
d	Dexamethasone
DSU	Decision Support Unit
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
EORTC	European Organization for Research and Treatment of Cancer
EQ-5D	EuroQol-5-dimension Questionnaire
ERG	Evidence Review Group
HR	Hazard ratio
HR-QoL	Health-related quality of life
ICER	Incremental cost-effectiveness ratio
IMiD	Immunomodulatory drug
IRC	Independent Review Committee
ITT	Intention-to-treat
IV	Intravenous
KM	Kaplan–Meier
MID	Minimal important difference
MM	Multiple myeloma
NHS	National Health Service
NICE	National Institute of Health and Care Excellence
OR	Odds ratio
ORR	Overall response rate
OS	Overall survival
PFS	Progression-free survival
PSS	Personal Social Services
QALY	Quality adjusted life year
R	Lenalidomide
RCT	Randomised controlled trial
SCT	Stem cell transplantation

SD	Standard deviation
SLR	Systematic literature review
SmPC	Summary of Product Characteristics
STA	Single Technology Appraisal
TEAE	Treatment-emergent adverse effect
TTD	Time-to-treatment discontinuation
TTP	Time to progression

1 Executive summary

1.1 Critique of the decision problem in the company's submission

Evidence on the clinical and cost effectiveness for carfilzomib in a doublet (Cd) and a triplet (CRd) regimen in the management of multiple myeloma has previously been reviewed as part of the Technology Appraisal process (TA457), with the committee recommending:

- Cd as an option for treating multiple myeloma in adults, only if:
    - people have had only 1 previous therapy, which did not include bortezomib; and
    - the company provides carfilzomib with the discount agreed in the patient access scheme.

The triplet combination of CRd at third line (3L) was considered but not recommended. The clinical and cost effectiveness of CRd at second line (2L) was not discussed as part of TA457.

For the decision problem that is the focus of this STA, which is a part review of TA457, the company submitted evidence on the clinical effectiveness of CRd as a 2L treatment for those with multiple myeloma, and specifically those who have undergone prior treatment with a bortezomib-based regimen (2L prior bortezomib). Thus, the company's submission is narrower than the final scope issued by the National Institute for Health and Care Excellence (NICE), which specified the population to be adults with multiple myeloma who had received at least one prior therapy. As a consequence of the restriction of the population to those receiving CRd at 2L after a bortezomib-based regimen, the sole relevant comparator of interest available through routine commissioning becomes Rd.

Evidence in support of the clinical effectiveness of CRd in the management of multiple myeloma at 2L is derived from ASPIRE, a randomised controlled trial enrolling adults with multiple myeloma who had received one or more previous lines of therapy, which was reviewed in TA457. Revised estimates of comparative clinical effectiveness for CRd versus Rd at 2L based on more mature data are available for only PFS and OS (cut-off date of December 2017) compared with data presented in TA457. Analysis of response rates by the Independent Review Committee (IRC) and capture of health-related quality of life (HRQoL) outcomes ceased on demonstration of a benefit in PFS and, thus, results for those outcomes are based on data from the interim analysis (June 2014).

1.2 Summary of the key issues in the clinical effectiveness evidence

Considering the evidence informing estimates of effect for CRd versus Rd in the 2L setting, the Evidence Review Group's (ERG's) key reservations around the data are:

- estimates of effect are derived from *post hoc* subgroups from the ASPIRE trial, which was reviewed as part of TA457;
    - estimates derived from *post hoc* subgroups are at a higher risk of bias than those reported for the full trial population;
- the company provided data for a subgroup in which a proportion of people had not received bortezomib as part of their last regimen, and a proportion of people who had undergone treatment with lenalidomide (2L prior bortezomib), which does not reflect NICE approved first-line treatment for multiple myeloma. The ERG considers the subgroup in which all people had received one line of prior treatment that included bortezomib and no lenalidomide (2L prior bortezomib/no prior lenalidomide), to be more relevant to the decision problem and requested characteristics and results for this subgroup from the company at the clarification stage.
- as would be expected, imbalances were noted in some baseline characteristics between those given CRd and those administered Rd in the *post hoc* subgroups. The direction of bias introduced by the differences in baseline characteristics, and the impact on estimates of relative treatment effect, is unclear.
- updated estimate of PFS informing this STA is based on assessment by investigator as IRC ceased assessing results after demonstration of benefit in PFS at interim analysis;
    - ASPIRE is an open label trial and assessment of PFS is potentially at risk of bias.

To mitigate against the imbalances in baseline characteristics, and to address the limitations associated with use of data derived from a *post hoc* subgroup, the company carried out an inverse probability weighted (IPW) analysis to generate estimates for PFS and OS for CRd versus Rd in the *post hoc* subgroups. In TA457, results from subgroup analyses adjusted to account for imbalances in baseline characteristics arising from non-randomised groups were accepted by the committee. The ERG considers that the company's IPW analysis to adjust subgroup data for imbalances can be considered appropriate for decision-making. Additionally, the company highlights that for PFS, "*there is a consistent treatment effect across baseline covariate subgroups*". As hazard ratios (HRs) derived from an ITT population of an RCT are, by their nature, more robust than those generated from a subgroup analysis, the ERG considers that the results from the ITT population are relevant to

the STA. A summary of PFS and OS for the ITT population, and the 2L prior bortezomib/no prior lenalidomide and 2L prior bortezomib subgroups, is presented in Table A.

Table A. Summary of PFS and OS for CRd versus Rd for the ITT population of ASPIRE and the two post hoc subgroups evaluating CRd as a second-line treatment

Outcome	ITT[a]	2L prior bortezomib/no prior lenalidomide[b]	2L prior bortezomib[b]
PFS	0.659 (0.553 to 0.784)	[redacted]	[redacted]
OS	0.794 (0.667 to 0.945)	[redacted]	[redacted]

Results are presented as Hazard ratio with accompanying 95% confidence interval.
[a] Unadjusted analysis.
[b] Results of inverse probability weighted analysis, adjusted for covariates selected using stepwise logistic regression.
Abbreviations: CRd, carfilzomib, lenalidomide and dexamethasone; ERG, evidence review group; ITT, intention to treat; OS, overall survival; PFS, progression-free survival; Rd, lenalidomide and dexamethasone.

Although the ERG predominantly considers the company's approach to identification of relevant covariates for the IPW appropriate, the ERG considers it important to highlight that the regression analyses [redacted] for specific individual covariates. The ERG considers that the results could suggest that the identified covariates are potential treatment effect modifiers. In particular, adjustment for prior SCT and for β2-microglobulin level suggest that, compared with Rd, treatment with CRd is associated with a [redacted]. As data are derived from *post hoc* subgroup analyses, the ERG emphasises that any inferences from the results are hypothesis generating.

1.3 Summary of the key issues in the cost effectiveness evidence

The ERG considers the key issues with the cost-effectiveness analysis are as follows:

- As mentioned in Section 1.2, the company's subgroup of 2L prior bortezomib that is used for the base-case analysis includes a proportion of patients that received lenalidomide (Section 4.2.2). In England, bortezomib in combination with lenalidomide is not an approved regimen. In response to ERG clarification questions, the company provided scenario analysis for the 2L prior bortezomib/no prior lenalidomide subgroup, which the ERG deems more appropriate for the analysis and is used for the ERG base-case analysis.

- The company's approach to estimate OS for the Rd arm is based on a hybrid of extrapolated ASPIRE IPW OS data and real-world evidence from a French registry of multiple myeloma patients, MyelomaToul.
    - For the CRd arm, OS is also based on extrapolated ASPIRE IPW OS data and MyelomaToul data adjusted using the IPW OS hazard ratio (HR) from ASPIRE (Section 4.2.5). The company chose this approach as they deemed the survival estimates based solely on ASPIRE using the Weibull distribution, which they deemed the best-fitting distribution to the observed data, produced pessimistic results for the Rd arm.
    - The ERG consulted its clinical experts who confirmed that longer-term survival estimates for Rd patients based on ASPIRE are conservative. However, the ERG considers that the company's adjustment of Rd survival results in survival that is inflated for CRd compared with the extrapolated estimates based on IPW ASPIRE data.
    - As such, the ERG considers that the company could have chosen a more clinically plausible extrapolation of the ASPIRE data to use for the base-case. The company confirmed that if they used MyelomaToul to validate their extrapolations, the exponential distribution would have been appropriate to estimate OS. The ERG considers that the exponential distribution produced similar survival estimates for Rd compared with company's base-case estimates.
    - Furthermore, the CRd OS survival estimates are based entirely on mature ASPIRE OS data, which the ERG deems is appropriate and reduces the uncertainty in the analysis.
- As an illustrative scenario, the ERG tested the impact of utilising ITT hazard ratios (HRs) for PFS and OS for the reasons highlighted in Section 1.2.
- Pre-progression utility values in the model capture both mean increase in utility from baseline for both treatment arms as well as treatment-specific increase in utility if a patient is on CRd (Section 4.2.7.1). Change from baseline was the outcome of the utility model so the mean change from baseline is estimated from the individual effects of each covariate that is adjusted for. However mean change in utility over time was [redacted] for CRd than the Rd, even though all patients have progression-free disease. Furthermore, clinical expert advice sought by the ERG suggests that there is no clinical reason for there to be a treatment-specific utility benefit in addition to the benefit provided by any gains in

progression-free survival. Thus, the ERG considers that it is more appropriate for pre-progression utility values for both treatment arms to be equal and that difference in pre-progression quality-adjusted life-years (QALYs) should be determined by length of time spent in the progression-free health state.

- Other issues in the cost-effectiveness analysis that were investigated but found to have minimal impact on the ICER were alternative modelling of time-to-treatment discontinuation for CRd (Section 4.2.5.1), changes to assumptions for adverse events (Section 4.2.6.1), use of investigational drugs for subsequent treatment in ASPIRE (Section 4.2.8.8), alternative weighting of subsequent treatment costs and uncertainty around monitoring costs (Section 4.2.8.8).

1.4 Summary of the ERG's preferred assumptions and resulting ICER

The ERG's preferred assumptions for the cost-effectiveness analysis of CRd compared with Rd are as follows:

- 2L prior bortezomib/no prior lenalidomide subgroup – Section 4.2.5.1 & 6.2;
- Jointly fitted exponential distribution for OS – ASPIRE only – Section 4.2.5.1;
- Removal of treatment effect and average increase in utility for cycle 3 onwards for pre-progression health state utility value – Section 4.2.7.3.

Results of the ERG preferred base-case deterministic ICER compared with the company base-case deterministic ICER, including the confidential patient access scheme (PAS) of [redacted] for carfilzomib, are presented in Table B. The PSA ICER for the ERG preferred base-case is £55,530. A confidential appendix is supplied alongside this report with the confidential PAS's for the comparator lenalidomide and the subsequent therapies panobinostat, pomalidomide and bortezomib applied.

Table B. Deterministic cost-effectiveness results – company vs ERG base-case

Intervention	Total costs	Total QALYs	Δ costs	Δ QALYs	ICER £/QALY
Corrected company base-case					
Rd	[redacted]	2.58	-	-	-
CRd	[redacted]	3.96	60,467	1.38	**43,952**
ERG preferred base-case					
Rd	[redacted]	2.40			
CRd	[redacted]	3.44	53,017	1.04	**50,960**

Abbreviations: CRd, carfilzomib, lenalidomide and dexamethasone; ERG, evidence review group; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; Rd, lenalidomide and dexamethasone.

1.5 Summary of exploratory and sensitivity analyses undertaken by the ERG

Table C presents the ERG's exploratory analysis for the cost-effectiveness of CRd compared with Rd.

Table C. ERG exploratory analysis

Scenario	Section in ERG report	CRd		Rd		ICER £/QALY
		Costs (£)	QALYs	Costs (£)	QALYs	
Corrected company base-case	*6.1*	[redacted]	3.96	[redacted]	2.58	43,952
Corrected company scenario for the 2L prior bortezomib/no prior lenalidomide subgroup	*6.2*	[redacted]	3.94	[redacted]	2.58	40,335
Jointly fitted exponential distribution for OS – ASPIRE only	*4.2.5.1*	[redacted]	3.68	[redacted]	2.52	45,919
PFS and OS CRd curves using ITT PFS and OS HR applied to company scenario PFS and OS	*4.2.5.1*	[redacted]	3.26	[redacted]	2.58	76,716
PFS and OS CRd curves using ITT PFS HR applied to company scenario Rd PFS curve and ITT OS HR applied to ERG preferred Rd OS curve	*4.2.5.1*	[redacted]	3.16	[redacted]	2.52	81,593
Weibull distribution for CRd TTD	*4.2.5.1*	[redacted]	3.94	[redacted]	2.58	40,552
No treatment effect applied for pre-progression health state utility value	*4.2.7.3*	[redacted]	3.96	[redacted]	2.64	41,303
No average increase in baseline utility from cycle 3 onwards	*4.2.7.3*	[redacted]	3.68	[redacted]	2.43	43,583
Subsequent therapy based on ASPIRE and inclusion of investigational drugs cost for subsequent therapy	*4.2.8.8*	[redacted]	3.94	[redacted]	2.58	42,657
Assuming a 50% increase in costs for routine monitoring in the PFS health state	*4.2.8.8*	[redacted]	3.94	[redacted]	2.58	40,903
Alternative weighting of subsequent treatment costs	*4.2.8.8*	[redacted]	3.94	[redacted]	2.58	40,253

Abbreviations: 2L, second-line; CRd, carfilzomib plus lenalidomide and dexamethasone; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; ITT, intention-to-treat; OS, overall survival; PFS, progression-free survival; QALY, quality-adjusted life-year; Rd, lenalidomide plus dexamethasone; TTD, time-to-treatment discontinuation

2 Introduction and background

2.1 Introduction

The company producing carfilzomib (Kyprolis®; Amgen) submitted to the National Institute for Health and Care Excellence (NICE) clinical and economic evidence in support of the effectiveness of carfilzomib (C) in combination with lenalidomide (R) and dexamethasone (d) for the treatment of adults with multiple myeloma. Specifically, the company presents evidence on comparative clinical effectiveness of CRd versus Rd for those who have received only one prior bortezomib-based therapy, which is narrower than the final scope issued by NICE.[1] Herein is a critique of the company's submission (CS) to the Single Technology Appraisal (STA), together with supplementary information, where necessary, provided by the company during the clarification process.

2.2 Background

Within Section B.1 of the CS, the company provides an overview of:

- carfilzomib, including its mode of action, dose and method of administration (Section B.1.2);
- multiple myeloma, including prevalence, prognosis and disease management (Section B.1.3).

The Evidence Review Group (ERG) considers the CS to present an accurate overview of carfilzomib.

The current treatment pathway for multiple myeloma is complex and rapidly changing, with multiple treatments approved at some lines of therapy and a lack of options at other lines. Given that the company is proposing restricting use of CRd to the second-line setting and after treatment with a bortezomib-based regimen, a decision with which the ERG's clinical experts agree (discussed in greater detail in Section 2.3.1), the ERG considers it would be beneficial to simplify the company's overview of the treatment pathway to focus on treatment options available at second line in UK clinical practice (Figure 1).

As the company highlights, various factors are considered when deciding on treatment, including comorbidities, age, general health status, and prior myeloma treatment. The preferred first-line treatment for patients younger than 65 years and who are physically fit is high-dose chemotherapy with stem cell transplant (SCT). Patients deemed eligible for SCT initially undergo induction therapy with a bortezomib-based regimen to reduce the number of myeloma cells in the bone marrow (Figure 1).[2] However, many patients are not suitable for SCT and will be treated with pharmacotherapy alone.[3] NICE recommends a thalidomide-based regimen as a first-line treatment

for patients who are ineligible for SCT.[4] Alternative options for those who are contraindicated or unable to tolerate thalidomide are Rd or a bortezomib-based therapy (Figure 1).[4, 5]

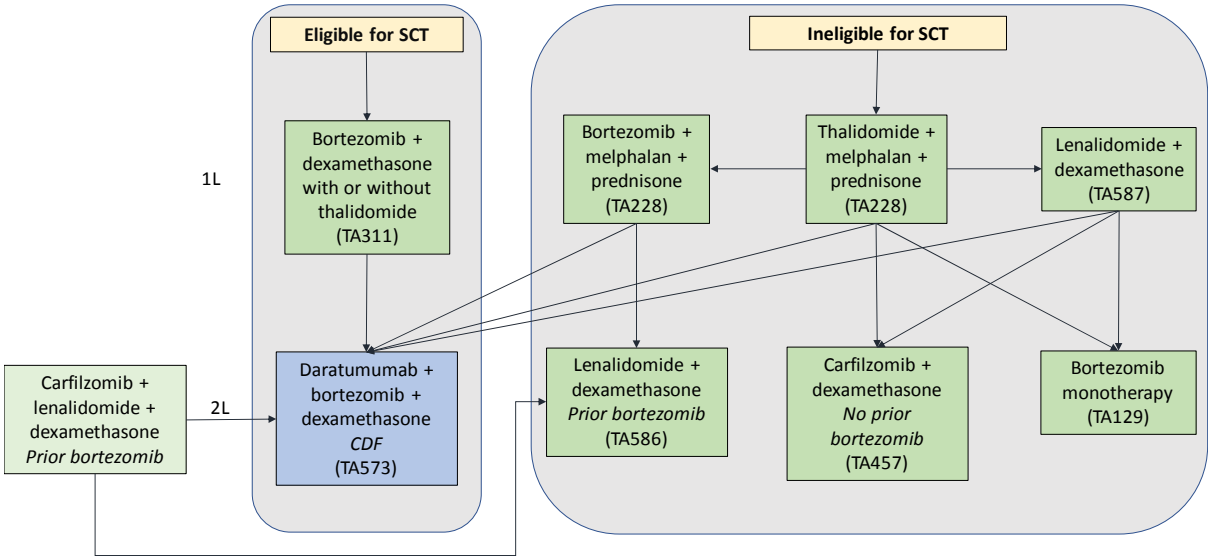
Based on the company's interpretation of the treatment pathway for multiple myeloma, the ERG considers that the company is positioning CRd as a second-line treatment for people who have had prior bortezomib-based treatment, irrespective of eligibility for SCT. However, based on NICE guidance, whether a person undergoes SCT influences the treatment options available at second line (Figure 1). At the time of writing, for those who receive SCT, no treatment option is available in the second-line setting as part of routine commissioning. Daratumumab (D) in combination with bortezomib (V) and dexamethasone (d; DVd) for second-line treatment after SCT became available in April 2019 through the Cancer Drugs Fund (CDF).[6] DVd was recommended with no stipulation on eligibility for SCT or type of prior therapy, and so is also an option for those deemed to be ineligible for SCT. Remaining treatment options at second line for those who have not undergone SCT at that time are:

- Rd;[7]
- Cd;[8]
- bortezomib monotherapy.

However, Rd is recommended after prior bortezomib-based treatment, and Cd is available to those who have not received prior bortezomib (Figure 1).

The ERG's clinical experts fed back that bortezomib monotherapy is rarely given as more effective treatment options are available at second line: relevant comparators for CRd are discussed in greater detail in Section 2.3.3.

Figure 1. Current pathway for first- and second-line treatment of multiple myeloma based on NICE guidance, and the proposed position of CRd



Abbreviations: 1L, first line; 2L, second line; C, carfilzomib; CDF, Cancer Drugs Fund; d, dexamethasone; NICE, National Institute for Health and Care Excellence; R, lenalidomide; SCT, stem cell transplant; TA, Technology Appraisal.

2.3 Critique of the company's definition of the decision problem

The company provided a summary of the final scope issued by the NICE, together with their rationale for any deviation from the final scope (Table 1).[1] The company highlights that the submission differs from the final scope primarily in terms of the population of interest to the decision problem (Table 1 and Table 2). The differences between the decision problem addressed in the company submission (CS) and the scope are discussed in greater detail in the sections that follow.

Table 1. Summary of decision problem (adapted from Table 1 in Document B, pages 9–12)

	Final scope issued by NICE	Decision problem addressed in the submission
Population	Adults with multiple myeloma who have had at least 1 previous therapy	Adults with multiple myeloma who have received only one prior therapy with bortezomib
Intervention	Carfilzomib plus lenalidomide and dexamethasone	Per final scope
Comparator(s)	For people who have had 1 previous therapy: • carfilzomib plus dexamethasone; • lenalidomide plus dexamethasone; • bortezomib. For people who have had 2 previous therapies: • lenalidomide plus dexamethasone; • panobinostat plus bortezomib and dexamethasone. For people who have had 3 or more previous therapies: • lenalidomide plus dexamethasone • panobinostat plus bortezomib and dexamethasone; • pomalidomide plus dexamethasone.	For people who have received one prior therapy with bortezomib: • lenalidomide plus dexamethasone. An additional analysis is also presented versus DVd which is currently recommended for use within the Cancer Drugs Fund as a treatment option for adults who have had one prior therapy.
Outcomes	The outcome measures to be considered include: • progression-free survival; • overall survival; • response rates (for example complete response); • time to next treatment; • adverse effects of treatment; • health-related quality of life.	Per final scope
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.	Per final scope

	The availability of any patient access schemes for the intervention or comparator technologies will be taken into account.	
Subgroups to be considered	If the evidence allows, subgroup analyses based on type and number of lines of previous therapy will be considered	Patients who have received one prior therapy with bortezomib
Special considerations, including issues related to equity or equality	None included	None included

Abbreviations: CDF, Cancer Drugs Fund; CRd, Carfilzomib in combination with lenalidomide and dexamethasone; CS, company submission; DVd, Daratumumab in combination with bortezomib and dexamethasone; ERG, Evidence Review Group; NHS, National Health Service; N/A, not applicable; NICE, National Institute for Health and Care Excellence; Rd, Lenalidomide and dexamethasone; TA, Technology Appraisal.

Table 2. Rationale for deviation from decision problem (adapted from Table 1 in Document B, pages 9–12)

	Company's rationale if different from the scope	ERG comment
Population	CRd is not positioned for use in patients who have received more than one prior therapy as it is anticipated to be used earlier in the treatment pathway in clinical practice	Based on feedback from the ERG's clinical experts, the ERG considers the company's rationale for focusing on those receiving CRd at second line and after prior bortezomib at first line to be appropriate (discussed in greater detail in Section 2.3.1). As part of the clarification process, the ERG requested that the company generate subgroups for CRd and Rd as per the population of interest to the STA (discussed in greater detail in Section 2.3.1).
Intervention	N/A	Schedule of CRd assessed in key RCT on clinical effectiveness of triplet combination (ASPIRE[9]) restricts use of carfilzomib to 18 cycles, whereas carfilzomib could be given for more cycles in UK clinical practice (dosing schedule reported in Section 2.3.2). Maximum of 18 cycles implemented in economic evaluation.
Comparator(s)	People who have received one prior therapy: • Amgen proposes that CRd will be used primarily as an alternative treatment option to Rd in patients who have received one prior therapy with bortezomib. This positioning is aligned with clinical experts' opinion on appropriate use of CRd in UK clinical practice, the primary evidence base underlining this appraisal, the reimbursed population of the primary comparator, and where CRd is likely to derive the most benefit for patients;	Restriction of the population of interest to CRd at second line after prior bortezomib results in narrowing of the relevant comparators for CRd to Rd and bortezomib monotherapy, based on the final scope issued by NICE. In the CS, the company focuses on comparison of CRd with Rd. The ERG agrees with the company's rationale for not considering re-challenge with bortezomib (discussed in greater detail in Section 2.3.3). At the time of writing, DVd is recommended only for use within the Cancer Drugs Fund, and, therefore, is outside of the remit of the STA process and is not assessed further by the ERG.

	• In addition, Amgen proposes that a comparison versus DVd remains informative to the decision problem given the high expected uptake of DVd in clinical practice following the CDF recommendation; • Amgen does not propose that CRd will be used as an alternative treatment to bortezomib re-challenge as it is anticipated that use bortezomib will be limited in this population, due to the availability of superior regimens with alternative mechanisms of action and the standard clinical practice of switching between drug classes with different mechanisms of action. This position is aligned with the recent conclusion of the NICE Committee during TA586 where treatment re-challenge with bortezomib was not considered to be an appropriate comparator to lenalidomide plus dexamethasone in the population under consideration. As such, bortezomib is not considered to be a relevant comparator within this appraisal. People who have received at least two prior therapies: • As outlined above, Amgen does not propose that CRd will be used in patients who have received at least two prior therapies; • CRd was previously appraised as a 3rd-line treatment option (NICE TA457) and was not recommended for use in this setting.	
Outcomes	N/A	In the CS, for those receiving CRd at second line after prior bortezomib, unadjusted and adjusted analyses are reported for only progression-free survival and overall survival for CRd versus Rd, with analyses based on more mature data than presented in an earlier TA evaluating carfilzomib in the treatment of multiple myeloma (TA457[1]). Results for response rate, time to next treatment, health-related quality of life and adverse effects are presented for the full population of the ASPIRE RCT.[9] Analysis of response to treatment by the Independent Review Committee and capture of health-related quality of life outcomes ceased on demonstration of a benefit in PFS and, thus, results are based on data from the interim analysis (June 2014). Given that progression-free survival and overall survival are the only clinical outcomes informing the economic analysis, the ERG considers that no

		clinically important estimates of comparative effectiveness for the subgroup of interest have been omitted from the CS. As part of the clarification process, the company provided estimates of relative treatment effect for PFS and OS based on a revised subgroup requested by the ERG (discussed in Section 2.3.1)
Economic analysis	N/A	N/A
Subgroups to be considered	Amgen propose to consider a subgroup of the marketing authorisation as the primary population of interest in this appraisal. Specifically, patients who have received prior bortezomib are the most appropriate population for consideration given: • this positioning is aligned with clinical expert opinion on the optimal use of CRd in UK clinical practice; • the most relevant comparator, Rd, is recommended by NICE in this subgroup and a comparison is supported by robust head-to-head evidence; and • in this position CRd is likely to derive the most benefit for patients.	The ERG considers it appropriate to present the *post hoc* subgroup as the primary population for the decision problem that is the focus of this STA (discussed in greater detail in Section 2.3.1).
Special considerations, including issues related to equity or equality	N/A	N/A

Abbreviations: CDF, Cancer Drugs Fund; CRd, Carfilzomib in combination with lenalidomide and dexamethasone; CS, company submission; DVd, Daratumumab in combination with bortezomib and dexamethasone; ERG, Evidence Review Group; NHS, National Health Service; N/A, not applicable; NICE, National Institute for Health and Care Excellence; Rd, Lenalidomide and dexamethasone; TA, Technology Appraisal.

2.3.1 Population

In 2016, the marketing authorisation for carfilzomib was extended as follows, "*Kyprolis [carfilzomib] in combination with either lenalidomide and dexamethasone or dexamethasone alone is indicated for the treatment of adult patients with multiple myeloma who have received at least one prior therapy*".[10] In line with the marketing authorisation, the final scope issued by NICE specifies the population of interest for this part review of a previous technology appraisal (TA; TA457[8]) to be adults with multiple myeloma who had received at least one prior therapy, with no restriction to a particular line of treatment (Table 1).[1]

In TA457, the company submitted evidence on the clinical and cost effectiveness for carfilzomib in a doublet (Cd) and a triplet (CRd) regimen in the management of multiple myeloma at specific lines within the treatment pathway:[11]

- Cd at second line;
- CRd at second line (prior therapy comprised bortezomib);
- CRd at third line (prior therapy did not include lenalidomide or carfilzomib).

After reviewing the evidence, NICE recommended:[8]

- Cd as an option for treating multiple myeloma in adults, only if:
    - people have had only 1 previous therapy, which did not include bortezomib; and
    - the company provides carfilzomib with the discount agreed in the patient access scheme.

NICE did not recommend the triplet combination of CRd at 3L, citing that overall survival (OS) data were immature, the life expectancy criterion for the end of life consideration was not met and the incremental cost-effectiveness ratios (ICERs) were higher than normally accepted as a cost-effective use of NHS resources.[8]

During the decision-making process, clinical experts present at the Committee meeting fed back that consideration of Cd and CRd and second and third line settings, respectively, was appropriate.[12] Thus, additional details on deliberation on the clinical and cost effectiveness of CRd at second line as part of TA457 are not available in the committee papers.

In the part review reported here, the company presents evidence on CRd at only second line after prior bortezomib in the first-line setting. The company's reasons for focusing on use of CRd at in this setting are:

- the clear unmet need for triplet therapies that target multiple pathways and enable deeper and more durable responses, as well as improved survival outcomes, earlier in the pathway;
- feedback from clinical experts that CRd will offer the greatest benefit to patients in the second-line setting;
    - in the pivotal ASPIRE trial, patients at second line demonstrated improved clinical outcomes compared with later lines, which supports the value of CRd being used early in the pathway;
- an alignment with the reimbursement criteria of the most relevant comparator (Rd), which is supported by a phase 3 randomised comparison;
- the subgroup for which CRd offers the greatest economic value given the substantial clinical benefit observed in this population.

The ERG's clinical experts agree with the company that there remains an unmet need for clinically effective treatments at second line for the management of multiple myeloma, and that CRd is likely to offer the most benefit at the proposed position.

In the CS, the company highlights that the Appraisal Committee for TA457 determined the evidence presented on use of CRd at 3L to be insufficient to establish cost-effectiveness in that setting, in part due to uncertainty arising from immature OS data from ASPIRE. Despite there now being more mature OS data for CRd at 3L, given that the triplet combination was not recommended as an option at this position in the treatment algorithm, the ERG considers it a pragmatic decision for the company to no longer pursue use of CRd at 3L in multiple myeloma.

Given that Cd has been recommended as a second-line treatment for those who received a regimen not including bortezomib, the ERG's clinical experts agree with the company's restriction of use of CRd to second line after prior bortezomib-based therapy.

In support of the proposed positioning of CRd, the company presented estimates of progression-free survival (PFS) and OS derived from a subgroup described as having received one prior therapy with bortezomib. The ERG noted that the subgroup included a proportion of people who had not received bortezomib as part of their last round of therapy ([redacted]), as well as people who had

undergone treatment with lenalidomide in their last regimen ([redacted]). Given that the company is positioning CRd at the second-line setting and after prior bortezomib, as part of the clarification process, the ERG requested that the company generate a new subgroup comprising people who had undergone only one round of therapy that was bortezomib-based and who had not received prior lenalidomide, and to provide revised estimates of PFS and OS for the new subgroup (discussed in greater detail in Section 3.3). The ERG's requested exclusion of those who had received lenalidomide as part of their first-line treatment regimen because no lenalidomide-based regimen is recommended by NICE as a treatment option in this setting. As part of the clarification process, the company highlighted that the subgroup presented in the CS comprised those who had received one prior regimen and had received prior bortezomib. The company commented that the inclusion of those who had not received bortezomib in their last regimen is a consequence of the definition of "last regimen" implemented in ASPIRE. The ERG could not locate a definition for "last regimen" in the CS or CSR. The ERG agrees with the company that people in England could receive a lenalidomide-based regimen at first line as per NICE guidance, if they are judged to be ineligible for SCT, but the available combination does not include bortezomib. Therefore, given the proposed position of CRd in the treatment pathway, the ERG maintains that its requested subgroup more closely reflects the characteristics of people who would likely be eligible for treatment with CRd in clinical practice in England.

In terms of the relevant comparators for CRd at second line (discussed in greater detail in Section 2.3.3), the ERG notes that applying recommendations from TA586[7] on use of Rd at second line could further confine the population who would be eligible for CRd to those who are deemed to be ineligible for SCT at the time of assessment or who cannot tolerate thalidomide. The ERG notes the two studies that informed TA586 included people who had undergone SCT and who had received prior thalidomide.[13, 14] The evidence informing the TA586 was derived from the full trial populations and not from the subgroup of those who were ineligible for SCT or who could not tolerate thalidomide. Additionally, eligibility for SCT or whether a person could tolerate thalidomide were not inclusion criteria for ASPIRE,[9] and, furthermore, have not been specified as baseline characteristics of the subgroup requested by the ERG.

2.3.2 Intervention

The dosing schedule for each drug comprising the triplet regimen of CRd as administered in ASPIRE,[9] and as reported in the Summary of Product Characteristics (SmPC) for carfilzomib,[15] is presented in Table 3. As noted in Table 1, in ASPIRE, use of carfilzomib, but not lenalidomide or dexamethasone,

was restricted to 18 cycles, which is not in line with the marketing authorisation. The ERG's clinical experts fed back that they might consider continuing beyond 18 cycles, if available as an option, for some patients after carrying out a benefit–risk assessment, as advised in the SmPC: [8, 15] data are limited on the tolerability and toxicity of carfilzomib beyond 18 cycles.[8, 15]

The company reports that, in ASPIRE, carfilzomib was administered for a median of 18 cycles (range: 1 to 18 cycles) and a median duration of 72 weeks (range: 1 to 93.1 weeks), which corresponded to the maximum protocol-defined carfilzomib treatment duration.[11] The median relative dose intensity of carfilzomib was 93.7%.

Table 3. Dose and schedule of treatment for carfilzomib, lenalidomide and dexamethasone

Treatment	Route of administration	Dose	Regimen	Treatment duration
Carfilzomib	IV (10 minute infusion)	Starting dose of 20 mg/m^2 on days 1 and 2 of cycle 1 (maximum dose 44 mg). If tolerated, dose should be increased to target dose of 27 mg/m^2 (maximum dose 60 mg).	**Cycles 1–12**: Given on days 1, 2, 8, 9, 15 and 16 of each 28-day treatment cycle.[a] **Cycles 13–18**: Given on days 1, 2, 15 and 16 of each 28-day cycle.	ASPIRE:[9] given for a maximum of 18 cycles, unless discontinued early for disease progression or unacceptable toxicity Median treatment duration: 72 weeks
Lenalidomide	Oral	25 mg	Daily on days 1–21 of each 28-day cycle.	ASPIRE:[9] could be continued after 18 cycles until treatment until progression of disease or unacceptable toxicity. Median treatment duration: • CRd group: 85 weeks; • Rd group: 57 weeks
Dexamethasone[b]	Oral or IV	40 mg	Days 1, 8, 15, and 22 of each 28-day cycle.	ASPIRE:[9] could be continued after 18 cycles until treatment until progression of disease or unacceptable toxicity. Median treatment duration: • CRd group: 80 weeks; • Rd group: 49 weeks

[a] Each 28-day cycle is considered one treatment cycle.
[b] Dexamethasone should be administered 30 minutes to 4 hours before carfilzomib.
Abbreviations: IV, intravenous; m^2, metre-squared; mg, milligram.

2.3.3 Comparators

In the CS, the company presents a matching adjusted indirect comparison on comparative clinical effectiveness of CRd versus daratumumab (D) in combination with bortezomib (V) and dexamethasone (d; DVd) at second line after prior bortezomib. At the time of writing, DVd is recommended only for use within the Cancer Drugs Fund,[6] and, therefore, is outside of the remit of the STA process and is not assessed further by the ERG.

As per the final scope issued by NICE, the relevant comparators for management of multiple myeloma at second line are:[1]

- Cd for those who have received only one previous therapy that did not include bortezomib;
- Rd for those who have received only one prior therapy that included bortezomib;
- bortezomib monotherapy for those who are at first relapse and who have undergone, or are unsuitable for, bone marrow transplantation.

In the CS, the company presents evidence on the comparative clinical effectiveness of only CRd versus Rd for the subgroup of interest, which is derived from the key RCT, ASPIRE, comparing the two treatment regimens. With a focus on implementation of CRd at second line for those whose regimen at first line included bortezomib, Cd is no longer a relevant comparator.

TA586[7] deemed that re-challenge with bortezomib-based therapy was not an appropriate comparator for Rd in the population under consideration. Thus, bortezomib monotherapy is not considered to be a relevant comparator for the population that is the focus of this STA. The ERG's clinical experts agree that people receiving a bortezomib-based regimen at first line would not undergo subsequent re-challenge with bortezomib monotherapy.

The ERG agrees that Rd is the only relevant comparator for CRd at second line after prior bortezomib and, to avoid confusion, reiterates that recommendations from TA586 specify that the population of interest for use of Rd in this setting is limited to those who cannot have a SCT (at the time of assessment) or cannot tolerate thalidomide, and who have already had bortezomib.[7] The ERG also emphasises that the evidence informing TA586 was derived from the full trial population of two studies that included people who had undergone SCT and treatment with thalidomide.[13, 14] The limitation on use of Rd at second line, as in whether Rd is considered only for those ineligible for SCT or who cannot tolerate thalidomide or also includes those who undergo SCT, is not clear from the final scope issued by NICE for the decision problem that is the focus of this STA.[1] The ERG highlights

that, at the time of writing, the NICE pathway for management of multiple myeloma lists no treatment option available through routine commissioning at second line for those who undergo SCT.[16]

3 Clinical effectiveness

The sections below discuss the evidence submitted by the company in support of the clinical effectiveness of carfilzomib (C) in combination with lenalidomide (R) and dexamethasone (d) as a second-line treatment for adults with multiple myeloma whose previous therapy included bortezomib (rationale for narrowing of population outlined in Section 2.3). The Evidence Review Group (ERG) has critiqued the details provided on:

- methods implemented to identify, screen and data extract relevant evidence;
- clinical efficacy of CRd in the subgroup of interest;
- assessment of comparative clinical effectiveness of CRd against relevant comparators in the subgroup of interest;
- safety profile of CRd.

A detailed description of an aspect of the company submission (CS) is provided only when the ERG disagrees with the company's assessment or proposal, or where the ERG has identified a potential area of concern that the ERG considers necessary to highlight for the Committee.

3.1 Critique of the methods review

The company undertook a broad systematic literature review (SLR) with the objective of identifying randomised controlled trials (RCTs) assessing the clinical efficacy and safety of carfilzomib and other therapies in the treatment of multiple myeloma. The company's SLR was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and The Cochrane Collaboration.[17, 18] Full methods and results of the SLR are reported in Appendix D of the CS and a summary of the methods with comments from the ERG about the appropriateness of the methods adopted are presented in Table 4.

The purpose of the SLR was to identify all relevant studies that could inform the comparison of CRd with other interventions for multiple myeloma. As stated in earlier sections, Rd is the only comparator relevant to this appraisal as daratumumab with bortezomib and dexamethasone (DVd), the only other treatment option at second line for patients previously treated with bortezomib, is currently available through the Cancer Drugs Fund (CDF) and not through routine commissioning. Relevant studies identified in the SLR are therefore limited to those of CRd and Rd.

Sixty three studies reported across 397 publications were identified for inclusion in the SLR, however, these included studies assessing any of the broad list of interventions specified in the inclusion criteria (CS, Appendix D, Table 17). One study relevant to the decision problem was identified (ASPIRE),[9] providing direct evidence on the clinical effectiveness of CRd versus Rd. All other studies were not described or discussed further in the CS.

Overall, the ERG found the company's SLR to be of reasonable quality and likely to have identified all studies relevant to the decision problem, despite limiting inclusion to English-language publications.

Table 4. Summary of ERG's critique of the methods implemented by the company to identify evidence relevant to the decision problem

Systematic review step	Section of CS in which methods are reported	ERG assessment of robustness of methods
Data sources	Appendix D.1.1	**The ERG considers the sources and dates searched appropriate.** MEDLINE, EMBASE, PubMed, The Cochrane Library, latest search date: 11 August 2019. Trial registries (ISRCTN registry, WHO ICTRP, clinicaltrials.gov), conference proceedings (ASH, ASCO, ESMO, EHA, IMW), regulatory bodies (EMA, FDA), HTA agencies (NICE, CADTH, SMC, AWMSG), reference lists of reviews. Latest search update: August 2019
Literature searches	Appendix D.1.1, Tables 1–16	**The ERG is satisfied that searches would have identified all evidence relevant to the decision problem.** Search strategies combined comprehensive terms for the population and interventions, medical subject headings, and study design filters
Inclusion criteria	Appendix D.1.1, Table 17	**The ERG considers it likely that no relevant evidence was excluded based on the eligibility criteria used.** Inclusion criteria were broader than the NICE final scope, especially listed interventions of interest, which were considerably broader than the scope and the company's positioning of CRd. No explanation was provided for the rationale for the broad inclusion criteria, or for the subsequent exclusion of the majority of studies. The ERG assumes studies were excluded because they were not relevant to the decision problem. Limited to English-language publications.

Screening and data extraction	Appendix D.1.1, Figure 1	**The ERG considers the methods for screening described to be robust. Details on data extraction were not reported.** Independent duplicate screening and data extraction by two reviewers against predefined criteria; discrepancies resolved by consensus/with a third reviewer, screening results summarised in a PRISMA diagram.
Tool for quality assessment of included study or studies	Appendix D.3, Table 18	**The ERG agrees with the quality assessment tool used for the key trial, ASPIRE, but the company's assessment lacks details to support the assessment.** It is unclear if quality assessment was done by one or two reviewers and, if so, whether the assessments were done independently. ASPIRE was assessed based on the NICE guidance for companies. Limited details were provided in the CS for the judgement on each of the questions. However, the ERG notes that greater detail on the quality assessment is available in TA457.[8]

Abbreviations: ASCO, American Society of Clinical Oncology; ASH, American Society of Hematology; AWMSG, All Wales Medicines Strategy Group; C, carfilzomib; CADTH, Canadian Agency for Drugs and Technologies; CS, company submission; d, dexamethasone; EMA, European Medicines Agency; ERG, Evidence Review Group; ESMO, European Society for Medical Oncology; FDA, Food and Drug Administration; HTA, Health Technology Assessment; ICTRP, International Clinical Trials Registry Platform; ISRCTN, International Standard Randomised Controlled Trials Number; NICE, National Institute for Health and Care Excellence; R, lenalidomide; SMC, Scottish Medicine Consortium; WHO, World Health Organisation.

3.2 Critique of trials of the technology of interest, the company's analysis and interpretation

The ERG reiterates that the population relevant to the decision problem is a subgroup of those enrolled in ASPIRE,[9] and, moreover, is not a pre-specified subgroup. As a subgroup, and, in particular a *post hoc* subgroup, relevant estimates of comparative clinical effectiveness for CRd versus Rd are at a higher risk of bias than those reported for the full trial population. Finally, ASPIRE was not powered to detect a statistically significant difference in clinically relevant outcomes in the subgroup of interest to the decision problem.

In subsequent sections, the ERG focuses on aspects of trial design, conduct and external validity of ASPIRE that are of import to this STA because the listed areas have previously been covered in greater depth in TA457,[8] the original TA evaluating CRd versus Rd for the management of multiple myeloma. The ERG's critique of the internal validity of ASPIRE is available in Table 5. The ERG agrees with the company's assessment of ASPIRE as being at overall low risk of bias, based on the trial conduct and analyses for the full trial population.

Considering the *post hoc* subgroup that forms the basis of the CS, as noted in Section 2.3.1, data are derived from a subgroup in which a proportion of people have not received bortezomib, and others have undergone treatment with lenalidomide, as part of their last treatment regimen (hereafter referred to as 2L prior bortezomib). Estimates of PFS and OS for CRd versus Rd for those forming the 2L prior bortezomib inform the company's base-case analysis of cost effectiveness of CRd. For reasons outlined in 2.3.1, the ERG's preferred subgroup is that comprising people who received

carfilzomib at 2L after one line of prior bortezomib-based therapy and no lenalidomide (2L after prior bortezomib and no lenalidomide). The ERG notes that the two *post hoc* subgroups have similar baseline characteristics for the CRd and Rd treatment groups, and also comparable hazard ratios (HRs) are derived for PFS and OS for CRd versus Rd (discussed in greater detail in relevant sections). Hereafter, the ERG focuses its critique on data and results derived from the subgroup receiving CRd and Rd 2L after prior bortezomib and no lenalidomide. For comparative purposes, data for the 2L prior bortezomib subgroup that informs the company's base case are also presented. Key differences between the two *post hoc* subgroups are highlighted where applicable.

Table 5. Summary of ERG's critique of the design and conduct of ASPIRE, the trial evaluating the technology of interest to the decision problem

Aspect of trial design or conduct	Section of CS in which characteristic is reported	ERG's critique
Trial conduct[9]		
Randomisation	Section B.2.5 (page 31)	Appropriate. Randomisation carried out by IVRS. People randomised 1:1 to CRd versus Rd. Randomisation stratified by: • β2-microglobulin level (<2.5 vs ≥2.5 mg/L); • previous bortezomib therapy (no vs yes); • previous lenalidomide therapy (no vs yes).
Concealment of treatment allocation	Section B.2.5 (page 31)	Appropriate. Treatment allocation concealed through use of IVRS at randomisation.
Baseline characteristics	Section B.2.5 (page 31)	Baseline characteristics were well balanced between CRd and Rd groups in the ITT population. Imbalances in baseline characteristics were noted in the 2L prior bortezomib subgroup, as expected.
Masking appropriate	Section B.2.5 (page 31)	Open label design. However, primary analyses for disease progression-related outcomes (e.g., PFS and ORR) were based on assessment by a blinded IRC, including the primary outcome of PFS.
No difference between groups in treatments given, other than intervention versus control	Section B.2.5 (page 31)	No evidence to suggest that standard of care differed between treatment groups
Dropouts (high drop out and any unexpected imbalance between groups)	Section B.2.5 (page 31)	Low rate of loss to follow-up (1 person lost to follow-up from Rd group).
Outcomes assessed	Section B.2.5 (page 31)	No evidence to suggest that additional outcomes were assessed and not reported. All clinically relevant outcomes reported. Primary outcome was PFS as determined by IRC. Investigator-assessed PFS reported as a secondary outcome. Other secondary outcomes included: • OS; • ORR; • Time to response;

		• Best response; • Disease control rate; • Duration of disease control; • HRQoL (as assessed by EORTC QLQ-C30 GHS/QoL).
ITT analysis carried out	Section B.2.5 (page 31)	Yes ITT population formed the basis for analyses of efficacy and a PP population (all patients who received ≥1 dose of study drug) informed analyses of safety and tolerability.
Subgroup analyses	Section B.2.5 (page 31)	*Post hoc* subgroup analysis forms the basis of the submission that is the focus of this STA.
Statistical analysis plan		
Sample size	Section B.2.4 (page 30)	Calculation informed by median PFS for Rd (high-dose dexamethasone) derived from a phase III study. Sample size of 526 PFS events required at the time of the final analysis to give the desired power.
Power	Section B.2.4 (page 30)	Calculated sample size gives the study 90% power to detect a 33% increase in median PFS associated with CRd compared with Rd (14.9 months with CRd vs 11.2 months with Rd). A 33% increase in median PFS for CRd corresponds to a 25% decrease in risk of progression compared with Rd (i.e., HR 0.75) at a one-sided significance level of 0.025.
Analysis for estimate of effect	Section B.2.4 (page 30) Section B.2.7.7 (pages 47–49)	An interim analysis was performed after approximately 420 events had occurred (80% of the planned total). If there was a significant between-group difference in PFS at the interim analysis, secondary end points would be sequentially tested in the order of OS, ORR, and HRQoL, each at a one-sided significance level of 0.025. PFS and OS were compared between treatment groups with the use of a log-rank test stratified according to the factors used for randomisation. Hazard ratios were estimated by means of a stratified Cox proportional-hazards model. Distributions were summarized with the use of the Kaplan–Meier method. For the *post hoc* subgroup analyses, the company presents an IPW treatment effect: methods implemented in the IPW analysis are discussed in more detail in Section 3.3.1.1.

Abbreviations: C, carfilzomib; CI, confidence interval; CS, company submission; d, dexamethasone; EORTC QLQ-C30 GHS/QoL, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 Global Health Status/Quality of Life; ERG, Evidence Review Group; IPW, inverse probability weighted; IRC, Independent Review Committee; ITT, intention to treat; IVRS, interactive voice response system; mg, milligram; PFS, progression-free survival; ORR, overall response rate; OS, overall survival; PP, per protocol; R, lenalidomide; STA, Single Technology Appraisal.

3.2.1 Baseline characteristics

Baseline characteristics for the subgroup comprising people receiving carfilzomib 2L after prior bortezomib and with no lenalidomide, as provided by the company during clarification at the request of the ERG, are available in Appendix 9.1 (Table 37): baseline characteristics of the full trial population of ASPIRE (Table 38) and the subgroup of 2L prior bortezomib (Table 39) are also presented in Appendix 9.1.

As noted in TA457,[8] baseline characteristics for the full trial population of ASPIRE were well balanced between the treatment groups (Appendix 9.1; Table 38). The ERG's clinical experts highlighted that, as would be expected in a clinical trial, the enrolled population is slightly younger and has a better performance status (i.e., lower ECOG scores) than people typically presenting with multiple myeloma in clinical practice. After discussion, the committee for TA457 concluded that the population forming ASPIRE was generalisable to the UK population likely to be eligible for treatment with carfilzomib.[12]

As would be expected for non-randomised, *post hoc* subgroups, the ERG notes imbalances in some baseline characteristics between those given CRd and those administered Rd after a bortezomib-based regimen and no prior lenalidomide (Appendix 9.1; Table 37). Imbalances that require particular consideration are those characteristics that are considered to be factors that would influence prognosis, and those that are potential modifiers of treatment effect. The company consulted with clinical experts to identify key prognostics factors, a list of which is provided in Section 3.3.1.1: the ERG's advisors agreed with the factors identified by the company as impacting prognosis. One example of a marked imbalance in key characteristics is mean time since initial diagnosis, which is [redacted] for those allocated to Rd compared with those receiving CRd ([redacted] months with CRd vs [redacted] with Rd), which could introduce bias [redacted] of treatment with Rd. However, the ERG also notes that the standard deviation accompanying mean time since initial diagnosis is also [redacted] for the Rd group ([redacted] [95% CI: [redacted]] with CRd vs [redacted] [95% CI: [redacted]] with Rd), suggesting a [redacted] in time since initial diagnosis in those forming the Rd group compared with the CRd arm (Appendix 9.1; Table 37): 95% CI calculated by the ERG. By contrast, in the 2L prior bortezomib subgroup, median time since diagnosis is [redacted] in the CRd and Rd treatment groups at [redacted] and [redacted] years, respectively, but with a marked difference in the maximum time since diagnosis between groups ([redacted] years with CRd vs [redacted] years with Rd; Table 39).

In the 2L prior bortezomib no lenalidomide subgroup, differences between treatment groups were observed in the proportion of people refractory to prior bortezomib ([redacted]/74 [redacted] with CRd vs [redacted]/66 [redacted] with Rd), prior SCT ([redacted]/74 [redacted] with CRd vs [redacted]/66 [redacted] with Rd) and age of 75 years and older ([redacted]/74 [redacted] with CRd vs [redacted]/66 [redacted] with Rd). Similar differences were noted for the 2L prior bortezomib subgroup (Table 39).

The direction of bias introduced by the differences in baseline characteristics, and the impact on estimates of relative treatment effect, is unclear. To account for the imbalances between treatment groups, the company carried out an inverse probability weighted (IPW) analysis to adjust patient-level data for covariates identified by clinical experts as prognostic factors. The ERG's critique of the methods implemented by the company to carry out the IPW analyses is available in Section 3.3.1.1.

3.2.2 Outcome assessment

As noted in Table 1, revised estimates of comparative clinical effectiveness for CRd versus Rd that are based on more mature data are available in the CS for only PFS and OS, for both the ITT population of ASPIRE and the subgroup of those receiving treatment at 2L after prior bortezomib. Analysis of response rates by the Independent Review Committee (IRC) and capture of health-related quality of life (HRQoL) outcomes ceased on demonstration of a benefit in PFS and, thus, results for those outcomes are based on data from the interim analysis (June 2014).

Estimates of comparative clinical effectiveness for clinical outcomes at the interim analysis have been reported and critiqued as part of TA457.[8] Here, the ERG focuses on the robustness of the effect estimates generated for PFS and OS for the subgroup of interest to the STA.

For completeness, the ERG provides a brief summary of response rates, HRQoL, time to next treatment (TTNT) and adverse effects in the ITT population of ASPIRE. As noted in TA457, statistical significance of the difference between groups in secondary outcomes was only to be tested in a fixed sequence if the null hypothesis for the primary outcome of PFS (interim or final) was rejected. At the interim analysis, a statistically significant difference was found between treatment groups in PFS and, thus, significance of difference between groups for other outcomes was tested, starting with OS. At the interim analysis, the p-value boundary for OS to trigger testing of the next outcome in the sequence was not met and so formal statistical testing for the remaining secondary endpoints was precluded. Thus, any reported p-values for ORR, HRQoL and TTNT are descriptive in nature.

3.3 Clinical effectiveness results

As noted earlier, the ERG's preferred subgroup is that in which people received CRd 2L after prior bortezomib and with no prior treatment with lenalidomide. The company's base case is based on their preferred subgroup for CRd at 2L, which includes a proportion of people who received prior lenalidomide. For reference purposes, unadjusted and IPW-adjusted estimates of PFS and OS for the subgroup preferred by the company (received CRd at 2L after bortezomib) are also presented.

Estimates of comparative treatment effectiveness for PFS and OS reported in the CS are based on an additional 3 years of follow up compared with the data presented in TA457. Median follow-up at the time of the interim analyses (June 2014), which were evaluated in TA457, and at the time of the primary OS analysis (data cut-off of April 2017), which are reported here, are available in Table 6. Event rates for the full trial population at the time of the analysis are also provided in Table 6. The ERG notes that the sample size required at the time of the final analysis to give the desired power was 526 PFS events (Table 5). At the time of the primary OS analysis, 516 PFS events had occurred. As a statistically significant result was identified at the interim analysis of PFS, and also at the primary OS analysis, the ERG considers the results in the ITT population to be robust.

In TA457, the Committee recognised the limitations and uncertain outcomes associated with using data derived from subgroups that were not prespecified. The Committee also acknowledged that the company had attempted to mitigate against the uncertainty from using *post hoc* data through identifying additional covariates through a Cox proportional hazards model, and adjusting imbalances in baseline characteristics accordingly to provide estimates of efficacy for carfilzomib and its comparators. For consistency, here, the ERG focuses on the estimates of PFS and OS for CRd versus Rd generated from IPW-adjusted analyses based on data from the ERG's preferred subgroup. However, the ERG recognises that generation of *post hoc* subgroups renders the data produced to be observational in nature, and that any analyses derived from *post hoc* subgroups are considered to be hypothesis generating. In the CS, for the ITT population of ASPIRE, the company comments that, "*based on stepwise Cox regression modelling, there was a lack of evidence of treatment-covariate interactions for PFS suggesting an overall consistent treatment effect across the baseline covariate subgroups*". As the relative treatment effect for CRd versus Rd is consistent, irrespective of subgroup, to mitigate against uncertainty associated with *post hoc* subgroup analyses reported here, the ERG considers HRs derived from the ITT population of ASPIRE are informative. For comparison purposes, PFS and OS results for the ITT population in ASPIRE are presented alongside those for those receiving CRd at 2L after prior bortezomib, but with no lenalidomide (Sections 3.3.1.2 and

3.3.1.3 for PFS and OS, respectively). The ERG notes that, although the relative treatment effect of CRd versus Rd is constant irrespective of treatment group, there could be differences between treatment groups in absolute gain or loss of time to progression or death in the individual subgroups.

Table 6. Summary of median follow-up times and number of events on which PFS and OS analyses are based for the ITT population of ASPIRE

	PFS		OS	
Data cut-off	**CRd**	**Rd**	**CRd**	**Rd**
Interim (June 2014), follow-up months (95% CI)	31.4 (30.7 to 31.9)	30.1 (28.8 to 31.4)	32.3 (31.7 to 33.2)	31.5 (30.8 to 32.5)
Number of events	431		305	
Primary OS (April 2017), follow-up months	48.8 ([redacted]	48.0 [redacted]	67.1 [redacted]	67.1 [redacted]
Number of events	516		513	

Abbreviations: C, carfilzomib; CI, confidence interval; CS, company submission; d, dexamethasone; PFS, progression-free survival; OS, overall survival; R, lenalidomide.

3.3.1 *Progression-free survival and overall survival in* post hoc *subgroup*

3.3.1.1 *Inverse probability weighted analysis to derive effect estimates for relevant subgroup*

To account for imbalances in baseline characteristics, and to address the limitations associated with use of data derived from a *post hoc* subgroup, the company carried out an IPW to generate estimates for PFS and OS for CRd versus Rd in the subgroup of interest to the STA: details of methodology followed are available in Section B.2.7.2 (page 47) of the CS. The ERG agrees with the company's approach to mitigate against the issues arising from use of a *post hoc* subgroup.

Based on details available in the CS, the ERG had reservations on two aspects of the IPW:

- covariates accounted for in the IPW (discussed in subsequent section);
- use of Cox regression model to select covariates for the IPW (discussed in subsequent section).

Covariates accounted for in the IPW

In the CS, the company reports that they implemented a stepwise (backwards and forwards) Cox regression model to select covariates that should be accounted for in the analyses from a list of characteristics identified by clinical experts as being prognostic of outcomes in multiple myeloma.

In terms of the covariates assessed for inclusion in the regression analyses, the company reports that clinical experts identified the characteristics below as influencing prognosis:

- number of prior lines of therapy;
- prior exposure to lenalidomide or bortezomib;
- age (<65 vs ≥65 years);
- Eastern Cooperative Oncology Group performance status score (0 vs 1 or 2);
- creatinine clearance (<50, 50–80, or ≥80 mL/min);
- time since diagnosis;
- time since last relapse;
- International Staging System stage (I vs II or III);
- prior SCT;
- β2-microglobulin (<3.5 vs ≥3.5 mg/L);
- refractory to last prior treatment;
- cytogenetic risk status (high, standard, or unknown/missing).

As highlighted earlier, the ERG's clinical experts agreed that the characteristics listed are those likely to influence prognosis, and went on to comment that the extent of impact on prognosis will differ across the characteristics.

The ERG recognises that the most relevant characteristics have been considered by the company but comments that it is unclear from the CS what criterion has been applied to add or remove a covariate from the model for IPW analysis based on the company's preferred subgroup. The ERG notes that similar issues were raised in TA457, with the ERG commenting, "*The ERG has concerns about the lack of justification and use of a large number of covariates in the Cox proportional hazards models to estimate the efficacy of Cd and CRd in these* post hoc *subgroups of ENDEAVOR and ASPIRE*".[12]

During clarification, the company helpfully outlined the approach used to identify covariates to be included in the IPW estimate of comparative treatment effectiveness for PFS and OS, and reported the HR and 95% CI for CRd versus Rd after adjustment for an individual covariate, as well as an estimate of effect adjusted for all retained covariates. Details of estimates of effect for CRd versus Rd for included covariates are presented in Table 7.

Although the ERG predominantly considers the company's approach to identification of relevant covariates appropriate, the ERG considers it important to highlight that the regression analyses [redacted] for some covariates. The ERG considers that the results could suggest that the characteristics are potential treatment effect modifiers. In particular, adjustment for prior SCT and for β2-microglobulin level suggest that, compared with Rd, treatment with CRd is associated with a [redacted] (Table 7): [redacted] (Table 7). Similar [redacted] was noted in the IPW analyses presented in the CS relating to the subgroup preferred by the company. During clarification, the ERG queried whether the reported effect estimates were for, [redacted] irrespective of treatment received. The company confirmed that the estimates presented were for CRd versus Rd after adjustment for the individual covariate. The company commented that [redacted]. The ERG agrees that [redacted] are likely to have different characteristics [redacted] but considers that there is no clear clinical rationale [redacted]. As data are derived from *post hoc* subgroup analyses, the ERG emphasises that any inferences from the results are hypothesis generating.

Table 7. Results generated using covariates selected through the Cox proportional hazards regression model based on December 2017 data cut-off (adapted from Table 2 of the company's response to clarification)

Covariate	CRd versus Rd, 2L after bortezomib and no prior lenalidomide	
	PFS HR (95% CI)	OS HR (95% CI)
Treatment (CRd vs Rd)	[redacted]	[redacted]
Prior stem cell transplantation (yes vs no)	[redacted]	[redacted]
Age (≥65 vs <65)	[redacted]	[redacted]
ECOG status (1-2 vs 0)	[redacted]	[redacted]

Creatinine clearance (≥50 - <80 vs other)		
Creatinine clearance (≥80 vs other)		
Time from diagnosis		
Time from last relapse		
ISS stage (II-III vs I)		
β2-microglobulin (≥3.5 vs <3.5 mg/L)		
Refractory to last prior treatment (yes vs no)		

Abbreviations: 2L, second line; C, carfilzomib; CI, confidence interval; d, dexamethasone; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; ISS, International Staging System; OS, overall survival; PFS, progression-free survival; R, lenalidomide.

Use of Cox regression model to select covariates for the IPW

IPW utilises a logistic regression model to estimate the probability (propensity score) for a particular person of receiving a specific treatment (e.g., CRd or Rd) given confounding variables (covariates) of the patient.[19] The inverse of the estimated probabilities is applied to reweight the population and adjust for imbalances in the included covariates. A key assumption is that all confounders have been measured and properly modelled in the regression model. The ERG has reservations around the use of the Cox regression model to select the variables that are subsequently modelled by logistic regression. The ERG considers it could be more appropriate to select covariates using the same regression method applied to generate the IPW.

The ERG is unaware of formal guidance on how adjusted survival estimates in oncology should be generated when there are imbalances in baseline characteristics between treatment groups. Technical Support Document (TSD) 14 produced by the NICE Decision Support Unit (DSU) outlines various methodologies to survival analysis and provides guidance on assessing suitability of each method for a particular case, but methods to account for analyses based on adjusting survival for imbalances arising from use of *post hoc* subgroup analyses are not covered in this TSD.[20] Additionally, TSD17 outlines use of observational data to inform estimates of treatment effectiveness and covers methods on how to adjust for confounders, including IPW. Guidance in TSD17 highlights that the utility of IPW depends on how well the model for the propensity score predicts the probability of treatment, and that the propensity score should be sufficiently flexible, which can be achieved using a parametric model (e.g., probit or logit): the choice of parametric model can have an impact on the results.[21]

During clarification, the company gave a detailed description of the methods followed to generate the IPW-adjusted estimates of PFS and OS, which were as follows:

- the treatment indicator and the clinician-identified covariates were considered in a Cox proportional hazards model, and an automated stepwise variable selection procedure was performed using the stepAIC function in R, which minimises the AIC. Treatment-covariate interactions were not tested due to constraints related to sample size.
- a logistic regression model was subsequently conducted in which the treatment indicator was defined as the dependent variable and the covariates identified in the stepwise selection Cox model were used as independent variables. The retained variables for PFS and OS are summarised in Table 10.
- survival analyses were conducted on the weighted dataset.

The ERG highlights that, as requested during the clarification process, the company additionally used logistic regression to select covariates for which to retain in the IPW analyses, and provided results for IPW- adjusted PFS and OS.

In support of the use of the Cox regression model for covariate selection, as part of the clarification process, the company stated that, "*the logistic regression model can be interpreted as an approach where one searches and adjusts for covariates that are strongly related to the treatment received. However, the subgroup data is coming from a well-conducted randomised clinical trial where patients were randomly assigned to treatments. Therefore, in our view a more appropriate approach is to identify which covariates are strongly related to the outcome and adjust for imbalances in these covariates*".

The company also commented that resulting AIC for the model based on the stepwise selection within the logistic model were higher than those obtained when applying the stepwise selection within the Cox proportional hazard model, suggesting that selection of covariates using the Cox proportional hazards might provide a better representation of the data. The ERG disagrees with the company that the lower AIC associated with the final Cox proportional hazards regression implies that the model is a better representation of the data. AIC estimates the quality of each model relative to each of the other models in that analysis, and the lowest score identifies the best fitting model for that data set. The ERG considers that using different regression techniques to identify the covariates generates different data sets and thus the AIC scores are not directly comparable.

The ERG notes that similar estimates of comparative treatment effectiveness for PFS and OS are generated from IPW analyses adjusted for covariates identified using the Cox proportional hazards regression and the logistic regression. In their base case, the company utilises estimates derived

from covariates selected with the Cox proportional hazards regression model. For completeness, the ERG presents results from both analyses (Sections 3.3.1.2 and 3.3.1.3).

3.3.1.2 Progression-free survival

The ERG notes that PFS assessed by the IRC was the primary outcome in ASPIRE, and was met at the time of the interim analysis (data cut-off June 2014). Thus, as highlighted by the company, assessments of PFS after June 2014 are based on determinations by investigators and are not supported by determinations from an IRC. Given that ASPIRE was an open label study, the ERG notes that the determination of progression subsequent to June 2014 is at increased risk of bias.

At a cut-off date of December 2017, PFS for the ERG's preferred subgroup was based on a median follow-up of [redacted] and [redacted] months in the CRd and Rd groups, respectively (Table 8), which is [redacted] to that of the ITT population of ASPIRE (cut-off date of April 2017): Kaplan–Meier (KM) plot for PFS for the ITT population of ASPIRE is presented in Figure 2.

Without adjustment for imbalances in baseline characteristics, CRd was associated with an absolute increase in median PFS of [redacted] months compared with Rd (median PFS [months]: [redacted] [95% CI: [redacted] to [redacted]] with CRd vs [redacted] [95% CI: [redacted] to [redacted]] with Rd). Treatment with CRd was associated with a [redacted] in risk of progression or death (PFS), with the difference between CRd and Rd [redacted] in PFS compared with Rd (HR [redacted]; 95% CI: [redacted] to [redacted]; Table 8 and Figure 3).

After IPW adjustment for imbalances in key baseline characteristics (either method for stepwise selection of covariates), the [redacted] associated with treatment with CRd in the unadjusted analysis [redacted]. The difference between CRd and Rd in PFS [redacted], with [redacted] in risk of progression or death from [redacted] to [redacted] or to [redacted] for Cox proportional hazards and logistic regression analyses, respectively (Table 8 and Figure 4).

The ERG notes that the absolute difference in PFS is [redacted] when the restricted mean value is considered, with CRd associated with an improvement in PFS of [redacted] months [redacted] Rd (Table 8). The [redacted] in the median and mean values of PFS [redacted].

Table 8. Estimates of effect for progression-free survival for ITT population of ASPIRE and subgroup of those receiving CRd at 2L after prior bortezomib and no prior lenalidomide (ERG favoured subgroup) (adapted from Table 12 of the CS and Tables 4 and 5 of the company's response to clarification)

	ASPIRE ITT population April 2017 cut off		2L prior bortezomib/no prior lenalidomide December 2017 cut off PFS determined by investigators				2L prior bortezomib December 2017 cut off PFS determined by investigators			
			Unadjusted		IPW adjusted		Unadjusted		IPW adjusted	
	CRd (N = 396)	Rd (N = 396)	CRd (N = 74)	Rd (N = 66)	CRd (N = 68)	Rd (N = 69)	CRd (N = 93)	Rd (N = 73)	CRd (N = 82)	Rd (N = 81)
Total number of events, n (%)	244 (61.6%)	272 (68.7%)								
• Progression					NR	NR			NR	NR
• Death					NR	NR			NR	NR
Median PFS (95% CI), months	26.1 (23.2 to 30.3)	16.6 (14.5 to 19.4)								
Restricted mean PFS time (95% CI) [SE]	NR	NR			NR	NR			NR	NR
Median follow-up (95% CI), months	48.8	48.0								
Mean follow-up (95% CI), months	NR	NR			NR	NR			NR	NR
HR CRd vs Rd (95% CI) unadjusted	0.659 (0.553 to 0.784)				NA				NA	

HR CRd vs Rd (95% CI) adjusted for stratification variables[a]	NR	[redacted]	NA	[redacted]	NA
HR CRd vs Rd (95% CI) IPW-adjusted (stepwise selection within Cox model)	NA	NA	[redacted][b]	NA	[redacted][d]
HR CRd vs Rd (95% CI) IPW-adjusted (stepwise selection within logit model)	NA	NA	[redacted][c]	NA	[redacted][e]

[a] Stratification factors applied in ASPIRE were: β2-microglobulin level (<2.5 mg/L vs ≥2.5 mg/L), previous therapy with bortezomib (no vs yes), and previous therapy with lenalidomide (no vs yes).
[b] Variables adjusted for: [redacted].
[c] Variables adjusted for: [redacted].
[d] Variables adjusted for: [redacted].
[e] Variables adjusted for: [redacted].
Abbreviations: 2L, second line; AIC, Akaike 's Information Criterion; C, carfilzomib; CI, confidence interval; CS, company submission; d, dexamethasone; ERG, Evidence Review Group; HR, hazard ratio; IPW, inverse probability weighted; ITT, intention to treat; NA, not applicable; NR, not reported; PFS, progression-free survival; R, lenalidomide; SE, standard error.

Figure 2. Kaplan–Meier plot for unadjusted progression-free survival as determined by investigator for the ITT population from ASPIRE based on April 2017 cut off (reproduced from CS, Figure 6, page 40)

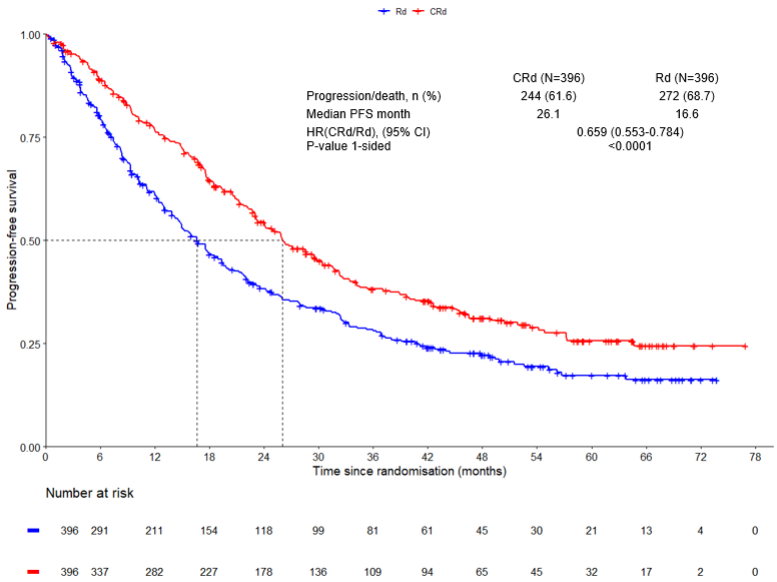


Figure 3. Kaplan–Meier plot for unadjusted progression-free survival for the subgroup receiving CRd at 2L after prior bortezomib and no lenalidomide (reproduced from Figure 1 of the company's response to clarification)

[redacted]

Abbreviations: 2L, second line; C, carfilzomib; d, dexamethasone; R, lenalidomide.

Figure 4. Kaplan–Meier plot for IPW-adjusted progression-free survival for the subgroup receiving CRd at 2L after prior bortezomib and no lenalidomide (reproduced from Figure 2 of the company's response to clarification; covariates selected using Cox proportional hazards regression)

Abbreviations: 2L, second line; C, carfilzomib; d, dexamethasone; R, lenalidomide.

Figure 5. Kaplan–Meier plot of IPW-adjusted PFS in the 1 prior therapy, prior bortezomib subgroup (ASPIRE, 5 December 2017 data cut; reproduced from the CS, Figure 9, page 50)

3.3.1.3 *Overall survival*

More mature data are now available to inform the analysis of OS, with a median follow-up of 67.1 months for the ITT population of ASPIRE and a total of 513 OS events (513/792 [64.8%]; Table 9): KM plot for unadjusted OS for ITT population of ASPIRE is presented in Figure 6.

In the subgroup of those receiving CRd or Rd at 2L after prior bortezomib and no lenalidomide, CRd was associated with an [redacted] in median survival of [redacted] months compared with Rd, and [redacted] in risk of death of [redacted], [redacted], the difference between treatments in OS [redacted] statistical significance (HR [redacted]; 95% CI: [redacted] to [redacted]; Table 9 and Figure 7). However, IPW analysis generates [redacted] for CRd compared with Rd, with [redacted] in risk of death from [redacted] (covariates selected by stepwise logistic regression), with the difference between groups [redacted] (HR [redacted]; 95% CI: [redacted] to [redacted]; Table 9 and Figure 8).

As is expected with OS, results are potentially confounded due to people moving on to non-randomised treatments due to progression of disease. Limited data are available in the CS on subsequent therapies received in the subgroup of interest to the STA. As part of the clarification process, the company provided details on treatments given at 3L for the ERG's preferred subgroup, and treatments given as subsequent treatments for the ITT population of ASPIRE (please see Table 32 in the company's response to clarification questions). The ERG noted that [redacted] at 3L, with [redacted] available in the NHS for the 3L setting (e.g. [redacted]). The proportion of people receiving individual therapies [redacted] across treatment groups, with the [redacted]. [redacted] people in the CRd group were given subsequent treatment with an investigational drug compared with Rd ([redacted] [[redacted]] with CRd vs [redacted] [[redacted]] with Rd). Conversely, a [redacted] ([redacted] [[redacted]] with CRd vs [redacted] [[redacted]] with Rd). The ERG's clinical experts commented that they would likely give bortezomib or ixazomib at third line to someone treated with a non-proteasome-inhibitor containing regimen (e.g., Rd) at second line.

Taking the ERG's reservations around the potential for confounding due to subsequent treatments, the ERG considers that the results for OS should be interpreted with a measure of caution.

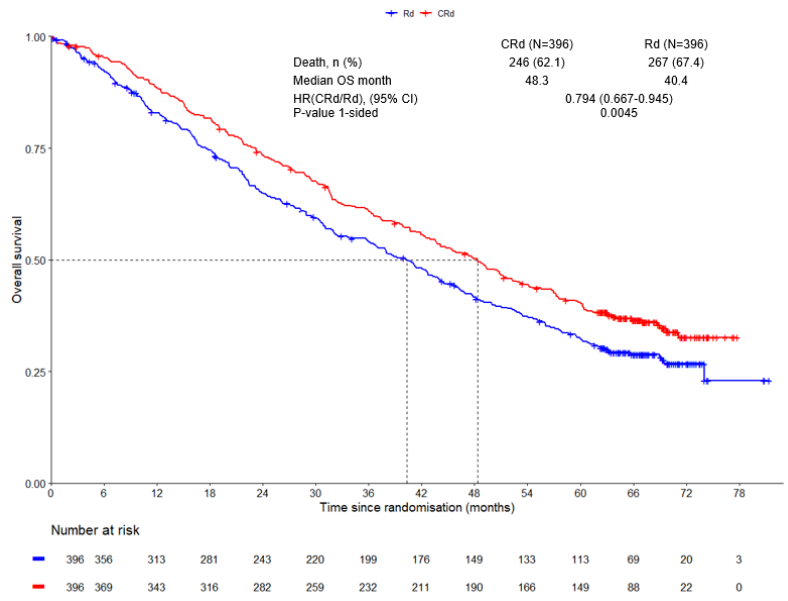
Table 9. Estimates of effect for overall survival for ITT population of ASPIRE and subgroup of those receiving CRd at 2L after prior bortezomib and no prior lenalidomide (ERG favoured subgroup) (adapted from Table 13 of the CS and Tables 8 and 9 of the company's response to clarification)

	ASPIRE ITT population April 2017 cut off		2L prior bortezomib/no prior lenalidomide December 2017 cut off				2L prior bortezomib December 2017 cut off			
			Unadjusted		IPW adjusted		Unadjusted		IPW adjusted	
	CRd (N = 396)	Rd (N = 396)	CRd (N = 74)	Rd (N = 66)	CRd (N = 69)	Rd (N = 68)	CRd (N = 93)	Rd (N = 73)	CRd (N = 82)	Rd (N = 81)
Total number of events, n (%)	246 (62.1%)	267 (67.4%)								
Median OS (95% CI), months	48.3 (42.4 to 52.8)	40.4 (33.6 to 44.4)								
Restricted mean OS time (95% CI) [SE]	NR	NR			NR	NR			NR	NR
Median follow-up (95% CI), months	67.1	67.1								
Mean follow-up (95% CI), months					NR	NR			NR	NR

HR CRd vs Rd (95% CI) Unadjusted	0.794 (0.667 to 0.945)	[redacted]	NA	[redacted]	NA
HR CRd vs Rd (95% CI) adjusted for stratification variables[a]	NR	[redacted]	NA	[redacted]	NA
HR CRd vs Rd (95% CI) IPW-adjusted (stepwise selection within Cox model)	NA	NA	[redacted][b]	NA	[redacted][d]
HR CRd vs Rd (95% CI) IPW-adjusted (stepwise selection within logit model)	NA	NA	[redacted][c]	NA	[redacted][e]

[a] Stratification factors applied in ASPIRE were: β2-microglobulin level (<2.5 mg/L vs ≥2.5 mg/L), previous therapy with bortezomib (no vs yes), and previous therapy with lenalidomide (no vs yes).
[b] Variables adjusted for: [redacted].
[c] Variables adjusted for: [redacted].
[d] Variables adjusted for: [redacted].
[e] Variables adjusted for: [redacted].
Abbreviations: 2L, second line; AIC, Akaike 's Information Criterion; C, carfilzomib; CI, confidence interval; CS, company submission; d, dexamethasone; ERG, Evidence Review Group; HR, hazard ratio; IPW, inverse probability weighted; ITT, intention to treat; NA, not applicable; NR, not reported; OS, overall survival; R, lenalidomide; SE, standard error.

Figure 6. Kaplan–Meier plot for unadjusted overall survival for the ITT population from ASPIRE based on April 2017 cut off (reproduced from CS, Figure 7, page 40)



Abbreviations: 2L, second line; C, carfilzomib; d, dexamethasone; R, lenalidomide.

Figure 7. Kaplan–Meier plot for unadjusted overall survival for the subgroup receiving CRd at 2L after prior bortezomib and no lenalidomide (reproduced from Figure 5 of the company's response to clarification)

Abbreviations: 2L, second line; C, carfilzomib; d, dexamethasone; R, lenalidomide.

Figure 8. Kaplan–Meier plot for IPW-adjusted overall survival for the subgroup receiving CRd at 2L after prior bortezomib and no lenalidomide (covariates selected using Cox proportional hazards regression model; reproduced from Figure 6 of the company's response to clarification)

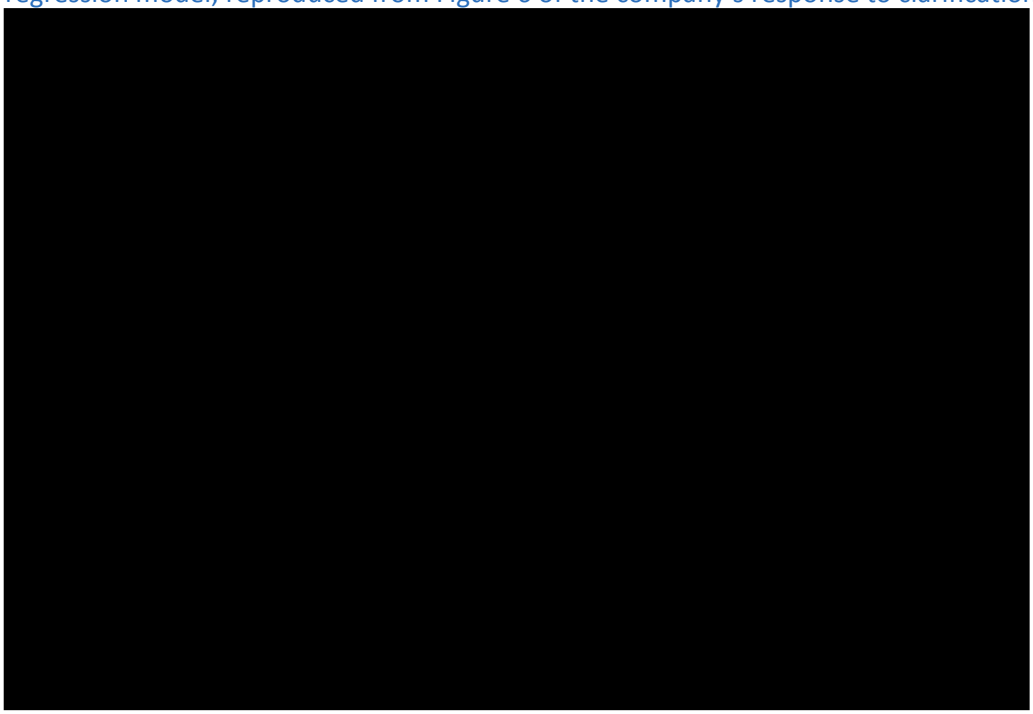


Figure 9. Kaplan–Meier plot of IPW-adjusted OS in the 1 prior therapy, prior bortezomib subgroup (ASPIRE, 5 December 2017 data cut; reproduced from the CS, Figure 9, page 50)

Abbreviations: 2L, second line; C, carfilzomib; d, dexamethasone; IPW, inverse probability weighted; R, lenalidomide.

3.3.2 Summary of other clinically relevant outcomes

A summary of results from ASPIRE for overall response rate and time to next treatment are available in Appendix 9.2.

3.3.2.1 Health-related quality of life

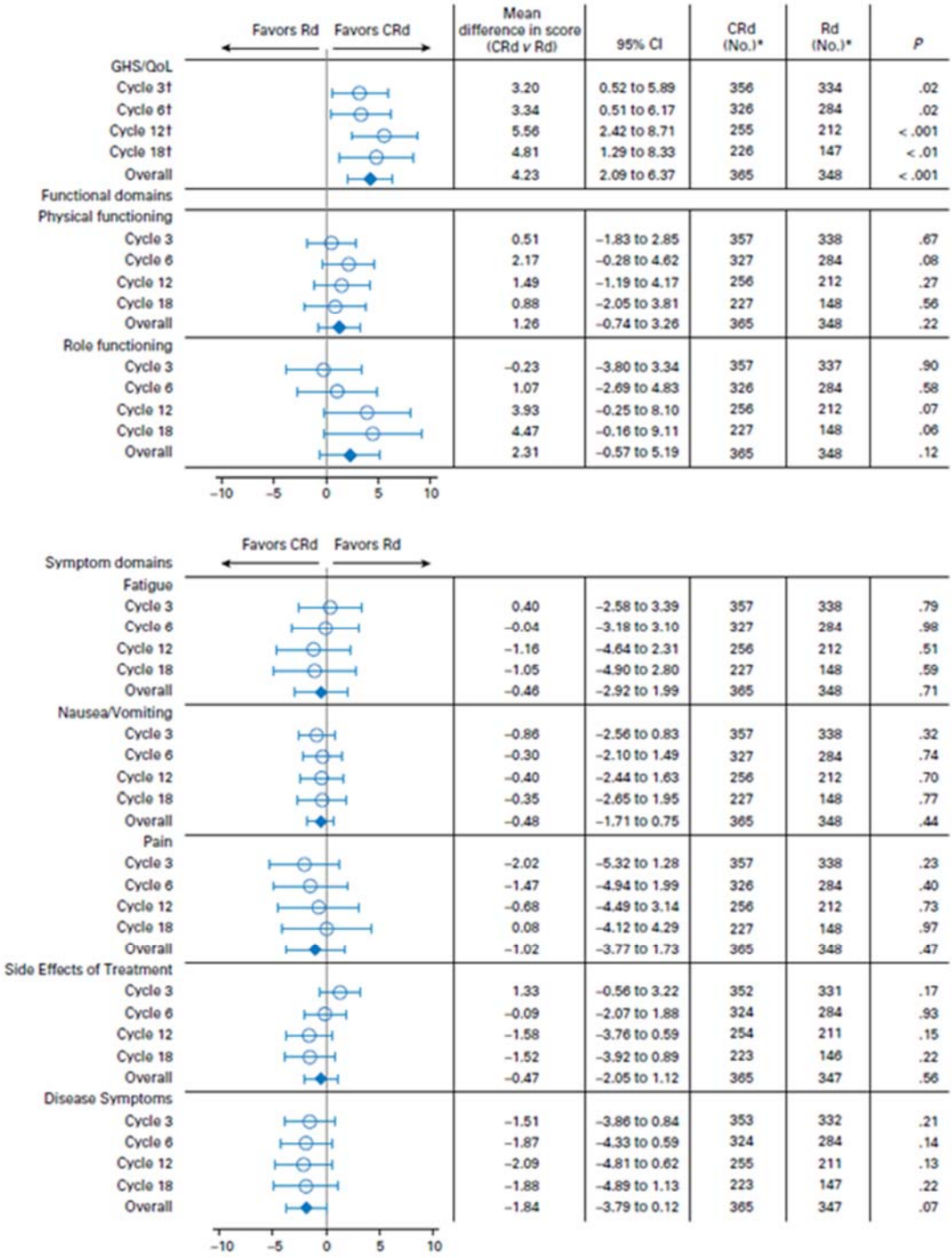
HRQoL was captured in ASPIRE using the EORTC QLQ-C30 questionnaire and the 20-item myeloma-specific EORTC QLQ-MY20 module. The company used the data on collected on EORTC QLQ-C30 score to predict an EQ-5D-3L utility score for each patient through application of a mapping algorithm.[22] As HRQoL data captured from ASPIRE have been used to inform the economic model, the results for HRQoL are presented here.

Analysis of HRQoL is based on results from the interim analysis (June 2014), as, like response, data on HRQoL was no longer collected on demonstration of a benefit of PFS.

Of the 792 people forming the ITT population, 713 (90%) completed at least 1 HRQoL assessment after baseline evaluation and were included in the analyses (CRd, n = 365; Rd, n = 348). Baseline QLQ-C30 and QLQ-MY20 subscale scores were similar between treatment groups.

Over 18 cycles of treatment, global health status scores as assessed using QLQ-C30 GHS/QoL were statistically significantly higher for the group receiving CRd compared with those treated with Rd (two-sided p <0.001; Figure 10). The minimal important difference (MID) for between-group differences on QLQ-C30 GHS/QoL is 5 points.[23-26] Based on the predefined threshold, the MID between CRd and Rd was met at cycle 12 (MID = 5.56) and was approached at cycle 18 (4.81). No statistically significant differences between CRd and Rd were recorded on other components of the HRQoL tools and no other MID was met, but a trend in favour of CRd was observed in differences across subscales (Figure 10).

Figure 10. Treatment difference in EORTC QLQ-C30 and myeloma-specific EORTC QLQ-MY20 module based on the interim analysis data cut-off for the ASPIRE population[a,b] (reproduced from the CS, Figure 8, page 43)



[a] Based on patients completing at least 1 post-baseline HRQoL assessment.

[b] Values shown are the adjusted least squares mean treatment difference in scores from a restricted maximum likelihood-based model for repeated measures under the assumption of missing at random. Scores are adjusted for baseline score, baseline score by visit interaction and the randomisation stratification factors (β2-microglobulin levels [<2.5 mg/L vs ≥2.5 mg/L], prior bortezomib (no vs. yes), and prior lenalidomide (no vs. yes).

Abbreviations: C, carfilzomib; CI, confidence interval; CS, company submission; d, dexamethasone; EORTC, European Organization for Research and Treatment of Cancer; HRQoL, health-related quality of life; R, lenalidomide.

3.3.2.2 *Adverse effects*

The CS (Section B.2.10, pages 62–67) gives a detailed overview of the adverse effects experienced by people enrolled in ASPIRE. Here, the ERG provides an overview of adverse effects, with a focus on those that have been included in the economic model, or those that have been omitted from the model and the ERG considers important to include.

Safety and tolerability data derived from ASPIRE and reported in the CS are based on the data cut-off of 28 April 2017, which includes approximately 3 additional years of follow-up compared with the interim analysis presented in TA457.[8] The company comments that the results based on longer follow-up are consistent with those from the interim analysis presented in TA457 and no new risks have been identified. The company highlights that there was no additional exposure to carfilzomib during longer term follow-up, as all people in the CRd group had completed carfilzomib treatment before the cut-off date for the interim analysis. As per the protocol for ASPIRE, people could continue treatment with Rd in both groups. At the time of the primary OS analysis data cut-off, [redacted] ([redacted]) and [redacted] ([redacted]) people in the CRd and Rd groups, respectively, remained on study treatment.

People continued allocated study treatment longer in the CRd arm than the Rd arm, with median treatment duration of [redacted] weeks and [redacted] weeks, respectively (April 2017 cut-off date).

Adverse effects accounted for in the economic model are:

- Neutropenia;
- Anaemia;
- Thrombocytopenia;
- Cataract;
- Hyperglycaemia;
- Lymphopenia;
- Hypertension;
- Fatigue;
- Hypokalaemia;
- Hypophosphataemia;
- Pneumonia.

Serious adverse reactions that could occur during treatment with carfilzomib that are not included in the economic model are cardiac disorders (e.g., congestive cardiac failure, pulmonary oedema,

decreased ejection fraction),[15] which the ERG's clinical experts advised was an important omission (discussed in greater detail in Section 4.2.6). The Summary of Product Characteristics (SmPC) for carfilzomib reports cardiac disorders as a special warning and precaution for use.[15] The SmPC details that cardiac toxicity typically occurs early in the course of treatment but also advises that people are assessed for cardiovascular risk factors before starting treatment with carfilzomib.[15]

Cardiac failure and ischaemic heart disease occurred [redacted] in the CRd group compared with the Rd group (Table 10). [redacted] were also more common with CRd than with Rd (Table 10). For the adverse effects considered in the economic model, with the exception of lymphopenia, a larger proportion of people receiving CRd experienced the event compared with people allocated to Rd (Table 10).

Table 10. Selected adverse events of interest from the ASPIRE safety population based on the April 2017 data cut-off (adapted from CS, Tables 25 [page 64] and 26 [page 66])

Adverse effect	CRd (N = 392) n (%)		Rd (N = 389) n (%)	
Preferred term	All Grades	Grade ≥3	All Grades	Grade ≥3
Cardiac failure	[redacted]	[redacted]	[redacted]	[redacted]
Ischaemic heart disease	[redacted]	[redacted]	[redacted]	[redacted]
Venous thromboembolic events	[redacted]	[redacted]	[redacted]	[redacted]
Peripheral neuropathy	[redacted]	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]	[redacted]
Neutropenia	157 (40.1)	122 (31.1)	136 (35.0)	107 (27.5)
Anaemia	169 (43.1)	73 (18.6)	158 (40.6)	68 (17.5)
Thrombocytopenia	115 (29.3)	66 (16.8)	94 (24.2)	51 (13.1)
Cataract[a]	44 (11.2)	20 (5.1)	37 (9.5)	17 (4.4)
Hyperglycaemia[a]	50 (12.8)	21 (5.4)	39 (10.0)	18 (4.6)
Lymphopenia[a]	13 (3.3)	11 (2.8)	14 (3.6)	8 (2.1)
Fatigue	131 (33.4)	32 (8.2)	124 (31.9)	26 (6.7)
Hypokalaemia	116 (29.6)	41 (10.5)	58 (14.9)	23 (5.9)
Hypophosphataemia[a]	57 (14.5)	35 (8.9)	33 (8.5)	20 (5.1)
Pneumonia	91 (23.2)	63 (16.1)	66 (17.0)	47 (12.1)

[a] Taken from Clinical Study Report.[11]
Abbreviations: C, carfilzomib; CS, company submission; d, dexamethasone; R, lenalidomide.

3.4 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

As highlighted in Section 2.3.3, the ERG does not consider daratumumab (D) in combination with bortezomib (V) and dexamethasone (d) at 2L after prior bortezomib to be a valid comparator for the STA reported here. The indirect comparison between CRd and DVd, presented by the company in the CS, is therefore not described or critiqued in this report.

3.5 Conclusions of the clinical effectiveness section

Evidence in support of the clinical effectiveness of CRd in the management of multiple myeloma at 2L is derived from ASPIRE, a randomised controlled trial enrolling adults with multiple myeloma who had received one or more previous lines of therapy. Thus, the population relevant to the decision problem is a subgroup of those taking part in ASPIRE, and, moreover, is not a pre-specified subgroup. As a *post hoc* subgroup, relevant estimates of comparative clinical effectiveness for CRd versus Rd in those receiving treatment at 2L after prior bortezomib are at a higher risk of bias than those reported for the full trial population.

Considering the *post hoc* subgroup that forms the basis of the CS and informs the company's base case in their economic evaluation, data presented by the company are derived from a subgroup in which a proportion of people have not received bortezomib, and others have undergone treatment with lenalidomide, as part of their last treatment regimen (2L prior bortezomib). No lenalidomide-based regimen is recommended by NICE as a treatment option in combination with bortezomib in the first-line setting. Thus, as part of the clarification process, the ERG requested a second *post hoc* subgroup comprising people who had received bortezomib-based regimen as their first treatment and excluding those who had received lenalidomide as part of their first-line regimen (2L prior bortezomib/no lenalidomide). The ERG notes that the two *post hoc* subgroups have similar baseline characteristics for the CRd and Rd treatment groups, and also that comparable hazard ratios (HRs) are derived for PFS and OS for CRd versus Rd.

As would be expected for non-randomised, *post hoc* subgroups, the ERG noted imbalances in some baseline characteristics between those given CRd and those administered Rd for both subpopulations. The direction of bias introduced by the differences in baseline characteristics, and the impact on estimates of relative treatment effect, is unclear. To account for imbalances in baseline characteristics, and to address the limitations associated with use of data derived from a *post hoc* subgroup, the company carried out an inverse probability weighted (IPW) analysis to generate estimates for PFS and OS for CRd versus Rd in the subgroups of people receiving CRd at 2L, for both the company's and ERG's preferred subgroup. In TA457, results from subgroup analyses adjusted to account for imbalances in baseline characteristics arising from non-randomised groups were accepted by the committee. The ERG agrees with the company's approach to mitigate against the issues arising from use of a *post hoc* subgroup. In the CS, the company highlights that for PFS, "*there is a consistent treatment effect across baseline covariate subgroups*". As HRs derived from an

ITT population of an RCT are, by their nature, more robust than those generated from a subgroup analysis, the ERG considers that the results from the ITT population are also relevant to the STA.

In their IPW analysis, the company implemented stepwise Cox regression analysis to select covariates for retention in the model that would subsequently be adjusted using logistic regression to generate IPW estimates. The ERG had reservations around the use of Cox regression to select covariates. On request, the company provided IPW analyses of PFS and OS in which covariates were selected using logistic regression. Similar HRs for PFS and OS are generated from IPW analyses adjusted for covariates selected using the Cox proportional hazards regression and the logistic regression.

Estimates of comparative treatment effectiveness for PFS and OS reported in the CS are based on an additional 3 years of follow up compared with the data presented in TA457. The ERG notes that PFS assessed by the IRC was the primary outcome in ASPIRE, and was met at the time of the interim analysis (data cut-off June 2014). Assessments of PFS after June 2014 are based on determinations by investigators and are not supported by determinations from an IRC. Given that ASPIRE was an open label study, the ERG notes that the determination of progression subsequent to June 2014 is at increased risk of bias.

For the 2L prior bortezomib/no prior lenalidomide subgroup, without adjustment for imbalances in baseline characteristics, CRd was associated with an absolute increase in median PFS of [redacted] months compared with Rd (median PFS [months]: [redacted] [95% CI: [redacted] to [redacted]] with CRd vs [redacted] [95% CI: [redacted] to [redacted]] with Rd). Treatment with CRd was associated with a [redacted] in risk of progression or death (PFS), with the difference between CRd and Rd [redacted] in PFS compared with Rd (HR [redacted]; 95% CI: [redacted] to [redacted]). After IPW adjustment for imbalances in key baseline characteristics (either method for stepwise selection of covariates), the [redacted] associated with treatment with CRd in the unadjusted analysis [redacted]. The difference between CRd and Rd in PFS [redacted], with [redacted] in risk of progression or death from [redacted] to [redacted] or to [redacted] for Cox proportional hazards and logistic regression analyses, respectively.

In the subgroup of those receiving CRd or Rd at 2L after prior bortezomib and no lenalidomide, CRd was associated with an [redacted] in median survival of [redacted] months compared with Rd, and [redacted] in risk of death of [redacted], [redacted], the difference

between treatments in OS [redacted] statistical significance (HR [redacted]; 95% CI: [redacted] to [redacted]). However, IPW analysis generates [redacted] for CRd compared with Rd, with [redacted] in risk of death from [redacted] (covariates selected by stepwise logistic regression), with the difference between groups [redacted] (HR [redacted]; 95% CI: [redacted] to [redacted]). As is expected with OS, results are potentially confounded due to people moving on to non-randomised treatments due to progression of disease. The ERG noted that [redacted] at 3L, with [redacted] available in the NHS for the 3L setting (e.g. [redacted]). The ERG notes that similar estimates of comparative treatment effectiveness for PFS and OS are generated from IPW analyses for the company's and ERG's preferred subgroups.

Although the ERG predominantly considers the company's approach to identification of relevant covariates appropriate, the ERG considers it important to highlight that the regression analyses [redacted] for some individual covariates. The ERG considers that the results could suggest that the characteristics are potential treatment effect modifiers. In particular, adjustment for prior SCT and for β2-microglobulin level suggest that, compared with Rd, treatment with CRd is associated with a [redacted] (Table 7): [redacted] (Table 7). Similar [redacted] was noted in the IPW analyses presented in the CS relating to the subgroup preferred by the company. During clarification, the ERG queried whether the reported effect estimates were for, [redacted] irrespective of treatment received. The company confirmed that the estimates presented were for CRd versus Rd after adjustment for the individual covariate. The company commented that [redacted]. The ERG agrees that [redacted] are likely to have different characteristics [redacted] but considers that there is no clear

clinical rationale

[redacted]. As data are derived from *post hoc* subgroup analyses, the ERG emphasises that any inferences from the results are hypothesis generating.

4 Cost effectiveness

4.1 ERG comment on the company's review of cost effectiveness evidence

The company performed a systematic literature review (SLR) to identify published studies of economic evaluation, health-related quality of life (HRQoL), resource-utilisation, and costs, relating to patients with relapsed or refractory multiple myeloma (R/RMM) who have received at least one prior therapy. The SLR was an update of the company's original appraisal (TA457)[27] and was conducted most recently on 16th March 2018 in anticipation of this part-review of the appraisal. A summary of the ERG's critique of the company's SLR is given in Table 11.

Table 11. Summary of ERG's critique of company's SLR

Systematic review step	Section of CS in which methods are reported			ERG assessment of robustness of methods
	Cost effectiveness evidence	HRQoL evidence	Resource use and costs evidence	
Search strategy	Appendix G	Appendix G	Appendix G	The search was performed around 2 years ago, so it may not include all the latest evidence.
Inclusion/exclusion criteria	Appendix G	Appendix G	Appendix G	Appropriate
Screening	Appendix G	Appendix G	Appendix G	Appropriate
Data extraction	Appendix G	Appendix G	Appendix G	Appropriate
Quality assessment of included studies	Appendix G	Appendix G	Appendix G	Appropriate

Abbreviations: CS, company submission; ERG, evidence review group; HRQoL, health related quality of life.

The company's SLR resulted in the inclusion of 43 economic evaluations, 15 cost/resource use studies and 22 HRQoL studies.

The company's SLR was generally sound but was performed around 2 years ago and therefore may have missed relevant studies published since then. Despite this, the ERG considers the sources used by the company throughout the analysis to be generally reasonable and unlikely to be limited by the restriction of the SLR date.

4.2 Summary and critique of company's submitted economic evaluation by the ERG

4.2.1 NICE reference case checklist

Table 12 summarises the ERG's appraisal of the company's economic evaluation against the requirements set out in the NICE reference case checklist for the base-case analysis, with reference to the NICE final scope outlined in Section 2.

Table 12. NICE reference case checklist

Element of health technology assessment	Reference case	ERG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	All relevant health effects for adult patients with multiple myeloma who have received only one prior therapy with bortezomib have been included.
Perspective on costs	NHS and PSS	All relevant costs have been included and are based on the NHS perspective.
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	Cost-utility analysis with fully incremental analysis has been provided by the company.
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Lifetime horizon (40 years).
Synthesis of evidence on health effects	Based on systematic review	The company performed an appropriate systematic review.
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	QALYs using data from the EORTC QLQ-C30 and the myeloma-specific EORTC QLQ-MY20 taken from ASPIRE and mapped to the EQ-5D-3L.
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	EORTC QLQ-C30 and the myeloma-specific EORTC QLQ-MY20 reported directly from the subgroup of interest in ASPIRE, mapped to obtained EQ-5D-3L utility values.
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	The subgroup of interest from ASPIRE is representative of the UK population.
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	The economic evaluation matches the reference case.

Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Costs included in the analysis have been sourced using NHS reference costs[28], MIMS[29], eMIT[30] and published literature and are reported in pounds sterling for the price year 2018.
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Discount rate of 3.5% has been used for both costs and health effects.

Abbreviations: eMIT, Drug and pharmaceutical electronic market information tool; EORTC QLQ-C30, European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire C30; EQ-5D-3L, EuroQoL five dimensions three levels; ERG, evidence review group; MIMS, monthly index of medical specialities; NHS, national health service; PSS, personal social services; QALY, quality adjusted life year

4.2.2 Population

The population considered by the company for this single technology appraisal (STA) is adult patients with multiple myeloma who have received only **one** prior therapy with bortezomib (hereafter referred to as the 2L prior bortezomib subgroup). The population under consideration is a restricted sub-population of the marketing authorisation (MA) for the triplet therapy, carfilzomib in combination with lenalidomide and dexamethasone (hereafter referred to as CRd), which does not restrict prior therapy to bortezomib.

The restricted population proposed by the company is a deviation from the NICE final scope, which proposes the relevant population to be adult patients with multiple myeloma who have received **at least** one prior therapy. The company justify the positioning of CRd for the 2L prior bortezomib subgroup as they state it reflects the need for triplet therapies earlier in the pathway, greater benefit of the treatment is demonstrated in this subgroup and thus offers the greatest economic value, and lastly, it aligns with the NICE recommendation for Rd, which is deemed the most relevant comparator. The ERG's clinical experts agreed that there is an unmet need in the second-line setting. Furthermore, the ERG considers that not exploring subgroups where cost-effectiveness cannot be demonstrated is appropriate and pragmatic.

However, as discussed in Section 2.3.1, the ERG noted that the company's subgroup included a proportion of people who had not received bortezomib as part of their last round of therapy ([redacted]), as well as people who had undergone treatment with lenalidomide in their last regimen ([redacted]). Given that the company is positioning CRd at the 2L setting and after prior bortezomib, as part of the clarification process, the ERG requested that the company generate a new subgroup comprising people who had undergone only one round of therapy that was bortezomib-based and who had not received prior lenalidomide, and to provide revised estimates of

PFS and OS for the new subgroup (hereafter referred to as 2L prior bortezomib/no prior lenalidomide) and incorporate these into the cost-effectiveness analysis.

The company provided revised cost-effectiveness results for the 2L prior bortezomib/no prior lenalidomide subgroup as a scenario only and maintained that the 2L prior bortezomib subgroup analysis is more appropriate because patients could receive lenalidomide as first-line treatment in combination with bortezomib. Thus, the company did not change its base-case assumptions. However, in England, bortezomib plus lenalidomide is not an approved therapy at first-line. As such, the ERG considers the 2L prior bortezomib/no prior lenalidomide subgroup to be more reflective of patients who would be eligible for CRd and Rd in England and has implemented this subgroup for the ERG base-case analysis (Section 6.4).

4.2.3 Interventions and comparators

The intervention under consideration for the economic analysis is CRd, which is a triplet therapy consisting of carfilzomib in combination with lenalidomide and dexamethasone.

The comparators considered by the company are Rd, which is doublet combination therapy of lenalidomide and dexamethasone, and daratumumab plus bortezomib and dexamethasone (DVd). However, DVd is only available through the Cancer Drugs Fund and is not approved for use in routine commissioning. Therefore, NICE has advised that DVd is not a relevant comparator for this analysis and is not discussed further in this ERG report.

The company's choice to limit the comparator to Rd, based on the restriction of the population to the 2L prior bortezomib subgroup, only partially reflects the NICE final scope. The NICE final scope splits the population by line of therapy and outlines comparators for each subgroup. For the 2L subgroup, the comparators of interest in the NICE final scope are Rd, carfilzomib in combination with dexamethasone (Cd) and bortezomib monotherapy. However, the company's restriction to one prior therapy with bortezomib removes Cd and bortezomib monotherapy as comparators and ignores the third- and fourth-line subgroups. As mentioned in Section 4.2.2, the ERG considers the company's justification to restrict to the 2L prior bortezomib subgroup reasonable and as such considers that Rd is the most relevant comparator at second-line of therapy.

The dosing regimen for the individual components of CRd and Rd (carfilzomib, lenalidomide and dexamethasone) is presented in Table 13.

Table 13. Treatment dosing regimen

Treatment	Dose	Dose regimen	Treatment duration
Carfilzomib	Starting dose of 20mg/m^2 on days 1 and 2 of cycle 1 (maximum dose of 44mg). Target dose of 27mg/ m^2 thereafter (maximum dose of 60mg).	**Cycles 1-12**: 10-minute IV infusion on days 1,2,8,9,15 and 16 of a 28-day treatment cycle. **Cycles 13-18**: 10-minute IV infusion on days 1,2,15 and 16 of a 28-day cycle.	Up to 18 cycles
Lenalidomide	25mg per dose	One tablet, taken orally on days 1-21 of a 28-day treatment cycle.	Treatment until progression of disease or unacceptable toxicity.
Dexamethasone	40mg per dose	20 tablets, taken orally on days 1, 8, 15 and 22 of a 28-day treatment cycle.	Treatment until progression of disease or unacceptable toxicity.

Abbreviations: IV, intravenous; m^2, metre-squared; mg, milligram.

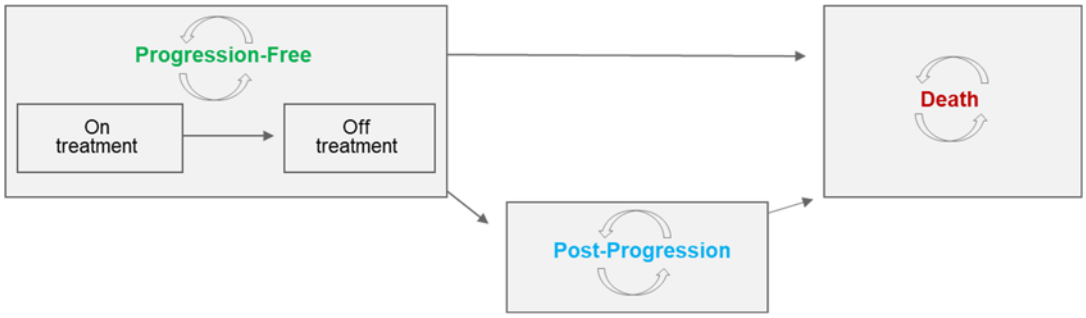
Time to treatment discontinuation (TTD) for carfilzomib, lenalidomide and dexamethasone in the CRd and Rd arms is based on data from the ASPIRE trial, extrapolated over a lifetime horizon using standard parametric survival distributions (described further in Section 4.2.5). It should be noted that in ASPIRE, treatment for carfilzomib was capped to 18 cycles and this is reflected in the economic analysis. For lenalidomide and dexamethasone, discontinuation of treatment was primarily due to disease progression or because of unacceptable toxicity.

4.2.4 Modelling approach and model structure

A single *de novo* economic model was developed in Microsoft© Excel to assess the cost-effectiveness of CRd compared with Rd for the treatment of adult patients with multiple myeloma who have received at least one prior therapy with bortezomib (2L prior bortezomib subgroup).

The model structure is based on a partitioned survival analysis structure, with three health states: progression-free, progressed and dead. The progression-free health state is further sub-divided into progression-free and on-treatment and progression-free off-treatment. Figure 11 presents the company's model schematic. The company state that the chosen model structure is in line with previous HTA oncology models, specifically in the area of multiple myeloma.[4, 7, 31-33]

Figure 11. Model structure (adapted from the schematic presented in the company's economic model)



All patients enter the model in the progression-free health state and are assumed to start treatment on CRd or Rd. During each model cycle, patients in the progression-free health state can be either on-treatment or off-treatment if they are experiencing unacceptable toxicity. Furthermore, from the progression-free health state, patients can transition to either the progressed health state when they experience disease progression or die (thus transitioning to the dead health state). When patients transition to the progressed health state, they remain there until death.

Extrapolations of clinical outcomes data, including progression-free survival (PFS), overall survival (OS) and TTD, using standard parametric curves are implemented in the model to estimate the proportion of patients occupying a health state in any given model cycle. PFS is used to estimate the proportion of patients occupying the progression-free health state, OS is used to model the death state and TTD is used to estimate the proportion of patients who are progression-free and on-treatment. The proportion of patients occupying the progressed health state for any given cycle is calculated as the difference between OS and PFS per cycle. A detailed description of how the survival curves were estimated and implemented in the model is provided in Section 4.2.5.

A model cycle length of 28-days with half-cycle correction applied was implemented in the model and is reflective of a treatment cycle length for carfilzomib. The model time horizon was set to 40 years, considered by the company to be sufficiently long enough to capture a lifetime as the median age in ASPIRE at baseline was 64 years. The perspective of the analysis was based on the UK national health service (NHS), with costs and benefits discounted using a rate of 3.5%, as per the NICE reference case.[34]

4.2.4.1 ERG Critique

The ERG considers the structure of the company's model is appropriate, capturing all relevant health states and clinically plausible transitions between health states that are largely similar to other appraised oncology models. The 28-day cycle length used in the model is suitable to capture important changes in the health state of patients, allowing for robust estimates of costs and benefits to be calculated for each treatment. Half-cycle correction has been appropriately applied in the model to prevent over or under-estimation of costs and quality-adjusted life-years (QALYs).

4.2.5 Treatment effectiveness

Overview of the company's approach to survival analysis

Treatment effectiveness estimates in the economic model for CRd and Rd are calculated using extrapolations of ASPIRE inverse probability weighted (IPW) Kaplan Meier (KM) PFS and OS data for the 2L prior bortezomib subgroup (company base-case). At the request of the ERG, the company also provided a scenario where alternative treatment effectiveness estimates for CRd and Rd are based on extrapolations of IPW KM PFS and OS data for the 2L prior bortezomib/no prior lenalidomide subgroup, which is discussed further in Section 4.2.5.1. The data cut-off point for all analyses was 5 December 2017.

For the company's base-case analysis, OS estimates used in the economic model incorporate extrapolated real-world data from the MyelomaToul registry. Time-on-treatment estimates in the model for carfilzomib, lenalidomide and dexamethasone for each treatment arm are based on extrapolations of TTD KM data for the 2L prior bortezomib subgroup from ASPIRE.

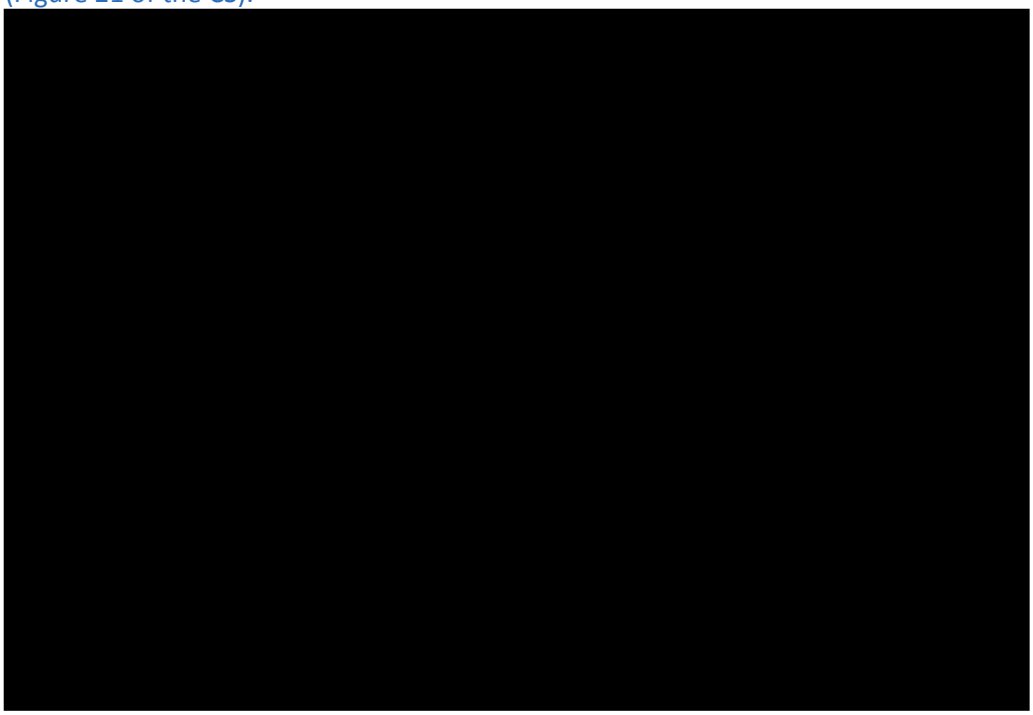
The company first assessed whether the assumption of proportional hazards (PH) held for PFS and OS outcomes from ASPIRE for both the intention-to-treat (ITT) population, as well as the 2L prior bortezomib subgroup using log-cumulative hazard plots. The company used the outcomes of the PH assessment to decide to either jointly or separately fit survival distributions. Extrapolations of the KM data were then performed using standard parametric survival distributions (exponential, Weibull, Gompertz, log-normal, log-logistic and generalised gamma). For the extrapolation of the MyelomaToul registry data, the company also assessed piecewise exponential models with different time-point cut-offs.

The process of curve selection recommended in the NICE decision support unit technical support document (DSU TSD) 14 was implemented by the company to select an appropriate distribution for the extrapolation of each outcome.[20] The company assessed the fit of each modelled curve against the KM data using statistical goodness of fit statistics, including Akaike information criterion (AIC) and Bayesian information criterion (BIC) statistics, visual inspection of the curves and clinical plausibility of the extrapolation over the time horizon of the model.

Progression-free survival

Based on AIC/BIC statistics and visual fit, the company selected the generalised gamma distribution for the PFS extrapolation, presented in Figure 12. Plots of all the assessed distributions compared with the KM data and AIC/BIC statistics can be found in Appendix M.5 of the CS.

Figure 12. PFS curves used for the company's base-case analysis; 2L prior bortezomib subgroup (Figure 21 of the CS).



Abbreviations: CS, company submission; CRd, Carfilzomib plus lenalidomide and dexamethasone; KM, Kaplan Meier; PFS, progression-free survival; Rd, lenalidomide plus dexamethasone.

A comparison of the IPW KM PFS curves in Figure 12 shows that the curves cross at around 66 months after randomisation (please refer to Figure 32, Appendix M of the CS for a more detailed presentation of the KM curves). The company state this is due to the small numbers at risk towards the end of the data cut-off (5 December 2017), such that one event causes a substantial change in the KM curve. The crossing of the curves was deemed clinically implausible by the company and its

clinical experts as the treatment effect for OS remained consistent throughout follow-up. Furthermore, the KM PFS curve for the ITT population (Figure 26, Appendix M of the CS) demonstrated a consistent separation of the curves for CRd and Rd and the log-cumulative hazard plots demonstrated that the PH assumption holds (Figure 40, Appendix M of the CS).

Thus, the company chose to model PFS jointly instead of separately as they state that the ITT data for PFS are more informative to decide on the approach to modelling the 2L prior bortezomib subgroup data as they are based on more patients and demonstrate consistency of the treatment effect for CRd.

Overall survival

The company explored whether the assumption of PH held for the IPW KM OS data for the 2L prior bortezomib subgroup to determine the choice of jointly or separately modelling the parametric survival curves. Based on the log-cumulative hazards plots, presented in Figure 19 of Appendix M 3.2 of the CS, the company concluded that the PH assumption held and jointly modelled the OS curves for CRd and Rd.

The company explored the statistical and visual fit of standard parametric distributions to the IPW KM OS data, as well as the clinical plausibility of the extrapolations. The company selected the Weibull distribution as the best fit but found that the estimates of survival produced for the Rd curve towards the end of the extrapolation (0% at 20 years) were conservative when compared with survival estimates of 11% at 25 years, presented for the technology assessment of Rd (TA586), though the ERG for TA586 found the estimates implausible.[7]

As such, the company used real-world data from a French registry of multiple myeloma patients, MyelomaToul, to inform the extrapolations of OS for both the Rd and the CRd arms of the model.[35] The company digitised published data from the registry of patients treated with second-line lenalidomide (n=1,890) and explored three piecewise exponential models with cut off points of 48, 60 and 72 months to extrapolate the data. The company stated that all three models visually fit the data well and chose the piecewise exponential model with the cut-off point of 72 months as it had the best statistical fit (lowest AIC value). The exponential model pieces can be defined as period one, which is months 0 to 72 and period two, which is 72 months onwards.

In their clarification response, the company confirmed that standard parametric curves (exponential, Weibull, Gompertz, log-logistic, lognormal and generalised gamma) were also explored but found that the piecewise exponential model (no cut-off stated) had the best statistical fit.

Based on the piecewise exponential model for the MyelomaToul data, a survival probability for one cycle was estimated separately for period one and period two. The company then calculated an adjusted MyelomaToul survival curve (referred to as the matched MyelomaToul curve in the CS) to account for the difference in the mortality rate between the registry data and the IPW subgroup data from ASPIRE. The adjusted curve was calculated by applying time-dependent hazard ratios (HR) to the survival probability for one cycle for period one and then period two.

The company calculated the time-dependent HRs by fitting a Cox model to the MyelomaToul KM data and the IPW KM data for the 2L prior bortezomib subgroup. The company selected time-dependent HRs to adjust the MyelomaToul registry data because up to month 10 the two data sets overlapped and thereafter separated out (Figure 13). As such, the HR for the period 0-10 months was 1.01 and for 11 months onwards, the HR was 2.04. The company explored the use of a constant HR in a scenario, presented in Section 5.2.

Figure 13. Comparison of Kaplan-Meier overall survival data for MyelomaToul and ASPIRE (2L prior bortezomib subgroup) (Figure 17 of the CS)

Abbreviations: 2L, second-line; CS, company submission; CRd; pB, prior bortezomib; Rd, lenalidomide plus dexamethasone.

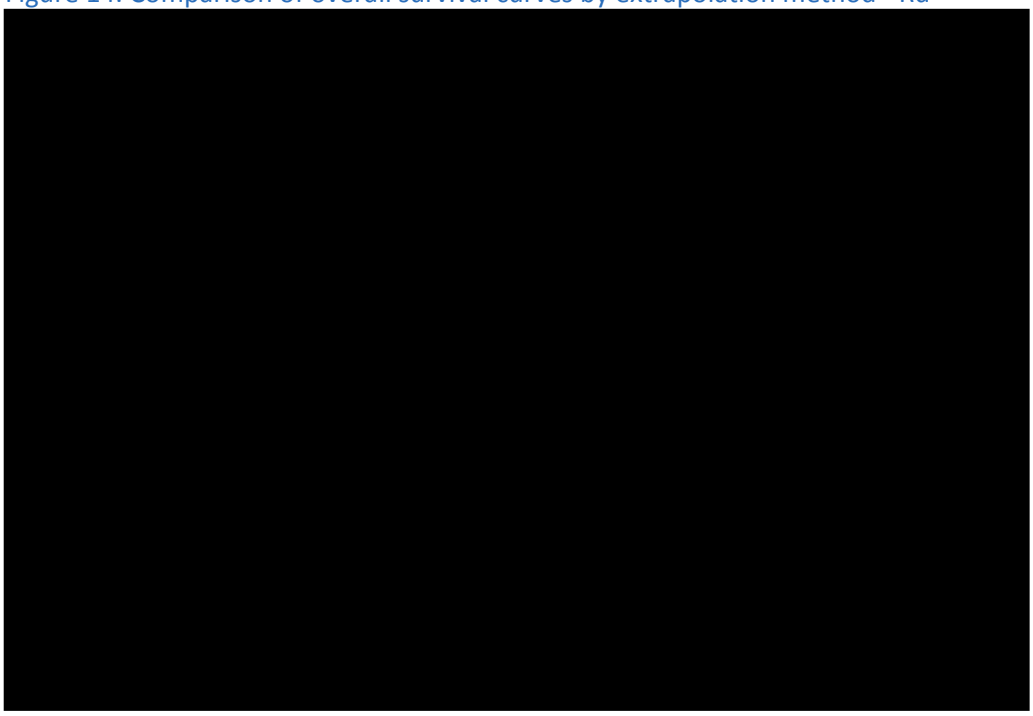
The company's base-case OS curve for Rd is a hybrid of the Weibull survival curve, based on IPW KM subgroup data, truncated to month 72 and then from month 72 onwards, the hazards from the adjusted MyelomaToul piecewise exponential survival curve are applied to the survival proportion estimated in the previous cycle. To estimate the CRd OS curve, first the company applied the IPW OS HR for the subgroup derived from ASPIRE ([redacted]) to the adjusted MyelomaToul Rd OS curve to calculate the per-cycle hazards. Then, for the first 72 months, the ASPIRE Weibull OS curve for CRd was used and thereafter the hazards from the first step were applied to survival proportion estimated in the previous cycle to construct the remaining portion of the OS curve. Table 14, Figure 14 and Figure 15 present comparisons of OS predictions for the Weibull extrapolation of ASPIRE IPW subgroup data and the hybrid method using MyelomaToul data.

Table 14. Comparison of overall survival predictions by extrapolation method

OS assumptions	10 years		20 years	
	CRd	Rd	CRd	Rd
ASPIRE Weibull distribution	16%	5%	2%	0%
Adjusted MyelomaToul model + HR	21%	9%	9%	1%

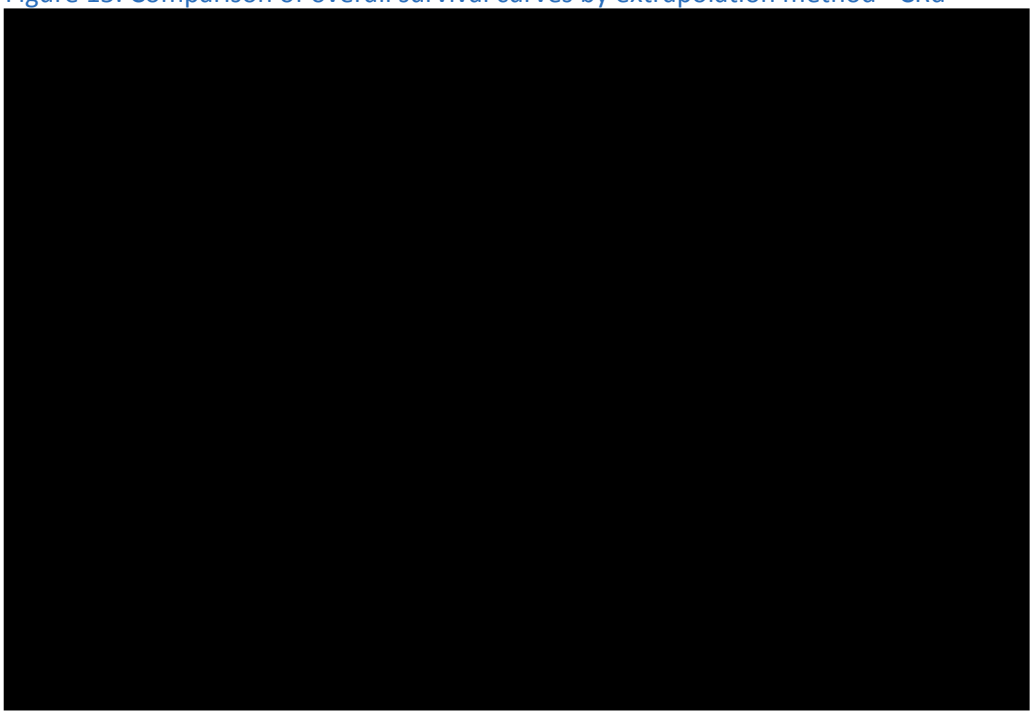
Abbreviations: CRd, carfilzomib plus lenalidomide and dexamethasone; HR, hazard ratio; ITT, intention-to-treat; OS, overall survival; Rd, lenalidomide plus dexamethasone

Figure 14. Comparison of overall survival curves by extrapolation method - Rd



Abbreviations: KM, Kaplan Meier; Rd, lenalidomide plus dexamethasone.

Figure 15. Comparison of overall survival curves by extrapolation method - CRd



Abbreviations: CRd, carfilzomib plus lenalidomide and dexamethasone; KM, Kaplan Meier.

Time-to-treatment discontinuation

Time-to-treatment discontinuation for each treatment in the CRd and Rd arms was modelled separately as the company states that patients may discontinue different components of combination therapy at different times. As such, IPW TTD KM subgroup data from ASPIRE for carfilzomib, lenalidomide and dexamethasone for CRd and Rd were used to inform the survival extrapolations. It should be noted that in ASPIRE, carfilzomib treatment was capped at 18 treatment cycles. Thus, the company truncated the carfilzomib survival extrapolation to 18 model cycles. In addition, the company states that as PFS is longer for patients on CRd compared with Rd, and treatment duration with lenalidomide and dexamethasone is also longer, lenalidomide and dexamethasone have been modelled separately for CRd and Rd. In the model, TTD is capped to PFS to ensure patients are not accruing treatment costs if they have disease progression.

Table 15 presents the parametric survival distributions selected by the company for use in the base case analysis, based on AIC/BIC statistics and visual fit of the curve to the KM data. Plots of all the assessed distributions compared with the KM data and AIC/BIC statistics can be found in Appendix M.6 of the CS.

Table 15. Selected TTD survival distributions for components of CRd and Rd (Table 30 of the CS)

Treatment component	CRd	Rd
Carfilzomib	Gompertz	-
Lenalidomide	Exponential	Log-logistic
Dexamethasone	Exponential	Log-logistic

Abbreviations: CRd, Carfilzomib plus lenalidomide and dexamethasone; CS, company submission; Rd, lenalidomide plus dexamethasone; TTD, time to treatment discontinuation.

4.2.5.1 ERG critique

The company's base-case cost-effectiveness analysis is based on the IPW 2L prior bortezomib subgroup from ASPIRE. As mentioned in Sections 2.3 and 4.2.2, this subgroup includes patients who have received prior lenalidomide, which the ERG considers does not reflect UK clinical practice. Thus, the ERG's critique of treatment effectiveness is based on the IPW 2L prior bortezomib/no prior lenalidomide subgroup data from ASPIRE and the analysis provided by the company in their response to ERG clarification questions. It should be noted that the methods of analysing the data remain the same as in the company base-case and it is only the underlying data sources and extrapolations that have been updated (presented in Figures 8, 9 and 10 of the company's response to ERG clarification questions). Table 16 presents a comparison of the treatment effectiveness parameters used for the company's base-case and the company's scenario for the 2L prior bortezomib/no lenalidomide subgroup.

Table 16. Comparison of treatment effectiveness parameters for company base-case vs company scenario for the 2L prior bortezomib/no lenalidomide subgroup

Model parameter	Company base case (2L prior bortezomib)		Company scenario (2L prior bortezomib/no prior lenalidomide)	
	CRd	Rd	CRd	Rd
PFS	Joint fitted generalised gamma		Joint fitted generalised gamma	
OS	Joint fitted Weibull (first 72months), then MyelomaToul Rd with ASPIRE IPW OS HR applied for the remainder of the model	Joint fitted Weibull (first 72 months) + matched MyelomaToul (piecewise exponential, cut-off at 72 months)	Joint fitted Weibull (first 72 months), then MyelomaToul Rd with ASPIRE IPW OS HR applied for the remainder of the model	Joint fitted Weibull (first 72 months) + matched MyelomaToul (piecewise exponential, cut-off at 72 months)
TTD - carfilzomib	Gompertz	-	Exponential	-
TTD – lenalidomide	Exponential	Log-logistic	Exponential	Log-logistic
TTD - dexamethasone	Exponential	Log-logistic	Exponential	Log-logistic

IPW OS HR (CRd vs Rd)	[redacted]	-	[redacted]	-
Time dependent HRs for MyelomaToul adjustment	-	1.02 before 10 months, 2.04 thereafter	-	[redacted]

Abbreviations: 2L, second-line; CRd, Carfilzomib plus lenalidomide and dexamethasone; HR, hazard ratio; IPW, inverse probability weighted; OS, overall survival; PFS, progression-free survival; Rd, lenalidomide plus dexamethasone; TTD, time to treatment discontinuation.

As mentioned in Section 3.4, the ERG considers the company's IPW analysis to adjust the ASPIRE ITT data for the 2L prior bortezomib/no prior lenalidomide subgroup is reasonable. The ERG's main concern with the modelling of treatment effectiveness is how the company has estimated OS, using real-world data to adjust mature trial-based data. The company extrapolated ASPIRE trial data but found the estimates for key time points (10 and 20 years) for the Rd arm did not pass clinical validity based on a comparison of estimates produced by previous TAs (TA586, TA573, TA457)[7, 27, 36]. Namely, the company deemed the estimates produced by the best-fitting Weibull curve for Rd to be pessimistic, predicting survival at 10 and 20 years to be 5% and 0%, respectively. Using data from the MyelomaToul registry for the 2L lenalidomide population, the company estimated what they believed to be more clinically plausible survival estimates of 9% and 1% for 10 and 20 years (Table 14).

The company also provided results from a multistate model based on ASPIRE ITT data (Appendix N of the CS) which estimated survival at 20 years to be between 1.9% and 3%. Even though the estimates are not based on the subgroup of interest, the company state the multi-state model results are generalisable to the subgroup of interest. The ERG highlights that the model was not submitted to the ERG and estimates of survival for CRd were not provided for comparison. However, the ERG considers that it was not necessary to investigate the model further, as mature trial data from ASPIRE for the subgroup of interest are available and as mentioned previously, the three-state model is appropriate.

In the statistical analysis report for MyelomaToul, produced specifically for Amgen, the ERG found that the subgroup data used in the modelling is not adjusted for "only one prior therapy that was a bortezomib-based regimen", which would match the company base-case population.[35] In the report, of patients not undergoing SCT (referred to as a graft; second plot of Figure 15), approximately 50% of patients received a bortezomib-based regimen as their first-line treatment and nearly 30% of patients received therapy classed as "other". The ERG assumes that the analyses were bespoke for Amgen and thus considers that the company could have requested a subgroup analysis of OS for patients who only received a bortezomib-based treatment as their first-line therapy and then went

on to 2L lenalidomide. The mixture of first-line treatments may be an influential factor on OS for 2L lenalidomide patients from MyelomaToul as OS in this group is longer than that of 2L Rd patients who had one prior treatment with bortezomib and no lenalidomide from ASPIRE (Figure 16).

The ERG acknowledges that the company has adjusted the data to account for the mortality difference between the two datasets, but because the shape of the tail of the adjusted MyelomaToul curve is different to the ASPIRE KM curve (Figure 16), the adjustment influences the extrapolation of the data and results in an increase in survival in the tail compared with Weibull extrapolation of the ASPIRE data (see Figure 14). Furthermore, as can be seen in Figure 16, the company's adjustment of the MyelomaToul data shows that only 1% are alive from year 12 onwards, rather than the 20 years reported by the company.

Figure 16. Comparison of OS KM for 2L lenalidomide treated patients in MyelomaToul and ASPIRE 2L prior bortezomib/no prior lenalidomide (taken from the economic model)

Abbreviations: 2L, second-line; KM, Kaplan Meier; MT, MyelomaToul; Rd, lenalidomide with dexamethasone.

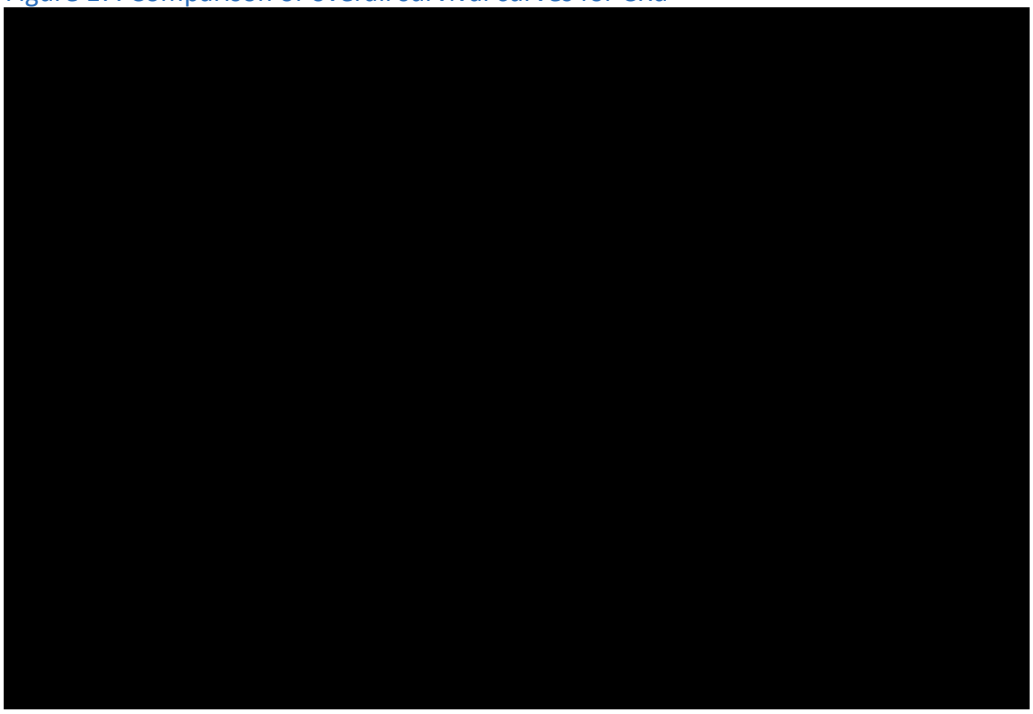
The ERG consulted its clinical experts who confirmed that longer-term survival estimates for Rd patients based on ASPIRE are conservative. However, the consequence of the company's adjustment when using real-world evidence is that survival is inflated for CRd compared with the estimates based on IPW ASPIRE data presented in Figure 15, improving its cost-effectiveness.

Where trial data are available DSU TSD 14 recommends selecting a different extrapolation based on trial data that produces more clinically valid estimates of survival.[20] In their response to the ERG's

clarification question B7, the company states that when using the MyelomaToul extrapolation to validate the ASPIRE extrapolation, the exponential distribution provides the most plausible long-term predictions of survival, with results comparable between the models (Table 17). However, the company considered their base-case approach more appropriate as the model had a better statistical fit to the observed data. Though in their main submission, the company states that all models for the ASPIRE OS data performed similarly well in terms of statistical fit. Moreover, for the company base-case subgroup (2L prior bortezomib) the exponential model was the second-best fitting distribution. For the ERG preferred subgroup (2L prior bortezomib/ no prior lenalidomide), the exponential model was statistically the best fit to the KM data.

Figure 17 presents a comparison of the different modelling approaches for CRd OS and it can be seen that the exponential distribution is less pessimistic than the Weibull distribution but is also less optimistic than the company's base-case approach using MyelomaToul data.

Figure 17. Comparison of overall survival curves for CRd



Abbreviations: CRd, carfilzomib plus lenalidomide and dexamethasone, KM, Kaplan Meier.

The ERG considers that 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[27] 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 for to limit bias and it maintains the observed treatment effect between the two trial arms, increasing the

robustness of the cost-effectiveness analysis. Therefore, the ERG deems it appropriate to revert to the company's survival modelling of the ASPIRE subgroup data wholly for CRd and Rd and considers the exponential model to be appropriate to model OS and explores this in a scenario presented in Table 17 and Section 6.3.

The ERG highlights an additional issue regarding the treatment effect for subgroups. In the CS the company states that "*based on stepwise Cox regression modelling, there was a lack of evidence of treatment-covariate interactions for PFS suggesting an overall consistent treatment effect across the baseline covariate subgroups"*. This statement infers that while the absolute benefit may be different based on the particular subgroup the relative benefit between the two treatment groups is consistent irrespective of subgroup. As such, the ERG considers that the HRs for PFS (HR 0.66) and OS (HR 0.794) derived from the ITT population are relevant for consideration and requested the company to provide a scenario applying the ITT HRs to the baseline Rd PFS and OS extrapolations to construct alternative CRd PFS and OS curves.

The company did not supply the requested scenario with their clarification response and instead provided what the ERG considers to be a circular argument for why it is inappropriate to use the ITT HRs. The company state that, "*ASPIRE was not primarily designed to detect significant treatment effects within subgroups, and consequently lacked power to detect significant treatment-covariates interactions. In addition, we also noted that there may be important differences in baseline characteristics across study arms in subgroups (particularly if the subgroup is constructed by multiple covariates such as for the current assessment) that confound the subgroup-specific treatment effect estimates"*.

From the company's statement, the ERG understands that the HRs for the base-case subgroup (2L prior bortezomib) and the ERG preferred subgroup (2L prior bortezomib/no prior lenalidomide) are likely to be confounded whereas the results from the randomised ITT population are not. Therefore, the ERG considers it is still relevant to explore the impact of applying the ITT HRs to construct alternative CRd PFS and OS curves and conducted the following two scenario analyses for the ERG preferred subgroup (2L prior bortezomib/no prior lenalidomide):

1. Applying the ITT PFS and OS HRs to the company's preferred PFS and OS survival curves for Rd.

2. Applying the ITT PFS HR to the company's preferred Rd PFS curve and the ITT OS HR to the ERG's preferred modelling of Rd OS using the exponential distribution to extrapolate ASPIRE IPW data.

Results of these scenarios can be found in Section 6.3 and a comparison of the OS predictions by extrapolation method are presented in Table 17.

Table 17. Comparison of overall survival predictions by extrapolation method for the 2L prior bortezomib/ no prior lenalidomide subgroup

OS assumptions	10 years		20 years	
	CRd	Rd	CRd	Rd
ASPIRE Weibull distribution	16%	5%	2%	0%
ASPIRE exponential distribution (ERG preferred)	**19%**	**8%**	**4%**	**1%**
Adjusted MyelomaToul model + HR (company base case)	**21%**	**9%**	**6%**	**1%**
ITT PFS and OS HRs applied to company scenario for PFS and OS for Rd	15%	9%	3%	1%
ITT PFS HR applied to company scenario Rd PFS curve and ITT OS HR applied to ERG alternative OS modelling for Rd using the exponential distribution for ASPIRE data only.	13%	8%	2%	1%

Abbreviations: CRd, carfilzomib plus lenalidomide and dexamethasone; ERG, evidence review group; HR, hazard ratio; ITT, intention-to-treat; OS, overall survival; PFS, progression-free survival; Rd, lenalidomide plus dexamethasone

Aside from the issues with OS, the ERG considers the modelling of PFS using the jointly fitted generalised gamma distribution is appropriate. Furthermore, the use of the log-logistic distribution to extrapolate TTD for lenalidomide and dexamethasone for the Rd arm of the model is reasonable.

The ERG had concerns with the modelling of TTD for CRd treatment components. Specifically, the Weibull distribution for the TTD modelling of carfilzomib, lenalidomide and dexamethasone for the CRd arm provided a better fit to the observed KM data then the company's base-case choice of the exponential distribution. However, a scenario using the ERG's preferred survival curves for the extrapolation of CRd TTD had minimal impact on the ICER. Results of the scenario can be found in Section 6.2.

4.2.6 Adverse events

For the base case analysis, the company included grade 3 or higher treatment-emergent adverse events (TEAEs) that were reported by at least 5% of patients in the safety population in either treatment arm of ASPIRE, presented in Table 18.

Table 18. Grade 3 or higher AEs implemented in the model (Table 47 of the CS)

Adverse events	CRd (%)	Rd (%)
Neutropenia	31.12	27.51
Anaemia	18.62	17.48
Thrombocytopenia	16.84	13.11
Cataract	5.10	4.37
Hyperglycaemia	5.36	4.63
Lymphopenia	2.81	2.06
Hypokalaemia	10.46	5.91
Fatigue	8.16	6.68
Hypertension	5.36	2.31
Hypophosphataemia	8.93	5.14
Pneumonia	16.07	12.08

Abbreviations: CRd, Carfilzomib plus lenalidomide and dexamethasone; Rd, lenalidomide plus dexamethasone

The company then estimated per-cycle probabilities of experiencing each adverse event using the following formula:

Per-cycle probability of AE = 1-EXP(((LN(1-incidence of AE))/mean number of treatment cycles in ASPIRE))

Table 19 presents the per-cycle AEs for each treatment arm included in the model.

Table 19. Probability of AEs per cycle implemented in the model (Table 47 of the CS)

Adverse events	CRd (%)	Rd (%)
Neutropenia	1.24%	1.39%
Anaemia	0.69%	0.83%
Thrombocytopenia	0.61%	0.61%
Cataract	0.17%	0.19%
Hyperglycaemia	0.18%	0.21%
Lymphopenia	0.09%	0.09%
Hypokalaemia	0.37%	0.26%
Fatigue	0.28%	0.30%
Hypertension	0.18%	0.10%
Hypophosphataemia	0.31%	0.23%
Pneumonia	0.58%	0.56%

Abbreviations: CRd, Carfilzomib plus lenalidomide and dexamethasone; Rd, lenalidomide plus dexamethasone

The impact of AEs on patients' quality of life is considered in the model and is described further in Section 4.2.7, while the costs of managing AEs are discussed in Section 4.2.8.

4.2.6.1 ERG critique

After consultation with the ERG's clinical experts, cardiac failure was found to be an omission from the model. In ASPIRE, [redacted] of CRd patients and [redacted] of Rd patients experienced grade 3 or higher cardiac failure. Furthermore, the company presented grade 3 or higher adverse events of interest (which included cardiac failure) that were also not included in the analysis (Table 26 of the CS). The ERG requested the company to provide a scenario where grade 3 or higher adverse events of interest are included in the model in addition to the TEAEs.

The company advised the ERG that it was not possible to provide the requested scenario within the timeframe to respond to ERG clarification questions and instead took a pragmatic approach to provide a scenario where costs of cardiac failure are included in the model and a second scenario where AE costs are increased by 50%. Both scenarios were found to have minimal impact on the ICER. Details of the scenarios can be found in Table 25 to Table 28 of the company's response to ERG clarification questions.

Overall, the ERG considers that AEs are not a primary driver of cost-effectiveness in the model and that any amendments to how these are incorporated in the economic model are unlikely to have a substantial impact on the ICER.

4.2.7 Health-related quality of life

4.2.7.1 Health-State Utility Values

The ASPIRE study did not collect utility data directly but did collect HRQoL data using two disease-specific measures; the cancer-specific European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC QLQ-C30) and the myeloma-specific EORTC QLQ-MY20. Using these data, the company applied a published mapping algorithm by Proskorovsky *et al.* 2014[22], to predict an EQ-5D-3L utility score for each patient based on their EORTC QLQ-C30 score.

This mapping study was used in the original TA457 appraisal based on an SLR of mapping studies. The company did not perform an update to this SLR but instead searched the University of Oxford Health Economics Research Centre mapping database in April 2016 to identify any more recently published studies that may be relevant. Only one study was identified but was not considered further as it was based on newly diagnosed MM patients (MYELOMA-IX). The Proskorovsky *et al.*

2014 algorithm was, therefore, used again as per the original TA457, as well as for the NICE appraisal of panobinostat (TA380).[22, 27, 31]

The predicted EQ-5D-3L utility values were then analysed using a repeated-measures mixed-effects linear regression model. The company stated that the regression model included subject-level random intercepts to account for repeated measures, and fixed effects included treatment group, baseline characteristics, and a time-dependent progression covariate. The outcome of the model was defined as change in utility from baseline.

The regression was performed in two steps. The first step assessed the significance of the effect of each potential covariate in a univariate model to determine if it was associated with the outcome based on a p-value threshold of 0.2. The next step was to include the covariates that were associated with the outcome in a multivariate regression model with a backwards stepwise variable selection procedure performed to remove variables that became non-significant at each step based on a threshold p-value of 0.1. For categorical variables, the company included the variable if at least one of the categories had a p-value < 0.2 and excluded if none of the categories had a p-value < 0.1. The resulting significant variables that were associated with affecting the outcome were carfilzomib treatment, baseline utility, ECOG performance, progression, age, neutrophil count, measurable disease category, and number of prior therapies. The final model results are given in Table 20.

Table 20. Final utility regression model results (Table 34 of the CS)

Covariate	Value	SE	p-value
(Intercept)	0.467	0.042	0.000
CRd (vs Rd)	0.016	0.009	0.075
Progression	-0.047	0.008	0.000
Baseline utility	-0.403	0.025	0.000
Age	-0.001	0.001	0.010
ECOG PS 1	-0.032	0.010	0.001
ECOG PS 2	-0.044	0.019	0.020
Absolute neutrophil count ≥ 1.5 × 109/L	-0.033	0.016	0.036
Measurable disease category: SPEP only	-0.025	0.013	0.050
Measurable disease category: UPEP only	0.009	0.020	0.637
Number of prior therapies: ≥ 2	-0.031	0.009	0.001

Abbreviations: CRd, carfilzomib/lenalidomide/dexamethasone; ECOG PS, Eastern Cooperative Oncology Group Performance Status; Rd, lenalidomide/dexamethasone; SE, standard error; SPEP, serum protein electrophoresis; UPEP, urine protein electrophoresis.

The mean predicted change from baseline for the full population was estimated to be 0.0145 and for the 2L prior bortezomib subgroup, the estimated mean change from baseline was 0.047.

For the economic model, the company used the mapped EORTC QLQ-C30 baseline utility value from the ASPIRE study based on patients with one prior therapy with bortezomib (0.714) for cycles 1 and 2. For patients in the later cycles of the pre-progression health-state, the company added the mean change from baseline estimate of 0.047 for the CRd treatment group (0.761), and from the resulting value, the company took off the treatment effect of 0.016 for the Rd treatment group (0.745). From this value, the company removed the effect estimated for progression, 0.047, and used this as the post-progression utility value for patients for both the CRd and Rd treatment groups (0.698).

Table 21. Base case health-state utility values (adapted from Table 36 of the CS)

Health state	CRd	Rd
Pre-progression (cycles 1 and 2)	0.714	0.714
Pre-progression (later cycles)	0.761	0.745
Post-progression	0.698	0.698

Abbreviations: CRd, carfilzomib/lenalidomide/dexamethasone; Rd, lenalidomide/dexamethasone.

4.2.7.2 Adverse Event Disutility values

The company modelled the impact of AEs based on the event rates observed in the ASPIRE study for treatment-related AEs that occurred in at least 5% of patients in either treatment group. The event rates are discussed in more detail in Section 4.2.6. The company used disutility values sourced from various publications. The disutility values applied as well as the sources are detailed in Table 22.

Table 22. Disutility values for AEs (adapted from Table 35 of the CS)

Adverse event	Disutility	Duration (Days)	Duration-adjusted utility decrement (per event)	Source
Neutropenia	0.145	13.20	0.005	NICE TA573[36]
Anaemia	0.310	10.70	0.009	
Thrombocytopenia	0.310	14.10	0.012	
Cataract	0.140	182.63	0.070	NICE TA297[37]
Hyperglycaemia	0.060	4.02	0.001	Disutility stated to be from Wehler *et al.* (2018): hard copy of the paper and complete reference details were not provided; Duration estimated as weighted average length of stay from NHS reference costs 2017/18; Non-elective inpatients long stay: Fluid or Electrolyte Disorders, with Interventions, KC05G to KC05N.
Lymphopenia	0.065	15.50	0.003	NICE TA573[36]
Hypertension	0.000	0.00	0.000	
Fatigue	0.115	14.60	0.005	

Hypokalaemia	0.200	0.02	0.000	Consistent with assumption made in NICE TA510[38]
Hypophosphataemia	0.000	0.00	0.000	Assumption.
Pneumonia	0.190	12.00	0.006	NICE TA573[36]

4.2.7.3 ERG critique

As mentioned previously, the ERG considers that the relevant population for this appraisal is the 2L prior bortezomib/no prior lenalidomide subgroup. In response to ERG clarification questions, the company provided the equivalent utility values for the ERG's preferred subgroup. This population showed a lower baseline utility value of [redacted] and the resulting change from baseline over time was greater at [redacted]. The resulting utility values are given alongside those for the company's base case population in Table 23. The methodology for estimating the utility values remains unchanged from the company base-case.

Table 23. Health-state utility values used in the economic model

Health state	Company base case (2L prior bortezomib)		Company scenario (2L prior bortezomib/no prior lenalidomide)	
	CRd	Rd	CRd	Rd
Pre-progression (cycles 1 and 2)	0.714	0.714	[redacted]	[redacted]
Pre-progression (later cycles)	0.761	0.745	[redacted]	[redacted]
Post-progression	0.698	0.698	[redacted]	[redacted]

Abbreviations: 2L, second-line; CRd, carfilzomib/lenalidomide/dexamethasone; Rd, lenalidomide/dexamethasone.

The ERG has two primary concerns with regard to the company's estimation of health state utility values (HSUVs). One issue relates to the company's use of the estimated mean change in utility over time to increase the HSUVs for model cycles 3 onwards, in addition to changes that relate to progression or treatment effects for instance. Change from baseline was the outcome of the utility model so the mean change from baseline is estimated from the individual effects of each covariate that is adjusted for. However mean change in utility over time was [redacted] for CRd than the Rd, even though all patients have progression-free disease.

In addition, clinical expert advice sought by the ERG suggested that there was no clinical reason for there to be a treatment-specific utility benefit in addition to the benefit provided by any gains in progression-free survival. They considered that there may be a quicker response to treatment in patients receiving carfilzomib (in CRd) compared to Rd but there would be no additional benefit beyond being progression-free.

Therefore, the ERG considers the company's application of both mean change in utility over time for the pre-progression health state and treatment-specific values may be unreliable and may overestimate the overall quality-adjusted life-years (QALYs) in favour of carfilzomib. The ERG recommends applying treatment utilities based on progression status alone without a treatment effect applied or an increase in utility from baseline. The ERG has included these assumptions in the ERG's preferred base case, presented in Section 6.4.

A secondary issue that the ERG was concerned about the lack of information on the company's variable selection procedure for the adjustment of utility values and the inclusion of urine protein electrophoresis (UPEP), which was not statistically significant. However, as a result of their response to ERG clarification questions, the company provided more details on their methods and highlighted UPEP was part of a categorical variable called "Measurable disease category". This variable also included serum protein electrophoresis (SPEP) as a category and this had a significant p-value of 0.05, and therefore, the whole categorical variable was included.

The ERG considers that even though the effect estimate for "UPEP only" was relatively small at 0.009, it may have been more appropriate to specify the model differently where categorical variables produced levels with non-significant effect estimates. Particularly for variables like UPEP and SPEP, which could have been included as separate independent variables rather than a single categorical variable. This may have made the variable selection procedure more robust and provided potentially more reliable results but unlikely to have a large impact on the results.

Lastly, the ERG was concerned that the company's SLR was performed nearly two years ago but considers the sources of evidence used to be reasonable and that the date of the SLR is unlikely to have missed any evidence that could have impacted on utility estimates.

4.2.8 Resource use and costs

In the economic analyses, the company included the costs of drug acquisition, administration of drugs, concomitant medications, routine monitoring, treatment of AEs and the costs of palliative care. Each of these is described in the following subsections.

4.2.8.1 Drug acquisition

The company sourced the unit costs for each of the branded drugs in the model using the Monthly Index of Medical Specialties (MIMS)[29], while for generic drugs the company used the electronic market information (eMIT) tool[30].

Carfilzomib and lenalidomide both have a patient access scheme (PAS), and both provide a simple discount on the list price to the health care provider. For carfilzomib, the simple discount is [redacted]. A confidential appendix accompanies this document to provide the results of the cost-effectiveness analysis with the comparator PAS for lenalidomide as well as the carfilzomib PAS applied. A summary of the drug acquisition costs relating to the actual doses received in ASPIRE for the 2L prior bortezomib subgroup, and assuming no wastage, is given in Table 24. Where applicable, the prices with the PAS discounts applied are given in brackets.

Further details of the regimens for the intervention and comparator are given in Section 4.2.3.

Table 24. Drug acquisition costs per 28-day cycle

Health state	CRd List prices (PAS prices)	Rd List prices
Carfilzomib	Cycle 1: £4,230 ([redacted]) Cycle 2-12: £4,630 ([redacted]) Cycles 13-18: £3,087 ([redacted])	NA
Lenalidomide	£4,050	£4,058
Dexamethasone	£16	£16
Total	**Cycle 1: £8,295 ([redacted])** **Cycle 2-12: £8,695 ([redacted])** **Cycles 13-18: £7,152 ([redacted])**	**£4,075**

Abbreviations: CRd, carfilzomib with lenalidomide and dexamethasone; PAS, patient access scheme; Rd, lenalidomide with dexamethasone.

The company also accounted for the relative dose intensity (RDI) of each of the regimens to factor in doses that were not received and therefore did not incur costs. The RDIs were calculated as the percentage of planned doses that were actually received and these were multiplied by the drug acquisition costs per cycle. The RDIs for each regimen in each treatment group are given in Table 25.

Table 25. Relative dose intensity

Regimen	CRd	Rd
Carfilzomib	90.72%	NA
Lenalidomide	80.27%	79.46%
Dexamethasone	79.93%	82.90%

Abbreviations: CRd, carfilzomib with lenalidomide and dexamethasone; Rd, lenalidomide with dexamethasone.

4.2.8.2 Administration costs

Administration costs were included for carfilzomib based on the simple parenteral chemotherapy at first attendance cost code (SB12Z) from NHS reference costs 2018[28]. Specifically, it was based on an outpatient setting cost, which was estimated to be £174.40 per administration. The overall administration costs per cycle were estimated as £1,010 for cycles 1-12, and £674 for cycles 13 onwards. The difference is a result of the reduced frequency of doses after cycle 12.

For lenalidomide and dexamethasone, no administration costs were assumed, as these are oral drugs that do not require any resource use for administration.

Further details on the regimens for the intervention and comparator are given in Section 4.2.3.

4.2.8.3 Concomitant Medication Costs

The costs of concomitant medications were applied in the model based on those received in the ASPIRE trial. The medications received were valacyclovir, lansoprazole and aspirin. The proportions of patients receiving these medications in each group of the ASPIRE trial were used to estimate a weighted per-cycle cost to be applied in the model. The estimated costs per-cycle were £5.88 for the CRd group and £4.27 for the Rd group. Further details can be found in Table 43 of the CS.

4.2.8.4 Routine Monitoring Costs

The company included costs of routine monitoring in addition to the costs incurred from administration of drugs. The expected resource use was estimated by the company based on a non-interventional, observational chart review study using retrospective data collected from medical records of patients with symptomatic multiple myeloma.[39]

To collect data for the chart review, 56 oncologists and haematologists in the UK were asked to complete electronic forms to provide retrospective data on patient characteristics, treatments, response, costs and resource use.[39] Costs included outpatient consultations, lab tests, scans and other relevant procedures, and were separated by on-treatment and off-treatment for the pre-progression phase but did not split by treatment regimen as the average cost of resource use was considered similar across treatment regimens. Post-progression costs were also considered separately and were not treatment specific but did consider the subsequent treatment phase separately from the best supportive care phase.

A summary of the costs used in the economic model, inflated to 2018 prices using the PSSRU hospital and community health services pay and prices index[40], are summarised in Table 26.

Table 26. Monitoring costs per 28-day cycle

Health state	Costs per 28-day cycle (inflated to 2018 prices)
Progression-free (on treatment)	£94.51
Progression-free (off treatment)	£64.32
Post-progression (on subsequent treatment)	£94.51
Post-progression (BSC)	£194.78

Abbreviations: BSC, best supportive care; CRd, carfilzomib with lenalidomide and dexamethasone; PAS, patient access scheme; Rd, lenalidomide with dexamethasone.

4.2.8.5 Adverse Event Costs

The company included the costs associated with treating AEs for both the CRd and Rd groups based on the safety population of the ASPIRE trial. The company restricted the AEs included in the model to those that were grade 3 and above and occurred in at least 5% of patients in at least one group of the ASPIRE trial. Further detail of AEs included in the economic model is given in Section 4.2.6.

The unit costs applied to the proportion of AEs estimated for each model cycle were based on either inpatient, outpatient, day case or general practice treatment settings depending on the AE. Details of the specific AEs can be found in Table 48 on page 112 of the CS.

Unit costs for each AE in each setting were based on NHS reference costs 2018. Further details can be found in Table 49 on page 113 of the CS. The total cost of AE treatment per model cycle for the CRd treatment group was estimated to be £54.40, while for the Rd treatment group it was estimated to be £56.15.

4.2.8.6 Subsequent Treatment Costs

The company included the costs of subsequent treatments that would be expected to be received by patients in each of the treatment groups of the ASPIRE trial. Following either CRd or Rd as the primary treatment, the company assumed that patients would subsequently receive panobinostat in combination with bortezomib and dexamethasone (PVd) followed by pomalidomide in combination with dexamethasone (Pd), based on the current treatment pathway in England and Wales and the proposed positioning of CRd. A treatment-free interval of three cycles was included in the model, based on data from ASPIRE which estimated time between progression and start of subsequent treatment. The treatment-free interval was assumed to be the same, irrespective of prior lines of therapy.

Unit costs of the regimens were sourced from MIMS[29] or eMIT[30] as per the primary intervention and comparator regimens. The company stated in the CS that they assumed that 80% of patients would receive 3L therapy and that 20% received no treatment but did not specify their assumptions regarding 4L treatment. The company's model appears to assume that PVd should be received by 100% of patients and Pd by 66% of patients, based on a Kantar Health chart review.[41] The total cost of PVd estimated per-cycle was £8,432 and the estimated cost of Pd per-cycle was £8,900. The resulting cost per-cycle applied for both the CRd and Rd treatment groups in the model was £7,295. The company assumed a duration of five months for PVd based on median duration from the PANORMA-1 trial, and a duration of four months for Pd based on the pomalidomide NICE appraisal[32], resulting in a total of nine cycles for subsequent therapy.

The company included an administration cost of £89 per cycle for bortezomib based on the specialist nursing, cancer related, Adult, Face to face cost code (N10AF) from NHS reference costs 2018[28]. The company did not include administration costs for panobinostat, lenalidomide, pomalidomide and dexamethasone as these are oral treatments.

4.2.8.7 Palliative Care Costs

All patients are assumed to incur costs of palliative care covering resources used in the 90 days prior to death. The company used estimates from Georghiou and Bardsley 2014[42], which were inflated to 2018 prices using the PSSRU hospital and community health services pay and prices index[40]. A summary of these costs is presented in Table 27.

Table 27. Palliative care costs per 28-day cycle

Health state	Costs per 28-day cycle (inflated to 2018 prices)
District nurse	£308
Nursing and residential care	£1,141
Hospice care (in-patient)	£609
Hospice care (final 3 months)	£4,985
Marie Curie nursing service	£609
Total	**£7,653**

Abbreviations: BSC, best supportive care; CRd, carfilzomib with lenalidomide and dexamethasone; PAS, patient access scheme; Rd, lenalidomide with dexamethasone.

4.2.8.8 ERG critique

As mentioned previously, the ERG considers that the relevant population for this appraisal is the 2L prior bortezomib/no prior lenalidomide subgroup. In response to ERG clarification questions, the

company provided updated RDI for each of the regimens (Table 28) and weighted average cost per dose for lenalidomide for CRd and Rd (Table 29).

Table 28. Relative dose intensity by subgroup

Regimen	Company base case (2L prior bortezomib)		Company scenario (2L prior bortezomib/no prior lenalidomide)	
	CRd	Rd	CRd	Rd
Carfilzomib	90.72%	NA	[redacted]	[redacted]
Lenalidomide	80.27%	79.46%	[redacted]	[redacted]
Dexamethasone	79.93%	82.90%	[redacted]	[redacted]

Abbreviations: 2L, second-line; CRd, carfilzomib with lenalidomide and dexamethasone; NA, not applicable; Rd, lenalidomide and dexamethasone.

Table 29. Weighted average lenalidomide cost per dose by subgroup

Treatment arm	Company base case (2L prior bortezomib)	Company scenario (2L prior bortezomib/no prior lenalidomide)
CRd	£192.84	[redacted]
Rd	£193.24	[redacted]

Abbreviations: 2L, second-line; CRd, carfilzomib with lenalidomide and dexamethasone; Rd, lenalidomide with dexamethasone.

The ERG considers the company's methods regarding the estimation of unit costs and resource use to be generally reasonable. However, the ERG highlights two issues regarding monitoring costs and subsequent treatment, which warrant further investigation.

An issue that could have an important impact on the cost-effectiveness results is the subsequent treatment costs that are applied for both CRd and Rd in the economic model. The company's application of costs relating to the anticipated treatment pathway in England may seem plausible; however, it may not necessarily reflect the treatments received in the ASPIRE trial from which the treatment effectiveness estimates were acquired. This potentially causes bias in the economic analysis and the ERG considers that it is more appropriate to apply treatment costs based on the treatments received by patients in the 2L prior bortezomib subgroup of the ASPIRE trial. This then aligns the treatment effectiveness data with the costs of the treatments that have impacted on those data. The potential drawback with this approach is that some patients may have received treatments that are not recommended by NICE and, therefore, may have prices that do not reflect a cost-effective use of resources.

In response to the ERG's clarification questions, the company provided details of the subsequent treatments received by patients in the ASPIRE trial (Table 30). The company also supplied the simplified analysis in which subsequent treatment costs in the model were estimated based on some

of the key treatments received in the ASPIRE trial, which included Vd, Pd and Rd as subsequent treatments. This resulted in total per-cycle costs of £2,497 and £2,032 for CRd and Rd, respectively.

Bortezomib appears to be the key treatment that has a relatively large difference in usage across the treatment groups. The ERG's clinical experts advised that it is reasonable that more patients on Rd would be given bortezomib as a third-line treatment compared with CRd patients.

However, there is also a notable difference in investigational drugs, which appears to be largely monoclonal antibodies including daratumumab, based on the footnotes in the company's table (Table 32 of the company's response to clarification document). Daratumumab is an expensive and effective drug, and therefore, the company's omission of this from their estimation of subsequent treatment costs is likely to underestimate the total costs. The benefits, however, are likely to have overestimated the overall survival observed in the ASPIRE trial and therefore it is important that these costs are included to align with the overall survival. The ERG has provided a scenario analysis to include investigational drugs in the subsequent treatment costs with the assumption that costs are based on daratumumab costs. The results of this scenario are given in Section 6.2.

The ERG considers that the company may have misinterpreted the evidence it has used in its approach to weighting costs for subsequent treatments. In the economic model, 80% of progressed patients go on to receive subsequent therapy. However, the company has assumed that of those 80% of patients, 66% of patients will receive fourth- and fifth-line treatment, based on data from a conference poster.[41] However, the ERG considers that the fourth-line cohort in the study is a percentage of the total cohort and not a sub-population of the third-line cohort, as has been assumed in the economic-model. The ERG has conducted a scenario, where the weighting of subsequent treatment costs assumes 80% of costs for third-line treatment and 66% of costs for fourth- and fifth-line treatments. Results of the scenario are presented in Section 6.2.

A secondary issue, raised by the ERG's clinical experts, was that monitoring costs seemed quite low and were likely to be an underestimate of the true monitoring costs for 2L multiple myeloma patients. However, the ERG reviewed relevant submissions from previous appraisals and noted that for the daratumumab appraisal (TA573) the routine monitoring costs were actually lower and these were accepted by the ERG and subsequently the committee.[36]As such, the ERG considers the company's estimates to be conservative and acceptable. Nonetheless, the ERG tested the impact of increasing the routine monitoring costs in the PFS health state by 50% and found that this had a minimal impact on the ICER. The full results of this scenario are given in Section 6.3

The ERG had some concerns regarding the resource use assumed for the treatment of AEs based on clinical expert opinion but found that changes in the cost assumptions had minimal impact on the ICER.

Table 30. Subsequent antimyeloma therapies reported for ≥2% of patients in any treatment arm of the intent-to-treat population (Adapted from Table 32 of the company's clarification response)

	2L / prior bortezomib			2L / prior bortezomib / no prior lenalidomide		
	CRd (N=93) n (%)	Rd (N=73) n (%)	Mean DOT	CRd (N=74) n (%)	Rd (N=66) n (%)	Mean DOT
Nr of patients experienced progression	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nr. of patients treated with ≥1 antimyeloma therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Antineoplastic agents						
Bortezomib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cyclophosphamide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Doxorubicin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Melphalan	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pomalidomide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bendamustine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Carfilzomib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Etoposide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cisplatin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Immunosuppressants						
Lenalidomide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Thalidomide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Corticosteroids						
Dexamethasone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prednisone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
All other therapeutic products						
Investigational drug‡	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Blood substitutes and perfusion solutions						
Blood and related products	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: 2L, second-line; CRd, carfilzomib with lenalidomide and dexamethasone; DOT, duration of treatment; Rd, lenalidomide with dexamethasone.

5 Cost-effectiveness results

5.1 Company base-case results

The results of the company's base-case analysis are given in Table 31, showing an incremental cost-effectiveness ratio of £43,952 per QALY gained for CRd versus Rd. These results include the company's agreed PAS for carfilzomib, which provides a discount of [redacted] on the list price.

Table 31. Company's base case results

Interventions	Total Costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Rd	[redacted]	4.08	2.58	-	-	-	-
CRd	[redacted]	6.62	3.96	60,467	2.54	1.38	43,952

Abbreviations: CRd, carfilzomib with lenalidomide and dexamethasone; ERG, evidence review group; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; Rd, lenalidomide and dexamethasone.

5.2 Company's sensitivity analyses

5.2.1 Probabilistic sensitivity analysis

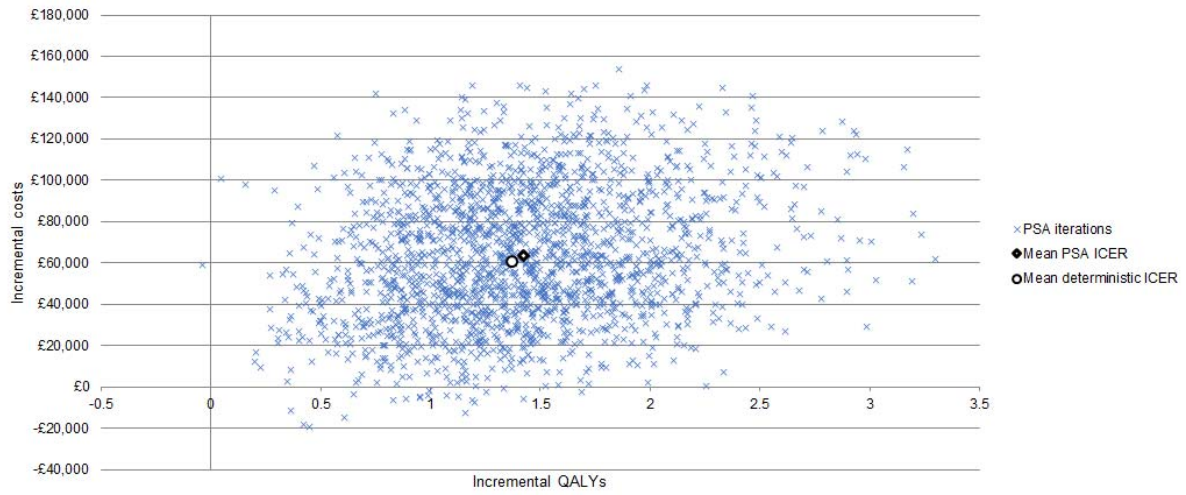
The company conducted a probabilistic sensitivity analysis (PSA) based on 2,000 samples. In response to ERG clarification questions, the company provided a corrected analysis after the ERG identified an unusual clustering of points on the cost-effectiveness plane produced when the ERG ran 10,000 samples in the company's economic model. The corrected PSA results are presented in Table 32, and a scatterplot of the 2,000 sampled costs and QALYs on the cost-effectiveness plane are presented in Figure 18.

Table 32. Company's PSA results

Interventions	Total Costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Rd	[redacted]	4.08	2.58	-	-	-	-
CRd	[redacted]	6.78	4.00	63,873	2.70	1.42	44,902

Abbreviations: CRd, carfilzomib with lenalidomide and dexamethasone; ERG, evidence review group; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; Rd, lenalidomide and dexamethasone.

Figure 18. Scatterplot of PSA samples on cost-effectiveness plane (pairwise – CRd vs Rd)

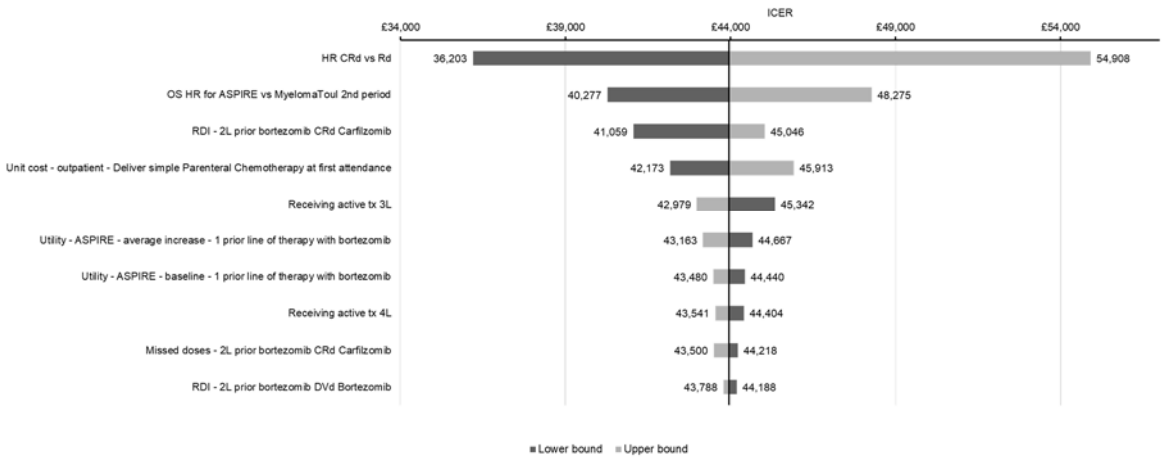


Abbreviations: CRd, Carfilzomib plus lenalidomide and dexamethasone; PSA, probabilistic sensitivity analysis; Rd, lenalidomide plus dexamethasone.

5.2.2 One-way sensitivity analyses

The company conducted a range of one-way sensitivity analyses (OWSAs) to test the impact that plausible changes on parameters have on the overall results. The tornado plot in Figure 19 shows the parameters that had the greatest impact, with the OS HR for CRd versus Rd having the greatest impact, resulting in ICERs ranging from £36,203 to £54,908 per QALY.

Figure 19. Tornado plot of OWSA results

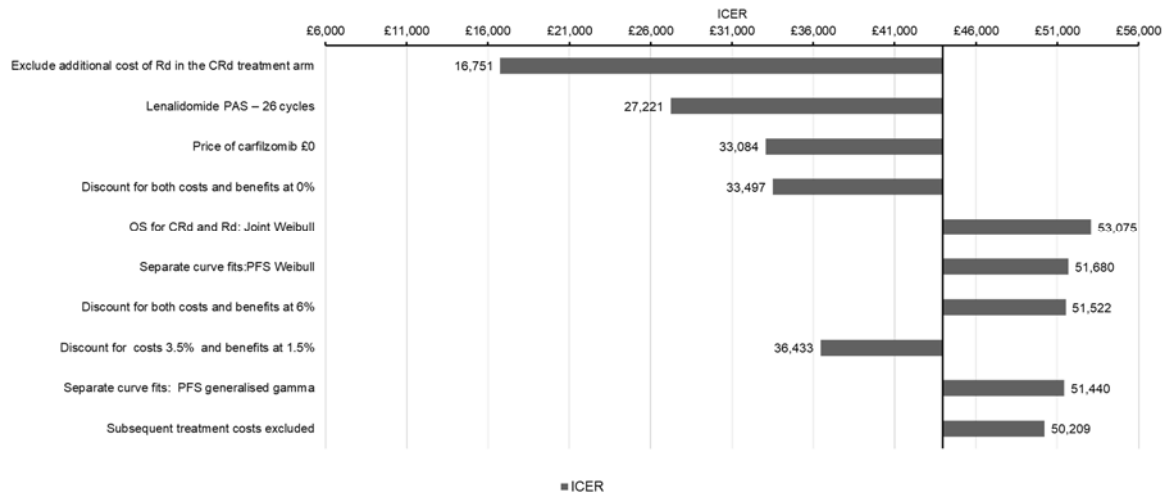


Abbreviations: 2L, second-line; 3L, third-line; 4L, fourth-line; CRd, Carfilzomib plus lenalidomide and dexamethasone; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; Rd, lenalidomide plus dexamethasone; RDI, relative dose intensity.

5.2.3 *Scenario analyses*

The company provided a range of scenario analyses around their base case, which are detailed in full in Table 56 on page 128 of the CS. The results of the scenarios that had the greatest impact are shown in the tornado plot in Figure 20.

Figure 20. Tornado plot of scenario analysis results



Abbreviations: CRd, Carfilzomib plus lenalidomide and dexamethasone; ICER, incremental cost-effectiveness ratio; OS, overall survival; PFS, progression-free survival; Rd, lenalidomide plus dexamethasone; RDI, relative dose intensity.

5.3 Model validation and face validity check

Quality assurance was performed by the external company who developed the model. A health economist not involved with model development reviewed the model for coding errors, inconsistencies and validity of model parameters.

6 Additional economic analysis undertaken by the ERG

6.1 Model corrections

The ERG did not identify any model errors.

6.2 Exploratory and sensitivity analyses undertaken by the ERG

In Section 4 of this report, the ERG has described several scenarios that warrant further exploration in addition to the company's own sensitivity and scenario analyses to ascertain the impact of these changes on the incremental cost-effectiveness ratio (ICER). The deterministic scenarios the ERG has produced are applied to the company's alternative cost-effectiveness scenario for the 2L prior bortezomib/no prior lenalidomide subgroup provided by the company in their response to ERG clarification questions and are as follows:

1. Implementation of the company's jointly fitted exponential distribution for ASPIRE inverse probability weighted (IPW) overall survival (OS) subgroup data - Section 4.2.5.1
2. Construction of progression-free survival (PFS) and OS curves for the carfilzomib with lenalidomide and dexamethasone treatment arm (hereafter to referred to as CRd) using intention-to-treat (ITT) PFS and OS hazard ratios (HRs) applied to the company scenario PFS and OS curves for the lenalidomide with dexamethasone treatment arm (hereafter referred to as Rd) - Section 4.2.5.1
3. Alternative construction of PFS and OS curves for CRd using the ITT PFS HR applied to the company scenario Rd PFS curve and ITT OS HR applied to ERG alternative OS modelling for Rd using the exponential distribution for ASPIRE data only - Section 4.2.5.1
4. Weibull distribution for CRd time-to-treatment discontinuation (TTD) – Section 4.2.5.1
5. No treatment effect applied for pre-progression health state utility value – Section 4.2.7.3
6. No average increase in baseline utility from cycle three onwards – Section 4.2.7.3
7. Combination of scenarios five and six.
8. Inclusion of investigational drugs in the company's subsequent treatment scenario using the ASPIRE trial data and assumed costs of daratumumab – Section 4.2.8.8
9. Assuming a 50% increase in costs for routine monitoring in the PFS health state – Section 4.2.8.8
10. Alternative approach to weighting costs of subsequent treatment – Section 4.2.8.8

6.3 ERG scenario analysis

Table 35 presents the results of the ERG exploratory analyses described in Section 6.2. Results reported include the company's proposed patient access scheme (PAS) of [redacted].

Table 35. Results of the ERG's scenario analyses

	Results per patient	Intervention - CRd	Comparator - Rd	Incremental value
0a	**Company base case**			
	Total costs (£)	[redacted]	[redacted]	£60,467
	QALYs	3.96	2.58	1.38
	ICER (£/QALY)			**43,952**
0b	**Company scenario for the 2L prior bortezomib/no prior lenalidomide subgroup**			
	Total costs (£)	[redacted]	[redacted]	54,626
	QALYs	3.94	2.58	1.35
	ICER (£/QALY)			**40,335**
1	**Jointly fitted exponential distribution for OS – ASPIRE only**			
	Total costs (£)	[redacted]	[redacted]	£3,017
	QALYs	3.68	2.52	1.15
	ICER (£/QALY)			**45,919**
2	**PFS and OS CRd curves using ITT PFS and OS HR applied to company scenario PFS and OS**			
	Total costs (£)	[redacted]	[redacted]	52,235
	QALYs	3.26	2.58	0.68
	ICER (£/QALY)			**76,716**
3	**PFS and OS CRd curves using ITT PFS HR applied to company scenario Rd PFS curve and ITT OS HR applied to ERG preferred Rd OS curve**			
	Total costs (£)	[redacted]	[redacted]	52,261
	QALYs	3.16	2.52	0.64
	ICER (£/QALY)			**81,593**
4	**Weibull distribution for CRd TTD**			
	Total costs (£)	[redacted]	[redacted]	54,918
	QALYs	3.94	2.58	1.35
	ICER (£/QALY)			**40,552**
5	**No treatment effect applied for pre-progression health state utility value**			
	Total costs (£)	[redacted]	[redacted]	54,626
	QALYs	3.96	2.64	1.32
	ICER (£/QALY)			**41,303**
6	**No average increase in baseline utility from cycle three onwards**			
	Total costs (£)	[redacted]	[redacted]	54,626
	QALYs	3.68	2.43	1.25
	ICER (£/QALY)			**43,583**
7	**Scenarios 5 and 6**			
	Total costs (£)	[redacted]	[redacted]	54,626
	QALYs	3.68	2.46	1.23
	ICER (£/QALY)			**44,438**
8	**Inclusion of investigational drugs cost for subsequent therapy based on ASPIRE**			

	Total costs (£)	[redacted]	[redacted]	57,768
	QALYs	3.94	2.58	1.35
	ICER (£/QALY)			**42,657**
9	**50% increase in costs for routine monitoring in the PFS health state**			
	Total costs (£)	[redacted]	[redacted]	55,396
	QALYs	3.94	2.58	1.35
	ICER (£/QALY)			**40,903**
10	**Alternative weighting of subsequent treatment costs**			
	Total costs (£)	[redacted]	[redacted]	54,512
	QALYs	3.94	2.58	1.35
	ICER (£/QALY)			**40,253**

Abbreviations: 2L, second-line; CRd, carfilzomib with lenalidomide and dexamethasone; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; ITT, intention-to-treat; OS, overall survival; PFS, progression-free survival; QALY, quality-adjusted life-year; Rd, lenalidomide plus dexamethasone; TTD, time-to-treatment discontinuation

6.4 ERG preferred assumptions

In this section, the ERG presents its base-case ICER for the 2L prior bortezomib/no prior lenalidomide subgroup. Deterministic results are presented in Table 36 and incorporate the company's patient access scheme (PAS) simple discount of [redacted]. The PSA ICER for the ERG preferred base-case is £55,530.

Table 36. ERG's preferred model assumptions

Preferred assumption	Section in ERG report	Cumulative ICER £/QALY
Company base case	*5.1*	**43,952**
Corrected company scenario for the 2L prior bortezomib/no prior lenalidomide subgroup	*4.2.5.1 & 6.2*	**40,335**
Jointly fitted exponential distribution for OS – ASPIRE only	*4.2.5.1*	**45,919**
Removal of treatment effect and average increase in utility for cycle three onwards for pre-progression health state utility value	*4.2.7.3*	**50,960**

Abbreviations: 2L, second-line; ERG, evidence review group; ICER, incremental cost-effectiveness ratio; OS, overall survival; QALY, quality-adjusted life-year

6.5 Conclusions of the cost-effectiveness sections

The final scope provide by the National Institute of Health and Care Excellence (NICE) listed that the relevant population to assess the cost-effectiveness of carfilzomib in combination with lenalidomide and dexamethasone (CRd) is adult patients with multiple myeloma who have received at least one prior therapy. The company deviated from the NICE final scope by restricting the proposed population to only one prior therapy with bortezomib (2L prior bortezomib subgroup). Based on advice from clinical experts, the ERG accepts the company's justifications for the positioning of CRd for the 2L prior bortezomib subgroup, which they state reflects the need for triplet therapies earlier in the pathway, greater benefit of the treatment is demonstrated in this subgroup and thus offers the greatest economic value, and lastly, it aligns with the NICE recommendation for Rd, which is deemed the most relevant comparator. Furthermore, the ERG considers that not exploring subgroups where cost-effectiveness cannot be demonstrated is appropriate and pragmatic.

However, as mentioned in Section 3.5, the company's subgroup analysis included a proportion of people who had not received bortezomib as part of their last round of therapy as well as people who had undergone treatment with lenalidomide in their last regimen. In response to ERG clarification

questions, the company provided scenario analyses for the subgroup excluding patients who had received prior lenalidomide (2L prior bortezomib/no prior lenalidomide), which the ERG considers more accurately represents the company's population of interest and as such is the subgroup considered for the ERG preferred analyses.

Overall, the ERG considers the company's approach to estimating PFS and TTD is appropriate and unbiased. With regards to the modelling of adverse events (AEs), the ERG had some concerns but on balance found that any changes to the modelling assumptions for AEs had minimal impact on the ICER and thus were not considered a primary driver of cost-effectiveness. Moreover, the ERG investigated the impact on the ICER of alternative assumptions for estimating monitoring costs and the inclusion of investigational drugs costs in the subsequent therapy pathway based on data from ASPIRE but found these did not produced a meaningful difference.

One of the primary issues with the cost-effectiveness analysis is the company's approach to estimating OS, using real-world data to adjust mature trial-based data. For the base-case analysis of OS for Rd, the company constructed a hybrid survival curve based on extrapolated ASPIRE IPW OS data and real-world evidence from a French registry of multiple myeloma patients, MyelomaToul. For the CRd arm, OS is also based on extrapolated ASPIRE IPW OS data and MyelomaToul data adjusted using the IPW OS HR from ASPIRE. The company chose this approach as they deemed the survival estimates based solely on ASPIRE using the Weibull distribution, which they deemed the best-fitting distribution to the observed data, produced pessimistic results for the Rd arm.

The ERG consulted its clinical experts who confirmed that longer-term survival estimates for Rd patients based on ASPIRE are conservative. However, the consequence of the company's adjustment when using real-world evidence is that survival is inflated for CRd compared with the extrapolated estimates based on IPW OS ASPIRE data. As such, the ERG considers that the company could have chosen a more clinically plausible extrapolation of the ASPIRE data to use for the base-case. The company confirmed that if they used MyelomaToul to validate their extrapolations, the exponential distribution would have been appropriate to estimate OS. The ERG considers that the exponential distribution produced similar survival estimates for Rd compared with company's base-case estimates. Furthermore, the CRd OS survival estimates are based entirely on mature ASPIRE OS data, which the ERG deems is appropriate and reduces the uncertainty in the analysis.

It should be noted that in the company submission (CS), the company highlight that for PFS, "*there is a consistent treatment effect across baseline covariate subgroups*". HRs derived from an ITT

population of an RCT are, by their nature, more robust than those generated from a subgroup analysis, which is based on *post-hoc* data where randomisation has been broken and the sample size reduced. However, this appraisal is a part-review of TA457 where results from subgroups adjusted to account for imbalances in baseline characteristics arising from non-randomised groups was accepted by the committee. As such, the ERG considers that the company's IPW analysis to adjust subgroup data for imbalances can be considered for appropriate for decision-making. However, as an illustrative scenario the ERG tested the impact of utilising ITT hazard ratios (HRs) for PFS and OS and found that it increased the ICER by almost £40,000 when combined with the other ERG preferences for modelling OS.

Separately from OS, the ERG had a concern with the assumptions made by the company for the estimation of utility values for the progression-free health state. Specifically, pre-progression utility values in the model capture both mean increase in utility from baseline for both treatment arms as well as treatment-specific increase in utility if a patient is on CRd. Change from baseline was the outcome of the utility model so the mean change from baseline is estimated from the individual effects of each covariate that is adjusted for. However mean change in utility over time was [redacted] for CRd than the Rd, even though all patients have progression-free disease. Furthermore, clinical expert advice sought by the ERG suggested that there was no clinical reason for there to be a treatment-specific utility benefit in addition to the benefit provided by any gains in progression-free survival. Thus, the ERG considers that it is more appropriate for pre-progression utility values for both treatment arms to be equal and that difference in pre-progression quality-adjusted life-years (QALYs) should be determined by length of time spent in the progression-free health state.

In conclusion, the ERG considers that the original uncertainty in TA457 has been resolved by more mature OS and PFS from ASPIRE.[27] As such, the ERG considers the ICER for the ERG preferred analysis to be robust.

7 End-of-Life

NICE end-of-life status should be applied when the following criteria are satisfied:

(i) the treatment provides an extension to life of more than an average of three months compared to current NHS treatment, and;

(ii) the treatment is indicated for patients with a short life expectancy, normally a mean life expectancy of less than 24 months.

The company state that second-line (2L) carfilzomib plus lenalidomide and dexamethasone (CRd) meets the first criterion of extension to life but does not meet the second criterion of short life expectancy. The ERG agrees with the company's evaluation and the case has not been made for end-of-life.

However, the company highlighted that for the appraisal of pertuzumab for HER2 positive metastatic cancer (TA509)[43], committees can use the following criteria to apply discretion and agree to end-of-life status for treatments for metastatic cancer when:

- OS without new drug exceeds 24 months;
- The new drug provides significant extension to life beyond three months, and;
- The new drug is combined with existing treatment, and;
- Both the existing treatment and the new drug are used until disease progression.

The company stated that 2L CRd meets these additional, discretionary criteria. However, the final appraisal document for TA509 stated that pertuzumab, "*has been available on the cancer drugs fund for several years and the committee recognised this as an exceptional circumstance. In this context, committee considered it reasonable to apply flexibility in its interpretation of the criteria for special consideration as a life-extending treatment for people with a short life expectancy, but that the weight applied to the quality adjusted life years gained would not be at the maximum allocated in other, more regular, circumstances where the end of life criteria have been applied*".[43]

Thus, the ERG does not consider the company's request for flexibility is warranted as CRd is not in the Cancer Drugs Fund for the subgroup under consideration in this appraisal.

8 References

1. National Institute for Health and Care Excellence. Carfilzomib for previously treated multiple myeloma (part review of TA457) (ID1493), 2019. Available from: https://www.nice.org.uk/guidance/gid-ta10510/documents/final-scope. Date accessed: 28 Jan 2020.
2. National Institute for Health and Care Excellence. Bortezomib for induction therapy in multiple myeloma before high-dose chemotherapy and autologous stem cell transplantation, 2014. Available from: https://www.nice.org.uk/guidance/TA311. Date accessed: 28 Jan 2020.
3. Kurteva E, Rajani S, Chadokufa S, Sider S, Sawney T, Buckingham R, et al. A case of de novo Inflammatory Bowel Disease (IBD) post thymic transplant in a patient with di George syndrome. *Journal of Pediatric Gastroenterology and Nutrition* 2018; **66**: 548.
4. Excellence NIfHaC. Bortezomib and thalidomide for the first-line treatment of multiple myeloma, 2011. Available from: https://www.nice.org.uk/guidance/TA228. Date accessed: 28 Jan 2020.
5. National Institute for Health and Care Excellence. Lenalidomide plus dexamethasone for previously untreated multiple myeloma, 2019. Available from: https://www.nice.org.uk/guidance/TA587. Date accessed: 28 Jan 2020.
6. National Institute for Health and Care Excellence. Daratumumab with bortezomib and dexamethasone for previously treated multiple myeloma, 2019. Available from: https://www.nice.org.uk/guidance/TA573. Date accessed: 28 Jan 2020.
7. National Institute for Health and Care Excellence. Lenalidomide plus dexamethasone for multiple myeloma after 1 treatment with bortezomib, 2019. Available from: https://www.nice.org.uk/guidance/TA586. Date accessed: 28 Jan 2020.
8. National Institute for Health and Care Excellence. Carfilzomib for previously treated multiple myeloma, 2017. Available from: https://www.nice.org.uk/guidance/TA457. Date accessed: 28 Jan 2020.
9. Stewart AK, Rajkumar SV, Dimopoulos MA, Masszi T, Spicka I, Oriol A, et al. Carfilzomib, lenalidomide, and dexamethasone for relapsed multiple myeloma. *N Engl J Med* 2015; **372**: 142-52.
10. European Medicines Agency. Kyprolis (carfilzomib). An overview of Kyprolis and why it is authorised in the EU, 2018. Available from: https://www.ema.europa.eu/en/documents/overview/kyprolis-epar-medicine-overview_en.pdf. Date accessed: 04 Feb 2020.
11. Amgen. Abbreviated Clinical Study Report: Onyx. A randomized, multicenter, Phase 3 study comparing carfilzomib, lenalidomide, and dexamethasone (CRd) vs lenalidomide and dexamethasone (Rd) in subjects with relapsed multiple myeloma. 2017.
12. National Institute for Health and Care Excellence. Carfilzomib for previously treated multiple myeloma. Final Appraisal Determination, 2017. Available from: https://www.nice.org.uk/guidance/ta457/documents/final-appraisal-determination-document. Date accessed: 04 Feb 2020.
13. Dimopoulos M, Spencer A, Attal M, Prince HM, Harousseau JL, Dmoszynska A, et al. Lenalidomide plus dexamethasone for relapsed or refractory multiple myeloma. *N Engl J Med* 2007; **357**: 2123-32.
14. Weber DM, Chen C, Niesvizky R, Wang M, Belch A, Stadtmauer EA, et al. Lenalidomide plus dexamethasone for relapsed multiple myeloma in North America. *N Engl J Med* 2007; **357**: 2133-42.
15. electronic Medicines Compendium (eMC). Kyprolis powder for solution for infusion, 2019. Available from: https://www.medicines.org.uk/emc/product/5061. Date accessed: 03 Feb 2020.
16. National Institute for Health and Care Excellence. Managing myeloma, 2020. Available from: https://pathways.nice.org.uk/pathways/myeloma#path=view%3A/pathways/myeloma/managing-myeloma.xml&content=view-index. Date accessed: 28 Jan 2020.

17. Centre for Reviews and Dissemination (CRD). CRD's guidance for undertaking reviews in healthcare, 2011. Available from: https://www.york.ac.uk/media/crd/Systematic_Reviews.pdf. Date accessed: 17 Feb 2020.
18. Higgins JPT GS. *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0*. Collaboration TC, editor2011.
19. Sperandei S. Understanding logistic regression analysis. *Biochem Med (Zagreb)* 2014; **24**: 12-8.
20. Latimer N. NICE DSU Technical Support Document 14: Survival analysis for Economic Evaluations Alongside Clinical Trials - Extrapolation with Patient-Level Data, 2013. Available from: http://www.nicedsu.org.uk/NICE%20DSU%20TSD%20Survival%20analysis.updated%20March%202013.v2.pdf. Date accessed: 01/03/2017.
21. National Institute for Health and Care Excellence: Decision Support Unit (NICE DSU). NICE DSU Technical Support Document 17: The use of observational data to inform estimates of treatment effectiveness in technology appraisal: methods for comparative individual patient data. , 2015. Available from: http://nicedsu.org.uk/wp-content/uploads/2016/03/TSD17-DSU-Observational-data-FINAL.pdf. Date accessed: 03 Mar 2020.
22. Proskorovsky I, Lewis P, Williams CD, Jordan K, Kyriakou C, Ishak J, et al. Mapping EORTC QLQ-C30 and QLQ-MY20 to EQ-5D in patients with multiple myeloma. *Health Qual Life Outcomes* 2014; **12**: 35.
23. Cocks K, King MT, Velikova G, Martyn St-James M, Fayers PM, Brown JM. Evidence-based guidelines for determination of sample size and interpretation of the European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30. *J Clin Oncol* 2011; **29**: 89-96.
24. Delforge M, Dhawan R, Robinson D, Jr., Meunier J, Regnault A, Esseltine DL, et al. Health-related quality of life in elderly, newly diagnosed multiple myeloma patients treated with VMP vs. MP: results from the VISTA trial. *Eur J Haematol* 2012; **89**: 16-27.
25. Kvam AK, Fayers P, Wisloff F. What changes in health-related quality of life matter to multiple myeloma patients? A prospective study. *Eur J Haematol* 2010; **84**: 345-53.
26. Kvam AK, Fayers PM, Wisloff F. Responsiveness and minimal important score differences in quality-of-life questionnaires: a comparison of the EORTC QLQ-C30 cancer-specific questionnaire to the generic utility questionnaires EQ-5D and 15D in patients with multiple myeloma. *Eur J Haematol* 2011; **87**: 330-7.
27. National Institute for Health and Care Excellence. Carfilzomib for previously treated multiple myeloma, 2017. Available from: https://www.nice.org.uk/guidance/TA457. Date accessed: 28 Jan 2020.
28. NHS improvement. National Schedule of Reference Costs 2017/18. Available from: https://improvement.nhs.uk/resources/reference-costs/. Date accessed: Oct 2019.
29. MIMS. Monthly Index of Medical Specialties (MIMS). Available at: https://www.mims.co.uk/.
30. Department of Health. Drug and pharmaceutical electronic market information tool (eMit) .
31. National Institute for Health and Care Excellence. Panobinostat for treating multiple myeloma after at least 2 previous treatments, 2016. Available from: https://www.nice.org.uk/guidance/TA380. Date accessed: 28 Jan 2020.
32. National Institute for Health and Care Excellence. Pomalidomide for multiple myeloma previously treated with lenalidomide and bortezomib, 2017. Available from: https://www.nice.org.uk/guidance/TA427. Date accessed: 28 Jan 2020.
33. National Institute for Health and Care Excellence. Lenalidomide for the treatment of multiple myeloma in people who have received at least 2 prior therapies, 2019. Available from: https://www.nice.org.uk/guidance/TA171. Date accessed: 28 Jan 2020.

34. National Institute for Health and Care Excellence (NICE). Guide to the methods of technology appraisal. 2013. Available from: https://www.nice.org.uk/process/pmg9/resources/guide-to-the-methods-of-technology-appraisal-2013-pdf-2007975843781. Date accessed: Feb 2019.
35. Expertise Ph. MyelomaToul Statistical Analysis Report. 2020.
36. National Institute for Health and Care Excellence. Daratumumab with bortezomib and dexamethasone for previously treated multiple myeloma, 2019. Available from: https://www.nice.org.uk/guidance/TA573. Date accessed: 28 Jan 2020.
37. National Institute for Health and Care Excellence. Ocriplasmin for treating vitreomacular traction, 2013. Available from: https://www.nice.org.uk/guidance/ta297. Date accessed: March 2020.
38. National Institute for Health and Care Excellence. Daratumumab monotherapy for treating relapsed and refractory multiple myeloma, 2018. Available from: https://www.nice.org.uk/guidance/TA510. Date accessed: 28 Jan 2020.
39. Amgen. Haematological Malignancy Research Network: Clinical Management and Outcomes in Multiple Myeloma. 2016.
40. Curtis L and Burns A. Unit Costs of Health and Social Care 2018. 2018. Available from: https://www.pssru.ac.uk/project-pages/unit-costs/unit-costs-2018/. Date accessed: February 2020.
41. Gonzalez-McQuire S YK, Flinois A, et al. Retrospective Chart Review Study to Evaluate the Cost of Care of Patients with Symptomatic Multiple Myeloma in the UK. *Poster presented at the ISPOR 21st Annual Meeting; May 21-25, 2016; Washington DC, United States* 2016.
42. Georghiou T, Bardsley M. Exploring the cost of care at the end of life. 2014.
43. National Institute for Health and Care Excellence. Pertuzumab with trastuzumab and docetaxel for treating HER2-positive breast cancer, 2019. Available from: https://www.nice.org.uk/guidance/ta509. Date accessed: March 2020.
44. International Myeloma Working Group. International Myeloma Working Group (IMWG) Uniform Response Criteria for Multiple Myeloma, 2020. Available from: https://www.myeloma.org/resource-library/international-myeloma-working-group-imwg-uniform-response-criteria-multiple. Date accessed: 06 Feb 2020.

9 Appendices

9.1 Baseline characteristics

Table 37. Baseline characteristics for the subgroup of people from ASPIRE who received carfilzomib 2L after bortezomib-based regimen and no lenalidomide (adapted from Table 3 provided as part of the company's response to clarification questions)

Characteristic	CRd	Rd
	(N = 74)	(N = 66)
Age group, n (%)		
• <65	[redacted]	[redacted]
• 65–74	[redacted]	[redacted]
• ≥75	[redacted]	[redacted]
ECOG performance status, n (%)		
• 0	[redacted]	[redacted]
• 1	[redacted]	[redacted]
• 2	[redacted]	[redacted]
Baseline creatinine clearance, n (%)		
• 30–<50 mL/min	[redacted]	[redacted]
• 50–<80 mL/min	[redacted]	[redacted]
• ≥80 mL/min	[redacted]	[redacted]
Time (months) since initial diagnosis		
• Mean (SD)	[redacted]	[redacted]
Time (months) since last relapse		
• Mean (SD)	[redacted]	[redacted]
Baseline ISS Stage, n (%)		
• Stage I	[redacted]	[redacted]
• Stage II	[redacted]	[redacted]
• Stage III	[redacted]	[redacted]
Baseline β2 microglobulin, n (%)		
• <3.5 mg/L	[redacted]	[redacted]
• ≥3.5 mg/L	[redacted]	[redacted]
Prior SCT, n (%)		
• Yes	[redacted]	[redacted]
• No	[redacted]	[redacted]
Prior therapy, n (%)		
• Bortezomib	[redacted]	[redacted]
• Lenalidomide	[redacted]	[redacted]
Refractory in any prior regimen, n (%)		
• Bortezomib	[redacted]	[redacted]

Abbreviations: C, carfilzomib; CS, company submission; d, dexamethasone; ECOG PS, Eastern Cooperative Oncology Group Performance Status; IMiD, immunomodulatory drug; ISS, International Staging System; ITT, intention-to-treat; max, maximum; min, minimum; NR, not reported; R, lenalidomide; SCT, stem cell transplantation; SD, standard deviation.

Table 38. Overview of baseline characteristics in ASPIRE (ITT population, adapted from CS, Table 7, page 27)

Characteristic	CRd (N = 396)	Rd (N = 396)	Total (N = 792)
Age, years, median (min, max)	64.0 (38.0, 87.0)	65.0 (31.0, 91.0)	64.0 (31.0, 91.0)
Female, n (%)	181 (45.7)	164 (41.4)	345 (43.6)
Race, n (%)			
• White	377 (95.2)	377 (95.2)	754 (95.2)
• Black	12 (3.0)	11 (2.8)	23 (2.9)
• Asian	1 (0.3)	3 (0.8)	4 (0.5)
• Native Hawaiian/Pacific Islander	[redacted]	[redacted]	[redacted]
• NR/other	6 (1.5)	4 (1.0)	10 (1.3)
Time since diagnosis, years, median (min, max)	3.0 (0.4, 19.7)[a]	3.2 (0.5, 27.3)	3.1 (0.4, 27.3)
Body surface area (m^2), mean (SD)	[redacted]	[redacted]	[redacted]
ECOG PS, n (%)			
• 0	165 (41.7)	175 (44.2)	340 (42.9)
• 1	191 (48.2)	186 (47.0)	377 (47.6)
• 2	40 (10.1)	35 (8.8)	75 (9.5)
ISS stage at diagnosis, n (%)			
• I	64 (16.2)	74 (18.7)	138 (17.4)
• II	99 (25.0)	94 (23.7)	193 (24.4)
• III	185 (46.7)	161 (40.7)	3 (43.7)
• Unknown	48 (12.1)	67 (16.9)	115 (14.5)
Calculated ISS stage at baseline, n (%)[b]			
• I	[redacted]	[redacted]	[redacted]
• II	[redacted]	[redacted]	[redacted]
• III	[redacted]	[redacted]	[redacted]
• Unknown	[redacted]	[redacted]	[redacted]
Cytogenetic risk (%)[c]			
• High	48 (12.1)	52 (13.1)	100 (12.6)
• Standard	147 (37.1)	170 (42.9)	317 (40.0)
• Unknown	201 (50.8)	174 (43.9)	375 (47.3)
Number of prior regimens			
• Median (min, max)	2.0 (1, 4)	2.0 (1, 4)	2.0 (1, 4)
• 1, n (%)	184 (46.5)	157 (39.6)	341 (43.1)
• 2, n (%)	[redacted]	[redacted]	[redacted]
• 3, n (%)	[redacted]	[redacted]	[redacted]
• 4, n (%)	[redacted]	[redacted]	[redacted]
Prior therapy received, n (%)			
• SCT	217 (54.8)	229 (57.8)	446 (56.3)
• Bortezomib	261 (65.9)	260 (65.7)	521 (65.8)
• Lenalidomide	79 (19.9)	78 (19.7)	157 (19.8)

• Thalidomide	[redacted]	[redacted]	[redacted]
• Pomalidomide	[redacted]	[redacted]	[redacted]
• Any IMiD[d]	233 (58.8)	229 (57.8)	462 (58.3)
• Bortezomib and IMiD	146 (36.9)	139 (35.1)	285 (36.0)
• Corticosteroids	[redacted]	[redacted]	[redacted]
• Anthracycline	[redacted]	[redacted]	[redacted]
• Alkylators	[redacted]	[redacted]	[redacted]
Received in last regimen, n (%)			
• Bortezomib	[redacted]	[redacted]	[redacted]
• Lenalidomide	[redacted]	[redacted]	[redacted]
Refractory to last regimen, n (%)	110 (27.8)	119 (30.1)	229 (28.9)

[a] N = 395 for this analysis.

[b] ISS sponsor-derived using central laboratory data for β2-microglobulin and local laboratory data for serum albumin.

[c] The high-risk group consisted of patients with the genetic subtypes t(4; 14), t(14;16), or deletion 17p in ≥ 60% of plasma cells. The standard-risk group consisted of patients without t(4; 14), t(14;16), and < 60% of plasma cells with deletion 17p. The unknown risk group included patients with FISH results that could not be analysed or from whom samples were not collected.

[d] Lenalidomide, thalidomide, or pomalidomide.

Abbreviations: C, carfilzomib; CS, company submission; d, dexamethasone; ECOG PS, Eastern Cooperative Oncology Group Performance Status; FISH, fluorescence in situ hybridisation; IMiD, immunomodulatory drug; ISS, International Staging System; ITT, intent-to-treat; max, maximum; min, minimum; NR, not reported; R, lenalidomide; SCT, stem cell transplantation; SD, standard deviation.

Table 39. Baseline characteristics for people receiving treatment at second line after one prior therapy with bortezomib (ASPIRE; adapted from Table 19 of Appendix E)

	CRd (N = 93)	Rd (N = 73)	Total (N = 166)
Age, years			
• Median (min, max)	[redacted]	[redacted]	[redacted]
• Mean (SD)	[redacted]	[redacted]	[redacted]
Age group N(%)			
• <65	[redacted]	[redacted]	[redacted]
• 65–74	[redacted]	[redacted]	[redacted]
• >=75	[redacted]	[redacted]	[redacted]
Female, n (%)	[redacted]	[redacted]	[redacted]
Race, n (%)			
• White	[redacted]	[redacted]	[redacted]
• Black	[redacted]	[redacted]	[redacted]
• Asian	[redacted]	[redacted]	[redacted]
• Native Hawaiian/Pacific Islander	[redacted]	[redacted]	[redacted]
• NR/other	[redacted]	[redacted]	[redacted]
Ethnicity, N(%)			
• Hispanic or Latino	[redacted]	[redacted]	[redacted]
• Not Hispanic or Latino	[redacted]	[redacted]	[redacted]
BMI			
• N(%) Missing	[redacted]	[redacted]	[redacted]
• Mean (SD)	[redacted]	[redacted]	[redacted]
• Median (Min, Max)	[redacted]	[redacted]	[redacted]

Time since diagnosis, years	[redacted]	[redacted]	[redacted]
• Median (min, max)	[redacted]	[redacted]	[redacted]
Time from last relapse, months			
• N	[redacted]	[redacted]	[redacted]
• Median (min, max)	[redacted]	[redacted]	[redacted]
Time from last regimen, months			
• N	[redacted]	[redacted]	[redacted]
• Median (min, max)	[redacted]	[redacted]	[redacted]
Body surface area (m^2)			
• N	[redacted]	[redacted]	[redacted]
• Mean (SD)	[redacted]	[redacted]	[redacted]
Body surface area (m^2)			
• N(%) Missing	[redacted]	[redacted]	[redacted]
• <=2.2	[redacted]	[redacted]	[redacted]
• >2.2	[redacted]	[redacted]	[redacted]
Region, N (%)			
• Missing	[redacted]	[redacted]	[redacted]
• Europe	[redacted]	[redacted]	[redacted]
• North America	[redacted]	[redacted]	[redacted]
• ROW	[redacted]	[redacted]	[redacted]
ECOG PS, n (%)			
• 0	[redacted]	[redacted]	[redacted]
• 1	[redacted]	[redacted]	[redacted]
• 2	[redacted]	[redacted]	[redacted]
ECOG PS, n (%)			
• 0	[redacted]	[redacted]	[redacted]
• 1–2	[redacted]	[redacted]	[redacted]
Baseline Hemoglobin N(%)			
• Median (min-max)	[redacted]	[redacted]	[redacted]
• <105 g/L	[redacted]	[redacted]	[redacted]
• >=105 g/L	[redacted]	[redacted]	[redacted]
Absolute Neutrophil count N(%)			
• Median (min-max)	[redacted]	[redacted]	[redacted]
• <1.5 g/L	[redacted]	[redacted]	[redacted]
• >=1.5 g/L	[redacted]	[redacted]	[redacted]
Platelet count (10^9/L), N(%)			
• Median (min-max)	[redacted]	[redacted]	[redacted]
• <150	[redacted]	[redacted]	[redacted]
• >=150	[redacted]	[redacted]	[redacted]
Corrected Calcium (mg/dl), N(%)			
• N	[redacted]	[redacted]	[redacted]
• Median (min-max)	[redacted]	[redacted]	[redacted]
• <=11.5	[redacted]	[redacted]	[redacted]
• >11.5	[redacted]	[redacted]	[redacted]

• Missing	[redacted]	[redacted]	[redacted]
Serum Creatinine (umol/L)			
• Mean (SD)	[redacted]	[redacted]	[redacted]
• Median (Min, Max)	[redacted]	[redacted]	[redacted]
Creatinine Clearance Sponsor Calculated (mL/min)			
• N	[redacted]	[redacted]	[redacted]
• Median (Min, Max)	[redacted]	[redacted]	[redacted]
• <30	[redacted]	[redacted]	[redacted]
• 30–<50	[redacted]	[redacted]	[redacted]
• 50–<80	[redacted]	[redacted]	[redacted]
• ≥80	[redacted]	[redacted]	[redacted]
• Missing	[redacted]	[redacted]	[redacted]
Creatinine Clearance Reported (mL/min)			
• N	[redacted]	[redacted]	[redacted]
• Median (Min, Max)	[redacted]	[redacted]	[redacted]
• <30	[redacted]	[redacted]	[redacted]
• 30–<50	[redacted]	[redacted]	[redacted]
• 50–<80	[redacted]	[redacted]	[redacted]
• ≥80	[redacted]	[redacted]	[redacted]
ISS stage at diagnosis, n (%)			
• I	[redacted]	[redacted]	[redacted]
• II	[redacted]	[redacted]	[redacted]
• III	[redacted]	[redacted]	[redacted]
• Unknown	[redacted]	[redacted]	[redacted]
Calculated ISS stage at baseline, n (%)[a]			
• I	[redacted]	[redacted]	[redacted]
• II	[redacted]	[redacted]	[redacted]
• III	[redacted]	[redacted]	[redacted]
• Unknown	[redacted]	[redacted]	[redacted]
Measurable disease category at baseline N(%)			
• SPEP Only	[redacted]	[redacted]	[redacted]
• SPEP and UPEP	[redacted]	[redacted]	[redacted]
• UPEP Only	[redacted]	[redacted]	[redacted]
M-protein heavy chain isotype N(%)			
• IGA	[redacted]	[redacted]	[redacted]
• IGG	[redacted]	[redacted]	[redacted]
• IGD	[redacted]	[redacted]	[redacted]
• NOT DETECTED	[redacted]	[redacted]	[redacted]
M-protein light chain isotype N(%)			
• KAPPA	[redacted]	[redacted]	[redacted]
• LAMBDA	[redacted]	[redacted]	[redacted]

Baseline Beta 2 Microglobulin Level N(%)			
• <3.5	[redacted]	[redacted]	[redacted]
• >=3.5	[redacted]	[redacted]	[redacted]
• Missing	[redacted]	[redacted]	[redacted]
Baseline Beta 2 Microglobulin Level per Covance N(%)			
• <2.5	[redacted]	[redacted]	[redacted]
• >=2.5	[redacted]	[redacted]	[redacted]
• Missing	[redacted]	[redacted]	[redacted]
Presence of plasmacytoma N(%)			
• N(%) Missing	[redacted]	[redacted]	[redacted]
• Yes	[redacted]	[redacted]	[redacted]
• No	[redacted]	[redacted]	[redacted]
Presence of bone lesion N(%)			
• N(%) Missing	[redacted]	[redacted]	[redacted]
• Yes	[redacted]	[redacted]	[redacted]
• No	[redacted]	[redacted]	[redacted]
Cytogenetic risk (%)[b]			
• High	[redacted]	[redacted]	[redacted]
• Standard	[redacted]	[redacted]	[redacted]
• Unknown	[redacted]	[redacted]	[redacted]
Baseline Albumin (g/L)			
• N(%) Missing	[redacted]	[redacted]	[redacted]
• Mean (SD)	[redacted]	[redacted]	[redacted]
• Median (Min, Max)	[redacted]	[redacted]	[redacted]
Prior surgery for multiple myeloma N(%)			
• Yes	[redacted]	[redacted]	[redacted]
• No	[redacted]	[redacted]	[redacted]
Prior radiotherapy for multiple myeloma N(%)			
• Yes	[redacted]	[redacted]	[redacted]
• No	[redacted]	[redacted]	[redacted]
Prior hematopoietic cell transplant N(%)			
• Yes	[redacted]	[redacted]	[redacted]
• No	[redacted]	[redacted]	[redacted]
Prior therapy received, n (%)			
• SCT	[redacted]	[redacted]	[redacted]
• Bortezomib	[redacted]	[redacted]	[redacted]
• Lenalidomide	[redacted]	[redacted]	[redacted]
• Thalidomide	[redacted]	[redacted]	[redacted]
• Pomalidomide	[redacted]	[redacted]	[redacted]
• Any IMiD[c]	[redacted]	[redacted]	[redacted]
• Bortezomib and IMiD	[redacted]	[redacted]	[redacted]

Received in last regimen, n (%)			
• Bortezomib	[redacted]	[redacted]	[redacted]
• Lenalidomide	[redacted]	[redacted]	[redacted]
Refractory in Any Prior Regimen N(%)			
• Bortezomib	[redacted]	[redacted]	[redacted]
• Lenalidomide	[redacted]	[redacted]	[redacted]
• Bortezomib and IMiD	[redacted]	[redacted]	[redacted]
• Thalidomide	[redacted]	[redacted]	[redacted]
• Refractory to last regimen, n (%)	[redacted]	[redacted]	[redacted]
History of neuropathy N(%)			
• N(%) Missing			
• Yes	[redacted]	[redacted]	[redacted]
• No	[redacted]	[redacted]	[redacted]
Best response to last prior line regimen N(%)			
• Unknown	[redacted]	[redacted]	[redacted]
• Complete Response	[redacted]	[redacted]	[redacted]
• Partial Response	[redacted]	[redacted]	[redacted]
• Minimal Response	[redacted]	[redacted]	[redacted]
• Stable Disease	[redacted]	[redacted]	[redacted]
• Progressive Disease	[redacted]	[redacted]	[redacted]

[a] ISS sponsor-derived using central laboratory data for β2-microglobulin and local laboratory data for serum albumin

[b] The high-risk group consisted of patients with the genetic subtypes t(4; 14), t(14;16), or deletion 17p in ≥ 60% of plasma cells. The standard-risk group consisted of patients without t(4; 14), t(14;16), and < 60% of plasma cells with deletion 17p. The unknown risk group included patients with FISH results that could not be analysed or from whom samples were not collected.

[c] Lenalidomide, thalidomide, or pomalidomide.

Abbreviations: CRd, carfilzomib/lenalidomide/dexamethasone; ECOG PS, Eastern Cooperative Oncology Group Performance Status; IMiD, immunomodulatory drug; ISS, International Staging System; ITT, intent-to-treat; max, maximum; min, minimum; NR, not reported; Rd, lenalidomide/dexamethasone; SCT, stem cell transplantation

9.2 Overview of overall response rate and time to next treatment

9.2.1 Overall response rate

Primary analysis of overall response rate (ORR) was defined as achieving a partial response (PR) or better, and was based on classifications of response to treatment as evaluated by the IRC. Level of response was categorised as per criteria set out by the IMWG-URC (International Myeloma Working Group-Uniform Response Criteria),[44] with the exception of minimal response, which was based on European Group for Blood and Marrow Transplant (EBMT) criteria.

For the ITT population of ASPIRE, CRd was associated with a statistically significant higher ORR compared with Rd, with [redacted] ([redacted]/396) of people in the CRd group achieving a best response of at least a PR versus [redacted] ([redacted]/396) with Rd (odds ratio [redacted]; 95% confidence interval [CI]: [redacted]; p <0.0001; Table 40). Median time to response was 1 month for both CRd and Rd,

but a difference in mean time to response was noted (1.6 months with CRd vs 2.3 months for Rd; Table 40).

Table 40. Overall response rate as determined by the IRC for the ASPIRE ITT population (adapted from CS, Table 14, page 41)

Response	CRd (N = 396)	Rd (N = 396)
Best response[a]		
≥CR	126 (31.8)	37 (9.3)
• Stringent CR	56 (14.1)	17 (4.3)
• CR	70 (17.7)	20 (5.1)
≥VGPR	277 (69.9)	160 (40.4)
• VGPR	[redacted]	[redacted]
PR	[redacted]	[redacted]
Minimal response	[redacted]	[redacted]
Stable disease	[redacted]	[redacted]
Progressive disease	[redacted]	[redacted]
Not evaluable	[redacted]	[redacted]
ORR, n (%)[b] (95% CI of ORR)	345 (87.1) (83.4 to 90.3)	264 (66.7) (61.8 to 71.3)
p-value (one-sided)[c]	<0.0001[d,e]	
OR (95% CI)	[redacted]	
Time to response		
• Mean, months (SD)	1.6 (1.39)	2.3 (2.42)
• Median, months	1	1

[a] Best response was defined as a patient's best response during the study.
[b] Defined as patients who had a best response of sCR, CR, VGPR, or PR.
[c] Unadjusted p-value from Cochran–Mantel–Haenszel chi-square test with β2-microglobulin levels (<2.5 mg/L vs ≥2.5 mg/L), prior bortezomib (no vs yes), and prior lenalidomide (no vs yes) as stratification factors.
[d] p-value is statistically significant (per hierarchical testing strategy described in Siegel *et al.* 2018.
[e] Reported as a two-sided p-value (p <0.0001) in Stewart *et al.* 2015.
Abbreviations: C, carfilzomib; CI, confidence interval; CR, complete response; CS, company submission; d, dexamethasone; ITT, intention to treat; OR, odds ratio; ORR, overall response rate; PR, partial response; R, lenalidomide; SD, standard deviation; VGPR, very good partial response.

9.2.2 Time to next treatment

TTNT was defined as the median time from randomisation to commencement of a new anti-myeloma treatment. At the time of the interim analysis (June 2014) presented in TA457,[8] CRd was associated with a statistically significantly longer TTNT than Rd, with median TTNT of 17.3 months and 12.1 months, respectively (hazard ratio [HR] 0.63; 95% CI: 0.50 to 0.78; p <0.0001; Table 41). The benefit in TTNT reported for CRd was maintained at a later data cut-off (April 2017), with TTNT of [redacted] months reported for CRd compared with [redacted] months for RD (HR 0.65; 95% CI: 0.53 to 0.79; p <0.0001).

Table 41. Time to next treatment for the ASPIRE ITT population (adapted from ERG report for TA457[8] and CS, Table 15, page 42)

	Interim analysis (data cut-off 16 June 2014)		Primary OS analysis (data cut off 28 April 2017)	
	CRd (N = 396)	**Rd (N = 396)**	**CRd (N = 396)**	**Rd (N = 396)**
Participants who started next treatment, n (%)	151 (38.1)	184 (46.5)	182 (46.0)	211 (53.3)
Time to next treatment, median months (min, max)	17.3 (0.46 to 37.6)	12.1 (0.26 to 33.5)	[redacted]	[redacted]
K–M estimate of time to next treatment, median months (95% CI)	37.6 (31.8 to NE)	24.5 (20.8 to 32.8)	39.0 (31.8 to 55.1)	24.4 (20.8 to 28.4)
Hazard ratio CRd:Rd (95% CI)	0.63 (0.50 to 0.78)		0.65 (0.53 to 0.79)	
Descriptive p-value (1-sided)[a]	<0.0001		<0.0001	
Median follow-up for time to next treatment, months (95% CI)	31.5 (30.7 to 32.0)	30.0 (29.3 to 31.2)	[redacted]	[redacted]

[a] Unadjusted p-value is from a stratified log-rank test with β2-microglobulin levels (<2.5 mg/L vs ≥2.5 mg/L), prior bortezomib (no vs yes), and prior lenalidomide (no vs yes) as stratification factors. P-value is for descriptive purposes only.

Abbreviations: C, carfilzomib; CI, confidence interval; d, dexamethasone; ITT, intention to treat; K–M, Kaplan–Meier; NE, not estimable; OS, overall survival; R, lenalidomide.

National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

ERG report – factual accuracy check

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

You are asked to check the ERG report to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies, you must inform NICE by **5pm** on **Tuesday 31 March 2020** using the below comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

The factual accuracy check form should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Issue 1 Error related to application of subsequent treatment

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 6.1 Model Corrections *"The evidence review group (ERG) identified an error in the company's application of subsequent treatments in that they did not apply the estimated value of 80% for the proportion of patients expected to receive third-line treatments."* ***Section 4.2.8.8 ERG Critique*** *"The ERG noted a minor discrepancy in the company's approach taken for subsequent treatments in that the percentage of patients receiving 3L subsequent treatment estimated to be 80% was not applied"*	Amgen believe reference to this error should be removed from the ERG report and the model correction removed from the ERGs Preferred ICERs (see Justification for amendment)	The ERG state that the company did not apply the estimated value of 80% for the proportion of patients expected to receive third-line treatments in the economic model. Therefore, to correct the error, the ERG used this percentage to calculate a weighted average acquisition and administration cost for subsequent treatments. However, Amgen do not agree that there is an error in the model and thus believe the correction is not required. The estimated value of 80% for the proportion of patients expected to receive a third-line treatment is in fact applied in the model to estimate the per cycle proportion of patients receiving subsequent treatments (see cell AI15 on Sheets CRd and Rd). Subsequently, the per cycle proportion of patients receiving subsequent treatments as well as the acquisition and administration costs of subsequent treatments are used to estimate the total cost of subsequent treatments in the trace. As a result, we believe that the percentage of patients receiving	Thank you for highlighting the issue. The ERG agrees with the company's suggested modification of setting cell AI15 in the traces to 100%. The ERG report has been amended to remove mention of a correction to the company base-case results and instead implements the modification as a scenario analysis in Section 6.2. All other ERG run scenarios and preferred analysis results have been updated, included confidential appendix.

		subsequent treatment is taken in to account twice when the correction is implemented. To avoid this, cell AI15 in the traces should be set to 100% when applying the ERG´s correction.	

Issue 2 Double counting of utility values

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 17, Page 86 "*Change from baseline was the outcome of the utility model so the mean change from baseline is estimated from the individual effects of each covariate that is adjusted for. Therefore, there is likely to be double-counting when the treatment effects and the progression values are also applied later, as these also impact the mean change in utility over time*."	"*Change from baseline was the outcome of the utility model so the mean change from baseline is estimated from the individual effects of each covariate that is adjusted for.* ~~*Therefore, there is likely to be double-counting when the treatment effects and the progression values are also applied later, as these also impact the mean change in utility over time*~~*"*	The covariates included in the utility model indicate how much the utility changes over time, on average, when the covariates value change by one unit. For example, if patients had more than 2 prior therapies, their change in utility over time is expected to be 0.031 smaller than those who had 1 prior therapy. In terms of treatment, the results of the utility model indicate that adjusting for the impact of all other covariates, treatment (CRd vs Rd) plays an independent role in explaining the change in utility over time. We acknowledge that the description of utilities was potentially not detailed enough in the submitted report given this way of estimating the utilities for the cost-effectiveness model was previously accepted by	Thank you for supplying the additional information and providing clarity. We have removed this sentence from the ERG report.

		NICE. Further, we do not believe it is correct to suggest there is likely to be double-counting of the utility values over time and that this rationale be removed. For clarity, we have provided more detail on the specific estimation of the utilities to demonstrate this position: • The average change in utility for CRd patients was estimated as follows: taking all patients in the subgroup, irrespective of the treatment they received (that is, overwriting the treatment indicator of Rd patients from zero to one, which is the treatment indicator of CRd patients, in the dataset), the predicted change from baseline was calculated for each time point over time given the regression coefficients of the utility model. Using the individual predictions over time, an average was calculated excluding measurement points for patients with progressive disease. This way of calculating the change in utility over time ensured that there is no double counting. In the cost-effectiveness model, the treatment effect of CRd and the	

		impact of progression was applied relative to the estimated mean utility value for CRd.	

Issue 3 Description of clinical plausibility of estimated survival

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 17, Page 102 "As such, the ERG considers that the company could have chosen a more clinically plausible extrapolation of the ASPIRE data to use for the base-case."	"As such, the ERG considers that the company could have chosen ~~a more~~ alternative, clinically plausible extrapolation of the ASPIRE data to use for the base-case."	We do not believe it accurate the claim by the ERG that their preferred approach is 'more' clinically plausible than the Amgen base case estimates, which were considered to be plausible and reasonable estimates of survival by clinical experts. The ERGs claim is not appropriately justified and the wording should thus be amended in their report.	This is not a factual error.

Issue 4 Interpretation of multi-state transition model

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 77 "The company also provided results from a multistate model based on ASPIRE ITT data	Proposed additional context: "*The company drew two key conclusions from the multistate modelling approach. Firstly, later progression is associated with longer post-progression survival, which translates to non-*	The purpose and conclusions of the multi-state modelling analysis are not fully reflected in the ERG report. We believe this context is important to capture as it adds to the rationale provided to support the base case	This is not a factual error.

(Appendix N of the CS) which estimated survival at 20 years to be between 1.9% and 3%. Even though the estimates are not based on the subgroup of interest, the company state the multi-state model results are generalisable to the subgroup of interest. The ERG highlights that the model was not submitted to the ERG and estimates of survival for CRd were not provided for comparison. However, the ERG considers that it was not necessary to investigate the model further, as mature trial data from ASPIRE for the subgroup of interest are available and as mentioned previously, the three-state model is appropriate.”	*increasing death risk in the overall population longer term. Secondly, OS predicted by the multistate model suggested longer estimates than those predicted by the best fitting parametric distributions from the ASPIRE clinical trial.”*	survival analysis approach.	

(please cut and paste further tables as necessary)

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Technical report

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

This document is the technical report for this appraisal. It has been prepared by the technical team with input from the lead team and chair of the appraisal committee.

The technical report and stakeholder's responses to it are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the appraisal committee meeting.

The technical report includes:

- topic background based on the company's submission
- a commentary on the evidence received and written statements
- technical judgements on the evidence by the technical team
- reflections on NICE's structured decision-making framework.

This report is based on:

- the evidence and views submitted by the company, consultees and their nominated clinical experts and patient experts and
- the evidence review group (ERG) report.

The technical report should be read with the full supporting documents for this appraisal.

Issue date: May 2020

1. Summary of the technical report

1.1 In summary, the technical team considered the following:

Issue		Technical team's preliminary judgement
1	**Positioning in the treatment pathway**	The treatment pathway for multiple myeloma is complex, and so further clinical input is required to confirm the company's positioning of carfilzomib is appropriate and that all relevant comparators have been considered
2	**Post-hoc subgroups to be considered**	The ERG's preferred subgroup (second line prior bortezomib and no prior lenalidomide) reflects the population that would likely receive carfilzomib in NHS clinical practice.
3	**Utility values used in the economic model**	It is unlikely that there are additional treatment-specific benefits with carfilzomib with lenalidomide and dexamethasone compared with lenalidomide plus dexamethasone, and so equal utility values should be used for the progression-free health state for both treatment groups.
4	**Extrapolation of overall survival**	A clinically plausible extrapolation of overall survival can be obtained entirely from the ASPIRE trial data, rather than a hybrid method using real-world data. The exponential distribution is likely to result in the most clinically plausible extrapolation of ASPIRE data and prediction of long-term survival, based on validation using real-world registry data.

1.2 The technical team recognised that the following uncertainties would remain in the analyses and could not be resolved:

- Subsequent treatment costs included in the model may not reflect those received in the ASPIRE trial and may include treatments not recommended by NICE. A scenario analysis found that including treatments from ASPIRE had a minimal impact on the incremental cost-effectiveness ratio (ICER).
- Certain investigational drugs (daratumumab) were omitted from the subsequent treatment costs included in the economic model. A

scenario analysis found that inclusion of these drugs had little impact on the ICER.

- It is not clear whether routine monitoring costs may be underestimated in the economic model. A scenario analysis found that increasing these costs had a minimal impact on the ICER.
- It is not clear whether the resource use assumed for the treatment of adverse events is appropriate, however changes in the cost assumptions had a minimal impact on the ICER.

1.3 The cost-effectiveness results include a commercial arrangement (patient access scheme) for carfilzomib.

1.4 Taking these aspects into account, for carfilzomib with lenalidomide and dexamethasone, the technical team's preferred assumptions result in an incremental cost-effectiveness ratio (ICER) of £50,960 per QALY gained (see Table 10) compared with lenalidomide plus dexamethasone, after only 1 prior therapy with bortezomib. This estimate does not include the commercial arrangement for lenalidomide, because this is confidential and cannot be reported here. Estimates that included this commercial arrangement would be lower than those reported above.

1.5 Based on the modelling assumptions, carfilzomib with lenalidomide and dexamethasone is unlikely to meet the end-of-life criteria (see Table 12: Other issues for information).

1.6 Carfilzomib with lenalidomide and dexamethasone is unlikely to be considered innovative (see Table 12: Other issues for information).

1.7 No equality issues were identified.

2. Topic background

2.1 Disease background – Multiple myeloma

- 4,799 new diagnoses of MM in England in 2017.
- Symptoms include bone pain, bone fractures, tiredness, infections, hypercalcaemia and kidney problems.
- Multiple myeloma is an incurable disease; therapy aims to prolong survival and maintain a good quality of life by controlling the disease and relieving symptoms.
- If the disease progresses after initial treatment, the choice of subsequent therapy is influenced by previous treatment and response to it, duration of remission, comorbidities and patient preference.
- The 5-year survival rate for adults with multiple myeloma in England and Wales is about 47%.

2.2 Carfilzomib with lenalidomide and dexamethasone

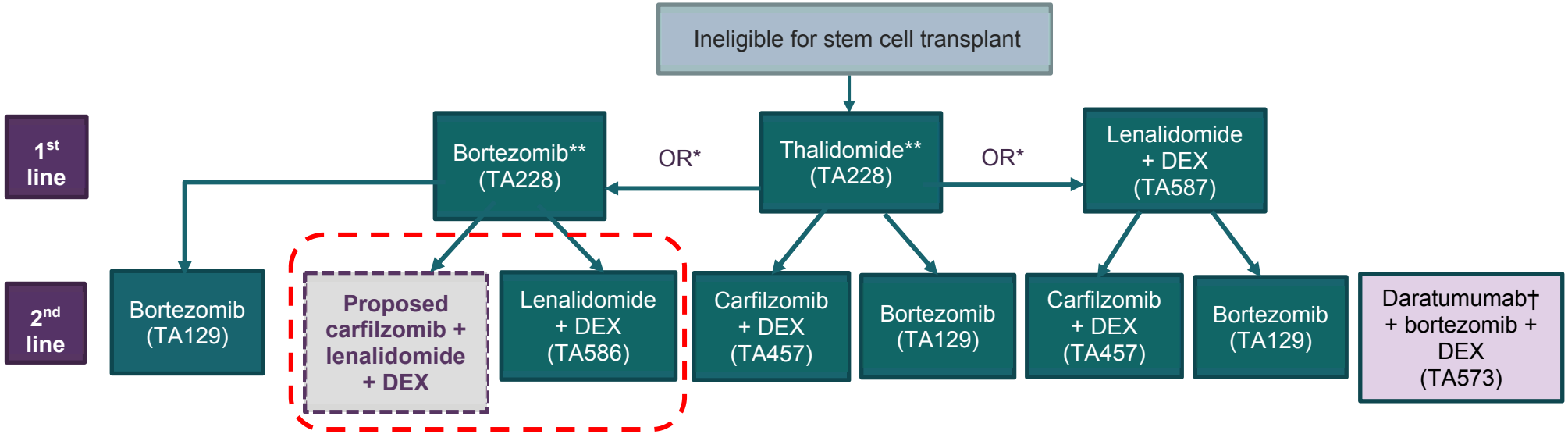
Table 2: Details of the technology being appraised

Marketing authorisation (granted November 2015)	Carfilzomib in combination with either lenalidomide and dexamethasone or dexamethasone alone is indicated for the treatment of adult patients with multiple myeloma, who have received at least one prior therapy.
Appraisal population	This is a part review of NICE technology appraisal 457 which recommends carfilzomib with dexamethasone as an option for treating multiple myeloma in adults, only if they have had only 1 previous therapy, which did not include bortezomib. This appraisal considers carfilzomib in a triplet regimen with lenalidomide and dexamethasone.
Mechanism of action	Carfilzomib is a selective proteasome inhibitor. Proteasome inhibition affects a number of cell signalling pathways, leading to cell arrest, and promotes apoptosis. Carfilzomib is the only irreversible proteasome inhibitor.
Administration	Intravenously

Price	The list price of carfilzomib is £1,056 for a 60-mg vial (excluding VAT). The company has a commercial arrangement (simple discount patient access scheme). This makes carfilzomib available to the NHS with a discount. The size of the discount is commercial in confidence. In combination with lenalidomide and dexamethasone: one course/cycle of carfilzomib consists of 28-day treatment. Assuming a body surface area of 1.79 m^2, the cost of cycle 1 is anticipated to be £4,663 per patient (at list price). For cycles 2 to 12, the cost of carfilzomib per cycle is £5,104 (at list price) and for cycles 13 onwards, the cost of carfilzomib per cycle is £3,402 (at list price).

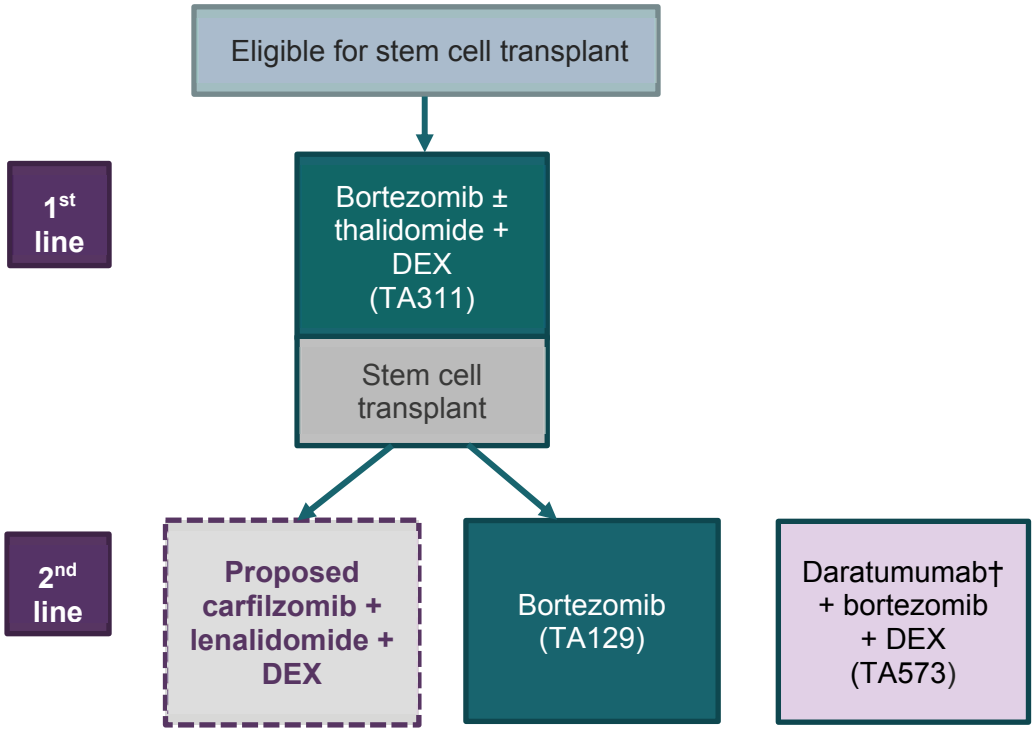
Treatment pathway

Figure 1: Treatment pathway for the management of multiple myeloma in those ineligible for stem cell transplant (adapted from Figure 1 in company submission and Figure 1 from ERG report)



NICE guidance recommendations are dependent on a person's previous treatment.
Red dashed line includes intervention and comparator included in the company's economic model
*OR if thalidomide is contraindicated or cannot be tolerated;
**Taken in combination with alkylating agent + corticosteroid.
† Currently recommended for use within the Cancer Drugs Fund (as a treatment option in people who have had 1 previous treatment) and therefore is not considered a comparator in this appraisal.
DEX = dexamethasone

Figure 2: Treatment pathway for the management of multiple myeloma in those eligible for stem cell transplant (adapted from Figure 1 of company submission and Figure 1 of ERG report)



NICE guidance recommendations are dependent on a person's previous treatment.
† Currently recommended for use within the Cancer Drugs Fund (as a treatment option in people who have had 1 previous treatment) and therefore is not considered as a comparator in this appraisal.
DEX = dexamethasone

2.2 Clinical evidence

The company presented direct evidence for carfilzomib with lenalidomide and dexamethasone compared with lenalidomide plus dexamethasone (NICE technology appraisal 586) from the ASPIRE trial. In addition, the company presented a matched adjusted indirect comparison of carfilzomib with lenalidomide and dexamethasone versus daratumumab with bortezomib and dexamethasone (NICE technology appraisal 573). As daratumumab with bortezomib and dexamethasone is recommended for use within the Cancer Drugs Fund and is not routinely commissioned, it is not considered as a relevant comparator in this appraisal (see NICE's position statement).

Table 3: Summary of RCT evidence for carfilzomib with lenalidomide and dexamethasone (adapted from Tables 3 and 5 in company submission)

	ASPIRE (n=792). Open-label, randomised, multicentre trial
Population and setting	• Adults with R/RMM who have received 1 to 3 prior therapies. • 129 centres across 20 countries in Europe, North America and Israel. 6 sites with 16 patients were enrolled in the UK.
Intervention	**Carfilzomib with lenalidomide and dexamethasone (28-day treatment cycles)** Cycles 1 to 12: • Carfilzomib 20 mg/m^2 IV on days 1 and 2 of cycle 1, escalating to 27 mg/m^2 on days 8, 9, 15, and 16 of cycle 1 and continuing on days 1, 2, 8, 9, 15, and 16 of cycle 2 to cycle 12 • Lenalidomide 25 mg orally on days 1 to 21 • Dexamethasone 40 mg oral or IV on days 1, 8, 15, and 22 Cycles 13 to 18: • Carfilzomib 27 mg/m^2 IV on days 1, 2, 15, and 16 • Lenalidomide 25 mg oral on days 1 to 21 • Dexamethasone 40 mg oral or IV on days 1, 8, 15, and 22 Cycle 19 and higher: • Lenalidomide 25 mg orally on days 1 to 21 • Dexamethasone 40 mg oral or IV on days 1, 8, 15, and 22

Comparator	**Lenalidomide and dexamethasone (28-day treatment cycles)** Cycle 1 and higher: • Lenalidomide 25 mg orally on days 1 to 21 • Dexamethasone 40 mg orally or IV on days 1, 8, 15, and 22
Primary outcomes	PFS
Secondary outcomes	OS, response rates, time to next treatment, adverse effects of treatment, HRQoL
Abbreviations: IV = intravenous; R/RMM = relapsed or refractory multiple myeloma; PFS = progression-free survival; OS = overall survival; HRQoL = health related quality of life	

2.3 Key trial results

Post-hoc subgroups

The company provided data for a post-hoc subgroup from the ASPIRE trial who received only 1 prior therapy with bortezomib (second line prior bortezomib). The ERG noted that in this subgroup, not all patients received prior bortezomib as part of their last treatment regimen and that some patients had undergone treatment with lenalidomide in their last regimen (see issue 2). The ERG therefore provided an alternative subgroup including patients from the ASPIRE trial who had received only 1 prior therapy with bortezomib and no lenalidomide (second line prior bortezomib/no lenalidomide).

To account for imbalances in baseline characteristics between treatment arms, the company conducted an inverse probability weighted (IPW) analysis to produce effect estimates for progression free survival and overall survival, after adjusting for several covariates identified by their clinical experts as being prognostic of outcomes in multiple myeloma.

ASPIRE trial data presented in company submission

Data from the ASPIRE trial informed the appraisal of carfilzomib and dexamethasone in NICE technology appraisal 457, which included comparative treatment

effectiveness results from the planned interim analysis (data cut-off June 2014). For this appraisal of **carfilzomib with lenalidomide and dexamethasone**, the company presented results from the pre-specified final analysis of mature data from the intention to treat (ITT) population of ASPIRE, and post-hoc subgroups relevant to the treatment positioning (data cut-off April 2017).

The company also presented results from an updated analysis for the ITT population and post-hoc subgroups which provided the most recent analysis of progression free survival and overall survival (data cut-off December 2017). For the post-hoc subgroups, the company performed an inverse probability weighted (IPW) analyses and presented results for adjusted progression-free survival and overall survival.

Table 4: Effectiveness results for the ITT population of ASPIRE (April 2017 data cut-off) (adapted from Tables 12 and 13 in company submission)

ASPIRE	Median (95% CI), months		HR CRd vs Rd	p value (1-sided, descriptive)
	CRd N = 396	Rd N = 396		
Progression-free survival	**26.1 (23.2 to 30.3)**	**16.6 (14.5 to 19.4)**	**0.659 (95% CI 0.553 to 0.784)**	**p=<0.0001**
Overall survival	48.3 (42.4 to 52.8)	40.4 (33.6 to 44.4)	0.794 (95% CI 0.667 to 0.945)	p=0.0045

Abbreviations: CRd = carfilzomib/lenalidomide/dexamethasone; Rd = lenalidomide/dexamethasone; ITT = intention to treat

Figure 3: Kaplan-Meier plot for unadjusted progression-free survival for the ITT population from ASPIRE (April 2017 data cut-off) (referenced from company submission, Figure 6)

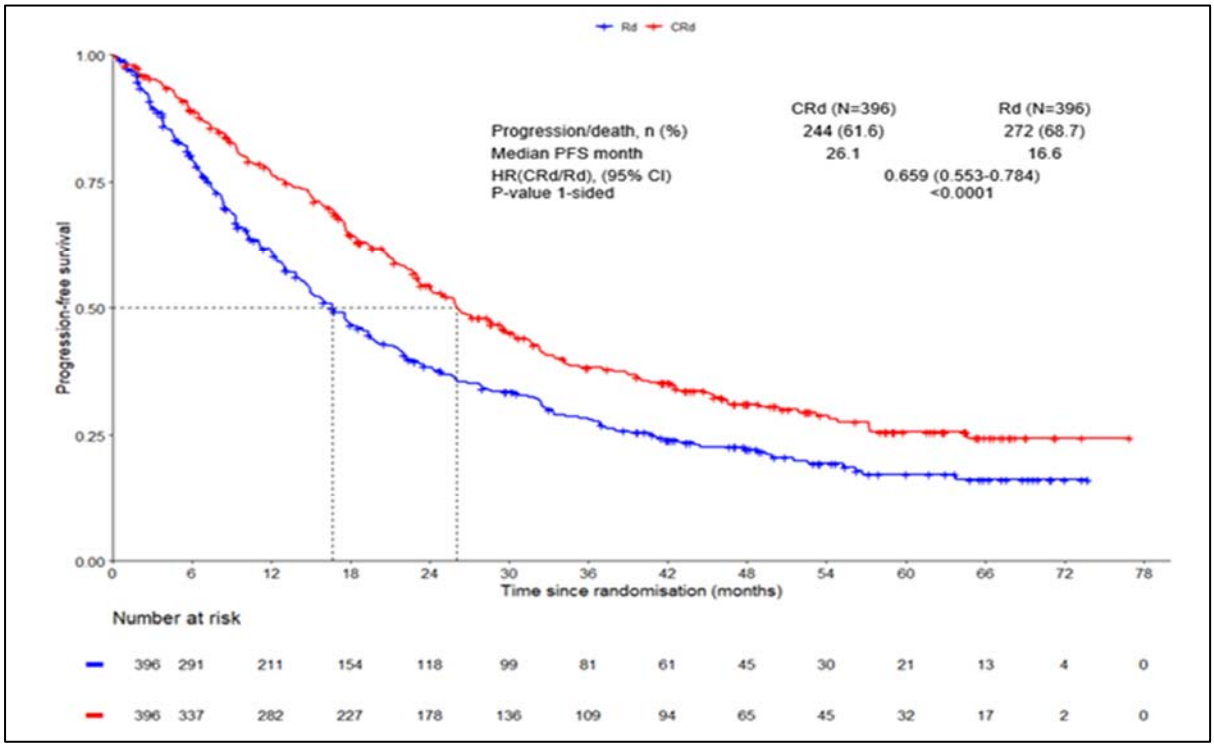


Figure 4: Kaplan-Meier plot for unadjusted overall survival for the ITT population from ASPIRE (April 2017 data cut-off) (referenced from company submission, Figure 7)

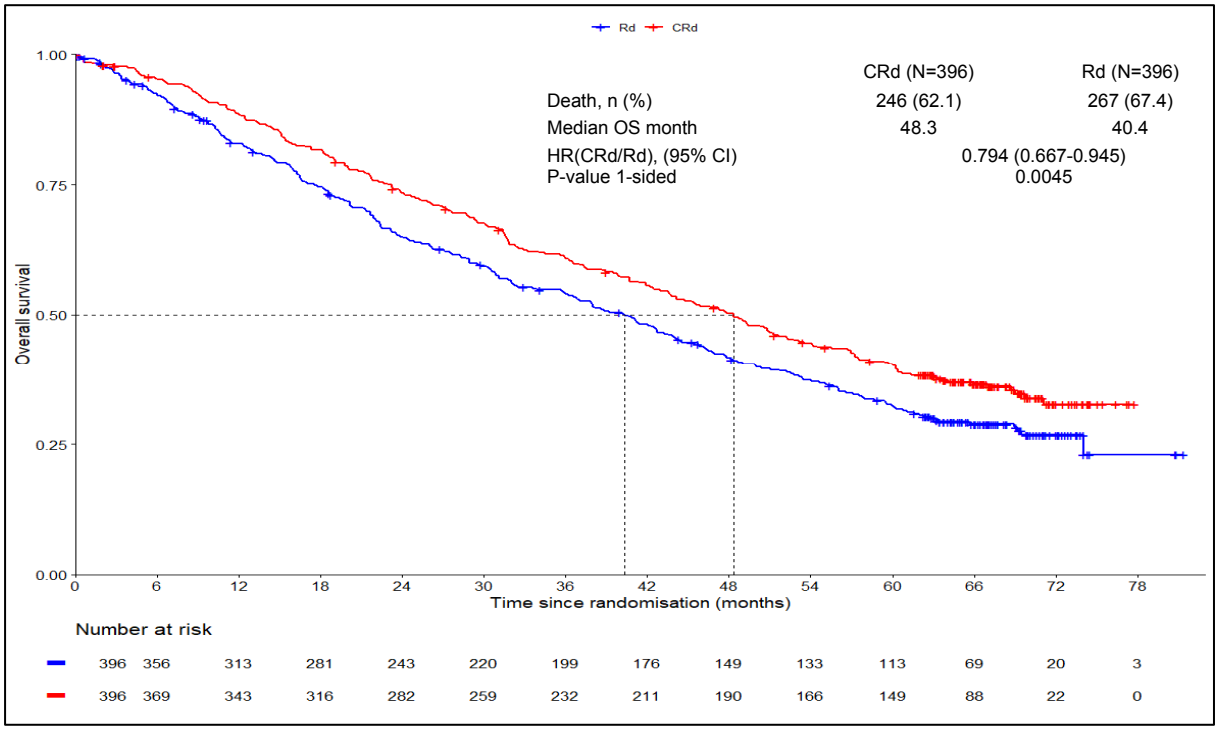


Table 5: Effectiveness results for the IPW adjusted company's post-hoc subgroup (second line prior bortezomib) of ASPIRE (December 2017 data cut-off) (adapted from Tables 5 and 9 of the company's response to clarification and Tables 8 and 9 of ERG report)

ASPIRE	Median (95% CI), months		HR CRd vs Rd
	CRd	Rd	
Progression-free survival	[redacted]	[redacted]	[redacted]
Overall survival	[redacted]	[redacted]	[redacted]

IPW-adjusted (stepwise selection within logit model)
Variables adjusted for:
[redacted]
Abbreviations: IPW, inverse probability weighted; CRd = carfilzomib/lenalidomide/dexamethasone; Rd = lenalidomide/dexamethasone

Figure 5: Kaplan-Meier plot for IPW adjusted progression-free survival for the company's post-hoc subgroup (second line prior bortezomib) from ASPIRE (December 2017 data cut-off) (referenced from company submission, Figure 9)

Table 6: Effectiveness results for the IPW adjusted ERG's post-hoc subgroup (second line prior bortezomib and no prior lenalidomide) of ASPIRE (December 2017 data cut-off date) (adapted from Tables 5 and 9 of the company's response to clarification and Tables 8 and 9 of ERG report)

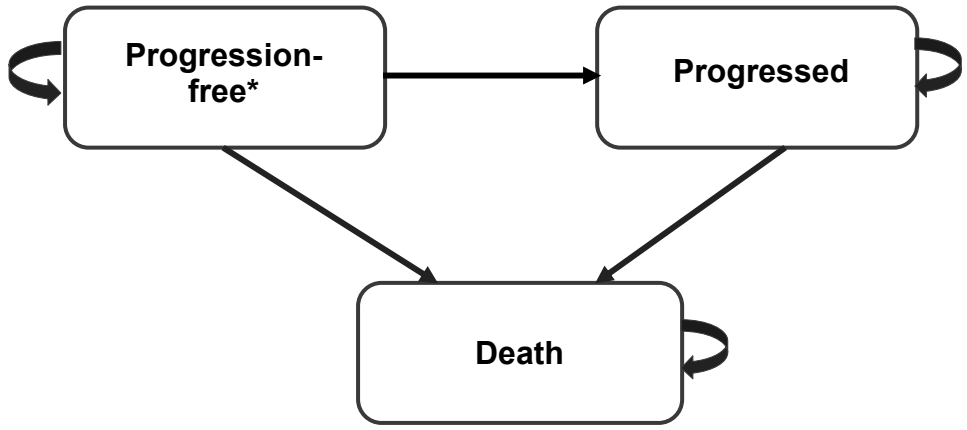
ASPIRE	Median (95% CI), months		HR CRd vs Rd
	CRd	Rd	
Progression-free survival	[redacted]	[redacted]	[redacted]
Overall survival	[redacted]	[redacted]	[redacted]

IPW-adjusted (stepwise selection within logit model), covariates selected using Cox proportional hazards regression
Variables adjusted for: [redacted]
Abbreviations: IPW, inverse probability weighted; CRd = carfilzomib/lenalidomide/dexamethasone; Rd = lenalidomide/dexamethasone; NA = not applicable.

Figure 6: Kaplan-Meier plot for IPW adjusted progression-free survival for the ERG's post-hoc subgroup (second line prior bortezomib and no lenalidomide) from ASPIRE (December 2017 data cut-off date) (referenced from company's response to clarification, Figure 2)

2.4 Model structure

Figure 7: Partitioned survival model structure (adapted from Figure 15 in company submission)



*** Patients in the progression-free health state can either be on-treatment and off-treatment (if experience unacceptable toxicity)**

Partitioned survival model:

- Three health states including progression-free, progressed and dead
- Cycle length of 28 days with half-cycle correction
- Lifetime time horizon (40 years)
- All patients enter the model at the progression-free health state and are assumed to start treatment.

2.5 Key model assumptions

Table 7: Summary of assumptions used in economic model (adapted from Table 52 in company submission and Table 10 in submission summary)

Variable	Assumption	Justification
Adjustment of baseline characteristics in the post-hoc subgroup of ASPIRE	The IPW approach was used to adjust for covariates of interest.	NICE technology appraisal 457 (Carfilzomib for previously treated multiple myeloma)

OS – CRd and Rd	OS for CRd and Rd was estimated using a Weibull distribution fit to ASPIRE and external data.	• Long-term extrapolations of OS using only ASPIRE trial data yielded unrealistic estimates comparing with survival data available from external sources. • The use of external data to inform OS extrapolation yielded more realistic estimates.
PFS – CRd and Rd	PFS for CRd and Rd was estimated using a generalised gamma distribution.	The generalised gamma was selected as this gave a plausible estimate of PFS.
Proportional hazards – CRd and Rd	Proportional hazards was assumed for PFS and OS through the use of jointly fitted curve distributions for CRd and Rd	<u>Post-hoc subgroup</u> • OS curves demonstrated sustained treatment effect that began at treatment initiation. • PFS curves crossed only when the number of patients at risk were very low. • Clinical experts supported the fact that it is clinically improbable that PFS would intersect but OS would not. <u>ITT population</u> See section B.3.3.1 in company submission.
TTD – CRd and Rd	TTD for CRd and Rd was estimated with the best fitting curve for each component treatment	All curves were indistinguishable in terms of statistical and visual fit in the observed period and there was little difference for Rd components, in the extrapolation period.
Lenalidomide and dexamethasone TTDs differ by treatment arm	The lenalidomide and dexamethasone components of CRd and Rd are modelled separately	The modelled time to discontinuation was observed to be different by treatment arm
Carfilzomib treatment duration in CRd	Treatment with carfilzomib when given in combination with lenalidomide and dexamethasone is assumed to cease after 18 cycles	In line with ASPIRE trial from which efficacy data for CRd were estimated
Utilities	• Utilities were assumed to be time and treatment-dependent in the progression-free health state • Based on ASPIRE data mapped from EORTC QLQ-C30 to EQ-5D	• HRQoL data from the ASPIRE study suggested differences in pre-progression utilities between treatments that varied over time. • Mapped utilities were preferred in NICE technology appraisal 457

Drug wastage	Drug wastage was not included	Carfilzomib drug wastage is expected to be minimal, given that 10 mg dose steps are possible
Subsequent treatments	Following CRd or Rd at second line the next treatments are FVd followed by Pd	Based on the current clinical pathway for patients with multiple myeloma in England and Wales
Acquisition costs	PAS discount applied to Carfilzomib. List price assumed for lenalidomide.	Lenalidomide PAS discount is commercially confidential. Base case ICERs are therefore based on the list price for lenalidomide.

Abbreviations Cd = carfilzomib/dexamethasone; CRd = carfilzomib/lenalidomide/dexamethasone; EORTC QLQ-C30 European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; EQ-5D: EuroQol-5 dimension; FVd = panobinostat/bortezomib/dexamethasone; HRQoL = health related quality of life; IPW = inverse probability weighting; OS = overall survival; Pd = pomalidomide/dexamethasone; PFS = progression-free survival; Rd = lenalidomide/dexamethasone; TTD = time to discontinuation; PAS = patient access scheme.

3. Key issues for consideration

Issue 1 – Positioning of carfilzomib in the treatment pathway

Questions for engagement	1. Is the positioning of carfilzomib appropriate in the treatment pathways for those eligible and ineligible for stem cell transplantation? 2. Have all the relevant comparators been considered?
Background/description of issue	Treatment positioning The marketing authorisation for carfilzomib states that "Kyprolis in combination with either lenalidomide and dexamethasone or dexamethasone alone is indicated for the treatment of adult patients with multiple myeloma who have received at least one prior therapy". **The company** have positioned carfilzomib with lenalidomide and dexamethasone in patients who have received only 1 prior therapy with bortezomib for the treatment of multiple myeloma, irrespective of eligibility for stem cell transplantation. The company states that this positioning is due to a clear unmet need for triple therapies earlier on in the treatment pathway and based on their clinical expert opinion that carfilzomib with lenalidomide and dexamethasone will offer the greatest benefit to patients as a second line treatment option. **The ERG's** clinical experts consider that the company's positioning of carfilzomib is appropriate and will offer the most benefit for patients. **The clinical expert** commented that the company's positioning of carfilzomib as part of a triplet therapy is clear in both treatment pathways. **The technical team** note that the company positioning is narrower than the marketing authorisation and the remit in the NICE scope. Relevant comparators **The company** consider lenalidomide and dexamethasone as the primary relevant comparator based on the proposed positioning of carfilzomib with lenalidomide and dexamethasone in the treatment pathway. The company also propose that daratumumab with bortezomib and dexamethasone should be considered as an additional comparator, given that it is recommended for

	use within the Cancer Drugs Fund as a second line treatment option for adults who have had one prior therapy (NICE technology appraisal 573). The company state that re-challenge with bortezomib is not likely to be a relevant, due to the availability of superior regimens with alternative mechanisms of action and the standard clinical practice of switching between drug classes with different mechanisms of action. **The ERG** agrees with the company that lenalidomide plus dexamethasone is the only relevant comparator that should be considered, based on the proposed positioning of carfilzomib with lenalidomide and dexamethasone. The ERG agrees with the company's rationale for not including re-challenge with bortezomib. **The clinical expert** commented that whilst lenalidomide plus dexamethasone was the main comparator, daratumumab with bortezomib and dexamethasone should also be considered as more than 80% of patients in England receive this as a second line treatment. The expert suggested that patients receiving bortezomib at first line may be re-challenged with a subsequent bortezomib based therapy in clinical practice, however this would most commonly be in combination with daratumumab and dexamethasone. **The technical team** note (as per NICE's position statement) that technologies that have been recommended by NICE for use in the Cancer Drugs Fund cannot be considered established practice and are therefore not considered as comparators in new appraisals.
Why this issue is important	The company are positioning carfilzomib for treating multiple myeloma in a subgroup of the ASPIRE trial population who have received only 1 prior therapy with bortezomib, which is narrower than the marketing authorisation for carfilzomib.
Technical team preliminary judgement and rationale	The treatment pathway for multiple myeloma is complex, therefore further clinical input is required to confirm the company's positioning of carfilzomib is appropriate and that all relevant comparators have been considered.

Issue 2 – Post-hoc subgroups to be considered

Questions for engagement	3. In clinical practice, is it possible for patients to receive lenalidomide and bortezomib as a first-line treatment even though this is not recommended in NICE guidance? 4. Which post-hoc subgroup of the ASPIRE trial reflects NHS clinical practice and should be included in the model?
Background/description of issue	**The company** presented clinical and cost-effectiveness results for carfilzomib with lenalidomide and dexamethasone versus lenalidomide plus dexamethasone in a subgroup of patients from the ASPIRE trial who received only 1 prior therapy with bortezomib (second line prior bortezomib). In their response to clarification, the company highlighted that their subgroup analysis is appropriate because patients could receive lenalidomide as a first-line treatment in combination with bortezomib. **The ERG note** that the company's base case consists of a subgroup of patients who had not all received prior bortezomib as part of their last treatment regimen [redacted] and that some patients had undergone treatment with lenalidomide in their last regimen [redacted] which they did not think reflected NICE-approved first-line treatment. Therefore, the ERG requested at clarification for a new subgroup to be incorporated in the analyses, consisting of patients who received only 1 prior bortezomib therapy and no prior lenalidomide. The ERG notes that the company provided this subgroup as a scenario only and therefore did not change its base-case assumptions. The ERG considers the second line prior bortezomib/no prior lenalidomide to be more reflective of clinical practice and has implemented this subgroup for the ERG base-case analysis.
Why this issue is important	The company and the ERG differ in their view of the most appropriate subgroup to include in the clinical and cost-effectiveness analyses. The choice of subgroup is likely to impact the company's base case ICER. Using the ERG's preferred subgroup (second line prior bortezomib/no prior lenalidomide): • The ICER reduces from **£43,952** in the company's base case to **£40,335**.
Technical team preliminary judgement and rationale	The technical team agree with the ERG's preferred subgroup (second line prior bortezomib/no prior lenalidomide), as this likely reflects the population that would receive carfilzomib in NHS clinical practice.

Issue 3 – Utility values used in the economic model

Questions for engagement	5. Are there additional treatment-specific benefits with carfilzomib with lenalidomide and dexamethasone compared with lenalidomide plus dexamethasone, other than gains in progression-free survival and overall survival? 6. Are the utility values used in the company's economic model appropriate and reliable for decision-making?
Background/description of issue	The EQ-5D was not administered in the ASPIRE trial and so mapped-utility values from a disease-specific questionnaire (EORTC QLQ-C30 to EQ-5D) were used in the company's economic model. To account for baseline imbalances in patient characteristics and utilities between treatment arms, the mapped utility values were assessed using a repeated-measures mixed-effects model. The outcome of the model was change from baseline utility and the mean change from baseline was estimated from the individual effects of each adjusted covariate. **The company** reported that treatment-specific utilities were incorporated in their cost-effectiveness model for their preferred subgroup (second line prior bortezomib). For cycles 1-2 in the progression-free health state, the company used the same baseline utility value as patients in ASPIRE with 1 prior therapy with bortezomib, for both treatment groups. For cycles 3 onwards in the pre-progression health state, the company added on the mean change in utility from baseline for both treatment groups, and then subtracted the utility difference between treatment groups for the lenalidomide plus dexamethasone group only. **The ERG** is concerned that utility values for the progression-free health state capture both the increase in mean utility from baseline for both treatments, as well treatment-specific increase in utility if a patient is on carfilzomib with lenalidomide and dexamethasone. The ERG notes that the mean change in utility over time was [redacted] for carfilzomib with lenalidomide and dexamethasone compared with lenalidomide plus dexamethasone, even though all patients have progression-free disease. The ERG clinical expert suggested that there was no clinical reason for there to be a treatment-specific utility benefit in addition to the benefit provided by any gains in progression-free survival. The ERG considers that the company's use of both mean change in utility over time and treatment-specific values may be unreliable and consider that it is more appropriate for the pre-progression utility values to be the same for both treatment arms.

	The clinical expert noted that other than gains in progression-free survival and overall survival, there would not be any additional treatment-specific benefit with carfilzomib with lenalidomide and dexamethasone over lenalidomide plus dexamethasone**.**
Why this issue is important	The choice of pre-progression utility values used in the economic model is likely to impact the ICER for the ERG's preferred subgroup (second line prior bortezomib/no prior lenalidomide): 1) Removal of treatment effect for pre-progression health-state utility value - the ICER increases from **£40,335** in the ERG base case to **£41,303**. 2) Removal of average increase in baseline utility from cycle 3 onwards – the ICER increases from **£40,335** in the ERG base case to **£43,583**. 3) The removal of both 1) and 2) – the ICER increases from **£40,335** in the ERG base case to **£44,438**.
Technical team preliminary judgement and rationale	It is unlikely that there are additional treatment-specific benefits with carfilzomib with lenalidomide and dexamethasone compared with lenalidomide plus dexamethasone. As such, the technical team agrees with the use of equal utility values for the progression-free health state for both treatment groups.

Issue 4 – Extrapolation of overall survival

Questions for engagement	7. Should data entirely from the ASPIRE trial be used in the economic model to extrapolate overall survival? 8. Is the Weibull or exponential distribution more appropriate for extrapolation of overall survival?
Background/description of issue	The company model has a lifetime time horizon (40 years), so overall survival needs to be extrapolated beyond the observed time period for the trials. The company calculated effectiveness estimates in the model for carfilzomib with lenalidomide and dexamethasone and lenalidomide plus dexamethasone, using extrapolations of ASPIRE inverse probability weighted (IPW) Kaplan-Meier (KM) progression-free survival and overall survival data. Treatment effectiveness estimates were calculated for both the company's preferred subgroup (second line prior bortezomib) and the ERG's preferred subgroup (second line prior bortezomib/no prior lenalidomide). **The company** selected the Weibull distribution as the best fit to the IPW KM overall survival data, but noted that estimates of survival for the lenalidomide plus dexamethasone curve were conservative towards the end of the extrapolation, when compared with estimates presented in NICE technology appraisal 586. As such, to estimate overall survival for the lenalidomide plus dexamethasone arm, the company extrapolated a hybrid of IPW KM overall survival data and real-world evidence from a French registry (MyelomaToul) of multiple myeloma patients who received lenalidomide as a second line treatment. To estimate overall survival for the carfilzomib with lenalidomide and dexamethasone arm, the company also conducted a similar hybrid extrapolation, with the MyelomaToul data adjusted using the IPW overall survival hazard ratio from the ASPIRE trial. **The company** highlighted in their response to clarification, that in NICE technology appraisal 457 data from a UK registry; Haematological Malignancy Research Network (HMRN) were available for the overall survival of patients receiving lenalidomide as a third line therapy. HMRN data were used in a scenario analysis to estimate the overall survival of lenalidomide and dexamethasone in patients with 2 prior therapies and no prior lenalidomide. The company highlighted that reliable and robust data from HMRN were not available for patients receiving lenalidomide as a second line treatment, at the time of data access. **The ERG's** clinical experts agreed that the longer-term survival estimates for patients treated with lenalidomide and dexamethasone were conservative. The ERG notes that the company have

adjusted the MyelomaToul data to account for the mortality difference between patients from the MyelomaToul registry and from the ASPIRE trial. The ERG is concerned that the company's adjustment of survival for the lenalidomide and dexamethasone arm, results in an inflation of survival for the carfilzomib with lenalidomide and dexamethasone arm, compared with estimates derived from the IPW ASPIRE data (see Table 9 below).

Table 9: Overall survival predictions by extrapolation method for the second line prior bortezomib/no prior lenalidomide subgroup (adapted from Table 17 in ERG report)

Overall survival extrapolation	10 years		20 years	
	CRd	Rd	CRd	Rd
ASPIRE Weibull distribution	16%	5%	2%	0%
Adjusted MyelomaToul model + HR	21%	9%	6%	1%
ASPIRE exponential distribution	19%	8%	4%	1%
Abbreviations: CRd = carfilzomib/lenalidomide/dexamethasone; Rd = lenalidomide/dexamethasone.				

The ERG also notes that the adjusted MyelomaToul data indicates that 1% of patients are alive at around year 12 onwards, compared with 20 years as reported by the company (see Figure 8 below).

Figure 8: Overall survival of second line lenalidomide treated patients in MyelomaToul and ASPIRE second line prior bortezomib/no prior lenalidomide (referenced from ERG report, Figure 16)

	 The ERG notes that in the company's response to clarification, the company state that when the MyelomaToul data was used to validate the extrapolation of overall survival from the ASPIRE trial, the exponential distribution provided the most clinical plausible predictions of longer-term survival. The ERG also notes that the exponential distribution produced similar survival estimates for lenalidomide plus dexamethasone compared with the company's base case estimates. The ERG considers that the exponential distribution was the best statistical fit to the IPW KM overall survival data for their preferred subgroup, being less optimistic than the company's base case using MyelomaToul registry data (see Figure 9 below).

	Figure 9: Comparison of overall survival curves for carfilzomib in combination with lenalidomide and dexamethasone (referenced from ERG report, Figure 17)  The ERG considers that the IPW overall survival data should be used for the base case analysis as it is based on mature trial data, and therefore a clinically plausible extrapolation of overall survival for carfilzomib with lenalidomide and dexamethasone can be estimated entirely from ASPIRE. **The technical team** note that the MyelomaToul registry data used in the economic model was not adjusted to match the company's base case.

Why this issue is important	The choice of distribution used for modelling overall survival is likely to impact the company's and ERG's preferred base case ICER. Using the exponential distribution for overall survival (from ASPIRE only): • The ICER increases from **£40,335** in the ERG base case to **£45,919**.
Technical team preliminary judgement and rationale	The technical team agree that a clinically plausible extrapolation of overall survival can be obtained entirely from the mature ASPIRE trial data. It is likely that the exponential distribution results in the most clinically plausible prediction of long-term survival with carfilzomib in combination with lenalidomide and dexamethasone, however further clinical input is required to validate this assumption in clinical practice.

4. Issues for information

Tables 10 to 12 are provided to stakeholders for information only and not included in the technical report comments table provided.

Table 10: Technical team preferred assumptions and impact on the cost-effectiveness estimate

Alteration	Technical team rationale	ICER*	Cumulative change
Company base case (second line prior bortezomib)	**–**	**£43,952**	**–**
1. ERG preferred subgroup: second line prior bortezomib/no prior lenalidomide	Technical team agree with the ERG's alternative subgroup - Issue 2	£40,335	-£3,617
2. Extrapolation of overall survival	Exponential distribution using only ASPIRE trial data - Issue 5	£45,919	+£5,584
3. Utilities	Removal of treatment effect and increase in utility from baseline for cycle 3 onwards for pre-progression health state utility value - Issue 4	£50,960	+£5,041
Cumulative impact of the technical team's preferred assumptions on the cost-effectiveness estimate	**–**	**£50,960**	**£7,008**

*including carfilzomib PAS (but not the lenalidomide PAS)

Table 11: Outstanding uncertainties in the evidence base

Area of uncertainty	Why this issue is important	Likely impact on the cost-effectiveness estimate
Subsequent treatment costs	Subsequent treatment costs included in the model may not reflect those received in the ASPIRE trial and may include treatments not recommended by NICE. The ERG noted that investigational drugs were omitted from subsequent treatment costs, which may underestimate the total costs included in the economic model.	The company conducted an analysis in which subsequent treatment costs for key treatments received in the ASPIRE trial including Vd, Rd and Pd were included in the model. Implementing the scenario had a small impact on the ICER. The ERG added investigational drugs (based on daratumumab costs) in the subsequent treatment costs based on ASPIRE, as a separate scenario analysis, and found this had a very little impact on the ICER.
Monitoring costs	The ERG's clinical experts noted that monitoring costs may be underestimated in the model.	The ERG conducted a scenario analysis increasing the routine monitoring costs by 50% and found this had a minimal impact on the ICER.
Adverse events	The ERG clinical experts raised concerns for the resource use assumed for the treatment of adverse events.	The ERG noted that changes in the cost assumptions had minimal impact on the ICER.

Abbreviations: Vd = bortezomib/dexamethasone, Rd = lenalidomide/dexamethasone; Pd = pomalidomide/dexamethasone

Table 12: Other issues for information

Issue	Comments
Inverse probability weighted (IPW) analysis	The company completed an IPW analysis to account for imbalances in baseline characteristics between treatment arms, arising from the use of a non-randomised post-hoc subgroup. The ERG deems that that the company's approach to identification of relevant covariates was appropriate, however noted that some of the covariates [redacted]. After adjustment, treatment with carfilzomib with lenalidomide and dexamethasone compared with lenalidomide plus dexamethasone, was associated with [redacted]. The company in response to the ERG's request at clarification, confirmed that the results of the regression analyses were treatment specific. Clinical experts contacted by the ERG and the technical team consider that the clinical rationale for these results are not clear. The ERG also highlighted that in NICE technology appraisal 457 (which did not use an IPW analysis to adjust results for the second line prior bortezomib/ no prior lenalidomide subgroup), the result presented for [redacted] is similar to results generated by the IPW analyses in this appraisal. The ERG concluded that the results from the IPW analyses are as reliable as those considered by the committee in NICE technology appraisal 457 and can be considered appropriate for decision-making.
Generalisability of ASPIRE	The ASPIRE trial was conducted across 129 sites in 20 countries in Europe, USA and Israel. Sixteen patients (2%) were enrolled in the UK across 6 sites. The company reports that progression-free survival and overall survival data were shown to be consistent irrespective of geographic region in the pre-specified ASPIRE subgroup analysis. Clinical experts contacted by the ERG and technical team highlighted that the population in the ASPIRE trial are slightly younger and have a lower Eastern Cooperative Oncology Group (ECOG) performance status than people typically presenting with multiple myeloma in clinical practice. The ERG clinical expert highlighted that this would be expected in a myeloma clinical trial. The technical team note that in NICE technology appraisal 457,the committee understood from the clinical expert that patients in myeloma trials are generally younger because they are more willing and able to travel to the treatment centre and because patients are being diagnosed earlier. The committee concluded that the ASPIRE trial could be generalised to UK clinical practice.
Stopping rule	In the ASPIRE trial, carfilzomib was stopped after 18 cycles whereas the marketing authorisation allows for treatment until progression or unacceptable toxicity. The company state that the rationale for this stopping rule is due to the limited data

Issue	Comments
	on the tolerability and toxicity of carfilzomib beyond 18 cycles. The technical team note that treatment costs for carfilzomib were not included in the company's economic model after 18 cycles.
Drug wastage	The company have not included drug wastage in the model as they expect carfilzomib drug wastage to be minimal. The company conducted a scenario analysis to include drug wastage and found that implementing the scenario had a minimal impact on the ICER. The ERG considers that drug wastage is not a primary driver of cost-effectiveness in the model and agree with the company that this assumption does not have a meaningful impact on the ICER. The ERG considers that drug wastage is likely to occur in clinical practice.
Adverse events	The ERG noted that cardiac disorders were omitted in the economic model as a serious adverse reaction. The ERG's clinical experts highlighted that the Summary of Product Characteristics (SmPC) for carfilzomib reports cardiac disorders as a special warning and a precaution for use. Cardiac failure, ischemic heart disease, hypertension and venous thromboembolic events occurred [redacted] in those receiving carfilzomib with lenalidomide and dexamethasone compared with lenalidomide plus dexamethasone.
Cancer Drugs Fund	The company has not expressed an interest in carfilzomib being considered for funding through the Cancer Drugs Fund, due to mature efficacy data available from the APIRE trial directly comparing carfilzomib with lenalidomide and dexamethasone to lenalidomide plus dexamethasone. The technical team consider that carfilzomib is unlikely to be a candidate for the Cancer Drugs Fund.
End-of-life criteria	The company state that in the proposed second line positioning, carfilzomib with lenalidomide and dexamethasone meets the extension to life criterion but does not meet the short life expectancy criterion. The company highlighted that it did however meet the end-of life criteria considered in the appraisal of pertuzumab with trastuzumab and docetaxel for treating HER2-positive breast cancer (NICE technology appraisal 509). The technical team note that the flexibility in the application of the end-of-life criteria was accepted in this case as an exceptional circumstance. The technical team note that whilst there is flexibility in the application of end-of-life criteria, carfilzomib is unlikely to meet end-of-life criteria.
Innovation	The company considers that carfilzomib with lenalidomide and dexamethasone is innovative in being a triplet regimen. However, the technical team considers that all relevant benefits associated with the drug are adequately captured in the model.
Equality considerations	No equalities issues were identified by the company.

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NICE National Institute for Health and Care Excellence

Technical engagement response form

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

As a stakeholder you have been invited to comment on the technical report for this appraisal. The technical report and stakeholder's responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

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Deadline for comments by 5pm on Wednesday 10 June 2020.

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- Do not use abbreviations.
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- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, 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 engagement 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.

About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**Amgen Ltd**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**NA**

Questions for engagement

Issue 1: Positioning of carfilzomib in the treatment pathway	
1. Is the positioning of carfilzomib appropriate in the treatment pathways for those eligible and ineligible for stem cell transplantation?	**Amgen believe that the positioning put forward in our company submission is appropriate within the context of the multiple myeloma clinical pathway** **Our proposed positioning reflects:** o the clear unmet need for triplet therapies that target multiple pathways and enable deeper and more durable responses, as well as improved survival outcomes, earlier in the pathway;[1, 2] o feedback from clinical experts suggests that carfilzomib in combination with lenalidomide and dexamethasone (CRd) will offer the greatest benefit to patients in the 2L setting;[3] o In the pivotal ASPIRE trial, patients at 2L demonstrated improved clinical outcomes compared with later lines (post hoc subgroup analysis, see Section B.2.7 of main submission dossier), which supports the value of CRd being used early in the pathway. o an alignment with the reimbursement criteria of the most relevant comparator, lenalidomide in combination with dexamethasone (Rd), which is supported by a Ph3 randomised comparison; o and the subgroup within which CRd offers the greatest economic value given the substantial clinical benefit observed in this population. Amgen also maintain that CRd should be considered as a treatment option irrespective of transplant eligibility, which is consistent with the clinical evidence base from the Ph3 ASPIRE trial (primary clinical data source), and feedback from clinical experts (n=6) received during a 2019 advisory board as to the most appropriate positioning of CRd in the treatment pathway.

2. Have all the relevant comparators been considered?	**Although Rd is the primary relevant comparator in the appraisal, consideration should be given to the comparison versus daratumumab in combination with bortezomib and dexamethasone (DVd), and the challenges of demonstrating cost-effectiveness within combination therapies should be recognised.** Amgen agree that as per the positioning outlined in Issue 1.1, a comparison of CRd versus Rd is of primary relevance to this appraisal. However, there are specific issues related to combination therapies, whereby the new technology is penalised by increased costs of background therapy, that we feel are not well recognised in the technical report. This is relevant for CRd – the increased time spent in progression free survival (PFS) due to the increased efficacy of adding carfilzomib to Rd results in patients incurring incremental costs associated with additional Rd which is given until progression. In the extreme case, this issue can lead to new combination therapies being unable to demonstrate cost-effectiveness even at zero price, as the prolonged use of the background therapy is not considered cost-effective at usual willingness to pay thresholds[1]. **The issue is demonstrated in the Amgen base case analysis, where [redacted] of the total CRd acquisition cost was associated with Rd and only [redacted] comprised of carfilzomib (analysis conducted at lenalidomide list price). Even when considering the previously applied complex 26-cycle cap for lenalidomide, [redacted] of the total CRd acquisition cost was associated with Rd and only [redacted] comprised of carfilzomib.** [redacted] In an exploratory analysis where the treatment duration of Rd was assumed equivalent in both arms, the ICER reduced markedly from £43,952 per QALY in the base case to £16,751 per QALY (analysis conducted at lenalidomide list price). Although we recognise the 'combination issue' is broader than the CRd appraisal in isolation, 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 degree to which CRd is penalised by increased background therapy is amplified beyond which would typically be expected for other combination therapies. • [redacted]

[1] NICE DSU Report - Assessing Technologies that are Not Cost-Effective at a Zero Price http://nicedsu.org.uk/methods-development/not-cost-effective-at-0/

	• In the proposed 2L positioning, CRd meets the extension to life criterion but does not meet the short life expectancy criterion. However, we were 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.[4] We believe CRd meets these criteria and thus there is a case for additional flexibility to be applied during the decision making process. We believe the issues surrounding combination therapies as it relates to the comparison of CRd versus Rd are important for Committee decision making context and should be reflected in the associated Committee Papers following this consultation. In addition, and as outlined in our submission dossier, Amgen maintain that a comparison versus DVd is an important and informative component of this appraisal. 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 in to account outside of the reference case. Clinical experts have consistently informed Amgen that DVd would be a relevant comparator and is widely used in the proposed positioning of CRd in this appraisal; indeed, as noted in the Technical Engagement Report, the clinical expert consulted by NICE suggested as many as 80% of patients receive DVd in England as a second-line treatment. Amgen conducted a matched-adjusted indirect comparison to explore the relative efficacy of CRd versus DVd and the analysis resulted in [redacted] We acknowledged the considerable uncertainty with this analysis in our submission dossier, primarily due to the immature survival data for DVd; however, clinical expert opinion (n=6) sought during a 2019 advisory board considered results indicating an improved PFS and at least comparable OS to be reasonable in the absence of direct comparative data. In the economic evaluation base case, CRd was found to be a ***dominant*** treatment strategy, providing increased benefit for a cost saving of *£55,317* (analysis conducted at lenalidomide and daratumumab list prices). Given the current use of DVd in clinical practice 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 should be included for Committee deliberations.

Issue 2: Post-hoc subgroups to be considered	
3. In clinical practice, is it possible for patients to receive lenalidomide and bortezomib as a first-line treatment even though this is not recommended in NICE guidance?	**Amgen maintain that the most appropriate population for CRd Guidance is the 2L prior bortezomib subgroup. We recognise that the 'strict' interpretation of the clinical pathway results in a reduced ICER and may be informative for decision making; however, the final guidance should reflect clinical practice and remain clinically relevant.**
4. Which post-hoc subgroup of the ASPIRE trial reflects NHS clinical practice and should be included in the model?	As outlined in our response to clarification questions, the subgroup used in our submission dossier is defined on two variables: **1)** number of prior regimens = 1; **2)** prior bortezomib = 1 [yes]. This subgroup is consistent with the proposed positioning of CRd detailed in our response to Issue 1 and with the Guidance of the primary comparator in this appraisal, Rd (TA586). We acknowledge that the ERGs preferred subgroup (ie. addition of a further 'no prior lenalidomide' restriction) reflects a 'strict' interpretation of the NICE approved clinical pathway and that this leads to reduction in the ICER – therefore, it may be informative for a Committee to consider but we would caution that this does not necessarily reflect clinical practice in England and that further restriction of this population could result in suitable patients unwittingly becoming ineligible for an effective 2L treatment. After consultation with clinical experts, we believe it is plausible that a minority of patients could be exposed to prior lenalidomide and still be considered eligible for treatment with CRd. Furthermore, there is a concern that including additional restrictions for CRd during this appraisal could lead to downstream challenges as front-line therapy changes in the future. It is worth noting that that the clinical and cost-effectiveness results in the Amgen preferred and ERG preferred subgroups remain largely consistent. An overview of PFS data is provided in Table 1 below:

Table 1: Data for the IPW-adjusted PFS as determined by investigators (data cut-off December 2017)

	2L/prior bortezomib/no prior lenalidomide		2L/prior bortezomib	
	CRd (N=68)	Rd (N=69)	CRd (N=82)	Rd (N=81)
Median PFS (95%CI)	[redacted]	[redacted]	[redacted]	[redacted]
HR; CRd vs Rd (95% CI) IPW-adjusted (stepwise selection within Cox model)	[redacted]		[redacted]	

Abbreviation: CRd = carfilzomib/lenalidomide/dexamethasone; HR = hazard ratio; IPW = Inverse probability weighting; PFS = Progression-free survival; Rd = lenalidomide/dexamethasone

The ICER reduces from £43,952 to £40,335 per QALY for the Amgen and ERG preferred subgroups, respectively (analyses conducted at lenalidomide list price).

In conclusion, although we recognise that the ERGs preferred subgroup may be relevant for the Committee to consider, we do not believe it is the most-appropriate population for which to issue Guidance.

Issue 3: Utility values used in the economic model

5. Are there additional treatment-specific benefits with carfilzomib with lenalidomide and dexamethasone compared with lenalidomide plus dexamethasone, other than gains in progression-free survival and overall survival?

6. Are the utility values used in the company's economic model appropriate and reliable for decision-making?

Amgen consider that there is a clear case for a treatment-specific utility impact beyond 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 reflects clinical expert opinion and the high-quality health-related quality of life (HRQoL) data collected during the pivotal Ph3 trial.

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.[5, 6] 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]

	[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. Nevertheless, the of use of treatment specific utility values are also justified by the HRQoL data reported in the ASPIRE clinical trial. HRQoL was included as a pre-specified secondary endpoint measured by the QLQ-C30 GHS/QoL subscale – this provided a measure of the overall impact of MM and its treatment from the patient's perspective. Completion of the baseline questionnaire was excellent (94.1% of randomly assigned patients) and compliance remained high for subsequent measurements (>82% across all measurement cycles). CRd was found to improve global health status with significantly higher QLQ-C30 GHS/QoL scores compared to Rd ($p < 0.001$) and point estimates favoured CRd across the functional and symptom domains. Subsequently, the mixed effects model based on the mapping of QLQ-C30 scores to EQ-5D found that patients who received CRd had a statistically significantly larger average increase in utility than patients who received Rd after adjusting for baseline imbalances. Overall, we believe that the HRQoL 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. Indeed, Amgen's approach for estimating utilities in MM was also preferred by the ERG in the unrelated TA573 appraisal of DVd in 2019. Finally, it is worth noting that the ERGs preferred utility values recommended two changes to Amgen's base case model – in addition to the removal of a treatment specific utility, it is suggested to remove an improvement in utility values from Cycle 3 onwards. As per the above argumentation, the ERGs preferred approach is inconsistent with the response and HRQoL data observed in the ASPIRE clinical trial and contradictory to previously accepted approaches in this disease area. In conclusion, we believe there is a strong justification to maintain the utility values used in the company base case evaluation, as these are supported by both clinical data and feedback received from clinical experts consulted by Amgen.

Issue 4: Extrapolation of overall survival	
7. Should data entirely from the ASPIRE trial be used in the economic model to extrapolate overall survival?	**Amgen believe that real world evidence sources incorporated in our submission dossier provide reliable and informative data to capture plausible long-term survival extrapolations. We maintain that parametric extrapolation from the ASPIRE clinical trial may result in 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.** **<u>External Data</u>** As noted in our response to clarification questions, there are several pieces of published evidence that make Amgen believe that extrapolating survival solely based on data from the ASPIRE trial may provide overly pessimistic long-term survival estimates (in particular, the statistically best-fitting Weibull model): 1. The Weibull model fitted to ASPIRE subgroup data estimates survival proportions for Rd patients at 10, and 20 years to be 5% and 0%, respectively (see Table 29 in the company submission). These estimates are more conservative than those predicted by the manufacturer in the technology appraisal submitted to NICE for Rd in relapsed/refractory multiple myeloma (TA586). In TA586, the company estimated survival at 25 years for patients starting on Rd to be 11%.[7] Although the ERG assessing the submission deemed this to be too high, an alternative more plausible value was not reported. In the recent FAD for the NICE appraisal of DVd, clinical experts in the UK estimated that around 5-10% of current second-line patients would be expected to survive to 10 years.[8] The 10-year survival probability estimated by a Weibull model fitted exclusively to ASPIRE data is notably at the lower end of this range. We feel it is important to note that the estimate provided by experts during the final appraisal of DVd reflects the survival probability in clinical practice and the survival probability of patients enrolled in clinical trials are generally higher than in routine clinical practice. 2. Long-term OS data with more than 8 years of follow-up for Rd-treated patients was recently published for a Czech/Slovakian registry cohort (Registry of monoclonal Gammopathies; RMG).[9] In the published analysis, OS data were presented based on patients who received 1-3 prior therapies and were treated outside of clinical trials. Adopting a similar approach to that used with the MyelomaToul dataset (and detailed in our response to clarification questions) the predicted survival for Rd in the 2L setting was between 2.9%-5.7% and 13.7%-15.4%, for 20-year and 10-year, respectively. This data supports the conclusion that some patients may achieve a long-term durable response to treatment and can have plausible survival rates greater than that predicted by extrapolation from the ASPIRE clinical trial. 3. In 2016, Amgen submitted carfilzomib/dexamethasone (Cd) to NICE as a part of appraisal TA457 to assess the cost-effectiveness of Cd versus bortezomib/dexamethasone (Vd) using subgroup data from the phase 3
8. Is the Weibull or exponential distribution more appropriate for extrapolation of overall survival?	

	ENDEAVOR randomised controlled trial. In the submission, reference was made to the DOXIL-MMY-3001 study, which was highlighted as the study with the longest follow-up for OS with bortezomib-treated relapsed/refractory multiple myeloma patients.[10] The study was considered to represent a rich external data source from which clinical plausibility of the OS extrapolation for Vd could be meaningfully assessed. Specifically, in the bortezomib monotherapy arm of the DOXIL-MMY-3001 study, the proportion of patients alive after 9 years was estimated to be about 13% and the shape of the survival curve started to display a flattening shape after about 4-5 years. This dataset underlines the importance of considering real-world data for survival extrapolations and demonstrates that relatively high proportions of patients with multiple myeloma can survive long-term. . **Multistate Model – exploratory analysis of ASPIRE** Amgen also conducted additional exploratory analyses of the ASPIRE clinical trial to assess the feasibility of parametric models to inform long-term OS projections. Survival estimation via parametric extrapolation in an area-under-the-curve model structure is only determined by the time-to-death data observed and is not explicitly linked to the timing of earlier progression events. Specifically, extrapolation of OS depends only upon prior trends in mortality rates (unless external information on hazard rates beyond the trial period is incorporated), and is not explicitly linked to information on the non-fatal progression event. This exploratory analysis used a multistate modelling approach applied to data from all Rd patients in ASPIRE[2] to assess differences in long-term OS extrapolations versus the standard parametric extrapolation approaches. The multistate explicitly considered clinical events to be related; that is, it modelled transitions between health states to take in to account the underlying disease process. Consequently, survival predictions performed by the multistate modelling approach are expected to differ from the those prepared by the standard curve fitting approach. These analyses are detailed in full in our original submission dossier although were not included for consideration in the technical engagement report. Two key conclusions were drawn based on the multistate modelling approach: 1. Later progression (or increased progression free survival) was associated with longer post-progression survival, which translated to a non-increasing risk of death in the overall population 2. OS predicted by the multistate model suggested longer estimates than those predicted by the Weibull model and were consistent with the external MyelomaToul data. Although these analyses were conducted in the ITT population and not directly applicable to the subgroup under consideration for this appraisal, we believe that they can inform the most appropriate extrapolation approach. It is our view that parametric distributions based on observed ASPIRE data that do not reflect the

2 Data from the Rd arm of the full ASPIRE trial population was used to be able to estimate reliable parameters for the multistate model, a larger dataset is preferred (please see a discussion of the challenges associated with multistate modelling in the NICE DSU Technical Support Document 19).

potential for decreasing hazards after the trial follow-up likely underestimate long-term survival and that real-word data from the MyelomaToul registry provides a more clinically plausible outcome.

Clinical Expert Opinion

Amgen sought validation of the projected survival outcomes in our base case economic evaluation in a 2019 advisory board (n=6 clinicians present) and feedback confirmed that current estimates were clinically plausible. Indeed, it was noted that 10-year survival projections may underestimate survival in clinical practice which is consistent with feedback received during other NICE appraisals in multiple myeloma. We also note that this is a view shared by the ERG's clinical expert as stated in the Technical Engagement Report; '*The ERG's clinical experts agreed that the longer-term survival estimates for patients treated with lenalidomide and dexamethasone were conservative.*'

Although the Amgen's base case and the ERGs preferred case provide similar estimates of survival (10-year and 20-year survival rates within 2% [absolute]), relatively minor changes in long term survival rates can have a meaningful impact on the resulting ICERs. We believe it is important to consider the evidence that suggests survival estimation via ASPIRE is conservative and utilise longer-term external data where possible to inform decision making.

Finally, we suggest it is informative to consider previously accepted estimates of long-term survival by NICE within the multiple myeloma disease area. Of particular relevance, is the TA573 appraisal of DVd in which the FAD states that the Committee preferred the ERG's more conservative survival estimate for the daratumumab combination at 20 years of 11% (see Table 2). Feedback from clinical experts during the advisory board found that long-term survival with CRd was expected to be at least comparable with DVd, particularly given the improved PFS suggested in the indirect comparison. Given this, it can reasonably be concluded that Amgen's base case estimate of 20-year survival remains conservative and that the ERGs base case prediction estimates approximately 1/3 of the 20-year survival that experts have previously deemed to be clinically plausible.

Table 2: Comparison of 20-year survival rates

	20-year survival	
	Rd	**CRd**
Amgen Base Case – RWE (MyelomaToul) informed long-term extrapolation	**1%**	**6%**
ERG Base Case – parametric extrapolation from ASPIRE	**1%**	**4%**
NICE Committee Preferred Assumptions for DVd (TA583) - 2L	**DVd**	
	11%	

	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 in to account clinically plausible long-term survival extrapolations.

References

1. Balijevic M, Holstein S. Evidence-Based Support for Triplet Therapies in Multiple Myeloma. The ASCO Post. 2017.
2. National Institute for Health and Care Excellence. Appraisal consultation document – Daratumumab with bortezomib for previously treated multiple myeloma. Available from: https://www.nice.org.uk/guidance/gid-ta10174/documents/appraisal-consultation-document (Accessed 7 February 2019) 2018.
3. Cello Health Insight. Kyprolis Customer Insight Program. 2018.
4. National Institute for Health and Care Excellence (NICE). Pertuzumab (with trastuzumab and docetaxel) for HER2 positive metastatic breast cancer [ID523]. Committee meeting 4 slides. 8 May 2017.
5. Osborne TR, Ramsenthaler C, Siegert RJ, Edmonds PM, Schey SA, Higginson IJ. What issues matter most to people with multiple myeloma and how well are we measuring them? A systematic review of quality of life tools. Eur J Haematol. 2012;89(6):437-57.
6. Gulbrandsen N, Hjermstad MJ, Wisloff F, Nordic Myeloma Study Group. Interpretation of quality of life scores in multiple myeloma by comparison with a reference population and assessment of the clinical importance of score differences. Eur J Haematol. 2004;72(3):172-80.
7. National Institute for Health and Care Excellence (NICE). Lenalidomide plus dexamethasone for multiple myeloma after 1 treatment with bortezomib. Technology appraisal guidance TA586 2019 [10 July 2019]. Available from: https://www.nice.org.uk/guidance/ta586.
8. National Institute for Health and Care Excellence. Daratumumab with bortezomib for treating relapsed or refractory multiple myeloma [ID974] Final Appraisal Determination 2019 [21 March 2019]. Available from: https://www.nice.org.uk/guidance/indevelopment/gid-ta10174/documents.
9. Maisnar V, Stefanikova Z, Spicka I, Pour L, Minarik J, Flochova E, et al. Lenalidomide and dexamethasone in treatment of patients with relapsed and refractory multiple myeloma—analysis of data from the Czech Myeloma Group Registry of Monoclonal Gammopathies. Neoplasma. 2019;66(3):499-505.
10. Orlowski RZ, Nagler A, Sonneveld P, Bladé J, Hajek R, Spencer A, et al. Randomized phase III study of pegylated liposomal doxorubicin plus bortezomib compared with bortezomib alone in relapsed or refractory multiple myeloma: combination therapy improves time to progression. Journal of Clinical Oncology. 2007;25(25):3892-901.

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- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
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About you

Your name	**Dr Karthik Ramasamy**
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**UKMF/ BSH/ Royal College of Physicians/ Royal College of pathologists**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**Research Grants/ Speaker Honoraria/ Advisory Board – Celgene, Janssen, Takeda, Amgen Advisory Board – Abbvie/ Sanofi**

Questions for engagement

Issue 1: Positioning of carfilzomib in the treatment pathway	
1. Is the positioning of carfilzomib appropriate in the treatment pathways for those eligible and ineligible for stem cell transplantation?	**Yes**
2. Have all the relevant comparators been considered?	**Should consider adding DVD as comparator - majority of patients are receiving DVD as second line therapy in clinical practice**
Issue 2: Post-hoc subgroups to be considered	
3. In clinical practice, is it possible for patients to receive lenalidomide and bortezomib as a first-line treatment even though this is not recommended in NICE guidance?	**In clinical practice VRD is not current standard of care in England. Patients who receive SCT following a Bortezomib based induction are eligible for licensed Lenalidomide maintenance therapy. This is currently under consideration with NICE. There are patients who received Lenalidomide maintenance therapy following SCT in a private setting.** **During COVID-19 pandemic, patients have been switched from Bortezomib to Lenalidomide based induction therapy and therefore would have had exposure to both agents in first line setting.** **Patients treated in trials during first line of therapy would have been exposed to Lenalidomide and bortezomib combination induction therapy or Lenalidomide in maintenance setting.**
4. Which post-hoc subgroup of the ASPIRE trial reflects NHS clinical practice and should be included in the model?	**Second line therapy and prior Bortezomib exposure**

Issue 3: Utility values used in the economic model	
5. Are there additional treatment-specific benefits with carfilzomib with lenalidomide and dexamethasone compared with lenalidomide plus dexamethasone, other than gains in progression-free survival and overall survival?	**Addition of Carfilzomib to Lenalidomide and dexamethasone improves QoL in the GHS. Although this is an open label study and therefore a degree of bias in reporting, significantly higher proportions of patients have responded and do respond within first 4 cycles. It is clinically plausible this would be associated with improved QoL parameters.**
6. Are the utility values used in the company's economic model appropriate and reliable for decision-making?	**Outside my area of expertise**
Issue 4: Extrapolation of overall survival	
7. Should data entirely from the ASPIRE trial be used in the economic model to extrapolate overall survival?	Overall survival continues to improve in myeloma and this is driven by early diagnosis and availability of effective treatment combinations. Aspire trial started recruiting almost 10 years ago and reported in 2014. Data from other trials if available (provided entry criteria are similar) or real world evidence sources could be considered if the population if interest are comparable.
8. Is the Weibull or exponential distribution more appropriate for extrapolation of overall survival?	Weibull appears more conservative, exponential distribution is more clinically plausible

NICE National Institute for Health and Care Excellence

Technical engagement response form

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

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We need your comments and feedback on the questions below. You do not have to answer every question. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be summarised and used by the technical team to amend or update the scientific judgement and rationale in the technical report.

Deadline for comments by 5pm on Wednesday 10 June 2020.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

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About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**Myeloma UK – Stakeholder**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**N/A**

Questions for engagement

Issue 1: Positioning of carfilzomib in the treatment pathway	
1. Is the positioning of carfilzomib appropriate in the treatment pathways for those eligible and ineligible for stem cell transplantation?	Yes
2. Have all the relevant comparators been considered?	Yes according to NICE guidance on comparators. We would note that daratumumab (Darzalex), bortezomib (Velcade) and dexamethasone (DVD) is not included as a comparator due to CDF status. While we understand the rationale for this and that it is an agreed policy position for NICE, DVD is likely to be most clinician's first treatment of choice at second line, unless there are specific contraindications or clinical reasons why the patient should not receive it. It is the case therefore that the real world standard treatment will not be used as a comparator.
Issue 2: Post-hoc subgroups to be considered	
3. In clinical practice, is it possible for patients to receive lenalidomide and bortezomib as a first-line treatment even though this is not recommended in NICE guidance?	Yes this is possible although those patients who do receive it may be more likely to do so consecutively rather than as a combination. The treatment sequencing effect as it relates to use of carfilzomib (Kyprolis) lenalidomide (Revlimid) and dexamethasone KRd is the same. For example

	a patient may receive velcade as part of their induction therapy. Following on from this it may be possible for some patients to receive lenalidomide maintenance post HDT-ASCT. In the current context of COVID – 19 some patients may also receive velcade based induction prior to stem cell harvest and then be placed on longer term lenalidomide prior to deferred transplant. It is difficult to say what size this patient population may be, but it could be significant. Post HDT-SCT lenalidomide and dexamethasone has also have been accessed by significant number of patients via the Myeloma XI trial. Access to lenalidomide maintenance is currently being appraised by NICE (TA475). Should that appraisal be approved, then significant numbers of patients will have had both bortezomib and lenalidomide prior to second line. (5800 patients are diagnosed each year and around one third of those receive a stem cell transplant; so over 1900 patients could be eligible to receive lenalidomide maintenance.) Lenalidomide maintenance post HDT-SCT and the combination of lenalidomide, veclade and dexamethasone will also have been privately prescribed. Therefore it is likely that a number of patients could have received velcade and lenalidomide before 2nd line and a proportion of this patients will not be refractory to lenalidomide (for example, because there lenalidomide was stopped to enable them to progress with deferred autologous transplant.)
4. Which post-hoc subgroup of the ASPIRE trial reflects NHS clinical practice and should be included in the model?	As stated above there could be a significant portion of the patient population who will have received velcade and lenalidomide and a proportion of these patients will not be refractory to

	lenalidomide. They should be able to access this treatment combination option and its associated benefits. The post-hoc subgroup of the ASPIRE trial presented by the company reflects NHS clinical practice and should be included in the model. It should be noted that the difference between the ICER base is not significantly large.
Issue 3: Utility values used in the economic model	
5. Are there additional treatment-specific benefits with carfilzomib with lenalidomide and dexamethasone compared with lenalidomide plus dexamethasone, other than gains in progression-free survival and overall survival?	Yes. The ASPIRE study did not contain a generic, preference-based utility measure; however, it did contain two disease-specific HRQoL measures: the EORTC QLQ-C30, a questionnaire developed to assess HRQoL in cancer patients, and the EORTC QLQ-MY20, a questionnaire developed to assess HRQoL in MM patients. In this disease specific questionnaire KRd was associated with a significantly higher HRQoL compared to Rd over 18 cycles of treatment, with clinically meaningful differences observed between the two treatment arms. To date, carfilzomib is the only novel treatment in MM to demonstrate improvement in patient reported QoL metrics. It must be noted that since the questionnaire was open label and not conducted blind then it could be susceptible to subconscious bias. However feedback from patients and clinicians is that there is a rapid HRQoL benefit delivered when receiving Carfilzomib and Dexamethasone alone. With that in mind and that the disease-specific HRQoL measures shows improved QoL through the trial data we feel that this should be included as a treatment specific benefit alongside PFS and OS.

6. Are the utility values used in the company's economic model appropriate and reliable for decision-making?	As stated above we feel that the utility value presented by the company reflects feedback we have received from patients and clinicians. Therefore we feel that this is appropriate and reliable for decision making.
Issue 4: Extrapolation of overall survival	
7. Should data entirely from the ASPIRE trial be used in the economic model to extrapolate overall survival?	Overall survival (OS) is clearly very important to patients and their families and it is right that treatments are scrutinised on their ability to deliver this. However, it is increasingly difficult to reach a median OS in myeloma trials. A 10 year horizon curve using data from the ASPIRE trial to extrapolate OS is reasonable. In our view it is almost impossible to have a meaningful discussion about OS over a 20 year horizon.
8. Is the Weibull or exponential distribution more appropriate for extrapolation of overall survival?	No Comment

NICE National Institute for Health and Care Excellence

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

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About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	Janssen
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None

Questions for engagement

Issue 1: Positioning of carfilzomib in the treatment pathway	
1. Is the positioning of carfilzomib appropriate in the treatment pathways for those eligible and ineligible for stem cell transplantation?	The company positioning seems appropriate.
2. Have all the relevant comparators been considered?	Yes. It should be noted that TA457 (carfilzomib and dexamethasone) is currently under review and the guidance may be re-issued with an extended recommendation for Cd to be used in second line after bortezomib. In this case, Cd will be a comparator for CRd.
Issue 2: Post-hoc subgroups to be considered	
3. In clinical practice, is it possible for patients to receive lenalidomide and bortezomib as a first-line treatment even though this is not recommended in NICE guidance?	Access for lenalidomide and bortezomib as first-line is only possible via individual funding request.
4. Which post-hoc subgroup of the ASPIRE trial reflects NHS clinical practice and should be included in the model?	No comment.
Issue 3: Utility values used in the economic model	
5. Are there additional treatment-specific benefits with carfilzomib with lenalidomide and dexamethasone compared with lenalidomide plus	CRd achieved with significantly higher QLQ-C30 GHS/QoL scores compared to Rd over 18 cycles of treatment, therefore it seems reasonable to use different treatment-specific benefits utilities for CRd and Rd in the economic model.

dexamethasone, other than gains in progression-free survival and overall survival?	
6. Are the utility values used in the company's economic model appropriate and reliable for decision-making?	Mapped-utility values from a disease specific questionnaire (EORTC QLQ-C30 to EQ-5D) is a valid approach.
Issue 4: Extrapolation of overall survival	
7. Should data entirely from the ASPIRE trial be used in the economic model to extrapolate overall survival?	Real world evidence is relevant to confirm trial extrapolations. Clinical experts consulted by the ERG deemed the lenalidomide and dexamethasone extrapolation as conservative, therefore seems appropriate to consider Rd RWE.
8. Is the Weibull or exponential distribution more appropriate for extrapolation of overall survival?	No comment

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

ERG response to Amgen technical engagement comments

June 2020

Source of funding

This report was commissioned by the National Institute for Health Research Systematic Reviews Programme as project number 129575/T.

Issue 1: Positioning of carfilzomib in the treatment pathway

The view of the Evidence Review Group (ERG) is unchanged from the ERG report. In summary, the NICE pathway for multiple myeloma indicates that whether a person undergoes stem cell transplant (SCT) influences the treatment options available in the second-line setting. At the time of writing, for those who receive SCT, no subsequent treatment is available as part of routine commissioning. Daratumumab (D) in combination with bortezomib (V) and dexamethasone (d; DVd) for second-line treatment (irrespective of SCT status) became available in April 2019 through the Cancer Drugs Fund (CDF). However, as DVd is only available through the CDF, the treatment is outside the remit of a Single Technology Appraisal (STA) and so was not considered by the ERG.

Recommendations from NICE Technology Appraisal 586 (TA586) for the second-line treatment of multiple myeloma specify that the population of interest for use of lenalidomide in combination with dexamethasone (Rd) in this setting is limited to those who cannot have a SCT (at the time of assessment) or cannot tolerate thalidomide, and who have already had bortezomib. The ERG also emphasised that the evidence informing TA586 was derived from the full trial population of two studies that included people who had undergone SCT and treatment with thalidomide. The limitation on use of Rd at second line, as in whether Rd is considered only for those ineligible for SCT or who cannot tolerate thalidomide or also includes those who undergo SCT, was not specified in the final scope issued by NICE for the decision problem that is the focus of this STA.

Issue 2: *Post-hoc* subgroups to be considered

The view of the ERG is unchanged from the ERG report. The ERG's preferred subgroup for treatment with carfilzomib in combination with Rd (CRd) in the second-line setting remains those who have received prior bortezomib but no prior treatment with lenalidomide. As highlighted by the ERG's clinical experts, and underscored by responses from stakeholders, bortezomib in combination with lenalidomide is not clinical practice in the NHS in England. At the time of writing of the ERG report, people who have received bortezomib and lenalidomide as a first-line treatment are likely to have been treated in a private setting or had access to the combination through enrolment in a clinical trial. The ERG appreciates that as a result of the COVID-19 pandemic, as highlighted by stakeholders, first-line regimens in multiple myeloma may have changed, with some people switching from bortezomib-based to lenalidomide-based induction therapy. The ERG considers that the impact of the change in induction treatment is difficult to quantify, with lack of data on the proportion of people affected and uncertainty around the length of time that COVID-19 will continue to affect clinical services.

Issue 3: Utility values used in the economic model

The view of the ERG is unchanged from the ERG report. The company suggest that there is a link between objective response rate (ORR) and health related quality of life (HRQoL) improvement but has not provided any evidence to quantify how improvements in ORR translate to an improvement in HRQoL utility values. However, as mentioned in the ERG report, clinical expert advice sought by the ERG suggested there may be a quicker response to treatment in patients receiving carfilzomib (in CRd) compared to Rd but that there was no clinical reason for there to be a treatment-specific utility benefit in addition to the benefit provided by gains in progression-free survival.

Furthermore, due to the open-label nature of the ASPIRE trial, there may be a degree of information bias in the patient responses to the HRQoL questionnaires depending on whether a patient was on the intervention treatment or not. This is also acknowledged in the stakeholder responses to technical engagement from a clinical expert and Myeloma UK. As such, the ERG considers its approach to remove the treatment specific utility gain, as well as mean increase in utility from cycle three onwards provides a conservative estimate of the ICER.

Issue 4: Extrapolation of overall survival

The view of the ERG is unchanged from the ERG report. The company state that their extrapolations based on ASPIRE clinical trial data may underestimate long-term survival. However, the committee for TA457 concluded that the population forming ASPIRE was generalisable to the UK population likely to be eligible for treatment with carfilzomib and as mentioned in the ERG report, the company states that when using the MyelomaToul extrapolation to validate the ASPIRE extrapolations, the exponential distribution provides the most plausible long-term predictions of survival. It is the ASPIRE exponential distribution that has been used for the ERG preferred analysis.

The company also state that, "*Although the Amgen's base case and the ERGs preferred case provide similar estimates of survival (10-year and 20-year survival rates within 2% [absolute]), relatively minor changes in long term survival rates can have a meaningful impact on the resulting ICERs*". However, it is important to reiterate that in Figure 17 of the ERG report between year six and year 30 of the company preferred extrapolation and the exponential distribution preferred by the ERG, the overall survival difference is substantially inflated in favour of carfilzomib, driving the difference in the ICERs.

Furthermore, the company discuss their multi-state model to inform the most appropriate extrapolation of overall survival. However, as mentioned in the ERG report and stated by the

company, the model is based on the ITT population and not directly applicable to the subgroup of interest for this appraisal. As such, the ERG does not deem the multistate model warrants further consideration.