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Daratumumab in combination with bortezomib and dexamethasone for treating relapsed or refractory multiple myeloma (Review of TA573)

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Declared competing interests of the authors and advisors

- The authors declare none
- Dr Bird declares none
- Dr Parrish declares advisory board membership and speaker fees from BMS/Celgene (manufacturer of lenalidomide and pomalidomide) and speaker fees from Janssen (manufacturer of bortezomib, daratumumab and doxorubicin).
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Rider on responsibility for report

The view expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

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Contributions of authors

Inês Souto Ribeiro critically appraised the health economic systematic review, critically appraised the economic evaluation, and drafted the report; Emma Maund critically appraised the clinical effectiveness systematic review, and drafted the report; Neelam Kalita critically appraised the health economic systematic review, critically appraised the economic evaluation, and drafted the report; David Scott critically appraised the clinical effectiveness systematic review, and drafted the report; Jo Picot critically appraised the clinical effectiveness systematic review, drafted the report and is the project co-ordinator and guarantor.

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LIST OF ABBREVIATIONS

1PL	One prior line
AE	Adverse event
AIC	Akaike information criterion
ASCT	Autologous stem cell transplant
Bd	Bortezomib and dexamethasone
BMI	Body mass index
CAA	Confidential commercial access agreement
Cd	Carfilzomib in combination with dexamethasone
CI	Confidence interval
CR	Complete response
CRD	Centre for Reviews and Dissemination
CrI	Credible interval
CS	Company submission
CSR	Clinical study report
DBd	Daratumumab in combination with bortezomib and dexamethasone
DSU	Decision support unit
ECOG	Eastern Cooperative Oncology Group
EORTC-QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire
EQ-5D-5L	EuroQol Five Dimensions Questionnaire
EAG	Evidence Review Group
HR	Hazard ratio
HRQoL	Health-related quality of life
ICER	Incremental cost effectiveness ratio
ILd	Ixazomib with lenalidomide and dexamethasone
IMWG	International Myeloma Working Group
IPCW	Inverse probability of censoring weights
ISS	International staging system
ITT	Intent-to-treat
IV	Intravenous
KM	Kaplan-Meier
Ld	Lenalidomide and dexamethasone
MAIC	Matching-Adjusted Indirect Comparison

MIMS	Monthly index of medical specialities
MM	Multiple myeloma
MRD	Minimal residual disease
NA	Not applicable
NE	Not evaluable
NHS	National Health Service
NICE	National Institute for Health and Clinical Excellence
NIHR	National Institute for Health Research
NMA	Network meta-analysis
NR	Not reported
ORR	Overall response rate
OS	Overall survival
PAS	Patient Access Scheme
Pd	Pomalidomide and dexamethasone
PFS	Progression-free survival
PPS	Post-progression survival
PR	Partial response
PSA	Probabilistic sensitivity analysis
PSS	Personal social services
QALY	Quality-adjusted life year
RCT	Randomised controlled trial
RRMM	Relapsed/refractory multiple myeloma
SACT	Systemic Anticancer Therapy
SC	Subcutaneous
sCR	Stringent complete response
SD	Standard deviation
SHTAC	Southampton Health Technology Assessments Centre
TEAE	Treatment emergent adverse event
TTD	Time to treatment discontinuation
TTNT	Time to next therapy/treatment
UK	United Kingdom
US	United States
VGPR	Very good partial response

1 EXECUTIVE SUMMARY

This summary provides a brief overview of the key issues identified by the external assessment group (EAG) as being potentially important for decision making. It also includes the EAG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Sections 1.3 to 1.6 explain the key issues in more detail. Background information on the condition, health technology, evidence and information on the issues are in the main EAG report.

All issues identified represent the EAG's view, not the opinion of the National Institute for Health and Care Excellence (NICE).

1.1 Overview of the EAG's key issues

Table 1 Summary of EAG's key issues

Issue number	Summary of issue	EAG report sections
1	Uncertainty about overall survival in the Systemic Anticancer Therapy (SACT) dataset	3.3
2	Absence of real-world data for second-line patients receiving bortezomib plus dexamethasone (Bd)	3.3 and 3.7
3	Naïve comparison of overall survival (OS) rates from the NHS Digital Newly Diagnosed Multiple Myeloma (NDMM) Standing Cohort study (patients did not receive daratumumab) and the SACT dataset (patients received daratumumab plus bortezomib and dexamethasone [DBd])	3.3 and 3.9
4	Difference in the OS estimates for DBd obtained from the real-world evidence-SACT database and the company's trial CASTOR	3.3 and 4.2.6
5	Extrapolation of OS in the Bd arm	4.2.6

The key differences between the company's preferred assumptions and the EAG's preferred assumptions are:

- The company uses the baseline characteristics (age and gender distribution) from the CASTOR trial, while we prefer to use the baseline characteristics from the SACT dataset.

- The company uses the Gompertz parametric function to extrapolate OS in the Bd arm whereas we prefer the exponential distribution.
- The company uses Monthly Index of Medical Specialities (MIMS) prices for the drugs included in the model while we prefer to use eMIT prices where available, as recommended by NICE.

We note that our changes to baseline characteristics and Bd arm OS extrapolation do not capture the more fundamental uncertainties arising from the limitations of the comparative evidence between the real world and trial data.

1.2 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a quality-adjusted life year (QALY). ICER is the ratio of the extra cost for every QALY gained.

Table 2 reports the company's cost effectiveness base case results using the patient access scheme (PAS) price of daratumumab, and list prices for other drugs. The results, which were updated in response to EAG clarification questions B10b, B10c, B11a, B11b, B13b, B15 and B16, show that DBd is [redacted] and yields [redacted] than Bd, resulting in an ICER of [redacted] per QALY. DBd dominates carfilzomib (Cd) as it is [redacted] and yields [redacted] than Cd.

The company's model results were most sensitive to shorter time horizons and to the adjustment of OS for the subsequent treatments not available in England.

Table 2 Company's revised base case results at CDF review (discounted at 3.5%; PAS price for daratumumab)

	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER vs comparator
Comparison with Bd					
Bd	[redacted]	[redacted]			
DBd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Comparison with Cd					
Cd	[redacted]	[redacted]			
DBd	[redacted]	[redacted]	[redacted]	[redacted]	Dominates

Source: Reproduced from clarification responses Tables 27 and 28
Bd = bortezomib plus dexamethasone; Cd = carfilzomib plus dexamethasone; DBd = daratumumab plus bortezomib plus dexamethasone; ICER = incremental cost-effectiveness ratio; PAS = patient access scheme; QALYs = quality-adjusted life-years.

1.3 The decision problem: summary of the EAG's key issues

No key issues were identified with respect to the decision problem. Although the company focus on a population narrower than that specified in the NICE scope, this is consistent with the company submission (CS) population for TA573 and with the NICE recommendation for use of DBd in the Cancer Drugs Fund (CDF). Similarly, the company's omission of combination chemotherapy as a comparator for the population who have had one prior line (1PL) of therapy is also consistent with the NICE committee's earlier agreement that chemotherapy would be replaced by bortezomib retreatment at second-line.

1.4 The clinical effectiveness evidence: summary of the EAG's key issues

Issue 1 Systemic Anticancer Therapy (SACT) dataset

Report section	3.3 SACT dataset
Description of issue and why the EAG has identified it as important	The SACT dataset provides evidence from a large number of NHS patients treated with DBd in England ([redacted]). However, there are three points to bear in mind: • Median OS has not been reached for the SACT cohort and median follow-up for OS ([redacted]) • Only three baseline patient characteristics (age, sex and Eastern Cooperative Oncology Group [ECOG] performance status) are reported for the SACT dataset, with almost a quarter of patients missing data for performance status. Median age of patients in the SACT dataset ([redacted]) is older than in the one previous therapy subgroup of the CASTOR trial (63 years and 64 years in the DBd and Bd arms respectively). The extent to which differences in population characteristics between SACT and CASTOR have influenced OS is uncertain, particularly as some characteristics, such as [redacted] were not reported for SACT patients. • Some patients in the SACT dataset could have received [redacted] The use of ILd at second-line may have had an impact on OS in the SACT database, but as the number of patients who received ILd is unknown, it is not possible to judge how likely or large any impact may have been.
What alternative approach has the EAG suggested?	None
What is the expected effect on the cost-effectiveness estimates?	Unknown
What additional evidence or analyses might help to resolve this key issue?	The following additional evidence or clinical opinion might help resolve this key issue: • Continued collection of SACT cohort data until median OS is reached. • Additional information on effect modifiers and important prognostic factors for the SACT cohort, including ISS disease staging and refractory status and advice from clinical experts to help understand the influence these characteristics have on OS. • Knowledge of the number of patients in the SACT dataset who received [redacted] and advice from clinical experts to help understand the influence this may have had on OS.

Issue 2 Absence of real-world data for second-line patients receiving Bd

Report section	3.3 SACT dataset 3.7 Unanchored matching-adjusted indirect comparison (MAIC) of CASTOR versus SACT
Description of issue and why the EAG has identified it as important	The SACT dataset only provides information for patients who received DBd during the period of managed access. We do not have equivalent real-world data for patients treated with the comparators Bd or Cd. The CS provides a comparison of DBd OS data from the 1PL CASTOR population versus the SACT dataset (CS Figure 19, reproduced in Figure 7 of this report) so the difference in OS between these two data sources can be clearly seen. Although difficult, due to the lack of data, there is a need to explore what plausible real-world Bd curves might look like to inform decision making.
What alternative approach has the EAG suggested?	The EAG suggested in clarification question B4: • Plotting the Bd CASTOR data on CS Figure 19. This would allow the relative positions of the Bd CASTOR Kaplan-Meier (KM) plot and the SACT KM plot to be observed (does the Bd CASTOR OS KM plot lie above or below the SACT OS KM plot?). It would also enable the reader to imagine more easily what a real-world Bd KM plot might look like if the relative benefit observed in CASTOR holds in the real world. • Use the relative benefit from CASTOR to create a simulated Bd dataset from the SACT DBd data and plot this on CS Figure 19. This is not an ideal approach but, in the absence of Bd real world data, it could help the committee to explore the clinical plausibility of the company's assertion that the relative benefit of CASTOR will apply in the real world. The company did not consider our suggestions methodologically appropriate so neither was taken up.
What is the expected effect on the cost-effectiveness estimates?	Unknown
What additional evidence or analyses might help to resolve this key issue?	The suggested approaches above could be explored to help resolve this key issue.

Issue 3 Naïve comparison of OS rates from the NHS Digital NDMM Standing Cohort study (did not receive daratumumab) and the SACT dataset (received DBd)

Report section	3.3 SACT dataset, 3.9 NHS Digital NDMM Standing cohort study
Description of issue and why the EAG has identified it as important	In the absence of real-world data for second-line patients treated with Bd, the company made a naïve comparison between patients from the NHS Digital newly diagnosed multiple myeloma (NDMM) standing cohort who did not receive daratumumab during their course of treatment and people in the SACT dataset who received DBd. 24-month survival among first-line autologous stem cell transplant (ASCT)-negative patients from the NHS Digital NDMM standing cohort who had not received daratumumab during their course of treatment was [redacted], among ASCT-positive patients it was [redacted]. In the SACT cohort that received DBd, [redacted] were ASCT-positive patients, the remainder were ASCT-negative patients. In this mixed ASCT-/ASCT+ population the 24-month OS was [redacted]. CS section B.2.10.6 compares the [redacted] OS rate at 24 months in the 1PL subgroup of the SACT dataset to the [redacted] 24-month survival among first-line ASCT-negative patients from the NDMM standing cohort who had not received daratumumab during their course of treatment and states this "*gives confidence that although absolute differences exist between CASTOR and SACT, the relative benefit observed in CASTOR is likely to hold in the real world*". The EAG believes that the 24-month OS in a group containing a mix of ASCT-negative and ASCT-positive patients who had not received daratumumab would be higher than 54% because of the greater OS rate for ASCT-positive patients.
What alternative approach has the EAG suggested?	Clinical advice or further analyses from the NDMM standing cohort might help the committee understand what 24-month survival is in a mixed ASCT-negative/ASCT-positive population. This would help in making a naïve comparison with results from the SACT dataset. The EAG notes however that the mix of ASCT-negative/ASCT-positive patients differs between the NHS Digital NDMM standing cohort ([redacted] in the whole cohort, the proportion among those who did not receive daratumumab is unknown) and the SACT cohort ([redacted]).
What is the expected effect on the cost-effectiveness estimates?	These data are not included in the cost-effectiveness model but are provided to help the committee judge whether the relative benefit of DBd versus Bd treatment in CASTOR holds in the real world.
What additional evidence or analyses might help to resolve this key issue?	Clinical advice could be sought or further analysis of the NDMM standing cohort could be requested to help resolve this key issue.

1.5 The cost-effectiveness evidence: summary of the EAG's key issues

Issue 4: Difference in the OS estimates for DBd obtained from the real-world evidence-SACT database and the company's trial- CASTOR

Report section	Sections 3.3 and 4.2.6
Description of issue and why the EAG has identified it as important	The SACT dataset has demonstrated that the patients treated with DBd in UK practice were on average older and less fit than those in the company's trial-CASTOR. This suggests that the OS and progression-free survival (PFS) extrapolations based on the trial data that are used in the company's base case are likely to be more favourable than one would expect in routine NHS practice.
What alternative approach has the EAG suggested?	The EAG used the baseline patient characteristics (age and gender split) from the SACT dataset for our preferred base case. We also tested this assumption in the company's base case model.
What is the expected effect on the cost-effectiveness estimates?	EAG base case ICER (including the SACT patient demographics) is [redacted] per QALY for DBd versus Bd while Cd is dominated by DBd. Using the company's approach (CASTOR demographics) reduces the ICER to [redacted] per QALY for DBd versus Bd and Cd remains dominated. However, this analysis does not adjust for other prognostic factors which might differ between the SACT and CASTOR populations.
What additional evidence or analyses might help to resolve this key issue?	An exploratory scenario analysis using an OS extrapolation for DBd fitted to the SACT KM data and OS for Bd estimated by applying the CASTOR hazard ratio (HR) to the fitted SACT DBd extrapolation might help to resolve this issue. This would generate an exploratory Bd curve that the experts could take a view on regarding the plausibility of the company's assertion that the relative benefit observed in CASTOR is likely to hold in the real world.

Issue 5: Extrapolation of OS in the Bd arm

Report section	Section 4.2.6
Description of issue and why the EAG has identified it as important	The company's selection of Gompertz distribution to extrapolate Bd OS underestimates the effectiveness of the comparator, as their base case predicts a survival rate of 0% at 10 years. This is inconsistent with the estimates from other cost-effectiveness studies and EAG expert advice on the current and original submission TA573, where the survival lies between 8-20% at 10 years.
What alternative approach has the EAG suggested?	The EAG used the exponential distribution in our base case, which provides goodness of fit with the lowest Akaike information criterion (AIC) and Bayesian information criterion (BIC) statistics after Gompertz and predicts a survival rate of 11.6% at 10 years. Our predicted estimate reflects clinical expert feedback to the EAG and aligns with those reported in other studies in the literature, discussed in Section 5.3.4 of this report.
What is the expected effect on the cost-effectiveness estimates?	EAG base case ICER (including the exponential distribution for Bd OS) is [redacted] per QALY for DBd versus Bd while Cd is dominated by DBd. Using the company's approach (Gompertz distribution) reduces the ICER to [redacted] per QALY for DBd versus Bd and Cd remains dominated.
What additional evidence or analyses might help to resolve this key issue?	Further expert advice on the plausibility of the OS estimates for Bd at 10 years in UK NHS practice.

1.6 Other issues: summary of the EAG's view

The EAG identified the following other issues that may inform decision-making, but which we do not consider a 'key issue':

- An unanchored MAIC has been conducted using appropriate methods to compare the real-world SACT population who received DBd with the DBd 1PL arm of the CASTOR trial. However, the principle of including all prognostic factors and treatment effect modifiers cannot be met because of the limited information on baseline characteristics for the SACT dataset. This means the results from the unanchored MAIC are fundamentally unreliable.
- While additional EuroQol Five Dimensions Questionnaire (EQ-5D)-5L data was collected in CASTOR pre- and post-progression beyond the cut-off for the original submission, these were not used to update the CDF revised model. Further information about the company's additional EQ-5D-5L data from CASTOR (which are currently being assessed) would be helpful to assess whether these differ to the values used in the model, and if so, the impact on the overall cost-effectiveness

results. The EQ-5D utility values should be calculated in accordance with recommendations in the 2022 NICE health technology evaluations manual.

1.7 Summary of EAG's preferred assumptions and resulting ICER

The EAG preferred model assumptions are as follows:

- **Baseline age and proportion of male:** based on the SACT database. Age: [redacted] and Proportion of male: 59%
- **Extrapolation of Bd OS curve:** Exponential distribution
- **Drug costs:** Use of eMIT prices.

It is worth noting that the above assumptions do not capture the more fundamental uncertainties arising from the limitations of the comparative evidence between real world and trial data as described above.

Table 3 reports the EAG preferred base case results for DBd vs Bd and Cd which shows that the ICER of DBd versus Bd changes from [redacted] per QALY in the company's revised base case, to [redacted] per QALY. DBd dominates Cd in the company's revised and EAG preferred base cases.

Table 3 EAG's preferred model assumptions (discounted at 3.5%; PAS price for daratumumab)

Scenario	Comparator	Incremental		
		Costs	QALYs	ICER (£/QALY)
Company's revised model	Bd	[redacted]	[redacted]	[redacted]
	Cd	[redacted]	[redacted]	Dominates
+ Patient age and gender from SACT ([redacted], 59% males)	Bd	[redacted]	[redacted]	[redacted]
	Cd	[redacted]	[redacted]	Dominates
+ Bd – Extrapolation of OS (Exponential)	Bd	[redacted]	[redacted]	[redacted]
	Cd	[redacted]	[redacted]	Dominates
+ Drug costs: based on eMIT	Bd	[redacted]	[redacted]	[redacted]
	Cd	[redacted]	[redacted]	Dominates
EAG preferred base case	Bd	[redacted]	[redacted]	[redacted]
	Cd	[redacted]	[redacted]	Dominates

Bd, bortezomib plus dexamethasone; Cd, carfilzomib plus dexamethasone; eMIT, drugs and pharmaceutical electronic market information tool; ICER, incremental cost-effectiveness ratio; OS, overall survival; PAS, patient access scheme; QALYs, quality adjusted life years; SACT, Systemic Anti-Cancer Therapy.

2 INTRODUCTION AND BACKGROUND

2.1 Introduction

This report is provided as part of the new managed access review (MAR) process which has replaced the CDF review process for cancer topics. In this report we provide a critique of the CDF review company's submission (CS) to NICE for the review of TA573[1] on the clinical effectiveness and cost effectiveness of daratumumab with bortezomib and dexamethasone (DBd) for treating relapsed or refractory multiple myeloma following the period of managed access within the Cancer Drugs Fund (CDF). Clarification on some aspects of the CS was requested on 8th September 2022. The company's response was received by the EAG on 26th September 2022.

The key area of uncertainty identified in TA573, which was to be addressed within the period of the managed access agreement (MAA),[2] was overall survival in daratumumab patients, in part because median overall survival (OS) had not been reached in the CASTOR trial.

The sources of data collection listed in the MAA are:

- the CASTOR phase III randomised controlled trial (RCT) comparing DBd with bortezomib and dexamethasone (Bd) among patients with relapsed Multiple myeloma (MM) who had received at least one prior line of therapy
- Data collected by Public Health England, including via the Systemic Anti-cancer Therapy (SACT) dataset

2.2 Background

2.2.1 Background information on disease area

The CS (section B.1.3.1) provides a clear overview of MM, including relapsed or refractory multiple myeloma (RRMM). We summarise the key aspects of the disease and its treatment from the CS together with supplemental information, where appropriate, below.

MM is a rare incurable blood cancer. In England approximately 5041people are newly diagnosed with MM each year (2016-2018 average), accounting for 2% of newly diagnosed cancers.[3] However, the incidence of MM has increased by approximately 33% since the 1990s and is predicted to rise by 11% between 2014 and 2035.[3]

MM is characterised by abnormal plasma cells, myeloma cells, which produce an abnormal non-functional type of antibody known as myeloma protein (also referred to as M protein or

para-protein).[4] Myeloma cells build up in the bone marrow and M proteins build up in the body causing serious complications such as hypercalcaemia, renal impairment, anaemia, bone disease and, less frequently, increased blood viscosity, infections, thrombosis and extramedullary disease (tumours which form outside of the bone marrow). RRMM is defined as disease that is nonresponsive while on salvage therapy (which is given when the disease does not respond to standard treatment), or progresses within 60 days of last therapy in patients who have achieved minimal response (MR) or better at some point previously before then progressing in their disease course.[5]

MM is more common in older people, males, Black people, those who are overweight or obese, and those with a family history of monoclonal gammopathy of unknown significance (MGUS) or multiple myeloma.[6]

Prognostic factors for MM include cancer stage, cytogenic profile and number of prior treatments.[7] In addition to these, one of the EAG clinical advisors considered the following as prognostic factors or treatment effect modifiers for patients with RRMM who have had one prior line of treatment: presence of circulating disease, renal impairment, patient-related factors (in particular frailty, age, comorbidities, mobility and views on frequent hospital visits) and therapy-related factors (particularly toxicity from front line therapy e.g. peripheral neuropathy).

A key feature of MM is that patients have multiple relapses, with each subsequent relapse associated with a reduction in the degree and duration of response to treatment, and a worse prognosis. All surviving patients eventually relapse from, or become refractory to, existing treatments (as depicted in CS Figure 1).

According to the latest data available from Cancer Research UK (2013 to 2017), five and 10-year survival rates for adults with MM in England are 52.3% and 29.1%, respectively.[8] The latest mortality data from Cancer Research UK (2017 to 2019) show that there were 2610 deaths annually from MM in England.[8] The CS does not report figures for survival in England specifically for RRMM.

MM and RRMM have detrimental effects on many aspects of quality of life for patients. These include:

- Physical effects due to symptoms of disease and side effects of treatment, which worsen as the disease progresses and affect ability to perform daily activities.[9-12]

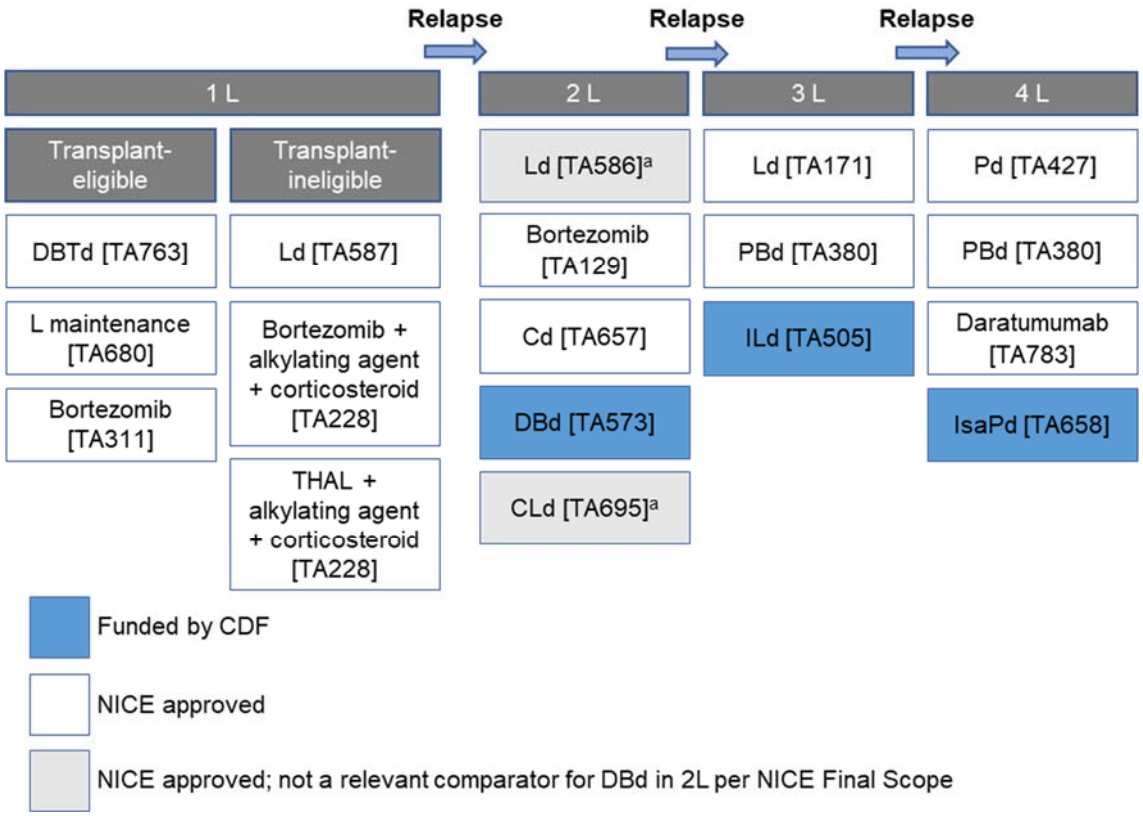
- Emotional/psychological effects due to side effects of treatments or effects of living with a chronic but ultimately fatal disease.[9; 10]
- Social difficulties with a decline in social contact and activities due to physical symptoms of the disease and side effects of treatment.[9; 11; 13; 14]
- Financial impact due to stopping work, or indirect costs, such as travel costs for attending appointments,[10; 12-14] which worsens with disease progression.[15]

Overall, patient health-related quality of life (HRQoL) worsens as the disease progresses.[9; 16]

Carers provide most of the care for patients with MM,[17] and their time spent caring increases as the disease progresses.[9] As with patients, the HRQoL of carers is also negatively affected. Carers suffer physical problems (e.g. fatigue, sleep disorders, exacerbation of per-existing health conditions),[17] emotional/psychological problems (e.g. anxiety, fear),[9; 17; 18] social problems (e.g. social isolation),[17] and financial problems (e.g. having to stop work or retire early).[13; 18]

Clinical management of MM

The treatment pathway has changed in terms of first and second-line treatments since the original CS for TA573. The CDF review CS (section B.1.3.2 and Figure 2 – reproduced as Figure 1 below) provides an overview of how multiple myeloma is now treated in England.



1L = first-line; 2L = second-line; 3L = third-line; 4L = fourth-line; Bd = bortezomib and dexamethasone; Cd =carflizomib and dexamethasone; CDF = Cancer Drugs Fund; CLd = carfilzomib, lenalidomide and dexamethasone; DBd = daratumumab, bortezomib and dexamethasone; DBTd = daratumumab, bortezomib, thalidomide and dexamethasone; IsaPd = isatuximab, pomalidomide and dexamethasone; ILd = ixazomib, lenalidomide and dexamethasone; L = lenalidomide; Ld = lenalidomide and dexamethasone; MM = multiple myeloma; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; PBd = panobinostat, bortezomib and dexamethasone; Pd = pomalidomide and dexamethasone; THAL = thalidomide; UK = United Kingdom

[a] Restricted to patients who received bortezomib in 1L

Source: reproduced from CS Figure 2

Figure 1 Current NHS clinical care pathway in England for the treatment of patients with MM

There are now four second-line treatments:

- Carfilzomib with dexamethasone and lenalidomide (NICE technology appraisal guidance [TA] 695[19]) and lenalidomide plus dexamethasone (NICE TA586[20]) have been have been introduced since the orginal CS. Both are only recommended for use in patients who have previously received boretozomib as first-line therapy.
- Bortezomib monotherapy (NICE TA129[21]) was previously limited to bortezomib naïve patients at the time of the original CS for NICE TA573[1] due to NHS England funding restrictions. Since the original CS, these funding restrictions have been lifted and

bortezomib monotherapy is now also available to patients who had a good response to the first course of bortezomib treatment. The EAG note that in clinical practice it seems bortezomib is used in combination with other drugs, rather than as a monotherapy - in first- and second-line treatments, one EAG advisor stated they use bortezomib in combination with dexamethasone, while a second EAG advisor stated they use an unlicensed three drug combination of bortezomib with cyclophosphamide and dexamethasone.

- At the time of the original CS, carfilzomib in combination with dexamethasone was not recommended in patients who have previously received bortezomib (NICE TA457[22]). This guidance has been now been superseded by NICE TA657[23] and patients can now receive this treatment regardless of prior first-line therapy received.

Of the current second-line treatments, two, bortezomib-based therapy and carfilzomib in combination with dexamethasone are specified as relevant second-line treatment comparators in the final NICE Final Scope for this appraisal. These comparators are the same as those in the original CS for TA573.

2.2.2 Background information on intervention

The company provides details of the technology under appraisal, daratumumab in combination with bortezomib and dexamethasone, in CS Table 2. Daratumumab (Darzalex®) is a human monoclonal antibody that binds the CD38 antigen that is expressed on MM tumour cells. It was granted marketing authorisation in April 2017, in combination with bortezomib and dexamethasone, for the treatment of adult patients with multiple myeloma who have received at least one prior therapy. Daratumumab can be administered as an intravenous (IV) infusion[24] or subcutaneous (SC) injection,[25] with a dose of daratumumab 16 mg/kg intravenously or 1,800 mg subcutaneously every week for weeks 1 to 9, every three weeks for weeks 10 to 24 and every four weeks from week 25 onward until disease progression. CS Table 2 states that in the UK, most patients receive daratumumab by subcutaneous injection because of its better tolerability compared to IV infusion but in the pivotal study, CASTOR, patients received daratumumab by IV infusion. All three EAG clinical advisors agreed that in England almost all daratumumab is administered subcutaneously. The EAG note that in patients with relapsed or refractory MM, subcutaneous daratumumab has been shown to be non-inferior to IV daratumumab in terms of efficacy, with a similar adverse event profile but lower rate of infusion related reactions.[26]

2.2.3 The position of intervention in the treatment pathway

CS Figure 2, reproduced as Figure 1 above, places DBd as a second-line treatment only. This is in line with the population specified in the original company submission and NICE's recommendation for DBd use within the CDF.

2.3 Critique of the company's definition of the decision problem

Table 4 summarises the decision problem addressed by the company in the CS in relation to the final scope issued by NICE and the EAG's comments on this.

Table 4 Summary of the decision problem

	Final scope issued by NICE	Company's decision problem	Rationale if different from the final NICE scope	EAG comments
Population	Adults with relapsed or refractory multiple myeloma who have had at least 1 previous therapy	Adults with relapsed or refractory multiple myeloma who have received 1 prior line of therapy (second-line patients)	Consistent with the original company submission (TA573), final analysis results from CASTOR demonstrate greatest clinical benefit in patients with one prior line of therapy The PFS/OS benefit, particularly at second-line, is driven by deeper and longer sustained responses associated with the use of combination therapy earlier in the disease course, while the disease is at a more treatment-sensitive stage compared with administration in later treatment lines.[27]	The population in the company's decision problem (second-line patients only) is narrower than that specified in the NICE scope but it is consistent with the CS population for TA573 and with the NICE recommendation for use of DBd in the Cancer Drugs Fund ("an option for treating relapsed multiple myeloma in people who have had 1 previous treatment").[1]
Intervention	Daratumumab in combination with bortezomib and dexamethasone	Daratumumab in combination with bortezomib and dexamethasone	N/A	Consistent with NICE scope
Comparators	For people who have had 1 prior line of therapy, depending on previous treatment: ▪ Bortezomib-based therapy	For people who have had 1 prior line of therapy: ▪ Bortezomib-based therapy	Positioning of DBd is in patients who have had 1 prior line of therapy Janssen does not consider combination chemotherapy a relevant comparator at second-line. In TA573, chemotherapy was only considered a	The comparators are appropriate for the population with relapsed or refractory multiple myeloma who have received 1 prior line of therapy. The NICE committee agreed that chemotherapy would be replaced by bortezomib retreatment at second-line (TA573 ACD 3.3[28]).

	▪ Carfilzomib in combination with dexamethasone ▪ Combination chemotherapy For people who have had 2 prior lines of therapy: ▪ Lenalidomide in combination with dexamethasone ▪ Panobinostat in combination with bortezomib and dexamethasone For people who have had 3 prior lines of therapy: ▪ Panobinostat in combination with bortezomib and dexamethasone ▪ Pomalidomide in combination with dexamethasone Daratumumab monotherapy	▪ Carfilzomib in combination with dexamethasone	relevant treatment option in the absence of NHS England funding for bortezomib retreatment. Subsequently, a treatment algorithm was developed by NHS England allowing retreatment with bortezomib at second-line. Ultimately, with the funding restriction regarding bortezomib retreatment lifted, the Committee concluded that, after initial therapy, relevant second-line treatment options included bortezomib-based therapy or carfilzomib plus dexamethasone	
Outcomes	The outcome measures to be considered include: ▪ OS ▪ PFS ▪ response rates ▪ Time to next treatment ▪ adverse effects of treatment	The outcome measures to be considered include: ▪ OS ▪ PFS ▪ TTD ▪ response rates (including minimal residual disease [MRD] negativity)	TTD is included as it is used in the economic model to capture the cost of treatment more accurately. MRD is also included as an outcome measure as it represents a more sensitive measure of disease burden than definitions of clinical response such as CR.	The company reports all the outcomes listed in the NICE scope. Time to next treatment is not listed as an outcome in the company's decision problem but is included within the CS (CS B.2.6.6).

	▪ HRQoL	▪ adverse effects of treatment ▪ HRQoL	MRD-negative status (i.e., undetectable clonal plasma [myeloma] cells) is associated with prolonged PFS and OS and is assessed in accordance with IMWG criteria.[29]	
Source: CS Table 1 with EAG comments added. 1L = first-line; CR = complete response; DBd = daratumumab, bortezomib and dexamethasone; HRQoL = health-related quality of life; IMWG = International Myeloma Working Group; MRD = minimal residual disease; MM = multiple myeloma; N/A: not applicable; NICE = National Institute for Health and Care Excellence; OS = overall survival; PFS = progression-free survival; TTD = time to treatment discontinuation				

3 CLINICAL EFFECTIVENESS

The CS includes the following pieces of clinical effectiveness evidence:

1) RCT evidence identified from the company's systematic review. This includes evidence from the company's CASTOR trial of DBd versus Bd in adults with relapsed or refractory multiply myeloma for the subgroup who had received one prior therapy (DBd n=122, Bd n=113, sections 3.2.1.1 to 3.2.6.3 of this EAG report) as well as evidence from the ENDEAVOR trial of carfilzomib (Cd) versus Bd in an indirect comparison enable an evaluation of DBd vs Cd.
2) Real-world evidence from the SACT dataset which comprises data from [redacted] people in clinical practice in England with RRMM who had received one prior line of therapy and who were treated with DBd via the CDF during the managed access period (sections 3.3 and 3.7 of this EAG report).
3) Real-world evidence from the NHS Digital newly diagnosed multiple myeloma (NDMM) standing cohort study, commissioned by Janssen ([redacted]). In the absence of any real-world data for second-line patients treated with Bd, the company makes a naïve comparison of OS rates between people in the SACT dataset (who received DBd) and people in the NDMM standing cohort who did not receive daratumumab during their course of treatment (section 3.9 of this EAG report).

In this and subsequent chapters we refer to the subgroup of patients from the CASTOR trial who had received one prior therapy as either the 1PL subgroup, the second-line subgroup or second-line patients.

3.1 Critique of the updated systematic review of clinical effectiveness evidence

Table 36 in Appendix 1 provides a summary of the EAG's critical appraisal of the company's systematic review of clinical effectiveness. Compared to the systematic review in the original CS, there were some modifications to the search strategy and eligibility criteria. In summary, these relate to a narrower population of interest (one prior treatment regimen versus at least one prior treatment) but a wider range of study designs (RCTs and non-RCT studies versus RCTs only). The EAG believe these changes to be appropriate. Overall, the EAG considers the systematic review conforms to accepted methodological standards in evidence synthesis and is at low risk of bias.

3.1.1 Studies included in the systematic review of clinical effectiveness evidence

The company's updated systematic review of RCTs included a total of seven RCTs,[30-36] reported in a total of 42 sources (CS Appendix D Figure 8; the EAG note that CS Appendix D.1.1. states 40 publications). These seven trials evaluated relevant second-line treatments of interest (DBd, Bd or Cd). Of these seven trials,

- One (CASTOR[30]) was the only head-to-head trial of DBd versus a relevant comparator (Bd) in adults with documented relapsed or refractory multiple myeloma
- Two (CASTOR and ENDEAVOR[30; 31]), were considered relevant, by the company, for a network meta-analysis (NMA) (see EAG report section 3.4)
- Five were considered irrelevant for an NMA by the company: four (BOSTON,[33] CANDOR,[32] IKEMA[35] and OPTIMISMM[36]) because they did not provide a network connection, and one (LEPUS[34]), which compared DBd to Bd, because the company deemed the population too dissimilar, in terms of a potential risk modifier (Asian ethnicity), to that of CASTOR and ENDEAVOR (CS Appendix D.1.3.3; (see EAG report section 3.4)). The EAG agrees with the company's decision.

The company's systematic review of non-RCTs (CS Appendix D Figure 10) found two non-RCTs[37; 38] that met the inclusion criteria. However, the company did not consider these relevant for an NMA given their comparative poor quality compared to the RCT evidence (CS Appendix D.1.3.3). The EAG believe this is acceptable and in line with NICE's current NICE health technology evaluations manual (section 3.3.2[39]).

As in the original CS, the focus of the company's updated systematic review of clinical effectiveness is the CASTOR RCT. The original CS had a data cut-off of 11 January 2018 (median follow-up 26.9 months). The CDF review CS presents updated data (see EAG section 3.2.3 for further details). Details of the study are provided in CS sections B.2.3.1 to B.2.3.6, and CS Appendix D.2.2 to 2.3.3.

3.2 Critique of studies of the technology of interest, the company's analysis and interpretation (and any standard meta-analyses of these)

3.2.1 Included study: CASTOR RCT

3.2.1.1 CASTOR RCT: Study characteristics

The CASTOR study[30] (study MMY3004; ClinicalTrials.gov number NCT02136134) is a multicentre, phase III, randomised, open-label trial which compares DBd with Bd in patients with RRMM who have received at least one prior line of treatment. The dosing of daratumumab and dexamethasone is consistent with the SmPC. Two of the EAG clinical

advisors commented on the dosing of bortezomib. Both agreed the total dosing of bortezomib in clinical practice was the same as in the CASTOR trial, but one advisor stated they administer bortezomib weekly rather than biweekly due to lower toxicity

A summary of the study's characteristics is presented in Table 5, below.

The EAG note that CS Table 11 states the trial was carried out at 117 sites across 16 countries, including the UK. However, the UK is not mentioned as a study location in CS section B.2.3.3, the original CS, the clinical study report (CSR), the supplementary material of the primary publication (Palumbo 2016) or the clinicaltrial.gov entry (NCT02136134). CS section B.2.3.3 states that of the 16 countries where the study was carried out, 11 were in the European region. The company confirmed in clarification response C1 that there were no study centres in the UK.

Table 5 CASTOR RCT study characteristics

Study characteristics	Intervention: DBd	Comparator: Bd
Design: Phase III open label, multicentre (16 countries, no UK centres), stratified RCT **Stratification criteria:** • ISS disease stage (I, II or III) • number of prior lines received (1 versus 2, or 3 versus ≥3) • use of prior bortezomib treatment (no versus yes). **Eligibility criteria:** • aged ≥18 years • documented evidence of relapsed or refractory multiple myeloma, as assessed against IMWG criteria. • ≥ 1 prior line of treatment • achieved at least a partial response to at ≥ 1 prior treatment	**Daratumumab:** IV infusion 16mg/kg weekly for the first 3 21-day cycles, then on day 1 of 21-day cycles 4 to 8 and every 4 weeks thereafter until disease progression or an unacceptable level of toxicity reached **Bortezomib:** SC at 1.3mg/m^2 on days 1, 4, 8, and 11 of each 21-day cycle. Up to eight 21-day bortezomib treatment cycles administered in total. **Dexamethasone:** orally at 20mg on days 1, 2, 4, 5, 8, 9, 11, and 12 of the first eight 21-day bortezomib treatment cycles (i.e. total dose of 160mg/cycle). During weeks when the patient received an infusion of daratumumab, dexamethasone was administered on infusion days	**Bortezomib:** SC at 1.3mg/m^2 on days 1, 4, 8, and 11 of each 21-day cycle. Up to eight 21-day bortezomib treatment cycles administered in total. **Dexamethasone:** orally at 20mg on days 1, 2, 4, 5, 8, 9, 11, and 12 of the first eight 21-day bortezomib treatment cycles (i.e. total dose of 160mg/cycle). During weeks when the patient received an infusion of daratumumab, dexamethasone was administered on infusion days at a dose of 20mg IV before the infusion.

• ECOG Performance Status score of 0, 1, or 2 **Number randomised:** N=498 (DBd: 251; Bd: 247) **Median length of follow up:** Primary endpoint (PFS), 50.2 months; secondary endpoints, including OS, 72.6 months **Number (%) with 1 prior line of treatment only** DBd: 122 (48.6); Bd: 113 (45.7)	at a dose of 20mg IV before the infusion. For patients >75 years of age, underweight (BMI<18.5), poorly controlled diabetes mellitus or prior intolerance/AE to steroid therapy, the dexamethasone dose could be administered at a dose of 20mg weekly.	For patients >75 years of age, underweight (BMI<18.5), poorly controlled diabetes mellitus or prior intolerance/AE to steroid therapy, the dexamethasone dose could be administered at a dose of 20mg weekly.
Source: partly reproduced from CS sections B.2.2, 2.3.1, 2.3.2, 2.3.3 and 2.3.4; CS Figure 3; CS Tables 6, 7, 8 and 11; and Appendix D Table 34 AE = adverse event; BMI = Body Mass Index; ECOG = Eastern Cooperative Oncology Group; IV = intravenous; OS = overall survival; PFS = progression free survival; SC = subcutaneous		

3.2.1.2 CASTOR RCT: Patients' baseline characteristics

The CASTOR RCT provides evidence for the company decision problem through analyses of a subgroup of patients in the trial population who have received one prior treatment only. Population characteristics for this subgroup are presented in CS Table 12 and CS Appendix D Table 34, and in Table 6 below.

Table 6 Characteristics of patients in the CASTOR RCT who had received one prior treatment only

Population characteristic		DBd (n=122)	Bd (n=113)
Age, years, mean (SD) [range]		[redacted]	[redacted]
Male, n (%)		[redacted]	[redacted]
Race, n (%)	White	[redacted]	[redacted]
	Asian	[redacted]	[redacted]
	Black or African American	[redacted]	[redacted]
	Other, unknown or not reported	[redacted]	[redacted]
Weight, kg, mean (SD) [range]		[redacted]	[redacted]
Time from MM diagnosis, years, mean (SD) [range]		3.6 (2.8) [0.7 to 14.9]	3.6 (2.5) [0.6 to 18.1]
Baseline ECOG score, n (%)	0	[redacted]	[redacted]
	1	[redacted]	[redacted]
	2	[redacted]	[redacted]
ISS staging, n (%)	I	[redacted]	[redacted]
	II		
	III		
Cytogenetic abnormality, n (%)[a]	Del17p	13 (14.3)	6 (7.6)
	T(4;14)	5 (5.5)	5 (6.3)
	T(14;16)	3 (3.3)	4 (5.1)
Cytogenetic risk stratification[b]	High risk	[redacted]	[redacted]
	Standard risk		
	Low risk	[redacted]	[redacted]
	Not done	[redacted]	[redacted]
Prior ASCT n (%)		[redacted]	[redacted]
Prior radiotherapy, n (%)		28 (23.0)	24 (21.2)
Prior cancer-related surgery, n (%)		[redacted]	[redacted]
Prior anthracyclines n (%)		[redacted]	[redacted]
Prior protease inhibitor, n (%)		65 (53.3)	59 (52.2)
Bortezomib		[redacted]	[redacted]
Prior IMiD, n (%)		[redacted]	[redacted]
Lenalidomide		15 (12.3)	33 (29.2)
Thalidomide		58 (47.5)	48 (42.5)
Refractory to IMiD only, n (%)		[redacted]	[redacted]
Refractory to Lenalidomide		6 (4.9)	18 (15.9)
Refractory to Thalidomide		8 (6.6)	7 (6.2)
Refractory to last line of prior therapy, n (%)		[redacted]	[redacted]

Source: Partly reproduced from CS Table 12, CS reference 99[40] and data provided for TA573 in the company's response to clarification question A6, Table 4 which is available from the NICE committee papers.[41]
a Cytogenetic abnormalities are based on FISH or karyotype testing; b Risk stratification is based on three factors: International Staging System (ISS); presence of chromosomal abnormalities of t(4; 14), del17 or del17p by fluorescence in situ hybridisation (FISH) or Karyotype testing and age; c Most of these patients were refractory to lenalidomide or thalidomide.

ASCT = autologous stem cell transplant; ECOG = Eastern Cooperative Oncology Group; IMiD = immunomodulatory drug; ISS = International Staging System; MM = multiple myeloma; SD = standard deviation

Overall, in patients who had received one prior treatment line only, baseline characteristics were well balanced between the two treatment arms. The EAG however note that proportionally more patients in the Bd group than in the DBd group received prior lenalidomide (Bd 29.2% vs DBd 12.3%), were refractory to immunomodulatory drug therapy (Bd 22.1% vs DBd 11.5%), and refractory to lenalidomide specifically (Bd 15.9% vs DBd 4.9%). During preparation of the EAG's report for TA573 the EAG's clinical advisors stated that these differences were unlikely to impact treatment effect. The EAG currently also note that approximately twice as many patients in the DBd group had loss of the short arm of chromosome 17 (Del17p), a prognostic indicator for poorer outcome in MM,[42] compared to the Bd group (14.3% vs 7.6%). During preparation of the EAG's report for TA573 the EAG's clinical advisors advised the baseline characteristics of the subgroup who received one prior treatment line only were representative of patients seen in clinical practice albeit slightly younger and with greater prior exposure to lenalidomide. They also highlighted that in clinical practice patients do not receive anthracycline. Two of the EAG's current clinical advisors confirmed they also hold the same opinion.

3.2.2 CASTOR RCT: Risk of bias assessment

The company's critical appraisal of study methodological quality and risk of bias of the CASTOR RCT is presented in CS section 2.5.1, and is based on Centre for Reviews and Dissemination criteria.[43] The assessment is identical to that presented in the original CS and, as previously, the EAG agrees with the company that the CASTOR RCT is at low risk of detection, attrition and reporting bias. However, as in the previous assessment, the EAG disagrees with the company that all CASTOR trial outcomes are at low risk of selection bias. The EAG considers that outcomes in the subgroup who received one prior treatment line only, are at an unclear risk of selection bias. This is due to:

- proportionally more patients in the Bd group receiving lenalidomide as a first-line therapy, and being refractory to their previous treatment, including specifically to lenalidomide (see Table 6). When reviewing the EAG's report for TA573 the EAG's clinical advisors stated the imbalances observed between trial arms for these factors were unlikely to impact on the treatment effect. However, in committee discussions for TA573 (NICE TA573[1] section 3.4), the Cancer Drugs Fund clinical lead suggested that the imbalance in patients receiving lenalidomide could bias results in favour of DBd.

- proportionally more patients in the DBd group having the 17p deletion (cytogenetic abnormality; Table 6), which the company argued at the committee meeting could bias results against DBd and which, as we noted above, is a prognostic indicator for poorer outcome in MM.[42]

Statistical analysis conducted by the company in response to the NICE appraisal consultation document for TA573 found no evidence of a statistical interaction between either previous lenalidomide use or 17p deletion and the overall survival benefit of DBd in the subgroup of patients who received one prior treatment only. However, the committee noted that the number of patients in the analysis may have been too small to detect an interaction and therefore uncertainty remained.[1] Despite this uncertainty, the committee nonetheless concluded that the second-line subgroup provided sufficient evidence for decision-making.[1]

Table 7 Company and EAG assessments of risk of bias

Criteria	Company's judgement	EAG judgement
SELECTION BIAS		
Was randomisation carried out appropriately?	Low risk	Low risk
Was the concealment of treatment allocation adequate?	Potential risk of bias as open label design	Probably low risk[a]
Were the groups similar at the outset of the study in terms of prognostic factors?	Low risk	**Unclear risk given imbalance in prior use of lenalidomide and in presence of 17p deletion**
DETECTION BIAS		
Were the care providers, participants and outcome assessors blind to treatment allocation?	Low, as an IDMC reviewed the data	Low risk for OS and TTD Probably low risk for PFS
ATTRITION BIAS		
Were there any unexpected imbalances in drop-outs between groups?	Low	Low risk, provided that outcomes are interpreted in the context of the expected imbalance[b]
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate	Low risk	Low risk

methods used to account for missing data?		
REPORTING BIAS		
Is there any evidence to suggest that the authors measured more outcomes than they reported?	Low risk	Low risk

Source: Partly reproduced from CS 2.5.1, CS Table 17, previous EAG report section 3.14, Table 8 and Appendix 1

[a] The company's response mistakenly refers to blinding, instead of allocation concealment. EAG's response is in relation to allocation concealment. Details of the interactive web response system used to randomise patients and whether it concealed allocation are not reported in the trial protocol, trial publication or abbreviated CSR, hence assessment of "probably low risk".

[b] most common reason for treatment discontinuation was death in both treatment arms, which was higher in the Bd arm versus DBd arm (68.8% versus 59%). Number of patients lost to follow up was identical between arms (1.6% in each arm) (CS section B.2.4.5)

Note: Text in bold highlights discrepancy between the company and EAG judgements of risk of bias

IDMC = Independent Data Monitoring Committee; OS = overall survival; PFS = progression free survival; TTD = time to treatment discontinuation

3.2.3 CASTOR RCT: Outcomes assessment

CS Table 6 and CS sections B.2.3.5 and B.2.3.6 provide information on outcomes assessed in the CASTOR trial. Appendix 2, Table 37 gives an overview of outcomes reported in the CDF review submission, including median follow up points, and whether data were reported for the 1PL subgroup or included in the NMA or base case economic model for 1PL patients.

In summary, outcome data in the CDF review submission are presented for the following data cuts:

1. The planned interim analysis (IA2) - 11 January 2018 (median follow-up 26.9 months). This was the data cut in the original CS for TA573.[1] The following outcomes had data reported at this timepoint in the CDF review submission:
    - Progression free survival (PFS), overall survival (OS), response outcomes, minimal residual disease (MRD) negativity and time to disease progression were reported for the 1 PL subgroup and the whole trial population (CS tables 18 and 21 and CS Appendix M).
    - Time to treatment discontinuation and PFS on subsequent line of therapy were reported for the 1PL subgroup (CS Table 21)
    - HRQoL was reported for the whole trial population (CS B.2.11).

2. The updated and final PFS analysis - 14 August 2019 (median follow-up 50.2 months). These data are new to this CDF review submission. The following outcomes had data reported at this time point:
    - PFS and MRD negativity were reported for the 1PL subgroup and the whole trial population (CS Tables 18 and 21, CS sections B.2.6.2, B.2.6.5, and B.2.7.2). PFS data for the 1PL subgroup were used in the NMA and in the base case economic model of 1PL patients.
    - Progression-free survival on subsequent therapy (PFS-2), time to treatment discontinuation (TTD), response outcomes were reported for the 1PL subgroup only (CS Table 21, CS section B.7.2.7 and CS Appendix E). The TTD data were used in the base case economic model of 1PL patients.

3. The final OS analysis with a clinical cut-off of 28 June 2021 (median follow-up 72.6 months). These data are new to this CDF review submission. The following outcomes had data reported at this time point:
    - OS (unadjusted) was reported for 1PL subgroup and whole trial populations. Data for the 1PL subgroup were used in the NMA of 1PL patients (CS Table 19 and CS section B.2.6.3)
    - OS adjusted for subsequent treatments were reported for the 1PL subgroup only. These data were used in the base case economic model of 1PL patients (CS Table 21 and CS section B.2.7.2).
    - Time to next therapy (TTNT), MRD negativity and PFS-2 and treatment duration were reported for the whole population (CS Table 18 and CS sections B.2.6.4 to B.2.6.7)
    - Adverse events were reported for the safety population (CS section B.2.12) and were provided for the 1 PL subgroup in response to clarification question A4. Adverse event data for the Bd arm only were used base case economic model of 1PL patients.

3.2.3.1 Efficacy outcome(s)

The key efficacy outcomes reported in the CS that match the decision problem and inform the economic model are:

- Overall survival (OS)

  OS was a secondary outcome in the CASTOR trial. It was measured from the date of randomisation to the data of death. Data for this outcome were still immature at the

time of the original CS and therefore the long-term effect of treatment on survival were unknown. As a condition of the managed access agreement, the company were required to report updated data on OS from the CASTOR trial in order to validate the extrapolation of the OS used in the economic model. As mentioned above, the company has provided the final OS analysis. The economic model appropriately uses OS adjusted for treatments that are not available in UK clinical practice or available only via the CDF (see section 4.2.6.3 of this report). However, as discussed in section 3.2.4 of this report, insufficient details were provided for the EAG to be certain that the methods had been applied correctly and with the same covariates as in the original submission for TA573.[1]

- Progression free survival (PFS)
  PFS was the primary outcome of the CASTOR trial, defined as the duration from the date of randomisation to either progressive disease, according to International Myeloma Working Group (IMWG) criteria,[44] or death, whichever occurred first (CS Table 11). Disease progression was assessed using a computerised algorithm, based on the IMWG criteria (CS table 11 and, Sonneveld 2022[45]). The amended statistical analysis plan[46] provides details of the algorithm and states that it was validated by an independent review committee in an earlier study (MMY2002, daratumumab monotherapy for patients with ≥ 3 lines of prior therapy or double refractory multiple myeloma).
- Time to treatment discontinuation (TTD)
  TTD was a post-hoc outcome (CS Table 6). The CDF review CS and the original CS do not provide a definition of TTD.

3.2.3.2 HRQoL outcomes

HRQoL was assessed in CASTOR using two tools, one disease specific (The European Organization for Research and Treatment of Cancer Quality of Life-Core 30 questionnaire (EORTC QLQ-C30)) and one generic (European Quality of Life Working Group Health Status Measure 5 Dimensions (EQ-5D-5L)). For both, the CDF review submission only reports data included in the original CS.

In the original appraisal both the EAG and committee agreed that the utility values derived from the CASTOR EQ-5D-5L lacked face validity.[1] Both the EAG and the committee therefore preferred the use of utility values from the ENDEAVOR trial[31] to be used in the base case analysis, which the company has utilised in the current submission.

The EAG asked the company if HRQoL data from CASTOR has been collected to update the utilities used for pre-and post-progression health states used in the original submission (clarification question B6). The company confirmed that they did collect updated data on HRQoL but did not provide it in the CDF review submission or in response to clarification question B6. The company stated they were "*conducting a feasibility assessment of including the additional data gathered since the original submission in an analysis and will provide an update at the next stage of this appraisal*." (Company clarification response B6).

3.2.3.3 Safety outcomes

Safety evaluations included: adverse event monitoring, physical examination, electrocardiogram monitoring, laboratory assessments, blood pressure and temperature measurements, and Eastern Cooperative Oncology Group (ECOG) performance. All adverse events, serious or non-serious, were reported from the time of signed informed consent to until 30 days following the last dose of study treatment.[46; 47] Adverse event data informing the economic model from the CASTOR trial were events Grade 3 or higher that were reported in at least 5% of patients in the Bd arm for the 1PL subgroup (DBd adverse event data came from another source as described in section 4.2.6.5 of this report).

EAG comment on outcomes assessment

Overall, the outcomes selected by the company are appropriate for the appraisal. The EAG notes that MRD negativity was included as an outcome in the original CS and in the CDF review CS (CS section B.2.3.5). It is defined as the absence of tumour plasma cells in a specified number (e.g.100 000) of bone marrow cells,[48] and has been shown to be associated with longer OS and PFS in patients with RRMM.[48] Two of the EAG clinical advisors who commented on MRD negativity both stated it is not routinely used in clinical practice in the NHS.

3.2.4 CASTOR RCT: Statistical methods

Overall, the statistical approach for the CASTOR trial described in the CDF review CS is the same as that described in the original CS. For clarity, the EAG has provided a summary of the statistical methods, with a brief critique, in Table 38 Appendix 3.

The EAG agrees that Inverse Probability of Censoring Weights (IPCW) method to adjust OS for subsequent treatments not routinely available on the NHS and therefore which could bias results, is appropriate. However, the EAG could not judge whether the methods were applied correctly, or whether the same baseline covariates and time-varying covariates were

included as per the original submission for TA573 because insufficient details were provided in CS section B.2.5.2 and CS Appendix M.

3.2.5 Efficacy results of the intervention study

In this section, the EAG focuses on the population that matches the decision problem (i.e. the 1 PL subgroup) and the outcomes of the CASTOR trial presented in the CS that match the decision problem and feed into the economic model. These outcomes are progression free survival (PFS), overall survival (OS) and time to discontinuation (TTD). Adverse event data, some of which feeds into the model, are presented in section 3.2.3.3

Outcomes reported in the CS for the 1 PL subgroup which do not feed into the economic model are summarised in section 3.2.6.

The EAG were unable to verify data presented for the OS final analysis, i.e. with a median follow up of 72.6 months, against the source document cited in the CS (Final OS analysis report, CS reference 94). This was because the document provided by the company for CS reference 94 was not the correct document.

3.2.5.1 Summary of results for overall survival

OS is a secondary outcome of the CASTOR trial and the key area of uncertainty in the original appraisal (TA573).[1] This was because OS data included in original CS were immature, and therefore the long-term effect of DBd on OS was unknown.

The CS presents the OS results for the CASTOR trial, with a median follow up of 72.6 months (1 PL subgroup CS B.2.7.1, B.2.7.2 and CS Appendix D section 3.2.3; whole trial CS B.2.6.3). In the whole trial population (which is not the focus of the appraisal), after a median follow up of 72.6 months, 319 deaths (64%) had occurred and fewer than half the patients in both arms were still alive. OS data were therefore mature in the whole trial population. Median OS was 49.6 months (95% confidence interval [CI] 42.2 to 62.3) in the DBd arm and 38.5 months (95% CI 31.2 to 43.2) for the Bd arm. For the 1 PL subgroup which is relevant to this appraisal, median OS was not reached in the DBd arm (95% CI 59.7 months to not evaluable), and 47.0 months (95% CI 32.6 to 58.7) in the Bd arm.

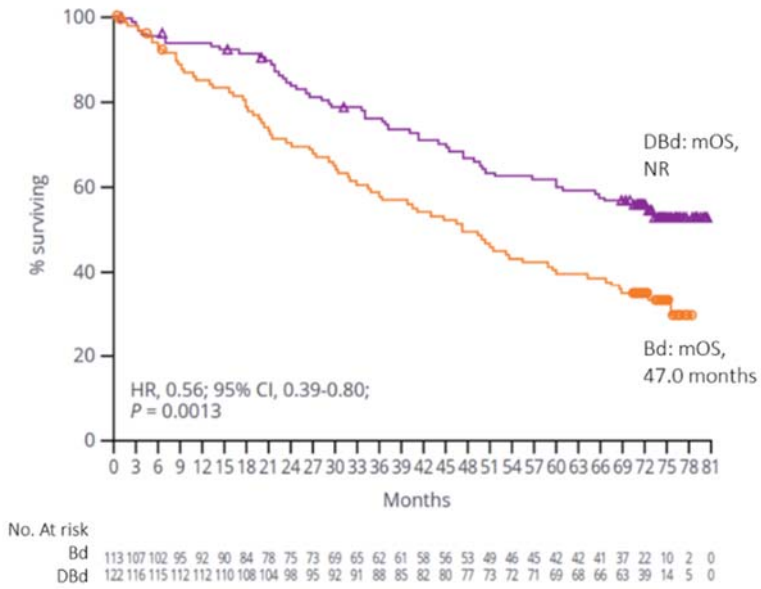
The improvement in OS with DBd was statistically and clinically significant, in the whole trial population (Hazard ratio [HR] 0.74, 95% CI 0.59 to 0.92, p=0.0075) and in the 1 PL

subgroup (HR 0.56, 95% CI 0.39 to 0.92, p=0.0013), signifying a 26% and 44% reduction in death in patients receiving DBd respectively (Table 8 and Figure 2).

Table 8 OS results for the CASTOR trial, median follow up 72.6 months

Parameter	Subgroup of 1PL patients		Total trial population	
	DBd (n=122)	Bd (n=113)	DBd (N=251)	Bd (N=247)
Events, n/N (%)	55 (45.1)	74 (65.5)	148 (59.0)	171 (69.2)[a]
Median OS (95% CI), months	NE (59.7, NE)	47.0 (32.6, 58.7)	49.6 (42.2, 62.3)	38.5 (31.2, 43.2)
HR, (95% CI) p-value	0.56 (0.39,0.80) 0.0013		0.74 (0.59, 0.92) 0.0075	

Source: Partly reproduced from CS Tables 20, 21 and 22
[a] CS Table 16 states that 170 (68.8%) of patients had died in the Bd arm at median follow up of 72.6 months but CS Table 20 states 171 deaths.
Bd = bortezomib and dexamethasone; CI = confidence interval; DBd = daratumumab in combination with bortezomib and dexamethasone; HR = hazard ration; NE = not evaluable, OS = overall survival



Source: Reproduced from CS Figure 11

Figure 2 Kaplan-Meier plot for OS among 1 PL patients treated with DBd compared with Bd in the CASTOR trial, median follow-up 72.6 months

Overall survival adjustment for CDF drugs and treatments not routinely commissioned in the England

As described in CS section B.2.5.2, CASTOR was an international multicentre trial therefore some participants received post-progression therapies unavailable in England. The number of patients in the 1 PL subgroup who received post-progression therapies unavailable in England were provided by the company in response to an EAG clarification question (clarification question A5). These data are shown in Table 9 below. Nearly twice as many patients in the Bd arm progressed and switched to subsequent therapies that were unavailable in England compared to the DBd arm (see Table 9).

Table 9 Switching proportions and sample sizes, in 1 PL subgroup

Treatment	No of patients	No. progressed	% progressed	No. switched to non-UK therapy	% switched to non-UK therapy
DBd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Reproduced from company clarification Table 5. The EAG assumes that although the company refers to therapies unavailable in the UK they are treating the UK as synonymous with England.
Bd = bortezomib and dexamethasone; DBd = daratumumab in combination with bortezomib and dexamethasone

As in the original CS, to reduce bias in the treatment effect related the use of post-progression therapies unavailable in England and the greater proportion of these being in the Bd arm, the company have adjusted the OS data using IPCW methods (see section 3.2.4 of this report)

CS section B.2.7.2 reports the results of the IPCW-adjusted OS data. The effect of the adjustment was a fall in the HR for OS (i.e. a greater reduction in the risk of death in comparison to the unadjusted data). In the 1 PL subgroup patients, the IPCW-adjusted HR was [redacted] (95% CI: [redacted]), representing a [redacted] reduction in risk of death for the DBd arm in comparison to the Bd arm, whereas the unadjusted HR reported in section 3.2.5.1 above represents a 44% reduction in risk of death for DBd versus Bd.

CS figure 12 (reproduced as Figure 3 below) shows the unadjusted and IPCW-adjusted OS curves for 1 PL patients on the same plot.

Source: Reproduced from CS Figure 12
Bd = bortezomib with dexamethasone; CI = confidence interval; DBd = daratumumab, bortezomib and dexamethasone; HR = hazard ratio; IPCW = Inverse Probability of Censoring Weighting; 1PL = one prior line of therapy; OS = overall survival

Figure 3 Kaplan-Meier curves for DBd and Bd OS in the CASTOR trial 1 PL subgroup pre- and post-IPCW adjustment

3.2.5.2 Summary of results for progression free survival

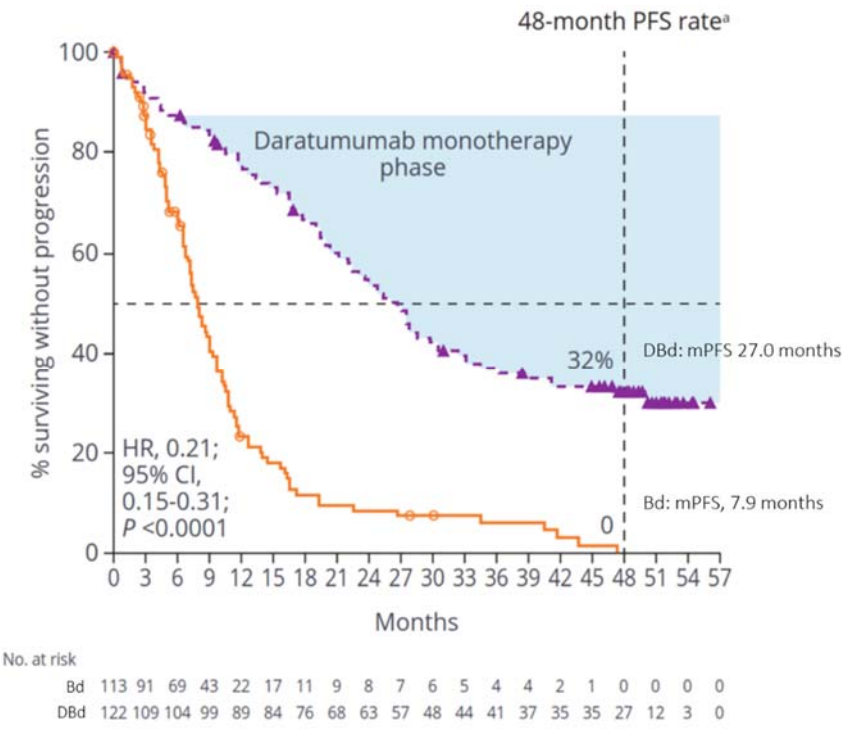
In the original appraisal (TA573),[1] the committee concluded that, based on CASTOR trial data with a median follow up of 27 months, DBd has both a statistically and clinically significant effect on progression free survival (PFS) compared with Bd.

The CDF review CS presents the PFS results for the CASTOR trial, with a median follow up of 50.2 months (subgroup of 1 PL patients CS section B.2.7.2 and CS Appendix D section 3.2.1; whole trial CS section B.2.6.2). In the whole trial population, a total of 396 progression events had occurred at a median follow up of 50.2 months. The proportion of PFS events occurring in the DBd arm was lower than that in the Bd arms for both the whole trial population and for the 1 PL subgroup (Table 10).

For 1 PL patients median PFS was approximately 19 months longer in the DBd arm than in the Bd arm (Table 10 and Figure 4). The improvement in PFS with DBd was statistically significant, with a HR of 0.21 (95% CI 0.15 to 0.31, p<0.0001) signifying a 79% reduction in the risk of disease progression or death in 1 PL patients receiving DBd.

Table 10 PFS results for the CASTOR trial, median follow up 50.2 months

Parameter	**Subgroup of 1PL patients**		**Total trial population**	
	DBd (n=122)	Bd (n=113)	DBd (N=251)	Bd (N=247)
Events, n/N (%)	[redacted]	[redacted]	187/251 (74.5)	209/247 (84.6)
Median PFS (95% CI), months	27.0 [redacted]	7.9 [redacted]	16.7 (13.1, 19.4)	7.1 (6.2, 7.7)
HR, (95% CI) p-value	0.21 (0.15, 0.31) p<0.0001		0.31 (0.24, 0.39) p<0.0001	
Source: Partly reproduced from CS Tables 19 and 23 Bd = bortezomib with dexamethasone; CI = confidence interval; DBd = daratumumab, bortezomib and dexamethasone; HR = hazard ratio; 1PL = one prior line of therapy; PFS: progression free survival				



Source: Reproduced from CS Figure 13

Figure 4 Kaplan-Meier plot for PFS among 1 PL patients treated with DBd compared with Bd in the CASTOR trial (median follow-up 50.2 months)

3.2.5.3 Time to treatment discontinuation

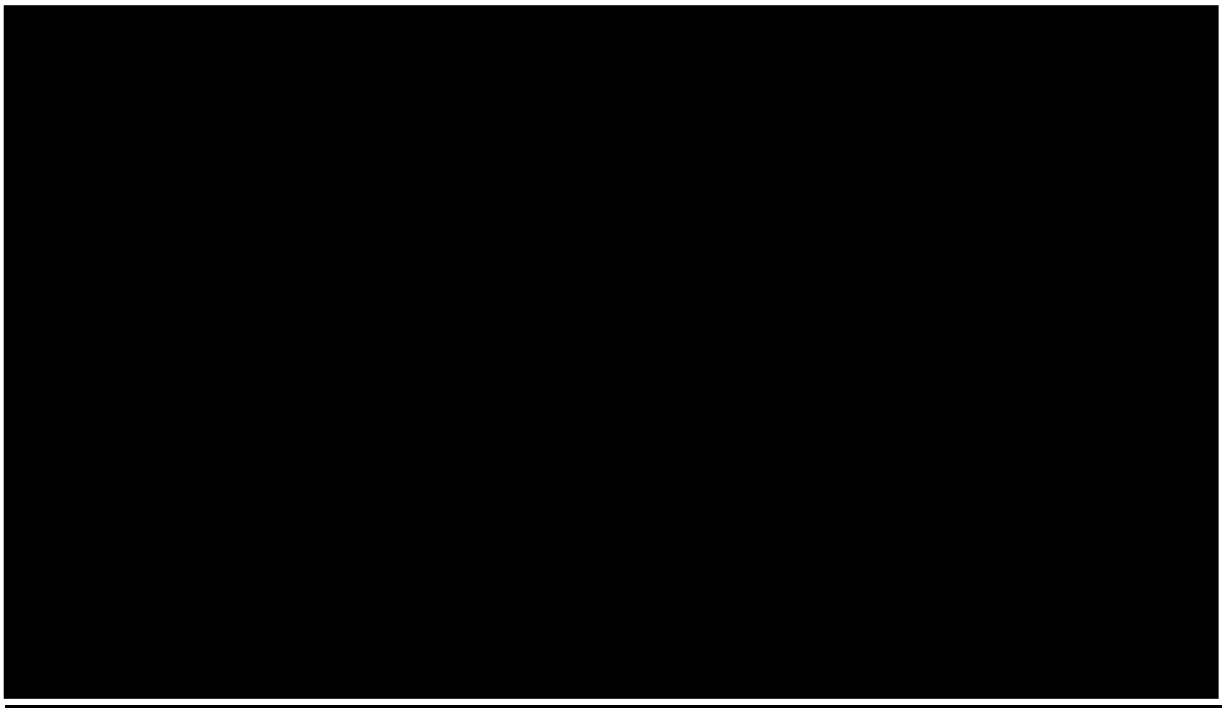
Time to treatment discontinuation (TTD) was a post-hoc outcome. As noted earlier in the report (EAG report section 3.2.3.1) the CS does not provide a definition for TTD. When interpreting the results for TTD, it is important to recognise that all patients received up to 8 cycles (21 days per cycle) of bortezomib whereas the daratumumab component of DBd was administered until disease progression or unacceptable toxicity.

The CS reports updated TTD data (median follow up 50.2 months) for the 1 PL subgroup only (CS section B.2.7.2, and CS Tables 21 and 24). Treatment with DBd was associated with a [redacted] in the risk of treatment discontinuation compared with Bd (HR [redacted], 95% CI [redacted] to [redacted]) (Table 11 and Figure 5).

Table 11 TTD results for the CASTOR trial (1 PL subgroup, median follow up 50.2 months)

Parameter	Subgroup of 1PL patients	
	DBd (n=122)	Bd (n=113)
Events, n/N (%)	[redacted]	[redacted]
Median TTD (95% CI), months	[redacted]	[redacted]
HR, (95% CI) p-value	[redacted]	

Source: Partly reproduced from CS section B.2.7.2 and CS Tables 21, 24
Bd = bortezomib with dexamethasone; CI = confidence interval; DBd = daratumumab, bortezomib and dexamethasone; HR = hazard ratio; NE = not evaluable 1PL = one prior line of therapy; TTD = time to treatment discontinuation



Source: Reproduced from CS Figure 15
Bd = bortezomib and dexamethasone; CI = confidence interval; DBd = daratumumab, bortezomib and dexamethasone; HR = hazard ratio; NE = not estimable; TTD = time to treatment discontinuation

Figure 5 TTD for patients being treated with DBd or Bd in the CASTOR 1 PL subgroup (median follow-up of 50.2 months)

3.2.6 Summary of secondary outcomes reported for the CASTOR trial 1 PL Subgroup

Secondary outcomes reported with updated data for the 1 PL subgroup but not included in the economic model were: MRD negative rate (CS section B.2.7.2), PFS on subsequent line of therapy (CS section B 7.7.2) and response rates (CS Appendix E Table 1)

Minimal residual disease

At 50.2 months median follow up, the MRD negative rate at 10^{-5} threshold (indicating that the number of tumour cells in the body has fallen below a detectable threshold) in the 1PL subgroup was higher in the DBd arm compared to the Bd arm ([redacted] vs. [redacted] respectively; odds ratio 7.19, 95% CI: 2.07, 24.92; p=0.000013; CS Table 21 and CS Appendix E).

Progression free survival on subsequent line of therapy

Progression free survival on subsequent line of therapy (PFS2), defined as the time interval between the date of randomisation to the date of progressive disease on the next line of subsequent treatment or death from any cause, was reported for the 1 PL subgroup at 50.2 months median follow up (CS section B.2.7.2)

Patients who had received DBd had a 63% reduction in the risk of disease progression or death on the first subsequent line of therapy compared with patients who had received Bd alone (HR 0.37, 95% CI 0.26 to 0.53, p<0.0001).

Response rates

For the 1 PL subgroup, at 50.2 months follow up, a statistically significant greater proportion of patients in the DBd arm achieved overall response rate, complete response or better and very good partial response or better compared to Bd arm (p=0.0007, p<0.0001, and p<0.0001 respectively) (Table 12).

Table 12 Response rate results in 1 PL subgroup for the CASTOR trial (response-evaluable population, follow-up of 50.2 months)

Response	DBd ([redacted])	Bd ([redacted])	P value
ORR, n (%)	[redacted] (92)	[redacted] (74)	0.0007
≥CR, n (%)	[redacted] (43)	[redacted] (15)	<0.0001
sCR, n (%)	17 (14)	5 (5)	NR
CR, n (%)	34 (29)	11 (10)	NR
≥VGPR, n (%)	[redacted] (77)	[redacted] (42)	<0.0001
VGPR, n (%)	40 (34)	30 (28)	NR
PR, n (%)	18 (15)	35 (32)	NR

Source: Partly reproduced from CS Appendix D.3.2.2 and Appendix E Table 1
Bd = bortezomib and dexamethasone; CR = complete response; DBd = daratumumab plus bortezomib and dexamethasone; NR = not reported; ORR = overall response rate; PR = partial response; sCR = stringent complete response; VGPR = very good partial response

3.2.6.1 HRQoL outcomes

As described in section 3.2.3.2, the company collected updated data on HRQoL from that presented on the original CS (company clarification response B6) but did not provide it in the CDF review CS.

3.2.6.2 Subgroup analyses

Subgroup analyses for the OS outcome in the whole trial population at 72.6 months of follow-up and subgroup analyses for the PFS outcome in the 1PL subgroup at either 50.2 months (three subgroups) or 47 months (1 subgroup) of follow-up are provided in the CS.

Pre-specified subgroup analysis of overall survival

CS Figure 10 presents results of the pre-specified subgroup analyses for the whole trial population. The OS benefit was greatest for those who had received 1 prior line of therapy only.

Subgroup analysis of PFS in 1 PL patients

Four subgroup analyses of PFS in 1 PL patients are presented in the CS (CS Appendix D section 3.2.4, CS Appendix D Table 39, CS Appendix E). The EAG believe that there are errors in reporting because, although some data are presented as 1PL subgroup, the numbers included in the analyses indicate they must be for the intent-to-treat (ITT) population.

3.2.6.3 Safety outcomes

The CS updates the evidence of treatment-emergent adverse events (TEAEs) in the safety population at the median follow-up of 72.6 months and this is summarised in Table 13 (in the original appraisal safety data were presented for a median 26.9 months of follow-up). In response to clarification question A3, the company confirmed that that the data for Bd at 72.6 months was the same as that at 26.9 months due to the maximum treatment period of eight 21-day cycles for Bd. After the start of treatment, the majority of patients experienced at least one TEAE (DBd 99.2%, Bd 95.4%, Table 13). A greater proportion of participants in the DBd arm experienced Grade 3/4 TEAEs compared with Bd (82.7% versus 62.9% respectively) but the DBd arm had a longer treatment duration compared to the Bd arm (where the maximum treatment period is eight 21-day cycles) and this may account for the difference. Similar proportions of patients discontinued treatment because of at least one TEAE in the two trial arms (DBd 9.3% versus Bd 10.7%).

Table 13 Summary of TEAEs at median 72.6 months of follow-up (CASTOR safety population).

	DBd (n=243)	Bd (n=237)
Any TEAE, n (%)	241 (99.2)	226 (95.4)
Grade 3/4 TEAE, n (%)	201 (87.2)	149 (62.9)
Serious TEAE, n (%)	134 (55.1)	81 (34.2)
TEAE leading to discontinuation, n (%)	26 (10.7)	22 (9.3)
TEAEs leading to death, n (%)	17 (7.0)	14 (5.9)
Source: Data reproduced from CS Table 33 Bd = bortezomib and dexamethasone; DBd = daratumumab plus bortezomib and dexamethasone; TEAE = treatment-emergent adverse event		

The most frequently reported TEAEs (≥20%) in the safety population are presented in Table 14. The most frequently reported TEAEs after a median follow-up of 72.6 months have remained consistent with those reported during the original appraisal when median follow-up was only 26.9 months. Only one additional TEAE (arthralgia) has been added to Table 14. A more detailed summary of TEAEs is provided in CS Table 34.

Table 14 Most frequently reported TEAEs

TEAEs (≥20%)	DBd (n=243)		Bd (n=237)	
	All grades≥20%	Grade 3/4	All grades≥20%	Grade 3/4
Common haematologic adverse event				
Thrombocytopenia, n (%)	145 (59.7)	112 (46.1)	105 (44.3)	78 (32.9)
Anaemia, n (%)	73 (30.0)	39 (16.0)	75 (31.6)	38 (16.0)
Common non-haematologic adverse events				
Peripheral sensory neuropathy, n (%)	122 (50.2)	11 (4.5)	90 (38.0)	16 (6.8)
Upper respiratory tract infection, n (%)	90 (37.0)	6 (2.5)	43 (18.1)	1 (0.4)
Diarrhoea, n (%)	88 (36.2)	10 (4.1)	53 (22.4)	3 (1.3)
Cough, n (%)	71 (29.2)	0	30 (12.7)	0
Fatigue, n (%)	57 (23.5)	13 (5.3)	58 (24.5)	8 (3.4)
Constipation, n (%)	56 (23.0)	0	38 (16.0)	2 (0.8)
Back pain, n (%)	54 (22.2)	6 (2.5)	24 (10.1)	3 (1.3)
Arthralgia, n (%)	49 (20.2)	4 (1.6)	14 (5.9)	0
Source: This is a modified and reduced version of CS Table 34 Bd = bortezomib and dexamethasone; DBd = daratumumab plus bortezomib and dexamethasone; TEAE = treatment-emergent adverse event				

The mode of administration of daratumumab has changed over time. Initially daratumumab was administered as an intravenous infusion and infusion-related reactions were a commonly expected adverse event (in the DBd arm of the CASTOR trial 45.3% of participants experienced an infusion related reaction). Since June 2020 however, a licence extension has been in place for the subcutaneous formulation of daratumumab. The company states that this is now used by most patients in UK clinical practice and is associated with an improved safety profile compared with intravenous daratumumab (CS section B.2.12.3). Clinical advisors consulted by the EAG agreed that this was the case.

In response to clarification question A4 the company provided results from a post-hoc analysis (conducted to enable inclusion of adverse events in the cost-effectiveness analysis) that focussed on the subgroup of CASTOR patients who received one prior line of therapy. This analysis included adverse events at Grade 3 or higher which occurred in at least 5% of patients in either CASTOR treatment arm. These results are summarised in Table 15. The most commonly experienced adverse event in both groups was thrombocytopenia, followed by pneumonia and anaemia in both groups and neutropenia in the DBd group. This is consistent with the most common grade 3/4 events that occurred in the total safety population.

Table 15 CASTOR 1PL subgroup – Cumulative probability of AEs during the treatment period (Final OS analysis)

Adverse Event	DBd	Bd
Neutropenia	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]
Lymphopenia	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]
Peripheral neuropathy	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]

Source: Reproduced from clarification question A4, Table 4
AE = adverse event; Bd = bortezomib and dexamethasone; Cd = carfilzomib and dexamethasone; DBd = daratumumab, bortezomib and dexamethasone.

3.2.7 Pairwise meta-analysis of intervention studies

There is only one RCT of DBd versus Bd so the CS does not include a meta-analysis.

3.3 SACT dataset

The SACT dataset is reported in CS sections B.2.3.8 (methodology), B.2.3.9 (baseline patient and disease characteristics), B.2.4.6 (study population), B.2.4.7 (statistical analyses) and B.2.8 (key results).

Overview of the SACT dataset

The SACT dataset provides information on the real-world treatment effectiveness of DBd in clinical practice in England for [redacted] people with RRMM who had received one prior line of therapy and who were treated via the CDF during the managed access period. This is a much larger cohort than the subgroup of patients in the CASTOR trial who had received one prior therapy (DBd n=122, Bd n=113). The data analysis was conducted by the National Disease Registration Service on behalf of NHS England and NHS Improvement in 2021.[49] The SACT dataset does not compare the effectiveness of DBd with other treatments for RRMM.

[redacted]

The SACT dataset includes [redacted] patients whose application for DBd treatment through the CDF was received between [redacted]. The included patients met the eligibility criteria listed in CS section B.2.3.8 [redacted]

Baseline characteristics

The only baseline characteristics provided in the SACT [redacted] Table 16 compares the baseline characteristics of patients in the SACT dataset and those in the one prior therapy subgroup of the CASTOR trial. [redacted]

We asked our clinical advisors about the differences in the baseline characteristics between the SACT dataset and CASTOR trial 1PL subgroup. There was agreement that the median baseline age of the SACT cohort ([redacted]) was a fair reflection of reality in the NHS in England. In the SACT dataset the lower proportion of SACT patients who had received prior ASCT and the higher proportion who had received previous treatment with bortezomib in comparison to CASTOR was viewed by one advisor as a reflection of SACT dataset being an older cohort, less likely to have been fit for ASCT at first-line treatment, and the commissioning position of bortezomib in the UK, respectively. Two clinical advisors thought the 7-year difference in median age between the CASTOR trial and the SACT dataset would either not have a large impact or might only have a modest impact on treatment outcomes. In contrast, another clinical advisor thought that the effect might be fairly significant because

an additional seven years in later life translates into a significant deterioration in frailty and organ function, and increase in comorbidities, and potentially financial and social changes such as a move from work to retirement. However, as one of our clinical advisors pointed out, these changes would have the same effect on the comparator group and that an improved response would be more impactful (rather than less impactful) in an older population because the chance of salvaging an older patient with an inferior treatment option is less than in a younger patient as the co-morbidities make it more likely that the patient will die at the current line of therapy.

Table 16 Comparison of baseline characteristics for the SACT dataset and CASTOR trial one prior line of therapy (1PL) subgroup

Characteristic	SACT cohort (DBd treatment) [redacted]	CASTOR TRIAL SUBGROUP	
		DBd, 1PL (n=122)	Bd, 1PL (n=113)
[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	63.0	[redacted]
[redacted]	[redacted]		
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]		
[redacted]	[redacted]		
[redacted]	[redacted]		
		[redacted] 47 (38.5)	[redacted] 38 (33.6)
[redacted]	[redacted]		
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]		[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	7 (5.7)	6 (5.3)
[redacted]	[redacted]	[a]	[a]
[redacted]	[redacted]	[a]	[a]
[redacted]	[redacted]		
[redacted]	[redacted]		
[redacted]	[redacted]	Prior B [b] 62 (50.8)	Prior B [b] 57 (50.4)
[redacted]	[redacted]	[redacted]	[redacted]

Sources: CS Table 12, CS Table 13 and, from TA573 clarification response A6 Table 4
[a] Only patients with an ECOG score of 0,1 or 2 were eligible for the CASTOR trial; [b] Reports prior bortezomib treatment but does not indicate that disease was not refractory to treatment so this is unknown.

ASCT = autologous stem cell transplant; B = Bortezomib; Bd = bortezomib and dexamethasone; DBd = daratumumab, bortezomib and dexamethasone; ECOG = Eastern Cooperative Oncology Group; SACT = Systemic Anti-Cancer Therapy

Influence of the Covid-19 pandemic

[redacted]. Many of these patients have therefore been treated during the COVID-19 pandemic (the World Health Organisation declared COVID-19 a pandemic on 11th March 2020). CS section 2.3.8, which describes the SACT study methodology, notes that patients included in the SACT dataset [redacted]. In response to clarification question B2a the company stated that the number of patients who received ILd was not presented in the SACT report. The company make the case that because some patients may have received ILd second-line and then received DBd third-line additional bias and uncertainty is introduced regarding the generalisability of the SACT data to the second-line population. The company state that the SACT results may underestimate DBd efficacy at second-line due to high usage at later lines. The EAG agrees the use of ILd at second-line during the COVID-19 pandemic may have had an impact, but it is difficult to ascertain how likely this is without knowing the exact number of patients in the SACT dataset who received ILd in the one prior line setting and who then went on to receive DBd. The company suggest that NHS England might be able to provide these data.

Generalisability of SACT

The SACT cohort comprises patients treated in the NHS and the results should therefore be more likely to reflect the outcomes of a typical 'real world' clinical practice than those outcomes observed under clinical trial conditions. However, we also note that follow-up for the SACT cohort was considerably shorter than for the CASTOR RCT and a longer follow-up would have been desirable, particularly as median overall survival was not reached (detailed results from SACT below). Furthermore, as noted above, it is possible that access to ILd at second-line during the COVID-19 pandemic may have reduced the generalisability of the SACT dataset.

Summary of the SACT dataset results

The SACT report[49] [redacted].

Table 17 shows the results from the SACT dataset. [redacted]

Table 17 Comparison of OS and treatment duration results from the SACT dataset and the one prior therapy subgroup of the CASTOR RCT

Outcome	SACT dataset DBd [redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
Source: Draws on data from CS Table 25 and CS section B.2.8.2 DBd = daratumumab, bortezomib and dexamethasone; OS = Overall survival; SACT = Systemic Anti-Cancer Therapy	

EAG conclusion

The SACT dataset is representative of a population in England receiving treatment for relapsed multiple myeloma who have had one previous treatment. The dataset included 2,545 patients, a considerably larger number than the DBd arm subgroup of the CASTOR trial who had received one prior therapy (n=122). Patients in the SACT dataset are older, and as a consequence possibly more frail, than the participants in the CASTOR trial but, because only limited population characteristics are reported, other population characteristics cannot be compared. Follow up in the SACT dataset was much shorter than in the company trial and median OS was not reached. The extent to which differences in population characteristics influenced OS is uncertain, particularly as some characteristics, such as [redacted] were not reported for SACT patients. Similarly, the extent to which access to ILd at second-line during the COVID-19 pandemic may have influenced OS in the SACT dataset is unknown.

3.4 Critique of studies included in the indirect comparison and/or multiple treatment comparison

3.4.1 Rationale for ITC

The company's updated systematic review did not identify any RCTs that compared DBd with Cd, the other comparator relevant for the population of RRMM patients who have had one prior therapy. Therefore the company updated the NMA from their earlier submission for TA573[1] which the EAG critiqued in their previous report.[51] Here we present a brief summary of the company's methods and indicate which aspects of the company's NMA have been updated since the CS submitted for TA573.

3.4.2 Identification, selection and feasibility assessment of studies for ITC

The company's updated systematic review identified three RCTs of relevant treatments for people with RRMM who have received one prior therapy (CS Table 27). One was the company's own CASTOR study,[30; 52] one the ENDEAVOR study[31] of Cd versus Bd which was included in the company's earlier indirect comparison for TA573 and one new RCT, the LEPUS trial[34] which, like CASTOR, compares DBd with Bd.

3.4.3 Clinical heterogeneity assessment

The company conducted a 'feasibility assessment' and determined that only CASTOR and ENDEAVOR were relevant to the ITC for the one prior therapy RRMM population. The LEPUS RCT was excluded because the population was not similar enough to align with the CASTOR or ENDEAVOR trial populations. In particular, the LEPUS RCT enrolled only Chinese patients whereas the CASTOR and ENDEAVOR populations were predominantly of white ethnicity (CASTOR 1PL subgroup 86%, ENDEAVOR ITT population 75%). The company state there is "*the potential risk of effect modification introduced by variations in Asian ethnicity*" (CS section B.2.10) and list subgroup data by race from four studies in support of this. The EAG note that, in common with subgroup analyses generally, caution must be observed in the interpretation of these data. The proportion of Asian participants in studies was typically less than 25% and confidence intervals for the Asian subgroup data overlapped with those of the comparison subgroup. The EAG also notes that no baseline characteristics are reported for the subgroup who had received one prior therapy at baseline in the LEPUS trial but comparing the LEPUS ITT population with the CASTOR and ENDEAVOR 1PL subgroups the LEPUS trial participants were slightly younger (median age 61 years versus 63 to 66 years across the arms of the other two trials) and a slightly higher proportion had ISS stage 1 disease (50% versus 46% and 48% in CASTOR and ENDEAVOR respectively). Finally, outcome data from the LEPUS RCT is immature. In the one prior therapy subgroup at 8.2 months follow-up median PFS was not reached in the DBd arm (a hazard ratio is reported) and OS data are not reported for this subgroup in the trial publication.[34]

On balance, the EAG agrees that the LEPUS trial should not be included in the company's base case, but we asked the company to add a scenario analysis that included the LEPUS trial (clarification question A7). The company provided this analysis (the results are reported in section 3.6.3 below.

3.4.4 Similarity of treatment effects and Risk of bias assessment for studies included in the ITC

As the ITC includes the same two studies as for the original assessment for TA573 the EAG has not reassessed these studies.

3.5 Critique of the ITC

3.5.1 Methods of the ITC

The company have used the same NMA structure and coding (using a Bayesian approach), that was used and accepted in the original assessment TA573. The EAG has not reassessed this as it was previously accepted as being fit for purpose. Instead, the EAG describes below which data inputs have been updated since TA573.

3.5.2 Updated data inputs to the NMA

Three inputs to the NMA have been updated as shown in Table 18, the PFS and OS hazard ratios and associated confidence intervals from the CASTOR trial, and the OS hazard ratio and confidence intervals for the ENDEAVOR trial. The inputs for the response outcomes have not been updated. As described above the EAG asked the company to include the LEPUS trial in a scenario analysis so these input data are also included in Table 18 below.

Table 18 Updated data inputs to the NMA

TRIAL	Current CS		Status, previous value
CASTOR	PFS HR [95% CI]	0.21 [0.05, 0.30] a	Updated. Previous value for TA573 was 0.23 [0.16, 0.33]
	OS HR [95% CI]	0.56 [0.39, 0.80] b	Updated. Previous value for TA573 was 0.50 [0.30, 0.84]
ENDEAVOR	PFS HR [95% CI]	0.45 [0.33, 0.61] a	No change (no updated data available)
	OS HR [95% CI]	0.77 [0.58, 1.02] b	Updated. Previous value for TA573 was 0.83 [0.61, 1.14]
In Scenario analysis only			
LEPUS [c]	PFS HR [95% CI]	0.40 (0.21-0.77)	Not applicable, not included in TA573
	OS HR [95% CI]	[redacted]	Not applicable, not included in TA573

[a] Source of data CS Appendix D Figure 15, [b] Source of data CS Appendix D Figure 16, [c] Source of data response to clarification question A7.

TRIAL	Current CS	Status, previous value
CS = company submission; DBd = daratumumab, bortezomib and dexamethasone; HR = hazard ratio, OS = Overall survival; PFS = progression-free survival		

3.6 Updated results from the indirect comparison

The results from the company's indirect comparison are presented in CS Table 30 (with additional detail including forest plots in Appendix D, section D.3.5) for the following outcomes: PFS, OS, Overall response (ORR), very good partial response or better (VGPR or better), complete response or better (CR or better). As already described response outcome data from CASTOR have not been updated since the previous STA (CS Appendix D Table 37) therefore we are not presenting the results for response outcomes here (note that the NMAs for response outcomes do not contribute data to the economic model). The EAG has validated the OS and PFS results by rerunning the analysis with our own code.

3.6.1 Progression-free survival

After updating the input data for the CASTOR trial but with the input for ENDEAVOR remaining the same as for TA573, the results were unchanged (hazard ratios in favour of DBd and the probability of DBd being the best treatment of 100% vs Bd and 99.9% vs Cd, Table 19).

Table 19 NMA results for PFS

Comparison	Subgroup of 1 prior therapy patients	
	HR (95% CrI)	Probability[a]
DBd vs Bd	0.21 [0.15, 0.30]	100%
DBd vs Cd	0.47 [0.29, 0.75]	99.9%

[a] Probability of DBd being better than the comparator
Source: CS Table 30 and CS Appendix D Figure 15
Bd = bortezomib and dexamethasone; Cd = carfilzomib and dexamethasone; CrI = credible interval; DBd = daratumumab, bortezomib and dexamethasone; HR = hazard ratio

3.6.2 Overall survival

After updating the input data for the CASTOR and ENDEAVOR trials, the reduction in the risk of death for the DBd versus Bd was 44% (compared with 50% in the TA573) and the probability of DBd being the best treatment increased very slightly to 99.9% (from 99.6% in TA573). In comparison to Cd, the reduction in the risk of death was 27% (compared with 40% in TA573) and the probability of DBd being the best treatment has fallen slightly to 91.5% (from 95% in TA573).

Table 20 NMA results for OS

Comparison	Subgroup of 1 prior therapy patients	
	HR (95% CrI)	Probability[a]
DBd vs Bd	0.56 [0.39, 0.80]	99.9%
DBd vs Cd	0.73 [0.46, 1.14]	91.5%

[a] Probability of DBd being better than the comparator
Source: CS Table 30 and CS Appendix D Figure 16
Bd = bortezomib and dexamethasone; Cd = carfilzomib and dexamethasone; CrI = credible interval; DBd = daratumumab, bortezomib and dexamethasone; HR = hazard ratio

3.6.3 Scenario analysis including the LEPUS trial

In response to clarification question A7 the company ran scenario analyses including the LEPUS trial of DBd vs Bd which was conducted in a Chinese population.

For the outcome of PFS the fixed effect meta-analysis of CASTOR and LEPUS gave a hazard ratio of [redacted] with an I^2 statistic of 65.3%. As a consequence of the heterogeneity implied by the I^2 statistic, the company ran both a fixed-effect and random-effects NMA. The results of the fixed-effect NMA were comparable to the base-case results without LEPUS. The results of the random-effects NMA were comparable for DBd versus Bd whereas for DBd versus Cd the wider credible intervals crossed one (indicating insufficient evidence that the groups are statistically significantly different).

For the outcome of OS the results of a fixed effect meta-analysis combining data from the CASTOR and LEPUS studies yielded a hazard ratio of [redacted] with an I^2 of 0% suggesting little or no heterogeneity. In the fixed-effects NMA the hazard ratio for DBd versus Bd was [redacted] and for DBd versus Cd [redacted] Both results were comparable to the base case without LEPUS.

Table 21 Scenario NMA including LEPUS, results for PFS

Meta-analysis (CASTOR & LEPUS)				
Comparison	**HR (95% CI)**	**Qpval**	**I^2**	**tau**
DBd vs Bd (Fixed effect)	[redacted]	[redacted]	[redacted]	[redacted]
NMA Scenario (CASTOR, LEPUS & ENDEAVOR)				
Comparison	**HR (95% CrI)**	**Probability[a]**		
DBd vs Bd (fixed effect)	[redacted]	[redacted]		

DBd vs Cd (fixed effect)	[redacted]	[redacted]
DBd vs Bd (random effects)	[redacted]	[redacted]
DBd vs Cd (random effects)	[redacted]	[redacted]

[a] Probability of DBd being better than the comparator
Source: Clarification question A7 response Tables 12 and 13
Bd = bortezomib and dexamethasone; Cd = carfilzomib and dexamethasone; CrI = credible interval; DBd = daratumumab, bortezomib and dexamethasone; HR = hazard ratio

Table 22 Scenario NMA including LEPUS, results for OS

Meta-analysis (CASTOR & LEPUS)				
Comparison	**HR (95% CI)**	**Qpval**	**I^2**	**tau**
DBd vs Bd (Fixed effect)	[redacted]	[redacted]	[redacted]	[redacted]
NMA Scenario (CASTOR, LEPUS & ENDEAVOR)				
Comparison	**HR (95% CrI)**	**Probability[a]**		
DBd vs Bd (fixed effect)	[redacted]	[redacted]		
DBd vs Cd (fixed effect)	[redacted]	[redacted]		

[a] Probability of DBd being better than the comparator
Source: Clarification question A7 response Tables 12 and 13
Bd = bortezomib and dexamethasone; Cd = carfilzomib and dexamethasone; CrI = credible interval; DBd = daratumumab, bortezomib and dexamethasone; HR = hazard ratio

3.7 Critique of the Unanchored MAIC [redacted]

3.7.1 Methods of the Unanchored MAIC [redacted]

The unanchored matching adjusted indirect comparison (MAIC) method can be used for a pairwise indirect treatment comparison between two single arms from different studies (i.e. no common comparator) when individual level patient data are available for one single arm ([redacted]) and summary data are available for the other ([redacted]). However, as the NICE Decision Support Unit (DSU) Technical Support document[53] cautions, there is an assumption in an unanchored MAIC that absolute outcomes can be predicted from the covariates. This means that it is assumed that all effect modifiers and prognostic factors are accounted for, but in practice this very strong assumption is usually considered impossible to meet. The failure to meet this assumption leads to an unknown amount of bias in the unanchored estimate.

The company state their analysis followed the method of Signorovitch et al.[54] and a guideline from the NICE DSU, with the NICE DSU Technical Support Document 16 cited (Adjusting

Survival Time Estimates in the Presence of Treatment Switching[55]). The EAG would have expected the NICE DSU Technical Support Document 18 to be cited (Methods for population-adjusted indirect comparisons in submissions to NICE[53]) but it is possible that an incorrect reference has been cited in error.

The methodological steps the company took for their unanchored MAIC are summarised briefly below:

- [redacted] The MAIC was conducted by [redacted]
- [redacted]

[redacted]

- [redacted] were obtained by converting the SACT Kaplan-Meier curve images into numbers with x and y coordinates (i.e. time and survival probabilities) using Engauge Digitizer.
- [redacted] and analysed together using weighted Cox proportional hazard models.

[redacted]

EAG conclusion

Whilst the MAIC appears to have been conducted correctly (albeit neither the programming code nor data were provided to the EAG for verification), the principle of including all prognostic factors and treatment effect modifiers in the analysis has not been met and cannot be met because of the limited information on baseline characteristics for the SACT dataset. Additional data baseline characteristics need to be reported for the SACT dataset in order for it to be more useful in this context, however if it had been possible to match more baseline characteristics the reduction in effective sample size would likely have been greater. The severe limitations of the MAIC should be considered when viewing the results from it in section 3.8 below.

3.8 Results from the Unanchored MAIC [redacted]

The company report the results of the unanchored MAIC in CS Figure 19 which is reproduced here (EAG report Figure 6). This figure shows:

- [redacted]
- [redacted]

[redacted]

As can be seen from Figure 6 [redacted] between the OS outcomes from the [redacted]. As it was unclear to the EAG why the adjusted Kaplan Meier curve for [redacted] should move upwards following matching we asked the company if they could provide a reason (clarification question A10). In response the company [redacted]. The EAG agrees with this conclusion.

1 PL = one prior line; Dara = daratumumab; DVd = DBd = daratumumab, bortezomib and dexamethasone; HR = hazard ratio; MAIC = matching-adjusted indirect comparison; NA = not available; OS = overall survival; SACT = Systemic Anti-Cancer Therapy.

Source: reproduction of CS Figure 19

Figure 6 DBd OS data from [redacted] (MAIC)

Although the MAIC is considered unreliable by both the company and the EAG, the EAG believes there is a need to explore the validity of the company's assertion that, despite differences between [redacted], the relative benefit observed in CASTOR is likely to hold in the real world. Therefore, in clarification question B4, the EAG asked the company to:

- provide a comparison of the Bd OS data from CASTOR (1PL population) versus SACT (MAIC)
- use the relative benefit from CASTOR to create a simulated Bd dataset from the SACT DBd data and plot this on CS Figure 19 and then to comment on the clinical plausibility of this simulated Bd data.

In response to our first request the company limited themselves to considering whether it would be appropriate to conduct a Bd CASTOR vs DBd SACT MAIC. This the company viewed as inappropriate, given the limitations of the [redacted] MAIC they had already reported as being unreliable. Whilst the EAG agrees that a further MAIC would not be beneficial, we did want to see the Bd CASTOR Kaplan-Meier (KM) data plotted on CS Figure 19 (EAG Figure

6) because we believe that being able to visualise the two arms of the CASTOR trial (DBd and Bd) and the single arm DBd SACT data on the same plot could be helpful to the NICE committee.

The EAG was also aware that our second request, to create a simulated Bd dataset by applying the relative benefit from CASTOR to the SACT DBd data, was far from ideal. However, we were again looking to find a way to help the committee explore how realistic it is to assume that the relative benefit of CASTOR will apply in the real world. The company declined to perform this analysis because they did not consider it methodologically appropriate for the reasons given in their response to clarification question B4. In brief these reasons were:

- The phase III CASTOR study of DBd versus Bd is the primary source of data collection in the MAA
- the challenges in simulating a comparable Bd curve from the DBd SACT data set
    - potential for selection bias if DBd patients are not representative of patients that would be treated with Bd in clinical practice
    - bias if DBd patients in SACT were treated at a later line due to the influence of the COVID-19 pandemic which permitted treatment with ILd at second-line
    - the methodology would rely on proportional hazard but there is evidence that the assumption of proportional hazards between the DBd and Bd arms does not hold.

[redacted]

Finally, as described earlier in section 3.3 of this report, we asked our clinical advisors about the differences between the SACT cohort and CASTOR trial population. There were differing views about the extent to which the age difference between the two populations might affect treatment outcomes ranging from ‘minimal’ to ‘might be fairly significant’. Unfortunately, there is no information from the SACT dataset on other potential prognostic factors and treatment effect modifiers (these might include characteristics such as ISS disease staging, refractory status to last line of previous therapy/immunomodulatory agents, cytogenic profile, renal impairment). Therefore, it is difficult to understand the reasons for the observed difference between OS in the SACT dataset and OS in the 1PL subgroup of the CASTOR trial.

EAG conclusion

The unanchored MAIC analysis, in the EAG’s opinion, is considered undependable. Our opinion is supported by the observation that [redacted] (CS Figure 19 and clarification response A10); this is counterintuitive. The [redacted] patients do much worse in terms of overall survival

than [redacted] patients (CS Figure 19), presumably because [redacted] is in a healthier population, but because few baseline characteristics are reported for the [redacted] dataset the true reasons for this are not known. The EAG asked two clarification questions to facilitate exploration of the company's assertion that the relative benefit observed in CASTOR is likely to hold in the real world. However, the company declined to answer both questions as they considered them methodologically inappropriate.

3.9 NHS Digital NDMM Standing cohort study

The SACT dataset and the results from it only provide information for people who received DBd as a second-line treatment. There is no equivalent real-world data for second-line patients treated with Bd. Therefore, the company has drawn on data from the NHS Digital newly diagnosed multiple myeloma (NDMM) standing cohort which includes people who did not receive daratumumab during their course of treatment and makes a naïve comparison of OS rates for this NDMM cohort and people in the SACT dataset (who received DBd).

[redacted]

The NHS NCRAS standing cohort report states that "results and figures are contained in Excel tables that accompany this report"[56] but the EAG was not supplied with a full copy of these figures and tables. The EAG has only had access to the summary of the main findings. We therefore requested a table of the baseline characteristics of participants in the NDMM cohort study (Clarification question A11a). The company supplied this information and the full baseline characteristics can be found in the company's response to clarification question 11, Table 15. Characteristics for the non-CDF incident myeloma cancer patients that could be compared with the CASTOR trial 1PL subgroup are reported in Table 23. In the CASTOR trial more than half of the patients in the 1PL subgroup had received prior ASCT whereas among patients in the NDMM cohort fewer than 20% received ASCT. This may be due to the difference in age profile of the NDMM cohort compared to the trial (the weighted average for the age of the non-CDF ASCT positive and ASCT negative patients combined is [redacted]). The proportion of males was very similar in the NDMM cohort and the CASTOR IPL subgroup. Due to the high proportions of missing data for baseline ECOG score and ISS staging it is not possible to draw conclusions about any similarities/differences between the NDMM cohort and the CASTOR IPL subgroup.

The EAG believes that the whole cohort ([redacted]) comprises patients who have received a variety of treatments, but without access to the full copy of figures and tables that accompany the NHS NCRAS standing cohort report[56] we cannot provide any details.

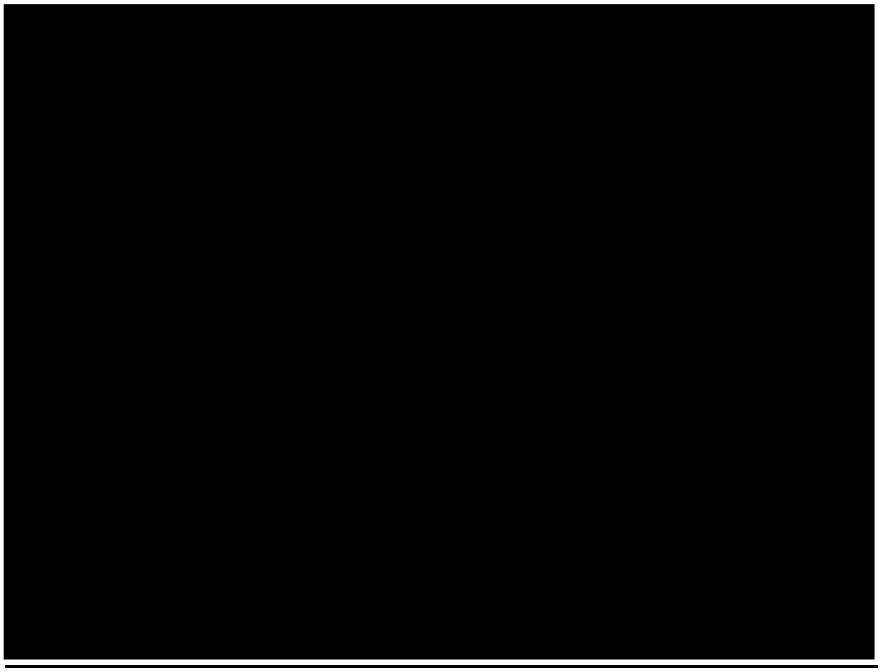
Table 23 Comparison of the baseline characteristics for the Non-CDF incident myeloma cancer patients and the CASTOR trial 1PL subgroup patients

	[redacted]		CASTOR trial 1PL subgroup	
	[redacted]	[redacted]	DBd, 1PL (n=122)	Bd, 1PL (n=113)
Prior ASCT	-	-	[redacted]	[redacted]
Age, years, n (%)				
<65	[redacted]	[redacted]	[redacted]	[redacted]
65 to 74	[redacted]	[redacted]	47 (38.5)	38 (33.6)
≥75			8 (7.0)	17 (15.0)
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	63.0	64.0
Range	[redacted]	[redacted]	30 to 84	40 to 85
Sex, n (%)				
Male	[redacted]	[redacted]	[redacted]	[redacted]
Baseline ECOG score, n (%)				
0	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	58 (47.5)	51 (45.1)
2	[redacted]	[redacted]	7 (5.7)	6 (5.3)
3	[redacted]	[redacted]		
4	[redacted]	[redacted]		
Missing	[redacted]	[redacted]		
ISS staging[b], n (%)				
I	[redacted]	[redacted]	57 (46.7)	51 (45.1)
II	[redacted]	[redacted]	42 (34.4)	44 (38.9)
III	[redacted]	[redacted]	23 (18.9)	18 (15.9)
Missing	[redacted]	[redacted]		

Source: CS Table 12 and clarification question A11 Table 15; TA573 clarification response A6 Table 4
[a] Calculated by the EAG
[b] [redacted] For the CASTOR trial ISS staging was based on the combination of serum β2-microglobulin and albumin.
ASCT= autologous stem cell transplant; Bd = bortezomib and dexamethasone; CDF = Cancer Drugs Fund; DBd = daratumumab, bortezomib and dexamethasone; ECOG= Eastern Cooperative Oncology Group; SD= standard deviation; ISS= International Staging System

[redacted] Because the CASTOR study and the SACT dataset included a mix of patients both eligible for and ineligible for ASCT, the EAG asked the company to provide the 24-month survival data for the transplant-eligible patients (Clarification question A12a). [redacted] The company provided a Kaplan-Meier plot showing front-line OS outcomes from the NDMM Standing Cohort Study for patients that either did or did not receive ASCT as their initial

therapy (Figure 7). The EAG notes that the number at risk for ASCT-negative patients in Figure 7 ([redacted]) is not the same as the number reported above ([redacted]), the reason for this is not clear but may be due to slight differences in how the populations are defined.



Source: Reproduction of Figure 2 from the company's response to clarification question A12
The company's figure includes this note: [redacted]
ASCT = autologous stem cell transplant

Figure 7 Kaplan-Meier OS for patients in the NDMM Standing Cohort Study who either did or did not receive ASCT

[redacted] this "*gives confidence that although absolute differences exist between CASTOR and SACT, the relative benefit observed in CASTOR is likely to hold in the real world*". We believe that the 24-month OS in a group containing a mix of ASCT-negative and ASCT-positive patients who had not received daratumumab would be higher than [redacted]

It was not possible for the company to provide PFS estimate for the NDMM cohort because this outcome is not reported (company response to clarification question A11b).

It seemed from the company's cited reference for the NDMM cohort[56] that OS and TTNT data were available for patients receiving bortezomib and dexamethasone at 2L or carfilzomib and dexamethasone at 2L, so the EAG requested this. The company's full response can be found in answer to clarification question A13, but in summary, the company explained that there are limitations to such analyses because:

- some necessary data items are not routinely available
- there are issues of data quality
- baseline characteristics for second-line patients are not available
- median follow-up of less than 24 months

The company therefore considered that it would not be "*methodologically appropriate nor robust to use unpublished exploratory analysis for comparator second-line treatments from the NDMM Standing Cohort Study to inform the NICE Decision Problem for DBd*".

3.10 Conclusions on the clinical effectiveness evidence

- The CS includes updated evidence (median follow-up for OS is 72.6 months, median follow-up for PFS 50.2 months) from the CASTOR trial for the subgroup of patients who had received one prior therapy which is relevant to this CDF review (DBd n=122, Bd n=113).
- In the 1PL subgroup median OS was not reached in the DBd arm (95% CI 59.7 months to not evaluable) and was 47.0 months (95% CI 32.6 to 58.7) in the Bd arm. Median PFS was approximately 19 months longer in the DBd arm than in the Bd arm. The improvements in OS and PFS with DBd versus Bd were statistically significant. Other clinical efficacy outcomes were reported and these are also in favour of DBd.
- TEAEs reported for the safety population after a median follow-up of 72.6 months remain consistent with those reported during the original appraisal (follow-up 26.9 months). A post-hoc analysis of adverse events in the 1PL subgroup is consistent with events in the full safety population.
- Real world data from [redacted] people with RRMM who had received one prior line of therapy and who were treated with DBd via the CDF during the managed access period shows NHS patients are [redacted]
- The NMA was well conducted and OS and PFS results have been validated by the EAG. DBd has the probability of being the best treatment when compared with Bd and Cd.
- A MAIC used to [redacted]. The MAIC was well conducted but lacks validity as many prognostic factors and treatment effect modifiers could not be included. Nevertheless, with CASTOR DBd and SACT KM data plotted together it is clear that SACT patients OS is not as good as for CASTOR DBd patients. The true reasons for this are not known.
- In the absence of real-world data for patients receiving Bd, the company has made a naïve comparison of OS rates between people in the NHS Digital NDMM Standing cohort study who were not treated with daratumumab and people in the SACT

dataset (who received DBd). [redacted]. The EAG believes that the 24-month OS for people who had not received daratumumab would be [redacted] if there was a mix of ASCT-negative and ASCT-positive patients.

4 COST EFFECTIVENESS

4.1 EAG comment on company's review of cost-effectiveness evidence

The company performed three systematic literature reviews (SLRs) to identify published studies of: i) cost-effectiveness (CS Appendix G), ii) health related quality of life (CS Appendix H), and iii) costs/healthcare resources (CS Appendix I), for patients with RRMM who had received one prior therapy.

We presume that the company's SLRs were updates of their original appraisal TA573, although there is a lack of clarity about the update searches. It appears there was at least one update search in between the searches carried out on 22nd August 2017 for the original submission TA573 and the searches conducted for this submission in May 2020, which were further updated in May 2022.

The company's SLRs resulted in the inclusion of 23 economic evaluations, 21 cost/resource use studies, and eight HRQoL studies. We use four of these studies, including one UK-based NICE appraisal (briefly summarised below) for validation of the company's findings (see Section 5.3.4 of this report).

Model submitted for NICE appraisal TA695

The model for this appraisal included patients with multiple myeloma who had previously received at least one prior therapy and used a partitioned survival approach with three health states: progression-free, progressed, and dead. It used parametric PFS, and OS curves fitted to ASPIRE trial data, with adjustments for the subgroup of interest. The analysis followed the NICE reference case, with an NHS and personal social services perspective, 3.5% annual discount rate for costs and effects, lifetime horizon (40 years), 28-day model cycle and a half-cycle correction. The cost-effectiveness evidence using DBd as a comparator was not presented to the committee due to NICE's position statement on the CDF.

> **EAG conclusions:** Overall, the company's searches were reasonable. There remains some uncertainty about the date limits applied, however, we do not anticipate any relevant published studies have been missed.

4.2 Summary and critique of the company's submitted economic evaluation

4.2.1 NICE reference case checklist

Table 24 NICE reference case checklist

Element of health technology assessment	Reference case	EAG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	It meets the NICE reference case, no change from the original submission TA573
Perspective on costs	NHS and PSS	
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	
Synthesis of evidence on health effects	Based on 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.	
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	
Source of preference data for valuation of changes in health-related quality of life	Representative sample 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	
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	
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	

4.2.2 Model structure

In response to clarification question B5a, the company submitted a revised version of their CDF review model with an Excel functionality capable of replicating the incremental cost effectiveness ratios (ICERs) used in the committee's decision making at the point of CDF entry (discussed later in Section 5.3 of this report). In addition to the functionality to revert to the original inputs, the company's revised version of the model also includes corrections

applied in response to EAG clarification questions B10b, B10c, B11a, B11b, B13b, B15 and B16. All discussion and results reported below relates to this revised CDF review model.

The model has a partitioned survival structure with three main health states: pre-progression, post-progression and death, which the TA573 committee considered acceptable. The pre- and post-progression states are subdivided into 'on' and 'off' treatment stages, as shown in CS Figure 20. This structure has not changed for the current CDF review, but the company have made some changes to the following model assumptions and parameters as listed below. This list does not include the changes made by the company in response to EAG clarification questions B10b, B10c, B11a, B11b, B13b, B15 and B16.

- Baseline population characteristics including age and sex (section 4.2.3)
- Updated PFS (section 4.2.6.2), OS (section 4.2.6.3) and TTD (section 4.2.6.4) data from the final data cut of CASTOR
- NMA results informing the HRs for PFS and OS (sections 3.5.2 and 3.6)
- Updated life tables for general population mortality (section 4.2.6.3)
- Incidence of adverse events for the DBd arm based on the COLUMBA trial (to reflect the safety profile of daratumumab administered via subcutaneous injection) (section 4.2.6.5)
- Distribution of subsequent treatments and the percentage of patients continuing subsequent treatments (section 4.2.8)
- Patient Access Scheme (PAS) discount for daratumumab (section 4.2.8)
- Costs associated with drugs, administration, monitoring, adverse events, and terminal care (section 4.2.8)

We critique the above aspects in the following sections of the report, except for the NMA results which have already been critiqued (sections 3.5.2 and 3.6).

4.2.3 Population

The modelled cohort is based on the second-line population in the CASTOR trial receiving DBd. The company revised the baseline patient characteristics in their base case as follows. In TA573, the mean age of the modelled cohort was 63.3 years and the proportion of females 41.3%. This was obtained from the 1PL subgroup in the CASTOR trial (including patients in both arms and that received one prior therapy). In the current appraisal, the mean age of the modelled cohort is 62.6 years and proportion of females 40.85% as it is based only on patients in the DBd arm that received one prior therapy.

We note that there are differences between the patients in the CASTOR trial and those treated with daratumumab in the SACT dataset: patients in the trial were younger, and consequently likely to be fitter, than those generally seen in clinical practice in England. The median age of the patients with one prior therapy in the CASTOR trial was 63.0 years whereas the median age of those in the SACT dataset was [redacted].

EAG conclusions: The SACT dataset comprises patients treated with daratumumab in UK practice. This indicates that clinicians will offer daratumumab to patients who are on average older and less fit than those in the trial. We have previously discussed the uncertainty around how this might affect treatment outcomes (see section 3.3). We therefore use the baseline patient characteristics derived from the SACT dataset ([redacted], male: 59%) in the EAG preferred assumptions, discussed in Section 6. The clinical experts advising the EAG agree that the SACT characteristics might be more reflective of the patients treated with daratumumab in UK NHS clinical practice.

4.2.4 Interventions and comparators

The intervention and comparators included in the company's base case cost-effectiveness analysis are consistent with their original submission TA573 and the NICE scope for second-line patients with multiple myeloma. All the treatments are implemented as per their respective marketing authorisation and according to their licensed dosing regimens.
The following treatments were included:

- *Intervention arm:* Daratumumab + bortezomib + dexamethasone (DBd)
- *Comparator arms:* Bortezomib + dexamethasone (Bd) and Carfilzomib + dexamethasone (Cd)

Chemotherapy was excluded as a comparator. This aligns with clinical practice as discussed earlier in Section 2.3.

EAG conclusions: We agree with the company's approach and view that all the relevant comparators from the UK NHS perspective are included in their analyses.

4.2.5 Perspective, time horizon and discounting

The model uses a lifetime horizon (30 years from an initial mean age of 62.6 years) in the base case. In accordance with the original submission TA573 and the NICE reference case, costs are estimated from the perspective of the NHS and personal social services and a discount rate of 3.5% per year is applied to both costs and quality-adjusted life years (QALYs). The model uses a weekly model cycle, with a half-cycle correction.

EAG conclusions: We agree with the company's approach.

4.2.6 Treatment effectiveness and extrapolation

The key parameters driving clinical effectiveness in the model are survival extrapolation functions of PFS, OS and time on treatment for the three included treatments. The company's approach is described in CS Section B.3.3. We present a summary, followed by our critique of the company's approach below.

4.2.6.1 Overview of methods for survival extrapolations

As in the original submission, the company fit independent survival curves to the CASTOR trial data for DBd and Bd; and use HR estimates from the NMA using CASTOR and ENDEAVOR to model survival curves for the Cd arm. Data from the final data cut of CASTOR on PFS, OS and time on treatment was used in the CDF review model.

For each survival outcome (OS, PFS and time on treatment), six parametric distributions were fitted: Exponential, Weibull, Log-normal, Log-logistic, Generalised gamma and Gompertz. NICE DSU guidance is cited in support of the selection of preferred distributions:

- assessing the proportional hazards assumption for OS and PFS comparisons including log-log plots (CS Figure 21 and Figure 28)
- assessing the long-term projections and validity of the survival assumptions through accelerated failure time models including quantile-quantile plots (CS Figure 22 and Figure 29)
- assessment of statistical (Akaike information criterion [AIC]/Bayesian information criterion [BIC]) fit to the KM data (CS Tables 37, 38, 41 and 42)
- estimation of smoothed hazard rates from CASTOR to compare changes in the observed hazard function over time against assumed hazards for each parametric model (CS Figure 24 and Figure 31)
- assessment of visual fit of the survival distributions to the KM data (CS Figures 23, 25, 26, 30 and 33)
- consideration of the plausibility of the extrapolations based on clinical expert opinion.

4.2.6.2 Progression-free survival extrapolations

DBd PFS (CS Section B.3.3.1.1)

- Updated CASTOR trial KM data up to four years, beyond which the data are extrapolated (CS Figure 25)

- KM data was used up to four years as none of the parametric curves could follow the trial results between years 2 and 4.
- The exponential distribution was chosen to extrapolate PFS beyond the trial period.
- The company noted that the Gompertz distribution, used in the original submission TA573, had a poor statistical fit as it showed a continuous decrease in hazards without capturing the initially higher hazards, as shown in the smoothed hazard rates from the CASTOR trial (CS Figure 24).

Bd PFS (CS Section B.3.3.1.1)

- To maintain consistency with the DBd arm, CASTOR trial KM data was used up to four years, beyond which the exponential distribution was fitted for the company's base case (CS Figure 26).
- While the log-logistic curve provided the best fit based on AIC and BIC statistics (CS Table 38), feedback the company received from their clinicians did not provide a clear preference for long-term extrapolation as all the fitted curves provided similar estimates at five years and 10 years.

Cd PFS (CS Section B.3.3.1.1)

- A HR of 0.45 (95% credible interval 0.41 to 0.51) compared with Bd from CASTOR was estimated from the NMA and applied until the end of fixed duration of Bd (which was 24 weeks). This is consistent with the original submission TA573.
- Beyond 24 weeks, an adjustment factor of 1.36 (95% credible interval 0.913 to 2.027) was applied to the HR of 0.45 to account for between trial differences (CS Table 39). This adjustment addressed a concern of the appraisal committee in the original submission (TA573) that the effectiveness of DBd compared to Cd was overestimated in the company's NMA in TA573 as no adjustment was made to correct the differences in treatment duration of bortezomib in Bd arms of CASTOR (where the number of Bd cycles was restricted to eight) versus ENDEAVOR (where patients were treated to progression).
- The adjustment factor of 1.36 translated to a HR of 0.332 [estimated using the calculation: (1/1.36)*0.45] that is applied to Bd arm beyond 24 weeks.

Probability of death during PFS

[redacted]

EAG conclusions:

- The company's comparison of observed PFS with the model predicted PFS indicates that the choice of survival curves fitted to the observed data is reasonable.
- The clinical expert advising the EAG feels that the PFS estimates are realistic but suggested that PFS at 10 years is too high in the DBd arm ([redacted]) while it is unlikely to be [redacted] in the Bd arm, as modelled by the company. We note, however, that the company's choice of curve (KM up to four years followed by the exponential distribution) provides the lowest estimate at 10 years in the DBd arm. For Bd, all the parametric distributions provide similar estimates (around [redacted]).
- We conducted a scenario analysis using log-logistic curve for Bd PFS as it provided the best statistical fit (see Section 6.1).
- To explore the impact on overall cost-effectiveness results, we also conducted scenario analyses by fitting a range of distributions to the PFS curves for both DBd and Bd arms, with and without using KM data up to four years (as discussed in Section 6.1). We note that the model results are not sensitive to the use of KM data up to a given timepoint compared to use parametric curves fitted to the whole data.
- The current appraisal addressed the concerns raised by the appraisal committee in the original submission in TA573 regarding adjustment of HR for Cd vs Bd. They applied the same adjustment factor accepted by the committee in the original submission.
- Overall, we agree with the company's approach.

4.2.6.3 Overall survival extrapolations

Adjustments for treatments not available on the NHS (CS Section B.3.3.1.2)

The company's OS estimates are adjusted for treatments that are not available in UK clinical practice or available only via the CDF. This is appropriate as many patients in the CASTOR trial (65% in the Bd arm versus 37% in the DBd arm) received such treatments, which introduced bias in the OS analyses. The IPCW approach was used for the adjustment (for details, see Section 3.2.4).

DBd OS (CS Section B.3.3.1.2)

- The company chose a log-logistic curve, which gave initially increasing hazard rates before a plateau and then gradual decline. The company argued that this is justified based on the high rate of MRD negativity (surrogate for estimating long-term survival associated with improved OS) observed among patients in the DBd arm compared

to patients in the Bd arm, which indicates a decline in mortality hazard with DBd as time passes (CS Figure 31, reproduced below in Figure 8).

- The smoothed trial curve, shown in CS Figure 31 alongside the hazard figures obtained from curve fitting, indicates that hazard rates increase up to 38 months (equivalent to the cut-off for the maximum follow up available in the original company submission), remain relatively constant between months 38 and 48 and thereafter rapidly decrease.
- The company's long-term predictions of DBd are shown below in Figure 9, reproduced from CS Figure 32.

Figure 8 Smoothed hazard rates from the CASTOR trial data and fitted parametric hazard functions, DBd: OS (reproduced from CS Figure 31)

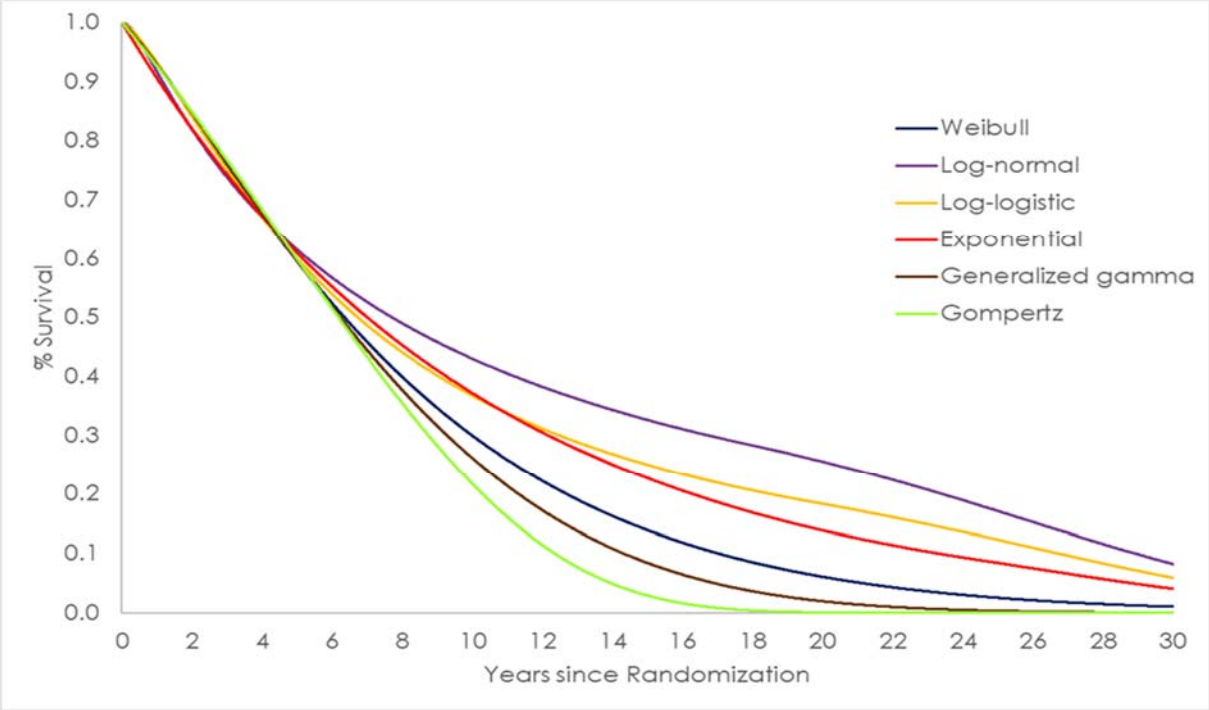


Figure 9 Company's long-term prediction of DBd (reproduced from CS Figure 32)

Bd OS (CS Section B.3.3.1.2)

- The company chose a Gompertz curve, based on AIC/BIC statistics, clinical expert feedback and visual inspection (CS Figure 33).

Cd OS (CS Section B.3.3.1.2)

- Similar approach applied as for modelling PFS Cd. A HR of 0.77 (95% credible interval 0.70 to 0.85) compared with Bd was estimated from the NMA and applied to the modelled Bd curve from CASTOR until the end of fixed duration of Bd treatment (which was 24 weeks).
- Beyond 24 weeks, an adjustment factor of 1.46 (95% credible interval 0.684 to 2.662) was applied to the HR of 0.77 to account for between trial differences (CS Table 43).
- This value translates to an HR of 0.526 [estimated using the calculation: (1/1.46)*0.77] that is applied to Bd arm beyond 24 weeks (CS Figure 34).

General population mortality rates

- Updated National Life Tables - 2018-2020 National Life Tables, England and Wales (ONS).
- Applied as a lower limit to the modelled mortality rates, as in the TA573 model.

EAG conclusions:

DBd:

- To compare the modelled DBd OS estimates with real world evidence, we present a comparison of the SACT KM data, the CASTOR KM data and the modelled extrapolations from trial data in Figure 10 below. We note a significant difference between the real-world evidence, the trial data, and the company's extrapolations: the SACT data indicates significantly lower OS for patients treated with DBd. We discuss this in detail in Section 5.3.3 of this report.
- The exponential and Gompertz distributions provide the best statistical fits to the company's trial data in terms of BIC and AIC respectively (CS Table 41). However, the exponential provides a constant hazard and the Gompertz a constantly increasing hazard, which do not reflect the plateau and subsequent decline in the smoothed hazard function from the CASTOR data (as shown in Figure 8 above). The company's choice of log-logistic for the DBd OS extrapolation does provide the closest approximation to the smoothed hazard estimates from the trial and would be reflective of the prognostic value of MRD negativity (which is associated with longer PFS and OS). However, given the lower OS estimates from the SACT data we also report a more conservative Gompertz scenario to ascertain its impact on the overall cost-effectiveness results in EAG analysis (Section 6 below).
- The log-normal distribution provides a more rapid initial increase in hazard which declines over a longer period than the log-logistic, which is reflective of the prognostic value of MRD negativity. Therefore, to provide a range of the possible cost-effectiveness results, we conduct an optimistic scenario using this distribution in our additional analyses in Section 6 of this report.
- Consultation with our expert indicated that the company's OS modelled estimates appear optimistic. He suggested that the Weibull distribution is a reasonable reflection of survival in RRMM patients receiving DBd (based on Figure 8 above) as he expects an early high rate of death followed by a potential drop and then a slow climb. For that reason, we conduct a scenario using the Weibull distribution in our additional analyses (see Section 6 below).
- Based on the available trial evidence, we agree with the company's assumption to use the log-logistic curve to extrapolate long-term survival for their base case. However, we view that there remains uncertainty whether the modelled OS estimates are reflective of UK clinical practice due to its difference from the SACT OS estimate, which is based on real world evidence.

Figure 10 Comparison of DBd OS estimates: SACT, CASTOR-KM and parametric survival extrapolations (adapted by EAG from CS Figure 19 and data in the model)

Bd:

- Comparing the OS estimates of Bd at 10 and 20 years, we note that the survival rate is 0% at 10 years for the company's base case (Table 25). This is inconsistent with the estimates obtained in the original submission TA573 where the survival was estimated at 10% at 10 years. Furthermore, the experts advising the EAG in the current submission as well as in TA573 expected the survival rate at this timepoint to be higher.
- The exponential curve followed the Gompertz curve closely in terms of goodness-of-fit (AIC statistic is 3rd lowest after Gompertz and Weibull, respectively and lowest BIC statistic after Gompertz, which is identical with Weibull). Furthermore, it predicted a survival rate of 11.6% at 10 years, which is close to the estimates suggested by the clinical experts to the EAG in TA573 (between 15-20%). Therefore, we view that the exponential distribution is best suited to extrapolate long term OS estimates for the Bd arm. We use this in our EAG analyses, shown in Section 6.

Table 25 Comparison of Bd OS

OS	Gompertz (company's base case)	Exponential	Weibull	Log-logistic	Log-normal	Generalised gamma	Other studies/ experts[a]
10 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
20 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[a] See details about other studies' estimates and the estimates from experts in section 5.3.4 below.							

Cd:

- We agree with the company's approach.

4.2.6.4 Time on Treatment

- DBd: KM data from CASTOR trial up to four years, thereafter exponential
- Bd: KM data from CASTOR trial up to four years, thereafter exponential
- Cd: A hazard of 0.477 between PFS and time on treatment, based on TA457

EAG conclusions: While the company modelled time on treatment independent to PFS, they used the same distribution for consistency. We view this is a reasonable adjustment. Furthermore, they appropriately restricted the treatment duration in the model to avoid any time on treatment exceeding PFS.

4.2.6.5 Adverse events

- Adverse events of Grade 3 or higher reported in at least 5% of patients in any treatment arm were included in the economic model.
- In contrast to the original appraisal TA573, adverse event data for DBd were taken from the subcutaneous injection arm of the COLUMBA trial.
- For Bd and Cd, the company used the same probabilities of adverse events as in the original submission TA573 (from CASTOR and ENDEAVOR trials, respectively).

EAG conclusions: We consider the company's approach to estimating adverse event probabilities and the data sources used in the cost-effectiveness model are appropriate. We agree that the adverse event profile of DBd should reflect the current administration route of daratumumab in the UK NHS practice (subcutaneous).

4.2.7 Health related quality of life (HRQoL)

The company applied the same approach as in the original submission TA573 for incorporating HRQoL data in the cost-effectiveness analysis. Utilities were applied to each

health state and utility decrements due to adverse events were estimated based on the treatment-specific adverse event rates, their duration and associated disutilities.

For the base case, health state utilities for PFS and post-progression survival (PPS) were obtained from TA457 (ENDEAVOR) as shown in CS Table 46. These values were preferred by both the EAG and the appraisal committee in the original appraisal TA573. No changes were made to the utility impact of adverse events from those used in the original submission.

While additional HRQoL data from CASTOR was collected in pre- and post-progression beyond the original submission, these were not used to update the CDF revised model (see company's response to the EAG clarification question B6). As mentioned earlier (Section 3.2.3) the company intends to provide these data in the next stage of this appraisal.

EAG conclusions: The company's approach to estimating utilities is consistent with the original submission TA573 and therefore appropriate. Further information about the additional HRQoL data collected from CASTOR (which are currently being assessed by the company) would be helpful to assess whether they affect the cost-effectiveness results.

4.2.8 Resources and costs

In general, the company's resource use assumptions have not changed from those in the analysis at CDF entry. Unit costs have been updated for all drugs in the model, drug administration, monitoring, adverse events, and other resource use.

The economic model includes the following costs:

- Drug acquisition
- Drug administration and co-medication
- Subsequent treatment
- Follow up monitoring and care
- Adverse events; and
- Terminal care

The company's base case uses a simple Patient Access Scheme (PAS) discount for daratumumab and list prices for all drugs (CS Table 48). We present results including all available PAS/CAA agreements in a confidential addendum to this report.

Drug costs are informed by dosing of treatment regimens, which in turn, are dependent on patient characteristics including body weight (mean [redacted], from CASTOR trial) and/or body

surface area (1.87m^2, from CASTOR trial). The company base case assumptions regarding drug wastage and dose intensity (CS Table 49) are consistent with their original submission TA573. Drug administration costs are summarised in CS Table 50 and co-medications in CS Table 52.

The model included costs associated with subsequent treatments, using a simple approach wherein a proportion of patients who discontinued from the initial modelled treatment continue to a basket of potential treatment options. This basket consisted of treatments which were received by patients in CASTOR, with adjustment for treatments not available in England. The proportion of patients receiving subsequent treatment was updated and obtained from the last data cut of CASTOR for DBd and Bd (87% for DBd and 94% for Bd). For Cd, the company assumed the lower of the proportions observed for DBd and Bd (i.e., 87%). The economic model assumed the same duration of subsequent treatment (9 months) for each RRMM treatment as in the original submission TA573. The distribution of subsequent treatment per treatment arm is presented in CS Table 53 and the treatment acquisition costs of subsequent treatments are summarised in CS Table 55.

Consistent with the original submission, the company assumed the same routine follow-up care costs per health state for all the comparators. Costs of treating the included adverse events (CS Table 58) and a one-time cost of £8,014 for terminal care at death were also included in the economic model.

The EAG noted a few inconsistencies in the cost inputs for: intravenous drug administration, oral drug initiation, co-medication unit costs, cost of haematologist, blood type determination, and administration cost for oral treatment initiation. The company corrected these estimates in their responses to clarification questions B10(b), B10(c), B11(a), B11(b), B13(b), B15, and B16 respectively and updated their revised model. Further details on the company's corrections are discussed in Section 5.3. While none of these corrections individually resulted in significant changes to the total costs, collectively, they reduced the base case ICER from [redacted] to [redacted]. Finally, NICE recommends the use of eMIT prices for drugs to improve transparency. Therefore, in our additional analyses (in Section 6), the EAG use the eMIT prices for the following drugs shown below in Table 26.

Table 26 Drug prices used in the EAG base case versus company's base case

Comparator	Pack Size	Strength	Company base case price (MIMS)	EAG base case price (eMIT)
Bortezomib	1	3.5mg	£533.67	£213.27
Dexamethasone	50	8mg	£120.01	£27.15
Thalidomide	28	50mg	£298.48	£297.35
Prednisolone	30	4mg	£6.19	£7.37 (eMIT price at 5mg, no price found for 4mg)
Paracetamol	100	500mg	£3.78	£0.47
Methylprednisolone	1	125mg	£4.75	£7.60
Aciclovir	56	400mg	£2.66	£1.78
Antiemetics (Domperidone)	100	10mg	£2.23	£1.09
Source: Draws on information from CS Table 48 and CS Table 52				

EAG conclusions:

According to our clinical experts, the modelled distribution of subsequent treatments showed in CS Table 55 is not reflective of UK practice as the majority of patients is currently being treated with CDF approved drugs. We acknowledge that the NICE process restricts what can be included as subsequent treatment by not allowing the inclusion of treatments in the CDF. In these circumstances, we consider the company's assumption reasonable with no other plausible scenarios that we can possibly run.

We note a minor inconsistency between the estimates from the EAG clinical experts and the company's modelled estimates regarding the frequency of routine follow-up care of patients with RRMM. However, we consider that this will not affect the model results significantly as the costs of these resources are negligible and will be balanced between the treatment arms.

The company's correction of the cost inputs, identified by the EAG in the clarification response stage of this appraisal, lowered the base case ICER marginally from [redacted] to [redacted]. In summary, the EAG considers that the company's approach to costing is consistent with the original submission TA573, related NICE guidance and therefore appropriate.

5 COST EFFECTIVENESS RESULTS

5.1 Company's cost effectiveness results

The company's cost effectiveness results with the committee's preferred assumptions at CDF entry (provided in response to clarification question B5) reported an ICER of [redacted] per QALY for DBd compared to Bd, and dominance of DBd over Cd (see Table 27). Their deterministic base case results for the current appraisal are reported in CS Section B.3.8.1, Tables 63 and 64. Revised versions of these tables were provided in response to EAG clarification questions B10b, B10c, B11a, B11b, B13b, B15 and B16 and are reproduced below in Table 28.

Table 27 Cost effectiveness results at CDF entry (discounted at 3.5%; PAS price for daratumumab)

	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER vs comparator
Comparison with Bd					
Bd	[redacted]	[redacted]			
DBd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Comparison with Cd					
Cd	[redacted]	[redacted]			
DBd	[redacted]	[redacted]	[redacted]	[redacted]	Dominates

Source: Clarification response B5 and EAG replication from company model submitted 26/09/2022
Bd = bortezomib plus dexamethasone; Cd = carfilzomib plus dexamethasone; DBd = daratumumab plus bortezomib plus dexamethasone; ICER = incremental cost-effectiveness ratio; PAS = patient access scheme; QALYs = quality-adjusted life-years.

Table 28 Company's revised base case results at CDF review (discounted at 3.5%; PAS price for daratumumab)

	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER vs comparator
Comparison with Bd					
Bd	[redacted]	[redacted]			
DBd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Comparison with Cd					
Cd	[redacted]	[redacted]			
DBd	[redacted]	[redacted]	[redacted]	[redacted]	Dominates

Source: Reproduced from clarification responses Tables 27 and 28
Bd = bortezomib plus dexamethasone; Cd = carfilzomib plus dexamethasone; DBd = daratumumab plus bortezomib plus dexamethasone; ICER = incremental cost-effectiveness ratio; PAS = patient access scheme; QALYs = quality-adjusted life-years.

The deterministic ICERs for the company's new base case are [redacted] per QALY gained for the comparison with Bd. Cd is dominated by DBd as the latter yields lower costs and more QALYs. These results include all the revisions listed in Section 4.2.2 above, the corrections made in response to EAG clarification questions B10b, B10c, B11a, B11b, B13b, B15 and B16 and the PAS price discount of [redacted] for daratumumab. The EAG replicated these reported ICERs using the revised version of the company's model submitted with their response to clarification questions on 26th September 2022.

We note that these analyses are conducted at list prices for all drugs except daratumumab, so do not reflect agreed discounts that are available within the NHS. We present results including PAS price discounts for comparators and subsequent treatments in a confidential addendum to this report.

5.2 Company's sensitivity analyses

5.2.1 Deterministic sensitivity analyses

One-way deterministic sensitivity analyses are reported in tornado plots. CS Figures 40 and 41 report the original analyses while Figures 3 and 4 of the company's clarification responses report the revised deterministic sensitivity analyses. These results suggest that the ICERs are most sensitive to changes in OS assumptions.

5.2.2 Scenario analysis

The company's scenario analyses are reported in CS Tables 68-70. Shortening the model time horizon had the greatest impact in the model results, followed by not adjusting the OS to the subsequent treatments not available in England. We consider that there are other plausible scenarios (not run by the company) that would also have a substantial impact on the cost-effectiveness results. See section 6 below for additional EAG analysis.

5.2.3 Probabilistic sensitivity analysis

The company report probabilistic sensitivity analysis (PSA) results in CS section B.3.9.1 (original analysis) and in Table 29, Figure 5, and Figure 6 of the company's clarification responses (revised analysis). For the comparison with Bd, the reported probabilistic ICER [redacted]) is similar to the deterministic result [redacted]). For the comparison with Cd, the probabilistic results are consistent with the deterministic results as DBd dominates Cd (company's clarification responses, Table 29).

The EAG re-ran the PSA in the revised model and obtained consistent results compared to the deterministic ones: [redacted] per QALY for the comparison with Bd, and DBd dominates Cd.

5.3 Model validation and face validity check

5.3.1 Company's model validation

The company describes their approach to model validation in CS section B.3.11. The cost-effectiveness model was internally reviewed for quality-assurance, which included: validation of the logical structure of the model, mathematical formulas, sequences of calculations, model inputs and appropriateness of distributions used in PSA. Also, an evaluation of the face validity of predicted results was conducted.

Validation with two expert advisory boards was carried out to understand the RRMM treatment pathway, unmet need, clinical outcomes, diagnostic requirements, and the appropriateness of the survival analyses (adjustment and extrapolation).

The company compared PFS and time on treatment model predictions against the median PFS and time on treatment estimates from the clinical trials CASTOR and ENDEAVOR. CS Table 65 shows strong consistency between model predictions and CASTOR outcomes. We note that the median PFS and time on treatment from ENDEAVOR is slightly longer than the respective model predictions.

5.3.2 EAG model verification procedures

The EAG conducted a range of manual checks to verify model inputs, calculations, and outputs ('white box' tests) on the company model submitted on 12th August 2022:

- Checking parameter inputs against values in the CS, excel model and cited sources.
- Checking all model outputs against results cited in the CS, including the base case, PSA and DSA and company's scenarios.
- Checking the calculations within the "Model engine" sheet
- Running a range of tests by changing the input parameters and checking if results are plausible ('black box' tests)

Due to time constraints, we could not repeat all of the above checks on the revised company model that was submitted on 26th September 2022 as part of their response to the EAG clarification questions. We did complete the following tests on this model version:

- Re-running all of the company's results (including sensitivity analyses).

- Replicating the results from the model submitted on 12th August 2022 by applying the relevant changes to the revised model.
- Reproducing the results from the CDF entry model that was used as the basis for this submission (see Table 27 above).

The model is generally well-implemented, and the inconsistencies identified were resolved in the company's response to EAG clarification questions. In their updated version of the model submitted on 26th September 2022, the company amended the inputs and assumptions raised by the EAG in clarification questions B10b, B10c, B11a, B11b, B13b, B15 and B16.

5.3.2.1 Reproducing the results at CDF entry using the revised version of the model submitted by the company on 26th September 2022

As a response to EAG clarification question B5, the company included a new functionality in the Excel model submitted on 26th September 2022 allowing us to automatically revert the revised model inputs to the ones used in the original submission at the time of CDF entry. The original inputs were taken from the model version: ""ID974_daratumumab_ERG analysis_no PAS ACiC_Revised Base Case 2Aug2018_NoPAS.xlsm". However, as pointed out by the company, running this Excel functionality leads to slightly different results as compared to the original model (see Table 17 of the company's clarification responses).

Contrary to the company's response to clarification question B5, we were able to reproduce the same results as in the original model at CDF entry (ICER of [redacted] for DBd versus Bd). We ran the Excel functionality, analysed the list of changes provided by the company as response to clarification question B5(b) and implemented additional changes based on our own examination of the model. Appendix 4 presents the list of changes included in the company's Excel functionality and the additional changes that the EAG implemented to the revised model to obtain the results at CDF entry.

5.3.3 Validation of DBd survival data against SACT data

The Managed Access Agreement for the CDF review stipulates the collection of further overall survival data in daratumumab patients.[2] Sources of data collection stated in this document include the CASTOR trial as well as the SACT dataset.[2] See sections 3.3, 3.7, 3.8 and 4.2.6 above for more details on the SACT dataset and the comparison between CASTOR trial and SACT dataset.

The company did not include the SACT data in the economic model, neither did they conduct a scenario analysis testing the impact of baseline characteristics or survival outcomes from the SACT dataset. Nevertheless, they provided a comparison of the trial overall survival outcomes against the SACT results (see CS Figure 19, reproduced in Figure 6 above). This shows that mortality is higher for SACT than CASTOR patients. As previously discussed in section 4.2.3 above, the SACT population receiving daratumumab is on average older and therefore likely to be less fit than those in the CASTOR trial, which might explain the poorer survival. This suggests that the DBd results from the company's model (based on CASTOR overall survival inputs) may not be generalisable to routine NHS use.

5.3.4 Validation of survival outcomes against data from other studies

The company did not provide any comparisons of the extrapolated OS estimates with external data for the population of interest. In Table 29 below, we compare the company's life years (LY), and survival estimates for the intervention and comparators with several cost-effectiveness studies. These studies, except TA457, were identified through the systematic literature review of cost-effectiveness evaluations conducted by the company (CS Appendix G) and were selected based on the population of interest (adults with multiple myeloma who have had at least one prior line of therapy), interventions in comparison (DBd, Bd and Cd), country in which they were conducted (UK setting or similar) and outcomes available (LYs, OS estimates). TA457 was used by the Evidence Review Group in the original submission TA573 for cross-validation purposes.

Table 29 Comparison of LYs and OS estimates for DBd, Bd and Cd

Treatment	DBd			Bd			Cd		
Outcome	LYs	OS		LYs	OS		LYs	OS	
		10y	20y		10y	20y		10y	20y
Company's model	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TA695 (UK)[19]	6.62	19%	4%	-	-	-	-	-	-
Isatuximab (Sarclisa) (Canada)[58]	-	-	-	-	-	-	5.66 [c]	-	-
Dolph et al. 2021 (US)[59]	-	-	-	3.90 [b]	12%	2%	-	-	-
Zhang et al. 2018 (US)[60]	2.169 [b]	35%	1.743 [b]		8%	-	-	-	-
TA457 [d] (UK)[22]	-	-	-	3.34	12%	2%	5.87	-	-

[a] As discussed in section 4.1, DBd was not accepted by the committee as a comparator in TA695.
[b] Discounted at 3%
[c] Discounted at 1.5%
[d] Based on committees preferred assumptions (Weibull used to extrapolate OS)
Bd = bortezomib plus dexamethasone; Cd = carfilzomib plus dexamethasone; DBd = daratumumab plus bortezomib plus dexamethasone; Lys = life years; TA = technology appraisal.

Based on the above information, we note that:

- The company's 10-year OS estimate for DBd is comparable with the US based study by Zhang et al.[60] However, for Bd, other studies (Zhang et al.;[60] Dolph et al[59] and TA457[22]) show a higher proportion of patients alive at 10 and 20 years than the company's model. The estimates from these studies, ranging between 8%-12%, are consistent with the clinical expert feedback to the EAG.
- For Cd, the Canadian appraisal applied a discount rate of 1.5% which makes the comparison with the current model inappropriate.[58] Despite the company including the adjustment factor agreed in TA573, we note that TA457 shows higher estimates than the company's model.[22] This is potentially due to the company's underestimation of OS in the Bd arm (as discussed above) as the survival for Cd is modelled relative to Bd (as explained in section 4.2.6).

EAG conclusions on the company's model validation

- Our model checks did not identify any additional errors or inconsistencies in the company's model submitted on 26th September 2022.

- We believe that the company could have provided a more comprehensive validation, including cross validity checks against relevant cost-effectiveness studies and NICE technology appraisals.
- We expect the ICER to increase if SACT data were to be used in the model to extrapolate overall survival, however due to the limitations with the SACT dataset (as discussed in Section 3.3) it is not possible to accurately estimate its quantitative impact on the cost-effectiveness results.
- OS for Bd is potentially underestimated in the company's model (compared to other studies, as discussed above, and EAG expert clinical feedback), which is corroborated by the lower LYs predicted by the company compared to TA457 for Cd. Therefore, in the EAG preferred base case, we use exponential distribution to extrapolate OS in the Bd arm (see section 6 below for further EAG analyses).

5.4 EAG corrections to the company model

We have not identified additional errors or inconsistencies in the company's model apart from those described earlier (see section 5.3.2) and corrected by the company as part of their responses to EAG clarification questions. Therefore, we did not make any corrections to the updated version of the company's model.

5.5 EAG summary of key issues and additional analyses

A full summary of EAG observations on key aspects of the company's economic model and additional analyses is presented in Table 30.

Table 30 EAG summary of key issues and additional analyses

Aspect	Company analyses	EAG analyses (scenarios)	EAG preferred
Model structure and characteristics			
Population baseline characteristics	• Based on CASTOR: • Age: 62.6 years • Males: 59.1%	• Based on SACT • Age: [redacted] years • Males: [redacted]	SACT population baseline characteristics
Survival estimates			
Extrapolation of OS	DBd • Base case: Log-logistic • Scenario: Exponential Bd • Base case: Gompertz	DBd • Gompertz (pessimistic) • Log-normal (optimistic) • Weibull (based on expert advice) Bd • Exponential	DBd: Same as company Bd: Exponential Cd: Same as company

Aspect	Company analyses	EAG analyses (scenarios)	EAG preferred
	• Scenario: Weibull Cd • Base case: HR vs. Bd • No scenarios	Cd • No additional scenarios	
Extrapolation of PFS	DBd • Base case: KM up to 4 years + exponential • Scenario: KM up to 4 years + Weibull Bd • Base case: KM up to 4 years + exponential • Scenario: KM up to 4 years + Weibull Cd • Base case: HR vs. Bd • No scenarios	DBd • Exponential • Gompertz (company base case in TA573) Bd • KM up to 4 years + Log-logistic • Exponential • Log-logistic • Gompertz (company and EAG base case in TA573) Cd • No additional scenarios	Same as company
Extrapolation of TTD	DBd • Base case: KM up to 4 years + exponential • Scenario: KM up to 4 years + Weibull Bd • Base case: KM up to 4 years + exponential • Scenario: KM up to 4 years + Weibull Cd: • Base case: HR vs. PFS curve • No scenarios	DBd • Exponential • Gompertz (company base case in TA573) Bd • KM up to 4 years + Log-logistic • Exponential • Log-logistic • Gompertz (company and EAG base case in TA573) Cd • No additional scenarios	Same as company
Costs and resource use			
Drug costs	• Based on MIMS	• Based on eMIT (as recommended by NICE)	Based on eMIT
Bd = bortezomib plus dexamethasone; Cd = carfilzomib plus dexamethasone; DBd = daratumumab plus bortezomib plus dexamethasone; EAG = Evidence Assessment Group; HR = hazard ratio; KM = Kaplan Meier; OS=overall survival; PFS = progression free survival; SACT = Systemic Anti-Cancer Therapy; ToT = time on treatment			

6 EAG'S ADDITIONAL ANALYSES

6.1 Exploratory and sensitivity analyses undertaken by the EAG

We performed a range of additional scenario analyses on the company revised base case model based on the key aspects summarised in Table 30 above. Results of these analyses are based on the PAS price for daratumumab (Table 31).

Table 31 Additional analyses conducted by the EAG on the company's revised cost effectiveness model (discounted at 3.5%; PAS price for daratumumab)

Scenario		Comparator	Incremental		
			Costs	QALYs	ICER (£/QALY)
Company's revised model		Bd	[redacted]	[redacted]	[redacted]
		Cd			Dominates
Patient age and gender from SACT ([redacted], 59% males)		Bd	[redacted]	[redacted]	[redacted]
		Cd			Dominates
DBd - Extrapolation of OS	Gompertz	Bd	[redacted]	[redacted]	[redacted]
		Cd			Dominates
	Log-normal	Bd	[redacted]	[redacted]	[redacted]
		Cd			Dominates
	Weibull	Bd	[redacted]	[redacted]	[redacted]
		Cd			Dominates
Bd – Extrapolation of OS	Exponential	Bd	[redacted]	[redacted]	[redacted]
		Cd			Dominates
DBd and Bd - Extrapolation of PFS and ToT	Exponential	Bd	[redacted]	[redacted]	[redacted]
		Cd			Dominates
	Gompertz	Bd	[redacted]	[redacted]	[redacted]
		Cd			Dominates
Bd - Extrapolation of PFS and ToT	KM up to 4 years + Log-logistic	Bd	[redacted]	[redacted]	[redacted]
		Cd			Dominates
	Log-logistic	Bd	[redacted]	[redacted]	[redacted]
		Cd			Dominates
Drug costs: based on eMIT		Bd	[redacted]	[redacted]	[redacted]
		Cd			Dominates

Bd = bortezomib plus dexamethasone; Cd = carfilzomib plus dexamethasone; DBd = daratumumab plus bortezomib plus dexamethasone; eMIT = drugs and pharmaceutical electronic market information tool; ICER = incremental cost-effectiveness ratio; KM = Kaplan Meier; OS = overall survival; PAS = patient access scheme; PFS = progression free survival; QALYs = quality adjusted life years; SACT = Systemic Anti-Cancer Therapy; ToT = time on treatment

Table 31 shows that using the Gompertz curve to extrapolate OS in the DBd arm has the highest impact on the cost-effectiveness results (ICER increases from [redacted] to [redacted] per QALY versus Bd). Other scenarios that have a sizeable impact on the cost-effectiveness results are: Weibull extrapolation of OS in the DBd arm (ICER increases from [redacted] to [redacted] per QALY); Gompertz extrapolation of PFS and time on treatment in the DBd and Bd arms (ICER increases from [redacted] to [redacted] per QALY versus Bd); and exponential extrapolation of OS in the Bd arm (ICER increases from [redacted] to [redacted] per QALY versus Bd). The remaining

scenarios have less impact on the cost-effectiveness results (ICERs change by less than £4,000 per QALY).

None of the scenarios tested by the EAG changed the direction of the cost-effectiveness results for DBd against Cd. DBd yields lower costs and higher QALYs than Cd, i.e., DBd dominates Cd in all scenarios.

6.2 EAG's preferred assumptions

The EAG preferred model assumptions are as follows:

1. **Baseline age and gender of population**: [redacted] and 59.1% of males (based on SACT dataset).
2. **Extrapolation of OS for Bd**: Use of exponential parametric curve.
3. **Drug costs:** based on eMIT prices where available (as per NICE's recommendation).

6.2.1 Results from the EAG preferred model assumptions

Table 32 shows the cumulative cost-effectiveness results of applying the EAG preferred model assumptions to the company's revised base case. Incorporating the EAG's assumptions leads to an increase of the ICER from [redacted] to [redacted] per QALY for the comparison of DBd against Bd. For the comparison against Cd, DBd is dominant. These results include the PAS price of daratumumab, with other comparators and subsequent treatments at list price. We report results including all available PAS discounts in a confidential addendum to this report.

The assumption that has the biggest impact on the cost-effectiveness results is using an exponential distribution to extrapolate OS in the Bd arm.

Table 32 EAG's preferred model assumptions (discounted at 3.5%; PAS price for daratumumab)

Scenario	Comparator	Incremental		
		Costs	QALYs	ICER (£/QALY)
Company's revised model	Bd	[redacted]	[redacted]	[redacted]
	Cd	[redacted]	[redacted]	Dominates
+ Patient age and gender from SACT ([redacted], 59% males)	Bd	[redacted]	[redacted]	[redacted]
	Cd	[redacted]	[redacted]	Dominates
+ Bd – Extrapolation of OS (Exponential)	Bd	[redacted]	[redacted]	[redacted]
	Cd	[redacted]	[redacted]	Dominates
+ Drug costs: based on eMIT	Bd	[redacted]	[redacted]	[redacted]
	Cd	[redacted]	[redacted]	Dominates
EAG preferred base case	Bd	[redacted]	[redacted]	[redacted]
	Cd	[redacted]	[redacted]	Dominates

Bd = bortezomib plus dexamethasone; Cd = carfilzomib plus dexamethasone; eMIT = drugs and pharmaceutical electronic market information tool; ICER = incremental cost-effectiveness ratio;

OS = overall survival; PAS = patient access scheme; QALYs = quality adjusted life years; SACT = Systemic Anti-Cancer Therapy.

6.2.2 Scenario analyses conducted on the EAG preferred model assumptions

We performed a range of scenario analyses on the EAG base case. We replicate the company's scenarios, as previously described in section 5.2.2 (Table 33 below), and conduct additional scenarios (as shown in Table 34 below).

The ICER of the EAG preferred model is most sensitive to the following assumptions: Gompertz extrapolation of OS, PFS and time on treatment in both DBd and Bd arms, Weibull extrapolation of OS in the DBd arm, shorter time horizons and alternative discount rates. We note that DBd dominates Cd in all scenarios except when Gompertz is used to extrapolate OS in the DBd arm: in this scenario DBd is less costly and less effective with an ICER of [redacted] per QALY.

Table 33 Company's scenario analyses using the EAG's preferred model assumptions (discounted at 3.5%; PAS price for daratumumab)

Scenario	Comparator	Incremental		
		Costs	QALYs	ICER (£/QALY)
EAG's preferred base case	Bd	[redacted]	[redacted]	[redacted]
	Cd	[redacted]	[redacted]	Dominates
Unadjusted OS	Bd	[redacted]	[redacted]	[redacted]
	Cd	[redacted]	[redacted]	Dominates
PFS/ToT extrapolation: KM+Weibull for DBd and Bd	Bd	[redacted]	[redacted]	[redacted]
	Cd	[redacted]	[redacted]	Dominates
OS extrapolation: Weibull for Bd	Bd	[redacted]	[redacted]	[redacted]
	Cd	[redacted]	[redacted]	Dominates
OS extrapolation: Exponential for DBd	Bd	[redacted]	[redacted]	[redacted]
	Cd	[redacted]	[redacted]	Dominates
Subsequent treatment duration: 13 months	Bd	[redacted]	[redacted]	[redacted]
	Cd	[redacted]	[redacted]	Dominates
Subsequent treatment duration: 15 months	Bd	[redacted]	[redacted]	[redacted]
	Cd	[redacted]	[redacted]	Dominates
Time horizon: 5 years	Bd	[redacted]	[redacted]	[redacted]
	Cd	[redacted]	[redacted]	Dominates
Time horizon: 10 years	Bd	[redacted]	[redacted]	[redacted]
	Cd	[redacted]	[redacted]	Dominates
Time horizon: 20 years	Bd	[redacted]	[redacted]	[redacted]
	Cd	[redacted]	[redacted]	Dominates
Allow vial sharing	Bd	[redacted]	[redacted]	[redacted]
	Cd	[redacted]	[redacted]	Dominates
Dose intensity option off	Bd	[redacted]	[redacted]	[redacted]
	Cd	[redacted]	[redacted]	Dominates
Discount rate: Costs 0%, Benefits 0%	Bd	[redacted]	[redacted]	[redacted]
	Cd	[redacted]	[redacted]	Dominates
Discount rate: Costs 0%, Benefits 1.5%	Bd	[redacted]	[redacted]	[redacted]
	Cd	[redacted]	[redacted]	Dominates
Discount rate: Costs 0%, Benefits 6%	Bd	[redacted]	[redacted]	[redacted]
	Cd	[redacted]	[redacted]	Dominates
Discount rate: Costs 1.5%, Benefits 0%	Bd	[redacted]	[redacted]	[redacted]
	Cd	[redacted]	[redacted]	Dominates
Discount rate: Costs 1.5%, Benefits 1.5%	Bd	[redacted]	[redacted]	[redacted]
	Cd	[redacted]	[redacted]	Dominates
Discount rate: Costs 1.5%, Benefits 6%	Bd	[redacted]	[redacted]	[redacted]
	Cd	[redacted]	[redacted]	Dominates
Discount rate: Costs 6%, Benefits 0%	Bd	[redacted]	[redacted]	[redacted]
	Cd	[redacted]	[redacted]	Dominates
Discount rate: Costs 6%, Benefits 1.5%	Bd	[redacted]	[redacted]	[redacted]
	Cd	[redacted]	[redacted]	Dominates
Discount rate: Costs 6%, Benefits 6%	Bd	[redacted]	[redacted]	[redacted]
	Cd	[redacted]	[redacted]	Dominates

Bd = bortezomib plus dexamethasone; Cd = carfilzomib plus dexamethasone; DBd = daratumumab plus bortezomib plus dexamethasone; EAG = Evidence Assessment Group; ICER = incremental cost-effectiveness ratio; KM = Kaplan Meier; OS = overall survival; PAS = patient access scheme; PFS = progression free survival; QALY = quality adjusted life years; ToT = time on treatment.

Table 34 Additional scenario analyses using the EAG's preferred model assumptions (discounted at 3.5%; PAS price for daratumumab)

Scenario		Comparator	Incremental		
			Costs	QALYs	ICER (£/QALY)
EAG's preferred base case		Bd	[redacted]	[redacted]	[redacted]
		Cd	[redacted]	[redacted]	Dominates
Patient age and gender from CASTOR		Bd	[redacted]	[redacted]	[redacted]
		Cd	[redacted]	[redacted]	Dominates
DBd - Extrapolation of OS	Gompertz	Bd	[redacted]	[redacted]	[redacted]
		Cd	[redacted]	[redacted]	[redacted]
	Log-normal	Bd	[redacted]	[redacted]	[redacted]
		Cd	[redacted]	[redacted]	Dominates
	Weibull	Bd	[redacted]	[redacted]	[redacted]
		Cd	[redacted]	[redacted]	Dominates
Bd – Extrapolation of OS	Gompertz	Bd	[redacted]	[redacted]	[redacted]
		Cd	[redacted]	[redacted]	Dominates
DBd and Bd - Extrapolation of PFS and ToT	Exponential	Bd	[redacted]	[redacted]	[redacted]
		Cd	[redacted]	[redacted]	Dominates
	Gompertz	Bd	[redacted]	[redacted]	[redacted]
		Cd	[redacted]	[redacted]	Dominates
Bd - Extrapolation of PFS and ToT	KM up to 4 years + Log-logistic	Bd	[redacted]	[redacted]	[redacted]
		Cd	[redacted]	[redacted]	Dominates
	Log-logistic	Bd	[redacted]	[redacted]	[redacted]
		Cd	[redacted]	[redacted]	Dominates
Drug costs: based on MIMS		Bd	[redacted]	[redacted]	[redacted]
		Cd	[redacted]	[redacted]	Dominates

SW 'Southwest quadrant' ICER: i.e., DBd less costly and less effective than Cd

Bd = bortezomib plus dexamethasone; Cd = carfilzomib plus dexamethasone; DBd = daratumumab plus bortezomib plus dexamethasone; EAG = Evidence Assessment Group; ICER = incremental cost-effectiveness ratio; KM = Kaplan Meier; OS = overall survival; PAS = patient access scheme; PFS = progression free survival; QALYs = quality adjusted life years; ToT = time on treatment.

6.3 Conclusions on the cost effectiveness evidence

The company's current cost-effectiveness analysis is an updated version of that used in the original appraisal TA573. The model structure, and most of the inputs and assumptions have not changed since last time. Therefore, our critique is focused on the parameters that were updated and that are listed in section 4.2.2 above.

The key issues identified by the EAG related to the cost-effectiveness evidence are:

1. **The difference between real-world SACT dataset and CASTOR trial estimates for OS in the DBd arm**. The company's base case uses OS estimates from CASTOR, however the SACT data shows lower survival for patients receiving DBd in UK NHS clinical practice. We note that the SACT patients are older than those in the trial, which suggests that CASTOR data may not be generalisable to routine NHS

practice. Therefore, we used the baseline characteristics (age and gender distribution) from the SACT dataset in the EAG preferred base case, which increases the ICER. We expect that using the SACT survival data in the current model would increase the ICER considerably more.

2. **Extrapolation of OS in the Bd arm**. The company's base case used a Gompertz distribution to extrapolate OS in the Bd arm, which seems to underestimate the expected survival of Bd compared to other cost-effectiveness studies included in the EAG validation (see section 5.3.4 above) and EAG expert clinical feedback. In the EAG preferred base case, we use the exponential distribution as it provides a good statistical fit and predicts a survival rate of 11.6% at 10 years.

In addition to the above issues, we also noted that the company collected additional HRQoL data from the CASTOR trial, although these were not updated in the current CDF revised model. For transparency and completeness, we consider that the additional HRQoL data should be presented, and a scenario conducted to assess its impact on the overall cost-effectiveness results.

The incorporation of the EAG's preferred assumptions in the economic model leads to an increase in the ICER for DBd versus Bd from [redacted] to [redacted] per QALY using the PAS price of daratumumab (and list prices for other drugs). The EAG preferred ICER is most sensitive to changes in assumptions related to: Gompertz extrapolations of OS, PFS and time on treatment in both DBd and Bd arms, Weibull extrapolation of OS in the DBd arm, shorter time horizons, and alternative discount rates.

However, we note that the company model and EAG base case and scenarios are not capable of capturing the underlying uncertainty raised by the difference in survival observed between real world evidence and trial data. The short follow-up of SACT dataset combined with the lack of data on prognostic factors and the absence of real-world data for patients treated with Bd and Cd are some of the reasons that hamper the use of real world data in the cost-effectiveness model.

7 SEVERITY

The company conducted a severity analysis, using the NICE recommended QALY shortfall calculation. Inputs for the calculation, shown in CS Tables 59 and 60, were obtained from: i) the CASTOR trial (cohort characteristics including population starting age and sex distribution and OS extrapolation), ii) TA457 (for health state utilities), and iii) UK Life tables and sex and age adjusted utilities based on Hernandez Alava et al 2022. The results of the QALY shortfall analysis, presented in CS Table 61, reported a proportional shortfall of 25%. This implied that DBd did not meet the criteria for a severity weight as the proportional shortfall was less than 85%.

EAG conclusions:

- We note an error in the calculations of the QALY shortfall in CS Table 61.
- We have not identified any errors in the calculations of the QALY shortfall in the company's revised version of the model submitted on the 26th September 2022 (see Table 35 below).
- We conclude that the intervention does not meet the criteria for applying a severity modifier for the company's and EAG base case (proportional shortfall <85%).

Table 35 QALY shortfall analysis

Treatment	Remaining QALYS without disease	Remaining QALYS with disease	Absolute shortfall	Proportional shortfall	QALY weight
Company's base case analysis					
DBd	11.77	[redacted]			
Bd		[redacted]	[redacted]	[redacted]	1.00
Cd		[redacted]	[redacted]	[redacted]	1.00
50/50 Bd Cd		[redacted]	[redacted]	[redacted]	1.00
EAG preferred assumptions					
DBd	9.10	[redacted]			
Bd		[redacted]	[redacted]	[redacted]	1.00
Cd		[redacted]	[redacted]	[redacted]	1.00
50/50 Bd Cd		[redacted]	[redacted]	[redacted]	1.00
Source: produced by the EAG from the company's revised model					

8 References

1. National Institute for Health and Care Excellence (NICE). Daratumumab with bortezomib and dexamethasone for previously treated multiple myeloma. Technology appraisal guidance [TA573] 2019 [updated 10 April. Available from: https://www.nice.org.uk/guidance/ta573.
2. National Institute for Health and Care Excellence. Cancer Drugs Fund. Managed Access Agreement. Daratumumab with bortezomib and dexamethasone for previously treated multiple myeloma [TA573], 2019.
3. Cancer Research UK. Myeloma incidence statistics. 2022 [Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/myeloma/incidence accessed 21 September 2022.
4. Cancer Research UK. What is myeloma? 2022 [accessed 21 September 2022.
5. 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(18):4691-5. doi: 10.1182/blood-2010-10-299487
6. NHS. Overview - Multiple myeloma 2021 [Available from: https://www.nhs.uk/conditions/multiple-myeloma/ accessed 21 September 2022.
7. Palumbo A, Rajkumar SV, San Miguel JF, et al. International Myeloma Working Group consensus statement for the management, treatment, and supportive care of patients with myeloma not eligible for standard autologous stem-cell transplantation. *J Clin Oncol* 2014;32(6):587-600. doi: 10.1200/JCO.2013.48.7934
8. Cancer Research UK. Myeloma survival statistics 2020 [Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/myeloma/survival#heading-Zero accessed 6 June 2022.
9. Hulin C, Hansen T, Heron L, et al. Living with the burden of relapse in multiple myeloma from the patient and physician perspective. *Leukemia Research* 2017
10. Parsons JA, Greenspan NR, Baker NA, et al. Treatment preferences of patients with relapsed and refractory multiple myeloma: a qualitative study. *BMC Cancer* 2019;19(1):264. doi: 10.1186/s12885-019-5467-x [published Online First: 2019/03/27]
11. He J, Duenas A, Collacott H, et al. Patient Perceptions Regarding Multiple Myeloma and Its Treatment: Qualitative Evidence from Interviews with Patients in the United Kingdom, France, and Germany. *Patient* 2021;14(5):613-23. doi: 10.1007/s40271-021-00501-7 [published Online First: 2021/03/10]
12. Terpos E, Mikhael J, Hajek R, et al. Management of patients with multiple myeloma beyond the clinical-trial setting: understanding the balance between efficacy, safety and tolerability, and quality of life. *Blood Cancer J* 2021;11(2):40. doi: 10.1038/s41408-021-00432-4 [published Online First: 2021/02/20]
13. Myeloma UK. Measuring patient preferences. An exploratory study to determine how patient preferences data could be used in health technology assessment (HTA). Project report., 2019.
14. LeBlanc MR, LeBlanc TW, Leak Bryant A, et al. A Qualitative Study of the Experiences of Living With Multiple Myeloma. *Oncol Nurs Forum* 2021;48(2):151-60. doi: 10.1188/21.Onf.151-160 [published Online First: 2021/02/19]
15. Gupta S, Clancy Z, Doane MJ. Assessing patient-reported outcomes and work productivity along the multiple myeloma (MM) patient journey. *Value in Health* 2018;21
16. 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. *Supportive Care in Cancer* 2013;21(2):599-607.
17. Kurtin S, Lilleby K, Jacy Spong R. Caregivers of multiple myeloma survivors. *Clinical journal of oncology nursing* 2013;17(6):25.

18. 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. *Psycho-oncology* 2011;20(1):88-97.
19. National Institute for Health and Care Excellence (NICE). Carfilzomib with dexamethasone and lenalidomide for previously treated multiple myeloma. Technology appraisal guidance [TA695] 2021 [Available from: https://www.nice.org.uk/guidance/ta695.
20. National Institute for Health and Care Excellence (NICE). Lenalidomide plus dexamethasone for multiple myeloma after 1 treatment with bortezomib. Technology appraisal guidance [TA586] 2019 [Available from: https://www.nice.org.uk/guidance/ta586.
21. National Institute for Health and Clinical Excellence (NICE). NICE Technology Appraisal Guidance 129: Bortezomib monotherapy for relapsed multiple myeloma, 2007.
22. National Institute for Health and Care Excellence (NICE). NICE Technology appraisal guidance 457: Carfilzomib for previously treated multiple myeloma 2017 [Available from: https://www.nice.org.uk/guidance/ta457 accessed January 2017.
23. National Institute for Health and Care Excellence (NICE). Carfilzomib for previously treated multiple myeloma. Technology appraisal guidance [TA657] 2020 [Available from: https://www.nice.org.uk/guidance/ta657.
24. Janssen. DARZALEX (daratumumab) 20 mg/ml concentrate for solution for infusion. Summary of Product Characteristics, 2022.
25. Janssen. DARZALEX (daratumumab), 1,800 mg solution for injection. Summary of Product Characteristics, 2022.
26. Mateos MV, Nahi H, Legiec W, et al. Subcutaneous versus intravenous daratumumab in patients with relapsed or refractory multiple myeloma (COLUMBA): a multicentre, open-label, non-inferiority, randomised, phase 3 trial. *Lancet Haematol* 2020;7(5):e370-e80. doi: 10.1016/S2352-3026(20)30070-3 [published Online First: 2020/03/28]
27. Landgren O, Iskander K. Modern multiple myeloma therapy: deep, sustained treatment response and good clinical outcomes. *Journal of Internal Medicine* 2017
28. National Institute for Health and Care Excellence. Daratumumab with bortezomib for previously treated multiple myeloma. Appraisal consultation document, 2018.
29. Kumar S, Paiva B, Anderson KC, et al. International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma. *Lancet Oncol* 2016;17(8):e328-46. doi: 10.1016/S1470-2045(16)30206-6
30. Palumbo A, Chanan-Khan A, Weisel K, et al. Daratumumab, Bortezomib, and Dexamethasone for Multiple Myeloma. *N Engl J Med* 2016;375(8):754-66. doi: 10.1056/NEJMoa1606038
31. Dimopoulos MA, Moreau P, Palumbo A, et al. Carfilzomib and dexamethasone versus bortezomib and dexamethasone for patients with relapsed or refractory multiple myeloma (ENDEAVOR): a randomised, phase 3, open-label, multicentre study. *Lancet Oncol* 2016;17(1):27-38. doi: 10.1016/S1470-2045(15)00464-7
32. Dimopoulos M, Quach H, Mateos MV, et al. Carfilzomib, dexamethasone, and daratumumab versus carfilzomib and dexamethasone for patients with relapsed or refractory multiple myeloma (CANDOR): results from a randomised, multicentre, open-label, phase 3 study. *Lancet* 2020;396(10245):186-97. doi: 10.1016/S0140-6736(20)30734-0 [published Online First: 2020/07/20]
33. Grosicki S, Simonova M, Spicka I, et al. Once-per-week selinexor, bortezomib, and dexamethasone versus twice-per-week bortezomib and dexamethasone in patients with multiple myeloma (BOSTON): a randomised, open-label, phase 3 trial. *Lancet* 2020;396(10262):1563-73. doi: 10.1016/S0140-6736(20)32292-3 [published Online First: 2020/11/16]
34. Lu J, Fu W, Li W, et al. Daratumumab, Bortezomib, and Dexamethasone Versus Bortezomib and Dexamethasone in Chinese Patients with Relapsed or Refractory

Multiple Myeloma: Phase 3 LEPUS (MMY3009) Study. *Clin Lymphoma Myeloma Leuk* 2021;21(9):e699-e709. doi: 10.1016/j.clml.2021.04.012 [published Online First: 2021/06/11]
35. Moreau P, Dimopoulos MA, Mikhael J, et al. Isatuximab, carfilzomib, and dexamethasone in relapsed multiple myeloma (IKEMA): a multicentre, open-label, randomised phase 3 trial. *Lancet* 2021;397(10292):2361-71. doi: 10.1016/s0140-6736(21)00592-4 [published Online First: 2021/06/08]
36. Richardson PG, Oriol A, Beksac M, et al. Pomalidomide, bortezomib, and dexamethasone for patients with relapsed or refractory multiple myeloma previously treated with lenalidomide (OPTIMISMM): a randomised, open-label, phase 3 trial. *Lancet Oncol* 2019;20(6):781-94. doi: 10.1016/s1470-2045(19)30152-4 [published Online First: 2019/05/18]
37. Pantani L, Zamagni E, Zannetti BA, et al. Bortezomib and dexamethasone as salvage therapy in patients with relapsed/refractory multiple myeloma: analysis of long-term clinical outcomes. *Ann Hematol* 2014;93(1):123-8. doi: 10.1007/s00277-013-1828-8 [published Online First: 2013/07/19]
38. Yoo KH, Gang GW, Yi JH, et al. P975: Interim Analysis of Phase II Study of Daratumumab in Combination with Bortezomib and Dexamethasone in Patients with Multiple Myeloma who Received 1 Prior Line of Therapy (KMM1906). European Hematology Association (EHA) Congress 2022: HemaSphere: Abstract Book for the 27th Congress of the European Hematology Association., 2022.
39. National Institute for Health and Care Excellence. NICE health technology evaluations: the manual, 2022.
40. Janssen. Data on file. Patient characteristics for 1 prior line subgroup in CASTOR study, 2021.
41. National Institute for Health and Care Excellence. Single Technology Appraisal. Daratumumab in combination with bortezomib for treating relapsed or refractory multiple myeloma [ID974]. Committee Papers., 2018.
42. Corre J, Perrot A, Caillot D, et al. del(17p) without TP53 mutation confers a poor prognosis in intensively treated newly diagnosed patients with multiple myeloma. *Blood* 2021;137(9):1192-95. doi: 10.1182/blood.2020008346 [published Online First: 2020/10/21]
43. Centre for Reviews and Dissemination. Systematic reviews: CRD's guidance for undertaking reviews in health care. York Publishing Services Ltd.: CRD, 2009.
44. Palumbo A, Sezer O, Kyle R, et al. International Myeloma Working Group guidelines for the management of multiple myeloma patients ineligible for standard high-dose chemotherapy with autologous stem cell transplantation. *Leukemia* 2009;23(10):1716-30. doi: 10.1038/leu.2009.122
45. Daratumumab plus bortezomib and dexamethasone Versus bortezomib and dexamethasone alone in patients with previously treated multiple myeloma: overall survival results from the phase 3 CASTOR trial. 3rd European Myeloma Network (EMN) Meeting; 2022; Virtual.
46. Janssen. Statistical Analysis Plan. Phase 3 Study Comparing Daratumumab, Bortezomib, and Dexamethasone (DVd) vs Bortezomib and Dexamethasone (Vd) in Subjects With Relapsed or Refractory Multiple Myeloma. Amendment 1, 2016.
47. Janssen. Clinical Protocol. Phase 3 Study Comparing Daratumumab, Bortezomib and Dexamethasone (DVd) vs Bortezomib and Dexamethasone (Vd) in Subjects With Relapsed or Refractory Multiple Myeloma, 2014.
48. Dimopoulos MA, Moreau P, Terpos E, et al. Multiple myeloma: EHA-ESMO clinical practice guidelines for diagnosis, treatment and follow-up(†). *Ann Oncol* 2021;32(3):309-22. doi: 10.1016/j.annonc.2020.11.014 [published Online First: 2021/02/08]

49. NHS England and NHS Improvement. Daratumumab with bortezomib and dexamethasone for previously treated multiple myeloma – data review: Systemic anti-cancer therapy (SACT) Final Report., 2022.
50. Cope S, Toor K, Popoff E, et al. Critical Appraisal of Published Indirect Comparisons and Network Meta-Analyses of Competing Interventions for Multiple Myeloma. *Value Health* 2020;23(4):441-50. doi: 10.1016/j.jval.2019.11.003 [published Online First: 2020/04/25]
51. Kalita N, Pickett K, Lord J, et al. Daratumumab in combination with bortezomib and dexamethasone for treating relapsed or refractory multiple myeloma: A Single Technology Appraisal: SHTAC, 2018.
52. Mateos MV, Sonneveld P, Hungria V, et al. Daratumumab, Bortezomib, and Dexamethasone Versus Bortezomib and Dexamethasone in Patients With Previously Treated Multiple Myeloma: Three-year Follow-up of CASTOR. *Clin Lymphoma Myeloma Leuk* 2020;20(8):509-18. doi: 10.1016/j.clml.2019.09.623 [published Online First: 2020/06/03]
53. Phillippo D, Ades T, Dias S, et al. NICE DSU Technical Support Document 18: Methods for population-adjusted indirect comparisons in submissions to NICE, 2016.
54. Signorovitch JE, Sikirica V, Erder MH, et al. Matching-adjusted indirect comparisons: a new tool for timely comparative effectiveness research. *Value Health* 2012;15(6):940-7. doi: 10.1016/j.jval.2012.05.004 [published Online First: 2012/09/25]
55. National Institute for Health and Care Excellence (NICE). NICE DSU Technical Support Document 16: Adjusting Survival Time Estimates in the Presence of Treatment Switching. July 2014., 2014.
56. NHS NCRAS. Standing Cohort Study of Newly Diagnosed Multiple Myeloma (NDMM) Patients in England. Report v1.0. May 2022., 2022.
57. Public Health England. Data on File. Standing Cohort Study of newly diagnosed multiple myeloma (NDMM) patients in England. Report covering diagnoses between January 2015 to December 2019, with follow-up to September 2021 inclusive. , 2022.
58. Canadian Agency for Drugs and Technologies in Health (CADTH). To evaluate the eligibility for reimbursement of isatuximab, in combination with carfilzomib and dexamethasone for the treatment of patients with multiple myeloma who have received at least one prior therapy., 2022.
59. Dolph M TG, Leong H. Cost Effectiveness of Triplet Selinexor-Bortezomib-Dexamethasone (XVd) in Previously Treated Multiple Myeloma (MM) Based on Results from the Phase III BOSTON Trial. Cost Effectiveness of Triplet Selinexor-Bortezomib-Dexamethasone (XVd) in Previously Treated Multiple Myeloma (MM) Based on Results from the Phase III BOSTON Trial. . *Pharmacoeconomics* 2021;39(11):1309-25.
60. Zhang TT WS, Wan N, Zhang L, Zhang Z, Jiang J. Cost-effectiveness of Daratumumab-based Triplet Therapies in Patients With Relapsed or Refractory Multiple Myeloma. *Clin Ther* 2018;40(7):1122-39.

9 Appendices

Appendix 1

Table 36 EAG appraisal of systematic review methods

Systematic review components and processes	EAG response (Yes, No, Unclear)	EAG comments
Was the review question clearly defined using the PICOD framework or an alternative?	See EAG comments	CS section B.2.1 provides the research question. The only research design it explicitly refers to is RCTs. However, the research question in CS Appendix D.1.1 refers to "RCT and non-RCT evidence" and CS section B.2.1 goes onto describe "non-RCT publications" taken into consideration.
Were appropriate sources of literature searched?	Yes	There was good coverage of appropriate sources of evidence, including grey literature (CS Appendix D.1.1).
What time period did the searches span and was this appropriate?	Unclear	The clinical effectiveness search for RCTs has been updated five times since the last search in the original CS. The last search for RCTs was performed on 16 May 2022 and for non-RCT studies on 2 March 2022 (CS Appendix D.1.1) No date limits were reported in any of the search strings. It is therefore unclear whether: i) databases were searched from inception, ii) there are any gaps in coverage between updates. Assuming there are no gaps in coverage then the search is relatively up to date at 3 months (RCTs) and 5 months (non-RCTs) old (CS Appendix D.1.1).
Were appropriate search terms used and combined correctly?	Yes	All the strategies were broad in that they did not include interventions or comparators. The searches in the original CS were not limited by study design but the update searches did include search strings for non-randomised studies, and separately for RCTs. A published RCT filter was not used, but it is unlikely that studies have been missed as a result (CS Appendix D.1.1).
Were inclusion and exclusion criteria specified? If so, were these criteria appropriate and relevant to the decision problem?	Yes Yes	The eligibility criteria for the systematic review in the original CS were modified for the company's CDF review submission (CS Appendix D Table 27), e.g. narrower population (one prior treatment regimen versus at least one prior treatment) but broader study design (RCTs and non-RCT studies versus RCTs only). Interventions specified in the inclusion criteria were: DBd, Bd, and Cd, which are relevant 2nd line treatments (see section 2.2.1). The modified inclusion and exclusion criteria are appropriate for the decision problem addressed in the company's CDF review submission.

Were study selection criteria applied by two or more reviewers independently?	Yes	Two independent investigators selected titles and abstracts, with disagreements resolved by discussion or arbitration by a third investigator (CS Appendix D.1.3.1) Full-text articles were reviewed by one investigator and all publications excluded were reviewed by a second investigator (CS Appendix D.1.3.2)
Was data extraction performed by two or more reviewers independently?	No	Data were extracted by one investigator and were checked against source publication by a second investigator. Discrepancies were resolved with a third investigator if necessary (CS Appendix D.1.4). The EAG considers this acceptable.
Was a risk of bias assessment or a quality assessment of the included studies undertaken? If so, which tool was used?	Yes	Risk of bias assessment was performed using the CRD assessment tool (CS Table 17).[43]
Was risk of bias assessment (or other study quality assessment) conducted by two or more reviewers independently?	No	Risk of bias was assessed by one investigator and checked by a second. The EAG considers this acceptable.
Is sufficient detail on the individual studies presented?	Yes	CS sections B.2.2 to B.2.7; CS appendices D to F.
If statistical evidence synthesis (e.g. pairwise meta-analysis, ITC, NMA) was undertaken, were appropriate methods used?	Yes	NMA structure and coding were the same as used in the original assessment for TA573 and are fit for purpose (CS section B.2.10 and CS appendix D). An unanchored MAIC was conducted using appropriate methods but is considered undependable due to limitations of the available data.
CS = company submission; Bd = bortezomib + dexamethasone; Cd = carfilzomib + dexamethasone; CDF = Cancer Drugs Fund; CRD = Centre for Reviews and Dissemination; DBd = daratumumab + bortezomib + dexamethasone; EAG = Evidence Assessment Group; ITC = indirect treatment comparison; NMA = network meta-analysis; MAIC = matching-adjusted indirect comparison; PICOD = population, intervention, comparator, outcomes, design; RCT = randomised controlled trial.		

Appendix 2

Table 37 CASTOR trial outcomes

Outcome specified in the scope and/ or decision problem	Outcomes reported in the CS (CASTOR trial)	Median follow-up (months)	Whole trial	1PL subgroup	Used in NMA of 1PL patients	Used in base case economic model (1PL patients)
OS	OS	*26.9*	□	□	—	—
		72.6[a]	□	□	□	—
	OS adjusted for subsequent treatment	72.6	—	□	—	□[b]
	OS subgroup analyses	72.6	□	—	—	—
PFS	PFS (primary outcome)	*26.9*	□	—	—	—
		47	—	□[c]	—	—
		50.2[d,e]	□	□	□	□[f]
Time to next treatment[g]	Time to next therapy	72.6	□	—	—	—
TTD	TTD	*26.9*	—	□	—	—
		50.2	—	□	—	□
Response rates, including Minimal Residual Disease (MRD) negativity	sCR	*26.9*	□	—	—	—
		50.2	—	□	—	—
	CR	*26.9*	□	—	—	—
		50.2	—	□	—	—
	VGPR	26.9	□	—	—	—
		50.2	—	□	—	—
	PR	50.2	—	□	—	—
	ORR	*26.9*	□	□	□	—
		50.2	—	□[h]	—	—
	VGPR or better	*26.9*	□	□	□	—
		50.2	—	□[h]	—	—
	CR or better	*26.9*	□	□	□	—
		50.2	—	□[h]	—	—
	MRD negativity	50.2	□	□	—	—

		72.6	[redacted]	—	—	—
AEs	AEs (safety and tolerability)	72.6	[redacted]	[redacted][i]	—	[redacted][j]
HRQoL	EORTC QLQ-C30	*26.9*	[redacted][k]	—	—	—
	EQ-5D-5L	*26.9*	[redacted][k]	—	—	—[l]
Outcomes not specified in scope or decision problem	PFS on subsequent therapy	50.2 72.6	— [redacted]	[redacted] —	— —	— —
	Treatment duration	72.6	[redacted]	—	—	—

Source: CS sections B.2.6.2 to B.2.6.7, B.2.7.1, B.2.7.2, B.2.11, B.2.12; CS Tables 18 to 24, CS Appendix D sections 3.2.2 and 3.2.4 and Tables 37 to 39; Appendix E, Clarification responses A3, A4 and Table 4.

Note: Outcomes in bold were specified in the scope and decision problem. Non-bold outcomes were specified in the company decision problem only. Median follow-up (months) in italics i.e., 26.9 months, is the data cut included in the original CS and is therefore non-updated data. Non-italicised median follow up (months) is updated data.

1PL = one prior line of therapy; AEs = adverse events; CR = complete response; EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life-Core 30 questionnaire; EQ-5D-5L = European Quality of Life Working Group Health Status Measure 5 Dimensions, 5 Levels; HRQoL = health related quality of life; ORR = overall response rate; OS = overall survival; PFS = progression free survival; PR = partial response; sCR = stringent complete response; TTD = time to treatment discontinuation; VGPR = very good partial response

[a] 12, 24, 36, 48 and 60 month survival rate (%) with 95% confidence intervals were also reported.
[b] OS data for DBd and Bd in the base case are taken from the CASTOR trial and adjusted for use of subsequent therapies not available in England.
[c] Patients with one prior line of therapy only who were lenalidomide exposed (CS Appendix D).
[d] Final PFS analysis was conducted at 50.2 months follow-up (data cut-off 14th August 2019)
[e] 12, 24, 36 and 48 month PFS rate (%) with 95% confidence intervals were also reported.
[f] PFS data for DBd and Bd taken from the CASTOR trial.
[g] specified in the scope, not specified in decision problem but results for this outcome presented in the CS.
[h] Reported in CS Appendix D.3.2.2 and Appendix E
[i] Grade 3 or higher events reported in at least 5% of patients in any treatment arm, specifically the following 8 outcomes: Grade 3+ neutropenia; Grade 3+ anaemia; Grade 3+ thrombocytopenia Grade 3+ lymphopenia; Grade 3+ pneumonia; Grade 3+ fatigue; Grade 3+ peripheral neuropathy; Grade 3+ hypertension.
[j] Only data for the Bd arm were included in the economic model. Data for the Bd arm at median follow-up 72.6 months are the same as presented for the median follow-up at 26.9 months due to the maximum treatment period for Bd of eight 21-day cycles.
[k] Reported narratively only
[l] Utility values from ENDEAVOR trial were used in base case analysis, as preferred by EAG and Committee in the original appraisal, instead of values from CASTOR trial.

Appendix 3

Table 38 Summary and EAG critique of the statistical methods used in the CASTOR trial

Sample size and power calculation	
Sample size of approximately 480 participants needed, taking into consideration an annual expected 5% dropout rate (SAP[46]). PFS (primary outcome): 295 PFS events provided 85% power to detect a 30% reduction in the risk of disease progression or death (HR=0.70) for DBd over Bd based on a log rank test with α =0.05 (two-sided).[46] The whole trial analysis presented in the original CS was undertaken when 362 progression events had occurred at a median follow-up of 26.9 months. OS (secondary outcome): 320 deaths provided approximately 80% power to detect a 27% reduction in the risk of death (HR=0.73) for DBd over BD based on a log-rank test (two-sided alpha=0.05).[46] The final OS analysis presented in the CDF review company submission took place after 319 deaths (99.7% of the planned 320 events) were observed at a median follow up of 72.6 months.	
EAG comment	Target sample size was reached with 498 patients (DBd N=251; Bd N=247) randomised and 480 (DBd N=243; Bd N=237) receiving study treatment, therefore the trial can be considered sufficiently powered for the intent to treat (ITT) population.
Analysis populations	
ITT: defined as subjects who have been randomly assigned to the Dbd or Bd group. Analysis of time-to-event outcomes (e.g., PFS, OS) were based on this population (CS section 2.4.2). The CS does not explicitly state whether this population was used for the post-hoc outcome of time to treatment discontinuation (treatment duration). Response-evaluable: defined as subjects who have a confirmed diagnosis of multiple myeloma and measurable disease at baseline or screening visit who received at least one administration of study treatment and have at least one post baseline disease assessment. Analysis of major secondary endpoints of ORR, rate of VGPR or better, and duration of and time to response were based on this population (CS section B.2.4.2). Safety population: defined as subjects who have received at least 1 administration of any study treatment (partial or complete), with patients grouped according to treatment actually received. All safety analyses were based on this population (CS section B.2.4.2).	
EAG comment	Appropriate analytical populations were used. Safety population, as a proportion of the total number randomised, was 96.3% thus there was minimal attrition bias.
Methods of analysis	
Time-to-event outcomes: Treatment groups compared using a stratified log-rank test The Kaplan–Meier method was used to estimate distributions. HRs and 95% CIs were	

estimated using a stratified Cox regression model with treatment as the sole explanatory variable (Trial protocol[47] section 11.3; SAP v.2 sections 5.2.2, 5.3.7.2;[46] CS Table 14; Sonneveld 2022[45]).

Binary outcomes: assessed using a stratified Cochran-Mantel-Haenszel test (CS Table 14)

Stratification factors used in the analyses were: ISS staging (I, II, III), number of prior lines therapy (1 vs. 2 or 3 vs. >3), and prior bortezomib treatment (no vs. yes) (CS section B.2.3.1))

Safety outcomes: Descriptive statistics (frequency, counts, percentages) were used (Trial protocol[47] section 11.11)

EAG comment	Appropriate analytical methods were used.

Disease progression assessments

Censoring rules for PFS and Time to disease progression

Patients who:

- started subsequent anticancer therapies for multiple myeloma without disease progression were censored at the last disease assessment before the start of subsequent therapies
- withdrew consent from the study before disease progression were censored at the last disease assessment before withdrawal of consent to study
- were lost to follow-up were censored at the last disease assessment before patients were lost to follow-up
- had not progressed and were still alive at the cut-off date for analysis were censored at the last disease assessment
- did not have any post-baseline disease assessment were censored at the randomisation

Censoring rules for OS

- if the patient was alive or the vital status was unknown, the patient's data was censored at the date the patient was last known to be alive.

EAG comment	Appropriate censoring criteria were used.

Missing data

The CS and SAP state that unless specified otherwise, no data imputation were/will be applied for missing safety and efficacy evaluations (CS section B.2.4.3, SAP v.2 section 2.8). However, the EAG note the SAP and a poster presenting CASTOR trial results with median follow up of 72.6 months, state that for analysis purpose, patients without MRD assessment are considered as having positive MRD (SAP v.2 5.3.6.1; Sonneveld 2022[45]).

EAG comment	The handling of missing data for MRD is conservative approach as it is likely to underestimate negative rates of minimal residual disease.

Adjustment of OS for receipt of subsequent treatments not used in England	
The Company used an Inverse Probability of Censoring Weights (IPCW) method to adjust OS for subsequent treatments received in CASTOR which were not routinely available on the NHS and therefore which could bias results. This applies to both treatment and control groups and is consistent with the methodology accepted in the original submission and TSD16.	
EAG comment	The EAG agrees the IPCW methodology is appropriate. However, limited data were provided to decide whether the methods were applied correctly, or whether the same baseline covariates and time-varying covariates were included as per the original submission.
Subgroup analyses	
The SAP states pre-specified subgroup analyses (SAP v.2 Table 1 and section 8.2.2) to be performed for the primary outcome of PFS, major secondary endpoints of ORR and OS and safety. The CS presents subgroup analyses for OS (the whole ITT population, with median follow up at 72.6 months only; CS B section 2.7.1). All were pre-specified in the SAP. Three of the subgroups were randomisation stratification factors in the CASTOR trial (ISS disease stage, the number of previous lines of therapy, previous treatment with bortezomib). The EAG note that results of the pre-specified subgroup analysis of baseline hepatic function were not reported. As per the managed access agreement section 7.1, the company produced a forest plot of subgroup analyses on OS (CS Figure 10).	
EAG comment	Subgroups analyses of OS in the CS were pre-specified, appropriate to this disease, and included those specified in the managed access agreement.
Bd = bortezomib and dexamethasone; CI = confidence interval; DBd = daratumumab, bortezomib and dexamethasone; HR = hazard ratio; ISS = International Staging System; ITT = Intention to treat; OS = Overall survival; ORR = overall response rate; PFS = Progression free survival; VGPR = very good partial response	

Appendix 4

Below we present the list of changes included in the company's Excel functionality (revised model submitted on 26th September 2022) and the additional changes that the EAG implemented to the revised model to obtain the same results as the ones reported in the CDF entry model.

Table 39 List of changes to the model submitted on 26th September 2022

Model submitted on 26th September 2022		Details	Included in company's CHANGE LOG
Excel tab	**Cells**		
Changes included in company's Excel functionality			
Clinical inputs	E15:E16	Curves to extrapolate PFS	No
Clinical inputs	E51:E52	Curves to extrapolate OS	No
Clinical inputs	E88	Pre-progression mortality	Yes
Treatment duration	F7:F8	Curves to extrapolate TTD	No

Model submitted on 26th September 2022		Details	Included in company's CHANGE LOG
Excel tab	**Cells**		
Treatment duration	G10	Median duration for "others"	Yes
Subsequent treatment	E20:E21, F19:F21, G19:G21, H19:H21	Proportion of patients receiving each subsequent treatment	Yes
Subsequent treatment	E32:E35	Percent of patients continuing on subsequent treatment	Yes
Medical Cost - Drug	D13:E13	Population body weight	Yes
Medical Cost - Drug	D21:F23	Dose intensity for DBd and Bd arms	Yes
Medical Cost - Drug	D34:F34	Daratumumab 1800mg	Yes
Medical Cost - Drug	F37, F39:F40	Drug costs for bortezomib, lenalidomide and dexamethasone	Yes, although wrongly labelled as thalidomide rather than lenalidomide by the company
Medical Cost - Drug	D60, D63:D65	Drug administration costs	Yes
Medical Cost - Drug	D78:E78, D80:E80, F78:F85	Cost of concomitant drugs, drug units and strength	Yes
Medical Cost - MRU	D8:D15	Monitoring costs	Yes
Medical Cost - MRU	D59	Terminal care costs	Yes
Adverse Events	D14:D21	Costs of adverse events	Yes
Adverse Events	G14:G21	Incidence of adverse events for DBd arm	Yes, although wrongly stated that incidence of adverse events for Bd arm also updated
PAS options	D22	PAS discount of daratumumab as intervention	Yes
PAS options	D26	PAS discount of daratumumab as subsequent treatment	Yes
NMA Results	Whole sheet	HR for PFS and OS	Yes
Parameter Estimates	Z9:AB21	Survival estimates for PFS	Yes
Parameter Estimates	Z27:AB39	Survival estimates for OS	No (CHANGE LOG states that changes were made to 'Param Est OS' sheet, which is not correct)
Parameter Estimates	Z45:AB57 (except AA45 and AA52)	Survival estimates for TTD	No (CHANGE LOG states that changes were made to 'Param Est OS' sheet, which is not correct)

Model submitted on 26th September 2022		Details	Included in company's CHANGE LOG
Excel tab	**Cells**		
Life Table	B4:B6	Baseline age and sex	Yes
Life Table	C10:D110	General population mortality	Yes
Additional changes implemented by the EAG			
Clinical inputs	C87	Pre-progression mortality	No
Medical Cost - Drug	D71:D72	Proportion of patients receiving IV or SC injections	No
Medical Cost - MRU	AA22	Blood test to determine blood type	No
Parameter Estimates	G85:H85, G92	Survival estimates for TTD	No
Drug Cost Calculations	CP14:CQ 14	Inclusion of blood type determination as part of the administration costs for daratumumab	No
Drug Cost Calculations	CP14	Exclusion of cost of oral drug administration for daratumumab	No
Drug Cost Calculations	CQ14:CQ 98	Formula of weekly administration costs for DBd	No
Drug Cost Calculations	CX14	Administration cost of POM-DEX	No
Model Engine	BM22	Formula of PFS MRU Cost	No

Bd = bortezomib plus dexamethasone; DBd = daratumumab plus bortezomib plus dexamethasone; HR = hazard ratio; IV = intravenous; OS = overall survival; PAS = patient access scheme; PFS = progression free survival; POM-DEX = Pomalidomide plus dexamethasone; SC = subcutaneous; TTD = time to treatment discontinuation