NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Daratumumab with bortezomib and dexamethasone for previously treated multiple myeloma (Managed Access Review of TA573) [ID4057]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

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The following documents are made available to stakeholders:

Access the **final scope and final stakeholder list** on the NICE website.

Pre-technical engagement documents

1. **Company submission** from Janssen

2. **Clarification questions and company responses**

3. **Patient group, professional group and NHS organisation submissions** from:
   a. Myeloma UK

4. **External Assessment Report** prepared by Southampton Health Technology Assessment Centre

Post-technical engagement documents

5. **Technical engagement response** from company

6. **External Assessment Group critique of company response to technical engagement** prepared by Southampton Health Technology Assessment Centre

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

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Daratumumab with bortezomib and dexamethasone for treating relapsed or refractory multiple myeloma [Review of TA573]

Document B

Company evidence submission

11 August 2022

File name	Version	Contains confidential information	Date
Janssen Evidence Submission for daratumumab in RRMM_Document B	1.0	Yes	11 August 2022

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Tables and figures

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

B.1.1 Decision problem

The submission focuses on part of the technology's marketing authorisation: adults with relapsed or refractory multiple myeloma who have received one prior line of therapy (i.e., second-line patients). The proposed positioning is consistent with the original submission for daratumumab in this indication (TA573, published 10 April 2019) which was narrower than the marketing authorisation because:

- There is a clear unmet need for triple therapies in the second-line setting in England and Wales;
- This position reflects where daratumumab in combination with bortezomib and dexamethasone (DBd) provides the greatest clinical benefit;
- This position optimises the cost-effectiveness of DBd, because of the substantial clinical benefit observed in second-line patients.

The decision problem addressed in this submission, compared with that defined in the final scope issued by NICE is summarised in Table 1.

Table 1 The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with relapsed or refractory multiple myeloma who have had at least 1 prior line of 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.[1]
Intervention	Daratumumab in combination with bortezomib and dexamethasone	Daratumumab in combination with bortezomib and dexamethasone	
Comparator(s)	For people who have had 1 prior line of therapy, depending on previous treatment: ▪ Bortezomib-based therapy ▪ 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	For people who have had 1 prior line of therapy: ▪ Bortezomib-based therapy ▪ Carfilzomib in combination with dexamethasone	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 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

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Outcomes	The outcome measures to be considered include: ▪ OS ▪ PFS ▪ response rates ▪ Time to next treatment ▪ adverse effects of treatment ▪ HRQoL	The outcome measures to be considered include: ▪ OS ▪ PFS ▪ TTD ▪ response rates (including MRD negativity) ▪ adverse effects of treatment ▪ HRQoL	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. 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.[2]

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; NICE = National Institute for Health and Care Excellence; OS = overall survival; PFS = progression-free survival; TTD = time to treatment discontinuation

B.1.2 Description of the technology being evaluated

A description of the technology being appraised, DBd, is presented in Table 2.

Table 2 Description of DBd

UK approved name and brand name	Daratumumab (Darzalex®)
Mechanism of action	Daratumumab is a targeted immunotherapy that binds with high affinity to tumour plasma cells expressing CD38+, a transmembrane glycoprotein. CD38+ is a distinct target from those of other approved agents for MM. High levels of CD38+ expression are found universally in the plasma cells of patients with MM.[3] Because of the clonal heterogeneity of MM, an immunotherapy approach targeting CD38+ cells is hypothesised to have broad therapeutic potential.[3] Preclinical data suggest that daratumumab is effective in vitro by killing CD38+ MM cells through multiple mechanisms including direct on-tumour and immunomodulatory actions.[3-5] The concept of clonal heterogeneity contributing to disease progression in MM led to the strategy of adopting combination therapies to eradicate both the dominant and minor clones.[6] Combination treatment strategies are now recommended for routine clinical practice by the IMWG.[7] CD38 is a distinct target from those of other approved agents for MM and this together with its high efficacy and favourable safety profile make daratumumab an ideal candidate for combination therapy. Synergism between daratumumab and other anti-myeloma agents including bortezomib has been demonstrated in preclinical mechanistic studies,[4,8,9] providing a scientific rationale for the DBd combination.
Marketing authorisation/CE mark status	Marketing authorisation was granted by the European Commission on 28 April 2017
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	The licensed indications for daratumumab in multiple myeloma are: ▪ 'In combination with lenalidomide and dexamethasone or with bortezomib, melphalan and prednisone for the treatment of adult patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant'.[10,11] ▪ 'In combination with bortezomib, thalidomide and dexamethasone for the treatment of adult patients with newly diagnosed multiple myeloma who are eligible for autologous stem cell transplant'.[10,11] ▪ 'In combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone, for the treatment of adults patients with multiple myeloma who have received at least one prior therapy.'[10,11] ▪ 'In combination with pomalidomide and dexamethasone for the treatment of adult patients with multiple myeloma who have received one prior therapy containing a proteasome inhibitor and lenalidomide and were lenalidomide refractory, or who have received at least two prior therapies that included lenalidomide and a proteasome inhibitor and have demonstrated disease progression on or after the last therapy.'[10,11] ▪ 'As monotherapy for the treatment of adult patients with relapsed and refractory multiple myeloma, whose prior therapy included a proteasome inhibitor and an immunomodulatory agent and who have demonstrated disease progression on the last therapy.'[10,11] Daratumumab is also indicated in combination with cyclophosphamide, bortezomib and dexamethasone for the treatment of adult patients with newly diagnosed systemic AL amyloidosis.[10,11]

Method of administration and dosage	Daratumumab can be administered through intravenous (IV) infusion or by subcutaneous (SC) injection. IV infusion: ▪ When used in combination with bortezomib and dexamethasone, daratumumab (16 mg/kg) is administered every week for weeks 1 to 9, every 3 weeks for weeks 10 to 24 and every 4 weeks from week 25 onward until disease progression.[11] SC injection: When used in combination with bortezomib and dexamethasone, daratumumab (1,800 mg) is administered every week for weeks 1 to 9, every 3 weeks for weeks 10 to 24 and every 4 weeks from week 25 onward until disease progression.[10] SC injection is widely used in the UK due to its convenience and favourable tolerability profile with IV infusion only used by a small minority of patients.[12] [redacted]
Additional tests or investigations	Initial blood test to type and screen serum prior to daratumumab administration.[10,11]
List price and average cost of a course of treatment	List Price 100 mg (IV infusion) = £360 (excl. VAT) List Price 400 mg (IV infusion) = £1,440 (excl. VAT) List Price 1,800 mg (fixed-dose vial) = £4,320.00 (excl. VAT)
Patient access scheme (if applicable)	[redacted]

AL = light chain amyloidosis; CE = Conformitè Europëenne; DBd = daratumumab, bortezomib and dexamethasone; IMWG = International Myeloma Working Group; MM = multiple myeloma; PAS = patient access scheme; PASLU = patient access schemes liaison unit; SmPC = Summary of Product Characteristics; UK = United Kingdom.

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

B.1.3.1 Disease overview

Disease background

Multiple myeloma (MM) is a rare haematological cancer and daratumumab has been designated an orphan drug in both the United States and Europe.[14,15] MM is characterised by the clonal proliferation of malignant plasma cells within the bone marrow and the overproduction of M proteins.[16] Over time, these components accumulate in adjacent skeletal structures, blood and multiple organs throughout the body, leading to serious complications.[16] While the precise mechanism that causes MM remains unknown, the combination of genetic abnormalities in plasma cells and selective pressure from the bone microenvironment has been used to explain progression to symptomatic disease.[17,18] Additionally, the coexistence of distinct tumour subclones displaying different drug sensitivities contributes to both the progression of the disease and the development of drug resistance.[17-20]

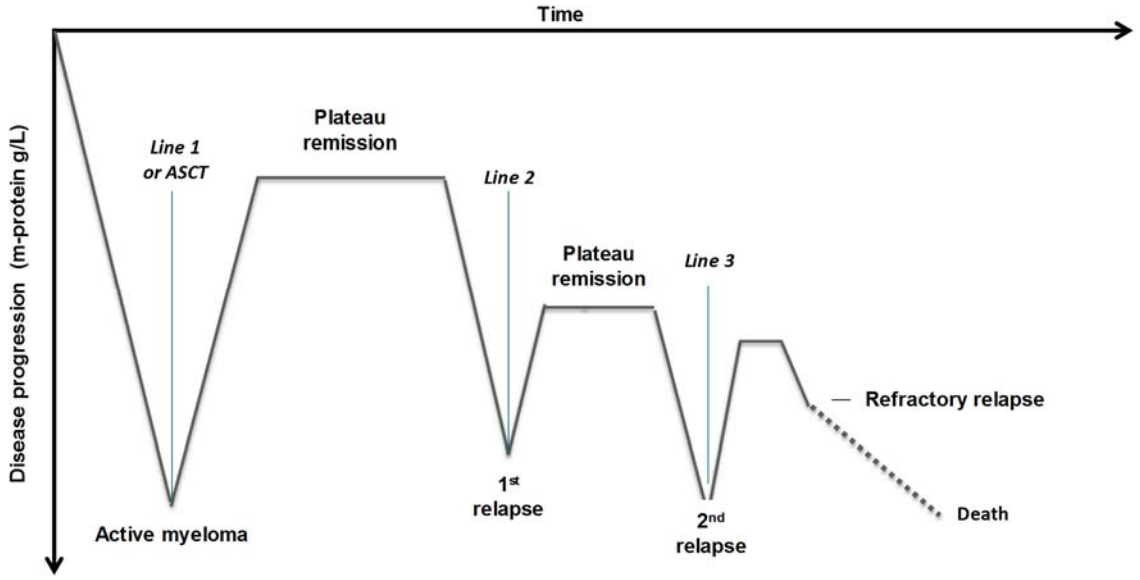
The development of symptomatic MM is associated with a variety of serious complications that require immediate treatment, including elevated calcium levels (hypercalcemia), renal impairment, anaemia and bone disease.[21] Less frequent complications of MM include

hyperviscosity syndrome (i.e., increased blood viscosity), infection, thrombosis and extramedullary disease.[22-24]

Relapsed refractory multiple myeloma (RRMM) is defined as a disease that is non-responsive while on salvage therapy or progresses within 60 days of last treatment in patients who have achieved a minimum response (MR) or better at some point previously, before then progressing in their disease course.[25]

MM is a heterogeneous disease in terms of the prognosis for patients and as a result can take a variable clinical course. Clinical outcomes, including overall survival (OS), vary depending on a number of prognostic factors, including International Staging system (ISS) stage, cytogenetic profile and number and type of prior treatments.[7,26,27] The disease is characterised by multiple relapses, with each relapse associated with a substantial reduction in depth and duration of response to treatment.[28] As a result, all surviving patients eventually relapse from, or become refractory to, existing treatments.[28] Consequently, with currently available therapies, the prognosis of relapsed patients is poorer than that of newly diagnosed patients, and with each successive relapse, prognosis deteriorates further (Figure 1).[28,29]

Figure 1 Disease and treatment progression of MM[29]



ASCT = autologous stem cell transplantation; MM = multiple myeloma.
Diagram is figurative and not to scale.

Epidemiology

MM accounts for approximately 1% of all cancers and 15% to 20% of haematological malignancies worldwide.[30] Based on data from 2016 to 2018, 5,041 people are diagnosed with MM annually in England, accounting for 2% of all new cancer cases.[31] Over the last decade, MM incidence rates have increased by approximately 11% in the United Kingdom (UK) and are projected to rise a further 11% between 2014 and 2035; the increase largely a reflection of the changing prevalence of risk factors and improvements in diagnosis and data recording.[31] Of people diagnosed with MM in the UK, 43% are aged 75 years and over (2016 to 2018).[31] MM is more common in men than in women, with 58% of cases in the UK occurring in men.[31]

Over the last two decades, considerable progress in the treatment of MM has improved patient survival.[32-34] Evidence suggests that global survival has more than doubled, increasing from approximately 3 years from 1985 to 1998 to approximately 6 to ≥8 years after 2006.[35-37] Despite this substantial improvement, which is largely attributed to the introduction of agents such as thalidomide, bortezomib and lenalidomide,[32-34] MM remains incurable and all surviving patients will eventually relapse.[28] The 5- and 10-year survival rates for adults with MM in England and Wales are approximately 52.3% and 29.1%, respectively (2013 to 2017).[38] There were 3,098 deaths annually from MM in the UK between 2017 and 2019.[39] However, these rates do not fully reflect anticipated survival improvements from the introduction of monoclonal antibodies including DBd since its recommendation on the Cancer Drugs Fund (CDF) in 2019.

Effect of RRMM on patients, carers and society

Patients with MM report worse symptoms and complications than those with other haematological malignancy including lymphoma or leukaemia.[40] The clinical burden of MM is influenced by both progressive disease symptoms and treatment-associated complications, such as weakness, fatigue, bone pain, peripheral neuropathy, weight loss, confusion, excessive thirst and constipation.[23,41-43] These complications can impact many aspects of patients' lives, including:[43-48]

- Reduced ability to perform daily activities
- Reduced participation in social activities, impact on relationships and isolation
- Impact on ability to maintain employment and financial status

Relapse in patients with MM is particularly detrimental to patient HRQoL; patients with RRMM have a worse prognosis and a greater symptomatic burden than patients with newly diagnosed MM due to the progressive nature of MM and the cumulative adverse effects of

treatment.[42,49] Observational data demonstrates that HRQoL decreases as patients move from their first treatment-free interval (TFI) to second-line treatment and subsequent treatment phases.[50] In a UK study of 370 patients with MM, the HRQoL profile of patients in their first TFI was superior for most parameters than in later treatment phases. This decline in HRQoL reflects the increasing symptom burden and cumulative toxicities as patients progress through treatment lines. Prolonging earlier remissions is therefore key to improving the quality of life of patients (Table 3).[50]

Table 3 Regression analyses of first treatment-free interval versus later treatment phases[50]

	First TFI vs second-line[a]			First TFI vs later stages[a]		
	B value	**SE**	**P value**	**B value**	**SE**	**P value**
EORTC QLQ-MY20						
Disease symptoms[b]	-2.26	3.27	0.490	3.59	2.56	0.161
Side effects[b]	8.14	2.22	<0.001	6.42	1.74	<0.001
Future perspectives	-8.28	3.74	0.027	-10.36	2.93	<0.001
Body image	-10.78	5.20	0.039	-11.21	4.07	0.006
EORTC-QLQ-C30 functioning domains						
Physical	-3.62	3.60	0.316	-9.69	2.82	0.001
Role	-9.89	4.88	0.043	-13.68	3.83	<0.001
Emotional	-5.88	2.99	0.050	-3.20	2.35	0.175
EQ-5D						
Cognitive	-2.95	3.57	0.409	-2.40	2.80	0.391
Social	-12.06	4.93	0.015	-13.99	3.86	<0.001
Utility	-0.059	0.038	0.122	-0.074	0.030	0.015
VAS	-0.061	0.030	0.044	-0.124	0.024	<0.001

EORTC-QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Core Questionnaire; EORTC-QLQ-MY20 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (multiple myeloma module); EQ-5D = EuroQol Five Dimensions Questionnaire; HRQoL = health-related quality of life; SE = standard error; TFI = treatment-free interval; VAS = Visual analogue scale.

[a]HRQoL during the first TFI relative to second and later treatment phases was measured using 11 ordinary least squares multiple regression analyses, with QLQ-C30 functional scales, MY20 scales, the EQ-5D utility index and VAS rating as dependent variables.

[b]For these subscales, a negative B coefficient is indicative of the first TFI being associated with worse HRQoL relative to the comparator treatment phase.

As patients move from their first TFI to second-line and subsequent treatment phases, HRQoL progressively declines and does not return to pre-first relapse levels.[50] In a European study, real-world evidence characterising the psychological burden of relapse on patients was collected through face-to-face interviews with 50 patients with RRMM and 30 haematologists across ten countries.[44] This study reported a trend of patients feeling more negative during relapse than when in remission, with the most profound emotional impact associated with the first relapse.[44] Additionally, patients reported deterioration in a number of physical and psychological factors upon change from stable disease to relapse or disease progression, including worsened energy levels, increased tiredness, impaired concentration,

ability to perform daily activities, decreased participation in social activities and overall quality of life.[44] In particular, multiple relapses were associated with a loss of hope for an extended period of remission and increasing distress over the exhaustion of effective treatment options.[44]

When considering an appropriate treatment for RRMM, it is important to consider the preferences of patients and their care team as well as the patient's individual situation.[42,43,46,51] Life expectancy, treatment effectiveness and longer remission periods are key priorities for patients, healthcare providers and carers, along with a reduction in adverse treatment effects and fatigue.[42,43,45,51] In a discrete choice experiment (DCE) involving patients with MM living in the UK, France or Germany (N=300, 29% with RRMM), patients placed most value on reduction in pain, decreased fatigue and increased life expectancy.[52] Quality of life/wellbeing, return to normal activities, social life and work are also of high value to patients living with MM.[45]

Most of the clinical management of MM is provided in the outpatient setting; therefore the bulk of care is informal and provided by caregivers.[53] Caregivers may perform complicated technical procedures (e.g. dressing changes, intravenous line care and injections), assist the patient with daily living, and attend appointments.[48,53,54] Therefore, the detrimental effects of MM on working life are not only experienced by patients, but also their caregivers.[48,53-55] Almost half (49%) of the partners of patients with MM report symptoms of anxiety and 14% report symptoms of depression.[55] The unmet need in supportive care is considerable and carers have specifically reported a need for help to manage the side effects and complications experienced by patients due to treatment for MM.[55]

Data specific to the economic burden of RRMM are limited. However, evidence suggests that patients with late-stage disease incur higher resource use and costs than those with early-stage disease due to the complications associated with the treatment of MM.[56-60]

B.1.3.2 Description of clinical pathway of care

Currently recommended treatments

MM is a treatable but incurable disease. Patients often require multiple lines of treatment, usually involving drug combinations with proteasome inhibitors (PIs) and/or immunomodulatory agents (IMiDs), with or without stem cell transplantation. Almost all surviving patients with MM eventually relapse from, or become refractory to, existing treatment options.[28] Consequently, the aims of treatment are to induce remission, delay progression, prolong survival and maximise quality of life.[61]

Choosing the most appropriate treatment for patients with RRMM is dependent on disease-, clinical- and patient-related factors; options may also be restricted by lack of response or sensitivity to components of the regimen used prior to relapse.[62-64] According to European guidelines (published in 2021), patients with RRMM not considered for salvage autologous stem cell transplantation (ASCT) therapy are typically treated with a triplet regimen of an antibody (daratumumab, isatuximab, elotuzumab), IMiD (i.e. thalidomide, lenalidomide or pomalidomide) and/or PI (i.e. bortezomib or carfilzomib), with the addition of dexamethasone to alleviate symptom burden.[62,64,65] Current clinical guidelines in the US also recommend a range of therapies for the management of RRMM, including triple therapies such as DBd.[64,66]

By contrast, the treatment pathway in England is heavily restricted, especially for patients with RRMM who have received one prior line of therapy (Table 4).[67-69] Carfilzomib in combination with lenalidomide and dexamethasone (CLd) is the only triple therapy recommended for routine commissioning in second-line patients with RRMM in England and is limited to patients who received first-line bortezomib. Consequently, there is therefore a significant unmet need for a safe and effective triplet regimen in the second-line setting (Table 4).[67-69]

Table 4 Triple therapies recommended in the US, Europe and England for patients with RRMM following one prior line of therapy[64,66-68]

United States[a] (NCCN)		Europe[b] (ESMO)		England (NICE)	
BLd	DLd	CLd	IsaCd	CLd[c]	
CLd	ILd	DLd	ILd	DBd (**CDF**)	
DBd	IsaCd	EloLd	Selinexor, Bd		
DCd		PBd	Ventoclax, Bd		
		DCd	DBd		

Bd = bortezomib and dexamethasone; BLd = bortezomib, lenalidomide and dexamethasone; CDF = Cancer Drugs Fund; CLd = carfilzomib, lenalidomide and dexamethasone; DBd = daratumumab, bortezomib and dexamethasone; DCd = daratumumab, carflizomib and dexamethasone; DLd = daratumumab, lenalidomide and dexamethasone; EloLd = elotuzumab, lenalidomide and dexamethasone; ESMO = European Society for Medical Oncology; ILd = ixazomib, lenalidomide and dexamethasone; ISaCd = isatuximab, carfilzomib and dexamethasone; Ld = lenalidomide and dexamethasone; NCCN = National Comprehensive Cancer Network; NICE = National Institute for Health and Care Excellence; PBd = Panobinostat, bortezomib and dexamethasone; RRMM = relapsed refractory multiple myeloma; UK = United Kingdom; US = United States

[a] NCCN preferred recommendations for patients with RRMM and 1 to 3 prior lines of therapy. **Patients with lenalidomide-refractory disease should be considered for a lenalidomide-free triplet regimen**.

[b] ESMO recommendations for patients with RRMM and 1 prior line of therapy for patients who did not previously receive daratumumab and are: sensitive/refractory to lenalidomide; sensitive to bortezomib; refer to the full publication for specific recommendations according to the treatment used in the front-line

[c] One prior line of therapy included bortezomib

Rationale for addition of DBd to the treatment pathway

One of the challenges of treatment to date has been to find options that effectively target and eliminate all clonal and subclonal mutations. Daratumumab binds to CD38, a protein that is overexpressed on the surface of MM cells. It works by targeting the tumour directly and indirectly, as well as uniquely modulating the immune system.[3,4] It is this combination of

direct and immunomodulatory effects that harnesses the body's own immune system to fight the disease that explains the deep responses and step-change in efficacy observed with daratumumab for this indication. Notably, [redacted] of patients receiving DBd in the second-line in England via the CDF remained alive at 24-months after initiating treatment.[70] This OS benefit is [redacted] to the OS of front-line patients with newly diagnosed transplant ineligible MM.[71] As documented in the standing cohort using NHS Digital datasets, [redacted] of [redacted] transplant ineligible patients survived to 24 months in response to front-line systemic therapy.[71]

The clinical benefit observed in second-line patients treated with DBd in the CASTOR study was also similar to that seen in newly diagnosed patients treated with existing drug therapies. That is, ORR with DBd was similar to ORR in DBTd treated patients and superior to all other front-line therapies. PFS with DBd was similar to that achieved with lenalidomide and superior to that achieved with bortezomib in the newly diagnosed transplant ineligible setting (Table 5).

Table 5 Comparison of front-line and second-line clinical outcomes for treatment regimens recommended by NICE

Treatment	ORR (%)	Median PFS (months)	Reference
Front-line (non-transplant)			
BMP	71	18.3	Velcade SmPC[72]
Ld	81	26.0	Facon 2018[73]
Front-line (transplant-eligible)			
BTd	85	55.5	Rosinol 2012[74]
DBTd	93	NE	Moreau 2019[75]
2L			
DBd	92	26.2	CASTOR (26.9 months follow-up)[76]
	N/A	27.0 months	CASTOR (50.2 months follow-up)[77]

2L = second-line; BMP = bortezomib, melphalan and prednisolone; BTd = bortezomib, thalidomide and dexamethasone; DBd = daratumumab, bortezomib and dexamethasone; DBTd = daratumumab, bortezomib, thalidomide and dexamethasone; FLNT = front-line non-transplant; FLT = front-line transplant; N/A = not applicable; NE= not estimable; Ld = lenalidomide and dexamethasone; NICE = National Institute of Healthcare and Excellence; ORR = overall response rate; PFS = progression free survival; SmPC = Summary of Product Characteristics.

The availability of a treatment option at first relapse that has demonstrated clinical outcomes similar to drug therapies at front-line, will help reduce relapse-associated anxiety in both patients and carers. This in turn, will provide patients and carers with a renewed sense of hope for a life-extending period of remission, which is not intrinsically captured in the QALY framework.[44]

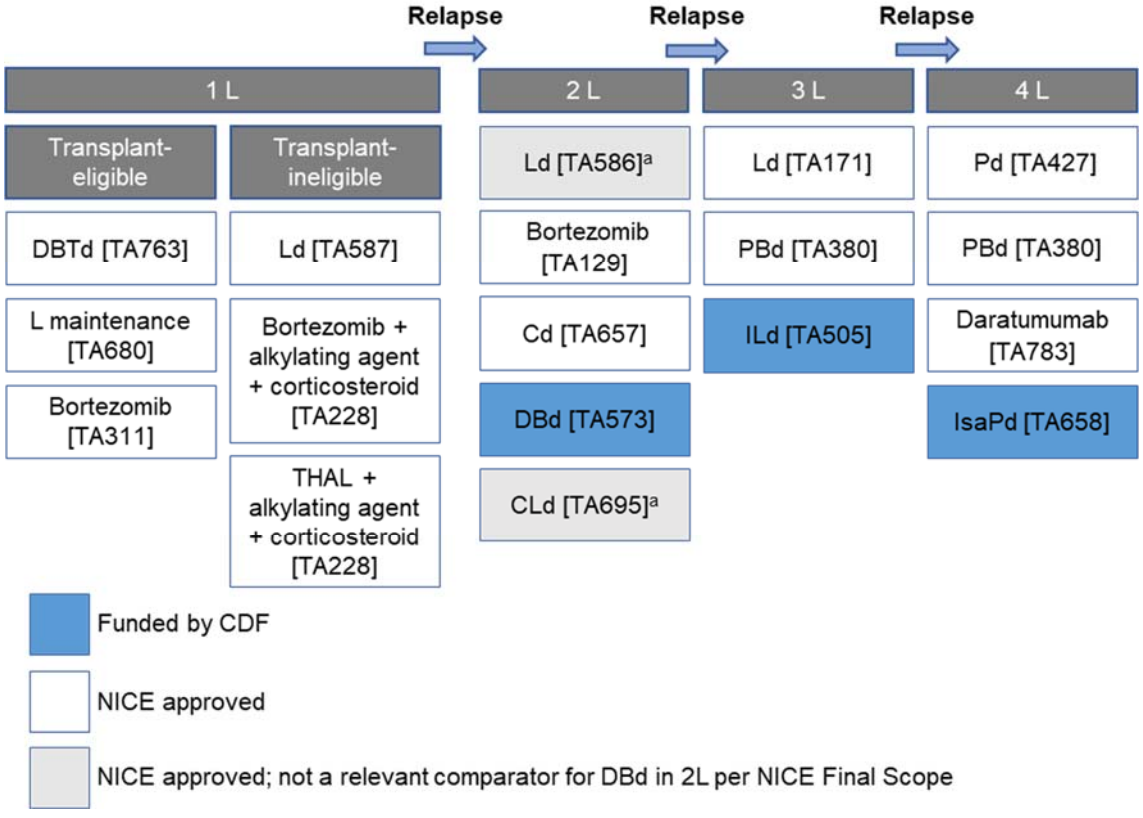
An additional benefit of offering DBd to patients with RRMM who have received one prior line

of therapy is the potential to increase therapeutic options for subsequent lines of therapy, as well as the number of UK patients eligible for recruitment into clinical trials. Eligibility for novel immunotherapies such as bispecifics and CAR-T for example, includes prior exposure to a CD38-targeting therapy.[78,79] None of these benefits are captured in the quality-adjusted life year (QALY) framework.

Furthermore, the proportion of patients eligible for a treatment decreases with each subsequent line of therapy due to death, disease progression, poor physical condition, toxicity and/or comorbidities.[80] These high attrition rates in MM coupled with diminishing survival benefits in later lines of therapy highlight the importance of using the most effective treatment option as early as possible to improve patients' survival.[81]

The clinical care pathway for MM patients in England is presented in Figure 2; including the proposed positioning of DBd as a second-line treatment option.

Figure 2 Current NHS clinical care pathway in England for the treatment of patients with MM[67-69,82-89]



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

B.1.4 Equality considerations

There are no equality issues arising in relation to this technology.

B.2 Clinical effectiveness

Summary of clinical effectiveness

- The efficacy and tolerability of DBd versus the directly relevant, active control Bd in patients with RRMM was assessed in a randomised, open-label, multicentre, phase III clinical trial, CASTOR (MMY3004)
- This submission is based on data from the CASTOR Final Analysis with a clinical cut-off of 28 June 2021 (median follow-up 72.6 months [>6 years]). Supportive data from the Primary PFS Analysis with a clinical cut-off of 14 August 2019 (median follow-up 50.2 months) is also presented where relevant
- Eligible patients were randomised to receive either DBd (n=251), or Bd (n=247)
- Baseline characteristics were balanced between arms, with a trial population broadly generalisable to clinical practice in the UK
- The greatest survival benefits gained from DBd were experienced by patients in their second-line of therapy. Within this prespecified subgroup, DBd provided compelling efficacy in relapsed or refractory patients, compared with Bd:
    - With a median follow-up of 50.2 months, the risk of disease progression or death was significantly lowered by 79% for patients treated with DBd compared with those receiving Bd (hazard ratio [HR]: 0.21; 95% CI: 0.15, 0.31; p<0.0001). The median PFS of patients treated with DBd or Bd was 27.0 months and 7.9 months, respectively
    - With a median follow-up of 72.6 months, the risk of death was significantly decreased by 44% for patients treated with DBd compared with those receiving Bd (HR: 0.56; 95% CI: 0.39, 0.80; p=0.0013).This survival benefit improved, following adjustment for subsequent therapies unavailable in the UK, as second-line patients treated with DBd had a [redacted]% reduction in risk of death compared to patients treated with Bd (HR: [redacted]; 95% CI: [redacted])
    - As presented in the 2018 submission for DBd (TA573), deeper responses were achieved in patients treated with DBd versus Bd, with improved ≥CR rates in the DBd group compared to the Bd group (42.9% versus 14.7%, respectively; median follow-up 26.9 months)
    - The MRD negativity rate as per the IMWG criteria, at the sensitivity threshold of 10^{-5}, was significantly higher for the DBd group at 50.2 months of follow-up (21.0%) compared with the Bd group (3.0%; p<0.000013). Now an accepted prognostic indicator, MRD-negativity inside the bone marrow is correlated with prolonged PFS and OS in patients with CR to therapy
- As previously reported, patient reported outcomes (PROs) for HRQoL (26.9 months median follow-up) were similar between treatment arms, indicating the addition of daratumumab to bortezomib and dexamethasone has no detrimental impact on HRQoL[76]
- The safety profile of the DBd regimen remained consistent with earlier analyses at median follow-up of 72.6 months
- Most patients treated with DBd or Bd had at least one treatment-emergent adverse event (TEAE) after the start of treatment (99.2% and 95.4%, respectively). The incidence of treatment discontinuations due to AEs in the ITT population was low and similar between the DBd and Bd treatment arms (10.7% and 9.3%, respectively; median follow-up 72.6 months)
- Limited data are also included from [redacted] patients who received DBd through the Cancer Drugs Fund (CDF) to evaluate the real-world effectiveness of DBd in England during the managed access period
    - With a median follow-up of [redacted] months, the survival rate was [redacted]% at 24 months (95% CI: [redacted]), with [redacted]% of patients still receiving treatment with DBd (95% CI: [redacted]). This compares favorably with a [redacted]% OS-rate at 24 months among patients with transplant ineligible NDMM in response to front-line systemic therapy.[71]

B.2.1 Identification and selection of relevant studies

To identify studies of daratumumab and potential comparator therapies for relapsed or refractory multiple myeloma (RRMM), a systematic literature review (SLR) of randomised controlled trial (RCT) evidence was conducted. To meet the objectives of the SLR, the following primary research question was addressed:

- What is the clinical efficacy and safety of daratumumab and relevant comparators in RCTs involving patients with RRMM who received 1PL of therapy?

Overall, 381 citations were assessed for eligibility during the SLR. Of these, 40 sources reporting on seven RCTs were considered relevant to patients with RRMM who were treated with 1PL of therapy only. An additional two non-RCT publications were also taken into consideration. From these studies, clinical evidence relevant to daratumumab are provided by the CASTOR RCT.

Following a feasibility assessment, only one other RCT, the ENDEAVOR study of carfilzomib, was considered relevant for comparative analyses. Five RCTs were excluded as they did not provide a network connection to a treatment of interest, or the population was not similar enough to align with CASTOR. Both CASTOR and ENDEAVOR included patients who had received 1PL of therapy and who presented with relapsed or refractory disease.

See Appendix D for full details of the process and methods used to identify relevant clinical efficacy data for this submission.

In addition, data from a study commissioned by NHS England and NHS Improvement evaluating the real-world effectiveness of DBd in patients with RRMM in England treated via the CDF are also available. Data were collected between 12 March 2019 and 1 June 2021, as a secondary source of evidence to attempt to reduce uncertainties surrounding long-term survival data raised by NICE in their decision to approve funding of DBd via the CDF (TA573 guidance for DBd in RRMM published 10 April 2019).[67]

B.2.2 List of relevant clinical effectiveness evidence

CASTOR (MMY3004) is a multicentre, phase III, randomised, open-label, active-controlled study comparing DBd with Bd among patients with RRMM who have received at least one prior line of treatment (Table 6).

Table 6 Clinical effectiveness evidence

Study	CASTOR (MMY3004)
Study design	Multicentre, phase III, randomised, open-label, active-controlled study comparing DBd with Bd
Population	Patients with relapsed or refractory multiple myeloma with at least one prior line of treatment
Intervention(s)	DBd: 16mg/kg intravenous daratumumab[a] administered weekly for the first 3 cycles (21 days/cycle), then every three weeks for Cycles 4 to 8 and then every 4 weeks thereafter Bortezomib was administered at a dose of 1.3mg/m2 SC twice weekly on Days 1, 4, 8, and 11 for eight 21-day cycles (Cycles 1 to 8) Dexamethasone was administered at a total dose of 80mg weekly in 2 out of 3 weeks for Cycles 1 to 8 (Days: 1, 2, 4, 5, 8, 9,11 and 12)
Comparator(s)	Bd: Bortezomib was administered at a dose of 1.3mg/m2 SC twice weekly on Days 1, 4, 8, and 11 for eight 21-day cycles (Cycles 1 to 8) Dexamethasone was administered at a total dose of 80mg weekly in 2 out of 3 weeks for Cycles 1 to 8 (Days: 1, 2, 4, 5, 8, 9,11 and 12)
Indicate if study supports application for marketing authorisation	Yes
Indicate if study used in the economic model	Yes
Reported outcomes specified in the decision problem[b]	▪ **Progression-free survival (PFS)** ▪ Overall response rate (ORR) ▪ **Overall survival (OS)** ▪ Health-related quality of life (HRQoL) ▪ **Adverse effects (AEs)**
All other reported outcomes[b]	▪ Time to disease progression (TTP) ▪ Rate of very good partial response (VGPR) or better ▪ Rate of complete response (CR) or better ▪ Time to response (TTR) ▪ Duration of response (DOR) ▪ Minimal residual disease (MRD) ▪ Time to next therapy (TTNT) ▪ Progression-free survival on the next line of therapy (PFS2) ▪ Best M-protein response ▪ Best response to first subsequent anticancer therapy ▪ Post-hoc outcomes:**Time to treatment discontinuation (TTD)**

[a] Daratumumab is also now available in a subcutaneous formulation, which demonstrated non-inferiority with intravenous daratumumab in RRMM in the COLUMBA study[10] and is the preferred method of administration in clinical practice in England.

[b] Bolded outcomes are those that are included in the economic model for DBd in RRMM (Section B.3)

Bd = bortezomib and dexamethasone; DBd = daratumumab, bortezomib and dexamethasone; SC = subcutaneously.

Following the appraisal of DBd in RRMM by NICE in 2019, DBd was recommended for the treatment of second-line RRMM patients in England via the CDF.[67] An analysis of the real-world effectiveness of DBd for patients with RRMM who had received one prior line of

therapy was conducted in 2021 by the National Disease Registration Service on behalf of NHS England and NHS Improvement.[70] The analysis included data collected in clinical practice in England from the Systemic Anti-Cancer Therapy (SACT) dataset on OS and treatment duration.[70]

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

B.2.3.1 CASTOR Study design

Patients in CASTOR were randomised 1:1 to receive DBd or Bd using a stratified block randomisation. Stratification factors included International Staging System (ISS; I, II or III) at screening, number of prior lines received (1 versus 2, or 3 versus ≥3) and the use of prior bortezomib treatment (no versus yes).[90]

The study consisted of the following three phases:[91]

- Screening Phase: up to 21 days prior to Cycle 1 (Day 1)
- Treatment Phase: from Cycle 1, Day 1 until study treatment discontinuation
- Follow-up Phase: from the End-of-Treatment Visit until death, loss to follow-up, consent withdrawal for study participation, or study end, whichever occurred first.

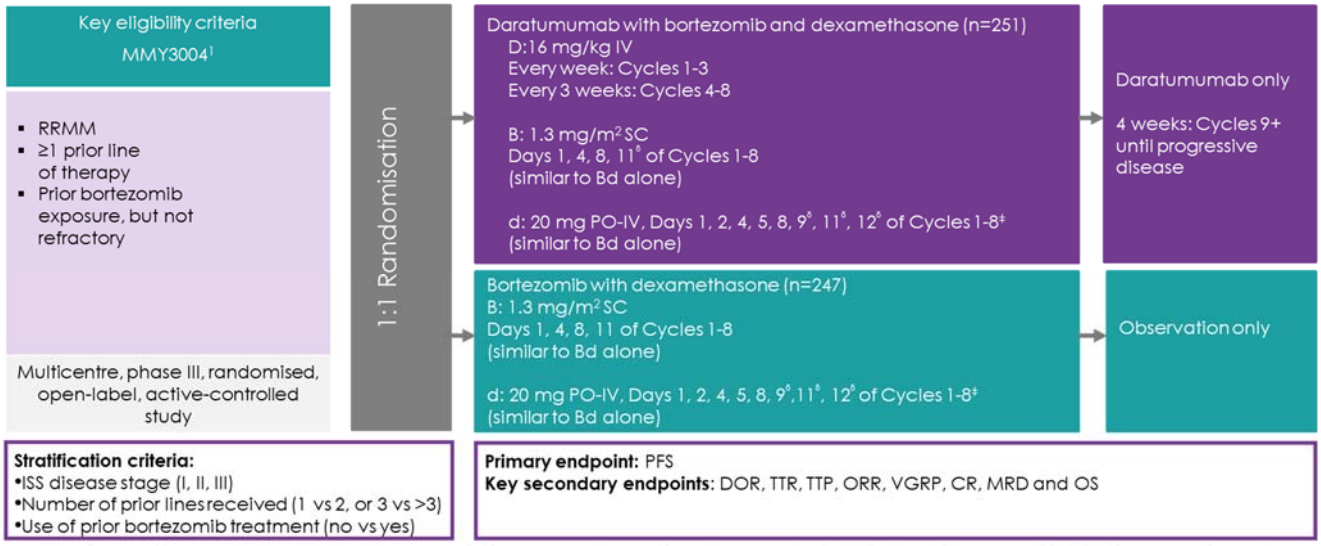
Patients were treated until disease progression or unacceptable toxicity. Disease evaluations included measurements of myeloma proteins, bone marrow examinations, skeletal surveys, assessment of extramedullary plasmacytomas and measurements of serum calcium corrected for albumin.[91]

Patients whose daratumumab treatment was discontinued could continue to receive bortezomib/dexamethasone. Patients who discontinued bortezomib could chose to continue with dexamethasone and/or daratumumab (DBd group only).[91]

Patients who were randomised to the Bd group received a maximum of 8 cycles of Bd followed by observation until disease progression or discontinuation for other reasons.[91]

An overview of the design of CASTOR is presented in Figure 3.

Figure 3 Overview of the CASTOR study design[91]



Bd = bortezomib and dexamethasone; DBd = daratumumab, bortezomib and dexamethasone; CR = complete response; DOR = duration of response; EOT = end-of-treatment; IV = intravenous; MRD = minimal residual disease; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; PO = orally; RRMM = relapsed refractory multiple myeloma; SC = subcutaneously; TX = study treatment; TTR = time to response; TTP = time to progression; VGPR = very good partial response

Based on the recommendations of an Independent Data Monitoring Committee (IDMC), the CASTOR study was unblinded to the sponsor at the first interim analysis due to the overwhelming efficacy of the daratumumab-containing combination regimen (see Section B.2.3.5). In addition, patients randomised to the control group were offered the option of treatment with daratumumab monotherapy after progressive disease was documented.[90]

Long-term survival follow-up commenced after observation of disease progression and continued every 16 weeks until patient death, loss to follow-up, consent withdrawal for study participation, or study end (defined as when approximately 320 deaths had occurred), whichever occurred first.[91]

B.2.3.2 Patient eligibility

Eligible patients had received at least one prior line of therapy, achieved at least a partial response to one or more of their prior therapies for MM and had documented progressive disease by IMWG criteria on or after their last regimen. All patients were required to have documented relapsed MM with measurable disease in the serum and/or urine as defined by the IMWG criteria.[91]

The inclusion and exclusion criteria for CASTOR are summarised in Table 7.

Table 7 CASTOR study inclusion and exclusion criteria[91]

Inclusion criteria	Exclusion criteria
▪ Aged ≥18 years ▪ Monoclonal plasma cells in the bone marrow ≥10% at some point in their disease history or presence of a biopsy proven plasmacytoma ▪ Measurable MM disease as defined by any of the following: o IgG MM: serum monoclonal paraprotein (M-protein) level ≥1.0g/dL or urine M-protein level ≥200mg/24 hours; or o IgA, IgD, IgE, IgM MM: serum M-protein level ≥0.5g/dL or urine M-protein level ≥200mg/24 hours; or o Light chain MM without measurable disease in the serum or the urine: Serum immunoglobulin free light chain ≥10mg/dL and abnormal serum immunoglobulin kappa lambda free light chain ratio ▪ Patients who have received at least 1 prior line of therapy for MM ▪ Patients must have achieved a response (PR or better) to at least one prior regimen ▪ Documented evidence of progressive disease on or after their last regimen. ▪ ECOG Performance Status score of 0, 1, or 2 ▪ For patients experiencing toxicities resulting from previous therapy, the toxicities must have resolved or stabilised to Grade ≤1 ▪ Women of childbearing potential must commit to either abstain continuously from heterosexual sexual intercourse or to use 2 methods of reliable birth control simultaneously. Contraception must begin 4 weeks prior to dosing ▪ Women of childbearing potential must have 2 negative serum or urine pregnancy tests at Screening, first within 10–14 days prior to dosing and the second within 24 hours prior to dosing ▪ Patients must sign an informed consent form indicating that he or she understands the purpose of and procedures required for the study and are willing to participate in the study	▪ Previous use of daratumumab or other anti-CD38 therapies ▪ Refractory to bortezomib, or another PI, like ixazomib and carfilzomib (i.e. patient had progression of disease while receiving, or within 60 days of ending, PI therapy). Ixazomib and carfilzomib were added as exclusion criteria in Amendment 1 when 40 patients were randomised ▪ Intolerant to bortezomib (i.e. discontinued due to any AE while on bortezomib treatment) ▪ Received anti-myeloma treatment within 2 weeks or 5 pharmacokinetic half-lives of the treatment before the date of randomisation (except the use of an emergency short course of corticosteroids before treatment) ▪ History of malignancy (other than MM) within 5 years before the date of randomisation (some exceptions apply) ▪ Received ASCT within 12 weeks before the date of randomisation or have previously received an allogenic SCT ▪ Patients planning to undergo a SCT prior to progression of disease on this study ▪ Known meningeal involvement of MM ▪ COPD or asthma ▪ Known seropositivity for HIV, hepatitis B or C ▪ Any concurrent medical condition or disease that is likely to interfere with study procedures or results ▪ Clinically significant cardiac disease ▪ Do not meet laboratory test requirements in terms of haemoglobin, platelet, AST, alkaline phosphate, bilirubin, creatinine clearance and serum calcium levels during the screening phase ▪ Known allergies, hypersensitivity, or intolerance to monoclonal antibodies, human proteins or their excipients, or known sensitivity to mammalian-derived products ▪ PCL or Waldenström's macroglobulinemia or POEMS syndrome or amyloidosis ▪ Patients who are known or suspected to not be non-compliant with the study protocol ▪ Pregnant or breastfeeding or planning to become pregnant ▪ Patients have received an investigational drug or used an invasive investigational medical device within 4 weeks before randomisation ▪ Major surgery within 2 weeks before randomisation, will not have fully recovered from surgery, or have surgery planned during the time they are expected to participate in the study

ASCT = autologous stem cell transplant; AST = aspartate aminotransferase; COPD = chronic obstructive pulmonary disease; ECOG = Eastern Cooperative Oncology Group; HIV = Human immunodeficiency virus; ISS = International Staging System; MM = multiple myeloma; PCL = Plasma cell leukaemia; PI = proteasome inhibitor; POEMS = Polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, skin changes; PR = partial response; SCT = stem cell transplant; SD = standard deviation.

B.2.3.3 Study site locations

CASTOR was conducted in 16 countries: 11 in the European region (Czech Republic [4 sites], Germany [10 sites], Hungary [4 sites], Italy [12 sites], Netherlands [8 sites], Poland [6 sites], Russian Federation [9 sites], Spain [6 sites], Sweden [7 sites], Turkey [7 sites], Ukraine [9 sites]), Australia (7 sites), Brazil (6 sites), the Republic of Korea (7 sites), Mexico (2 sites) and the US (13 sites).[91]

B.2.3.4 Study drugs

An overview of the study treatment and dosing is presented in Table 8.

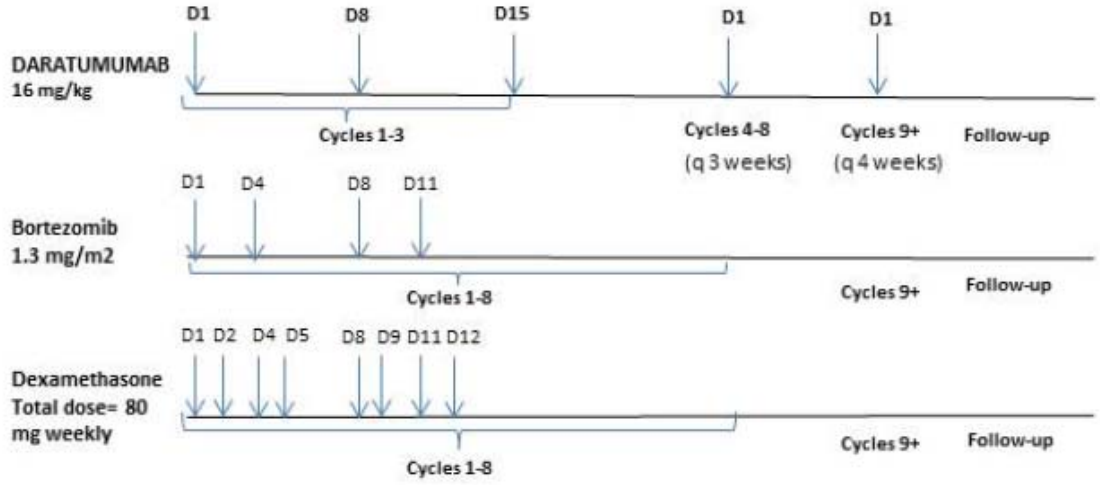
Table 8 Treatment combinations and dosing in CASTOR[91]

Study arms	**Intervention:** Daratumumab in combination with bortezomib and dexamethasone **Comparator:** Bortezomib in combination with dexamethasone
Drug dosing	**Daratumumab:** IV infusion 16mg/kg weekly for the first 3 cycles, on day 1 of cycles 4 to 8 and then 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. Eight bortezomib treatment cycles were administered **Dexamethasone:** orally at 20mg on days 1, 2, 4, 5, 8, 9, 11, and 12, of the first eight 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. 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. On the days of daratumumab administration, the scheduled dose of dexamethasone was administered as a premedication prior to infusion rather than taken by the patient at home. Pre-medication with oral dexamethasone up to 3 hours prior to the dose of daratumumab was another option available after the implementation of the protocol amendment.
Treatment duration	**Daratumumab**: until disease progression **Bortezomib**: eight 21-day treatment cycles **Dexamethasone**: eight 21-day treatment cycles

AE = adverse event; BMI = body mass index; IV – intravenous; SC = subcutaneous

A schematic representation of the dosing schedule is provided in Figure 4. The start of a cycle was defined as the start of any of the study treatments (daratumumab, bortezomib or dexamethasone).The Treatment Phase consisted of cycles of 21 days (Cycles 1-8) and 28 days (Cycle 9 and onwards). Patients continued to receive daratumumab until disease progression or unacceptable toxicity.[91]

Figure 4 Overview of the study dosing schedule in the CASTOR study[91]



D = day; q = daily.

For details of prior and concomitant therapy in CASTOR study, see Section 2.5 in Appendix D.

B.2.3.5 Outcome measures in the CASTOR study

The primary objective of CASTOR was to compare the efficacy of DBd with Bd alone in terms of progression-free survival (PFS). Assessment of response and disease progression was performed by a central laboratory and a validated computerised algorithm was used in line with the IMWG criteria of response. As a sensitivity analysis, additional investigator assessments of response and disease progression per the IMWG response criteria were performed.[25,90,92,93]

Key secondary objectives were to compare the efficacy of DBd with Bd for:[90]

- Time to disease progression (TTP)
- Overall response rate (ORR)
- Rate of very good partial response (VGPR) or better
- Time to response (TTR)
- Duration of response (DOR)
- Minimal residual disease (MRD)
- Overall survival (OS)
- Safety and tolerability

In addition to traditional assessment of response, IMWG guidelines now recommend consideration of MRD after each treatment stage in patients with a complete response (CR).[2] MRD is a new, more sensitive measure of disease compared with established definitions of clinical response in MM, where residual tumour cells are identified in the bone marrow based on the IMWG criteria described in Table 9.[2] Historically, MRD has not been measured at first relapse because it has generally been regarded as unobtainable.

Within CASTOR, MRD negativity was assessed using next generation sequencing (NGS) in bone marrow aspirates at three different thresholds (10^{-4}, 10^{-5} and 10^{-6}).[94] Aside from POLLUX (phase III RCT of daratumumab in combination with lenalidomide and dexamethasone versus lenalidomide plus dexamethasone), CASTOR was the first trial in RRMM patients to consider MRD.[95,96] MRD-negativity inside the bone marrow is now an accepted prognostic indicator of long-term patient outcome, being correlated with prolonged survival in patients with CR to therapy.[64,97] One meta-analysis found that compared to MRD-positive patients, patients negative for MRD had improved PFS (14 studies; HR 0.41 [95% CI: 0.36, 0.48]; p<0.0001) and OS (12 studies; HR 0.57 [95% CI: 0.46, 0.71]; p<0.0001).[98]

Table 9 IMWG criteria for MRD[2]

Response subcategory	Response criteria
Sustained MRD-negative	MRD negativity in the bone marrow confirmed ≥1 year apart by NGF, NGS, or both and by imaging (see flow MRD-negative category)
Flow MRD-negative	Absence of phenotypically aberrant clonal plasma cells by NGF on bone marrow aspirates using EuroFlow (or validated equivalent method) with a minimum sensitivity of 1 in 10^5 nucleated cells or higher
Sequencing MRD-negative	Absence of clonal plasma cells by NGS on bone marrow aspirate Presence of a clone is defined as <2 identical sequencing reads from bone marrow aspirates using the LymphoSIGHT platform (or validated equivalent method) with a minimum sensitivity of 1 in 10^5 nucleated cells or higher
Imaging-positive MRD-negative	MRD negativity as defined by NGF or NGS, plus at least one of the following criteria: Disappearance of every area of increased tracer uptake found at baseline or a preceding PET/CT Decrease to less mediastinal blood pool SUV Decrease to less than that of surrounding normal tissue

CT = computed tomography; IMWG = International Myeloma Working Group; MRD = minimal residual disease; NGF = next generation flow; NGS = next generation sequencing; PET = positron emission tomography; SUV = standardised uptake value.

These criteria are based on those used by Zamagni and colleagues and expert panel (IMPetUs; Italian Myeloma criteria for PET Use). Baseline positive lesions were identified by presence of focal areas of increased uptake within bones, with or without any underlying lesion identified by CT and present on ≥2 consecutive slices. Alternatively, SUVmax=2.5 within osteolytic CT areas >1 cm in size, or SUVmax=1.5 within osteolytic CT areas ≤1 cm in size were considered positive. Imaging should be performed once MRD negativity is determined by multiparameter flow cytometry or NGS.

Source: Kumar et al. 2016.

The following additional pre-specified efficacy analyses were explored within CASTOR:[92]

- Time to Subsequent Anticancer Therapy
- Best M-protein Response
- Progression-free Survival on the Next Line of Therapy (PFS2)
- Best response to First Subsequent Anticancer Therapy

Pre-specified assessment of functional status and well-being were assessed using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ-C30) and the EuroQol Five Dimensions Questionnaire (EQ-5D-5L).[92]

Post-hoc analyses of time to treatment discontinuation (TTD) were carried out to inform the economic model.

An overview of the efficacy and safety outcomes assessed in the interim and Final Analyses of CASTOR that are presented in this submission are summarised in Table 10.

Table 10 Summary of CASTOR data-cuts reported in the submission[77,91,94]

Data cut-off	Median follow-up	Populations included	Outcomes assessed	Rational for inclusion
11 January 2018	26.9 months	ITT and safety populations, patients with 1PL	Primary endpoint: PFS Secondary endpoints: ▪ ≥CR rate ▪ ≥VGPR ▪ MRD negativity ▪ ORR ▪ OS ▪ TTP ▪ Time to next treatment ▪ Time to response ▪ DOR ▪ PFS2 ▪ HRQoL ▪ Safety and tolerability	Interim OS analysis, efficacy and safety analyses [Data cut presented in the original company submission (TA573)]
14th August 2019	50.2 months	ITT and safety populations, patients with 1PL	Primary endpoint: PFS Secondary endpoints: ▪ PFS2	Primary PFS Analysis, updated efficacy analyses with longer-term follow-up
28th June 2021	72.6 months		Secondary endpoints: ▪ OS ▪ MRD ▪ Safety and tolerability	Final OS Analysis. updated efficacy and safety analyses with longer-term follow-up

CR = complete response; DOR = duration of response; HRQoL = health related quality of life; MRD = minimal residual disease; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; PFS2 = time to progression on the next line of therapy; 1PL = one prior line of therapy; TTP = time to progression; VGPR = very good partial response

B.2.3.6 Summary of methodology

A summary of the methodology used in CASTOR is presented in Table 11.

Table 11 Summary of trial methodology[91]

Trial	CASTOR (MMY3004)
Location	Multicentre: 117 sites across 16 countries
Trial design	Multicentre, phase III, randomised, open-label, active-controlled study of DBd vs. Bd Patients were randomised 1:1 (computer-generated randomization schedule) to receive either DBd (n=251) or Bd (n=247) Randomisation was stratified at screening by ISS, number of prior lines and prior use of bortezomib
Eligibility criteria for participants	Eligible patients had received at least 1 prior line of therapy and achieved at least a partial response to one or more of their prior therapies for MM, and had documented progressive disease by IMWG criteria on or after their last regimen. All patients were required to have documented relapsed multiple myeloma with measurable disease in the serum and/or urine as defined by the IMWG criteria
Trial drugs (the interventions for each group with sufficient details to allow replication, including how and when they were administered) **Intervention (n=243) and comparator (n=237)** **Permitted and disallowed concomitant medication**	Study treatment: daratumumab in combination with bortezomib and dexamethasone Study drug: daratumumab Daratumumab: IV infusion, 16mg/kg weekly for the first 3 cycles, on day 1 of cycles 4 to 8 and then every 4 weeks thereafter until disease progression or an unacceptable level of toxicity was reached Bortezomib: SC at a dose of 1.3mg/m^2 on days 1, 4, 8, and 11 of each 21-day cycle. Eight bortezomib treatment cycles were administered Dexamethasone: orally at a dose of 20mg on days 1, 2, 4, 5, 8, 9, 11, and 12, of the first eight bortezomib treatment cycles (i.e. total dose of 160mg per cycle). Administered at a dose of 20mg IV before the infusion during weeks when the patient received an infusion of daratumumab
Efficacy evaluation (including scoring methods and timings of assessments)	Serum and urine tests were performed every 21 days on the scheduled assessment day (±3 days) during Cycles 1 through 8. After Cycle 8 (beginning of Cycle 9) Disease assessments: serum protein electrophoresis, urine protein electrophoresis, and serum calcium corrected for albumin, were collected every cycle for the first 18 months of the study and every-other month thereafter. All responses (including PD based on biochemical investigations) required 2 consecutive assessments
Primary outcomes	PFS Defined as the time from the date of randomisation to the date of disease progression or death, whichever occurred first and assessed using computerised algorithm in accordance with IMWG criteria PFS based on investigator assessment was included in sensitivity analyses
Other outcomes used in the economic model/specified in the scope	▪ Rate of VGPR or better; ORR; OS; DOR; TTR; MRD; TTD ▪ Safety and tolerability ▪ EORTC QLQ-C30; EQ-5D-5L Disease progression and response outcomes assessed using computerised algorithm; outcomes assessment by investigator included in sensitivity analyses Safety data acquired during the study were reviewed on a regular basis by an unblinded IDMC member.

Pre-planned subgroups	Sex (male, female) Age (<65 years, ≥65 years) Race (White, others) Baseline renal function (≤60mL/min, >60mL/min) Baseline hepatic function (normal, impaired) Region (Western EU and US, other) ISS (I, II, III) Number of prior lines therapy (1, 2, 3, >3) Prior bortezomib treatment (no, yes) Prior IMiD (yes, no) Refractory to IMiD (yes, no) Refractory to last line of therapy (yes, no) Type of MM (IgG, non-IgG) High-risk (high risk, standard risk) ECOG performance score (0, ≥1)

Bd = bortezomib and dexamethasone; DBd = daratumumab, bortezomib and dexamethasone; DOR = duration of response; 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; IDMC = Independent Data Monitoring Committee; IMiD = immunomodulatory drug; ISS = International Staging System; IV = intravenous; MM = multiple myeloma; MRD = minimal residual disease; ORR = overall response rate; OS= overall survival; PD = progressive disease; PFS = progression-free survival; SC = subcutaneous; TTD = time to treatment discontinuation; TTP = time to disease progression; TTR = time to response; VGPR = very good partial response

B.2.3.7 Baseline patient and disease characteristics

A total of 498 patients (DBd: 251, Bd: 247) were randomised between 4 September 2014 and 15 September 2015 internationally across 16 countries. Demographic and baseline characteristics were well balanced between the two treatment groups with no categories having a difference of ≥10% (Table 12). The median age of the patient population was 64 years (range 30 to 88 years). All patients had received prior systemic therapy and 61% of patients had a prior autologous stem cell transplant (ASCT). The median number of lines of prior systemic therapies was 2 (range 1 to 10) and 47% of patients had received 1 line of prior therapy.[92]

Table 12 Characteristics of participants in CASTOR across treatment groups (intent-to-treat analysis set)[92,96,99,100]

	Bd, ITT (n=247)	**DBd, ITT (n=251)**	**Bd, 1PL (n=113)**	**DBd, 1PL (n=122)**
Age, years, n (%)				
<65	125 (50.6)	132 (52.6)	[redacted]	[redacted]
65 to 74	87 (35.2)	96 (38.2)	[redacted]	[redacted]
≥75	35 (14.2)	23 (9.2)	17 (15.0)	8 (7.0)
Mean (SD)	63.9 (9.8)	62.8 (9.7)	[redacted]	[redacted]
Median	64.0	64.0	64.0	63.0
Range	(33; 85)	(30; 88)	(40; 85)	(30; 84)

	Bd, ITT (n=247)	DBd, ITT (n=251)	Bd, 1PL (n=113)	DBd, 1PL (n=122)
Sex, n (%)				
Male	147 (59.5)	137 (54.6)	[redacted]	[redacted]
Ethnicity, n (%)				
Hispanic or Latino	24 (9.7)	17 (6.8)	[redacted]	[redacted]
Not Hispanic or Latino	212 (85.8)	227 (90.4)	[redacted]	[redacted]
Unknown	3 (1.2)	1 (0.4)	[redacted]	[redacted]
Not Reported	8 (3.2)	6 (2.4)	[redacted]	[redacted]
Race, n (%)				
White	219 (88.7)	216 (86.1)	[redacted]	[redacted]
Black or African American	6 (2.4)	14 (5.6)	[redacted]	[redacted]
Asian	11 (4.5)	12 (4.8)	[redacted]	[redacted]
American Indian or Alaska Native	1 (0.4)	1 (0.4)	[redacted]	[redacted]
Native Hawaiian or other Pacific Islander	0	1 (0.4)	[redacted]	[redacted]
Other	1 (0.4)	5 (2.0)	[redacted]	[redacted]
Unknown	2 (0.8)	0	[redacted]	[redacted]
Not Reported	7 (2.8)	2 (0.8)	[redacted]	[redacted]
Weight (kg)				
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median	76.0	77.0	[redacted]	[redacted]
Range	(37.5; 131.6)	(45.0; 134.8)	[redacted]	[redacted]
Height (cm)				
Mean (SD)	166.8 (10.0)	166.8 (10.0)	[redacted]	[redacted]
Median	167.0	167.0	[redacted]	[redacted]
Range	(139; 192)	(141; 194)	[redacted]	[redacted]
Baseline ECOG score, n (%)				
0	116 (47.0)	106 (42.4)	[redacted]	[redacted]
≥1			[redacted]	[redacted]
1	112 (45.3)	131 (52.4)	[redacted]	[redacted]
2	19 (7.7)	13 (5.2)	[redacted]	[redacted]
>2	0	0	[redacted]	[redacted]
Type of measurable disease[a], n (%)				
IgG	138 (55.9)	125 (49.8)	[redacted]	[redacted]
IgA	54 (21.9)	56 (22.3)	[redacted]	[redacted]
Other[b]	4 (1.6)	5 (2.0)	[redacted]	[redacted]
Urine only	36 (14.6)	40 (15.9)	[redacted]	[redacted]
Serum FLC only	14 (5.7)	25 (10.0)	[redacted]	[redacted]
NE	1 (0.4)	0	[redacted]	[redacted]
ISS staging[c], n (%)				

	Bd, ITT (n=247)	DBd, ITT (n=251)	Bd, 1PL (n=113)	DBd, 1PL (n=122)
I	96 (38.9)	98 (39.0)	51 (45.1)	57 (46.7)
II	100 (40.5)	94 (37.5)	44 (38.9)	42 (34.4)
III	51 (20.6)	59 (23.5)	18 (15.9)	23 (18.9)
Time from MM diagnosis to randomisation (years)				
Mean (SD)	4.8 (3.3)	4.7 (3.2)	[redacted]	[redacted]
Median	3.7	3.9	2.98	2.81
Range	(0.6; 18.6)	(0.7; 20.7)	(0.6; 18.1)	(0.7; 14.9)
Number of lytic bone lesions, n (%)				
None	50 (20.3)	56 (22.5)	[redacted]	[redacted]
1-3	43 (17.5)	50 (20.1)	[redacted]	[redacted]
4-10	55 (22.4)	53 (21.3)	[redacted]	[redacted]
>10	98 (39.8)	90 (36.1)	[redacted]	[redacted]
Any cytogenetic abnormality[d], n (%)				
Standard-risk	137 (78.7)	140 (77.3)	[redacted]	[redacted]
High-risk	37 (21.3)	41 (22.7)	[redacted]	[redacted]
Del17p	21 (12.1)	28 (15.5)	[redacted]	[redacted]
T(4;14)	15 (8.6)	14 (7.7)	[redacted]	[redacted]
T(14;16)	5 (2.9)	4 (2.2)	[redacted]	[redacted]
Total number of patients with any prior therapies for MM, n (%)				
Prior systemic therapy	247 (100.0)	251 (100.0)	[redacted]	[redacted]
Prior ASCT	149 (60.3)	156 (62.2)	[redacted]	[redacted]
Prior radiotherapy	59 (23.9)	63 (25.1)	[redacted]	[redacted]
Prior cancer-related surgery	35 (14.2)	33 (13.1)	[redacted]	[redacted]
Number of prior lines of therapy[e], n (%)				
1	113 (45.7)	122 (48.6)	113 (100)	122 (100)
2	74 (30.0)	70 (27.9)	0	0
3	32 (13.0)	37 (14.7)	0	0
>3	28 (11.3)	22 (8.8)	0	0
Mean (SD)	2.0 (1.4)	1.9 (1.2)	-	-
Median	2.0	2.0	1	1
Range	(1; 10)	(1; 9)	(1; 1)	(1; 1)
Prior therapy exposure, n (%)				
Prior PI	172 (69.6)	169 (67.3)	59 (52)	65 (53)
Bortezomib	164 (66.4)	162 (64.5)	57 (50.4)	62 (50.8)

	Bd, ITT (n=247)	DBd, ITT (n=251)	Bd, 1PL (n=113)	DBd, 1PL (n=122)
Carfilzomib	10 (4.0)	12 (4.8)	[redacted]	[redacted]
Ixazomib	7 (2.8)	12 (4.8)	[redacted]	[redacted]
Prior IMiD	198 (80.2)	179 (71.3)	[redacted]	[redacted]
Lenalidomide	120 (48.6)	89 (35.5)	[redacted]	[redacted]
Pomalidomide	7 (2.8)	7 (2.8)	[redacted]	[redacted]
Thalidomide	121 (49.0)	125 (49.8)	[redacted]	[redacted]
Prior corticosteroids	245 (99.2)	244 (97.2)	[redacted]	[redacted]
Dexamethasone	233 (94.3)	218 (86.9)	[redacted]	[redacted]
Prednisone	77 (31.2)	83 (33.1)	[redacted]	[redacted]
Prior alkylating agents	224 (90.7)	240 (95.6)	[redacted]	[redacted]
Prior anthracyclines	80 (32.4)	72 (28.7)	[redacted]	[redacted]
Prior PI+IMiD	129 (52.2)	112 (44.6)	[redacted]	[redacted]
Prior PI+IMiD+ALKY	121 (49.0)	112 (44.6)	[redacted]	[redacted]
Prior bortezomib+lenalidomide	89 (36.0)	75 (29.9)	[redacted]	[redacted]
Refractory status, n (%)				
PI only	4 (1.6)	3 (1.2)	[redacted]	[redacted]
IMiD only	90 (36.4)	74 (29.5)	[redacted]	[redacted]
Both PI and IMiD	7 (2.8)	9 (3.6)	[redacted]	[redacted]
Lenalidomide	81 (32.8)	60 (23.9)	16 (18.0)	6 (5.0)

1PL = one prior line; ALKY = alkylating agents; ASCT = autologous stem cell transplant; Bd = bortezomib and dexamethasone; DBd = daratumumab, bortezomib and dexamethasone; ECOG = Eastern Cooperative Oncology Group; FISH = fluorescence in situ hybridisation; FLC = free light chain; IMiD = immunomodulatory drug; ISS = International Staging System; ITT = intent-to-treat; MM = multiple myeloma; PI = proteasome inhibitor; MM = multiple myeloma; NE = not evaluable; SD = standard deviation

- = not available

[a]Includes patients without measurable disease in serum and urine.

[b]Includes IgD, IgM, IgE and biclonal.

[c]ISS staging is derived based on the combination of serum β2-microglobulin and albumin.

[d]Cytogenetic abnormalities are based on FISH or karyotype testing.

[e]Based on data recorded on prior systemic therapy eCRF page.

B.2.3.8 SACT Study methodology

The SACT analysis was conducted by the National Disease Registration Service (commissioned by NHS England and NHS Improvement) to evaluate the real-world effectiveness of DBd in England during the managed access period.[70]

The analysis included [redacted] patients who received DBd through the CDF (application for treatment received between [redacted]) and met the following eligibility criteria:[70]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

For the patients included in the dataset, the following conditions of treatment were observed:[70]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

To identify patients eligible for the study, NHS numbers were used to link SACT records to CDF applications for DBd recorded in the NHS England and NHS Improvement's Blueteq system. Treatment dates (regimen, cycle and administration dates) and primary diagnosis codes were used to ensure the correct SACT treatment records were matched to the corresponding CDF application.[70]

The following outcomes were evaluated in the study:[70]

- [redacted]
- [redacted]

B.2.3.9 Baseline patient and disease characteristics

Following the selection process presented in

Figure 5, [redacted] patients were included in the SACT analysis.[70]

Figure 5 Selection of patient cohort included in SACT data analysis[70]

[redacted]

CDF = Cancer Drugs Fund; SACT = Systemic Anticancer Therapy

Most patients were over [redacted], with a median age of [redacted].[70] A summary of the reported baseline patient characteristics and prior treatment status among patients treated with daratumumab included in the SACT dataset is presented in

Table 13.

Table 13 Patient and disease characteristics, SACT dataset analysis (N=)[70]

	SACT cohort (DBd treatment)

Bd = bortezomib and dexamethasone; DBd = daratumumab, bortezomib and dexamethasone; ECOG = Eastern Cooperative Oncology Group; SACT = Systemic Anti-Cancer Therapy

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

B.2.4.1 Summary of statistical analyses in the CASTOR study

In CASTOR, the primary endpoint of PFS was evaluated using a group sequential design with one prespecified interim analysis (see Section B.2.4.3 for details). For estimating statistical significance of the secondary endpoints, hierarchical testing was used to control for the Type I error rate. Major secondary endpoints were tested for significance sequentially (with a two-sided alpha level of 0.05) if significance was achieved for the primary endpoint in the interim analysis (see Section B.2.4.3 for details).[90,91]

A summary of the statistical analyses undertaken in this study is provided in Table 14.

Table 14 Summary of statistical analyses[92]

Trial	CASTOR (MMY3004)
Hypothesis objective	The primary efficacy endpoint is PFS. The null hypothesis is that there is no difference in PFS between DBd and Bd in patients with relapsed or refractory multiple myeloma The null hypotheses (H0) of no difference between DBd and Bd are also evaluated for the following major secondary objectives: ▪ TTP ▪ Rate of VGPR or better ▪ ORR ▪ OS These secondary hypotheses were tested in a sequential order as specified above
Statistical analysis	Analysis comparing groups for the primary hypothesis consisted of a stratified log-rank test A hierarchical testing approach was used to test secondary endpoints Stratified log-rank tests were used to assess time-to-event outcomes, with binary outcomes assessed using the stratified Cochran-Mantel-Haenszel test
Sample size, power calculation	Approximately 480 participants (240 per group) were required to provide 85% power to detect a reduction of 30% in the risk of either progression or death (Hazard ratio [DBd vs Bd] of 0.70) with a log-rank test (two-sided alpha=0.05) and 80% power to detect a 27% reduction in the risk of death (Hazard ratio=0.73) with a log-rank test (two-sided alpha=0.05)
Data management, patient withdrawals	Reason for withdrawal documented on the eCRF and source document
Censoring	Censoring rules were the same for both PFS and TTP: 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 Patients who withdrew consent from the study before disease progression were censored at the last disease assessment before withdrawal of consent to study Patients who were lost to follow-up were censored at the last disease assessment before patients were lost to follow-up Patients who had not progressed and were still alive at the cut-off date for analysis were censored at the last disease assessment Patients without any post-baseline disease assessment were censored at the randomisation For OS, if the patient was alive or the vital status was unknown, then the patient's data was censored at the date the subject was last known to be alive. For patients without confirmed response for the time to response analysis, and for patients who did not have documented evidence of progressive disease for the duration of response analysis, data was censored at the censoring date for TTP.

Bd = bortezomib and dexamethasone; DBd = daratumumab, bortezomib and dexamethasone; eCRF = Electronic case report form; PFS = progression free survival.

B.2.4.2 Study population and sample size in CASTOR

In CASTOR, 498 patients were randomised in the study (251 in the DBd group, 247 in the Bd group) and 480 patients received study treatment (243 in the DBd group, 237 in the Bd group). The sample size for this study was based on the alternative hypothesis of a 30% reduction in the risk of either progression or death. Under the exponential distribution, this benefit translates to a prolongation in median PFS from 10 months to 14.3 months. A total of 295 PFS events would provide a power of 85% to detect a reduction of 30% in the risk of

either progression or death (Hazard ratio [DBd versus Bd] of 0.70) with a log-rank test, assuming a two-sided significance level of 5%.[92]

Analysis of long-term OS was performed after 320 deaths had been observed (i.e., when two-thirds of the randomised patients had died). The study was designed to achieve approximately 80% power to detect a 27% reduction in the risk of death (hazard ratio=0.73) with a log-rank test (two-sided alpha=0.05), taking into consideration an annual dropout rate of 5%.[92]

Patient populations analysed in CASTOR

The primary endpoint and other time-to-event efficacy endpoints are based on the intent-to-treat (ITT) population, which includes all randomised participants. Analyses of major secondary endpoints of ORR, rate of VGPR or better and duration of and time to response is based on the response-evaluable population, defined as participants who have a confirmed diagnosis of multiple myeloma and measurable disease at baseline or screening visit, received at least one administration of study drug and have had at least one post baseline disease assessment.[92]

Safety outcomes, including AEs, were analysed in the safety population, which included 480 study participants who were randomised, received at least 1 dose of any study treatment, and for whom any safety data were recorded.[90,91]

Several pre-specified subgroup analyses were performed evaluating the primary efficacy endpoint of PFS, major secondary endpoints and safety endpoints:[92]

- Sex (Male, female)
- Age (<65 years, ≥65 years)
- Race (White, Others)
- Baseline renal function (≤60 mL/min, >60 mL/min)
- Baseline hepatic function (Normal, Impaired)
- Region (Western EU +US, Other)
- ISS (I, II, III)
- Number of prior lines therapy (1, 2, 3, >3)
- Prior bortezomib treatment (No, Yes)
- Prior IMiD (Yes, No)

- Refractory to IMiD (Yes, No)
- Refractory to last line of therapy (Yes, No)
- Type of MM (IgG, Non-IgG)
- High-risk (High risk, Standard risk)
- ECOG performance score (0, ≥1).

B.2.4.3 Statistical analyses in the CASTOR study

The primary analysis consisted of a stratified log-rank test for comparison of the PFS distribution between DBd and Bd using the ITT population.

The significance level to establish the superiority of DBd over Bd with regard to PFS was determined based on the observed number of PFS events at the interim analysis, using the O'Brien-Fleming boundaries as implemented by the Lan-DeMets alpha spending method.[91]

The Kaplan-Meier method was used to estimate the distribution of overall PFS for each treatment. The treatment effect (Hazard ratio) and its two-sided 95% confidence intervals were estimated using a stratified Cox regression model with treatment as the sole explanatory variable. Stratification factors used in the analyses were ISS staging (I, II, III), number of prior lines of therapy (1 versus 2 or 3 versus >3), and prior bortezomib treatment (no versus yes).[91]

The determination of dates for PFS events and dates for censoring is summarised in Table 15.

Table 15 PFS event and censoring method[91]

Situation	Date of progression or censoring	Outcome
Disease progression prior to start of subsequent anticancer therapy	Earliest date that indicates disease progression	PFS event
Death prior to start of subsequent anticancer therapy	Date of death	PFS event
No postbaseline disease assessment	Randomisation	Censored
Other (e.g. withdrawal of consent to study participation, lost to follow-up, start of subsequent anticancer therapy, etc.)	Date of last disease assessment prior to subsequent anticancer treatment	Censored

PFS = progression-free survival; TTP = time to disease progression.

Sensitivity analyses included:[91]

- PFS based on investigator assessment of progression

- PFS without censoring for subsequent anticancer therapies for participants who have not developed a confirmed progressive disease
- PFS by censoring for death or progression after more than one missed disease evaluation
- PFS derived for the per-protocol population
- PFS using an unstratified log-rank test.

Following testing for statistical significance of the primary endpoint of PFS, major secondary endpoints were sequentially tested as ordered below, each with an overall two-sided alpha of 0.05. A hierarchical testing approach as proposed by Tang and Geller (1999) was utilised, which strongly controls the Type I error rate.[101] Major secondary endpoints were ordered as follows:[91]

- TTP
- Rate of VGPR or better
- ORR
- MRD negativity rate
- OS

The determination of dates for time to disease progression (TTP) events and dates for censoring were similar to those described in Table 15 for PFS. Disease progression prior to the start of subsequent anticancer therapy was taken to be the earliest date that indicates disease progression. The date of death was determined as the death due to disease progression prior to the start of subsequent anticancer therapy. For OS, if the patient was alive or the vital status was unknown, then the patient's data was censored at the date that the patient was last known to be alive.[91]

Unless otherwise specified, no data imputation has been applied for missing safety and efficacy evaluations. For analysis and reporting purposes, missing or partial dates for adverse events (AE onset date; AE end date), concomitant therapies (start date; end date), MM diagnosis date, prior multiple myeloma therapies (start date; end date) and start date of subsequent anticancer therapy have been imputed.[91]

B.2.4.4 Summary of CASTOR data cuts

Two interim analyses and a final OS analysis were planned for this study. The first interim analysis evaluated safety and was performed after 80 patients had been treated for at least 8 weeks or discontinued study treatment.[91]

This submission includes data from the following analyses/data cuts:

- A top-line summary of results from the planned interim analysis (IA2) with a clinical cut-off of 11 January 2018 (median follow-up 26.9 months). IA2 evaluated cumulative interim safety and efficacy data and was performed when approximately 179 PFS events (60% of the total planned events) had occurred; these data were submitted to NICE as part of the original DBd submission in 2018.[76,91]
- The Primary PFS Analysis, with a clinical cut-off of 14 August 2019 (median follow-up 50.2 months).[77]
- The Final OS Analysis with a clinical cut-off of 28 June 2021 (median follow-up 72.6 months), which occurred after 319 deaths (99.7% of the planned 320 events) were observed.[77,94]

B.2.4.5 Participant flow in CASTOR

As of the clinical cut-off date of 28 June 2021 for the Final OS Analysis, all patients were considered as having discontinued the study as per protocol (no further data collection was planned). The most common reason for treatment discontinuation was death in both treatment groups (59% in the DBd group and 68.8% in the Bd group).[94]

Table 16 Summary of patient disposition at median follow-up 72.6 months (ITT population)[94]

	DBd, n (%)	Bd, n (%)	Total n (%)
Analysis set: intent-to-treat	251	247	498
Patients randomised but not treated[a]	8 (3.2)	10 (4.0)	18 (3.6)
Patients treated[a]	243 (96.8)	237 (96.0)	480 (96.4)
Patients who completed treatment[b]	0	133 (56.1%)	133 (27.7%)
Patients still on treatment[b]	30 (12.3)	0	30 (6.3)
Patients who discontinued study[a]	251 (100)	247 (100)	498 (100)
Withdrawal by patient	10 (4.0)	19 (7.7)	29 (5.8)
Death	148 (59.0)	170 (68.8)	318 (63.9)
Lost to follow-up	3 (1.2)	3 (1.2)	6 (1.2)
Other	3 (1.2)	3 (1.2)	6 (1.2)

Bd = bortezomib and dexamethasone; DBd = daratumumab, bortezomib and dexamethasone.

[a] Percentages are based on number of patients randomised.

[b] Percentages are based on number of patients treated.

If a participant withdrew after randomisation and after receiving at least one dose of study agent and before completion of the study, the reason for withdrawal was documented on the Electronic Case Report Form (eCRF) and source document. Participants who withdrew from the study were not replaced. The study agent assigned to the withdrawn participant was not

assigned to another participant. The procedures scheduled for End-of-Treatment Visit and Follow-up Visit were performed at the time of early withdrawal as specified in the Time and Events Schedule in the protocol.[92]

A participant was considered to have completed the study if he or she died before the end of the study, had not been lost to follow-up, or had not withdrawn consent from study participation. The study end was defined as when 320 deaths had occurred.[92]

Please refer to Appendix D for further details on participant flow.

B.2.4.6 Study population in the SACT dataset

The patient cohort in the SACT dataset analysis included patients with CDF applications for DBd treatment between [redacted]. A snapshot of SACT data was taken on [redacted].[70]

B.2.4.7 Statistical analyses in the SACT dataset

Overall survival

Overall survival was calculated for each patient as the [redacted]. For patients who remained alive, the [redacted] was carried out on [redacted]

Patients in the study cohort were either defined as: [70]

[redacted]

Treatment duration

To estimate the treatment duration, the [redacted].[70] Similarly, to estimate the treatment end date, the [redacted]

For patients who died between treatment administrations, the [redacted]

After calculation of the treatment duration, the treatment status of each patient was identified as:

- [redacted]
- [redacted]

B.2.5 Critical appraisal of the relevant clinical effectiveness evidence

B.2.5.1 Quality assessment of CASTOR

Study results published in a peer-reviewed journal were used as the primary source of data where available, clinical study reports (CSRs) were used as additional data sources.

A complete quality assessment of the CASTOR study can be seen in Table 17.

Table 17 Quality assessment results for parallel group RCTs

	CASTOR (MMY3004)	**Risk of bias**
Was randomisation carried out appropriately?	Yes, randomisation was carried out as per the pre-specified randomisation method; patients were randomised using a central IWRS	Low
Was the concealment of treatment allocation adequate?	CASTOR was open label. Concealment of treatment was not practical in CASTOR owing to the different dosing schedules. Potential bias was mitigated by use of an IDMC that was masked to treatment allocated	Potential risk of bias as open label design could have influenced investigator's assessment of PFS events
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes, demographic and baseline characteristics were well balanced between the two treatment groups with no categories having a difference of ≥10% (Table 12)	Low
Were the care providers, participants and outcome assessors blind to treatment allocation?	No, CASTOR was open-label and only Janssen were blinded to the results	Low, as an IDMC reviewed the data
Were there any unexpected imbalances in drop-outs between groups?	No, of the 498 patients randomised (251 in the DBd group and 247 in the Bd group), 480 received study treatment: 243 patients received DBd and 237 patients received Bd (see Section B.2.4.4)	Low
Is there any evidence to suggest that the authors measured more outcomes than they reported?	None	Low

	CASTOR (MMY3004)	Risk of bias
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes, the ITT population was used for analysis of the primary endpoint and other time-to-event efficacy endpoints, which included all randomised patients	Low

Bd = bortezomib and dexamethasone; DBd = daratumumab in combination with bortezomib and dexamethasone; IDMC = independent data monitoring committee; ITT = intent-to-treat; IWRS = interactive web response system; PFS = progression free survival; RCT = randomised controlled trial.

Adapted from Systematic reviews: CRD's guidance for undertaking reviews in health care (University of York Centre for Reviews and Dissemination).

B.2.5.2 Consideration of how closely the trials reflect routine clinical practice in England

CASTOR was a multicentre, international trial that enrolled participants generally representative of RRMM patients in England. While all patients were recruited outside the UK, all the sites were in countries with broadly similar demographics. In relation to the second-line subgroup, expert clinical opinion indicated that patients recruited in CASTOR were generally younger and fitter than clinical practice in England which is supported by a comparison of median age from the CASTOR trial versus SACT dataset (CASTOR 1PL: 63.0 years; SACT: [redacted] years).[70,99]

In comparison with the rest of Europe and the US, the treatment pathway for MM in England is heavily restricted. Therefore, the use of subsequent treatment in the trial differs from clinical practice in England.[70,92,102]

A post-hoc analysis, adjusting for the use of subsequent treatments not available in clinical practice in England has been undertaken to reduce bias and increase the generalisability of trial results to UK clinical practice. All methods recommended in NICE decision support unit (DSU) technical support document (TSD) 16 to adjust for such bias were explored.[103] However, the complexities of the data and the array of treatment switches meant that it was only possible to implement adjustment using the Inverse Probability of Censoring Weights (IPCW) method. This method censors patients upon treatment switch to a treatment that is not available in the UK, before reweighting the follow-up information for patients who remain at risk for the event to remove any censoring-related selection bias. For a description of the methods used for OS adjustment, see Appendix M.

B.2.6 Clinical effectiveness results of the relevant studies

B.2.6.1 Summary of key CASTOR clinical efficacy results

In the CASTOR study, data for PFS and secondary efficacy endpoints (including TTP and ORR) were collected at the second planned interim analysis (IA2) with a median follow-up of 26.9 months.[76] These data were presented in the previous DBd submission to NICE, and were the basis for NICE's recommendation in 2019 of DBd for a period of managed access via the CDF for second line patients with RRMM in England.[67] At 26.9 months follow-up, use of DBd was associated with a significantly greater reduction of risk of disease progression or death and a significantly greater ORR benefit, as well as improved TTP and MRD negativity rates compared with Bd.[76] These and additional endpoints, including time to response, duration of response, TTD and quality of life outcomes were presented in the original submission and can be found in Appendix M.

PFS data were subsequently updated with a median follow-up of 50.2 months, with an improvement in the observed treatment effect in favour of DBd with the IA2 data cut.[77] Final OS data were analysed at the latest data-cut in 2021 with a median follow-up of 72.6 months, along with the MRD-negativity rate, time to next therapy, and PFS2. Results for the updated PFS efficacy analysis and the final OS data-cut are presented as part of the current submission.[77,94]

The clinical benefit of DBd versus the directly relevant active comparator Bd is clearly demonstrated in updated efficacy data from CASTOR (Section B.2.6.2). In the updated PFS analysis at 50.2 months of follow-up, there was a 69% reduction in the risk of disease progression or death for DBd compared with Bd alone. Median PFS in the ITT population was 16.7 versus 7.1 months for patients treated with DBd and Bd, respectively; HR: 0.31 (0.24, 0.39), p<0.0001.[77]

At a median follow-up of 72.6 months, the final OS analysis showed a 26% reduction in risk of death in the DBd arm versus Bd arm in the ITT population (HR: 0.74 [0.59, 0.92], p=0.0075).[77] The rate of MRD negativity was also significantly higher among patients in the DBd arm compared with patients in the Bd arm (15.1% vs 1.6%, OR: 12.5% [95% CI: 4.13, 37.85]; p<0.0001) with evidence that MRD negativity is associated with improved OS.[77,94] Time to next therapy was significantly longer for patients treated with DBd than those treated with Bd (HR: 0.27, [95% CI: 0.21, 0.34]; p<0.0001) and the PFS of patients on a subsequent line of therapy (PFS2) was significantly longer among patients from the DBd vs the Bd treatment arm (HR: 0.43, [95% CI: 0.34, 0.54], p<0.0001).[77,94]

A top-line summary of results from IA2 (the primary PFS analysis presented in the original submission), the updated PFS analysis at 50.2 months and the Final OS Analysis are presented in Table 18.

Table 18 Summary of key clinical efficacy results from CASTOR (ITT population)[94,104,105]

Data cut (median follow-up)	**IA2 11 January 2018 (26.9 months)**		**Updated PFS Analysis 14th August 2019 (50.2 months)**		**Final OS Analysis 28th June 2021 (72.6 months)**	
Arm	**DBd**	**Bd**	**DBd**	**Bd**	**DBd**	**Bd**
PFS, n (%)	362/498 (72.6%)		396/498 (79.5%)		NR[a]	
PFS, HR (95% CI)	0.39 (0.28, 0.53)		0.31 (0.24, 0.39)		NR[a]	
p value	<0.0001		<0.0001		NR	
OS, n (%)	179/498 (36.0%)		NR		319/498 (64.0%)	
OS, HR (95% CI)	0.77 (0.57, 1.04) p=0.0884		NR		0.74 (0.59, 0.92)	
p value	0.0498		NR		0.0075	
Response, n (%)	351/474 (74.0%)		NR		NR	
ORR, % (95% CI)	84.6% (79.4, 88.9)	63.2% (56.7, 69.4)	NR	NR	NR	NR
OR (95% CI)	3.60 (2.24, 5.81)		NR		NR	
p value	<0.0001		NR		NR	
sCR+CR, n (%)	95/474 (20.0%)		NR		NR	
sCR	9.6% (6.2, 14.0)	2.6% (0.9, 5.5)	NR	NR	NR	NR
CR	20.4% (15.5, 26.1)	7.3% (4.3, 11.4)	NR	NR	NR	NR
≥CR	30.0% (24.3, 36.2)	9.8% (6.3, 14.4)	NR	NR	NR	NR
OR (95% CI)	4.67 (2.65, 8.25)		NR		NR	
p value	<0.0001		NR		NR	
VGPR, events (%)	124/474 (25.9%)		NR		NR	
VGPR	32.9% (27.0, 39.3)	19.2% (14.4, 24.9)	NR	NR	NR	NR
≥VGPR	62.9% (56.5, 69.0)	29.1% (23.3, 35.3)	NR	NR	NR	NR
OR (95% CI)	4.94 (3.23, 7.55)		NR		NR	
p value	<0.0001		NR		NR	

Data cut (median follow-up)	IA2 11 January 2018 (26.9 months)		Updated PFS Analysis 14th August 2019 (50.2 months)		Final OS Analysis 28th June 2021 (72.6 months)	
Arm	**DBd**	**Bd**	**DBd**	**Bd**	**DBd**	**Bd**
MRD, events (%)	34/498 (6.8%)		23/498 (5.0%)		61/498 (12.3%)	
MRD negativity rate, 10^{-5} sensitivity threshold (95% CI)	12% (8.2, 16.6)	1.6% (0.4, 4.1)	8.8% (5.6, 13.0)	1.2% (0.3, 3.5)	15.1% (10.9%, 20.2%)	1.6% (0.4%, 4.1%)
Odds ratio (95% CI)	8.25 (2.86, 23.78)		9.04 (2.52, 32.21)		12.50 (4.13, 37.85)	
p value	0.000001		0.0001		<0.0001	

Bd = bortezomib and dexamethasone; CI = confidence interval; CR = complete response; DBd = daratumumab, bortezomib and dexamethasone; HR = hazard ratio; ITT = intent-to-treat; MRD = minimal residual disease; NE = not evaluable; NR = not reported; OR = odds ratio; PR = partial response; sCR = stringent complete response; VGPR = very good partial response.

[a] Final PFS analysis was conducted at 50.2 months follow-up (data cut-off 14th August 2019)

An odds ratio >1 and a hazard ratio <1 indicates an advantage for DBd.

B.2.6.2 Primary endpoint: progression-free survival

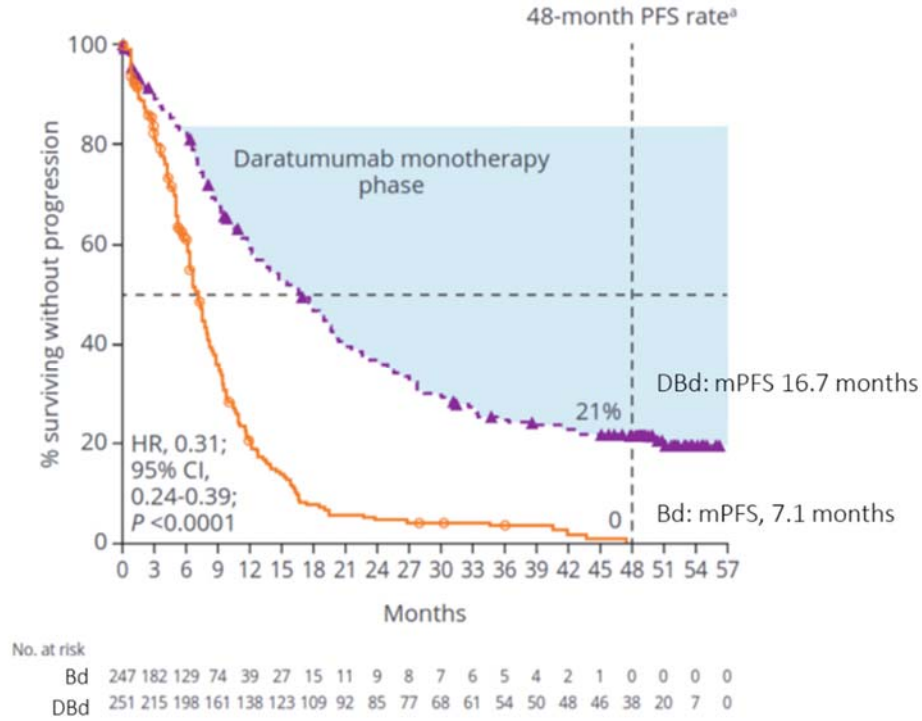
After a median follow-up of 50.2 months, a total of 187 (74.5%) PFS events had occurred in the DBd arm compared to 209 (84.6%) in the Bd arm.[105] The treatment effect in favour of DBd had improved relative to the outcomes of the IA2 analysis, with a statistically significant 69% reduction in the risk of disease progression or death compared with Bd (HR: 0.31; 95% CI: 0.24, 0.39; Figure 6 and Table 19).[77] The PFS rates remained consistently greater in the DBd arm compared with the Bd arm at 12 months through to 48 months after starting treatment (Table 19).[105] DBd can be considered significantly better than Bd in terms of helping patients control their myeloma for longer before worsening of the disease or death, which is a key treatment peference for patients with RRMM (Section B.1.3.1).[105]

Table 19 Summary of PFS in the CASTOR trial (ITT population) (data cut-off 14 August 2019)[77,94,105]

	DBd (n=251)	**Bd (n=247)**
Number of events (%)	187 (74.5%)	209 (84.6%)
Median (95% CI)	16.7 (13.1, 19.4)	7.1 (6.2, 7.7)
HR (95% CI)	0.31 (0.24, 0.39)	
p-value	<0.0001	
12-month PFS rate, % (95% CI)	59.1 (52.6, 65.0)	19.8 (14.7, 25.4)
24-month PFS rate, % (95% CI)	36.7 (30.6, 42.9)	4.6 (2.3, 8.1)
36-month PFS rate, % (95% CI)	24.5 (19.2, 30.2)	3.4 (1.4, 6.7)
48-month PFS rate, % (95% CI)	19.3 (14.1, 25.0)	0.0 (NE, NE)

CI = confidence interval; Bd = bortezomib and dexamethasone; DBd = daratumumab, bortezomib and dexamethasone; HR = hazard ratio; ITT = intent-to-treat; PFS = progression-free survival

Figure 6 Kaplan-Meier plot for progression-free survival among patients treated with DBd compared with Bd (CASTOR; ITT population; median follow-up 50.2 months)[77]



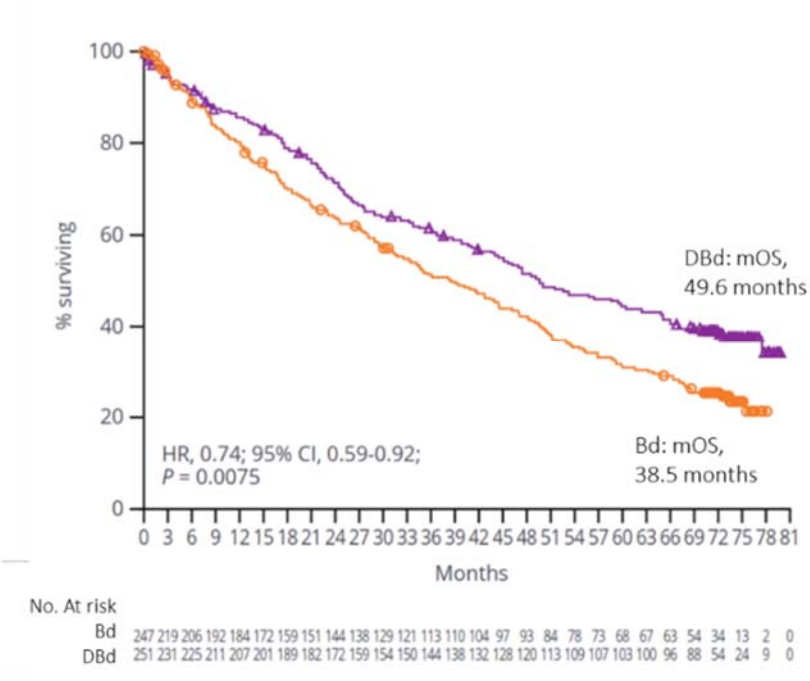
Bd = bortezomib and dexamethasone; DBd = daratumumab, bortezomib and dexamethasone; HR = hazard ratio; ITT = intent-to-treat; mPFS = median progression-free survival.[a] Kaplan-Meier estmates.

See Section B.2.7.2 for the subgroup analysis of PFS in second-line patients at 50.2 months follow-up.

B.2.6.3 Overall survival

After a median follow-up of 72.6 months, a total of 319 death events had occurred in CASTOR.[94] Median OS in the ITT population was 49.6 months (95% CI: 42.2, 62.3) in the DBd arm and 38.5 months (95% CI: 31.2, 43.2) in the Bd arm, reflecting the superiority of DBd with a statistically significant and clinically meaningful 26% reduction in the risk of death (HR 0.74; 95% CI: 0.59, 0.92, p=0.0075; Figure 7 and Table 20).[77]

Figure 7 Kaplan-Meier plot for overall survival among patients treated with DBd or Bd in the CASTOR trial (ITT population); median follow-up: 72.6 months.[77]



Bd = bortezomib and dexamethasone; DBd = daratumumab, bortezomib and dexamethasone; HR = hazard ratio; ITT = intent-to-treat; mOS = median overall survival; NR = not reached

In the DBd arm, survival rates were consistently greater than in the Bd arm from 12 months through to 60 months from starting treatment (Table 20).[94] In the patient preference DCE findings mentioned previously, patients placed a high value on increased life expectancy (Section B.1.3.1).[52]

Table 20 Summary of OS in the CASTOR trial (ITT population) (data cut-off 28th June 2021, median follow-up 72.6 months)[94]

	DBd (n=251)	Bd (n=247)
Number of events (%)	148 (59.0%)	171 (69.2%)
HR (95% CI)	0.74 (0.59, 0.92)	
p value	0.0075	
12-month survival rate, % (95% CI)	85.7% (80.7, 89.5)	80.1% (74.4, 84.7)
24-month survival rate, % (95% CI)	72.0% (65.8, 77.2)	63.9% (57.3, 69.7)
36-month survival rate, % (95% CI)	61.1% (54.6, 66.9)	51.3% (44.6, 57.6)
48-month survival rate, % (95% CI)	51.6% (45.1, 57.8)	42.2% (35.7, 48.6)
60-month survival rate , % (95% CI)	44.3% (37.9, 50.0)	30.9% (24.9, 37.0)

Bd = bortezomib and dexamethasone; CI = confidence interval; DBd = daratumumab, bortezomib and dexamethasone; HR = hazard ratio; ITT = intent-to-treat; OS = overall survival

See Section B.2.7.2 for the subgroup analysis of OS in second-line patients at 72.6 months follow-up.

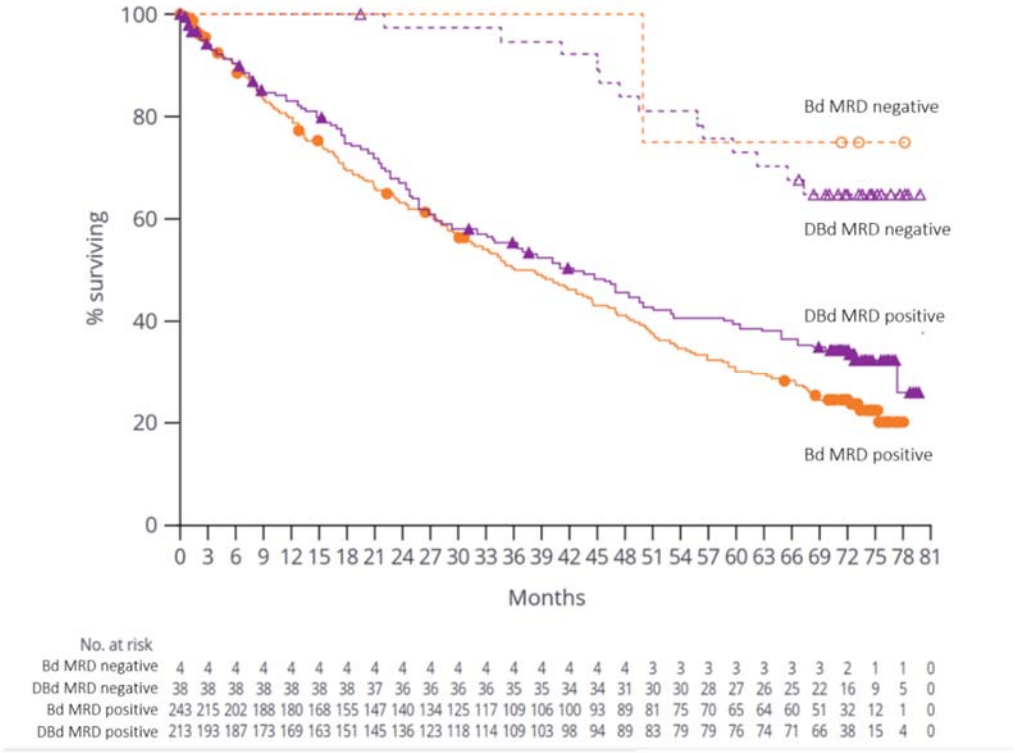
B.2.6.4 Treatment duration

At the time of Final Analysis, the median treatment duration was 13.4 months (range: 0.0-79.7 months) in the DBd group, and 5.2 months (range: 0.2-8.0 months) in the Bd group. The median duration of follow-up was similar in both treatment groups (72.5 months in the DBd group and 72.6 months in the Bd group).[94]

B.2.6.5 Minimal residual disease

In CASTOR, analysis at median follow-up of 72.6 months showed MRD-negative rates were more than 9 times higher in the DBd versus Bd arm at a threshold of 10^{-5} (15.1% versus 1.6%; OR: 12.50; 95% CI: 4.13, 37.85; p<0.0001).[77,94] Minimal residual disease negativity indicates that the level of tumour cells in the body has fallen below a detectable threshold, which is associated with longer survival without disease deterioration.[98,106] The impact of MRD negativity on OS can be seen in Figure 8.

Figure 8 Kaplan-Meier plot for overall survival based on MRD status among patients treated with DBd compared with Bd (CASTOR; intent-to-treat analysis set; median follow-up 72.6 months)[77]



Bd = bortezomib and dexamethasone; DBd = daratumumab, bortezomib and dexamethasone; MRD = minimal residual disease

B.2.6.6 Time to next therapy

At a median follow-up of 72.6 months, the median TTNT was 25.4 months (95% CI: 20.7, 29.1) for the DBd group and 9.7 months (95% CI: 8.4, 10.8) for the Bd group (HR 0.27, 95% CI: 0.21, 0.34; p<0.0001).[94]

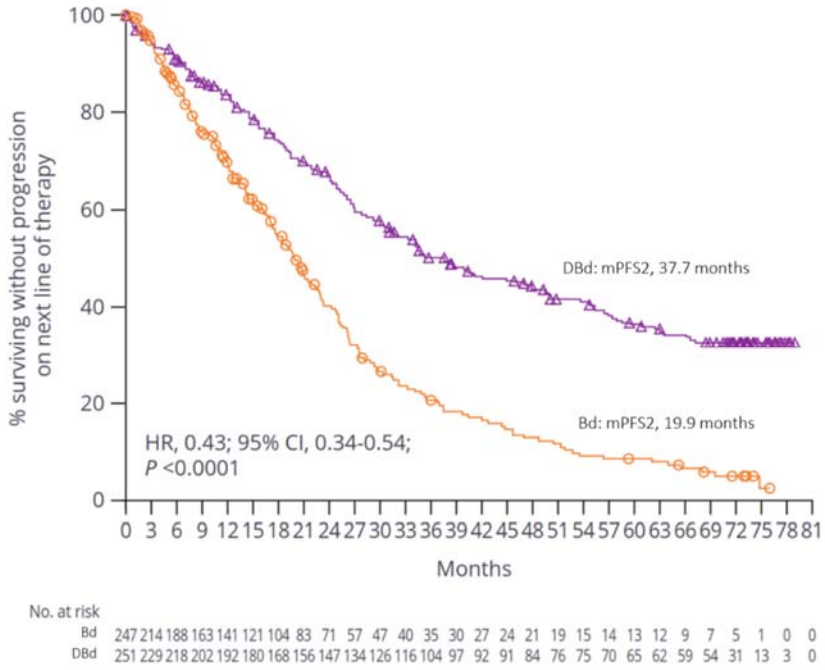
The data for TTNT in CASTOR are shown in Appendix D.3.2.8.

B.2.6.7 Progression-free survival on the subsequent line of therapy

At a median follow-up of 72.6 months, 66.3% of patients who had received treatment with DBd had gone on to receive subsequent therapy, compared with 84.4% of patients from the Bd arm.[77] PFS2 represents 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. From the CASTOR trial, patients who had received DBd had a 57% reduction in the risk of disease progression or death on the first subsequent line of therapy compared with patients who had received Bd alone.[77] Median PFS2 was 37.7 months for the DBd group and 19.9 months for the Bd group (HR 0.43, 95% CI: 0.34, 0.54; p<0.0001) (Figure 9).[77] The significantly prolonged PFS2 with DBd treatment further support the advantage of using daratumumab-based regiments as early as possible in the treatment sequence for patients with MM. As described previously (Section B.1.3.1), prolonging earlier remissions is key to improving the quality of life of patients.[50]

The data for PFS2 are unadjusted for the impact of subsequent therapies that are not available in England. As such, it is likely that the PFS2 benefit favouring DBd has been underestimated due to a higher proportion of patients in the Bd arm of CASTOR receiving such subsequent treatments.

Figure 9 Median Progression-Free Survival on Subsequent Therapy (mPFS2) Among Patients Treated with DBd or Bd in CASTOR (Follow-up: 72.6 Months)[77]



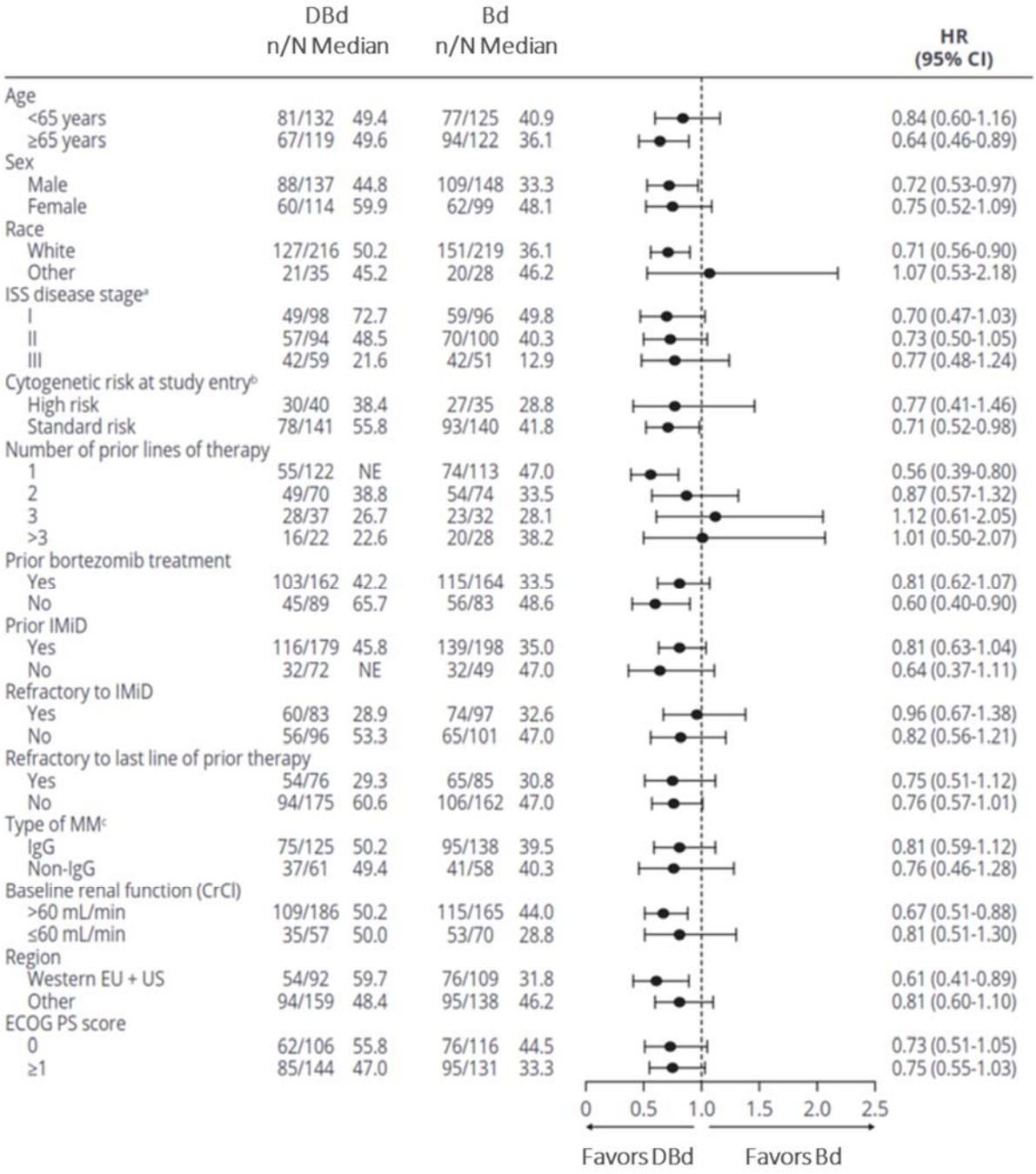
Bd = bortezomib and dexamethasone; DBd = daratumumab, bortezomib and dexamethasone; HR = hazard ratio; mPFS2 = median progression-free survival on subsequent therapy.

B.2.7 Subgroup analysis in CASTOR

B.2.7.1 Pre-specified subgroup analysis of overall survival

At 72.6 months of follow-up, OS was assessed in pre-specified subgroups, across which results were generally consistent (Figure 10).[77] When stratified according to the number of prior therapies received, the OS benefit was greatest for those who had received 1 prior line of therapy (Figure 10).[77] Further detail of analyses in patients who received 1 prior line of therapy are presented in Section B.2.7.2). Details of other pre-specified subgroups analyses including PFS are presented in Appendix M.

Figure 10 Subgroup analysis of OS in the CASTOR study (ITT population; follow-up: 72.6 months)[77]



Bd = bortezomib and dexamethasone; CrCl = creatinine clearance; DBd = daratumumab, bortezomib and dexamethasone; ECOG = Eastern Cooperative Oncology Group; EU = European Union; HR = hazard ratio; IMiD = immunomodulatory drug; ISS = International staging System; ITT = intent-to-treat; MM = multiple myeloma; OS = overall survival; PS = performance status; US = United States

B.2.7.2 Subgroup analyses in second-line patients

Data were analysed for the subgroup of patients who received one prior line of therapy:

- At 72.6 months follow up, when the Final OS Analysis was conducted
- At 50.2 months of follow-up, when the updated efficacy analysis was conducted for PFS and PFS2
- At 26.9 months of follow-up, when analyses for PFS, time to disease progression, treatment response, MRD negativity, and use of subsequent treatment were conducted

A summary of these results is presented in Table 21. Detailed results for efficacy outcomes from the Primary PFS Analysis and the Final OS Analysis are presented in Section B.2.7.2.

Table 21 Summary efficacy results in second-line patients from CASTOR[76,77,100,104,107,108]

Outcome		IA2 11 January 2018 (26.9 months)		Updated PFS Analysis 14th August 2019 (50.2 months)		Final OS Analysis 28th June 2021 (72.6 months)	
		DBd	**Bd**	**DBd**	**Bd**	**DBd**	**Bd**
Progression-free survival[a]	n/N (%)	60/122 (49.2)	94/113 (83.2)	[redacted]	[redacted]		
	Median (95% CI)	26.2 (21.19, NE)	7.9 (6.77, 9.03)	27.0 ([redacted])	7.9 ([redacted])	N/A	N/A
	HR (95% CI) p-value	0.23 (0.16, 0.33) p<0.0001		0.21 (0.15, 0.31) p<0.0001		N/A	
Progression-free survival on subsequent therapy	n/N (%)	[redacted]	[redacted]				
	Median (95% CI)	NE [redacted]	24.3 [redacted]	49.9 (NR, NR)	23.1 (NR, NR)		N/A
	HR (95% CI) p-value	0.32 (0.20, 0.51), <0.0001		0.37 (0.26, 0.53), p<0.0001		N/A	
Time to disease progression[a]	n/N (%)	[redacted]	[redacted]				
	Median (95% CI)	[redacted]	[redacted]	N/A	N/A	N/A	N/A
	HR (95% CI) p-value	[redacted]		N/A		N/A	
Time to treatment discontinuation	n/N (%)	67/119 (56.3)	41/111 (36.9)	[redacted]	[redacted]	N/A	N/A
	Median (95% CI)	23.98 (NR, NR)	NE	[redacted]	[redacted]	N/A	N/A
	HR (95% CI) p-value	0.41 (0.24, 0.69), p = 0.0009		[redacted]		N/A	
Overall survival	n/N (%)	25/122 (20.5)	40/113 (35.4)			55/122	74/113
	Median (95% CI)	NE (NE, NE)	NE (28.85, NE)	N/A	N/A	NE (59.7, NE)	47.0 (32.6, 58.7)
	HR (95% CI) p-value	0.50 (0.30, 0.84), p=0.0080		N/A		0.56 (0.39, 0.80), p=0.0013	
Overall response (sCR + CR + VGPR + PR)[b]	n/N	[redacted]	[redacted]				
	% ORR (95% CI)	92 [redacted]	74 [redacted]	N/A	N/A	N/A	N/A
	OR (95% CI) p-	[redacted] p<0.0007		N/A		N/A	

Outcome		IA2 11 January 2018 (26.9 months)		Updated PFS Analysis 14th August 2019 (50.2 months)		Final OS Analysis 28th June 2021 (72.6 months)	
		DBd	Bd	DBd	Bd	DBd	Bd
	value						
VGPR or better (sCR + CR + VGPR)[b]	n/N	[redacted]	[redacted]				
	% ORR (95% CI)	77 [redacted]	42 [redacted]	N/A	N/A	N/A	N/A
	OR (95% CI) p-value	[redacted] p<0.0001		N/A		N/A	
CR or better (sCR + CR)[b]	n/N	[redacted]	[redacted]				
	% ORR (95% CI)	43 [redacted]	15 [redacted]	N/A	N/A	N/A	N/A
	OR (95% CI) p-value	[redacted] p<0.0001		N/A		N/A	
MRD negativity (10^{-5})[a]	n/N	[redacted]	[redacted]	25/122	3/113		
	% MRD (95% CI)	16 [redacted]	3 [redacted]	21 (NR, NR)	3 (NR, NR)	N/A	N/A
	OR (95% CI) p-value	7.19 (2.07, 24.92) p=0.00082		NR, p=0.000013		N/A	

CI = confidence interval; CR = complete response; HR = Hazard ratio; MRD = minimal residual disease; N/A = not analysed; NE = not evaluable; NR = not reported; OR = odds ratio; PR = partial response; sCR = stringent complete response; VGPR = very good partial response.

[a] Analyses in the ITT population.

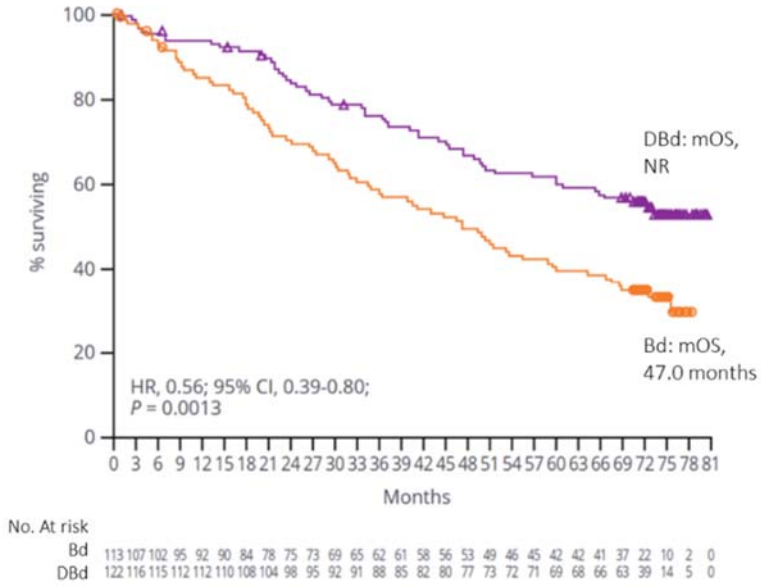
[b] Analyses in the response-evaluable population.

An odds ratio >1 and a Hazard ratio <1 indicates an advantage for DBd.

Overall survival in second-line patients

At median 72.6 months follow-up, DBd also demonstrated a statistically significant and clinically meaningful improvement in OS compared with Bd in patients who had been treated with one line of prior therapy (HR 0.56 [95% CI: 0.39, 0.80]; p=0.0013). Median OS was not reached in the DBd arm (95% CI: 59.7 months, NE), and was 47.0 months (95% CI: 32.6, 58.7) in the Bd arm (Figure 11 and Table 22).[77]

Figure 11 Kaplan-Meier plot for overall survival among patients treated with DBd or Bd in the CASTOR trial (patients with 1PL therapy); median follow-up: 72.6 months.[77]



1PL = one prior line of therapy; Bd = bortezomib and dexamethasone; DBd = daratumumab, bortezomib and dexamethasone; HR = hazard ratio; mOS = median overall survival; NR = not reached

Table 22 Summary of OS in the CASTOR trial (1 PL population) (data cut-off 28th June 2021, median follow-up 72.6 months)[77,94]

	DBd (n=122)	Bd (n=113)
Number of events (%)	55 (45.1%)	74 (65.5%)
HR (95% CI)	0.56 (0.39, 0.80)	
p value	0.0013	

Bd = bortezomib and dexamethasone; CI= confidence interval; DBd = daratumumab, bortezomib and dexamethasone; HR = hazard ratio; OS = overall survival; PL = prior line of therapy

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

As noted in Section B.2.6.7, treatment with DBd was associated with considerably less use of subsequent therapies not available in England compared with patients who had received

Bd (66.3% versus 84.4%, respectively).[77] The disparity in the extent of subsequent treatment received between the trial arms, as well as the higher proportion of patients receiving such treatment in the Bd arm, introduces bias into the OS analyses.

Consistent with the original company submission in 2018, adjustment for subsequent treatments was carried out using IPCW to reduce this bias. Following adjustment for subsequent treatments not available in clinical practice in England, the OS HR was [redacted] (95% CI: [redacted]) in the second-line population (Figure 12).[109]

Figure 12 Kaplan-Meier curves for DBd and Bd OS in the one prior-line population pre- and post-IPCW adjustment

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

For a description of the methods used for OS adjustment, see Appendix M.

Progression-free survival in second-line patients

In second-line patients, treatment with DBd was associated with a significantly greater PFS benefit compared with Bd. At median follow-up of 50.2 months, treatment with DBd was

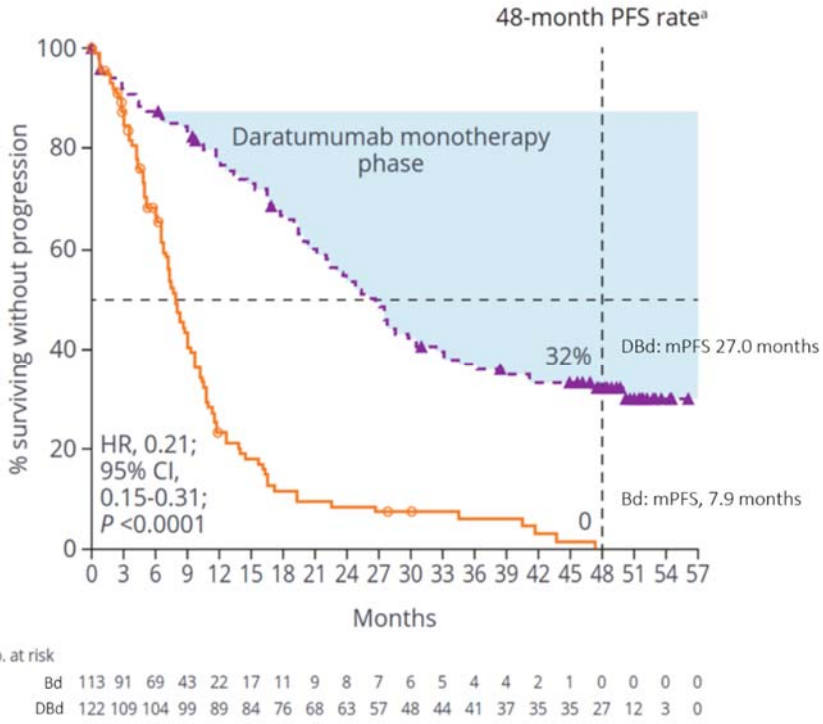
associated with an unprecedented 79% reduction in the risk of disease progression or death compared with Bd alone (HR 0.21, 95% CI: 0.15, 0.31; p<0.0001; Figure 13, Table 23).[77]

Table 23 Summary of PFS in the CASTOR trial (1PL population) (data cut-off 14 August 2019)[77]

	DBd (n=122)	Bd (n=113)
Number of events (%)	[redacted]	[redacted]
Median (95% CI)	27.0 [redacted]	7.9 [redacted]
HR (95% CI)	0.21 (0.15, 0.31)	
p value	<0.0001	
48-month PFS rate, % (95% CI)	32% [redacted]	0 [redacted]

CI = confidence interval; Bd = bortezomib and dexamethasone; DBd = daratumumab, bortezomib and dexamethasone; HR = hazard ratio; PFS: progression-free survival; PL = prior line of therapy

Figure 13 Kaplan-Meier plot for progression-free survival among second-line patients treated with DBd compared with Bd (CASTOR; intent-to-treat analysis set; median follow-up 50.2 months)[77]

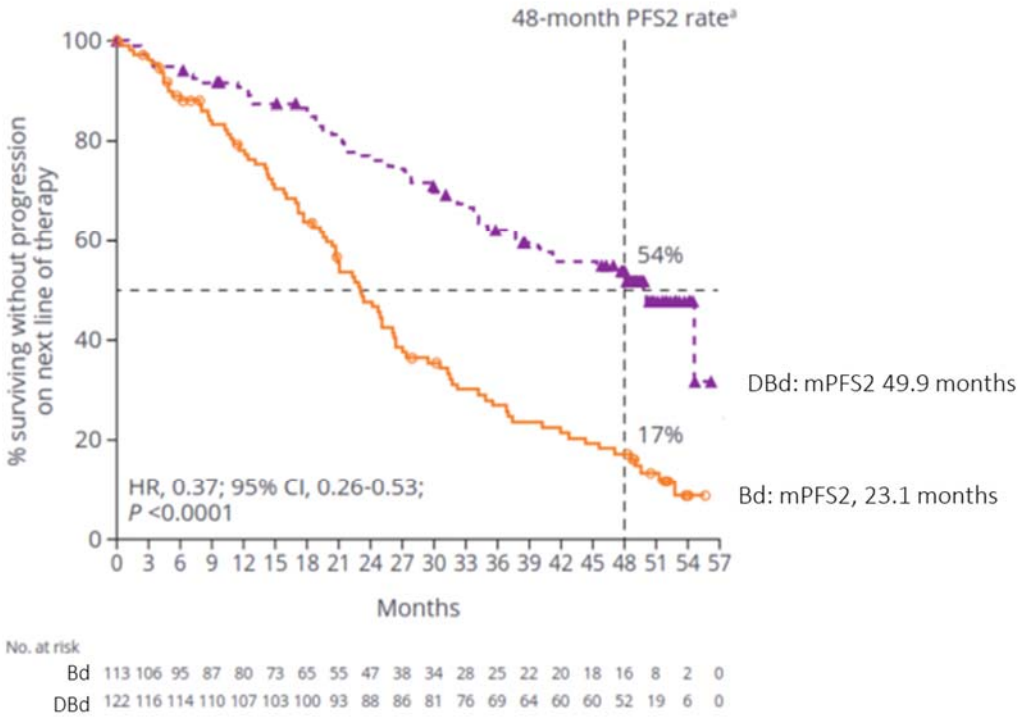


Bd = bortezomib and dexamethasone; DBd = daratumumab, bortezomib and dexamethasone; HR = hazard ratio; mPFS = median progression-free survival.[a]Kaplan-Meier estimate

Progression-free survival on subsequent therapy among patients who received DBd or Bd in the second-line

At 50.2 months of follow-up, patients who had been treated with DBd as a second-line therapy had longer PFS on a subsequent treatment regimen (PFS2) compared to patients who had received Bd in the second line (HR 0.37 [95% CI: 0.26, 0.53] p<0.0001) (Figure 14).[77] These results demonstrate a sustained benefit of daratumumab beyond progression.

Figure 14 Kaplan-Meier plot for progression-free survival on subsequent therapy for patients treated with DBd or Bd in the second-line (CASTOR; intent-to-treat analysis set; median follow-up of 50.2 months)[77]



Bd = bortezomib and dexamethasone; DBd = daratumumab, bortezomib and dexamethasone; HR = hazard ratio; mPFS2 = median progression-free survival 2.[a] Kaplan-Meier estmates.

Minimal residual disease in second-line patients

In second-line patients, the rate of MRD-negativity at 50.2 months of follow-up was significantly higher for patients treated with DBd compared with Bd (21% and 3%, respectively; p=0.000013).[100]

Time to treatment discontinuation in second-line patients

In second-line patients, treatment with DBd was associated with [redacted]; at a median follow-up of 50.2 months, the median TTD was was [redacted] months (95% CI: [redacted]) for patients in the DBd treatment arm and NE (95% CI: [redacted]) for patients treated with Bd (HR [redacted] [95% CI: [redacted]], p=[redacted]) (Table 24, Figure 15).[108]

Table 24 Summary of TTD in the CASTOR trial (1 PL population; median follow-up of 50.2 months)[108]

	DBd (n=122)	Bd (n=113)
Number of events (%)	[redacted]	[redacted]
HR (95% CI)	[redacted]	
p value	[redacted]	

Bd = bortezomib and dexamethasone; CI = confidence interval; DBd = daratumumab, bortezomib and dexamethasone; HR = hazard ratio; 1 PL = one prior line of therapy; TTD = time to treatment discontinuation

Figure 15 Time to treatment discontinuation for patients being treated with DBd or Bd in the second-line (CASTOR, intent-to-treat population, median follow-up of 50.2 months)[108]

[redacted]

Bd = bortezomib and dexamethasone; CI = confidence interval; DBd = daratumumab, bortezomib and dexamethasone; HR = hazard ratio; NE = not estimable; TTD = time to treatment discontinuation

B.2.8 Summary of key results from the SACT dataset analysis

Treatment duration and overall survival were evaluated in an analysis of real-world data from patients receiving treatment with DBd for RRMM funded through the CDF in England (based on the SACT dataset). SACT was specified as the secondary source of data collection per the Data Collection Agreement for TA573, with results providing evidence to inform the real-world survival outcomes of DBd in clinical practice in England.[70]

B.2.8.1 Overall survival

The median follow-up time for OS among the total SACT dataset population [redacted] was [redacted]. Median OS was [redacted]

[redacted] (see Section B.2.6.3).[70,77] At 24 months after starting treatment, the estimated OS was [redacted].[70]

Table 25 OS at 6, 12, 18 and 24 months for patients treated with DBd (SACT dataset)[70]

Time	OS (%)
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

CI = confidence interval; DBd = daratumumab-bortezomib-dexamethasone; OS = overall survival; SACT = Systemic Anti-Cancer Therapy

Figure 16 Kaplan-Meier plot for overall survival among patients treated with DBd (SACT data set, [redacted])[70]

[redacted]

DBd = daratumumab-bortezomib-dexamethasone; SACT = Systemic Anti-Cancer Therapy

B.2.8.2 Treatment duration

[redacted]. Among all patients in the SACT dataset, [redacted] had completed treatment by the latest follow-up [redacted]). Median follow-up was [redacted].[70] After [redacted] from starting treatment, [redacted] of patients were still receiving treatment with DBd (see

Table 26).[70]

Table 26 Rates of patients receiving DBd treatment at 6, 12, 18 and 24 months (SACT dataset)[70]

Time	Patients receiving treatment (%)
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

CI = confidence interval; DBd = daratumumab-bortezomib-dexamethasone

Median treatment duration was [redacted][70,94] See Figure 17 for the Kaplan-Meier plot of the estimated treatment duration for patients receiving DBd.

Figure 17 Kaplan-Meier plot for treatment duration estimate among patients receiving DBd (SACT dataset, [redacted])*[70]

[redacted]

DBd = daratumumab-bortezomib-dexamethasone; SACT = Systemic Anti-Cancer Therapy

A sensitivity analysis was conducted to evaluate treatment duration in a cohort of patients that continued their treatment with DBd for at least six months [redacted]. The median follow-up in this cohort was [redacted], with a similar treatment duration to the full cohort analysis: [redacted].[70]

B.2.9 Meta-analysis

As only one relevant trial evaluating DBd was identified, no meta-analysis is required.

B.2.10 Indirect and mixed treatment comparisons

Appendix D includes full details of the methodology for the indirect comparison or mixed treatment comparison.

The clinical SLR identified three RCTs that investigated DBd, Bd, or Cd as second-line treatments for RRMM and connected to a network with DBd (see Table 27 and Appendix D.1).

Table 27 RCTs identified in the SLR

Trial	Population	Intervention	Comparator	Outcomes assessed
CASTOR[100]	Patients with RRMM with at least 1PL of therapy	DBd	Bd	PFS, OS, ORR, VGPR or better, CR or better
LEPUS[110]	Patients with RRMM with at least 1PL of therapy	DBd	Bd	PFS, ORR
ENDEAVOR[111,112]	Patients with RRMM with one to three prior lines of therapy	Cd	Bd	PFS, OS, ORR, VGPR, sVGPR, CR, sCR

1PL = one prior line; Bd = bortezomib in combination with dexamethasone; Cd = carfilzomib in combination with bortezomib; CR = complete response DBd = daratumumab in combination with bortezomib and dexamethasone; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; RRMM = relapsed or refractory multiple myeloma; sCR = stringent complete response; sVGPR = stringent very good partial response; VGPR = very good partial response

Each study was reviewed as to its suitability for inclusion in an indirect or mixed treatment comparison, with consideration given to the data reported (e.g., KM data for OS and PFS) and the comparability of baseline characteristics. Following this review, it was determined that only two of the three RCTs identified were suitable for inclusion in the prospective network meta-analyses (NMA): CASTOR and ENDEAVOR.

The LEPUS study evaluated DBd vs. Bd in a Chinese population. It was not included in the NMA analyses because of (1) the lack of generalisability to the CASTOR and ENDEAVOR trials, where in the ITT population the closest-match populations represented 3.6% [Korean ethnicity] and 12.4% [Asian ethnicity], respectively (with ethnicity not reported for the 1PL subgroup); and (2) the potential risk of effect modification introduced by variations in Asian ethnicity. Potential signs of effect modification by Asian race were observed across studies in RRMM evaluating Bd and Cd, including the following trials:

- BOSTON, which compared Selinexor in combination with bortezomib and dexamethasone vs. Bd[113]
    - PFS HR of 0.57 (95% CI: 0.42, 0.79) for White race vs. 1.16 (0.61, 2.21) for other races
- CANDOR, which compared DCd vs. Cd[114]

- PFS HR of 0.63 (95% CI: 0.45, 0.88) for White race vs. 0.75 (0.26, 2.17) for Asian race

- ENDEAVOR, which compared Cd vs. Bd[111]
  - PFS HR of 0.52 (95% CI: 0.42, 0.65) for White race vs. 0.60 (0.31, 1.16) for Asian race

- IKEMA, which compared isatuximab in combination with carfilzomib and dexamethasone vs. Cd[115]
  - PFS HR of 0.53 (99% CI: 0.32, 0.88) in the ITT population vs. 0.64 (95% CI: 0.23, 1.77) for East Asian patients

To inform the decision problem, NMAs were carried out to enable a comparison of the remaining two trials, CASTOR and ENDEAVOR (DBd vs. Cd).

B.2.10.1 Summary of trials and network diagram

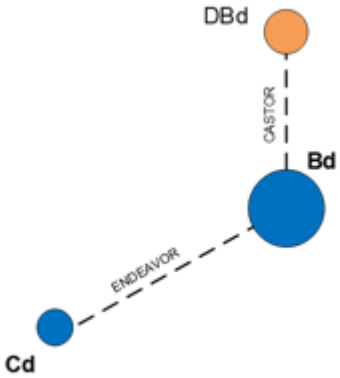
The trials used to carry out the base-case NMA are summarised in Table 28 and the resulting evidence network is provided in Figure 18.

Table 28 Summary of the trials used in base-case NMA

	Bd	DBd	Cd
CASTOR	Yes	Yes	
ENDEAVOR	Yes		Yes

Bd = bortezomib in combination with dexamethasone; Cd = carfilzomib in combination with dexamethasone; DBd = daratumumab in combination with bortezomib and dexamethasone

Figure 18 Evidence network



Bd = bortezomib in combination with dexamethasone; Cd = carfilzomib in combination with dexamethasone; DBd = daratumumab in combination with bortezomib and dexamethasone

B.2.10.2 Uncertainties in the indirect and mixed treatment comparisons

CASTOR and ENDEAVOR were phase III, open-label studies that included adults with RRMM who had received at least 1PL of therapy. Both trials stratified their randomisation by prior line of therapy (one vs. two or more) and reported subgroup analysis for patients who had received 1PL of therapy only. While CASTOR and ENDEAVOR were considered

sufficiently comparable for analysis, there was some heterogeneity in terms of study design with key differences summarised in Table 29 (see Appendix D.2 for full details).

Table 29 Comparative summary of key differences between CASTOR and ENDEAVOR methodologies

Trial number	CASTOR	ENDEAVOR
Eligibility criteria for participants	1. Excluded patients refractory to bortezomib 2. Bortezomib administered subcutaneously 3. Bd treatment duration limited until disease progression, unacceptable toxicity or up to eight cycles	Patients had to have a left ventricular ejection fraction of at least 40%. Patients had to have creatinine clearance of at least 15 mL/minute. Bortezomib administered intravenously or subcutaneously Bd treatment duration limited until disease progression or unacceptable toxicity with no upper limit on the number of cycles
Participant characteristics	4. 66% of patients with prior exposure to bortezomib in the ITT population; 51% patients with prior exposure to bortezomib in the 1PL population	54% patients with prior exposure to bortezomib in the ITT population; 42% patients with prior exposure to bortezomib in the 1PL population.

1PL = one prior line; Bd = bortezomib in combination with dexamethasone; ITT = intention to treat.

Participants from the 1PL population were similar with regard to age, ECOG performance status and ISS stage (see Appendix D.2.4). The differences in patient inclusion/exclusion criteria with respect to creatinine clearance and left ventricular ejection fraction are not expected to significantly impact the comparison of trials. Differences in bortezomib administration, are noted however, the cumulative dose of bortezomib was similar between studies and therefore efficacy is likely comparable.

The outcome data were analysed as reported for both of the studies, with the exception of VGPR or better and CR or better, which were calculated for the ENDEAVOR study by combining CR and sCR and VGPR and sVGPR.

The follow-up for ENDEAVOR was not reported within any of the studies identified from the SLR. It was assumed that the follow-up from ENDEAVOR was between 12 and 13 months which was calculated from the data cut-off of November 2014 (for the 1PL data)[112] and the data cut-off of July 2017 reported in a subsequent paper on the ITT population that also reported the median follow-up to be 44.3 months (Cd) vs. 43.7 months (Bd) at July 2017[116] (assuming 31 months between November 2014 and July 2017 would make the follow-up at November 2014 around 13 months [Cd] and 12 months [Bd]). In comparison, the follow-up from CASTOR was significantly longer at 50.2 months[100] for all outcomes other than OS and 72.6 months for OS.[77]

B.2.10.3 Efficacy results of the mixed treatment comparison

Table 30 describes the NMA results across the clinical efficacy outcomes assessed in the base-case analysis and Table 31 shows the probabilities of treatments being ranked the best. Individual forest plots for each of the outcomes are presented in Appendix D.3.5.1.

Table 30 NMA efficacy results

Outcome	PFS	OS	ORR	VGPR or better	CR or better
	HRs [95% CrIs] (probability of DBd being better than comparator)		ORs [95% CrIs] (probability of DBd being better than comparator)		
DBd vs. Bd	0.21 [0.15, 0.30] (100%)	0.56 [0.39, 0.80] (99.9%)	3.87 [1.82, 8.86] (100%)	4.50 [2.57, 8.03] (100%)	4.43 [2.36, 8.65] (100%)
DBd vs. Cd	0.47 [0.29, 0.75] (99.9%)	0.73 [0.46, 1.14] (91.5%)	1.62 [0.68, 4.10] (85.8%)	1.21 [0.62, 2.41] (70.5%)	2.81 [1.14, 6.99] (98.7%)

Bd = bortezomib in combination with dexamethasone; Cd = carfilzomib in combination with dexamethasone; CR = complete response; CrI = credible interval; DBd = daratumumab in combination with bortezomib and dexamethasone; HR = hazard ratio; NMA = network meta-analysis; OR = odds ratio; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; VGPR = very good partial response

Table 31 Overview of the treatment with the highest probability of being the best according to NMA base case

Outcome	PFS	OS	ORR	VGPR or better	CR or better
DBd	●	●	●	●	●
Cd					
Bd					

Bd = bortezomib in combination with dexamethasone; Cd = carfilzomib in combination with dexamethasone; CR = complete response; DBd = daratumumab in combination with bortezomib and dexamethasone; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; VGPR = very good partial response.

Green dot: treatment had highest probability of being the best in the NMA base case. [redacted]DBd had a statistical advantage in prolonging PFS vs. Bd and Cd. DBd had a statistical advantage in prolonging OS vs. Bd and there was a trend for DBd to improve OS vs. Cd. DBd also had a statistical advantage over Bd in achieving overall response, VGPR or better and CR or better. DBd had a statistical advantage over Cd in achieving CR or better and there was a similar trend for overall response and VGPR or better.

Across all outcomes, DBd had the highest probability of being the best treatment:

- PFS: 99.9%
- OS: 91.5%
- ORR: 85.8%
- VGPR or better: 70.5%

- CR or better: 98.7%

Further details of clinical efficacy outcomes from the mixed treatment comparison are available in Appendix D.3.5.1.

B.2.10.4 Investigation of statistical heterogeneity

Statistical heterogeneity is defined as an instance where a set of true relative treatment effects varies across studies; in other words, the observed treatment effects vary more than would be expected due to sampling error. For these analyses, there was only one study per comparison. Consequently, it is not possible to test for statistical heterogeneity or inconsistency in effects.

B.2.10.5 Unanchored MAIC CASTOR vs SACT

To compare the survival outcomes associated with use of DBd in real-world practice in the context of the outcomes demonstrated in clinical trial for patients with RRMM, an unanchored matching-adjusted indirect comparison (MAIC) was conducted that included the 1PL population in the DBd arm from the CASTOR study and the SACT dataset population. The MAIC was conducted by [redacted].

Methodology

The MAIC analysis for the SACT dataset versus data from CASTOR followed the method described by Signorovitch et al. and guidelines from the NICE DSU.[103,117] This method requires use of individual patient level data (IPD) from one study ([redacted]) and summary data from the other study ([redacted]). It accounts for cross-trial differences in patients' baseline characteristics (Table 32), which could bias the comparison. Patients with IPD that do not meet the inclusion/exclusion criteria of the comparator trial are removed and the remaining patients are reweighted with an approach similar to propensity score weighting (a tool widely used in observational research). After matching, treatment outcomes are compared across balanced trial populations.

Table 32 Baseline characteristics for the SACT dataset versus CASTOR 1PL population receiving DBd treatment[99,70,100]

Characteristic	SACT (N=[redacted])	CASTOR (N=122)
[redacted]		
[redacted]	[redacted]	63.0
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	N/A
[redacted]	[redacted]	N/A
[redacted]	[redacted]	N/A
[redacted]	[redacted]	N/A
[redacted]		
[redacted]	[redacted]	46 (37.7)
[redacted]	[redacted]	76 (62.3)

1PL = one prior line; DBd = daratumumab, bortezomib and dexamethasone; ECOG = Eastern Cooperative Oncology Group; NA = not available; SACT = Systemic Anti-Cancer Therapy

Following alignment of inclusion and exclusion criteria across trials, IPD from the remaining patients in the [redacted] cohort were then weighted such that mean values for relevant baseline parameters reflect the means reported in the [redacted] dataset. This was achieved [redacted] study, rather than [redacted] study. The weighting used the generalised method of moments to estimate propensity scores and has previously been described in detail by Signorovitch et al. It should be noted that the algorithm does not directly match median values; rather, it calculates the weights such that 50% of patients in [redacted] are within a value below the comparator's median value.[117]

The ability to adjust for multiple baseline factors depends on overlap between IPD and the population of the comparator. In general, matching larger numbers of baseline characteristics and adjusting for greater cross-trial baseline differences will require more extreme weights and will reduce the effective sample size. Effective sample size (Neff) is a measure which is derived from the weights and indicates the size of the original sample which contributes to the adjusted outcome.

Engauge Digitizer was used to convert the images of the KM curves from SACT into numbers with x and y coordinates (i.e., time and survival probabilities).[118] To ensure

accuracy, the digitised curve was overlaid onto the original image and visually compared against the original curves. These coordinates were then used to generate IPD (e.g., time and censoring status) for each curve using the method by Guyot et al.[119] The reweighted IPD from the [redacted] were then combined with the simulated IPD for [redacted] and analysed together using weighted Cox proportional hazard (PH) models. The impact of reweighting on the uncertainty was accounted for using the robust sandwich estimator for standard errors and consequently the confidence intervals for the HRs.[120] All MAIC analyses were conducted in SAS 9.4.

Results

Results demonstrate [redacted] between OS outcomes for the CASTOR and SACT datasets, which [redacted]. The observed (unadjusted) and adjusted CASTOR OS KMs and the SACT OS KM are presented in Figure 19.

Figure 19 DBd OS data from CASTOR (1PL population) versus SACT dataset (MAIC)[121]

[redacted]

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.

Discussion and limitations

The SACT dataset included a limited number of characteristics and it was not possible to match all variables (including [redacted]). In addition, any unreported or unobserved confounding factors that were not accounted for in the adjustment may lead to bias in the MAIC analysis. The length of OS follow-up was [redacted] Furthermore, differences in study design could bias the results. These limitations [redacted] between data from CASTOR and SACT.

B.2.10.6 Naïve comparison of data from SACT with the NHS Digital NDMM Standing Cohort Study

A naïve comparison of OS rates in clinical practice in England between SACT and a real-world evidence data set for NDMM from NHS Digital's National Cancer Registration and Analysis Service (NCRAS; [redacted]) indicated that the OS rate at 24 months for DBd in 1PL was [redacted] than the OS rate at 24 months for first-line for transplant-ineligible patients who did not receive daratumumab during their course of treatment [redacted]).[70,122] This highlights the strong benefits of DBd in the 1PL patient population in clinical practice in England and 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.

B.2.11 HRQoL

Patient reported outcomes (PROs) evaluating HRQoL were a major secondary endpoint in the CASTOR trial. At a median follow-up of 26.9 months, there was no significant detriment to overall HRQoL with the addition of daratumumab to bortezomib and dexamethasone; PRO results indicated that subjects in both the DBd and Bd groups who remained in the study maintained their HRQoL during treatment. Baseline values for all subscales of the EORTC-QLQ-C30 were comparable for patients treated with DBd and Bd and there was no significant difference between treatment groups at any time point. Similarly, baseline values for the EQ-5D-5L utility score and visual analogue scale (VAS) score were comparable for patients treated with DBd or Bd and there were no significant differences over time for most time points.

At a median follow-up of 26.9 months, there were also [redacted] in EORTC QLQ-C30 Global Health Status Scores for median time to improvement [redacted] or median time to worsening [redacted].[76] This means that patients treated with the DBd triple therapy combination benefit from improved PFS and OS with no significant detriment to overall HRQoL versus Bd. Moreover, the fact that HRQoL is maintained during treatment means a delay of further disability from the disease which is a key issue for patients.[123] [redacted], meaning that patients treated with DBd may experience additional QoL benefits following the [redacted] and can enjoy a better quality of life for longer than patients treated with Bd.[76] The economic model presented in this submission can therefore be considered as somewhat conservative, as the sustained treatment benefit gained associated with DBd is not captured (Section B.3.4.4).

B.2.12 Adverse reactions

To ensure all relevant safety evidence for daratumumab and potential comparator therapies was identified, systematic searches for additional AE data from non-randomised studies was carried out. These searches are in addition to the review of RCT safety evidence carried out as part of the clinical SLR (see Section B.2.10 and Appendix D). Most of the studies identified were short-term, small-scale studies that provided minimal supplementary safety data to RCTs identified through the clinical effectiveness SLR.

B.2.12.1 TEAE overall

At median follow-up of 72.6 months, most patients treated with DBd or Bd had at least one treatment-emergent adverse event (TEAE) after the start of treatment (99.2% and 95.4%, respectively).[94] Higher rates of grade 3 or 4 TEAEs were observed in patients treated with DBd compared with Bd 82.7% versus 62.9%); however, this may be largely attributable to the longer treatment duration for DBd versus Bd.[94]

The percentage of patients who discontinued treatment because of at least one TEAE was similar for both DBd and Bd (10.7% and 9.3%, respectively), suggesting that the tolerability of daratumumab is manageable.[77] A summary of TEAEs at 72.6 months of follow-up is provided in Table 33.

Table 33 Summary of TEAEs (CASTOR; safety population; median follow-up 72.6 months)[94]

	Bd (n=237)	DBd (n=243)
Any TEAE, n (%)	226 (95.4)	241 (99.2)
Grade 3/4 TEAE, n (%)	149 (62.9)	201 (87.2)
Serious TEAE, n (%)	81 (34.2)	134 (55.1)
TEAE leading to discontinuation, n (%)	22 (9.3)	26 (10.7)
TEAEs leading to death (Grade 5), n (%)	14 (5.9)	17 (7.0)

Bd = bortezomib and dexamethasone; DBd = daratumumab, bortezomib and dexamethasone; TEAE = treatment-emergent adverse event.

B.2.12.2 TEAE by preferred term

At median follow-up of 76.2 months, the most frequently reported TEAEs (≥20%) for the DBd group were: thrombocytopenia (60%), peripheral sensory neuropathy (50%), upper respiratory tract infection (37%), diarrhoea (36%), anaemia (30%), cough (29%), fatigue (24%), constipation (23%), and back pain (22%).[77] The most frequently reported TEAEs (≥20%) for the Bd group were: thrombocytopenia (44%), peripheral sensory neuropathy (38%), anaemia (32%), fatigue (25%) and diarrhoea (22%).[77] The three most common grade 3 or 4 adverse events reported in patients treated with DBd or Bd were thrombocytopenia (46.1% and 32.9%, respectively), anaemia (16.0% for both) and neutropenia (13.6% and 4.6%, respectively). Grade 3 or 4 infections were reported in 29.6% of patients in the DBd group and in 19% of patients in Bd group.[77] A summary of TEAEs reported in >15% of patients and Grade 3/4 by preferred term at 72.6 months of follow-up is provided in Table 34. Overall, no additional safety concerns were reported during the longer-term follow-up period in the CASTOR study.[77]

Table 34 TEAEs by preferred term (CASTOR; safety population, median follow-up 76.2 months)[77]

	Bd (n=237)		DBd (n=243)	
	All grades (≥15%)	**Grade3/4**	**All grades (≥15%)**	**Grade3/4**
Common haematologic adverse event				
Thrombocytopenia, n (%)	105 (44.3)	78 (32.9)	145 (59.7)	112 (46.1)
Anaemia, n (%)	75 (31.6)	38 (16.0)	73 (30.0)	39 (16.0)
Neutropenia, n (%)	23 (9.7)	11 (4.6)	48 (19.8)	33 (13.6)
Lymphopenia, n (%)	9 (3.8)	6 (2.5)	33 (13.6)	25 (10.3)
Common non-haematologic adverse events				
Peripheral sensory neuropathy, n (%)	90 (38.0)	16 (6.8)	122 (50.2)	11 (4.5)
Upper respiratory tract infection	43 (18.1)	1 (0.4)	90 (37.0)	6 (2.5)
Diarrhoea, n (%)	53 (22.4)	3 (1.3)	88 (36.2)	10 (4.1)
Cough, n (%)	30 (12.7)	0	71 (29.2)	0
Fatigue, n (%)	58 (24.5)	8 (3.4)	57 (23.5)	13 (5.3)
Constipation, n (%)	38 (16.0)	2 (0.8)	56 (23.0)	0
Back pain, n (%)	24 (10.1)	3 (1.3)	54 (22.2)	6 (2.5)
Arthralgia, n (%)	14 (5.9)	0	49 (20.2)	4 (1.6)
Peripheral oedema, n (%)	20 (8.4)	0	48 (19.8)	1 (0.4)
Dyspnoea, n (%)	21 (8.9)	2 (0.8)	47 (19.3)	10 (4.1)
Pyrexia, n (%)	28 (11.8)	3 (1.3)	46 (18.9)	5 (2.1)
Insomnia, n (%)	36 (15.2)	3 (1.3)	44 (18.1)	2 (0.8)
Pneumonia, n (%)	32 (13.5)	24 (10.1)	40 (16.5)	26 (10.7)
Bronchitis, n (%)	15 (6.3)	3 (1.3)	38 (15.6)	7 (2.9)
Nausea, n (%)	27 (11.4)	0	37 (15.2)	2 (0.8)
Hypertension, n (%)	8 (3.4)	2 (0.8)	30 (12.3)	18 (7.4)
Asthenia, n (%)	37 (15.6)	5 (2.1)	27 (11.1)	2 (0.8)

Bd = bortezomib and dexamethasone; DBd = daratumumab, bortezomib and dexamethasone; NA = not applicable; TEAE = treatment-emergent adverse event.

B.2.12.3 Subcutaneous formulation of daratumumab

A licence extension for a subcutaneous (SC) formulation of daratumumab was received in June 2020 and is now used by the majority of patients in UK clinical practice.[10] Non-inferiority between the weight-based IV formulation of daratumumab (which was used in CASTOR) and the SC formulation of daratumumab was demonstrated as part of the phase 3 COLUMBA (MMY3012) trial in patients with RRMM. Notably, use of the subcutaneous formulation of daratumumab was associated with an improved safety profile compared with intravenous daratumumab (see Appendix F for further detail).[10,12]

B.2.13 Ongoing studies

A summary of all completed and ongoing studies that should provide additional clinical evidence for daratumumab in RRMM in the next 12 months are shown in Table 35.

Table 35 Clinical trials for the evaluation of daratumumab in patients with relapsed/refractory MM disease

Study	Target indication/population	Primary objective	Phase	N	Efficacy hypothesis	Start Date	Completion date
NCT03768960[124]	Daratumumab as monotherapy in patients with RRMM previously treated with a PI and an immunomodulatory agent	This is a single arm study to confirm the safety profile of daratumumab in routine clinical practice, using incidence of TEAEs as the primary endpoint. Secondary endpoints: ORR, VGPR, PFS, TTR and HRQoL.	IV	150	This Phase IV study aims to confirm the efficacy of daratumumab in the setting of routine clinical practice	June 10, 2019	July 25, 2022
NCT03234972 (MY3009)[125]	DBd for patients with RRMM who have received ≥1 line of prior therapy for MM with PR or better to ≥1 line	This is an open label, randomised study comparing the efficacy DBd vs Bd in Chinese patients with RRMM. The primary endpoint is PFS. Additional endpoints: TTP, ORR, VGPR, TTR, DOR, OS and HRQoL	III	211	PFS is defined the time from date of randomisation to either PD or death, whichever occurs first (~4.5 years). PD is an increase of 25% from the lowest response value for serum M and urine M-protein	November 30, 2017	September 30, 2022
NCT03180736 MMY3013 (APOLLO)[126]	Daratumumab plus pomalidomide and dexamethasone for the treatment of patients with RRMM who received ≥1 prior treatment with both lenalidomide and a PI Patients had PD on or after the last treatment regimen; patients with only 1 prior line of therapy must have been found lenalidomide refractory on or within 60 days of the lenalidomide containing regimen	This is an open-label randomised study comparing daratumumab plus pomalidomide and low-dose dexamethasone, vs low-dose dexamethasone. The primary endpoint is comparison of PFS between treatment arms. Secondary endpoints include ORR, depth of response, DOR, time to next therapy, OS, HRQoL	III	304	PFS is defined as the time from randomisation to PD or death, whichever occurs first (up to ~3 years). Patients are assessed monthly, and PD is defined according to modified IMWG guidelines	June 12, 2017	June 1, 2022

Study	Target indication/population	Primary objective	Phase	N	Efficacy hypothesis	Start Date	Completion date
NCT02076009 MMY3003 (POLLUX)[127]	Daratumumab, lenalidomide and dexamethasone for the treatment of patients with RRMM who have received ≥1 prior treatment Patients had PD on or after their last treatment regimen	This is an open-label randomised study comparing daratumumab plus lenalidomide and dexamethasone vs lenalidomide and dexamethasone. The primary endpoint is PFS. Secondary endpoints include TTP, VGPR, MRD-negativity, ORR, OS, TTR and DOR	III	570	PFS is defined as duration from date of randomisation to PD or death, whichever occurs first. PD is defined using M-protein response values, size of existing/development of new bone lesions or soft tissue plasmacytomas, and development of hypercalcemia	May 23, 2014	August 30, 2024
NCT03158688 (CANDOR)[128]	Carfilzomib, daratumumab and dexamethasone for patients with RRMM who have received 1 to 3 prior therapies	This is an open-label, randomised study comparing carfilzomib, daratumumab and dexamethasone vs carfilzomib and dexamethasone. The primary endpoint is PFS. Secondary endpoints include OR, MRD-negative CR rate, OS, TEAEs, DOR, TTNT, TTP, TTR, HRQoL	III	466	PFS is defined as the time from randomisation to PD or death due to any cause, whichever occurs first. PD is defined using IMWG response criteria and assessed by IRC	June 13, 2017	April 15, 2022

Bd = bortezomib and dexamethasone; CR = complete response; DBd = daratumumab plus bortezomib and dexamethasone; DOR = duration of response; HRQoL = health-related quality of life; IRC = independent review committee; IMWG = International Myeloma Working Group; MM = multiple myeloma; MRD = minimal residual disease; NA = not available; OR = overall response; ORR = objective response rate; OS = overall survival; PD = progressive disease; PFS = progression-free survival; PI = proteasome inhibitor; PR = partial response; RRMM = relapsed or refractory multiple myeloma; TEAEs = treatment emergent adverse events; TTNT = time to next therapy; TTP = time to progression; TTR = time to response; VGPR = very good partial response

B.2.14 Interpretation of clinical effectiveness and safety evidence

The experience of relapse in patients with MM is particularly detrimental to patient HRQoL; patients with RRMM have a worse prognosis and a greater symptomatic burden than patients with newly diagnosed MM due to the progressive nature of MM and the cumulative adverse effects of treatment.[42,49] The proportion of treatment-eligible patients decreases with each subsequent line of therapy due to worsening prognosis.[80] High attrition coupled with diminishing survival in later lines of therapy highlight the importance of using the most effective treatment option as early as possible.[81] Moreover, most of the clinical management of MM is provided in the outpatient setting placing a high burden on informal care provided by caregivers.[53]

Life expectancy, treatment effectiveness and longer remission periods are key priorities for patients, healthcare providers and carers, along with a reduction in adverse treatment effects and fatigue.[42,43,45,51] Patients with RRMM have reported that they place most value on reduction in pain, decreased fatigue and increased life expectancy, with quality of life/wellbeing, return to normal activities, social life and work also of high value.[52]

Unlike European markets, where a wide variety of triplet regimens are recommended, the treatment pathway in England is heavily restricted, especially for patients with RRMM who have received one prior line of therapy. There is therefore a significant unmet need for a safe and effective triplet regimen in the second-line setting in England.[67-69] Currently in England, the use of anti-CD38 treatments is restricted to transplant-eligible patients with newly diagnosed MM.[84] Offering DBd to patients with RRMM not only increases later line therapeutic options for patients who have received one prior line of therapy, but also creates access to clinical trials which require prior exposure to anti-CD38 therapies, such as those evaluating bispecific antibodies and CAR-T.[78,79] Providing routine funding for anti-CD38 therapies in patients with RRMM can increase the probablility of access to future innovative medicines in England.

CASTOR demonstrated that the addition of daratumumab to a bortezomib and dexamethasone regimen resulted in unprecedented, substantial and consistent improvements in key clinical outcomes versus bortezomib and dexamethasone in patients with RRMM. DBd provided highly significant improvements with regards to the primary endpoint of PFS as well as for the secondary endpoints OS, TTP, ORR, rate of VGPR or better and MRD negativity rate compared with Bd. A key secondary endpoint, PROs on HRQoL were similar between DBd and Bd treatment arms, indicating that addition of daratumumab to bortezomib and dexamethasone has no detrimental impact on HRQoL.

After a median follow-up of 50.2 months, median PFS in the ITT population was significantly greater with DBd versus Bd (median: 16.7 versus 7.1 months respectively; HR, 0.31; 95% CI: 0.24, 0.39; p<0.0001).[77] An increase in PFS was consistently observed across all subgroups assessed, with the greatest benefit observed in second-line patients (median: 27.0 versus 7.9 months; HR 0.21, 95% CI: 0.15, 0.31; p<0.0001) (see Section B.2.7.2).[77]

Furthermore, after a median follow-up of approximately 6 years, treatment with DBd was associated with a 26% reduction in the risk of death in the overall population, and a 44% reduction in the risk of death in second-line patients. The estimated 78-month OS rate for patients with one prior line of therapy was 51.7% (95% CI: 41.9%, 60.7%) in the DBd arm and 28.8% (95% CI: 18.9%, 39.4%) in the Bd arm.[77] OS was generally consistent across subgroups with a pronounced effect in the 1 prior line subgroup. These survival results, together with those observed for daratumumab in combination with lenalidomide and dexamethasone in the phase 3 POLLUX study, demonstrate that patients receive an OS benefit with daratumumab-containing regimens in RRMM.[77]

The greater proportion of second-line patients surviving with DBd treatment further establishes the additional survival benefit offered by DBd compared with the standard of care in England, particularly for patients on second-line treatment. Moreover, these findings suggest that to maximise the prognosis of RRMM patients, DBd should be given as early as possible in the treatment pathway.

Additional evidence supporting the real-world clinical effectiveness of DBd was reported in clinical practice data from the SACT cohort of patients in England who received DBd for RRMM in patients previously treated with one prior line of therapy. The 24 month OS rate was [redacted], with a median treatment duration of [redacted].[70] This compares favourably with data from the NHS standing cohort study, which showed an OS-rate of [redacted] at 24-months for patients with transplant ineligible NDMM treated with front-line systemic therapy.[71]

An unanchored MAIC was conducted to assess survival outcomes for DBd in real-world practice (SACT patient cohort) in the context of data for DBd from CASTOR. There were [redacted] observed between the datasets; however, the comparison had limitations related to matching patient characteristics based on a limited number of baseline characteristics, follow-up and study design.

Due to the international design of the CASTOR trial, and highly restrictive NICE recommendations of RRMM treatments, many patients received subsequent treatment with

therapies not available in England (see Section B.2.5.2). Furthermore, as a consequence of the earlier progression of patients in the Bd arm, there is a disparity in the extent of subsequent treatment received between the trial arms (second-line patients: 37% for DBd versus 65% for Bd). The use of subsequent treatment not available in England, along with the higher proportion of patients in the Bd arm receiving such treatments, introduces bias into the OS analyses. As such, adjustment for subsequent treatments not available in clinical practice in England was carried out to reduce bias and increase the generalisability of trial results to English clinical practice.

Following adjustment, using inverse probability of censored weights (IPCW) methodology, the HR for OS was [redacted] (95% CI: [redacted]) in the second-line population (median 72.6 months follow-up), highlighting the survival benefit for patients receiving DBd in the CASTOR study.[109]

PRO data collected in CASTOR demonstrate that HRQoL is maintained during treatment with Bd or DBd, with no significant differences in EORTC QLQ-C30 Global Health Status Scores between treatment arms for median time to improvement (HR 0.99 [95% CI: 0.76, 1.29] p=0.9163) or median time to worsening (HR 0.94 [95% CI: 0.73, 1.20] p=0.5960).[76] Results are well-aligned with patient preference data in which quality of life/well-being, fewer side-effects, extended life, pain control and reduced treatment burden are highly valued.[45]

The safety of DBd was comparable with Bd across most safety endpoints, with a low and comparable number of treatment discontinuations due to adverse events for DBd and Bd (10.7% vs. 9.3%, respectively) in the CASTOR study. These results demonstrate that the safety profile of daratumumab in combination with Bd is consistent with the known safety profile of Bd alone and that of daratumumab as a monotherapy. Importantly, no new safety concerns were identified with the longer follow up.[76] Notably, in clinical practice bortezomib is often administered once weekly up to a maximum of 32 doses to reduce AEs, while in CASTOR bortezomib was administered more frequently according to its marketing authorisation (twice weekly for a maximum of 8 cycles); this difference is expected to have minimal impact on the relative effectivenss of DBd vs Bd since bortezomib was administered equally across both treatment arms. Furthermore, as reflected in the SmPC for daratumumab, use of the subcutaneous formulation is now representative of clinical practice in the UK, and is associated with an improved safety profile compared with the intravenous formulation used in CASTOR.

B.3 Cost effectiveness

B.3.1 Published cost-effectiveness studies

A systematic search of cost-effectiveness studies associated with RRMM was conducted to identify cost effectiveness analyses relevant to the decision problem. No published cost effectiveness studies relevant to the technology appraisal were identified. A summary list of published cost-effectiveness studies are presented in Appendix G.

B.3.2 Economic analysis

Janssen developed a *de novo* economic model for the original technology appraisal of DBd in 2019 which was used to evaluate the cost-effectiveness of DBd versus relevant comparators (TA573).[67] All variables and assumptions related to the selection of the model structure, inputs collected, and limitations were presented in the original company submission document available on NICE's website. The company submission for the reappraisal of DBd utilises the MS Excel Spreadsheet model submitted by Janssen following the original ACD response, and includes no structural changes to the model engine that was used for the original STA. Details of the analysis carried out based on updated data now available following a period of managed access on the CDF are presented below.

B.3.2.1 Patient population

Consistent with the original company submission, the modelled population in the economic evaluation of DBd is identical to the second-line population included in the CASTOR phase III clinical study. Inclusion and exclusion criteria for CASTOR are described in Section B.2.3.2. In line with the positioning of DBd, the model target population included adult patients with multiple myeloma who have received one prior therapy.

B.3.2.2 Model structure

The modelling approach and overall structure of the model presented in the original company submission has been maintained, which decision is supported by the significantly extended follow-up available (median 72.6 months vs 26.9 months, current submission vs original submission, respectively), the maturity of the data as well as the objective to support comparability of assumptions as well as results between the original and the updated company submissions, partitioned survival analyses (PartSA) were used in the model.

PartSA is a widely accepted approach in oncology indications and has been used in previous RRMM NICE technology appraisals.[86,129-134] As we are mindful, however, of the Company evidence submission for daratumumab in RRMM

limitations to the PartSA approach outlined in the technical support document (TSD)[135] from NICE's decision support unit (DSU), every effort has been made to validate the model extrapolations. All model extrapolations (particularly OS extrapolations) have been validated using a triangulation of external data, expert clinical opinion and examination of the underlying hazard function.

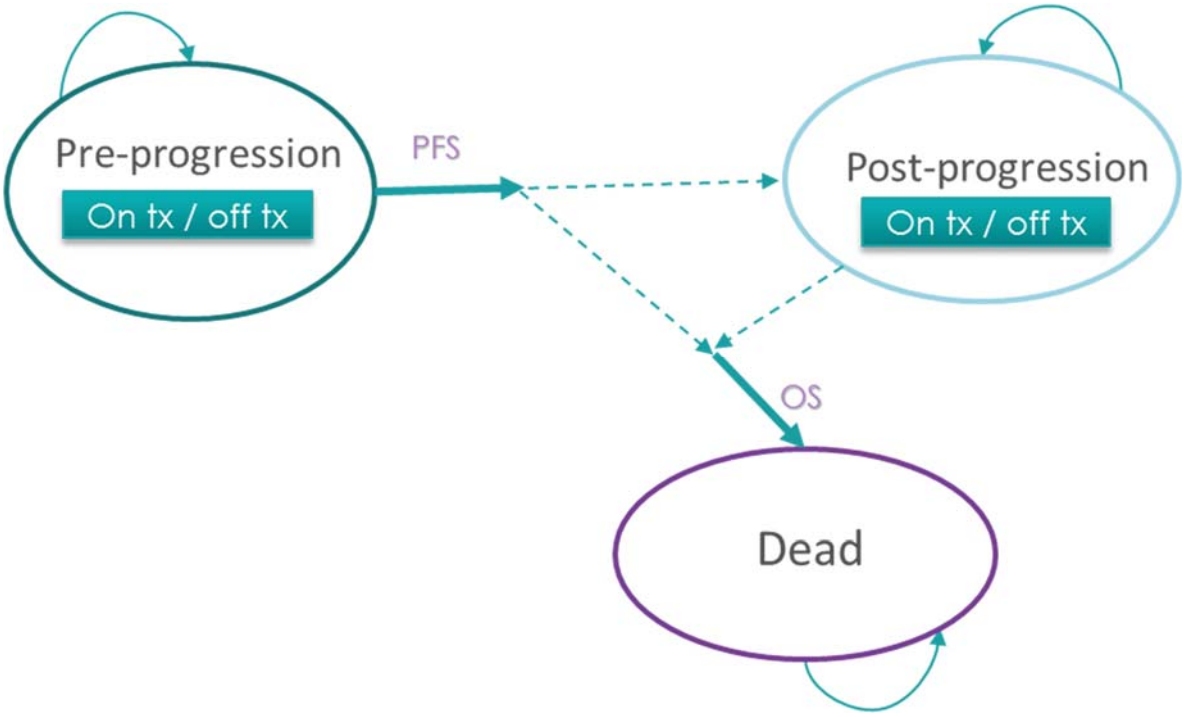
Clinical experts provided input on the appropriateness of the clinical pathway to ensure it reflected the key aspects of current clinical practice in England. Key aspects that were determined to affect both clinical outcomes and treatment decisions included:

- Duration of PFS;
- Duration of treatment;
- Treatment options in subsequent lines; and
- OS.

CASTOR[90] endpoints were consistent with the key clinical aspects identified in the review of the clinical and treatment pathways, and are indeed captured in the model structure as depicted in Figure 20. The model comprises three health states; pre-progression, post-progression and death directly capturing PFS and OS. Treatment status in both the pre-progression and post-progression states was also tracked to capture duration of treatment:

- Progression-free
  - On treatment
  - Off treatment
- Post-progression
  - On subsequent treatment
  - Off treatment/palliative care
  - Dead

Figure 20 Model diagram



OS = overall survival; PFS = progression-free survival; Tx = treatment

Dotted lines represent the fact the transitions between health states are not directly tracked, but proportions of patients in each health state are calculated through the partition approach at each time point.

Patients who are eligible for treatment entered the model, initiated treatment, and experienced an interval of PFS. Patients who experienced disease progression and did not die during the initial modelled line of treatment continued to the post-progression health state and could receive subsequent treatments. Patients could die at any time point in the model.

The PartSA approach applies treatment specific and independent PFS and OS curves for each comparator. The assumption is that at any time point:

- The proportion of patients falling under the PFS curve is in the pre-progression health state
- The proportion of patients falling above the OS curve is in the Dead health state
- Any remaining patients are in the post-progression health state

The model also captures the proportion of patients on- and off-treatment using the same partition approach:

- Patients falling under the TTD curve are on-treatment
- Patients between the TTD and PFS curves are in the pre-progression health state but off-treatment

Similarly, in the post-progression health state, the proportion of patients on subsequent treatment is captured based on the ratio of patients starting subsequent treatment after progression and their discontinuation from subsequent treatment either due to death or other reasons. The impact of differences in terms of treatment options in subsequent lines of treatment were captured by allowing for treatment-specific OS and a treatment-specific mix of subsequent treatments.

Costs and utilities were assigned to each health state and were applied according to the patients' disease progression status and the type of treatment received. As the model progressed, cost and utility data were summed per treatment arm, allowing for the calculation of differences in accumulated costs and effectiveness between comparators at model completion.

B.3.2.2.1 Model features

The base case analysis was conducted from the perspective of NHS England.

A 30-year time horizon was used in the base case. This time horizon was considered long enough to capture the long-term clinical and economic impacts of RRMM, an incurable disease requiring treatment until end of life. Given the median age of 62.6 years[91] for the second-line population of CASTOR (DBd arm), 30 years is considered to be a fair approximation of a lifetime time horizon. Although the median age of patients in clinical practice is higher (based on SACT dataset - [redacted] years), considering an external source to inform mean age is inconsistent with all other efficacy inputs in the model sourced from CASTOR, and would introduce bias into the calculations artificially decreasing overall survival due to general mortality impacting older patients.

Costs and health-related outcomes were discounted by 3.5% annually.

The model cycle-length is 1 week to adequately capture differences between dosing schedules regularly used in RRMM (e.g. where patients may receive treatment for two weeks and then no treatment for one week). Throughout the analysis, health benefit and cost calculations were half-cycle corrected by averaging the number of patients at the start and end of each cycle.

A summary of the model features is presented in Table 36, alongside a comparison with models included in previous NICE appraisals of treatments for RRMM as these were used to inform the base case model for daratumumab.

Table 36 Comparison of current and previous appraisals in the indication

Factor	Previous appraisals				
	TA171 (lenalidomide)[82]	**TA586 (lenalidomide post bortezomib)[69]**	**TA129 (bortezomib)[132]**	**TA457 (carfilzomib)[130]/ TA657[88] (review of TA457)**	**TA380 (panobinostat)[86]**
Summary of analytic methods	Discrete event simulation utilizing patient-level information	Partitioned survival model, 3 health states	Semi- Markov state transition model.	Partitioned survival model, 3 health states	Direct comparison survival analysis with data from clinical trials
Patient population	People with multiple myeloma who have received at least one prior therapy	Adults with multiple myeloma for whom thalidomide is contraindicated and whose disease has progressed after at least 1 prior treatment with bortezomib.	Patients who had experienced a 1st relapse of multiple myeloma	Patients with previously treated multiple myeloma	Patients who had received at least two prior lines of treatment including immunomodulatory drug (IMiD) and BOR based regimens.
Time horizon	30 years	25 years	15 years	40 years	25 years
Perspective	NHS&PSS		NHS	NHS	NHS&PSS
Discount	3.5%		3.5%	3.5%	3.5%
Cycle length	Continuous time model	4 weeks	3 weeks	4 weeks	3 weeks
Half-cycle correction	Not applied	Applied	N.A	Applied	N.A.
Treatment waning effect?	No, model driven by response rates	No, independently fitted curves	Hazard ratios for time to progression and overall survival Duration of treatment effects 3 years (based on median survival of the APEX trial)	No, independently fitted curves	HR for LEN/DEX relative to PANO/BOR/DEX changed at cycle 39, from 0.99 to 1.52
Source of utilities	van Agthoven (2004).		van Agthoven, 2004)	Mapping analysis using change from baseline from clinical trial applied to van Agthoven (2004)	Mapped utility values from trial Acaster et al. study

Source of costs	British National Formulary (BNF 65)	British National Formulary (BNF 65) Department of Health Electronic Market Information Tool (eMit) For monitoring costs NHS reference costs and ERG model (TA228)	APEX trial, NHS OutPatient Mandatory Tariff 2005/6, Bruce et al (1999), experts interviews		N.A.	N.A.
Factor	**Previous appraisals**				**Current appraisal**	
	TA505 (ixazomib)[85]	**TA427 (pomalidomide)[129]**	**ID1477 (isatuximab)[136]**	**TA510 (dara monotherapy)/ ID933**	**Chosen values**	**Justification**
Summary of analytic methods	Partitioned survival model, 3 health states	Partitioned survival model, 3 health states	Four-state partitioned survival model	Partitioned survival model, 3 health states	Partitioned survival model	Supports comparability of assumptions and results between the original and updated company submission
Patient population	Adult patients with multiple myeloma who have had 2 or 3 prior lines of therapy	Adults at third or subsequent relapse treated with LEN and BOR	Relapsed refractory multiple myeloma	Relapsed refractory multiple myeloma	Adult patients with multiple myeloma who have received one prior therapy.	Population identical to the second-line population included in the CASTOR phase III clinical study
Time horizon	25 years	15 years	15 years	15 years	30 years	Given the median age of 62.6 years for CASTOR population, 30 years is a fair approximation of a lifetime time horizon
Perspective	NHS and PPS	NHS	NHS and PPS	NHS and PPS	NHS&PSS	Aligns with NICE guide to the methods of technology appraisal
Discount	3.5%	3.5%	3.5%	3.5%	3.5%	Align with NICE guide to the methods of technology appraisal
Cycle length	1 week	1 week	1 week	1 week	1 week	Adequately captures differences between dosing schedules regularly used in RRMM (3 or 4 weeks)

Half-cycle correction	Applied	NR	Not applied	Not applied	Applied	
Treatment waning effect?	No, independently fitted curves	No, independently fitted curves	No	No	No, independently fitted curves	No treatment waning effect was applied in the base case analysis as there is no evidence to suggest if, or when, the treatment effect of daratumumab on survival would wane over time. Treatment waning was not considered in the previous NICE appraisals of daratumumab either (TA573 and TA510). Furthermore, scrutiny of the evolution of empirical hazards over time shows a decreasing pattern suggesting that treatment waning should not be considered.
Source of utilities	EQ-5D data from clinical trial	EQ-5D data collected in the trial	Utility data sourced from ICARIA study	Utility scores were mainly taken from the MM-003 trial.	Utilities derived based on ENDEAVOR (TA457)	Utilities were collected only at weeks 8 and 16 beyond relapse in CASTOR which did not allow for a robust analysis of PRO data.
Source of costs		Admin cost driven from TA311, monitoring, concomitant medication and AE costs from questionnaire filled by clinicians.	NHS reference costs, BNF and eMIiT	MIMs, NHS reference costs, BNF	MIMS UK Drug Database, National Schedule of Reference Costs 2020-2021	

B = bortezomib; C = carfilzomib; D = daratumumab; d = dexamethasone; EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; ERG = evidence review group; ICER = incremental cost effectiveness ratio; L = lenalidomide; LY = life year; N/A = not applicable; NHS = national health service; P = pomalidomide; QALY = quality adjusted life year.

B.3.2.3 Intervention technology and comparators

The intervention, DBd, is implemented within the model as per its marketing authorisation, and is given according to the recommended dosing regimen. The comparative treatments are also implemented as per their respective marketing authorisations and are given according to their licensed dosing regimens (e.g. up to 8 cycles for bortezomib).

As per the NICE scope for second-line patients, the following treatments were included in the base case comprising of patients with one prior line of treatment:

- Daratumumab+bortezomib+dexamethasone (DBd)
- Bortezomib+dexamethasone (Bd)
- Carfilzomib+dexamethasone (Cd)

The quality and the reliability of the evidence to allow comparison of relative clinical or cost-effectiveness of DBd against chemotherapies was inadequate. No evidence was identified for chemotherapy regimens used in current clinical practice. Furthermore, clinical expert opinion obtained during a recent advisory board meeting (see Appendix O for more details) confirmed that chemotherapies are not used in clinical practice in the UK in the 1 prior line setting. Most importantly it was also recognized by NHS England during the original appraisal of DBd that NHS England does not consider that cytotoxic chemotherapy is a reasonable comparator as 2nd line treatment.[67] As such, chemotherapies were not included as comparators in the below analyses.

B.3.3 Clinical parameters and variables

The key effectiveness inputs in the model are PFS, OS and time to treatment discontinuation (TTD).

B.3.3.1 Fitting of Parametric Distributions to Time to Event Data

To project time-to-event data for the entire model time horizon, the extrapolation of survival data beyond the trial period was required. Following recommendations by the NICE Decision Support Unit on survival data extrapolation, six parametric distributions were fitted to model OS, PFS and TTD data:

- Exponential
- Weibull
- Log-normal

- Log-logistic
- Generalised gamma
- Gompertz

To determine the most appropriate survival functions, model fits was assessed as follows:

- Testing the proportional hazard (PH) assumption by plotting the log cumulative hazard vs log time for both treatment arms and assessing whether their vertical distance is constant over time
- Plotting Quantile-Quantile-plots accelerated failure time models with a linear trendline, using the percentiles of the inverse survival functions for the intervention and comparator.
- Comparison of Akaike information criterion (AIC) statistics and Bayesian information criterion (BIC) statistics
- Estimation of smoothed hazard rates from CASTOR to compare changes in the observed hazard function over time against assumed hazards for each parametric model
- Visual comparison of the predicted curve from a given parametric function to the Kaplan-Meier (KM) curve from the patient data
- Assessment of the clinical validity of the extrapolated portion of the survival curves at key milestones

B.3.3.1.1 Progression-free Survival

Scrutiny of the PFS hazard curves from CASTOR indicated that there was a violation of the proportional hazards assumption between the treatment arms (Figure 21). In addition, Figure 22 (Quantile-Quantile-plot) suggests that accelerated failure time models should not be fitted jointly to the data. Due to these observations, DBd curves were fitted separately from Bd curves.

Figure 21 Log-(log) survival plot from the CASTOR trial data: progression-free survival

B = bortezomib; D = daratumumab; d = dexamethasone

Figure 22 Quantile-quantile-plot, accelerated failure time models with a linear trendline: progression-free survival

B = bortezomib; D = daratumumab; d = dexamethasone

Extrapolation of DBd PFS

Assessment of quality-of-fit

Long-term projection of PFS was assessed primarily on statistical and visual goodness-of-fit, examination of smoothed hazard rates vs projected hazards and the clinical plausibility of the longer-term projected tail. While PFS does not directly impact survival, it is an important determinant of quality of life.

Based on statistical quality of fit exponential (Bayesian information criteria - BIC) and Gompertz (Akaike information criteria - AIC) were calculated to be fitting the observed data most accurately, based on these curves having the lowest AIC and BIC values (see Table 37).

Table 37 Goodness-of-fit for parametric fitting to PFS in CASTOR and PFS at Different Landmark Points, DBd

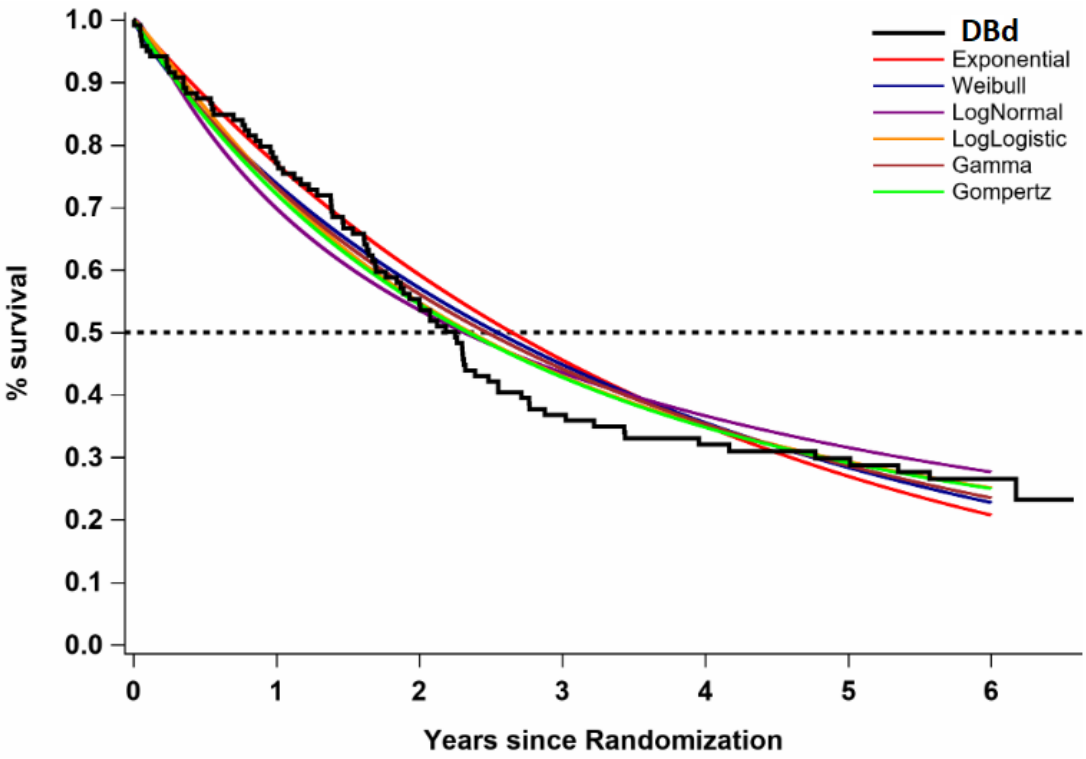
	DBd		Progression-free Survival		
Analysis	**AIC**	**BIC**	**5 years**	**10 years**	**20 years**
Weibull	812.6	818.2	28.5%	9.8%	1.4%
Log-normal	818.5	824.1	31.6%	18.2%	9.0%
Log-logistic	810.5	816.2	29.4%	15.6%	7.6%
Exponential	812.4	**815.2**	**27.1%**	**7.3%**	**0.5%**
Generalized gamma	813.9	822.3	28.8%	11.5%	2.6%
Gompertz	**809.7**	815.3	**29.2%**	**16.4%**	**11.0%**

AIC = Akaike information criteria; Bd = bortezomib and dexamethasone; BIC = Bayesian information criteria; DBd = daratumumab, bortezomib and dexamethasone; PFS = progression-free survival.

Bolded distributions indicate those with the best fit

Following the visual inspection of the trial results of DBd a change in the shape of the curve was observed. Due to this alteration simple parametric fitting was not able to consistently follow the trial results between years 2 and 4 (see Figure 23). To account for this deviation the KM curves were utilized up to 4 years after which point extrapolation of trial results was applied.

Figure 23 Parametric fitting to PFS in CASTOR, DBd



B = bortezomib; D = daratumumab; d = dexamethasone

Assessment of empirical hazards

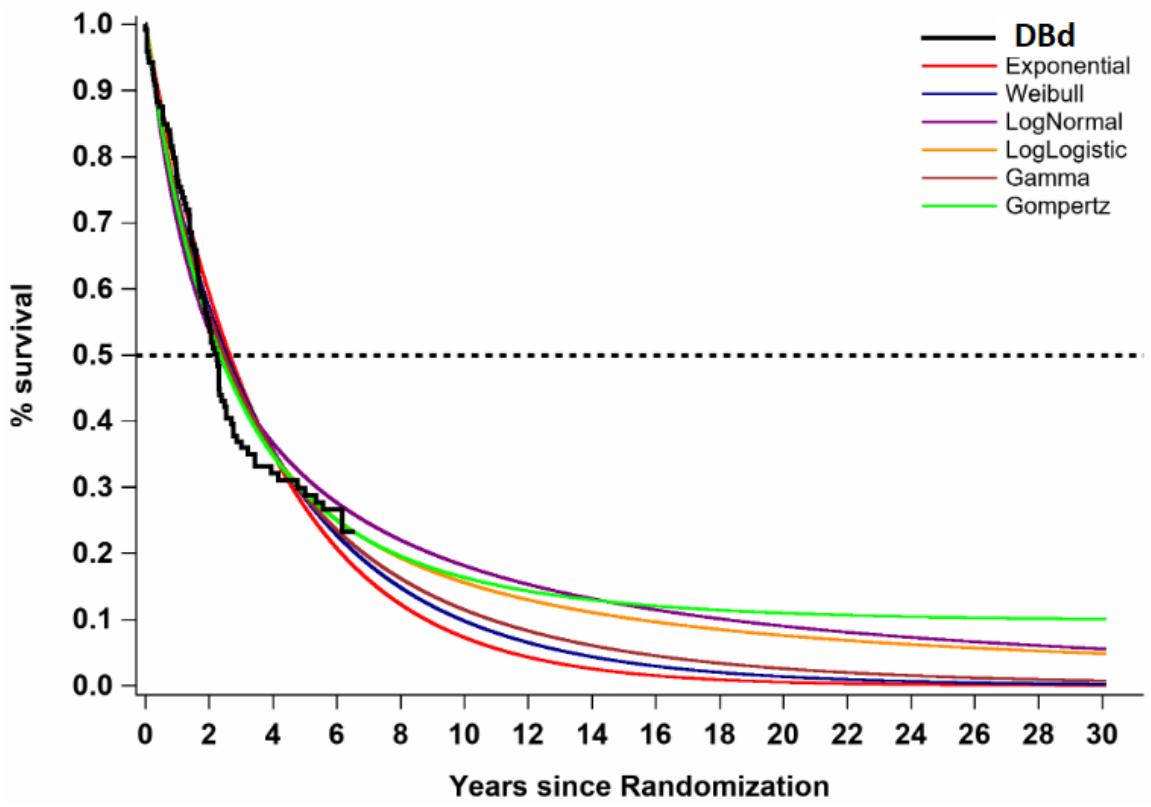
Next, the smoothed hazard curves plotted against the hazard figures derived from curve fitting exercise is in Figure 24. Figure 24 shows an initial decline followed by an increasing rate pattern observed with DBd until month 20 when the hazards start to decrease over time. At months 54-60 an increase in the hazards is observed, however this observation might be biased due to the low number of patients at risk (n=28-27) and should be used with caution for the basis of decision making. Contrary to these observations Gompertz showed a continuous decrease without capturing the initially higher hazards while Weibull provided continuously decreasing rates with a high baseline. For these reasons, Gompertz and Weibull were considered to be poor candidates for base case analysis. All other option were included in further evaluation for base case selection.

Figure 24 Smoothed Hazard Rates from the CASTOR Trial Data, DBd: PFS

Structured elicitation of clinical expert feedback

Consensus feedback from a recent clinical advisory board (see Appendix O) following a structured elicitation process confirmed that in a population similar to the one enrolled in CASTOR, approximately 10% of the patients would be expected to be progression-free 10 years beyond treatment initiation with DBd, which aligned best with the exponential and generalized gamma curves (Table 37 and Figure 25).

Figure 25 Parametric fitting to PFS in CASTOR, Long-term, DBd



B = bortezomib; D = daratumumab; d = dexamethasone

Conclusion

Considering the statistical quality of fit, the evolution of empirical hazards as well as clinical expert opinion, exponential was chosen to extrapolate observed data beyond 4 years (up to which timepoint KM data was used directly).

Extrapolation of Bd PFS

Assessment of quality-of-fit

Following the visual inspection of the trial results of Bd it was found that 87.61% patients progressed or died during the follow-up period, therefore a near-complete dataset was available for the estimation of Bd progression-free survival. To maintain consistency between the trial treatment arms, KM data was applied similarly to DBd until year 4 beyond which point the extrapolation of the Bd survival was needed.

Based on statistical quality of fit log-logistic was calculated to be fitting the observed data most accurately, based on having the lowest AIC and BIC values (see Table 38).

Table 38 Goodness-of-fit for parametric fitting to PFS in CASTOR and PFS at Different Landmark Points, Bd

	Bd		Progression-free Survival		
Analysis	**AIC**	**BIC**	**3 years**	**5 years**	**10 years**
Weibull	665.4	670.9	1.6%	0.0%	0.0%
Log-normal	659.6	665.0	4.0%	1.0%	0.1%
Log-logistic	**654.5**	**659.9**	**4.1%**	**1.5%**	**0.4%**
Exponential	671.0	673.8	3.6%	0.4%	0.0%
Generalized gamma	658.9	667.1	2.6%	0.3%	0.0%
Gompertz	658.9	677.9	2.6%	0.3%	0.0%

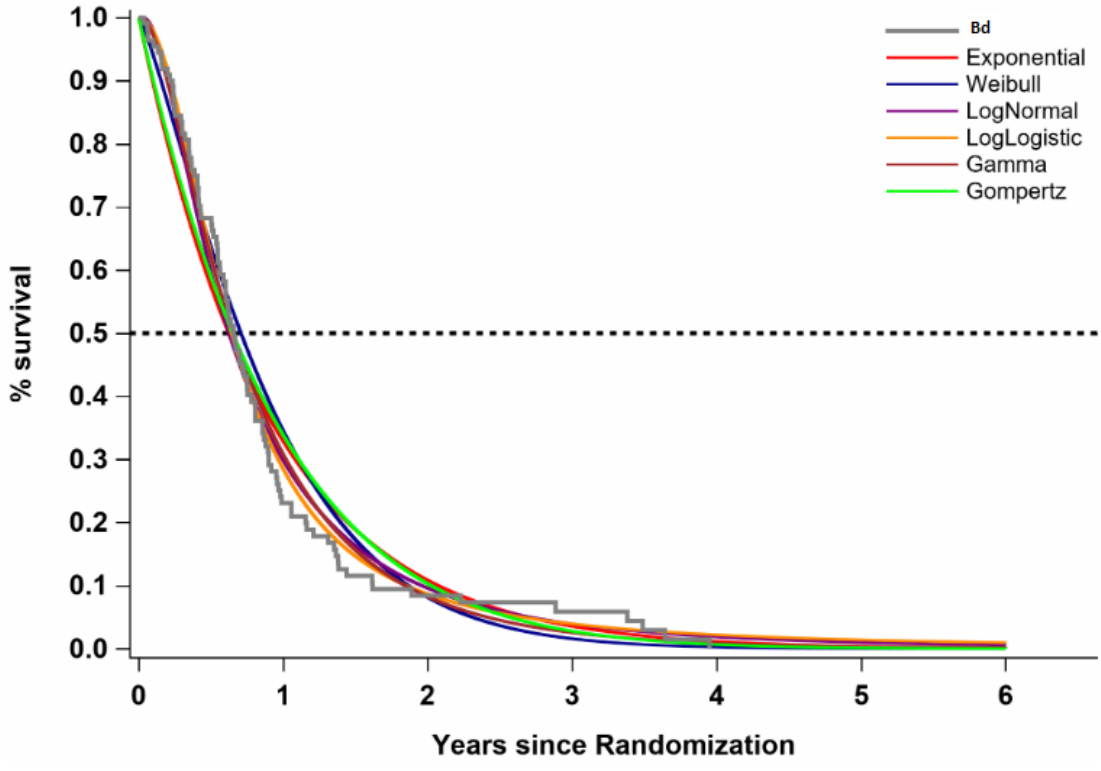
AIC = Akaike information criteria; Bd = bortezomib and dexamethasone; BIC = Bayesian information criteria; DBd = daratumumab, bortezomib and dexamethasone; PFS = progression-free survival.

Bolded distributions indicate those with the best fit

Structured elicitation of clinical expert feedback

Clinicians did not have a clear preference for long-term extrapolation of Bd as all curves followed the observed data relatively closely (Figure 26) and all curves provided similar survival estimates at 5 and 10 years (Table 38).

Figure 26 Parametric fitting to PFS in CASTOR, Bd



B = bortezomib; D = daratumumab; d = dexamethasone

Conclusion

To maintain consistency (Figure 26) between the distributions selected for PFS, exponential was selected to be used in the base case.

Extrapolation of Cd PFS

PFS of Cd was modelled by applying a HR calculated in the NMA to the reference curve of Bd projected PFS from CASTOR, which is consistent with the approach presented in the original company submission.

Following the review of the original company submission, the appraisal committee (AC) expressed concern that the effectiveness of DBd compared to Cd was overestimated in network meta analyses (NMA). This is because, unlike the appraisal of carfilzomib (TA457), no adjustment was made to correct for differences in the treatment duration of bortezomib in the Bd arms of CASTOR and ENDEAVOR; ENDEAVOR used a treat to progression approach, whereas CASTOR restricted the number of cycles of Bd to 8 (as per the marketing authorisation).

In response to the AC's review Janssen highlighted the importance of cumulative dose which was recognised in a retrospective analysis of the VISTA study that found a higher cumulative Bd dose was associated with significantly increased OS compared with a low cumulative Bd dose (age-adjusted HR, 0.561; p=0.00002).[137]

Janssen have estimated the cumulative dose of bortezomib received in the second-line populations of ENDEAVOR and CASTOR. The results indicate a marginal (2.0%) difference between the studies, with CASTOR associated with a higher cumulative dose than ENDEAVOR .[138]

Janssen concluded that, despite a similar cumulative dose of bortezomib between CASTOR and ENDEAVOR, there are notable differences in the LYG estimates for Cd between the updated economic model and those accepted in TA457 which implies that an adjustment is necessary. Therefore, the HR derived from the NMA was applied until the end of the fixed duration Bd phase (24 weeks), thereafter the HR was adjusted to account for between trial differences (see Table 39).

Table 39 HR of PFS

Comparator	HR versus Bd
Cd	0.45 (0.41, 0.51)
Adjustment factor beyond 24 weeks	1.36 (0.913, 2.027)

Bd = bortezomib and dexamethasone; Cd = carfilzomib and dexamethasone; HR = hazard ratio; PFS = progression-free survival.

Comparison of the median PFS estimated by the model for DBd, Bd versus CASTOR and Cd versus CASTOR and ENDEAVOR is summarised in Table 40.

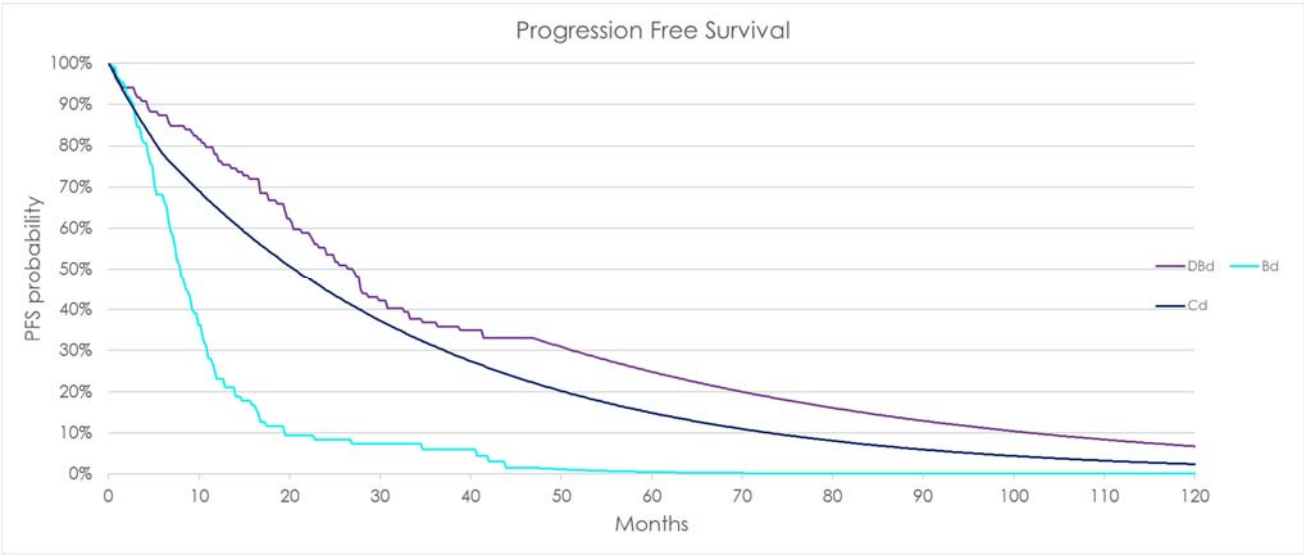
Table 40 Comparison of observed and predicted PFS

Treatment	Source	Median PFS per trial (months)	Median PFS per model (months)
DBd	Exponential fitting to KM data from trial	27.0	27.0
Bd	Exponential fitting to KM data from trial	7.9	7.9
Cd	HR applied to Bd PFS	22.2	20.7

Bd = bortezomib and dexamethasone; Cd = carfilzomib and dexamethasone; DBd = daratumumab, bortezomib and dexamethasone; HR = hazard ratio; KM = Kaplan-Meier; PFS = progression-free survival.

Figure 27 shows the PFS projections of DBd and Bd based upon a piecewise approach utilizing KM data directly until year 4, beyond which point parametric extrapolation is applied. PFS projections of Cd based upon a HR versus Bd. As PFS and OS were modelled independently in the survival partition model, in some circumstances the chosen survival functions may predict that PFS and OS cross. In order to prevent this, the model calculations effectively cap PFS with the OS curve, and so do not allow the PFS projection to cross the OS projection.

Figure 27 PFS curves for comparators in the base case analysis



Bd = bortezomib and dexamethasone; Cd = carfilzomib and dexamethasone; DBd = daratumumab, bortezomib and dexamethasone; PFS = progression-free survival.

B.3.3.1.2 Overall Survival

Extrapolation of OS is a key driver of the model and as such the clinical plausibility of long-term predictions have been thoroughly explored and externally validated.

Adjustment for treatments not available in the UK

Many patients in the CASTOR trial received subsequent treatment with therapies not available in UK clinical practice or available only via the CDF. A higher proportion of patients in the Bd arm received such treatments (65% in the Bd arm versus 37% in the DBd arm as their first subsequent therapy) which introduced bias into the OS analyses, affecting the cost-effectiveness analyses which make use of the OS evidence. To reduce this bias, adjustment for subsequent treatments not available in England was required.

NICE DSU technical support document 16 recommends use of available complex methods: Rank Preserving Structure Failure Time Models (RPSFTM); Iterative Parameter Estimation (IPE); Two-stage method and Inverse Probability of Censoring Weights (IPCW). All methods were explored. However, as a result of the nature of switching (to a variety of subsequent therapies) observed in CASTOR and the absence of a reasonable secondary baseline (required for the two-stage method), it was only possible to adjust using IPCW.

The IPCW method involves censoring patients upon treatment switch, then controlling for this potentially informative censoring by weighting the follow-up information for patients who remain at risk for the event with a similar prognosis such that the original composition of the treatment groups is recovered.

Proportional hazards assumption

Scrutiny of the OS hazard curves from CASTOR indicated that there was a violation of the proportional hazards assumption between the treatment arms (Figure 28). In addition, Figure 29 (Quantile-Quantile-plot) suggests that accelerated failure time models should not be fitted jointly to the data. Due to these observations, DBd curves were fitted separately from Bd curves.

Figure 28 Log-(log) survival plot from the CASTOR trial data: overall survival

Figure 29 Quantile-quantile-plot, accelerated failure time models with a linear trendline: overall survival

Bd = bortezomib and dexamethasone; Cd = carfilzomib and dexamethasone; DBd = daratumumab, bortezomib and dexamethasone; PFS = progression-free survival.

Extrapolation of DBd OS

Assessment of quality-of-fit

Parametric fitting to DBd in CASTOR[90] found little to differentiate survival distributions. The exponential and Gompertz functions were the best fitting according to the goodness-of-fit criteria (Table 41), with the exponential having the lowest BIC and Gompertz the lowest AIC), followed closely by the Weibull and log-logistic functions.

Table 41 Goodness-of-fit for adjusted OS from CASTOR

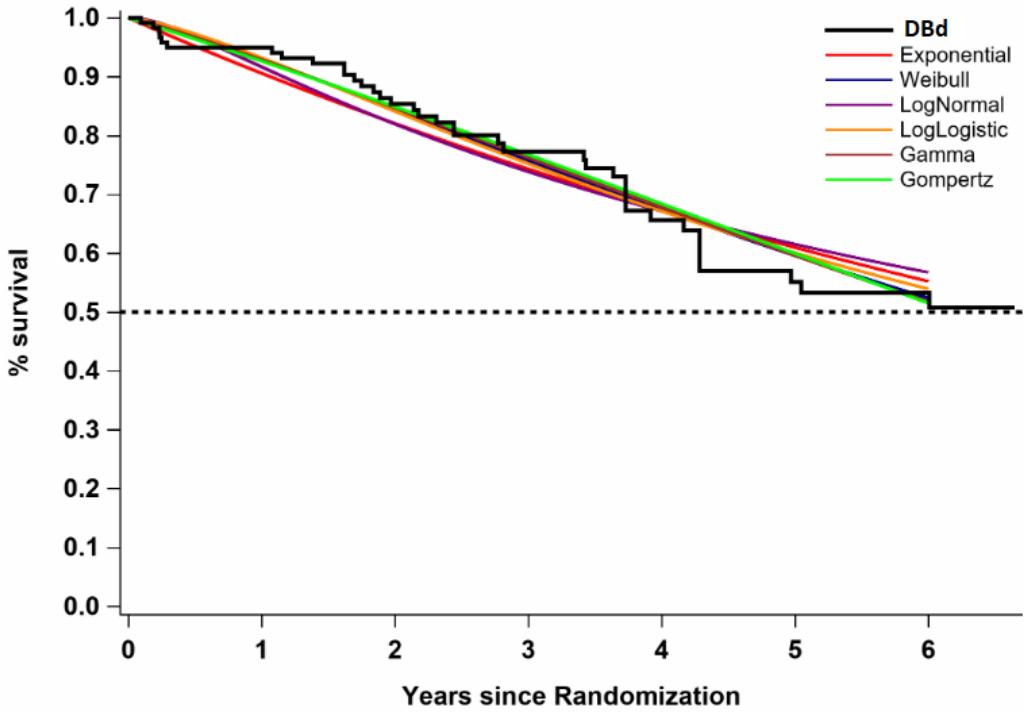
	DBd		Overall Survival		
Analysis	AIC	BIC	5 years	10 years	20 years
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalized gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

AIC = Akaike information criteria; BIC = Bayesian information criteria; DBd = daratumumab, bortezomib and dexamethasone; OS = overall survival.

Best statistical fit is in bold.

Following the visual inspection of the trial results of DBd most curves seem to fit the data reasonably well (Figure 30).

Figure 30 Parametric fitting to OS in CASTOR, DBd



DBd = daratumumab, bortezomib and dexamethasone.

Assessment of empirical hazards

Since the original company submission, the strong prognostic value of MRD negativity and its association with prolonged PFS and OS have been studied extensively. A robust meta-analysis[98,139] of 93 publications including 7,630 patients overall of which 1,224 patients had rrMM, showed that MRD is an appropriate surrogate for estimating long-term survival.

As noted in Section B.2.7.2, the rate of MRD negativity was significantly higher among patients in the DBd arm compared with patients in the Bd arm (15.1% vs 1.6%, OR: 12.5% [95% CI: 4.13, 37.85]; p<0.0001) with evidence that MRD negativity is generally associated with improved OS.

As time passes the influence of patients with MRD negativity on the risk of death will be more pronounced (as patients with poorer prognoses pass away). Consequently, it is anticipated that the mortality hazard with DBd would decrease as time passes.

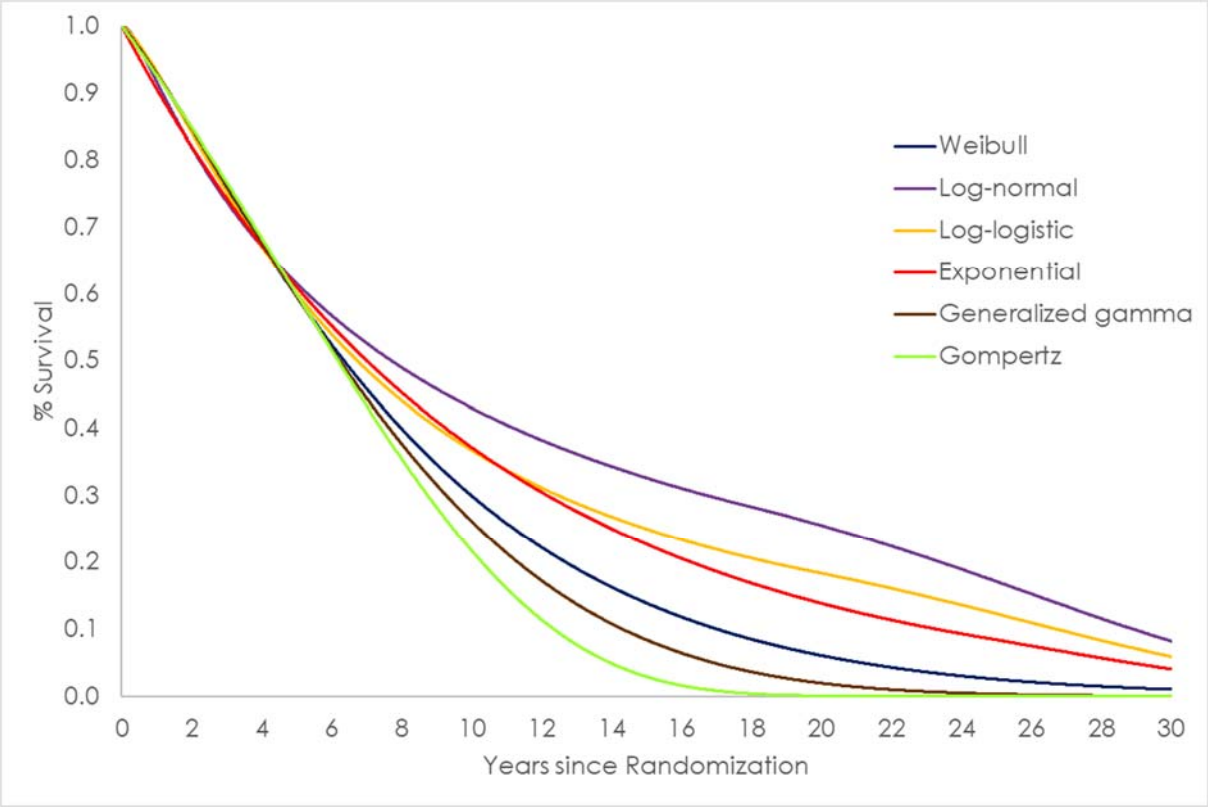
To examine whether such a shift in the hazards can be observed in the final data-cut the smoothed hazard curves along the hazard figures derived from curve fitting exercise were examined (Figure 31). The smoothed trial curve show that hazard rates increase over time up to month 38. Approximately this landmark is equivalent to the cut-off for the maximum follow-up available in the original company submission (denoted by a vertical yellow line in Figure 31). Subsequent to the initial increase, the hazard rate starts to rapidly decrease (month 48-54) following a period of constant rates between months 38 and 48. Based on the number of patients at risk [39-36 at months 48-54 with minimal decrease in the numbers until month 72 (21 patients a risk)] the observed decrease was considered to be relevant for decision making, however the steepness of the true curve is unclear. While Weibull showed similar properties in the original analysis to the smoothed curve left from the yellow line, the updated analysis supports Janssen's argument for the hazard curve to follow a decreasing pattern considering a longer time horizon.

Figure 31 Smoothed hazard rates from the CASTOR trial data, DBd: OS

Structured elicitation of clinical expert feedback

Consensus feedback from a recent clinical advisory board (see Appendix O) following a structured elicitation process confirmed that in a population similar to the one enrolled in CASTOR, approximately 35% of the patients would be expected to be alive 10 years beyond treatment initiation with DBd which aligned best with the exponential and log-logistic curves (Figure 32). Long-term projections based on log-normal, log-logistic and exponential are impacted by general mortality therefore its impact was incorporated into the curves presented below.

Figure 32 Long-term prediction of DBd



DBd = daratumumab, bortezomib and dexamethasone (DARA+BOR+DEX); OS = overall survival

Conclusion

Based on these observations, Janssen consider the log-logistic distribution most likely to reflect the true hazard curve of DBd with the hazard rate initially increasing before plateauing and gradual decline. Weibull was not considered an appropriate representation of the underlying hazard due to the constantly increasing rate which is not supported by the smoothed hazard plot for DBd from CASTOR. Following all the validation assessments detailed above, the log-logistic curve was chosen as the base case with exponential as a scenario analysis.

Extrapolation of Bd OS

Assessment of quality-of-fit

Parametric fitting to the Bd weighted KM data from CASTOR (following adjustment for subsequent treatments not available in England)[90] found that statistically, all distributions except generalized gamma were well matched to the trial period (Table 42). Generalized gamma had a relative gradient convergence of 0.008 and was as such convergence may be questionable therefore it was restricted to potentially be used in scenario analysis. Gompertz was the best fitting distribution according to the goodness-of-fit criteria (having the lowest AIC and BIC).

Table 42 Goodness-of-fit for adjusted OS from CASTOR

	Bd		Overall Survival		
Analysis	**AIC**	**BIC**	**5 years**	**10 years**	**20 years**
Weibull	411.1	416.5	25.2%	3.1%	0.0%
Log-normal	422.2	427.6	37.7%	20.1%	8.7%
Log-logistic	419.9	422.4	33.6%	15.3%	6.0%
Exponential	413.9	416.5	34.3%	11.7%	1.4%
Generalized gamma*	373.8	842.0	12.3%	0.0%	0.0%
Gompertz	406.7	412.1	**17.9%**	**0.0%**	**0.0%**

* Convergence may be questionable

AIC = Akaike information criteria; Bd = bortezomib and dexamethasone; BIC = Bayesian information criteria; OS = overall survival.

Best statistical fit is in bold.

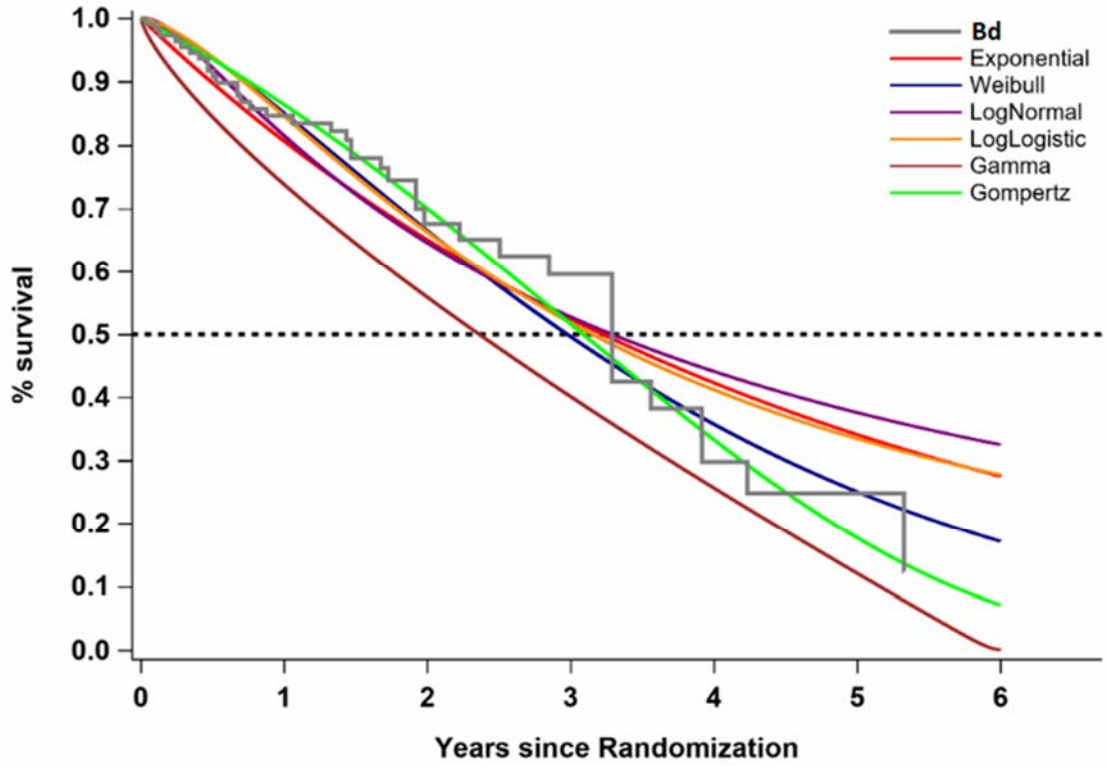
Structured elicitation of clinical expert feedback

Clinicians agreed that no patients are expected to be alive at 10 years.

Conclusion

Following the visual inspection of the trial results of Bd and based on clinical feedback, Gompertz seems to fit the data closest compared to the rest of the curves (Figure 33) and restricts survival so as not to exceed 10 years as suggested by the clinical experts. As a result of all the validation assessments detailed above, the Gompertz curve was chosen as the base case.

Figure 33 Parametric fitting to OS in CASTOR, Bd



Bd = bortezomib and dexamethasone.

Extrapolation of Cd OS

Similar to the modelling of PFS, OS for Cd was estimated by applying the HR for OS based upon the NMA to the Bd projected curves from CASTOR (Table 43) which was adjusted post-24 weeks to account for differences between Bd administration schedules in CASTOR and ENDEAVOR.

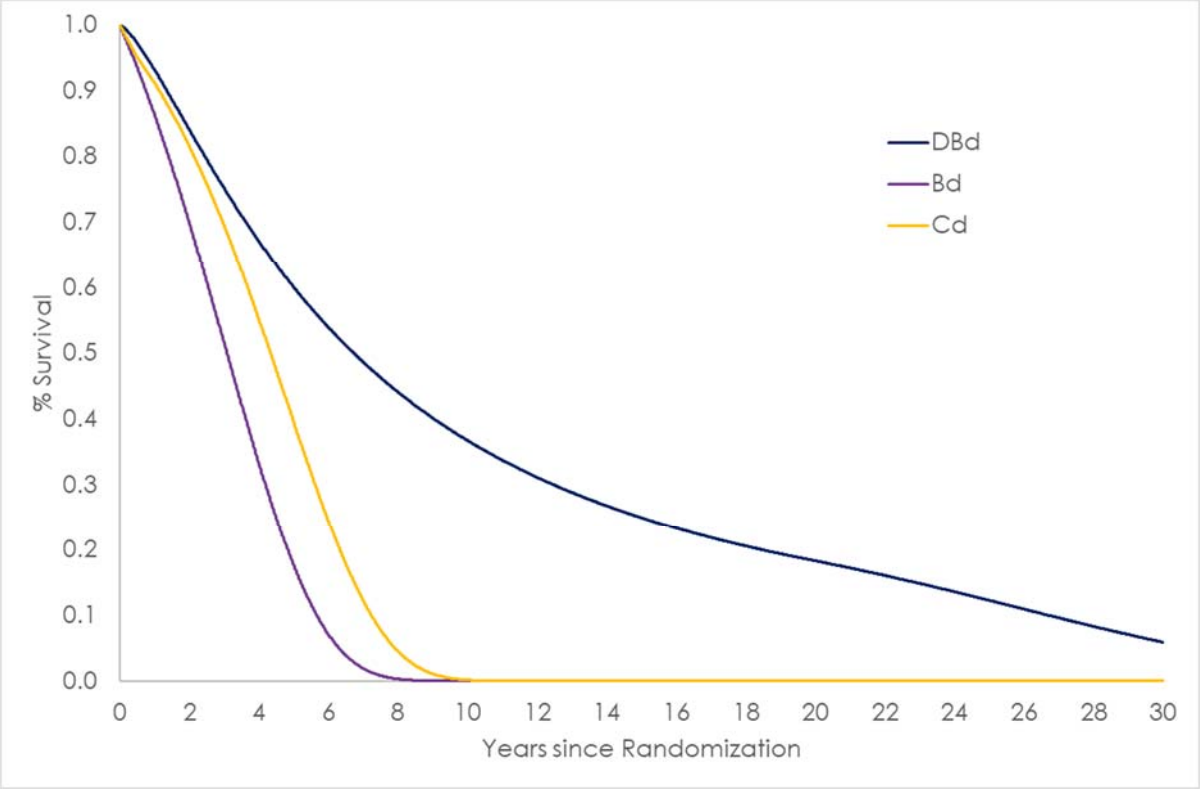
Table 43 HR of OS

Comparator	HR versus BD
Cd	0.77 (0.7, 0.85)
Adjustment factor beyond 24 weeks	1.46 (0.684, 2.662)

Bd = bortezomib and dexamethasone; Cd = carfilzomib and dexamethasone; HR = hazard ratio; OS = overall survival.

Figure 34 shows the resulting base case OS projections of Bd and DBd based upon direct trial KM extrapolation and projection of Cd based upon HRs versus Bd as reference curve.

Figure 34 OS for DBd network



Bd = bortezomib and dexamethasone (BOR+DEX); Cd = carfilzomib and dexamethasone (CAR+DEX); DBd = daratumumab, bortezomib and dexamethasone (DARA+BOR+DEX); OS = overall survival.

B.3.3.1.3 Probability of Death during PFS

As noted in the DSU guidance,[135] modelled survival endpoints that are structurally independent in a survival partition model can be problematic as there are several dependencies between the endpoints, e.g. both PFS and OS curves include the same pre-progression deaths. To account for this, the model explicitly estimates the number of death events within PFS to correctly predict numbers of patients starting subsequent therapies and dying in the post-progression period.

A constant ratio of death versus progression events was applied for each model cycle for patients in PFS health states. The probability of death was calculated based upon data from CASTOR (combined DBd and Bd patients), resulting in a probability of death of 6.56%. The probability of death during the PFS phase was assumed to be the same for all comparators. The incidence of progression was calculated as:

(PFST(n-1) – PFST(n)) *Ratio of Death during PFST(n-1)

B.3.3.1.4 Time on Treatment

A substantial part of the costs of treatment were attributed to the costs of medication which are related to the treatment duration, particularly for treat to progression regimens (unlike Bd, which is given for a fixed duration). There is a high positive correlation between time to treatment discontinuation (TTD) and efficacy (PFS in particular). In the CEM, treatment duration was modelled independently from efficacy, although the input parameters of the PFS and TTD curves are naturally correlated. TTD curves were assigned to each comparator arm as follows:

For DBd and Bd, parametric curves were fitted based on the individual patient level data (IPD) of CASTOR. This method makes the most comprehensive use of the trial data and provides TTD curves consistent with the efficacy inputs in terms of PFS and OS.

For Cd, a Proportional Hazard to PFS based upon the ENDEAVOR trial was used due to lack of more detailed information. TA457 reported a HR of 0.477 between PFS and TTD for Cd in patients who have received one prior line of therapy.[130]

Daratumumab is administered weekly for 3 cycles: every 3 weeks for cycles 4-8 and every 4 weeks thereafter until disease progression, toxicities or other.[90] All patients received up to 8 cycles (21 days per cycle) of bortezomib.

For consistency with PFS, the model reference case uses the Exponential curve for DBd and Bd in the base case (Table 44).

Table 44 Treatment duration

Treatment	Source	Median duration per trial (months)	Median duration in model (months)	Median PFS per model (months)
DBd	Exponential fitting to KM data from trial beyond month 47	[redacted]	[redacted]	[redacted]
Bd	Exponential fitting to KM data from trial beyond month 47	n/a[1]	n/a[2]	7.9
Cd	HR applied to PFS	[redacted]	[redacted]	[redacted]

1Patients who completed treatment on the Bd arm of CASTOR were censored and not considered to have discontinued treatment.

2Median was not reached, all patients discontinued treatment upon completion of 8 cycles

Bd = bortezomib and dexamethasone; Cd = carfilzomib and dexamethasone; DBd = daratumumab, bortezomib and dexamethasone; HR = hazard ratio; KM = Kaplan-Meier; PFS = progression-free survival.

To avoid conflicting long-term projection of TTD and PFS, the treatment duration was restricted in the model so as not to exceed PFS, regardless of the projection option chosen for TTD. Modelled time on treatment always remained very close to the PFS curve for DBd (Figure 35).

Figure 35 PFS and TTD comparison for DBd

DBd = daratumumab, bortezomib and dexamethasone (DARA-BOR-DEX); PFS = progression-free survival; TTD = time to treatment discontinuation; Tx = treatment; Cd = carfilzomib, dexamethasone

B.3.4 Measurement and valuation of health effects

B.3.4.1 Valuing Health Outcomes

Utility values were applied to each health state and event in the model to capture patient quality of life associated with treatment and disease outcomes.

In the original company submission utility values were derived from an analysis of EuroQoL Five-Dimension Five Level (EQ-5D-5L) data from CASTOR. Both the evidence review group (ERG) and the appraisal committee concluded that utility values derived from CASTOR did not have complete face validity. The reviewers argued that the post-progression utility value was unrealistically high for patients relapsing and concluded that values from TA457 (ENDEAVOR) should be used in the base case instead of values from CASTOR.

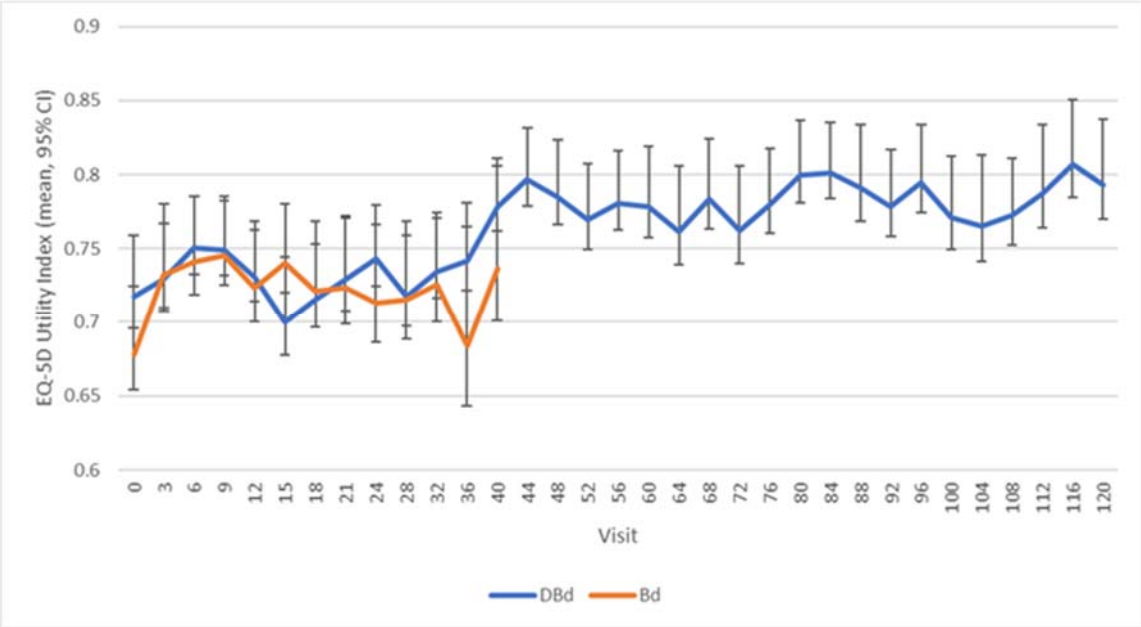
While Janssen believe that trial data should be preferred as a source of utility inputs given that they allow utility and efficacy data to be derived from the same population, Janssen understands the shortfalls of the PRO collection post-progression in CASTOR. Utilities were collected only at weeks 8 and 16 beyond relapse which did not allow for a robust analysis of PRO data. Due to these reasons and to support comparability or results between the original and current appraisal, utility values from ENDEAVOR (preferred by the ERG and Committee) are included in the base case analyses.

Results from CASTOR showed an initial increase in quality of life that remained relatively high throughout the trial. No statistically significant difference was found between treatment arms. Quality of life for DBd patients increased following cessation of Bd. This is expected given the favourable safety profile of daratumumab monotherapy. However, in the Bd arm of CASTOR, utility data were not collected following cessation of Bd. Therefore, observed improvements in utility for the monotherapy phase of DBd have not been implemented because of the absence of data at comparative time points for patients receiving Bd.

Results from CASTOR showed that there was an initial increase in quality of life that remained relatively high throughout the trial. No statistically significant difference was found between treatment arms. Quality of life for DBd patients increased following cessation of Bd. This is expected given the favourable safety profile of daratumumab monotherapy. However, in the Bd arm of CASTOR, utility data were not collected following cessation of Bd. Therefore, observed improvements in utility for the monotherapy phase of DBd have not been implemented because of the absence of data at comparative time points for patients receiving Bd (see

Figure 36).

Figure 36 EQ-5D-5L utility score – CASTOR[90]



Bd = bortezomib and dexamethasone; CI = confidence interval; DBd = daratumumab, bortezomib and dexamethasone; EQ-5D = EuroQoL five dimensions.

B.3.4.2 Health-related quality-of-life studies

For a list of studies identified by the SLR in which health-related quality of life was measured please see Appendix H.

B.3.4.3 Adverse reactions

Multiple myeloma is associated with a variety of complications such as hypercalcemia, renal impairment, anaemia and bone disease. As a result of these complications, patients with MM may experience and report a variety of disease-related symptoms. Treatment-related AEs are also common and include weakness, fatigue, bone pain, weight loss, confusion, excessive thirst and constipation, among others.

The daratumumab SmPC has now been updated to include the option to receive treatment via a subcutaneous injection at a recommended dose of 1,800 mg weekly for Weeks 0–9, every two weeks from Weeks 9–24, then every four weeks thereafter until disease progression. Administration of daratumumab via subcutaneous injection is now most representative of UK clinical practice and therefore acquisition costs and AEs have been updated to reflect this change in the base case.

As reported by Mateos et al,[12] the AE profile of daratumumab via subcutaneous injection is improved when compared with daratumumab via an intravenous injection.

The model uses a simple approach of relying on the cumulative probabilities of AE occurrence during the treatment period (Table 45). This is assumed to be independent of both PFS and treatment duration. Probabilities reported in Table 45 in the daratumumab arm were taken from the subcutaneous injection arm of the COLUMBA trial. Probabilities in the bortezomib arm were derived specifically based on the 1PL treatment group in CASTOR (final OS analysis).

The model includes AEs for which Grade 3 or higher events were reported in at least 5% of patients in any treatment arm in COLUMBA or CASTOR.[90] This inclusion rule was selected so as to capture AEs that would impact patients consistently enough to have validity in a real-world setting where AEs are monitored in a less strict manner compared with a clinical trial setting. Also, because in the model AEs affect both costs and utilities of patients receiving treatment, it is a conservative approach, as it ignores AEs such as dyspnoea or decreased lymphocyte count, that would have a higher occurrence for Cd and would therefore underestimate relative treatment costs and impact on utilities in favour of Cd.

Table 45 Cumulative probability of AEs during treatment period

Adverse Event	DBd	Bd	Cd
Neutropenia	13.1%	3.6%	0.9%
Anaemia	13.1%	9.0%	12.9%
Thrombocytopenia	13.8%	20.7%	6.5%
Lymphopenia	5.0%	3.6%	4.3%
Pneumonia	2.7%	9.0%	6.5%
Peripheral neuropathy	0%	6.3%	2.2%
Hypertension	3.1%	0.0%	10.3%
Source	COLUMBA SC arm	CASTOR – 1PL - Final OS analysis	ENDEAVOR

AE = adverse event; Bd = bortezomib and dexamethasone; Cd = carfilzomib and dexamethasone; DBd = daratumumab, bortezomib and dexamethasone.

B.3.4.4 Health-related quality-of-life data used in the cost-effectiveness analysis

Utility values were applied to each health state and event in the model to capture patient quality of life associated with treatment and disease outcomes (Table 46).

Utility decrements due to adverse events were calculated based on the treatment-specific rate of AEs (see above) and information on AE duration and its associated disutility from published literature identified by the SLR based on values reported in the pomalidomide NICE submission.[129] Recent data directly applicable in the analysis were not identified.

Treatment-specific AE rates imply treatment-specific AE-related utility decrements and, therefore, treatment-specific utilities. Decrements were applied as one-time decrements in baseline utility value at time 0.

Table 46 Summary of utilities applied in the model

Parameter	Mean Utility Value (SE)	SE	Reference
Utility during PFS	0.737	0.074	ENDEAVOR mapped values – ERG preferred base case (TA573)
Utility during PPS	0.665	0.067	
Adverse Events	**Duration of AE (Days)**	**Disutility**	**Reference**
Neutropenia	13.2	-0.145	Brown 2013/Partial Review TA171 (Bacelar 2014)[140]
Anaemia	10.7	-0.31	Brown 2013/Partial Review TA171 (Bacelar 2014)[140]
Thrombocytopenia	14.1	-0.31	Brown 2013/Partial Review TA171 (Bacelar 2014)[140]
Lymphopenia	15.5	-0.065	Assume lowest in range (Partial Review TA171 (Bacelar 2014))[140]
Pneumonia	12	-0.19	Brown 2013/Partial Review TA171 (Bacelar 2014)[140]
Fatigue	14.6	-0.115	Lloyd 2006[141]
Peripheral neuropathy	8	-0.065	Partial Review TA171 (Bacelar 2014)[140]
Hypertension	0	0	Assume no QoL impact, controlled by medication

AE = adverse event; EQ-5D = EuroQoL five dimensions; SE =standard error; PFS = progression-free survival' PPS = post-progression survival.

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

Cost categories in the model included:

- Costs of the treatments (drug acquisition and administration)
    - Applied for the duration of active treatment (determined by dosing regimen and treatment duration data from clinical trials)
- Costs of routine follow-up care
- Costs of unplanned events, such as AEs and progression
- Terminal care costs

Unit costs of drug acquisition, administration and resources used during routine follow-up were based on standard costing sources. AE costs were calculated based on the resources and average length of hospital stay involved in treatment of an episode.

Appendix I describes how relevant cost and healthcare resource use data for England were identified.

B.3.5.1 Intervention and comparators' costs and resource use

A summary of dosing information used to inform intervention and comparator costs is presented in Table 47. DBd and Bd dosing information was derived from CASTOR. Dosing for Cd was obtained from ENDEAVOR; the same published clinical trial included in the NMA.

Table 47 Summary of treatment regimen dosing

Treatment Regimens		Dose/ Administration	Administrations/ Cycle	Cycle Length (days)	Source
DBd					
Daratumumab	Cycle 1-3	16 mg/kg or 1800 mg per patient	3	21	CASTOR CSR[91]
	Cycle 4-9		1	21	
	Cycle 9 and above		1	28	
Bortezomib	all cycles (max 8 cycles)	1.3mg/m^2	4	21	
Dexamethasone	all cycles (max 8 cycles)	20 mg	8	21	
Bd					
Bortezomib	1-8 cycles	1.3 mg/m^2	4	21	CASTOR CSR[91]
Dexamethasone	1-8 cycles	20 mg	8	21	
Cd					
Carfilzomib	Cycle 1	20mg/m^2 56 mg/m^2	2 4	28	ENDEAVOR trial Dimopoulos 2016[111]
	Cycle 2 and above	56 mg/m^2	6	28	
Dexamethasone	all cycles	20 mg	8	28	

Bd = bortezomib and dexamethasone; Cd = carfilzomib and dexamethasone; DBd = daratumumab, bortezomib and dexamethasone.

A mean weight of [redacted]kg (SD [redacted]kg) was used for therapies that depend on weight to calculate dose in the network (based on the CASTOR second-line population, DBd arm). For therapies that depended on body surface area (BSA) to calculate dose, a value of 1.87m^2 was used, also based on the CASTOR trial population. The model assumes a distribution of weight and BSA around these means and optimises the number of vials used at each administration.

For treatments that are weight or BSA dependent, there is the potential that some drug will be wasted if perfect vial sharing is not practiced. When vial sharing is used, the model calculates the exact dose needed for the patients depending on their weight or BSA and multiplies it with the per milligram cost of the drug. The model is flexible to consider wastage, but the reference case of the model assumes vial sharing is not allowed. If wastage is considered, the dosing consumption per administration is rounded up to the closest integer number of vials.

Drug acquisition costs in the base case have been calculated assuming list prices for comparator drugs and the current patient access scheme (PAS) for daratumumab (see Table 48 below). Functionality is retained in the model, however, to consider the impact of existing patient access schemes (PASs), and confidential commercial access agreements (CAAs) for comparator and subsequent therapies.

Lenalidomide, for example, is available with a generic price following loss of exclusivity in January 2022, with further price erosion anticipated in the next 6-12 months as generic manufacturers continue to enter the market and supply is secured. However, as the discounts remain confidential, only generic list prices have been included in the model.

Table 48 Drug acquisition costs

Drug	Drug units (vials or capsules) per pack	Strength	Price per Pack	Source
Daratumumab	1	1800 mg	List price: £4,320.00 [redacted]	Source: MIMS UK Drug Database. Available by subscription. Access date: Apr 18, 2022.
Carfilzomib	1	60 mg	£1,056.00	
Bortezomib	1	3.5 mg	£533.67	
Dexamethasone	50	8.0 mg	£120.01	

B.3.5.2 Dose Intensity

The model considers both dose intensity and treatment discontinuation in the drug cost calculation.

Dose intensity was considered in the model and was used to adjust drug cost in proportion to the doses received in the trial. Patients in clinical trials, as in the real world, do not always receive full doses of treatments they are assigned. Therefore, data from clinical trials may better reflect the efficacy of the dose received rather than the intended dose (Table 49).

Treatment discontinuation accounted for treatment discontinuation due to progression, AEs, maximum treatment duration, or other non-clinical reasons. Patients' exposure to the regimen during the on-treatment period is reflected via relative dose intensity. Relative dose intensity is calculated as the doses per treatment cycle received divided by doses per cycle as per the trial design. Applying both factors in the calculation of drug cost ensures that the drug exposure is consistent with the efficacy data from CASTOR.

Dose intensity was considered separately for the components of combination treatments.

For the components of DBd and Bd combinations, the dose intensity was available from CASTOR. Cd dose intensity was assumed to be equal to DBd.

Table 49 Dose intensity

Dose Intensity	Component 1	BOR	DEX	Reference
DBd	95.09%	83.35%	89.63%	CASTOR
Bd	N/A	88.23%	91.62%	CASTOR
Cd	95.09%	N/A	89.63%	Assumption; same as DBd[1]

[1]Not available from trial publication

Bd = bortezomib and dexamethasone; Cd = carfilzomib and dexamethasone; DBd = daratumumab, bortezomib and dexamethasone.

B.3.5.3 Drug Administration Costs

The costs associated with administration are summarised in Table 50.

Administration of intravenous (IV) treatments (carfilzomib) requires an outpatient visit that may include additional nursing and pharmacist preparation time.

Administration of subcutaneous (SC) treatments (daratumumab – see Section B.3.4.3, bortezomib) requires an outpatient visit with a specialist cancer nurse.

On days where daratumumab and bortezomib are both administered, SC administration cost is applied only once.

Medications that are orally administered incur an administration cost at treatment initiation.

Table 50 Drug administration costs

Mode of Administration	Unit Cost	Source: National Schedule of NHS Costs - Year 2020-21 - NHS trusts and NHS foundation trusts
Each IV administration	£438.378	SB15Z - Deliver Subsequent Elements of a Chemotherapy Cycle - Outpatient
Each SC administration	£90.49	N10AF – Specialist Nursing, Cancer Related, Adult, Face to face
Oral drug initiation	£215.80	SB11Z – Deliver Exclusively Oral Chemotherapy - Outpatient

IV = intravenous; SC = subcutaneous.

B.3.5.4 Additional Medications (Co-medications)

Additional medications included pre- and post-infusion medications, concomitant medications and prophylactic medications. The requirements for additional medications for each comparator were based on the data sources available for their dosing schedule, including the prescribing information and representative clinical trials and summaries of product characteristics.

Only co-medications required for all patients were accounted for in the model. Additional medications that were provided to selected patients (e.g., patients at risk) were not included to reduce the risk of bias, as the proportion of such patients was not clearly reported for all comparators.

Pre- and post-infusion medications were defined as any drug, agent or fluids given prior to or following the administration of an agent, to prevent or minimise the occurrence of commonly expected AEs (e.g., infusion-related reactions [IRRs]). Pre-infusion and post-infusion medications included:

- Antihistamines (e.g., diphenhydramine)
- Corticosteroids (e.g., methylprednisolone)
- Antipyretics (e.g., paracetamol)
- Agents for hydration (e.g., sodium chloride [saline] solution).

Concomitant medications were defined as any drugs given in parallel with the active treatment regimens, excluding any drugs prescribed to manage AEs. Prophylactic medications were defined as any drugs or agents recommended for the prevention of potential AEs that were administered to patients prior to, or during, the course of treatment. For example, antibiotics and/or antivirals, antithrombotic and prophylactic use of granulocyte colony-stimulating factor (G-CSF) may be recommended for the prevention of infections, thrombosis and neutropenia, respectively. In cases where transfusions or growth factors are

required during AE management, the additional costs are already included in the average treatment costs.

Table 51 and Table 52 below present the recommendations, the schedule and unit costs applied in the model.

Table 51 Required additional medications for all patients reported for each comparator

Treatment	All patients
Daratumumab[11]	Administration requirement: Dilution with 0.9% sodium chloride Pre-infusion medication Administer approximately one hour prior to every infusion: IV corticosteroid (methylprednisolone 100 mg) Can decrease after second administration (methylprednisolone 60 mg IV) Oral antipyretics (paracetamol 650 to 1000 mg) Oral or IV antihistamine (diphenhydramine 25 to 50 mg) Post-infusion medication: Administer oral corticosteroid (20 mg methylprednisolone) to patients the first and second day after all infusions. After >4 infusions, if no major IRRs, these post-infusion medications may be discontinued
Bd[142]	Administration requirement: Three- to five-second bolus IV injection followed by a flush with sodium chloride 9 mg/ml (0.9%) solution for injection Co-medications: Antiviral prophylaxis is recommended in patients being treated with BOR Laxatives
Cd[111]	Co-medications: Sodium chloride solution or 5% glucose solution for injection immediately before and after CAR administration Antiviral prophylaxis Thromboprophylaxis is recommended Antiemetics

Bd = bortezomib and dexamethasone; Cd = carfilzomib and dexamethasone; IV = intravenous; IRR = infusion-related reactions.

Table 52 Co- medications

Co-medication	Drug Units (Vials or Capsules) per Pack	Strength	Price per Pack MIMS UK Drug Database. Available by subscription. Access date: Apr 18, 2022.	Dosage per administration
Methylprednisolone IV	1	125	£4.75	100
Prednisolone PO	30	4	£6.19	40
Paracetamol (acetaminophen)	100	500	£3.78	825
Diphenydramine	20	50	£4.46	37.5
Acyclovir	56	400	£2.55	400
Saline solution	1	50	£15.36	500
Thromboprofilaxis (LMWH)	10	40	£22.70	40
Laxatives	60	5	£2.70	10
Antiemetics (Domperidone)	100	10	£2.43	40

IV = intravenous; LMWH = Low-molecular-weight heparin.

Source: MIMS UK Drug Database. Available by subscription. Access date: Apr 20, 2022.

B.3.5.4.1 Subsequent treatments

Given that patients with MM receive multiple lines of treatment, subsequent treatments represent a considerable component of costs and health benefits. As such, modelling subsequent treatments is an important aspect of the cost-effectiveness assessment. The choice and efficacy of treatment in subsequent lines may depend on the treatment choices and efficacy in prior lines. This dependency creates a modelling challenge as, other than from CASTOR, there is little information available from clinical trials about:

- The number of subsequent treatment lines
- The treatments applied in subsequent lines
- The duration of subsequent treatments
- The clinical efficacy of subsequent treatment options, especially with regard to prior treatment history

Lacking this information, essential for the detailed modelling of subsequent treatment lines, the model used a simplified approach to incorporate their impact in the evaluation, in which patients discontinuing from the initial modelled treatment may continue to a basket of potential treatment options.

The proportion of patients continuing on subsequent treatment is a treatment specific model parameter. The proportion of patients receiving subsequent treatments was available for Company evidence submission for daratumumab in RRMM

DBd and Bd from CASTOR. For Cd this information was not available from the trial publications. Therefore, the base case uses a conservative approach by assuming the lower of the proportions observed for DBd and Bd.

The basket of subsequent treatment is composed of the set of treatments received by patients in CASTOR. The weights of the different subsequent treatments are specific to the initial modelled treatment ("primary treatment"). The model base case relies on a generic mix of available treatments in later lines and rules that prescribe whether a treatment may follow another treatment in prior lines. For example, it was assumed that no daratumumab treatment, either combination or monotherapy, would follow any daratumumab treatment in previous lines.

Since patients in CASTOR were able to receive therapies in subsequent lines of treatment which are not available in England, or are only available via the CDF, calculations were adjusted for availability of subsequent treatments from the UK perspective.

The duration of subsequent treatment is also a treatment-specific input that should depend upon the prior treatment history. However, again there is no relevant information available from the clinical trials. In addition, whilst duration of treatment is available from CASTOR, this information is also subject to selection bias; as it is typically patients with a worse prognosis that progress first. Consequently, for the base case, it was assumed that each RRMM treatment was followed by subsequent treatments of the same duration. As patients with MM typically receive treatment until death, median OS of third and later line patients (9 months) was assumed to be a reasonable proxy for the median duration of subsequent treatments.[143] This approach is supported by the literature; Yong and colleagues also reported similar lengths of subsequent therapies across seven European countries including the UK (e.g. a median of 6 months for third line treatment).[144] Given the median treatment duration, a constant discontinuation rate for subsequent treatments is modelled.

As the survival partition model approach already accounts for the efficacy of subsequent treatments in the OS estimates, only cost consequences of subsequent treatments were included to account for subsequent treatments. The distribution of subsequent treatment per treatment arm is summarised in Table 53, with percentage of patients continuing onto subsequent treatment displayed in Table 54. Table 55 summarises the acquisition cost of each subsequent therapy.

Table 53 Distribution of subsequent treatments

Subsequent Treatment	After DBd	After Bd	After Cd
Daratumumab monotherapy	0.0%	51.0%	51.0%
Ld	63.5%	32.4%	32.4%
Pd	36.5%	16.7%	16.7%

Bd = bortezomib and dexamethasone; Cd = carfilzomib and dexamethasone; DBd = daratumumab, bortezomib and dexamethasone; Ld = lenalidomide and dexamethasone; Pd = pomalidomide and dexamethasone.

Table 54 Percent of patients continuing on subsequent treatment

Primary treatment	Default	Source
DBd	87%	CASTOR[76]
Bd	94%	CASTOR[76]
Cd	87%	Assume same as lower % in CASTOR

Bd = bortezomib and dexamethasone; Cd = carfilzomib and dexamethasone; DBd = daratumumab, bortezomib and dexamethasone.

Table 55 Treatment acquisition cost of subsequent therapies

Drug	Drug Units (Vials or Capsules)	Strength	Price per Pack	Source
Daratumumab	1	1800 mg	List price: £4,320.00 [redacted]	MIMS UK Drug Database. Available by subscription. Access date: Apr 18, 2022.
POM	21	4 mg	£8,884.00	
LEN	21	25 mg	£3,057.60	
DEX	50	40.0 mg	£120.01	

D = daratumumab; d = dexamethasone; L = lenalidomide; POM = pomalidomide.

B.3.5.5 Health-state unit costs and resource use

B.3.5.5.1 Routine Follow-up Care Costs

Routine follow-up care costs were evaluated for each health state separately in the model. The types and frequencies of medical resource use were based on types and frequencies used in multiple NICE appraisals in MM (NICE TA228 [bortezomib and thalidomide for first-line treatment] and NICE TA338 [pomalidomide for RRMM]) as well as clinical opinion obtained at advisory board.[83,145] No evidence directly applicable to the analysis was identified, however findings of the SLR suggest that the monitoring frequency included in the submission broadly applicable to the UK setting (see Appendix I). The routine follow-up care was assumed to be the same for all comparators (Table 56).

Table 56 Unit costs and frequency of routine follow-up care use pre-progression (per week)

	Haematologist visit	Full blood count	Biochemistry	Protein electrophoresis	Immunoglobin	Urinary light chain excretion	Blood test to determine blood type (Daratumumab only)	Renal function test (Cd only)
Unit cost	£217.80	£3.63	£9.25	£1.85	£1.85	£1.85	£3.63	£18.50
Frequency[1]	0.23	0.21	0.19	0.13	0.12	0.05	1	0
Frequency for Cd before 8 weeks	0.23	1.00	0.19	0.13	0.12	0.05	0.00	1.00

[1]DBd, Bd and Cd (after 8 weeks)

Bd = bortezomib and dexamethasone; Cd = carfilzomib and dexamethasone; DBd = daratumumab. Bortezomib and dexamethasone.

Source: National Schedule of NHS Costs - Year 2020-21 - NHS trusts and NHS foundation trusts (consultant led and directly accessed pathology services)

After patients progress on any of the comparators, the model differentiates the frequency of use of care while on subsequent treatment or when patients no longer receive active treatment (Table 57).

Table 57 Frequency of routine follow-up care use post-progression (per week)

	Haematologist visit	Full blood count	Bio-chemistry	Protein electrophoresis	Immunoglobin	Urinary light chain excretion
On subsequent treatment	0.23	0.21	0.19	0.13	0.12	0.05
Off treatment	0.08	0.39	0.33	0.18	0.19	0.09

B.3.5.6 Adverse reaction unit costs and resource use

To account for differences in exposure time, treatment-specific cumulative probabilities for the second-line population over the whole trial durations were used to calculate an overall cost of AEs. A per patient overall AE cost was applied as a lump sum at the start of treatment. AE costs were calculated based on the National Schedule of Reference Costs (Year 2020-21), reporting the number of resources consumed/length of stay in hospital associated with each event (Table 58).[146] The table below presents the calculated average cost for each of the Grade 3 and 4 AEs. The costs of treating Grade 3 and 4 AEs were applied to the rates of each event for the intervention and comparators.

Table 58 Grade 3 or 4 adverse event costs

Adverse event	Cost (£)	Source
Neutropenia	£2,719.97	National Schedule of NHS Costs - Year 2020-21 - NHS trusts and NHS foundation trusts (non-elective long and short stay)
Anaemia	£1,763.03	
Thrombocytopenia	£2,534.21	
Lymphopenia	£2,039.05	
Pneumonia	£2,644.23	
Fatigue	£1,579.39	
Peripheral neuropathy	£1,933.29	
Hypertension	£924.08	

B.3.5.7 Miscellaneous unit costs and resource use

B.3.5.7.1 End of life cost

A one-time cost of £8,014 for terminal care was incurred at death.[147]

B.3.6 Severity

The severity of the condition, defined as the future health lost by people living with the condition with standard care in the NHS was calculated for the populations of interest. The extent of unmet health need is reflected by the absolute and proportional QALY shortfall.

Inputs for the QALY shortfall calculation are informed by clinical trials and published data. The cohort characteristics in the CASTOR trial are assumed to be representative of the patient population of interest, with a median age of 62.6 years and 59.1% being male.

Table 59 Summary features of QALY shortfall analysis

Factor	Value (reference to appropriate table or figure in submission)	Reference to section in submission
Sex distribution (male)	59.1%	0
Starting age	62.6 years	0

Health state utilities inputs were informed by the EQ-5D analysis based on TA457 (ENDEAVOR). For calculation of QALYs for patients without the condition over the remaining life expectancy, UK life tables and UK age and sex adjusted utilities based on Hernandez Alava et al. 2022 have been used.[148]

Table 60 Summary of health state benefits and utility values for QALY shortfall analysis

State	Utility value: mean
Progression-free	0.737
Progressed	0.665

Based on clinical feedback a 50%-50% split was chosen for Bd and Cd to calculate a weighted average of absolute shortfall for current standard of care. The results of the QALY shortfall analysis show that the technology does not meet the criteria for a severity weight according to proportional shortfall (at least 85%).

Table 61 Summary of QALY shortfall analysis

Treatment	Remaining QALYs without disease	Remaining QALYs with disease	SoC Weights	Remaining QALYs with disease – SoC Weighted	Absolute shortfall	Proportional shortfall	QALY weight
DBd	11.77	5.31	n/a	n/a	2.91	25%	1.00
Bd		2.03	50%	2.40			
Cd		2.77	50%				

B.3.7 Summary of base-case analysis inputs and assumptions

All inputs used in the model have been reported in Appendix N.

Table 62 outlines the assumptions made in the model.

Table 62 Model assumptions and justification

Area	Assumption	Justification
Time horizon	30 years	This time horizon was considered long enough to capture the long-term clinical and economic impacts of RRMM, an incurable disease requiring treatment until end of life. Given the median age of 63 years[76] for the CASTOR trial population, 30 years is a fair approximation of a lifetime time horizon
Cycle length	1 week	Sufficiently short to accurately capture clinical outcomes and differences in treatment administrations, i.e. the fact that patients only receive treatment on certain weeks
Discount	Both health benefits and costs were discounted at an annual rate of 3.5%	Per the Guidelines for the Economic Evaluation of Health Technologies in the UK
Extrapolation	OS and PFS curves were extrapolated. Curve selection based on statistical fit, clinical face validity of predictions and empirical hazards	Per DSU guidance
Treatment duration	DBd and Bd TTD modelled via fitted parametric curves based on trial information. Treatment duration for Cd was calculated by applying a HR to PFS obtained from TA457	Fitted curves most consistent with trial efficacy. For Cd approach is consistent with TA457

Area	Assumption	Justification
Subsequent treatments	Subsequent treatment modelled as a basket of potential treatment. For carfilzomib, the same percentage of patient receiving a subsequent treatment was applied as for daratumumab. Same duration for all comparators	Information on the proportion of patients receiving subsequent treatments and duration of subsequent treatment were not available from ENDEAVOR. Assuming the lower percentage receiving subsequent treatments observed in the two arms of CASTOR for carfilzomib is conservative.
Adverse event costs	Costs of adverse events are applied as a lump sum at the start of each treatment	Total exposure information is not publicly available for carfilzomib therefore it is not possible to calculate a per-person cycle-specific AE rate.
	The model includes AEs for which Grade 3 or higher events were reported in at least 5% of patients in any treatment arm in CASTOR	This inclusion rule captures important AEs It is also conservative, because it ignores AEs that would have a higher occurrence for carfilzomib.
Modelling approach	PartSA model	Supports comparability of assumptions and results between the original and updated company submission
Probability of death within PFS	The probability of death during the PFS phase was assumed to be the same for all treatments.	Data available only from CASTOR
Adjusted OS calculations	Inverse probability of censored weights (IPCW) methodology was used	All methods of adjustment recommended by NICE's DSU were explored. However, the complexities of the data and the array of treatment switches meant that it was only possible to implement adjustment using IPCW. The IPCW method involves censoring patients upon treatment switch, and then controlling for this potentially informative censoring by weighting the follow-up information for patients who remain at risk for the event with a similar prognosis such that the original composition of the treatment groups is recovered.
Utilities	The model uses the same utility for all patients in the pre- and post-progression health states. Utility values preferred by the ERG in TA573 were used (derived from ENDEAVOR, TA457)	Acknowledging the shortfalls of the trial design of CASTOR in terms of PRO collection, the critique of the ERG in TA573 related to the face validity of the utility analysis as well as supporting comparability between the original submission and the review of TA573, the utility values preferred by the ERG and the appraisal committee were applied.
Dose intensity	For carfilzomib, the same dose intensities were assumed as for the components of DBd	No dose intensity data were available from ENDEAVOR
Routine follow up care costs	Routine follow-up care was assumed to be the same for all treatments.	The types and frequencies of medical resource use were based on types and frequencies used in multiple NICE appraisals in MM

AE = adverse event; Bd = bortezomib and dexamethasone; Cd = carfilzomib and dexamethasone; DBd = daratumumab, bortezomib and dexamethasone; IPCW = Inverse probability of censoring weights; MM = multiple myeloma; NICE = National Institute of Health and Care Excellence; OS = overall survival; PFS = progression-free survival; PLD = patient level data; RRMM = relapsed and refectory multiple myeloma; TTD = time to treatment discontinuation; ERG = evidence review group.

B.3.8 Base-case results

B.3.8.1 Base-case cost-effectiveness analysis results

Table 63 and Table 64 present base case results of the model with the above-described assumptions and inputs. DBd was found to provide the highest LY and QALY gains among all treatments. Total costs associated with DBd were also higher than the comparator treatments'. As shown in Figure 37, Cd was dominated in the analysis by DBd. The ICER of DBd versus Bd was £31,034/QALY.

Due to the confidential nature of the carfilzomib PAS (and other PASs associated with subsequent treatment), and for consistency, it is important to note that the only PAS included in the remainder of this section is that for daratumumab when used in combination with Bd or as monotherapy. It is therefore challenging to determine the actual cost-effectiveness of DBd. However, based on the information available to Janssen, DBd is a cost-effective use of NHS resources when taking into account the wider context of innovation and benefits beyond the QALY.

Table 63 Base case results

Health Outcomes	DBd	Bd	Cd
LY accrued	[redacted]	[redacted]	[redacted]
LYs accrued: Progression Free Survival	[redacted]	[redacted]	[redacted]
LYs accrued: Post Progression Survival	[redacted]	[redacted]	[redacted]
QALY accrued	[redacted]	[redacted]	[redacted]
QALYs accrued: Progression Free Survival	[redacted]	[redacted]	[redacted]
QALYs accrued: Post progression Survival	[redacted]	[redacted]	[redacted]
QALYs accrued: Adverse Events	[redacted]	[redacted]	[redacted]
PFS Drug Cost	[redacted]	[redacted]	[redacted]
PFS Administration Cost	[redacted]	[redacted]	[redacted]
PFS Co-medication Cost	[redacted]	[redacted]	[redacted]
PFS Medical Resource Use	[redacted]	[redacted]	[redacted]
PPS Subsequent Treatment Drug Cost	[redacted]	[redacted]	[redacted]
PPS Medical Resource Use	[redacted]	[redacted]	[redacted]
Adverse Event Cost	[redacted]	[redacted]	[redacted]
Terminal Cost	[redacted]	[redacted]	[redacted]
Total Cost	[redacted]	[redacted]	[redacted]

Bd = bortezomib and dexamethasone; Cd = carfilzomib and dexamethasone; DBd = daratumumab, bortezomib and dexamethasone; LY = life year; PFS = progression-free survival; PPS = post-progression survival; QALY = quality-adjusted life year.

Table 64 Incremental cost-effectiveness results

Incremental results	Bd	Cd
Incremental costs	[redacted]	[redacted]
Incremental QALYs	[redacted]	[redacted]
Incremental LY	[redacted]	[redacted]
Cost per QALY gained	£31,034	Cd is dominated
Cost per LY gained	£21,718	Cd is dominated

Bd = bortezomib and dexamethasone; Cd = carfilzomib and dexamethasone; LY = life year; QALY = quality-adjusted life year.

Figure 37 Efficiency frontier plot for the reference scenario DARA+BOR+DEX

Bd = bortezomib and dexamethasone (BOR-DEX); Cd = carfilzomib and dexamethasone (CAR-DEX); DBd = daratumumab, bortezomib and dexamethasone (DARA-BOR-DEX); QALY = quality-adjusted life year.

B.3.8.2 Clinical outcomes from the model

Table 65 compares the median estimates of PFS from CASTOR and ENDEAVOR with model predictions. Importantly, results demonstrate strong consistency between CASTOR and the model results.

Table 65 Summary of model results compared with clinical data

Outcome	Treatment	Median clinical trial result (months)	Median model result (months)
PFS	DBd	27.01	27.01
	Bd	7.5	7.5
	Cd	22.2	20.7
TTD	DBd	[redacted]	[redacted]
	Bd	[redacted]	[redacted]
	Cd	[redacted]	[redacted]

[1]Patients who completed treatment on the Bd arm of CASTOR were censored and not considered to have discontinued treatment.

[2]Fixed duration treatment, median not reached

Bd = bortezomib and dexamethasone; DBd = daratumumab, bortezomib and dexamethasone; PFS = progression free survival.

B.3.9 Sensitivity analyses

B.3.9.1 Probabilistic sensitivity analysis

To account for the joint uncertainty of the underlying parameter estimates, second-order stochastic analysis was performed. Distributions used in the PSA are beta, gamma, log-normal and normal, per convention in economic analyses. The beta distribution is confined by the interval 0–1 and is typically used for inputs such as proportions and utility values. The gamma distribution is confined by the interval 0-∞ and is typically used for costs. The log-normal distribution is a normal distribution on the log scale and is typically used for sampling relative risks, ORs, and HRs. Treatment and AE costs, utilities for health states and HRs for OS were among the variables included in the PSA. The PSA was performed with 1,000 iterations.

The following preliminary assumptions for input parameter distributions and their SE/SD were applied:

- Cost inputs followed gamma distributions with an SE of 20% of default values.
- Pre-progression and post-progression utilities were assumed to follow beta distributions with the SEs calculated from the clinical trials, while AE disutility values were also assumed to follow the beta distribution, with an SE of 20% of default values.
- OS and PFS HRs were assumed to follow gamma distributions, with an SE calculated from the reported 95% CIs.
- Weight and BSA of patients was assumed to follow a normal distribution with the reported SD.

Correlation between survival curve parameters was considered using the Cholesky decomposition method to account for the correlation between the scale and shape parameters of the two- and three-parameter survival functions. The variance and covariance matrix of the survival function parameters were obtained from the curve-fitting procedure completed and are reported in Appendix P.

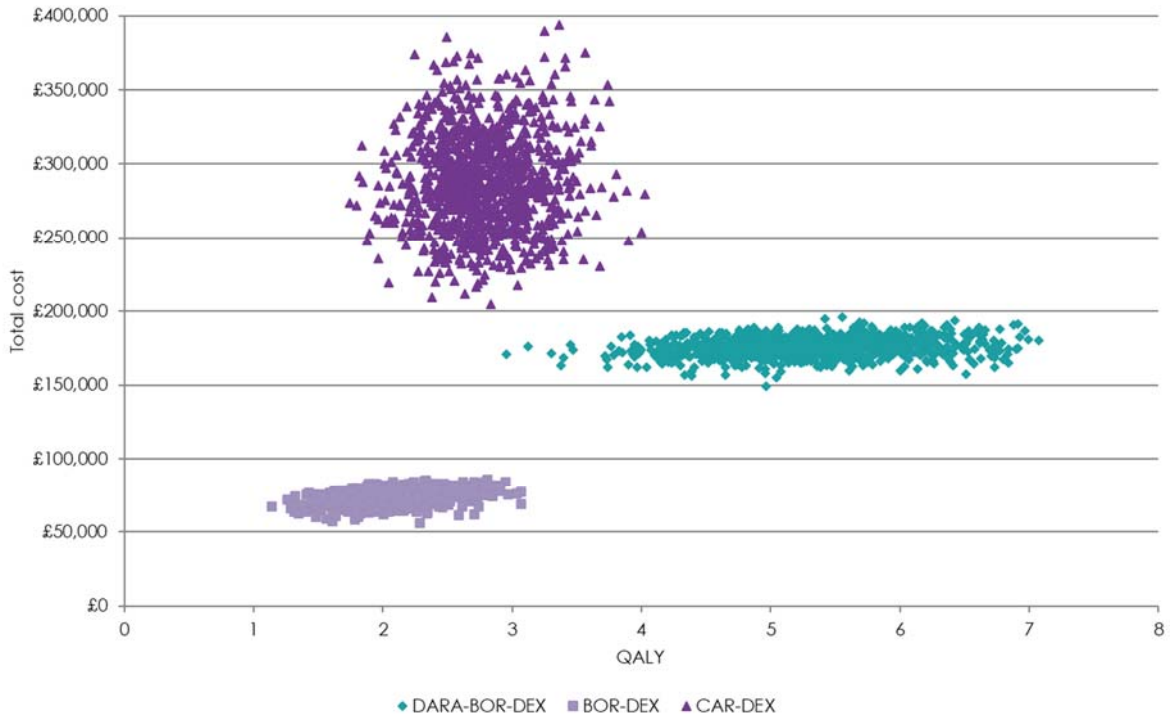
Results of the probabilistic analyses confirmed base case results. Cd was dominated and the ICER of DBd versus Bd calculated from the generated mean costs and mean QALY gains across the 1,000 random iterations was £31,470 (Table 66, Figure 38).

Table 66 Probabilistic analysis results

Comparator	Mean LYs	Mean QALYs	Mean Total cost	ICER
Bd	[redacted]	[redacted]	[redacted]	£31,470
Cd	[redacted]	[redacted]	[redacted]	Cd is dominated
DBd	[redacted]	[redacted]	[redacted]	N/A

Bd = bortezomib and dexamethasone; Cd = carfilzomib and dexamethasone; DBd = daratumumab, bortezomib and dexamethasone; ICER = incremental cost-effectiveness ratio; LY = life year; QALY = quality-adjusted life year.

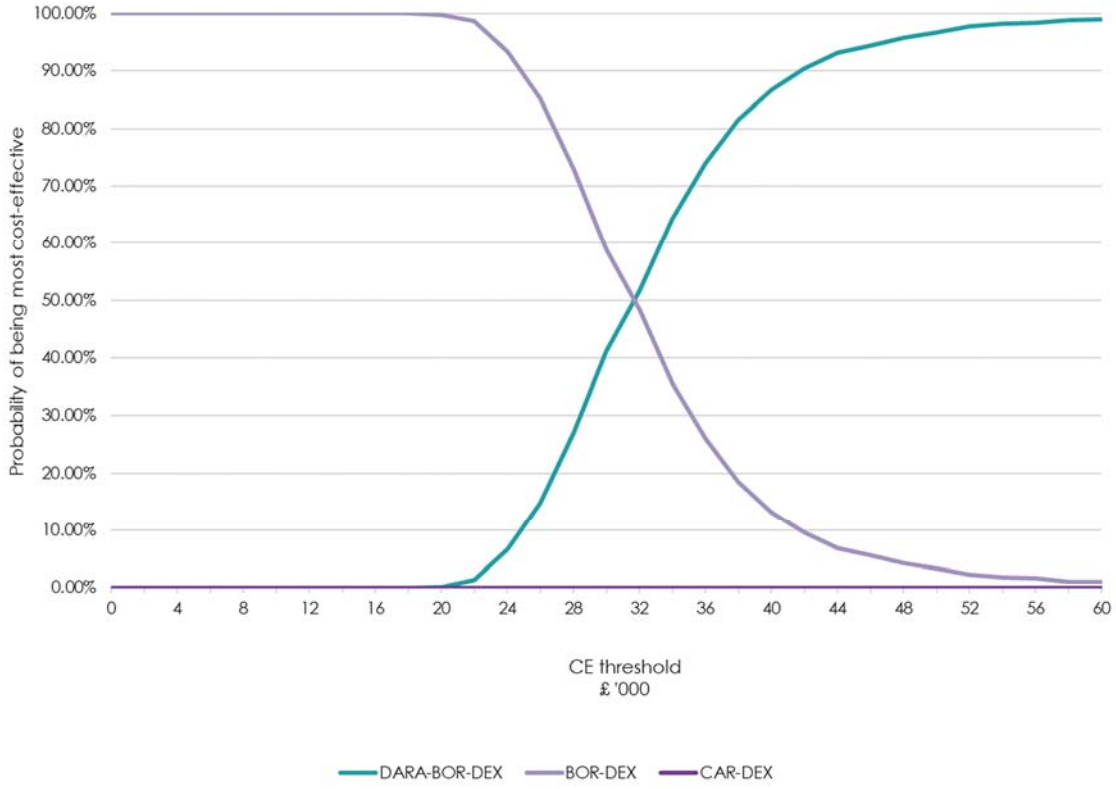
Figure 38 Probabilistic results on the cost-effectiveness plane



Bd = bortezomib and dexamethasone (BOR-DEX); Cd = carfilzomib and dexamethasone (CAR-DEX); DBd = daratumumab, bortezomib and dexamethasone (DARA-BOR-DEX); QALY = quality-adjusted life year.

Figure 39 depicts the cost-effectiveness acceptability curves. At the threshold of £30,000 /QALY, DBd had 100% and 42% chance of being cost-effective versus Cd and Bd, respectively, reaching 51.7% at a threshold of £32,000 /QALY.

Figure 39 Cost-effectiveness acceptability curves



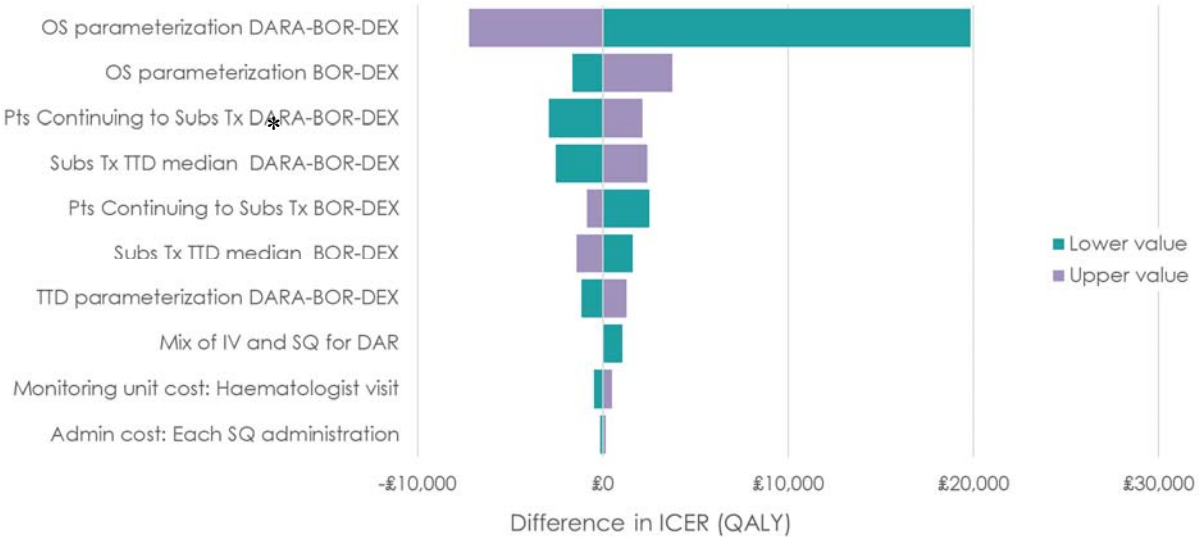
Bd = bortezomib and dexamethasone (BOR-DEX); Cd = carfilzomib and dexamethasone (CAR-DEX); DBd = daratumumab, bortezomib and dexamethasone (DARA-BOR-DEX); QALY = quality-adjusted life year.

B.3.9.2 Deterministic sensitivity analysis

All major model variables were tested in a number of one-way sensitivity analyses to identify model drivers and examine key areas of uncertainty. Where possible, CIs or published ranges were used as alternative values. In the absence of CIs or published ranges, upper and lower bounds tested in the one-way sensitivity analysis were calculated as ±20% of the mean base case value, as reported in Appendix N.

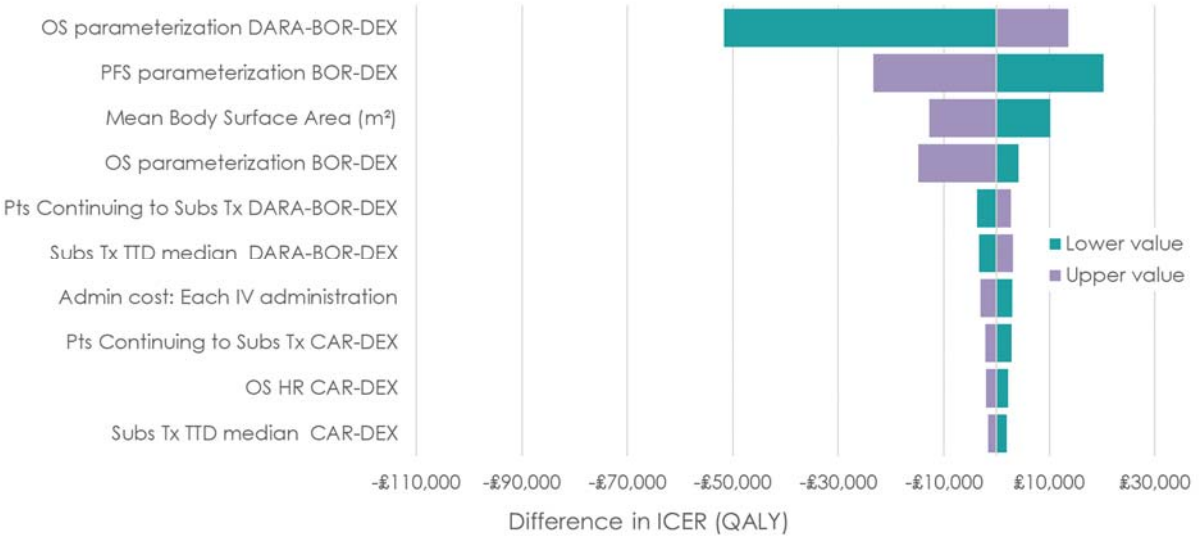
According to the result of the deterministic sensitivity analyses, OS assumptions have the largest influence on the calculated ICER of DBd versus Bd (Figure 40). Inputs related to subsequent treatment costs and treatment duration were also important determinants of the outcomes.

Figure 40 One-way sensitivity analysis DBd versus Bd



Bd = bortezomib and dexamethasone (BOR-DEX); DBd = daratumumab, bortezomib and dexamethasone (DARA-BOR-DEX); OS = overall survival; PFS = progression-free survival; Pts = patients; Subs = subsequent; TTD = time to treatment discontinuation; Tx = treatment.

Figure 41 One-way sensitivity analysis DBd versus Cd



Cd = carfilzomib and dexamethasone (BOR-DEX); DBd = daratumumab, bortezomib and dexamethasone (DARA-BOR-DEX); OS = overall survival; PFS = progression-free survival; Pts = patients; Subs = subsequent; TTD = time to treatment discontinuation; Tx = treatment.

B.3.9.3 Scenario analysis

Along with the base case, several scenarios were also examined to test the impact of various model assumptions.

B.3.9.3.1 Unadjusted overall survival

In the base case inverse probability of censoring weights (IPCW) methodology is used to adjust OS, to reduce bias since in the CASTOR trial many patients received subsequent treatment with therapies not available in UK clinical practice.

In the scenario analysis we evaluated an unadjusted OS approach extrapolating survival based on the direct observations from CASTOR.

B.3.9.3.2 Different survival curve functions to model PFS and OS

As mentioned in Section B.3.3.1, to project time-to-event data for the entire model time horizon, approaches for extrapolating survival data beyond the trial period were required. Given the relatively short follow-up available in CASTOR, when selecting the base case curves less weight was given to the statistical fits and more weight was given to the clinical face validity of the long-term PFS and OS projections to select the base case. In the scenario analysis other types of survival curves for PFS and OS were also tested as summarised in Table 67.

While the exponential function selected for the base case to extrapolate DBd PFS, the Weibull distribution was also a viable option for long-term projection. Therefore, the Weibull curve was also tested in a scenario analysis.

For Bd OS, clinical experts have indicated that besides the Gompertz function chosen as the base case, the Weibull distribution also predicted patient numbers to be alive at different time point which they found clinically reasonable.

Similarly, a scenario was also run where DBd OS was modelled using exponential function as conservative assumption, as according to clinical experts, DBd patients are expected to show a different mortality hazard than observed with older treatments.

Table 67 Alternative survival curve scenarios for PFS, OS and TTD

Survival curve modelling					
Curves		**Reference**	**Option 1**	**Option 2**	**Option 3**
PFS	DBd	Exponential	Weibull	Exponential	Exponential
	Bd	Exponential	Weibull	Exponential	Exponential
OS	DBd	Log-logistic	Log-logistic	Log-logistic	Exponential
	Bd	Gompertz	Gompertz	Weibull	Gompertz
Treatment duration	DBd	Exponential	Weibull	Exponential	Exponential
	Bd	Exponential	Weibull	Exponential	Exponential

Bd = bortezomib and dexamethasone; DBd = daratumumab, bortezomib and dexamethasone; OS = overall survival; PFS = progression-free survival; TTD = time to treatment discontinuation.

B.3.9.4 Summary of scenario analyses results

Results from scenario analysis using unadjusted OS data show a decrease in the relative survival benefit of DBd versus Bd and Cd. This is a direct consequence of the bias associated with the use of subsequent treatment not available in England. That is, the efficacy of comparator treatments is inflated due to higher proportions of patients receiving

currently unavailable therapies. The ICER of DBd versus Bd was £40,718 while DBd dominated Cd (Table 68).

Table 68 Results of unadjusted OS scenario

	DBd	Bd	Cd
Life-years (LY) accrued	[redacted]	[redacted]	[redacted]
LYs accrued: Progression Free Survival	[redacted]	[redacted]	[redacted]
LYs accrued: Post Progression Survival	[redacted]	[redacted]	[redacted]
Quality adjusted life-years (QALY) accrued	[redacted]	[redacted]	[redacted]
QALYs accrued: Progression Free Survival	[redacted]	[redacted]	[redacted]
QALYs accrued: Post progression Survival	[redacted]	[redacted]	[redacted]
Total Cost	[redacted]	[redacted]	[redacted]
Incremental costs		[redacted]	[redacted]
Incremental QALYs		[redacted]	[redacted]
Incremental LY		[redacted]	[redacted]
Cost per QALY gained		£40,718	Cd is dominated

Bd = bortezomib and dexamethasone; Cd = carfilzomib and dexamethasone; DBd = daratumumab, bortezomib and dexamethasone; LY = life years; OS = overall survival; QALY = quality-adjusted life year.

As shown in Table 69 and Table 70, most assumptions and alternative scenarios had relatively little impact on the economic evaluation results. Shortening the model time horizon had the greatest impact, followed by extrapolating DBd OS using an exponential function.

Table 69 Summary results of scenario analyses - cost per QALY gained

	Scenario		ICER (£) DBd vs Bd	ICER (£) DBd vs Cd
0	Base case		£31,034	DBd dominated Cd
1	Different survival curves	Unadjusted OS	£40,718	DBd dominated Cd
2		PFS Weibull	£32,071	DBd dominated Cd
3		Bd OS Weibull	£33,146	DBd dominated Cd
4		DBd OS exponential	£32,958	DBd dominated Cd
5	Longer subsequent treatment duration	13 months	£33,318	DBd dominated Cd
6		15 months	£34,532	DBd dominated Cd
7	Different time horizons	5 years	£97,699	DBd dominated Cd
8		10 years	£49,413	DBd dominated Cd
9		20 years	£34,358	DBd dominated Cd

	Scenario	ICER (£) DBd vs Bd	ICER (£) DBd vs Cd
10	Allow vial sharing	£30,954	DBd dominated Cd
11	Dose intensity option off	£32,597	DBd dominated Cd

Bd = bortezomib and dexamethasone; B = bortezomib; Cd = carfilzomib and dexamethasone; DBd = daratumumab, bortezomib and dexamethasone; ICER = incremental cost-effectiveness ratio; LY = life years; OS = overall survival; PFS = progression-free survival; TTD = time to treatment discontinuation; QALY = quality-adjusted life year.

Table 70 Summary results of scenario analyses for discount rates

Scenario 12						
Health benefit discount	**0%**		**1.5%**		**6.0%**	
Cost discount	ICER (£) DBd vs Bd	ICER (£) DBd vs Cd	ICER (£) DBd vs Bd	ICER (£) DBd vs Cd	ICER (£) DBd vs Bd	ICER (£) DBd vs Cd
0%	£24,750	DBd dominated Cd	£29,453	DBd dominated Cd	£46,169	DBd dominated Cd
1.5%	£23,017	DBd dominated Cd	£27,392	DBd dominated Cd	£42,937	DBd dominated Cd
6%	£19,151	DBd dominated Cd	£22,791	DBd dominated Cd	£35,725	DBd dominated Cd

Bd = bortezomib and dexamethasone; Cd = carfilzomib and dexamethasone; DBd = daratumumab, bortezomib and dexamethasone; ICER = incremental cost-effectiveness ratio.

B.3.10 Benefits not captured in the QALY calculation

Potential QoL benefits for daratumumab at 1PL are not captured in the economic model. The QoL of patients treated with DBd improved as patients moved into the monotherapy phase of treatment (Section B.3.4.1). These observed improvements in utility for the monotherapy phase of DBd were not included in the economic analyses due to the absence of data at comparative time points for patients receiving Bd. Please see

Figure 36.

In addition, it is important to mention that while patients in CASTOR received daratumumab via IV administration, clinical experts have confirmed that currently SC administration is routine practice across UK. The introduction of daratumumab SC significantly reduced the estimated chair time, which is particularly important at times of healthcare systems being under high pressure due to COVID-19. For daratumumab SC, the chair time was decreased by 97% versus daratumumab IV for first (from 456.9 to 13.3 minutes) and subsequent treatments (from 238.0 to 8.1 minutes).[149] In comparison, carfilzomib is administered via IV

infusion and more frequently, resulting in additional health care utilisation as well as stress for patients and HCPs. The wider benefits of SC vs IV administration on the NHS–especially while still recovering from pressure from the COVID-19 pandemic–is not captured in the economic model.

In comparison, carfilzomib is administered via IV infusion and more frequently, resulting in additional health care utilisation as well as stress for patients and HCPs.

Access to daratumumab at 1PL is pivotal for securing future MM innovations in the UK. Current clinical trials investigating novel immunological options, such as bispecific antibodies and CAR-T therapies, are investigating relapsed disease where patients are triple-class exposed, including to a CD38 mAb. As such, in addition to the clinical benefit that current patients would receive in the 1PL setting, access to DBd will mean UK myeloma patients in the relapsed setting will be eligible for participation in new clinical trials studying future innovations in anti-CD38 exposed patients.[150-154]

In addition, once regulatory approved, future access to these innovations will be facilitated since UK patients will be anti-CD38 exposed. The benefit of access to DBd in the context of future innovations is not explicitly captured in the QALY framework, and would potentially add additional QALYs to the DBd arm.

B.3.11 Validation

B.3.11.1 Validation of cost-effectiveness analysis

B.3.11.1.1 Internal validation

Throughout the validation process a comprehensive and rigorous quality check was fulfilled, including validating the logical structure of the model, mathematical formulas, sequences of calculations and the values of numbers supplied as model inputs. Unexpected model behaviour, implementation and typing errors were all identified by this review.

The process involved checking the intermediate calculations for references (whether they are linked to the correct cells, etc.) implementation (whether correct signs for the parameters are used, etc.), and evaluation of the face validity of predicted results. The expected function of parameters was checked with extreme value sensitivity analysis. The process also involved checking the functionality of any built-in Macro programs. Quality check was a repeatable process that produced a checklist spreadsheet indicating the specific tasks performed and their results returned.

The appropriateness of distributions used in the probabilistic analysis of the model was also checked. The model survival predictions were also checked against data observed in the clinical trials used as data sources.

B.3.11.1.2 External validation

External validation of the modelling approach and key assumptions was carried out in several stages. Firstly, a clinical advisory board attended by several NHS Consultant Haematologists with extensive and ongoing experience of treating patients with RRMM was run. The aim of this advisory board was to understand the RRMM treatment pathway, including unmet need, clinical outcomes, diagnostic requirements. Secondly, an advisory board attended by UK health economist experts with extensive experience of survival analyses (adjustment and extrapolation) was run.

B.3.12 Interpretation and conclusions of economic evidence

The economic analyses presented in this submission are robust, making best use of available data, minimising assumptions and capturing the novel mechanism of action of daratumumab. The PartSA approach allows for flexible modelling; where alternative long-term assumptions can be explored with ease.

Clinical expert advice was sought throughout the modelling process to assess the appropriateness of the modelled pathway and ensure key aspects of clinical care were captured. Consequently, clinical outcomes predicted by the economic model are consistent with those observed in CASTOR.

Due to the international design of CASTOR, many patients received subsequent treatment with therapies not available in England. This deviation from English clinical practice occurred in a higher proportion of patients treated with Bd than DBd (as a result of the earlier progression of patients receiving Bd); thereby introducing bias into the OS analyses.

All methods recommended in NICE DSU TSD 16 to adjust for such bias were explored. However, the complexities of the data and the array of treatment switches meant that it was only possible to implement adjustment using IPCW. Every method of adjustment is associated with theoretical and practical limitations; however, the IPCW method is robust, providing switching proportions are low and sample sizes are sufficient (as is the case in CASTOR). Moreover, the IPCW is a well-known method with a strong theoretical background that has been accepted in several NICE appraisals to date.

Where possible, model extrapolations have been validated using a triangulation of statistical fit, expert clinical opinion and consideration of empirical hazards. Extrapolation of OS is a key driver of the model results and as such has been thoroughly explored and externally validated. For bortezomib, given the maturity of the data base case selection was based on statistical and visual goodness-of-fit. For daratumumab, clinical plausibility of OS projections was assessed against clinical expert opinion and observation of empirical hazards.

A comprehensive and robust SLR was carried out to identify clinical evidence on comparators relevant to the decision problem in second-line patients. No evidence was identified pertaining to combination chemotherapy regimens that are used in clinical practice which finding was supported by clinical experts attending the advisory board stating that patients are not treated with chemotherapies in the 2nd line setting in clinical practice. Most importantly it was also recognized by NHS England during the original appraisal of DBd that NHS England does not consider that cytotoxic chemotherapy is a reasonable comparator as 2nd line treatment.[67] As a result, only comparisons against Bd and Cd were undertaken.

Evidence from CASTOR and ENDEAVOR were synthesised in Bayesian NMA to estimate the relative effectiveness of DBd versus Cd. Both CASTOR and ENDEAVOR are phase III, open-label RCTs including adult patients with RRMM who had received at least one prior line of therapy. Some heterogeneity with respect to study design exists between these studies; however, these differences are expected to have minimal impact on NMA results. Furthermore, baseline characteristics were similar with regards to key prognostic factors (age, cytogenetic risk status, number and type of prior therapies and ISS Stage). Moreover, both CASTOR and ENDEAVOR were stratified by number of prior treatment lines; in which pre-specified subgroup analyses were undertaken.

DBd dominated Cd. ICER of £31,034 per QALY was calculated versus Bd.

Sensitivity analyses (one-way and probabilistic) indicate that the base case cost-effectiveness results are robust with respect to parameter uncertainty. At a willingness-to-pay of £30,000, DBd has 42% chance of being the optimal treatment compared with Bd and a 100% chance of being the optimal treatment compared with Cd. Scenario analyses reveal that the base case cost-effectiveness results are sensitive to extrapolation of OS and robust with respect to extrapolation of PFS and TTD, utility and costing assumptions.

Results of the economic analyses demonstrate that DBd is a highly effective, life-extending treatment for patients with RRMM. DBd is predicted to provide [redacted] additional life years ([redacted] QALYs) versus Cd and [redacted] additional life years ([redacted] QALYs) versus Bd. This substantial

predicted OS benefit is supported by the highly significant and substantial clinical benefits (OS, PFS, ORR and MRD negativity) observed in CASTOR. Moreover, the innovative mechanism of action of daratumumab and synergy of effect with the current standard of care, Bd, is expected to fundamentally change the prognosis of patients, resulting in life expectancy akin to drug therapy outcomes in front-line patients.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Daratumumab with bortezomib and dexamethasone for previously treated multiple myeloma (Managed Access Review of TA573) [ID4057]

Clarification questions

August 2022

File name	Version	Contains confidential information	Date
ID4057 Clarification questions AIC CIC FINAL	**Final**	**Yes**	**25th September 2022**

Notes for company

Highlighting in the template

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

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Section A: Clarification on effectiveness data

Castor trial

A1. CS B.2.5.1 and CS Table 17 report the risk of bias assessment for the CASTOR trial only, including the judgements and reasons for each judgement. Appendix D Table 40 reports the judgement only for CASTOR and ENDEAVOR using criteria used that are worded differently to that in CS Table 17.

Please could the company present risk of bias assessments for CASTOR and ENDEAVOR using the same tool as CS Table 17 with judgements and reasons for each judgement. Please could the company also provide details of how the risk of bias assessment was performed, including confirmation of the tool used and the number of reviewers involved in the process.

The risk of bias assessment for CASTOR and ENDEAVOR is presented in Table **1** and was adapted from the Systematic reviews: CRD's guidance for undertaking reviews in health care (University of York Centre for Reviews and Dissemination). It was completed by one reviewer and validated by a second reviewer. In addition, the Cochrane risk of bias version 2 is also presented in Table **2** (completed by one reviewer and validated by a second). There were no differences between the two studies except for the unavailability of the ENDEAVOR protocol which meant the assessment for the domain 'is there any evidence to suggest that the authors measured more outcomes than they reported?' was unclear.

Table 1. Quality assessment results for parallel group RCTs

	CASTOR		ENDEAVOR	
	Notes	**Risk of bias**	**Notes**	**Risk of bias**
Was randomisation carried out appropriately?	Yes, randomisation was carried out as per the pre-specified randomisation method; patients were randomised using a central IWRS	Low	Yes, Patients were randomly assigned using an interactive voice and web response system.	Low
Was the concealment of treatment	CASTOR was open label. Concealment of treatment was not	Potential risk of bias as open label	ENDEAVOR was open label. Concealment of treatment was not	Potential risk of bias as open label

	CASTOR		ENDEAVOR	
	Notes	**Risk of bias**	**Notes**	**Risk of bias**
allocation adequate?	practical in CASTOR owing to the different dosing schedules. Potential bias was mitigated by use of an IDMC that was masked to treatment allocated	design could have influenced investigator's assessment of PFS events	practical in ENDEAVOR owing to the different dosing schedules. Potential bias was mitigated by use of an IRC that was masked to treatment allocated	design could have influenced investigator's assessment of PFS events
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes, demographic and baseline characteristics were well balanced between the two Treatment groups with no categories having a difference of ≥10%	Low	Yes, demographic and baseline characteristics were well balanced between the two Treatment groups with no categories having a difference of ≥10%	Low
Were the care providers, participants and outcome assessors blind to treatment allocation?	No, CASTOR was open-label and only Janssen were blinded to the results	Low, as an IDMC reviewed the data	No, ENDEAVOR was open-label	Low, as an IRC reviewed the data
Were there any unexpected imbalances in drop-outs between groups?	No, of the 498 patients randomised (251 in the DBd group and 247 in the Bd group), 480 received study treatment: 243 patients received DBd and 237 patients received Bd (see Section B.2.4.4)	Low	No, of the 929 patients randomised (464 in the Cd group and 465 in the Bd group), 919 received study treatment: 463 patients received Cd and 456 patients received Bd	Low
Is there any evidence to suggest that the authors measured more outcomes than they reported?	None	Low	Unclear as although a protocol was mentioned in the study, a copy of the protocol was not available to review	Unclear
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes, the ITT population was used for analysis of the primary endpoint and other time-to-event efficacy endpoints, which included all randomised patients	Low	Yes, the ITT population was used for analysis of the primary endpoint and other time-to-event efficacy endpoints, which included all randomised patients	Low

Bd = bortezomib and dexamethasone; Cd, carfilzomib and dexamethasone; DBd = daratumumab in combination with bortezomib and dexamethasone; IDMC = independent data monitoring committee; IRC = independent review committee; ITT = intent-to-treat; IWRS = interactive web response system; PFS = progression free survival; RCT = randomised controlled trial.

Adapted from Systematic reviews: CRD's guidance for undertaking reviews in health care (University of York Centre for Reviews and Dissemination).

Table 2. Cochrane Risk of Bias

Trial Name	CASTOR	ENDEAVOR
Risk of bias arising from the randomization process		
1.1 Was the allocation sequence random?	Yes	Yes
1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Yes	Yes
1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	No	No
Domain rating	**Low Risk**	**Low risk**
Risk of bias due to deviations from the intended interventions (*effect of assignment to intervention*)		
2.1 Were participants aware of their assigned intervention during the trial?	Yes	Yes
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Yes	Yes
2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the trial context?	No	No
2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA	NA
2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA	NA
2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Yes	Yes
2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	NA	NA
Domain rating	**Low Risk**	**Low risk**
Risk of bias due to missing outcome data		
3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Yes	Yes
3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?	NA	NA
3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	NA
3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	NA
Domain rating	**Low risk**	**Low risk**
Risk of bias in measurement of the outcome		
4.1 Was the method of measuring the outcome inappropriate?	No	No
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	No	No
4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?	No	No
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA	NA
4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	NA
Domain rating	**Low Risk**	**Low risk**
Risk of bias in selection of the reported result		
5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	Yes	No information

5.2. ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	No	No
5.3 ... multiple eligible analyses of the data?	No	Probably no
Domain rating	**Low Risk**	**Some concerns**

A2. When comparing baseline values of the CASTOR trial for DBd 1PL and Bd 1PL in CS Table 12 to CS reference 99, it appears that some values have been switched around (e.g. values in CS reference 99 for DBd 1PL height and weight are in the CS Table 12 Bd 1PL column and vice versa). Could the company confirm that the values in CS reference 99 are the correct baseline values for DBd 1PL and Bd 1PL.

We apologise for this error and confirm the values in CS reference 99 are the correct baseline values for DBd 1PL and Bd 1PL. Corrected values are included in the below table in bold.

Table 3. Characteristics of participants in CASTOR across treatment groups (intent-to-treat analysis set) - Corrected

	Bd, ITT (n=247)	**DBd, ITT (n=251)**	**Bd, 1PL (n=113)**	**DBd, 1PL (n=122)**
Age, years, n (%)				
<65	125 (50.6)	132 (52.6)	58 (51.3)	67 (54.9)
65 to 74	87 (35.2)	96 (38.2)	-	-
≥75	35 (14.2)	23 (9.2)	17 (15.0)	8 (7.0)
Mean (SD)	63.9 (9.8)	62.8 (9.7)	64.2 (9.88)	62.6 (9.83)
Median	64.0	64.0	64.0	63.0
Range	(33; 85)	(30; 88)	(40; 85)	(30; 84)
Sex, n (%)				
Male	147 (59.5)	137 (54.6)	65 (57.5)	74 (60.7)
Ethnicity, n (%)				
Hispanic or Latino	24 (9.7)	17 (6.8)	-	-
Not Hispanic or Latino	212 (85.8)	227 (90.4)	-	-
Unknown	3 (1.2)	1 (0.4)	-	-
Not Reported	8 (3.2)	6 (2.4)	-	-
Race, n (%)				
White	219 (88.7)	216 (86.1)	[redacted]	[redacted]
Black or African American	6 (2.4)	14 (5.6)	-	-
Asian	11 (4.5)	12 (4.8)	-	-
American Indian or Alaska Native	1 (0.4)	1 (0.4)	-	-

	Bd, ITT (n=247)	DBd, ITT (n=251)	Bd, 1PL (n=113)	DBd, 1PL (n=122)
Native Hawaiian or other Pacific Islander	0	1 (0.4)	-	-
Other	1 (0.4)	5 (2.0)	-	-
Unknown	2 (0.8)	0	-	-
Not Reported	7 (2.8)	2 (0.8)	-	-
Weight (kg)				
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median	76.0	77.0	[redacted]	[redacted]
Range	(37.5; 131.6)	(45.0; 134.8)	[redacted]	[redacted]
Height (cm)				
Mean (SD)	166.8 (10.0)	166.8 (10.0)	[redacted]	[redacted]
Median	167.0	167.0	[redacted]	[redacted]
Range	(139; 192)	(141; 194)	[redacted]	[redacted]
Baseline ECOG score, n (%)				
0	116 (47.0)	106 (42.4)	56 (49.6)	57 (46.7)
≥1			57 (50.4)	65 (53.3)
1	112 (45.3)	131 (52.4)	-	-
2	19 (7.7)	13 (5.2)	-	-
>2	0	0	-	-
Type of measurable disease[a], n (%)				
IgG	138 (55.9)	125 (49.8)	[redacted]	[redacted]
IgA	54 (21.9)	56 (22.3)	[redacted]	[redacted]
Other[b]	4 (1.6)	5 (2.0)	[redacted]	[redacted]
Urine only	36 (14.6)	40 (15.9)	[redacted]	[redacted]
Serum FLC only	14 (5.7)	25 (10.0)	[redacted]	[redacted]
NE	1 (0.4)	0	[redacted]	[redacted]
ISS staging[c], n (%)				
I	96 (38.9)	98 (39.0)	51 (45.1)	57 (46.7)
II	100 (40.5)	94 (37.5)	44 (38.9)	42 (34.4)
III	51 (20.6)	59 (23.5)	18 (15.9)	23 (18.9)
Time from MM diagnosis to randomisation (years)				
Mean (SD)	4.8 (3.3)	4.7 (3.2)	-	-
Median	3.7	3.9	2.98	2.81
Range	(0.6; 18.6)	(0.7; 20.7)	(0.6; 18.1)	(0.7; 14.9)
Number of lytic bone lesions, n (%)				
None	50 (20.3)	56 (22.5)	[redacted]	[redacted]
1-3	43 (17.5)	50 (20.1)	[redacted]	[redacted]
4-10	55 (22.4)	53 (21.3)	[redacted]	[redacted]
>10	98 (39.8)	90 (36.1)	[redacted]	[redacted]
Any cytogenetic abnormality[d], n (%)				
Standard-risk	137 (78.7)	140 (77.3)	66 (58.4)	73 (59.8)
High-risk	37 (21.3)	41 (22.7)	4 (3.5)	7 (5.7)

	Bd, ITT (n=247)	DBd, ITT (n=251)	Bd, 1PL (n=113)	DBd, 1PL (n=122)
Del17p	21 (12.1)	28 (15.5)	[redacted]	[redacted]
T(4;14)	15 (8.6)	14 (7.7)	[redacted]	[redacted]
T(14;16)	5 (2.9)	4 (2.2)	[redacted]	[redacted]
Total number of patients with any prior therapies for MM, n (%)				
Prior systemic therapy	247 (100.0)	251 (100.0)	[redacted]	[redacted]
Prior ASCT	149 (60.3)	156 (62.2)	[redacted]	[redacted]
Prior radiotherapy	59 (23.9)	63 (25.1)	-	-
Prior cancer-related surgery	35 (14.2)	33 (13.1)	[redacted]	[redacted]
Number of prior lines of therapy[e], n (%)				
1	113 (45.7)	122 (48.6)	113 (100)	122 (100)
2	74 (30.0)	70 (27.9)	0	0
3	32 (13.0)	37 (14.7)	0	0
>3	28 (11.3)	22 (8.8)	0	0
Mean (SD)	2.0 (1.4)	1.9 (1.2)	-	-
Median	2.0	2.0	1	1
Range	(1; 10)	(1; 9)	(1; 1)	(1; 1)
Prior therapy exposure, n (%)				
Prior PI	172 (69.6)	169 (67.3)	[redacted]	[redacted]
Bortezomib	164 (66.4)	162 (64.5)	57 (50.4)	62 (50.8)
Carfilzomib	10 (4.0)	12 (4.8)	[redacted]	[redacted]
Ixazomib	7 (2.8)	12 (4.8)	[redacted]	[redacted]
Prior IMiD	198 (80.2)	179 (71.3)	[redacted]	[redacted]
Lenalidomide	120 (48.6)	89 (35.5)	33 (29.0)	15 (12.0)
Pomalidomide	7 (2.8)	7 (2.8)	[redacted]	[redacted]
Thalidomide	121 (49.0)	125 (49.8)	[redacted]	[redacted]
Prior corticosteroids	245 (99.2)	244 (97.2)	[redacted]	[redacted]
Dexamethasone	233 (94.3)	218 (86.9)	[redacted]	[redacted]
Prednisone	77 (31.2)	83 (33.1)	[redacted]	[redacted]
Prior alkylating agents	224 (90.7)	240 (95.6)	[redacted]	[redacted]
Prior anthracyclines	80 (32.4)	72 (28.7)	[redacted]	[redacted]
Prior PI+IMiD	129 (52.2)	112 (44.6)	33 (29.0)	29 (24.0)
Prior PI+IMiD+ALKY	121 (49.0)	112 (44.6)	[redacted]	[redacted]
Prior bortezomib+lenalidomide	89 (36.0)	75 (29.9)	[redacted]	[redacted]
Refractory status, n (%)				
PI only	4 (1.6)	3 (1.2)	[redacted]	[redacted]
IMiD only	90 (36.4)	74 (29.5)	[redacted]	[redacted]
Both PI and IMiD	7 (2.8)	9 (3.6)	[redacted]	[redacted]
Lenalidomide	81 (32.8)	60 (23.9)	16 (18.0)	6 (5.0)

1PL = one prior line; ALKY = alkylating agents; ASCT = autologous stem cell transplant; Bd = bortezomib and dexamethasone; DBd = daratumumab, bortezomib and dexamethasone; ECOG = Eastern Cooperative Oncology Group; FISH = fluorescence in situ hybridisation; FLC = free light chain; IMiD = immunomodulatory drug; ISS = International Staging System; ITT = intent-to-treat; MM = multiple myeloma; PI = proteasome inhibitor; MM = multiple myeloma; NE = not evaluable; SD = standard deviation; NA = not available

[a]Includes patients without measurable disease in serum and urine.

[b]Includes IgD, IgM, IgE and biclonal.

[c]ISS staging is derived based on the combination of serum β2-microglobulin and albumin.

[d]Cytogenetic abnormalities are based on FISH or karyotype testing.

[e]Based on data recorded on prior systemic therapy eCRF page.

A3. In the summary of TEAEs (Table 33) for the Bd arm at median follow-up 72.6 months that data are the same as presented for the median follow-up at 26.9 months. The EAG presumes this is correct (due to the maximum treatment period for Bd of eight 21-day cycles) but please would the company confirm this.

We confirm the data for the Bd arm are the same at both follow-up points due to the maximum treatment period of eight 21-day cycles for Bd.

A4. CS Table 34 presents treatment emergent adverse events by preferred term, with median follow up of 76.2 months for the safety population in the CASTOR trial. Could the company please provide this data for patients with one prior line of therapy only.

For the subgroup of patients who received exactly 1 prior line of therapy, no pre-planned analysis was carried out that involved safety endpoints (such as adverse event [AE] rates). A post-hoc analysis was carried out to accommodate the inclusion of AEs in the cost-effectiveness analysis.

The analysis included AEs for which Grade 3 or higher events were reported in at least 5% of patients in any treatment arm in CASTOR. This inclusion rule was selected to capture AEs that would impact patients consistently enough to have validity in a real-world setting where AEs are monitored in a less strict manner compared with a clinical trial setting.

Table 4. Cumulative probability of AEs during treatment period - CASTOR – 1PL - Final OS analysis[1]

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]

AE = adverse event; Bd = bortezomib and dexamethasone; Cd = carfilzomib and dexamethasone; DBd = daratumumab, bortezomib and dexamethasone.

Adjustment of OS for subsequent treatments not available in clinical practice in England

A5. Priority question. Please provide an update on the switching proportions and samples sizes for the second-line patient group (i.e., an update of Table 32 in Appendix D from the 2018 company submission for TA573) and an update on the first subsequent therapy received not available in England (i.e., an update of Table 33 in Appendix D from the 2018 company submission for TA573).

The IPCW method involves censoring patients upon treatment switch to a treatment that is not available in England, and then reweighting the follow-up information for patients who remain in the study to remove any censoring-related selection bias. [redacted] % of patients ([redacted] out of [redacted] patients) in the Bd arm of CASTOR switched to treatments that are not available in England versus [redacted] % of patients ([redacted] out of [redacted] patients) in the DBd arm for the first subsequent therapy not available in England received. Note that daratumumab monotherapy was only adjusted for if received outside of the recommended fourth-line setting.

As greater proportion of patients on the control arm switched to efficacious subsequent treatments not available in England, we consider the unadjusted

analysis conservative and likely to underestimate the relative treatment effect of DBd vs Bd (unadjusted vs IPCW adjusted OS HR = [redacted] vs [redacted]).

Switching proportions and sample sizes are outlined in Table 5, while details of the first subsequent therapy received that is not available in England are provided in Table 6.

Table 5. Switching proportions and sample sizes, second-line patients

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

Bd = bortezomib and dexamethasone; DBd = daratumumab in combination with bortezomib and dexamethasone

Table 6. First subsequent therapy received not available in England, second-line patients

Subsequent therapies not available in England (allow Dara monotherapy at 4L)
[redacted]
[redacted]
[redacted]
[redacted]
[redacted]
[redacted]
[redacted]
[redacted]
[redacted]
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4L = fourth-line; Bd = bortezomib and dexamethasone; DBd = daratumumab in combination with bortezomib and dexamethasone

NMA and MAIC

A6. Priority question. Please summarise the evidence for prognostic factors and treatment effect modifiers.

Based on available baseline characteristics in the CASTOR and ENDEAVOR 1PL populations, the study populations were markedly similar (shown in Appendix D, Section D.2.4, Table 32 of the submission and repeated as Table **7** below). Therefore, investigations of treatment effect modifiers (or prognostic factors) were not expected to influence the interpretation of the NMA results.

Table 7. Baseline characteristics for CASTOR and ENDEAVOR (1PL population)

	1PL population	
Trial number	**Treatment group 1**	**Treatment group 2**
CASTOR (MMY3004)	Daratumumab + bortezomib + dexamethasone (n=122)	Bortezomib + dexamethasone (n=113)
Age	Median: 63.0 (range 30-84)	Median: 64.0 (range 40-85)
Sex	Male: 60.7%	Male: 57.5%
ECOG Performance Status	0: 46.7% ≥1: 53.3%	0: 49.6% ≥1: 50.4%
ISS Stage	I: 46.7% II: 34.4% III: 18.9%	I: 45.1% II: 38.9% III: 15.9%
Number of prior lines of treatment	1: 100%	1: 100%
ENDEAVOR	Carfilzomib + dexamethasone (n=232)	Bortezomib + dexamethasone (n=232)
Age	Median: 66 (36-89)	Median: 63.5 (39-88)
Sex	Male: NR	Male: NR
ECOG Performance Status	0: 47.4% 1: 44.8% 2: 7.8%	0: 56.5% 1: 39.7% 2: 3.9%
ISS Stage	I: 47% II: 29.3% III: 23.7%	I: 49.6% II: 26.7% III: 23.7%
Number of prior lines of treatment	1: 100%	1: 100%

Nonetheless, please find our qualitative assessment of treatment effect modifiers and prognostic factors below, based on subgroup analyses conducted across studies reporting 1PL data identified in the SLR. In each case, the studies examined PFS and used the whole cohort of the study (not the 1PL populations, **Table 8**).

Based on this assessment, the strongest evidence of effect modification was shown for:

- ISS disease staging
- Number of previous lines of therapy
- Baseline creatine clearance
- ECOG performance status

As baseline creatinine clearance was not reported for both CASTOR and ENDEAVOR, this represents a limitation of the analysis, as we do not know if the 1PL population of these studies were imbalanced with respect to this effect modifier. Similarly, the prognostic factors were also assessed in the whole cohort populations (not the 1PL populations) for the outcome PFS.

Due to data limitations prognostic factors were only assessable in the CASTOR and LEPUS trials, and not all risk factors considered in these trials were evaluable for prognostic effect due to immature PFS data (Table 9). Limited evidence indicated possible signs of the following being prognostic factors:

- ISS disease staging
- Number of previous lines
- Refractory to immunomodulatory agents
- Refractory to last line of previous therapy

Table 8. Effect modification

	CASTOR[2]	ENDEAVOR[3]	LEPUS[4]	BOSTON[5]	CANDOR[6]	IKEMA[7]	OPTIMISMM[8]
Age	Some	Yes	Yes	Some	Some	Some	Some
Sex	No	Some	Some	Some	No	NR	NR
ISS disease staging	Yes	Some	Yes	Yes	Some	Yes	Some
No. of previous lines	Yes	Some	Yes	Some	No	Some	Some
Previous stem cell transplantation	No	Some	NR	Some	NR	NR	No
Previous bortezomib therapy	Yes	Some	Some	NR	NR	NR	NR
Previous therapy with immunomodulatory agents	Some	Yes	Yes	NR	No	No	NR
Previous immunomodulatory agent and bortezomib	NR	Some	NR	NR	NR	NR	NR
Previous PI treatment	NR	NR	NR	Yes	Some	No	NR
Previous Lenalidomide	NR	Yes	NR	NR	Some	NR	NR
Previous Thalidomide	NR	No	NR	NR	NR	NR	NR
Refractory to Bortezomib	NR	Some	NR	NR	NR	NR	NR
Refractory to Bortezomib or ixazomib	NR	NR	NR	NR	Yes	NR	NR
Refractory to lenalidomide	NR	Yes	NR	NR	Yes	Some	Some
Disease refractory to previous immunomodulatory agent	Yes	NR	Yes	NR	Yes	NR	NR
Disease refractory to last line of previous therapy	No	NR	Some	NR	NR	NR	NR
Type of multiple myeloma	No	NR	No	NR	NR	NR	NR
Baseline creatine clearance	Yes	Yes	Yes	Some	Yes	NR	Some
Baseline renal function	NR	NR	Some	NR	NR	Yes	NR
Race	NR	No	NR	Yes	Yes	NR	NR
Ethnicity	NR	NR	NR	Some	NR	NR	NR

	CASTOR[2]	ENDEAVOR[3]	LEPUS[4]	BOSTON[5]	CANDOR[6]	IKEMA[7]	OPTIMISMM[8]
Geographical region	NR	Yes	NR	Yes	Yes	NR	NR
ECOG PS	NR	Yes	Yes	Yes	Yes	NR	No
Previous peripheral neuropathy	NR	No	NR	NR	NR	NR	NR
Baseline hepatic function	NR	NR	Yes	NR	NR	NR	NR
Cytogenic risk	NR	Yes	No	Yes	Some	Yes	No
Frailty	NR	NR	NR	No	NR	NR	NR

Key: Yes = evidence of effect modification; Some = some evidence of effect modification; No = evidence of no effect modification; NR = no evidence of effect modification reported
ECOG PS = Eastern Cooperative Oncology Group performance status; ISS = International Staging System; NR = not reported; PI = proteasome inhibitor

Table 9. Prognostic factor

	CASTOR	LEPUS
Age	No	No
Sex	NR	NR
ISS disease staging	Yes	No
No. of previous lines	Yes	No
Previous stem cell transplantation	NR	NR
Previous bortezomib therapy	No	No
Previous therapy with immunomodulatory agents	No	NR
Disease refractory to immunomodulatory agent	Yes	NR
Disease refractory to last line of previous therapy	Yes	NR
Disease refractory to immunomodulatory agent	NR	NR
Type of multiple myeloma	No	No
Baseline creatine clearance	NR	NR
Baseline hepatic function	NR	NR
Cytogenic risk	NR	No
ECOG PS	NR	NR

Key: Yes = evidence of a prognostic factor; No = evidence of no prognostic factor; NR = no evidence of a prognostic factor reported

ECOG PS = Eastern Cooperative Oncology Group performance status; ISS = International Staging System; NR = not reported

A7. Priority question. Please add a scenario analysis in the NMA adding the LEPUS trial.

The LEPUS study was evaluated in an entirely Chinese population. It was therefore not included in the base case NMA analyses because of (1) the lack of generalisability to the CASTOR and ENDEAVOR populations (where closest-match populations represented 3.6% [Korean ethnicity] and 12.4% [Asian ethnicity] of patients, respectively, in their main trial population [ethnicity was not reported for the 1PL subgroup]); and (2) the potential risk of effect modification introduced by variations in Asian ethnicity.

PFS and OS results from the LEPUS trial used in the scenario analysis are captured in Table 10 and Table 11 along with the results from CASTOR and ENDEAVOR. The results from CASTOR and LEPUS were pooled and are presented in Table 12. Given the moderate heterogeneity in the PFS results for DBd vs Bd in the two trials, we ran both a fixed effects and random effects model (I^2=65.3%, further justifying excluding LEPUS from the base case NMA). For OS, only a fixed-effect model was

run because no heterogeneity (I^2=0%) was observed (Table 12). Results of the NMAs are presented in Table 13.

The scenario analysis of PFS indicates that results are comparable to the base case analysis without LEPUS for the comparison of DBd vs Bd in both the fixed- and random-effects scenarios. Trends for DBd vs Cd were also comparable for PFS, although wider credible intervals (crossing the null) were observed in the random-effects comparison of DBd vs. Cd. This is to be expected given the high heterogeneity as a result of including the LEPUS trial.

The scenario analysis of OS indicates that results are comparable to the base case analysis without LEPUS.

In conclusion, adding the LEPUS trial does not change the general trends whereby DBd is favourable to Cd and Bd for PFS and OS.

Table 10. Progression-free survival among patients with 1PL RRMM (including LEPUS)

	CASTOR		ENDEAVOR		LEPUS	
Progression-free survival	**DBd (n=122)**	**Bd (n=113)**	**Cd (n=232)**	**Bd (n=232)**	**DBd (n=141)**	**Bd (n=70)**
Follow up	50.2 months		12-13 months[a]		25.1 months	
Median (95% CI)	27.0 (NR, NR)	7.9 (NR, NR)	22.2 (NR, NR)	10.1 (NR, NR)	17.5 (NR, NR)	6.0 (NR, NR)
HR (95% CI) p value	0.21 (0.15, 0.31) <0.0001		0.45 (0.33, 0.61) <0.0001		0.40 (0.21-0.77)	

Cd = carfilzomib and dexamethasone; CI = confidence interval; Bd = bortezomib in combination with dexamethasone; DBd = daratumumab in combination with bortezomib and dexamethasone; HR = hazard ratio; NR = not reported; PFS = progression-free survival

a : Data cut-off at November 2014. Based on a reported median follow up of 44.3mo (Cd) vs. 43.7mo (Bd) at July 2017, we assume that the 31 months between November 2014 and July 2017 would make the follow-up at November 2014 around 13 mo (Cd) and 12 mo (Bd).

Table 11. Overall survival among patients with 1PL RRMM (including LEPUS)

	CASTOR		ENDEAVOR		LEPUS	
Progression-free survival	**DBd (n=122)**	**Bd (n=113)**	**Cd (n=232)**	**Bd (n=232)**	**DBd (n=141)**	**Bd (n=70)**
Follow up	72.9 months		44 months		25.1 months	
Median (95% CI)	NE (59.7, NE)	47.0 (32.6, 58.7)	51.3 (NR, NR)	43.7 (NR, NR)	NR	NR
HR (95% CI) p value	0.56 (0.39, 0.80) 0.0013		0.771 (0.583, 1.018) NR		[redacted] NR	

Cd = carfilzomib and dexamethasone; CI = confidence interval; Bd = bortezomib in combination with dexamethasone; DBd = daratumumab in combination with bortezomib and dexamethasone; HR = hazard ratio; NR = not reported; PFS = progression-free survival

Table 12. DBd vs Bd pooled meta-analysis results

Outcome	Studies	Comparison	Effect	HR (95% CI)	Qpval	I^2	tau
OS	CASTOR, LEPUS	DBd vs Bd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PFS	CASTOR, LEPUS	DBd vs Bd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

CI = confidence interval; Bd = bortezomib in combination with dexamethasone; DBd = daratumumab in combination with bortezomib and dexamethasone; HR = hazard ratio; OS = overall survival; PFS = progression-free survival

Table 13. Updated PFS and OS NMA results to include LEPUS trial

	DBd vs. Bd	DBd vs. Cd
PFS HRs [95% CrIs] (probability of DBd being better than comparator)		
Previously submitted results using data from ENDEAVOR and CASTOR	[redacted]	[redacted]
Sensitivity analysis using data from ENDEAVOR, CASTOR and LEPUS [fixed effects]	[redacted]	[redacted]
Sensitivity analysis using data from ENDEAVOR, CASTOR and LEPUS [random effects]	[redacted]	[redacted]
OS HRs [95% CrIs] (probability of DBd being better than comparator)		
Previously submitted results using data from ENDEAVOR and CASTOR	[redacted]	[redacted]
Sensitivity analysis using data from ENDEAVOR, CASTOR and LEUPUS [fixed effects]	[redacted]	[redacted]

Cd = carfilzomib and dexamethasone; CrI = credible interval; Bd = bortezomib in combination with dexamethasone; DBd = daratumumab in combination with bortezomib and dexamethasone; HR = hazard ratio; OS = overall survival; PFS = progression-free survival

A8. Was simulated treatment comparison considered as an alternative to the MAIC? Please present the results if conducted or the rationale for not conducting.

Regarding the comparison between CASTOR and ENDEAVOR, an NMA was found to be the best approach given the availability of trial data and similarities between the two studies. Considering the comparison between DBd in CASTOR and DBd in the SACT database, neither MAIC nor simulated treatment comparison (STC) was appropriate given the limited data available from SACT. Janssen attempted to perform MAIC and reported results for overall survival, however due to major limitations of the analysis there is strong rational for not considering such analyses in the future. For more details, please see Section B1.

The implementation of STC requires derivation of a predictive equation using parametric survival methodology. The development of an equation would require substantially more information than available and reported in the final SACT report[14]. In addition, the implementation of an unanchored STC would require simulation of comparator-like trial data (since pseudo-IPD must be used for predicting OS and PFS in the comparator-like population). This is because the efficacy outcomes of interest are non-linear (i.e., OS and PFS are survival outcomes) and the impact of performing an unanchored indirect comparison on a different scale than that of the linear predictor introduces extra complexities with unknown impact on bias (see NICE DSU TSD 18, sections 2.3.2 and 2.3.3). Consequently, estimation of the standard errors of the effect estimates using bootstrapping techniques would be required.

Given this, and whilst acknowledging the limitations of the MAIC methodology, Janssen does not consider STC as a suitable alternative method.

A9. Priority question. Please provide a comparison of baseline characteristics of CASTOR and SACT post-matching. Please also provide a plot of patient weights.

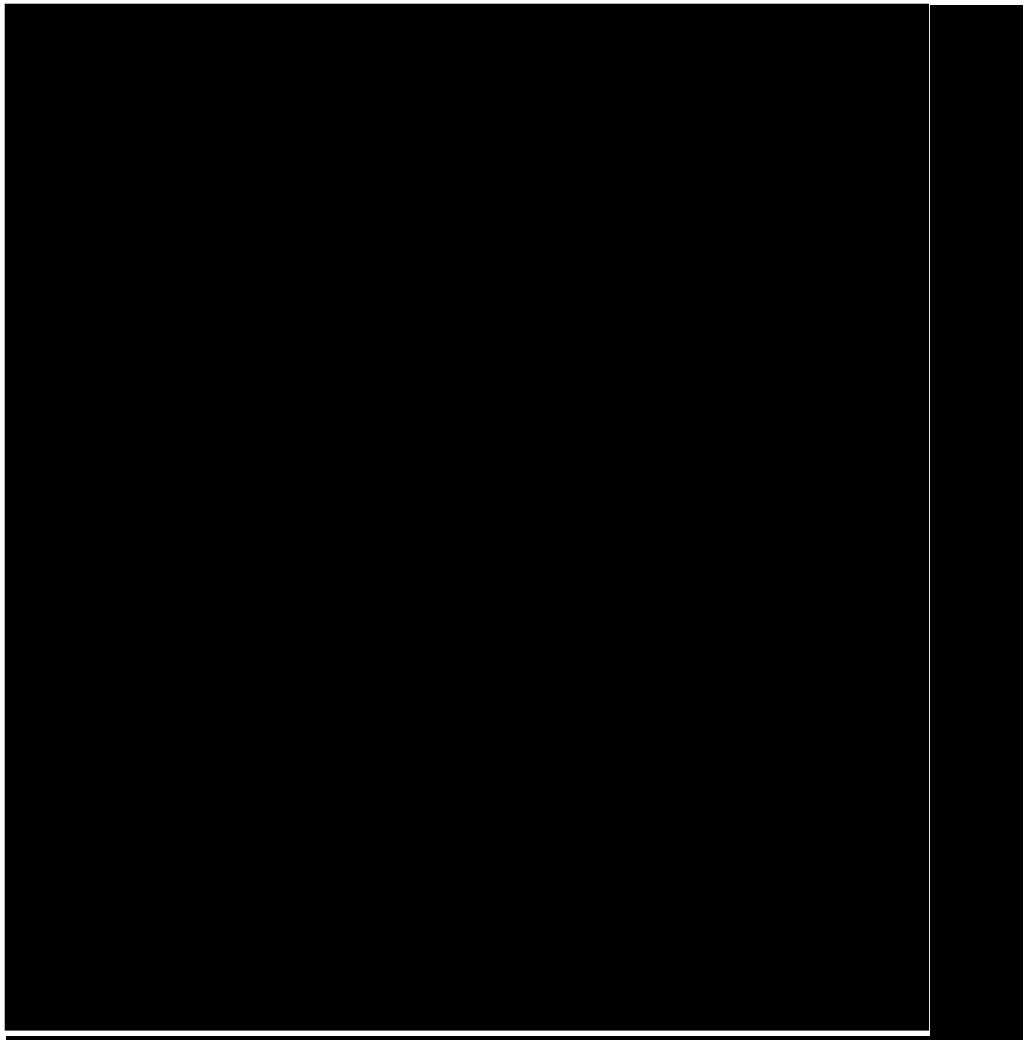
Baseline characteristics in CASTOR and SACT before and after matching are presented in Table 14. It should be noted that 23% of patients in the SACT dataset had missing ECOG performance status data. For the MAIC, it was assumed that the

missing data are random, and that the distribution of the observed patients was representative of the entire population. Histograms showing the patient weighting are shown in **Error! Reference source not found.**. As previously demonstrated in response to question A6, not all potential effect modifiers and prognostic factors are available for matching, hence a significant limitation to an unanchored MAIC as per DSU TSD 18. The DSU report states that during an unanchored MAIC all effect modifiers and prognostic variables should be adjusted for. Please see response to question A10 for further information.

Table 14. Baseline characteristics in CASTOR and SACT before and after matching for MAIC analysis[9]

-	[redacted]	[redacted]		[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]



A10. Priority question. It is unclear why the adjusted Kaplan Meier curve for CASTOR moves upwards following matching (Figure 19, document B). This appears counterintuitive given CASTOR appears to be in a healthier population than SACT (younger patients, more in ECOG 0). Please provide your rationale.

Janssen agrees that these results are counterintuitive and concludes that the unanchored MAIC of CASTOR versus SACT is fundamentally unreliable.

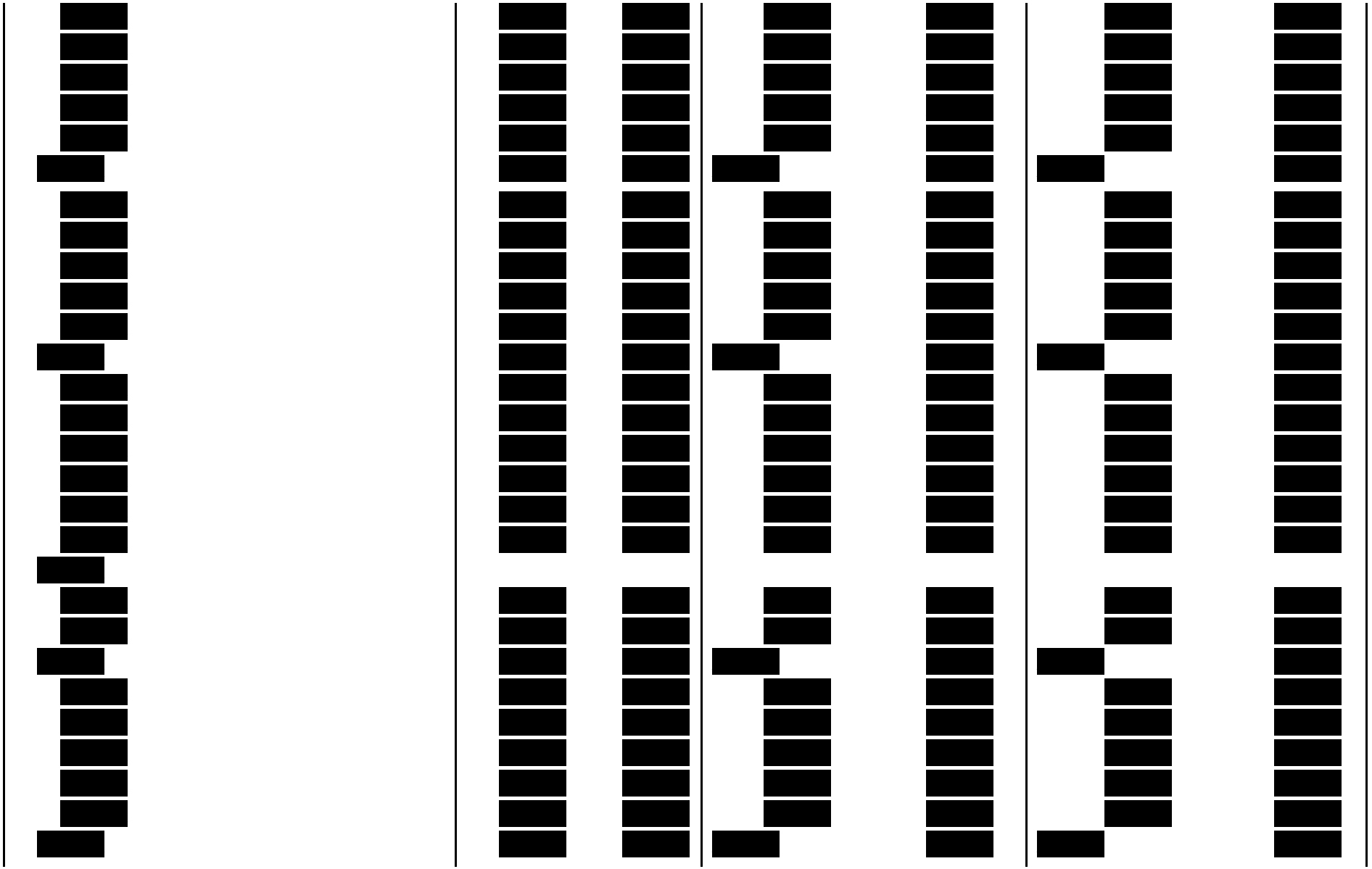
There are several limitations associated with the SACT data set including short median follow-up of only 7.4 months, progression-free survival not collected, and limited information regarding baseline patient and disease characteristics. As stated in DSU TSD 18, during an unanchored MAIC all effect modifiers and prognostic variables should be adjusted for. This is not the case for SACT where data on many baseline characteristics is missing, with corresponding impact on the robustness of any MAIC. Therefore, whilst Janssen explored a matching-adjusted indirect comparison (MAIC) of DBd from SACT versus DBd from CASTOR to inform generalisability of the trial evidence, the results remain highly uncertain and not robust as it was not be possible to adjust for all important prognostic markers and treatment effect modifiers. Furthermore, differences in study design could bias the results. These limitations preclude a meaningful unanchored MAIC analysis between data from CASTOR and SACT.

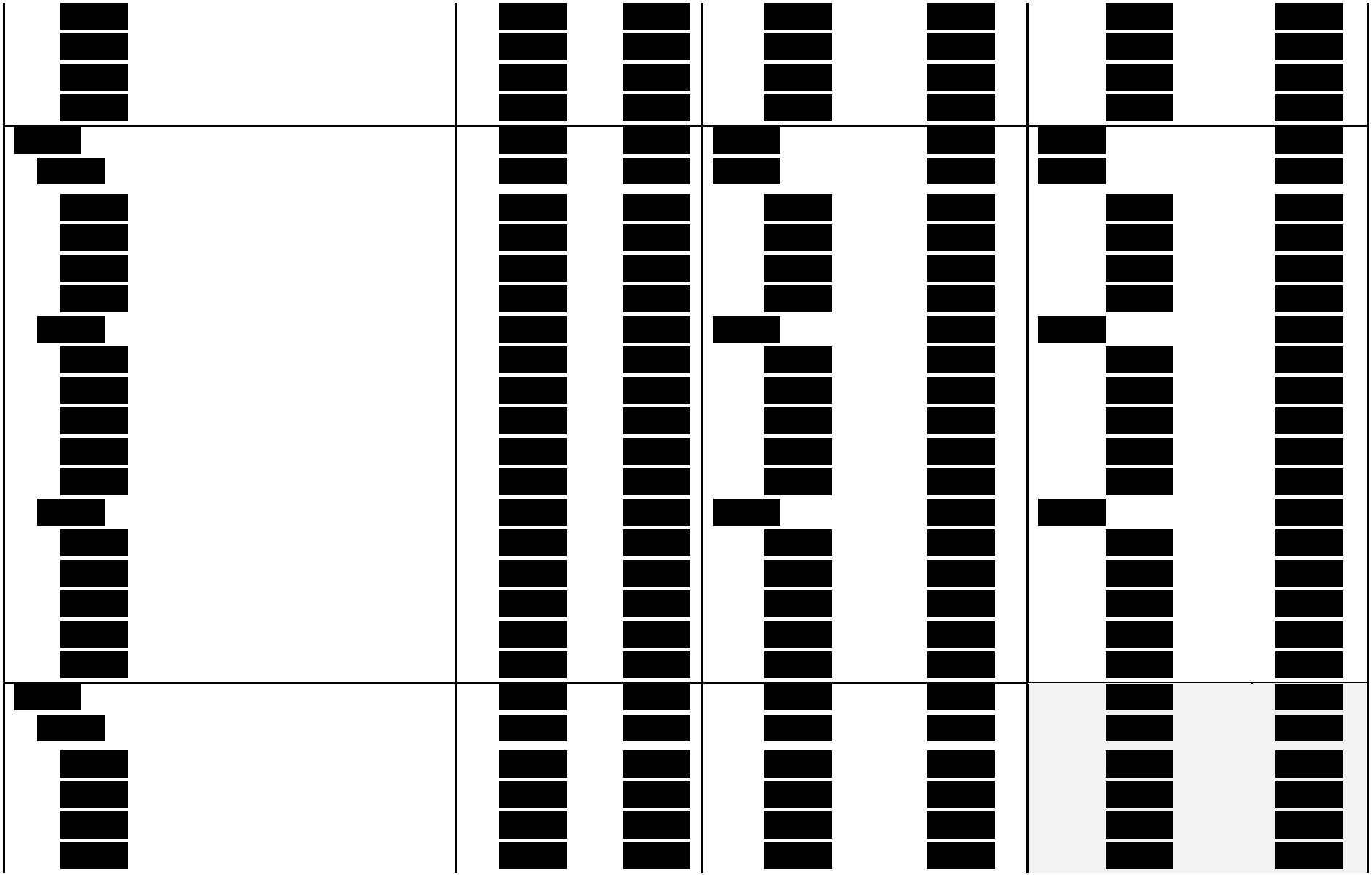
NHS Digital NDMM Standing Cohort Study

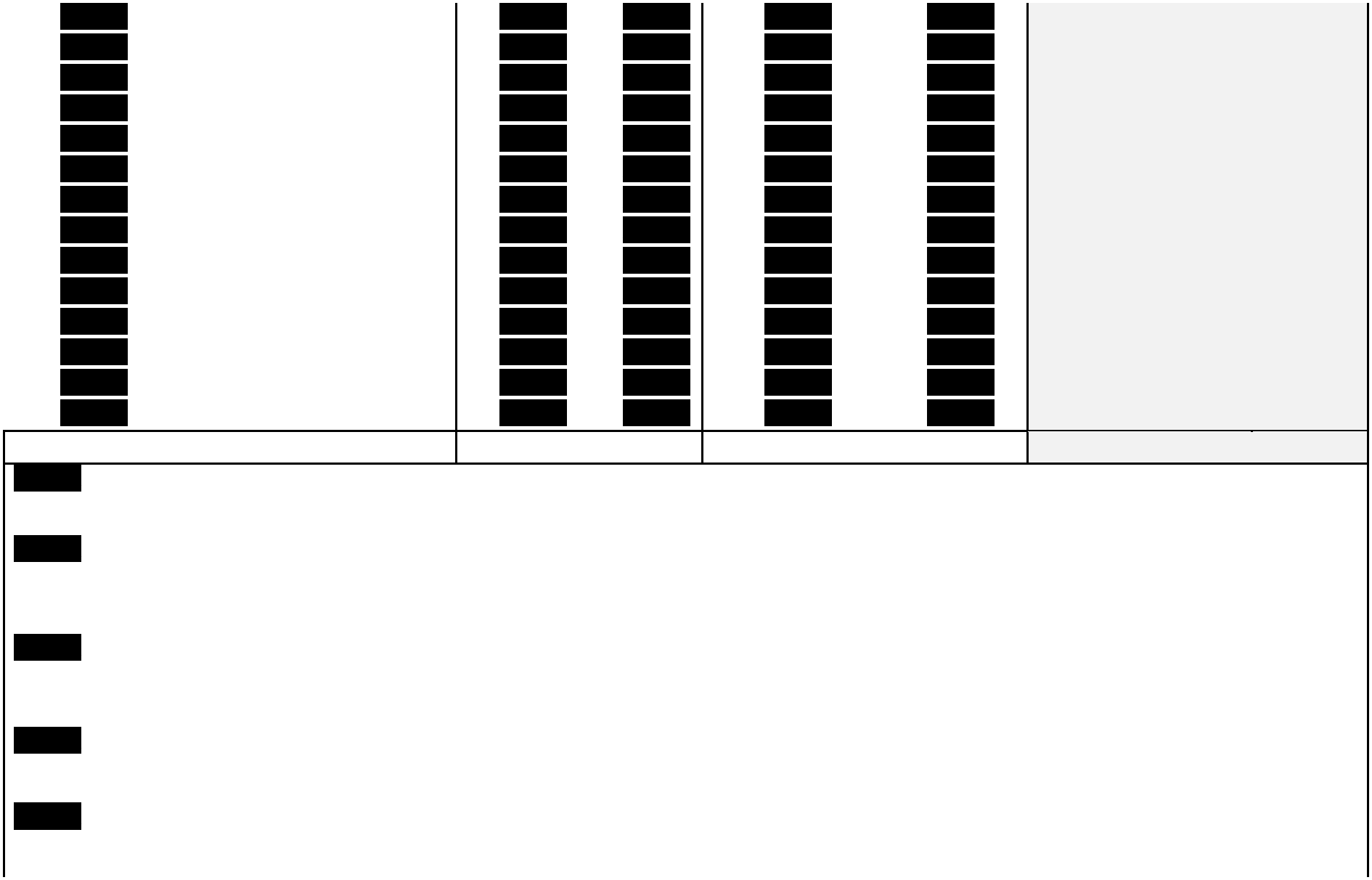
A11. Priority question. The reference for the NHS Digital NDMM Standing Cohort Study (NHS NCRAS_standing cohort.pdf) states that results and figures are contained in Excel tables that accompany the report. The reference 121.2022-05-17 NDMM results tables, report five (an excel spreadsheet) does not appear to contain all the tables from this report.

a) Please provide a table of the baseline characteristics of participants in the NDMM cohort study.

Please see Table 15 below for a summary of baseline characteristics for newly diagnosed patients stratified by transplant-eligibility from the NDMM Standing Cohort Study.







[redacted]

b) If available please provide PFS estimates in this cohort.

No variable is reported in SACT for determining lines of treatment, nor indicators of disease progression. As such, the NDMM Standing Cohort Study did not report PFS outcomes but rather analysed time-to-next-treatment (TTNT) as a proxy measure. Refer to Table 16 for a summary of front-line TTNT survival rates at 24-months stratified by transplant eligibility.

Table 16. Time-to-next-treatment for NDMM patients stratified by transplant eligibility

	ASCT-positive (%, 95% CI)	**ASCT-negative**
Survival at 24-months*	[redacted]	[redacted]

* TTNT calculated using the Kaplan-Meier estimator from the initiation of first-line therapy to death, censoring or the start of a new treatment line, whichever came first.

In the absence of robust and routinely recorded data concerning lines of therapy and disease progression, the NDMM Standing Cohort Study used a regimen- and cycle-based algorithm to derive lines of treatment. The analyses therefore relied upon a series

of predefined rules and there is a risk that some patients may be misclassified. As such, Janssen consider that the results should be interpreted with caution. Further rationale is provided in response to question A13.

A12. Priority question. The company provide the OS rate at 24 months for Dbd in the 1PL population for transplant-ineligible patients who did not receive daratumumab during their course of treatment.

a) Please can the company provide this outcome for transplant-eligible patients?

In the company submission, Janssen compared the OS rate at 24-months from SACT [redacted] versus front-line outcomes for transplant-ineligible patients who did not receive daratumumab during their course of treatment from the NDMM Standing Cohort Study ([redacted]

b) **If available please pr**ovide Kaplan-Meier plots of the OS data.

Please refer to Figure 2. for a comparison of front-line OS outcomes from the NDMM Standing Cohort Study for patients that received/did not receive an autologous stem cell transplant (ASCT) as initial therapy.

A13. Priority question. On page 12 of the cited reference 71 “NHS NCRAS_standing cohort.pdf” it states that OS and TTNT are reported separately for patients who received one of 12 listed options, two of these options being bortezomib and dexamethasone at 2L and carfilzomib and dexamethasone at 2L. Please provide these data.

The NDMM Standing Cohort Study was commissioned by Janssen in 2019 to identify a cohort of newly diagnosed multiple myeloma (NDMM) patients within NHS Digital (formerly, Public Health England) cancer and linked datasets. The aim was to follow the cohort over time to better understand the disease and treatment pathway, along with survival outcomes stratified by transplant-

eligibility. As an exploratory (non-prespecified) analysis, Janssen subsequently sought to understand survival outcomes for second-line patients however there are important limitations associated with such analysis.

As per our response to 11b above, analysis of second-line patients requires derivation of data items not routinely available within SACT. Derived data items are approximations of real-world data and may be subject to misclassification error with this risk exacerbated due to known issues with the quality of systemic treatment data submitted by NHS Trusts. Summarised below, these issues impact upon the ability to accurately derive lines of systemic treatment and disease progression:

- Missing cycles: there are instances where no cycle or only a single cycle is recorded within a treatment regimen;
- Split cycles: there are instances where each cycle within a regimen is incorrectly recorded under separate regimens;
- Merged regimens: there are instances where drugs that should form separate regimens are incorrectly listed under a single regimen.

Moreover, baseline characteristics for second-line patients are not available from the NDMM Standing Cohort Study. As such, any comparison is susceptible to bias due to the impact of confounding factors including age, ISS disease staging, cytogenetic risk, refractory status and the extent of any pre-existing comorbidities which have not been adjusted when conducting the univariate stratified Kaplan-Meier analysis. This limitation of RWE is acknowledged by the NICE real-world evidence framework[13] which recognises randomised controlled trials as the preferred source of evidence on the effects of interventions.

Given the limitations, and median follow-up of less than 24-months, Janssen considers it neither 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. This is particularly true in the context of this appraisal with over 6-years median follow-

up from CASTOR, a phase III randomised controlled trial against the directly relevant active comparator Bd, and the Primary source of data collection per the Managed Access Agreement[13].

Section B: Clarification on cost-effectiveness data

SACT dataset

B1. Priority question. The company make the case that SC administration for daratumumab is routine practice across the UK. Please could the company explain why [redacted], was this a condition of the Managed Access Agreement?

At the time of the recommendation to include DBd on the Cancer Drugs Fund (CDF) in 2019 daratumumab could only be administered intravenously, however, as discussed in CS B.2.12.3 Subcutaneous formulation of daratumumab, subcutaneous daratumumab was approved in June 2020. It is our understanding based on the feedback received during the clinical advisory board conducted by Janssen in 2022 that most patients switched to subcutaneous administration which is currently dominantly used in clinical practice over IV. The process of switching was expedited due to the significantly reduced time patients needed to spend in hospitals during the COVID-19 outbreak (please see CS B.3.10 Benefits not captured in the QALY calculation).

The term “intravenously” was included in the description by mistake (CS page 37), the SACT report does not mention any requirements about the route of administration of daratumumab. The exact wording in the report is: “The dosage schedule of daratumumab will be for weekly treatment given weeks 1-9 (a total of 9 doses), 3-weekly treatment in weeks 10 to 24 (a total of 5 doses) and 4-weekly treatment from week 25 onwards.”

B2. B.2.3.8 SACT study methodology

a) How many patients had interim ixazomib with lenalidomide and dexamethasone as a second-line therapy during the covid-19 pandemic. Are these patients included in the SACT dataset (if so, they received DBd as their 3rd therapy?).

Although, based on the report provided with the analysis, patients were allowed to receive ixazomib with lenalidomide and dexamethasone (ILd) in which case DBd could be administered in third line, the number of patients included based on this rule was not presented.

Janssen reviewed market share data available through IPSOS (Ipsos Healthcare Cancer Therapy Monitor – UK) and HARMONY market research data[18] which both show that ILd use exceeded 10% from 2020 in the 1 prior line setting and peaked at approximately 15% in Q1 of 2021. In these cases, DBd could be administered in 3rd line which includes additional bias and uncertainty around the generalizability of the SACT data to the second line population. SACT results may therefore underestimate DBd efficacy at 2L due to high usage at later lines, not fully generalisable to a 2L population.

NHS England (NHSE) could potentially provide details about the exact number of patients receiving ILd in the 1 prior line setting between 2019 and 2021.

b) Did the company apply any eligibility criteria additional to those listed on CS p.37 to select patients from the dataset supplied by NHS Digital England? If so, please explain these.

Company does not have access to patient level data used to conduct the analysis. All the inclusion criteria described in the report by National Disease Registration Service (NDRS) were reported in CS. We would like to clarify that the language that states that daratumumab was administered intravenously on page 37 of the CS was included incorrectly, no mention of route of administration is presented in the report by NDRS (please see B1 Priority question).

B3. Priority question. The company point out (B.2.14) that "in clinical practice bortezomib is often administered once weekly up to a maximum of 32 doses to reduce AEs, while in CASTOR bortezomib was administered more frequently according to its marketing authorisation (twice weekly for a maximum of 8 cycles)". What contribution does the company think this may have made to the difference between OS outcomes for the CASTOR and SACT datasets as shown in Figure 19?

Based on the feedback from clinical experts during the clinical advisory board conducted by Janssen in 2022 clinicians prefer to use once weekly bortezomib to minimize adverse events that could result in treatment discontinuation. To our knowledge there is variation in the use of bortezomib across practices in terms of frequency of administration, however clinical experts did not discuss that the efficacy of once weekly bortezomib would be dependent on the frequency of administration.

Furthermore, as presented in CS Section Extrapolation of Cd PFS (page 99), Janssen highlighted the importance of cumulative dose which was recognised in a retrospective analysis of the VISTA study that found a higher cumulative Bd dose was associated with significantly increased OS compared with a low cumulative Bd dose (age-adjusted HR, 0.561; p=0.00002)[17]. Regardless of the number of administrations per week bortezomib is administered to a maximum of 32 administrations both in CASTOR and clinical practice which would result in similar cumulative doses, hence it is expected that outcomes would be also similar.

In conclusion, we acknowledge the different dosing schedule in CASTOR vs SACT, however it is very difficult to interpet impact of this, given the limitations of the SACT data reported.

B4. Priority question. In CS Figure 19 the company provides a comparison of the DBd OS data from CASTOR (1PL population) versus SACT (MAIC).

- ***Please also provide a comparison of the Bd OS data from CASTOR (1PL population) versus SACT (MAIC).***

As per NICE DSU TSD 18, a robust unanchored MAIC requires that all effect modifiers and prognostic factors are accounted for[16]. The final SACT report, however, only reported limited information regarding key baseline patient and disease characteristics and excluded important prognostic variables including ISS disease staging and refractory status. In addition, any unreported or unobserved confounding factors that were not accounted for in the adjustment may lead to bias in the MAIC analysis. Combined, these limitations contributed to counterintuitive results for the comparison of DBd OS data from CASTOR versus SACT (refer to Company submission Section B.2.10.5 and response to clarification question A10). Given the known limitations of the SACT dataset, Janssen does not consider it appropriate to perform an unanchored MAIC to compare Bd OS data from CASTOR which would be subject to an unknown level of bias.

a) The company make the case that "<u>although absolute differences exist between CASTOR and SACT, the relative benefit observed in CASTOR is likely to hold in the real world</u>". Please would the company use the relative benefit from CASTOR to create a simulated Bd dataset from the SACT DBd data and plot this on CS Figure 19. Please comment on the clinical plausibility of this simulated Bd data.

Whilst Janssen acknowledge the important role of real-world evidence to support healthcare decision making, the NICE real-world evidence framework states that randomised controlled trials are the preferred source of evidence on the effects of interventions[13]. The phase III CASTOR study comparing DBd against the directly relevant active comparator, Bd, was also recognised as the primary source of data collection in the Data Collection Arrangement for TA573.

There are significant challenges associated with simulating a comparable Bd curve from the DBd SACT dataset. Such analysis would, for example, be susceptible to selection bias if the patients treated with DBd are not representative of patients that would otherwise be treated with Bd in clinical practice. Bias could also arise if DBd patients in SACT were treated at a later line due to the interim COVID guidelines permitting treatment of ixazomib with lenalidomide and dexamethasone as a second-line therapy (refer to clarification question B1.a). Applying the OS hazard ratio from CASTOR to the DBd SACT data also relies on proportional hazards, however scrutiny of the OS hazard curves from CASTOR provided clear evidence of violation of the proportional hazards assumption between treatment arms (refer to Company submission Section B.3.3.1.2). Finally, OS data from SACT is considered immature with [redacted] months median follow-up and [redacted] events compared to over 6-years and 45% events from CASTOR.

In summary, Janssen does not consider it methodologically appropriate to perform the requested analysis.
Please conduct a scenario using the DBd data from SACT.

Janssen does not consider it methodologically appropriate to naively compare trial versus real-world outcomes. As such, in the absence of SACT data collected for comparator treatments including Bd and Cd, we have not conducted a scenario analysis using DBd data from SACT.

Due to the significantly shorter follow-up, use of SACT data would also substantially increase the magnitude of uncertainty in the economic model and is therefore inappropriate where over 6 years of comparative RCT follow-up data is available. Janssen's approach is also consistent with the Data Collection Arrangement for TA573 which recognised CASTOR as the primary source of data collection and Public Health England's routine population-wide cancer data sets, including SACT, as the secondary source of data collection for this submission.

Replication of model results

B5. Priority question. Replication of model results.

a) Please include a model functionality in the current company's excel model that can replicate the ICERs used in the committee's decision making at the point of CDF entry.

Functionality was added to the excel model to include inputs used in the original submission. The inputs were extracted from the following model version: "ID974_daratumumab_ERG analysis_no PAS ACiC_Revised Base Case 2Aug2018_NoPAS.xlsm".
To automatically update the current model version with the original inputs select "Original" from the options in the dropdown in range "input.old.new.selection" on the Settings sheet. In addition, navigate to the "Scenarios" sheet and select the button "Reset".

From the options in the pop-up window select “Original inputs”. Resetting of inputs may take a couple of minutes, please wait until the model is fully executed (indicated by a progress bar).

There are minor differences between the results using the original versus the updated model due to the following reasons (see Table 17 for model results, differences are highlighted in bold text):

- Only IV daratumumab was included in the original model versus subcutaneous daratumumab in the new model. There is approximately £300 difference in the cost of treatment per admin making the subcutaneous daratumumab administrations cheaper. In addition, IV administration is more expensive than subcutaneous regardless of the treatment selected
- Since daratumumab monotherapy was included as a subsequent treatment option the treatment cost and amin unit cost difference of IV vs subcutaneous daratumumab also results in slight differences in subsequent treatment costs
- The application of blood type testing was corrected in the updated model, hence there is a slight difference compared to the original

Table 17. Comparison of Results (Updated Model vs Original Model)

	Updated model – original inputs			Original model - original inputs		
Health Outcomes (discounted at 3.5% per year)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Life-years (LY) accrued	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LYs accrued: Progression Free Survival	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LYs accrued: Post Progression Survival	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Quality adjusted life-years (QALY) accrued	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs accrued: Progression Free Survival	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs accrued: Post progression Survival	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

QALYs accrued: Adverse Events	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost Outcomes (discounted at 3.5% per year)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PFS Drug Cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PFS Administration Cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PFS Co-medication Cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PFS Medical Resource Use	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PPS Subsequent Treatment Drug Cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PPS Medical Resource Use	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adverse Event Cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Terminal Cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total Cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

b) Please present a summary of the step-by-step changes made by the company to the CDF entry model in order to obtain the company's current CDF review model with ICER of £[redacted].

Please see attached file for the list of changes.

TA573 - Change log 17Sept2022.docx

HRQoL

B6. Did the company collected any data on HRQoL in CASTOR to update the utilities for pre- and post-progression health states used in the original submission? If yes, can you please provide the updated utilities?

Data on HRQoL was collected in pre- and post-progression beyond the original submission, however they were not updated. The reason for this is that the key issue, i.e., face validity of post-progression utility was assumed not to change with the additional follow-up as the frequency of data collection did not change in CASTOR (done twice, at 8 and 16 weeks beyond progression). Janssen is 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.

Model clinical inputs

B7. CS Table 30 and Table 39 versus company's excel model Sheet!NMA results.

a) **Please clarify that in the company's excel model Sheet!NMA results, the cells in AB19 and AK18 are "CI High" and cells in AW19 and BF19 are "CI Low". This is inconsistent with the values reported in CS Table 30 and Table 39.**

The low and high values in the excel model have been swapped. The values have been corrected in the updated model version which have no impact on the base case results. Updated sensitivity analysis is presented in **Figure** .

b) **In CS Table 30, the high CI of HR for DBd vs Bd for PFS is reported 0.30 whereas the excel model in Sheet!NMA cell AW27 reports 0.31. Please clarify the inconsistency.**

The correct value is 0.306 which is the value included in the excel model.

B8. CS Table 54: the EAG is unable to locate the percentage of patients for DBd and Bd continuing on subsequent treatment from the pdf for reference 76. Please provide the appropriate reference containing these details and indicate where in the reference the values in Table 54 can be found.

We apologize for referencing the incorrect document. The derivation of proportion of patients was carried out as part of the trial data analysis conducted for the submission, therefore the correct reference is Janssen, data on file. Please see the number of patients who experienced progression and a subset of patients who received further treatments in the table below.

Table 18. Proportion of patients receiving subsequent treatment

Treatment	No. progressed	% Progressed	No. received subsequent therapy	% Received subsequent therapy
DBd	78	64%	68	87%
Bd	93	82%	87	94%

Bd = bortezomib and dexamethasone; DBd = daratumumab in combination with bortezomib and dexamethasone

B9. Adverse events. CS Table 45 excludes 'fatigue' as one of the adverse events for Bd and Cd but it is included in the excel model Sheet!Adverse events. Please explain this inconsistency.

CS Table 45 incorrectly excluded 'fatigue' as both CASTOR and ENDEAVOR reported relevant data. The excel model included rates correctly. Please see corrected table below.

Table 19. Cumulative probability of AEs during treatment period - Corrected

Adverse Event	DBd	Bd	Cd
Neutropenia	13.1%	3.6%	0.9%
Anaemia	13.1%	9.0%	12.9%
Thrombocytopenia	13.8%	20.7%	6.5%
Lymphopenia	5.0%	3.6%	4.3%
Pneumonia	2.7%	9.0%	6.5%
Fatigue	**–**	**4.5%**	**6.0%**
Peripheral neuropathy	0%	6.3%	2.2%
Hypertension	3.1%	0.0%	10.3%
Source	COLUMBA SC arm	CASTOR – 1PL - Final OS analysis	ENDEAVOR

AE = adverse event; Bd = bortezomib and dexamethasone; Cd = carfilzomib and dexamethasone; DBd = daratumumab, bortezomib and dexamethasone.

Costs

B10. Please explain the following inconsistencies:

a) In CS Table 48 and Table 55, the price of dexamethasone is reported as £120.01 but in the excel model Sheet!Medical Cost- Drug cellF39 the price used is £200.

We were not able to identify the input in the excel model as Sheet!Medical Cost- Drug cellF39 refers to the cost of lenalidomide. The cost of dexamethasone in the model is included in Sheet!Medical Cost- Drug cellF40 as £120.01 as reported in Table 48 and Table 55 in CS.

b) In CS Table 50, the cost of IV administration is reported as £438.378 but the National Reference costs 2020-21 report a unit cost of £471 for SB15Z.

The input selected for the base case analysis in CS assumes that patients would receive IV administration in an outpatient setting. This was a conservative approach as a higher IV unit cost would increase the total cost of carfilzomib treatment therefor making daratumumab an even more cost-effective option. The model has been updated with the IV unit cost of £471, the results are presented in Table 20.

Table 20. SB15Z Cost of IV administration

Currency Code	Service Description	Activity	National Average Unit Cost
SB15Z	Total	251,735	£ 471
SB15Z	Daycase and Reg Day/Night	191,524	£ 481
SB15Z	Outpatient	59,597	£ 438
SB15Z	Other	614	£ 477

c) In CS Table 50, the cost of oral drug initiation is reported as £215.80 but the National Reference costs 2020-21 report a unit cost of £245 for SB11Z.

Oral treatment initiation was assumed to be handled in an outpatient setting as 67% of the activity was reported to be outpatient service. This cost is assigned to all regimens included in the analysis therefore the impact of updating the input is minimal. Similarly, to B10b, results were updated using the recommended unit cost of £245 per initiation of oral administration.

Table 21. SB11Z Cost of oral administration

Currency Code	Service Description	Activity	National Average Unit Cost
SB11Z	Total	203,703	£ 245
SB11Z	Daycase and Reg Day/Night	67,164	£ 305
SB11Z	Outpatient	136,230	£ 216
SB11Z	Other	309	£ 308

B11. CS Table 52 Co-medications

a) Please provide the sources (including appropriate weblinks) from the MIMS UK Drug database for the specific unit costs of the following co-medications used in the model:

Source links for the selected co-medications included in the analyses are provided in the below table. Costs were updated where required due to changes in the costs since the initial input extraction.

Table 22. Co-medication Unit Costs and Source Links

Co-medication	Unit cost	Source Link
Prednisolone PO	£6.19	Link
Paracetamol (acetaminophen)	£3.78	Link
Diphenydramine	£4.72 (updated cost)	Link
Saline solution	£15.36	Link
Thromboprofilaxis (LMWH)	£22.70	Link
Laxatives	£2.68 (updated cost)	Link

b) The EAG noted inconsistencies in the prices of the following co-medications as reported in MIMS UK Drug Database. Please clarify:

Table 23. Co-medication Unit Costs

Co-medication	CS	EAG
Acyclovir	£2.55	£2.66
Domperidone	£2.43	£2.23

The model was updated with the unit costs referenced by the EAG. The results incorporating the correction are presented in **Table 27**.

B12. CS Table 55: the price of lenalidomide is stated as £3057.60 but EAG identified the cost for £25mg white cap, 21 as £4368.00 from the MIMS UK Drug Database. Revlimid | MIMS online Please clarify this inconsistency.

The CS incorrectly referenced the MIMS UK Drug Database as the correct source for the cost of lenalidomide is the British National Formulary (BNF). While Revlimid (lenalidomide) and Velcade (bortezomib) are both used in clinical practice, both drugs are available in generic form from multiple manufacturers, therefor the lowest available prices were selected for these drugs (see bolded rows in table below).

Table 24. Source of bortezomib and lenalidomide cost inputs

Description	Quantity	NHS Indicative Price	Manufacturer
Bortezomib 3.5mg powder for solution for injection vials - 3.5 mg	1 vial	£762.38	(Aspire Pharma Ltd); (Dr Reddy's Laboratories (UK) Ltd); (Pfizer Ltd); (Janssen-Cilag Ltd)
Bortezomib 3.5mg powder for solution for injection vials - 3.5 mg	1 vial	£648.02	(Sandoz Ltd); (Viatris UK Healthcare Ltd)
Bortezomib 3.5mg powder for solution for injection vials - 3.5 mg	**1 vial**	**£533.67**	**(Zentiva Pharma UK Ltd)**
Bortezomib 3.5mg powder for solution for injection vials - 3.5 mg	1 vial	£724.38	(medac UK)
Lenalidomide 25mg capsules	21	£3712.80	(Sandoz Ltd)
Lenalidomide 25mg capsules	21	£3931.20	(Teva UK Ltd)
Lenalidomide 25mg capsules	21	£4368.00	(Thornton & Ross Ltd)
Lenalidomide 25mg capsules	**21**	**£3057.60**	**(Zentiva Pharma UK Ltd)**

Source: British National Formulary (BNF) - (Hospital only)

B13. CS Table 56

a) Please provide the cost codes for the costs included in CS Table 56.

Please see costs codes and associated assumptions in the below table.

Table 25. Medical resource use cost codes

Costs	Cost code	Assumption
Haematologist	DAPS05	n/a
Biochemistry	DAPS04 - Clinical Biochemistry - U&E (5 Tests: Bicarbonate, Chloride, Potassium, Sodium, Urea)	Cost calculated as 5 times the cost of DAPS04 – consistent with the original submission
Protein electrophoresis	DAPS04 - Clinical Biochemistry	n/a
Immunoglobin	DAPS04 - Clinical Biochemistry	n/a
Urinary light chain excretion	DAPS04 - Clinical Biochemistry	n/a
Renal function test	DAPS04 - Clinical Biochemistry - 10 Tests: Albumin, Calcium total, Carbon dioxide (bicarbonate), Chloride, Creatinine, Glucose, Phosphorus inorganic (phosphate), Potassium, Sodium, Urea nitrogen (BUN)	Cost calculated as 10 times the cost of DAPS04 – consistent with the original submission

b) Please also explain the inconsistencies in the prices of Haematologist and biochemistry (as shown in the table below).

The cost of haematologist visit was incorrectly sourced using 'Clinical Haematology' in Sheet and cell OPROC!F9061. The updated results incorporating the correction are presented in Table 27. The cost of biochemistry was assumed to be 5 times the cost of DAPS04, which approach is consistent with the one presented in the original submission (please see table above).

CS Table 56: Unit costs of routine follow-up care use pre-progression

Costs	CS	EAG	EAG source
Haematologist	£217.80	£221.55	WF01D (NHS Ref cost Sheet!CL cellE501)
Biochemistry	£9.25	£1.85	DAPS04
Protein electrophoresis	£1.85		Please provide the cost code
Immunoglobin	£1.85		
Urinary light chain excretion	£1.85		
Renal function test	£18.50		Please provide the cost code

B14. CS Table 58. Please provide the NHS reference costs 2020-21 cost codes for all the AEs listed in this table.

Please see below the cost codes used to calculate adverse event management costs. All costs are based on weighted average costs using finished consultant episodes (FCE).

Table 26. NHS reference costs 2020-21 cost codes for adverse events

Adverse event	Cost code
Neutropenia	SA35 - Agranulocytosis
Anaemia	SA09 - Other Red Blood Cell Disorders (Includes: D63.0 Anaemia in neoplastic disease)
Thrombocytopenia	SA12 - Thrombocytopenia
Lymphopenia	SA08 - Other Haematological or Splenic Disorders
Pneumonia	DZ11 - Lobar, Atypical or Viral Pneumonia
Fatigue	WH17 - Admission Related to Social Factors (Includes: R53.X Malaise and Fatigue)
Peripheral neuropathy	AA26 - Muscular, Balance, Cranial or Peripheral Nerve Disorders, Epilepsy or Head Injury
Hypertension	EB04 - Hypertension

B15. Model cell 'Drug Cost Calculations'!CP13 states that the first administration cost for daratumumab and DBd includes the cost of blood type determination. Can you please clarify if this was included in the first administration cost of daratumumab and DBd and how?

The cost of blood type determination has been included as weekly recurring costs incorrectly following treatment with daratumumab (range MRUCostPerWeek.PFS row 1). A correction has been made to only include blood type determination once at treatment initiation (please refer to ='Model Engine'!BM22 in the excel model). The results incorporating the correction are presented in Table 27.

B16. Can you please clarify why you have not included the cost of oral administration to the cost of DBd as you have done for Bd and Cd arms? (please see model cells 'Drug Cost Calculations'!CQ14:CS14).

The cost of oral treatment initiation was mistakenly omitted from the calculations of daratumumab administration costs (both in combination with bortezomib and monotherapy). Furthermore, the cost of 1st administration was also incorrectly calculated using IV administration (both in combination with bortezomib and monotherapy) instead of SC admin. Both corrections were made in the excel model. The results incorporating the correction are presented in **Table 27**.

Model baseline characteristics

B17. The excel model cites the subgroup of population receiving 1 prior therapy in CASTOR to inform the estimates for proportion of males and females. Please clarify why the estimate of [redacted] from CS Table 12 (DBd arm) was not used?

We recognize the inconsistency in the use of inputs of patient characteristics included in the model. As much as possibly we prioritized using pooled values of the two treatment arms where appropriate which represent the overall population in CASTOR better. The input in the excel model was derived as the proportion of male patients in both DBd and Bd arms of the CASTOR trial instead of relying on the DBd arm only [redacted]. No changes were made to the model.

Section C: Textual clarification and additional points

C1. Please would the company confirm that mention of UK centres in Table 11 (Location row) is an error (in two other places, B.2.3.3 and B.2.5.2, the CS states there are no UK centres)

There are no UK study centres for CASTOR.[10] Study Centres are: Australia (7 sites), Brazil (6 sites), Czech Republic (4 sites), Germany (10 sites), Hungary (4 sites), Italy (12 sites), Korea (7 sites), Mexico (2 sites), Netherlands (8 sites), Poland (6 sites), Russian Federation (9 sites), Spain (6 sites), Sweden (7 sites), Turkey (7 sites), Ukraine (9 sites), United States of America (13 sites).[10]

C2. CS reference 92 should be the statistical analysis plan (SAP) for the CASTOR study but file 92.MMY3004_SAP.pdf is the protocol for CASTOR rather than the SAP (page 72 Section 11 "Statistical Methods" of the reference indicates that there should be a separate Statistical Analysis Plan). Please supply the SAP if possible.

The final SAP dated 2 November 2015 and Amendment 1 dated 2 March 2016 are enclosed.[11,12]

Updated Analysis

As a result of the initial review of the CS by the EAG, some of the clarification questions resulted in updates to the model inputs. Please refer to the following points above: B10b, 10c, B11a, B11b, B13b, B15 and B16. The updated analysis is presented in the section below. None of the corrections resulted in significant changes in the model outcomes, the base case ICER of DBd vs Bd slightly decreased from [redacted], while DBd dominates Cd.

Table 27. Updated base case results

Health Outcomes	DBd	Bd	Cd
LY accrued	[redacted]	[redacted]	[redacted]
LYs accrued: Progression Free Survival	[redacted]	[redacted]	[redacted]
LYs accrued: Post Progression Survival	[redacted]	[redacted]	[redacted]
QALY accrued	[redacted]	[redacted]	[redacted]
QALYs accrued: Progression Free Survival	[redacted]	[redacted]	[redacted]
QALYs accrued: Post progression Survival	[redacted]	[redacted]	[redacted]
QALYs accrued: Adverse Events	[redacted]	[redacted]	[redacted]
Costs			
PFS Drug Cost	[redacted]	[redacted]	[redacted]
PFS Administration Cost	[redacted]	[redacted]	[redacted]
PFS Co-medication Cost	[redacted]	[redacted]	[redacted]
PFS Medical Resource Use	[redacted]	[redacted]	[redacted]
PPS Subsequent Treatment Drug Cost	[redacted]	[redacted]	[redacted]
PPS Medical Resource Use	[redacted]	[redacted]	[redacted]
Adverse Event Cost	[redacted]	[redacted]	[redacted]
Terminal Cost	[redacted]	[redacted]	[redacted]
Total Cost	[redacted]	[redacted]	[redacted]

Bd = bortezomib and dexamethasone; Cd = carfilzomib and dexamethasone; DBd = daratumumab, bortezomib and dexamethasone; LY = life year; PFS = progression-free survival; PPS = post-progression survival; QALY = quality-adjusted life year.

Table 28. Updated incremental cost-effectiveness results

Incremental results	Bd	Cd
Incremental costs	[redacted]	[redacted]
Incremental QALYs	[redacted]	[redacted]
Incremental LY	[redacted]	[redacted]
Cost per QALY gained	[redacted]	[redacted]
Cost per LY gained	[redacted]	[redacted]

Bd = bortezomib and dexamethasone; Cd = carfilzomib and dexamethasone; LY = life year; QALY = quality-adjusted life year

The results of the one-way sensitivity analysis (**Figure** and **Figure**) and probabilistic sensitivity (**Table**, **Error! Reference source not found.** and **Error! Reference source not found.**) analysis remained consistent with the original outcomes. Updating the confidence intervals of the relative treatment effect of DBd vs Cd resulted in an increased impact of the OS hazard ratio which is currently listed as the 4th most influential model input when comparing DBd and Cd (**Figure**).

Figure 3. One-way Sensitivity Analysis Results (DBd vs Bd) - Updated

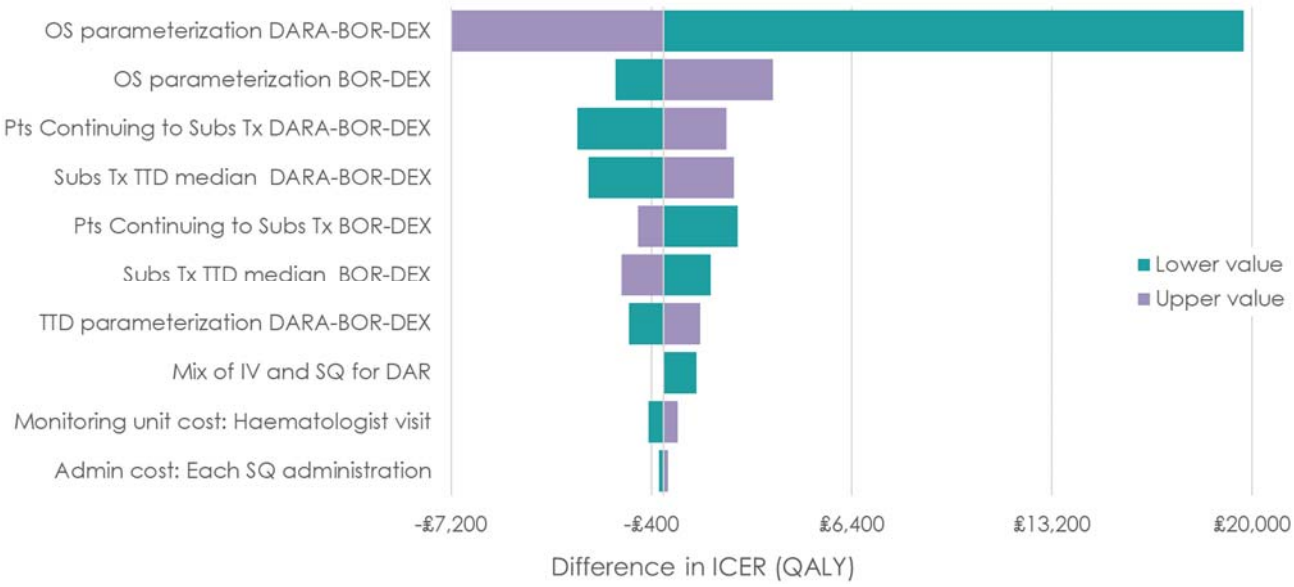


Figure 4. One-way Sensitivity Analysis Results (DBd vs Cd) - Updated

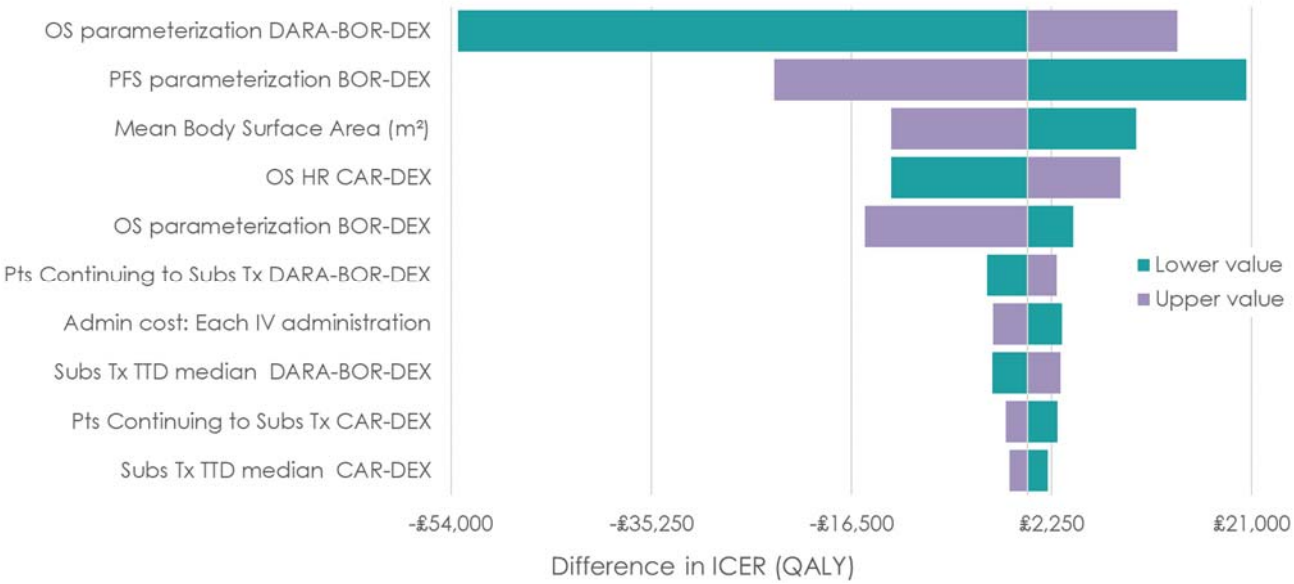


Table 29. Probabilistic Results - Updated

Comparator	Mean LY	Mean QALY	Mean Total cost	ICER
DBd	[redacted]	[redacted]	[redacted]	[redacted]
Bd	[redacted]	[redacted]	[redacted]	[redacted]
Cd	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

[redacted]

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Guidance review following a period of managed access - Patient organisation submission

Daratumumab with bortezomib and dexamethasone for previously treated multiple myeloma [ID4057]

Thank you for agreeing to give us your organisation's views on this treatment following a period of managed access. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

PLEASE NOTE: You do not have to answer every question. Your organisations involvement in the managed access agreement for this treatment is likely to determine which questions you can answer.

To help you give your views, please use this questionnaire with **NICE's guide for patient organisations "completing an organisation submission following a period of Managed Access for Technology Appraisals or Highly Specialised Technologies".** Please contact pip@nice.org.uk if you have not received a copy with your invitation to participate.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 20 pages.

NICE National Institute for Health and Care Excellence

This form has 8 sections

NICE National Institute for Health and Care Excellence

Section 1. About you

Table 1 Name, job, organisation

<table>
<tr><td>1. Your name</td><td>[redacted]</td></tr>
<tr><td>2. Name of organisation</td><td>Myeloma UK</td></tr>
<tr><td>3. Job title or position</td><td>[redacted]</td></tr>
<tr><td>4a. Provide a brief description of the organisation. How many members does it have?</td><td>Myeloma UK is the only organisation in the UK dealing exclusively with myeloma and its associated conditions. Our broad and innovative range of services cover every aspect of myeloma from providing information and support, to improving standards of treatment and care through research and campaigning. We are not a membership organisation and rely almost entirely on the fundraising efforts of our supporters. We also receive some unrestricted educational grants and restricted project funding from a range of pharmaceutical companies.</td></tr>
<tr><td>4b. Has the organisation received any funding from the company/companies of the treatment and/or comparator products in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list which was provided to you when the appraisal started]</td><td>
<table>
<tr><td>Name of Company</td><td>Grants and project specific funding</td><td>Gifts, Honoraria and Sponsorship</td><td>Total (£)</td></tr>
<tr><td>Celgene</td><td>-</td><td>5,000</td><td>5,000</td></tr>
<tr><td>BMS</td><td>40,000</td><td>-</td><td>40,000</td></tr>
<tr><td>Janssen-Cilag</td><td>25,000</td><td>950</td><td>25,950</td></tr>
</table>
The table above shows the audited 2021 income from the relevant manufacturers. Funding is received for a range of purposes and activities namely core grants, project specific work including clinical trials, and gifts, honoraria or sponsorship.
</td></tr>
</table>

If so, please state the name of company, amount, and purpose of funding.	
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	The information included in this submission has been gathered from the myeloma patients and carers we engage with through our research and services programmes, including: - We designed and widely circulated a Patient Treatment Survey specifically to support this appraisal. The survey was open to patients who have been treated with Daratumumab in combination with Velcade and dexamethasone (DVD) at second line of treatment. The survey received responses from 138 patients who shared their experience of being treated with DVD for myeloma. Therefore, this survey has important experience and insight data from a large number of patients whose clinical condition is highly relevant and have received the treatment being appraised. - A multi-criteria decision analysis study of 560 myeloma patients. The study, funded by Myeloma UK and run by the European Medicines Agency (EMA) and University of Groningen, explored patient preferences for different benefit and risk outcomes in myeloma treatment. It has also been informed by analysis of the experiences and views of patients, family members and carers gathered via our Myeloma Infoline, Patient and Family Myeloma Infodays and posts to our online Discussion Forum.

Section 2 Living with the condition and current treatment

Table 2 What it's like for patients, carers and families to live with the condition and current NHS treatment

6. What is it like to live with the condition?	***"Myeloma creeps up on you, engulfs you and, if you win the battle, leaves you wondering when it will come back."***

Consider the experience of living with the condition and the impact on daily life (physical and emotional health, ability to work, adaptations to your home, financial impact, relationships, and social life). For children, consider their ability to go to school, develop emotionally, form friendships and participate in school and social life. Is there any impact on their siblings?	Myeloma is a highly individual and complex cancer originating from abnormal plasma cells in the bone marrow. There is currently no cure, but treatment can halt its progress and improve quality of life. The complications of myeloma can be significant, debilitating and painful and include severe bone pain, bone destruction, kidney damage, fatigue and a depleted immune system which can lead to increased infections. Myeloma is also a relapsing and remitting cancer which evolves over time and becomes resistant to treatment. Most patients can be successfully retreated at relapse; however, remission is usually associated with diminishing duration and depth of response over time. Most patients can be successfully retreated at relapse; however, as patients multiply relapse their remission is usually associated with diminishing duration and depth of response over time. At first relapse the median time to next treatment is 13 months with only 58% of patients achieving a complete response/ very good partial response (CR/ VGPR) compared to 74% at diagnosis. At second relapse the time to next treatment reduces even further to 7 months with CR/ VGPR being achieved in less than half of patients.[1] ***"All the unknowns are hard. I would like to know everything because I want to be in control but with myeloma being so individual no one will give me a prognosis and I find this hard. My own guess is if I got one or two years of remission, I would be doing good. Now I am 18 months in remission, and I am finding it quite stressful going from my 3 monthly checkups in case things are beginning to change."*** Relapsed and multiple relapsed patients, the population covered in this appraisal, often experience an even more significant disease burden. They not only face a worse prognosis but also a greater symptomatic burden, due to the progressive nature of the disease and the cumulative effects of treatment which can result in reduced quality of life.[2]

[1] Bird and Boyd (2019) Multiple Myeloma: An Overview of Management Palliative Care and Social Practice 13:1-13 & Yong et.al (2016) Multiple Myeloma: Patient Outcomes in Real-World Practice Br J Heamatology 175:252-265

[2] Ramsenthaler, C., Osbourne, T.R. et al (2016) The impact of disease related symptoms and palliative care concerns on health related quality of life in multiple myeloma: a multi-centre study. BMC cancer 16:1 P.427

	Treatment side effects and frequent hospital visits have a social and practical impact on patients' lives, including significant financial implications. Reduction in mobility over time and a perceived increase in reliance on carers and family members, also impacts on patients' sense of control. ***"It has been really hard. Especially through the pandemic, the risk of infection was too great. My wife and I are both retired but we weren't able do much. We were not seeing many people or going out for meals, stuff like that. We have now been out more but you have got to be really careful."*** The individual and heterogeneous nature of myeloma means that some patients may tolerate a treatment well and others may not. In addition, myeloma evolves and becomes resistant to treatment. It is therefore essential to have a range of treatment options with different mechanisms of action at all stages of the myeloma pathway. ***"To say, "Well you already have a treatment." That's not good enough. You always have to show myeloma something new."***
7. What do carers experience when caring for someone with the condition?	<u>Family & Carers</u> ***"I feel angry that I'm not going to get the future I wanted, but the hardest thing to feel is how my life at the moment is in limbo"*** A Myeloma UK study into the experiences of carers and family members found that looking after someone with myeloma has a significant emotional, social, and practical impact: - 94% of carers are emotionally impacted and found the uncertainty of myeloma a major factor - 25% of those in work had been unable to work or had to retire early to care for the person with myeloma - 84% always put the needs of their relative or friend with myeloma before their own - Only 42% of carers were not given enough information at diagnosis about how myeloma may affect them[3]

[3] *A Life in Limbo: A Myeloma UK research report on the experience of myeloma carers in the UK* 2016: https://www.myeloma.org.uk/documents/a-life-in-limbo/

	Living with myeloma is therefore often extremely challenging physically and emotionally for patients, carers, and family members. ***"I had to think of my husband. You are in this as a team, it is not an individual battle."*** Family and carers have often spoken about the impact of a myeloma diagnosis on their own lives including a perceived lack of control, a change of roles/responsibilities within the household, daily lifestyle changes and missing out on important life events. ***"We had a role reversal. My husband used to do everything, but I now do it all. We actually moved house so it was something I could look after on my own when he relapses and goes back on treatment."*** ***"We have also altered what we eat. A lot more greens and a Mediterranean diet. When he was on treatment we slept in different rooms. I needed a full night's sleep to be able to take care of him throughout the day."*** ***"It has stopped us from travelling though it is hard to separate the myeloma from the restrictions due to COVID. You must be so careful...My daughter and her family live in New Zealand and my younger son lives in southern France. We used to go twice a year to see them both but now with myeloma and covid it's not really possible."***
8. What do patients and carers think of current treatments and care available on the NHS Please state how they help and what the limitations are.	Myeloma is an incredibly heterogenous condition with a large variability in age, comorbidities and fitness. Consequently, not all patients can receive the same treatment or intensity of dose. Therefore, treatment options must be based on the patient's fitness levels and ability to tolerate toxicities. As stated above the patient population covered in this appraisal who have had one prior therapy, the median time to next treatment is 13 months with only 58% of patients achieving a complete response/ very good partial response (CR/ VGPR).

	Patients and carers appreciate the wider range of effective treatments that are now available for treating relapsed myeloma which has delivered significant improvements in survival in myeloma over the past decade. However, myeloma remains a challenging cancer to treat, often particularly so for relapsed patients. For patients who relapse for the first time they have treatment options including: - Carfilzomib in combination with lenalidomide and dexamethasone (TA695) - Lenalidomide and dexamethasone (TA586) - Bortezomib monotherapy (TA129) - Carfilzomib and dexamethasone (TA657) - A small number of patients can also receive a second stem cell transplant. (The combination Ixazomib, lenalidomide and dexamethasone (TA505) is temporarily available at second line at an interim treatment option approved by NHS England during the pandemic.)[4] Of the options listed above lenalidomide is already approved for newly diagnosed patients as a maintenance treatment post HDT-SCT (TA680) and in combination with dexamethasone for patient who are ineligible for HDT-SCT (TA587). In clinical practice, lenalidomide is given as a treat until progression treatment meaning that many patients will become refractory to lenalidomide at their first line of treatment. The number of patients who can receive TA695 and TA586 will be diminishing. The current standard clinical practice in myeloma is to treat patients with as many treatments and with as many different mechanisms of actions up front as possible. Therefore, triplet and even quadruplet combinations are now standard therapy in myeloma. Therefore, this gap means that some patients must undergo sub-optimal treatment at a critical time in their disease pathway.

[4] NHS England interim treatment options during the COVID-19 pandemic https://www.nice.org.uk/guidance/ng161/resources/interim-treatment-change-options-during-the-covid19-pandemic-endorsed-by-nhs-england-pdf-8715724381 (accessed: 11/07/2022)

	Since Daratumumab in combination with Velcade and dexamethasone became available in 2019 it has become the standard treatment for myeloma after the 1st relapse.
9. Considering all treatments available to patients are there any unmet needs for patients with this condition? If yes please state what these are	The relapsing and remitting nature of myeloma, along with its heterogeneity and resistance to treatment means that a range of different treatment options at each point in the pathway is especially vital in myeloma. There have been welcome recent approvals at second line in the myeloma treatment pathway which has addressed to some extent what was a chronic unmet need. There is now considerable research evidence to show that longer and deeper remissions are gained in earlier relapses. Patients therefore deserve access to the widest possible range of effective treatments at the point in their myeloma where it has the greatest chance of delivering the best possible response. This combination will give patients a greater choice of options at this line of treatment and crucially give many patients access to a CD38 monoclonal antibody. (Daratumumab is available earlier in the treatment pathway as an induction/consolidation treatment for patients who can receive an HDT-SCT (TA763) however this is fixed at 6 cycles.) Overall, there is a need for a wide range of options at each stage of the treatment pathway given the heterogeneous and evolving nature of myeloma.

Section 3 Experience during the managed access agreement (MAA)

Table 3 Experience, advantages and disadvantages during the MAA

10. What are patients' and carers' experience of accessing and having the treatment?	<u>Patient experience</u> Our Patient Treatment Survey highlighted an overall positive experience with this treatment: • 87% of myeloma patients who had received daratumumab with bortezomib and dexamethasone rated their experience as *very positive* or *positive* (63% *very positive;* 24% *positive*)

• Please refer to the MAA re-evaluation patient submission guide	• 95% of myeloma patients who had received daratumumab with bortezomib and dexamethasone would recommend this treatment option to other patients. A small proportion of patients (8%) considered their experience of the treatment to be negative, and the remainder (5%) expressed a neutral opinion. *"The drugs were an effective treatment which has helped to get my myeloma into a plateau. The drugs brought my levels down very quickly, which is physically and mentally uplifting and positive."* <u>Impact of side effects</u> When asked to assess the impact of the treatment's side effects on their daily lives, patients shared mixed experiences. Over half (56%) reported that side effects had no or only a mild impact on their daily lives (15% *no impact,* 41% *mild impact*). Just over a third of respondents (35%) indicated that this impact was moderate, while the remaining proportion (9%) felt that the side effects had a high impact on their daily lives. *"I am able to lead my life in a relatively normal way, main side effect is tiredness but nothing that affects me too much."* *"The only notable side effect that I experienced was disruption to my sleep due to the dexamethasone and a bit of a swollen tummy! My life is unaffected and I am able to complete day to day activities."* Patients that shared more on the day-to-day impact of receiving DVD said that the side effects largely comprised of • Fatigue • Insomnia • Digestive issues <u>Method of administration</u>

	The majority of patients (92%) considered the way in which DVD was administered to be *very positive* or *positive* (70% *very positive,* 22% *positive*). Only 1% gave a negative assessment. *"Subcutaneous administration is fast and easy and no need to spend endless hours at the hospital"* *"I had it given intravenous, it was very easy, with no side effects or issues at all at the time."*
11. What do patients and carers think are the advantages of the treatment? Please refer to the MAA re-evaluation patient submission guide	We know from our engagement that patients value treatments which put their myeloma into remission for as long as possible, prolong their life and allow them to enjoy a normal day-to-day life. With evidence showing that that longer and deeper remissions are gained in earlier relapses, this triplet combination therapy can deliver longer PFS/OS compared to other therapies at second line of treatment. *"DVD treatment has kept my cancer in remission for currently 3 years and 1 month."* The CASTOR Clinical trial compared daratumumab, Velcade and dexamethasone (DVD) to the standard treatment of Velcade and dexamethasone (Vd). The results from the trial show that after 72.6 months of follow up median overall survival was 49.6 months for patients receive DVD vs 38.5 months for patients receiving Vd. The CASTOR study showed a statistically significant and clinically meaningful improvement in OS with D-Vd versus Vd (hazard ratio [HR], 0.74; 95% confidence interval [CI], 0.59-0.92; *P*=0.0075.[5] The ability to have daratumumab subcutaneously is now highly valued by patients. This is especially significant for patients who are receiving Daratumumab and want to reduce their risk of being exposed to infection such as COVID-19.

[5] Sonneveld, P et al Daratumumab plus bortezomib and dexamethasone versus bortezomib and dexamethasone alone in patient with previously treater multiple myeloma: Overall Survival results from the phase III CASTOR trial, HemaSphere: April 2022 - Volume 6 - Issue - p 12 doi: 10.1097/01.HS9.0000829588.31575.a9

	"At first I was having an intravenous infusion. When this was changed to an injection it was quicker and less intrusive. Spending less time at the hospital (especially during Covid) is much better." It is now becoming standard clinical practice to treat myeloma with as many treatments with different mechanisms of action as possible up front. Daratumumab is a CD38 monoclonal antibody and there is currently no treatment with this mechanism of action licensed for routine commissioning at this point in the treatment pathway. Finally, patients also desire treatments with minimal negative impact on quality of life, particularly those with as few side effects as possible and of low severity. In our engagement with patients across the myeloma pathway many have described daratumumab as a *"kinder"* treatment to take which does not increase toxicity in combination with other treatments. *"I found it a relatively 'kind' treatment, with few side effects other than bruising at the sites of my injections, and the inevitable ups and downs with dexamethasone."* That said, data shows that patients will accept even severe side effects if the treatment has a superior efficacy, suggesting that efficacy is the strongest driver of treatment choice. *"Although tough at the start (August 2019), the drugs were very quick and effective in bringing my myeloma under control again after my first relapse."* *"I had problems with blurred vision, constipation, fatigue, mild peripheral neuropathy in hands and feet and a kind of foggy feeling. I was never sick … Luckily as I was retired by the time of DVD, I didn't mind the side-effects and it was definitely well worth it for the amazing result!"* As described above, myeloma patients expressed largely positive views about their treatment with DVD and would recommend it to other patients. Given the option to elaborate on their reasons, patients highlighted the effectiveness in keeping their paraprotein levels low and the overall positive impact on their quality of life.

12. What do patients or carers think are the disadvantages of the treatment? Please refer to the MAA re-evaluation patient submission guide	Patients value treatments with fewer side effects with low severity ratings which stop when treatment ends. However, in practice patients will accept varying levels of toxicity in a treatment if it delivers good survival benefit and depending on the stage of their myeloma. The most common toxicities in the CASTOR trial were grade 3/4 thrombocytopenia (46.1%/32.9%), anaemia (16.0%/16.0%), neutropenia (13.6%/4.6%), lymphopenia (10.3%/2.5%), and pneumonia (10.7%/10.1%); and, side effects causing the discontinuation of treatment 10.7% vs 9.3%.[6] Overall adding daratumumab to Velcade and dexamethasone did not increase overall toxicity. The dosing schedule used is typical of real-world practice, and adverse events were clinically manageable and consistent with the known toxicities of daratumumab, Velcade and dexamethasone. Furthermore, some patients see symptoms and side effects as something to be expected as part of their disease and/or treatment, with many patients developing self-care strategies or accepting the immediate disadvantages in a trade-off for long-term gains. *"DVD administered between June and November 2019, some impact then on quality of life in that time but a small price to pay as it worked. Am currently leading a normal life apart from monthly infusions."* When discussing side effects with patients some were concerned about the level of toxicity that a triplet combination might bring. However, one patient did say: **"*The number of drugs, 3 or 4 is irrelevant to me, it's the effectiveness of the treatment."*** As outlined above, over a third of patients reported that the side effects of DVD treatment had a moderate impact on their daily lives, mainly due to the challenges of living with fatigue. While disadvantageous, this contrasts with the proportion (56%) who felt that there was no or only a mild impact.

[6] Sonneveld, P et al Daratumumab plus bortezomib and dexamethasone versus bortezomib and dexamethasone alone in patient with previously treater multiple myeloma: Overall Survival results from the phase III CASTOR trial, HemaSphere: April 2022 - Volume 6 - Issue - p 12 doi: 10.1097/01.HS9.0000829588.31575.a9

	Daratumumab can be given as an IV infusion. This does mean taking time out of the day to attend hospital. For some patients there are cost/capability issues associated with this and it can place an additional burden on carers who may have to accompany the patient to hospital. Our patient engagement has shown that there are also patients who welcome their treatment being delivered in the safety of a hospital environment and the opportunity to interact with clinical staff and other patients. However, mostly oral treatments are often valued by patients, particularly those who are working and have dependents. As said above the ability to have daratumumab subcutaneously would be highly appreciated by patients. Overwhelmingly though, clinical efficacy and the opportunity of a good remission outweighs any disadvantages in the method of administration.
13. What place do you think this treatment has in future NHS treatment and care for the condition? Consider how this treatment has impacted patients and how it fits alongside other treatments and care pathway.	We believe that this triple combination has a vital place in the Myeloma treatment pathway at 2nd line. Many patients will have received an IMiD in lenalidomide at first line of therapy and the ability to have a CD38 Monoclonal antibody and proteasome inhibitor at second line is highly valued by patients and clinicians. It is now becoming standard clinical practice to treat myeloma with as many treatments with different mechanisms of action as possible up front. Daratumumab is a CD38 monoclonal antibody and there is currently no treatment with this mechanism of action licensed for routine commissioning at this point in the treatment pathway. Therefore, this would remain an innovative change to the treatment pathway.

Section 4 Patients views on assessments used during the MAA

Table 4 Measurements, tests and assessments

14. Results from tests and assessments are used to help reduce uncertainty about the effectiveness of treatment. **How well do you think these tests and assessments worked in measuring the effectiveness of the treatment?**	The key data collection points used during the MAA were overall survival (OS), progression-free survival (PFS) and treatment duration. This data is easily collected and effective in understanding the key areas of clinical uncertainty. It is important that time on treatment – including when patients choose to stop taking treatment due to the negative impact of side effects or requesting a treatment break – is recorded accurately.
15. Were there any tests or assessments that were difficult or unhelpful from a patient's or carer's perspective?	The MAA does not provide detail on the type of tests or assessments carried out, however our assumption is that data in the study was captured through patient blood tests. This is the standard method of assessing paraprotein levels to determine disease progression and time of relapse. Myeloma patients get blood tests regularly so they are very used to them and this wouldn't have been an unusual or difficult process as part of data collection.
16. Do patients and carers consider that their experiences (clinical, physical, emotional and psychological) were captured adequately in the MAA tests and assessments? If not please explain what was missing.	It is unclear from the MAA what type of data relating to patient quality of life data was captured. With standard methods of quality of life data collection, like the EQ-5D survey, there is a risk that the whole holistic patient experience is not fully understood. A disease-specific tool like the Myeloma-Specific Patient Outcome Scale (MyPOS) questionnaire[7], designed specifically for use in the clinical setting, can be used to measure myeloma-specific quality of life issues including physical, emotional and psychological effects of treatment. We would recommend using the MyPOS tool to enable robust collection of the patient experience data.

[7] Palliative care Outcome Scale. MyPOS. Available at: https://pos-pal.org/maix/mypos.php

17. What outcomes do you think have not been assessed or captured in the MAA data? Please tell us why	Treatment side effects and the impact of these effects on patients' daily lives is not always accurately captured. Our patient treatment survey showed that over a third (35%) of myeloma patients experienced side effects that had a moderate impact on their daily lives. We feel that it is important to be able to capture this data effectively to take forward into clinical practice. One patient in our treatment survey commented that *"it's constant, week after week with no break for a slight body rest. My side effects last up to six days."*

Section 5 Patient population

Table 5 Groups who may benefit and those who declined treatment

18. Are there any groups of patients who might benefit more or less from the treatment than others? If so, please describe them and explain why.	A proportion of myeloma patients are intolerant of Velcade and therefore would not receive this treatment. There have been welcome recent approvals at second line in the myeloma treatment pathway which has addressed to some extent what was a chronic unmet need.
19. Were there people who met the MAA eligibility criteria who decided not to start treatment? Please state if known the proportion of eligible patients who did not start the treatment and any reasons for this.	Don't know

Section 6 Equality

20. Are there any potential equality issues that that should be taken into account when considering this condition and the treatment? See NICE's equality scheme for more details.

Section 7 Other issues

21. Are there any other issues that you would like the committee to consider?

Section 8 Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- There is a clear unmet need for this triplet combination therapy as it will give patients a greater choice of options at their second line of treatment and give many patients access to a CD38 monoclonal antibody. There is currently no treatment with this mechanism of action licensed for routine commissioning at this point in the treatment pathway.
- The Myeloma UK Patient Treatment Survey with 138 responses clearly demonstrates that patients who received daratumumab with bortezomib and dexamethasone had a positive experience and would recommend this treatment option to other patients.

- Clinical trial data and our survey confirm that daratumumab with bortezomib and dexamethasone delivers the benefits which are most important to patients: improved OS/PFS and good quality of life.
- Data from our survey shows that the side effects of this treatment combination have minimal impact on patients' daily lives and the advantages of its effectiveness outweigh the disadvantages of any moderate to high impact.
- The possibility to receive daratumumab subcutaneously is highly valued by patients.

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External Assessment Group Report commissioned by the NIHR Evidence Synthesis Programme on behalf of NICE

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

Produced by	Southampton Health Technology Assessments Centre (SHTAC)
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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).
- Dr Jenner declares receipt of honoraria in the last 12 months for advising Janssen for a different therapy in myeloma not relevant to the current appraisal.

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.

Confidential information

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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]

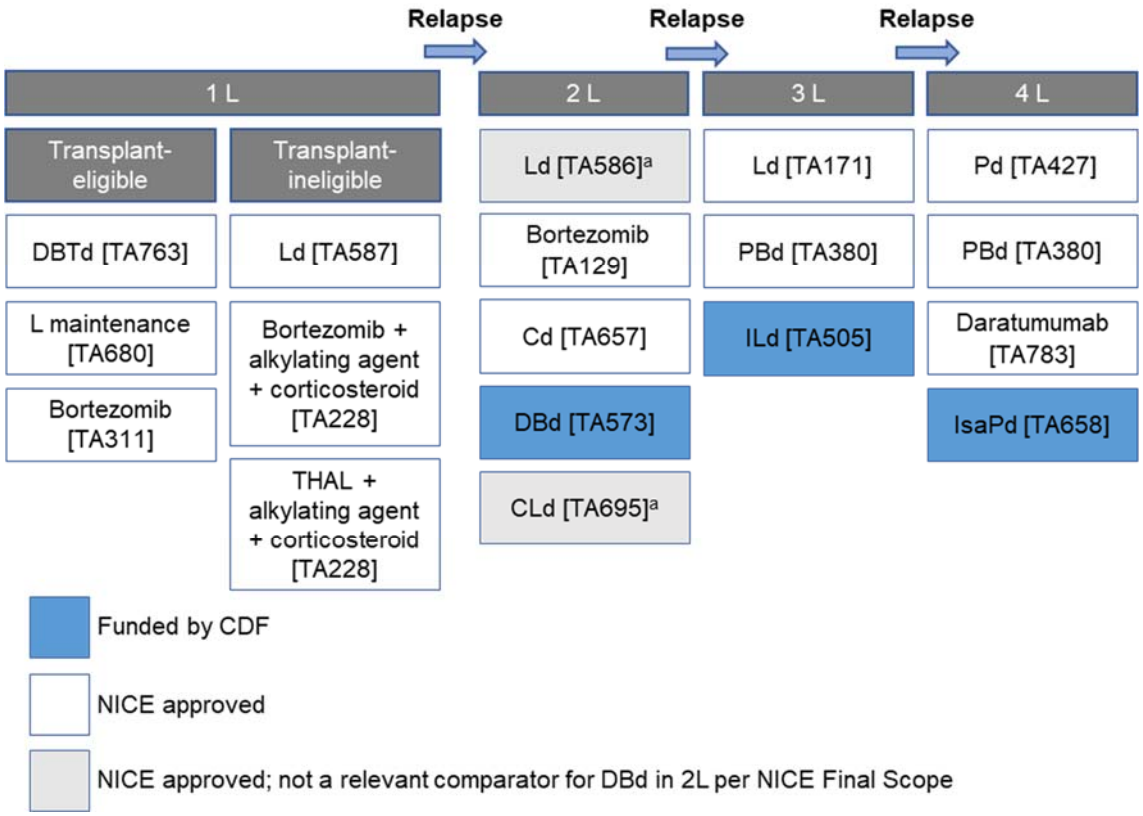
- Emotional/psychological effects due to side effects of treatments or effects of living with a chronic but ultimately fatal disease.[9; 10]
- Social difficulties with a decline in social contact and activities due to physical symptoms of the disease and side effects of treatment.[9; 11; 13; 14]
- Financial 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.

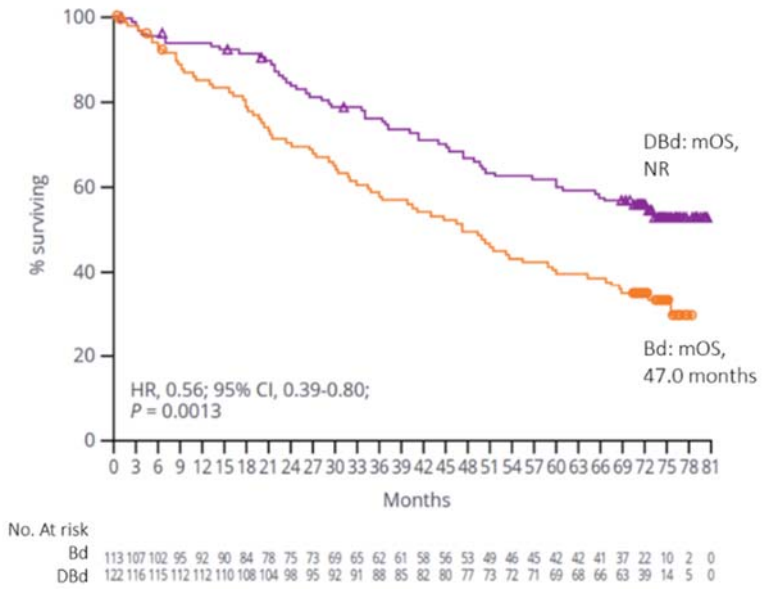
The improvement in OS with DBd was statistically and clinically significant, in the whole trial population (Hazard ratio [HR] 0.74, 95% CI 0.59 to 0.92, p=0.0075) and in the 1 PL

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

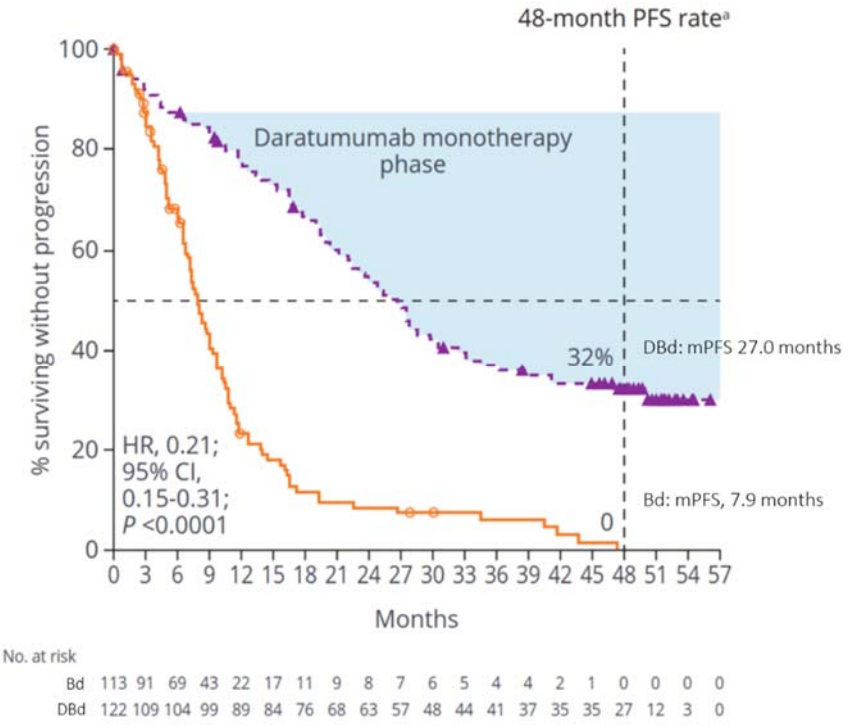
In the original appraisal (TA573),[1] the committee concluded that, based on CASTOR trial data with a median follow up of 27 months, DBd has both a statistically and clinically significant effect on progression free survival (PFS) compared with Bd.

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

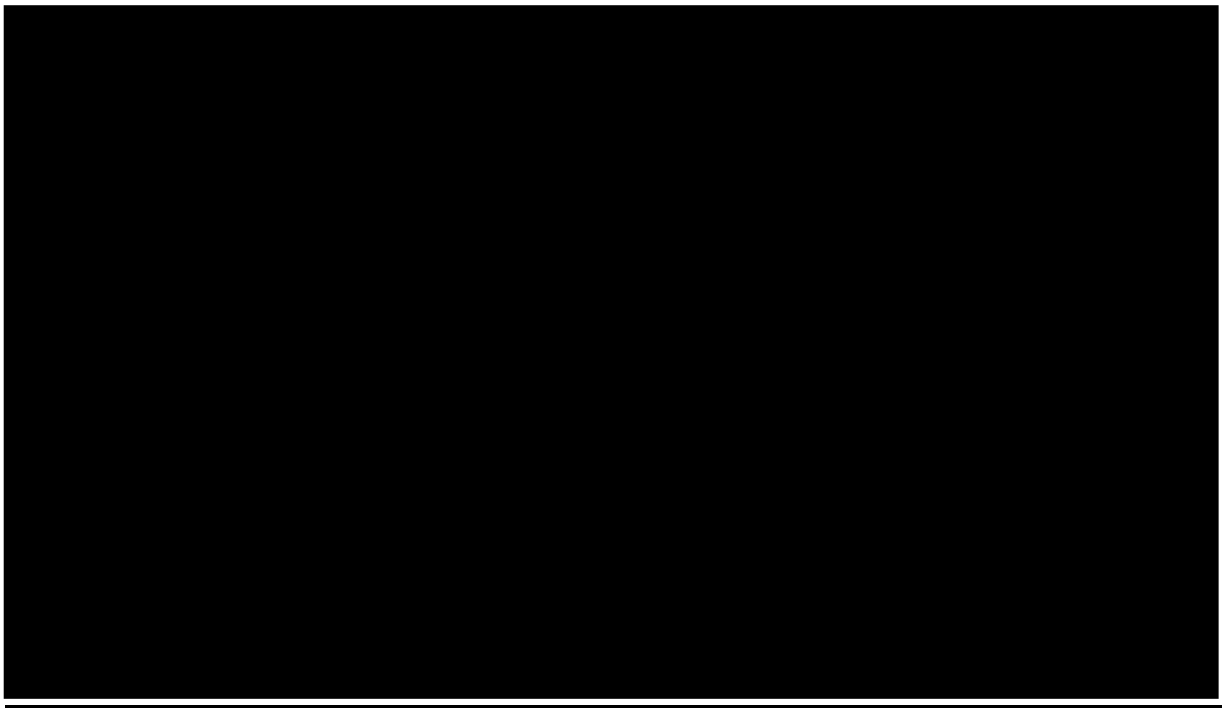
Time to treatment discontinuation (TTD) was a post-hoc outcome. As noted earlier in the report (EAG report section 3.2.3.1) the CS does not provide a definition for TTD. When interpreting the results for TTD, it is important to recognise that all patients received up to 8 cycles (21 days per cycle) of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

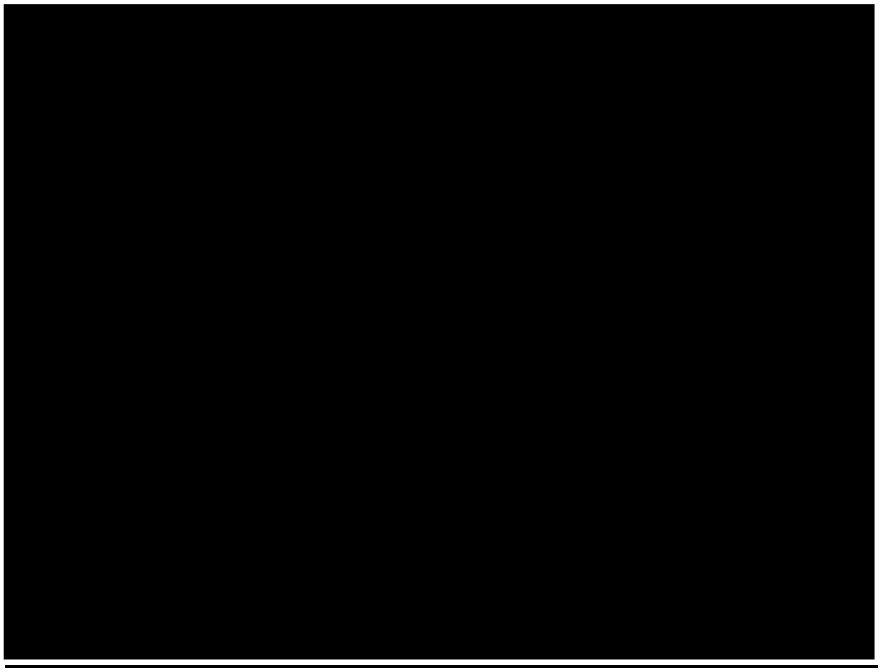
Table 23 Comparison of the baseline characteristics for the Non-CDF incident myeloma cancer patients and the CASTOR trial 1PL subgroup patients

	[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)

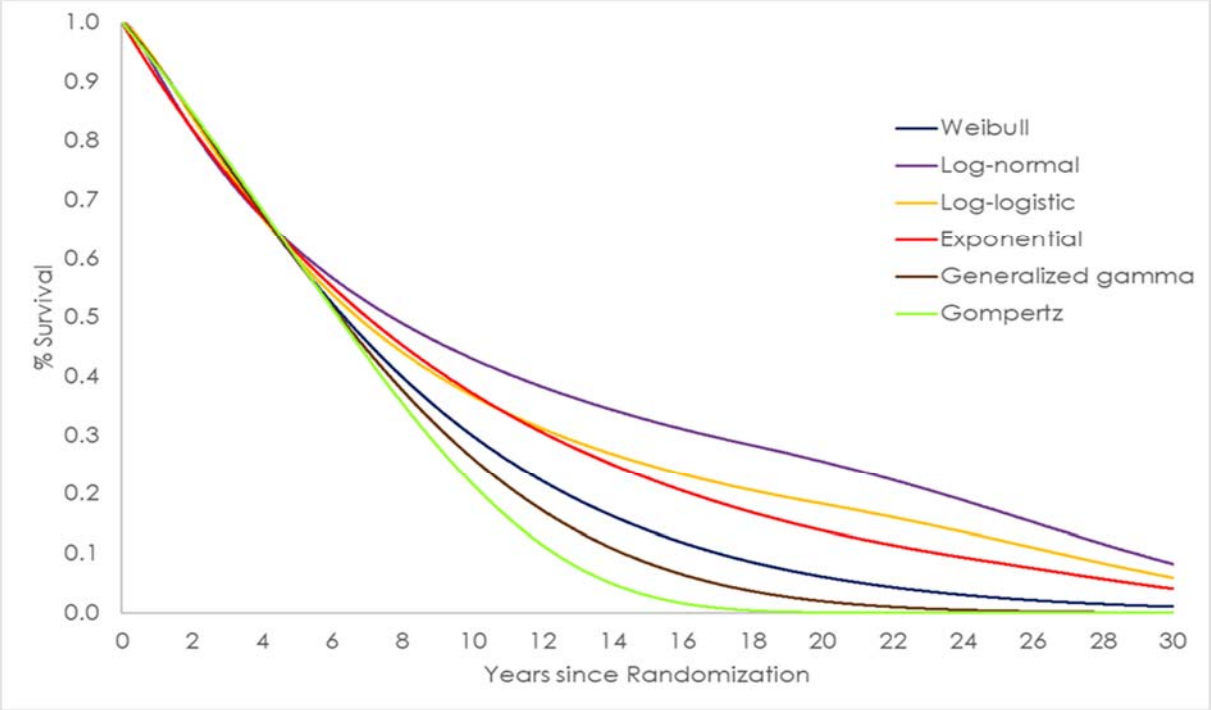


Figure 9 Company's long-term prediction of DBd (reproduced from CS Figure 32)

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					

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

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

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Daratumumab with bortezomib and dexamethasone for previously treated multiple myeloma

(Managed Access Review of TA573) [ID4057]

Technical engagement response form

As a stakeholder you have been invited to comment on the External Assessment Report (EAR) for this evaluation.

Your comments and feedback on the key issues below are really valued. The EAR and stakeholders' responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

We are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the EAR that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this evaluation, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include journal articles in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See the NICE health technology evaluation guidance development manual (sections 5.4.1 to 5.4.10) for more information.

The deadline for comments is **5pm** on **19th December 2022.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

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

Technical engagement response form

Daratumumab with bortezomib and dexamethasone for previously treated multiple myeloma (Managed Access Review of TA573) [ID4057]

NICE National Institute for Health and Care Excellence

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

Your name	[redacted]
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	Janssen-Cilag Ltd
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	N/A

About you

Table 1 About you

Key issues for engagement

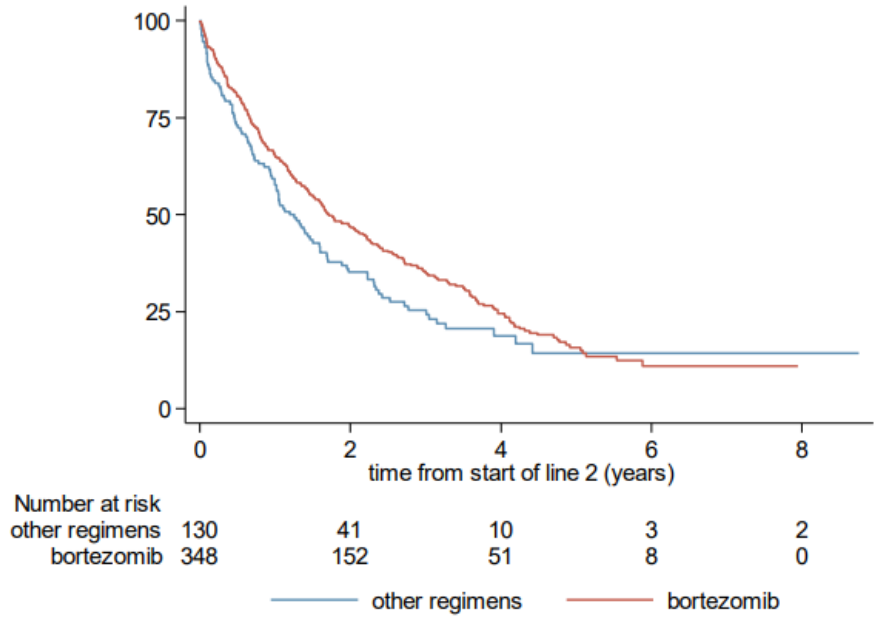
All: Please use the table below to respond to the key issues raised in the EAR.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
EAG Key Issue 1 Uncertainty about overall survival in the Systemic Anticancer Therapy (SACT) dataset	**No**	As per the Data Collection Arrangement (DCA) for TA573, the primary source of data collection for this CDF re-appraisal is the phase III CASTOR study comparing DBd against the directly relevant active comparator, Bd, with Public Health England (now NHS Digital) routine population-wide cancer data sets, including SACT, specified as a secondary data source. This is consistent with the Committee conclusions per the FAD, which noted the importance of further data collection from CASTOR to reduce longer-term survival modelling uncertainty for DBd. Randomised controlled trials are recognised by NICE as the gold standard in the evidence hierarchy and preferred source on the effects of interventions[1]. Whilst Janssen acknowledge that observational data collected via SACT is useful to inform absolute real-world clinical effectiveness of DBd, issues raised in the Company submission and by the EAG mean that results need to be interpreted with caution. Issues include: short median follow-up for OS of only [redacted] months (versus median follow-up of 72.6 months in CASTOR), and the unknown impact of ixazomib plus lenalidomide and dexamethasone (ILd) availability at second-line (as a result of COVID-19 guidelines introduced following the pandemic). As part of our clarification response, we noted that ILd use exceeded [redacted]% from 2020 in the one prior line setting and peaked at approximately [redacted]% in Q1 of 2021 based on IPSOS (Ipsos Healthcare Cancer Therapy Monitor – UK)[2] and HARMONY market research data[3]. In these

		cases, DBd could be administered in 3rd line which introduces additional bias and uncertainty around the generalisability of the SACT data to the second-line population. As such, SACT results may underestimate absolute DBd efficacy at 2L due to high usage at later lines, and not be fully generalisable to a 2L population. Moreover, with limited baseline characteristics reported in SACT, and no counterfactual collected for patients treated with standard of care, Bd, Janssen considers there is no robust means of using SACT data to estimate comparative (i.e., relative) effectiveness necessary to inform an economic evaluation. However, in order to further reassure the EAG and NICE committee we have explored additional analyses which we present in our response to Key Issue 2 below.
EAG Key Issue 2 Absence of real-world data for second-line patients receiving bortezomib plus dexamethasone (Bd)	**Yes**	The key area of clinical uncertainty identified in TA573 was overall survival in daratumumab patients, with clinical outcomes for Bd not specified as part of the DCA. Furthermore, it is not possible to have contemporaneous real-world data for the comparator, Bd, as this would have required randomisation of patients in clinical practice. As such, and given the limitations of the SACT dataset per Key Issue 1 above, Janssen considers there is no robust means to estimate real-world comparative (i.e., relative) effectiveness of DBd versus Bd. Nonetheless, Janssen understands the EAG's interest to understand real-world clinical outcomes for Bd given the difference in survival outcomes observed between CASTOR and SACT for DBd. To explore this uncertainty further, and assess whether the relative benefit from the trial is expected to hold in the real-world, Janssen has investigated alternate real-world evidence sources for standard of care and conducted the following exploratory analyses: • Overall survival for Bd patients from the Haematological Malignancy Research Network (HMRN) cohort study • Retrospective audit of second-line (non-DBd) outcomes from Leicester Royal Infirmary (LRI, part of the HONEUR Federated Data Network) • Extrapolation of DBd outcomes from SACT • Simulation of Bd OS curve using IPCW adjusted HR from CASTOR

		Expected real-world outcomes for Bd In Figure 1, we present Kaplan-Meier results for overall survival from the Haematological Malignancy Research Network (HMRN) cohort study referred to in the original Company Submission[4]. The HMRN is an ongoing population-based cohort that was established in the UK in 2004 to inform clinical practice and contribute to research in haematological malignancies. The HMRN region comprises a total population of 3.8 million (covering the area formerly served by the Yorkshire and the Humber & Yorkshire Coast Cancer Networks). The analysis reports second-line outcomes for adult patients diagnosed with multiple myeloma between 1st January 2008 to 31st August 2015. Although UK specific, 80% of patients included in the HMRN cohort were ineligible for autologous stem cell transplant (ASCT) compared with ~66% nationally suggesting a generally older and less fit patient population. The sample size of the study was 1,986, with 348 second-line patients receiving treatment with bortezomib-based therapy. **Figure 1: Kaplan-Meier plot for overall survival from the start of second-line treatment stratified by bortezomib versus other regimens; HMRN cohort study[5]**



Results from the HMRN cohort study demonstrate significantly lower outcomes for bortezomib-based therapy versus CASTOR, with median OS from the start of second-line treatment of 19.2 months and 39.5 months respectively. The shape of the survival curve is steep and, despite a gradual levelling-off and low number of patients at risk beyond year-4, the general trajectory indicates no patients are expected to be alive after 10-years. Whilst outcomes nationally may be higher due to a higher proportion of ASCT-eligible patients, this is not expected to alter the prognosis at 10-years from the start of second-line treatment. Janssen therefore consider the results most applicable to real-world clinical outcomes for Bd.

In Figure 22 below, we present Kaplan Meier analysis of overall survival from a retrospective audit of clinical outcomes for second-line patients from LRI. Data was collected as part of the

		Haematology Outcomes Network in Europe (HONEUR); a retrospective, observational cohort study utilising datasets from four European countries participating in a federated data network including the UK. Due to the low number of Bd patients, results for all non-DBd patients were analysed, covering the period from XXXX to XXXXXX. A summary of patient baseline characteristics and breakdown of second-line treatments are presented in Table 2 and **Error! Reference source not found.** respectively. [redacted]

		[redacted]

[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

[redacted]

[redacted]

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

With a median follow-up of [redacted] months, results from the retrospective LRI medical audit indicate similar outcomes to HMRN with median overall survival for second-line (non-DBd) patients of [redacted] months, and a trend indicating no patients expected to be alive beyond 10-years. It is

		notable that the population is older than SACT ([redacted]) and included fewer patients previously treated with a stem cell transplant ([redacted]). The basket of second-line treatments also includes a high proportion of lenalidomide-based therapy ([redacted]%) not in scope as a comparator for this appraisal. **Simulation of Bd OS outcomes in SACT** As outlined in our clarification question response, there are significant limitations to any attempt to simulate the Bd arm using the relative treatment effect observed in CASTOR. Briefly, our position is that: • Such analysis would be susceptible to selection bias if the patients treated with DBd are not representative of patients that would otherwise be treated with Bd in clinical practice. • Bias could also arise if DBd patients in SACT were treated at a later line due to the interim COVID guidelines permitting treatment (refer to clarification question B1.a). • Applying the OS hazard ratio from CASTOR to the DBd SACT data relies on proportional hazards, however, scrutiny of the OS hazard curves from CASTOR provided clear evidence of a violation of the proportional hazards assumption between treatment arms (refer to Company submission Section B.3.3.1.2). • OS data from SACT is immature with [redacted] months median follow-up and [redacted]% events compared to over 6 years median follow-up and [redacted]% events from CASTOR. Nevertheless, to explore this issue further, Janssen has conducted an exploratory analysis to generate a simulated Bd curve using the relative benefit observed in CASTOR which we present below. **Step 1: Extrapolate DBd outcomes from SACT** First, it was necessary to digitise the OS Kaplan-Meier (KM) curve for DBd from SACT using DigitizeIt software. This was required as Janssen has no access to patient level data from SACT. The Guyot algorithm was then used to generate simulated patient level data, before fitting standard parametric distributions using the FlexSurv function in R.

		To determine the most appropriate survival functions, model fits were assessed based on: • visual comparison of the predicted curve from a given parametric function to the KM curve from the patient data • statistical goodness-of-fit by the comparison of Akaike information criterion (AIC) statistics and Bayesian information criterion (BIC) statistics, and • assessment of the clinical validity of the extrapolated portion of the survival curves at key milestones. Visually all curves, with the exception of log normal, fitted the observed data well as expected given the short follow-up coupled with the large sample size. [redacted]

Abbreviation: KM = Kaplan-Meier

Statistical goodness-of-fit data (presented in Table 33) showed that the Weibull distribution is a good candidate as it ranked 1st based on AIC and 2nd based on BIC among the other distributions.

Table 3: Statistical goodness-of-fit

Analysis	Weibull	Log-normal	Log-logistic	Exponential	Generalized gamma	Gompertz
AIC	**10,955.80**	10,964.50	10,957.40	10,959.30	10,960.10	10,957.60
Rank	**1**	6	2	4	5	3
	10,967.50	10,976.20	10,969.10	**10,965.20**	10,977.60	10,969.30

BIC Rank	2	5	3	**1**	6	4

Abbreviation: AIC = Akaike information criterion; BIC = Bayesian information criterion

The proportions of patients alive at key milestones are presented in Table 4. The probability of death was restricted to be at least as high as observed in the general population. Mean age and gender distribution was based on the population included in the SACT data set.

Table 4: Proportion of patients alive at different milestones

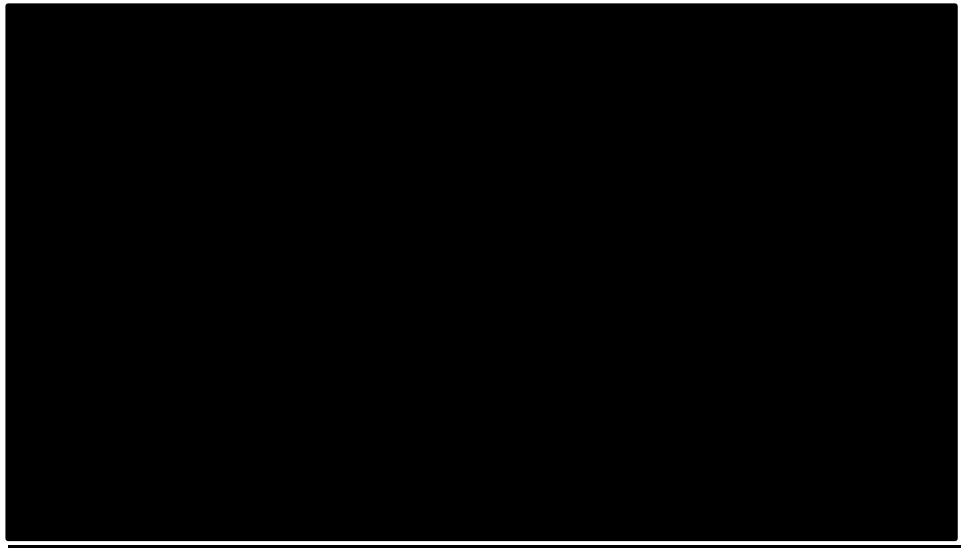
Years	Weibull	Loglogistic	Lognormal	Exponential	Generalized gamma	Gompertz
5 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
15 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
20 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
25 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
30 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Corresponding long-term projections are presented in Figure 4 below.

Figure 4: DBd SACT OS extrapolations, long-term

		 Abbreviation: KM = Kaplan-Meier Generalized gamma (light blue) provided unrealistically low estimates with [redacted]% of patients alive at 9 years, followed by exponential and Weibull ([redacted], respectively) and Gompertz, log-logistic and log-normal ([redacted], respectively). Following clinical expert feedback, Janssen selected the Weibull distribution (dark blue) as representative of real-world clinical outcomes expected for DBd in this patient population. **Step 2: Derive Bd OS curve using IPCW adjusted HR from CASTOR** In the following step, the inverse probability of censored weights (IPCW) hazard ratio (HR) from CASTOR was applied to the DBd reference curve to generate a simulated Bd curve. The IPCW HR of [redacted] was necessary to adjust for the impact of subsequent treatments not available in England as described in the original company submission (Appendix D.3.2.14.2 Method of adjustment). The resulting curves for DBd and Bd are presented in Figure 5.

[redacted]



* For the HMRN cohort, there are only 8 patients at risk of dying beyond year-6 therefore the observed plateau at the tail end of the curve needs to be interpreted with caution (marked red on the figure).

As illustrated in Figure 5, the simulated Bd curve provides a reasonable approximation to the real-world data, predicting a small proportion ([redacted]%) of patients to be alive at 10-years from the start of second-line treatment.

This estimate is closely in line with the clinical expert feedback Janssen received following an Advisory Board conducted in June 2022 using a structured elicitation method involving four English clinical experts which predicted zero patients alive.

The exploratory analysis presented above was undertaken to address concerns raised by the EAG, and provide a directional guide to help reduce residual uncertainty and support Committee

		decision making. Whilst the analysis needs to be interpreted with caution due to inherent limitations associated with a naïve comparison across different real-world data sources, and assumptions necessary to derive a simulated Bd curve, clinically plausible results provide reassurance that the relative treatment effect observed in CASTOR would hold in the real-world. Janssen also considers the lower median treatment duration for DBd observed in SACT of [redacted] months versus [redacted] months in CASTOR further supports the expected cost-effectiveness of DBd in the real-world setting.
EAG Key Issue 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])	**No**	Janssen would like to clarify that the purpose of presenting a naïve comparison of outcomes for DBd observed from the SACT dataset versus the NHS Digital newly diagnosed multiple myeloma (NDMM) standing cohort study was to put into context the survival outcomes against a similar real-world evidence data source. The purpose was not, as suggested by the EAG, to help inform whether the relative benefit of DBd versus Bd treatment in CASTOR holds in the real-world. In the Company Submission, Section B2.10.6, we note that despite absolute survival outcomes for DBd being lower in SACT versus CASTOR, the proportion of patients alive at 24-months ([redacted]%) compared favourably versus a large cohort of newly diagnosed patients in England (n= [redacted]) that did not receive an autologous stem cell transplant and did not go onto receive daratumumab as subsequent therapy [redacted]%). It's important to note that the 24-month survival rate per SACT is from the initiation of second-line therapy. As such, the survival rate from diagnosis for patients treated with DBd at second-line would be still higher, and the magnitude of difference versus the equivalent survival rate for newly diagnosed ASCT- patients from the standing cohort study greater. Janssen acknowledges that the standing cohort study was set-up for the purpose of understanding outcomes in newly diagnosed patients and the inherent limitations of a naïve comparison between different data sources however consider the results of interest given the national coverage of the NHS Digital data sets, large sample, and magnitude of the observed difference. They also help contextualise the results for DBd from SACT in the absence of contemporaneous real-world evidence for Bd.

EAG Key Issue 4 The difference in the OS estimates for DBd obtained from the real-world evidence-SACT database and the company's trial CASTOR	**No**	Janssen acknowledges that the patients included in SACT are significantly older and therefore expected to be frailer compared with CASTOR. As such, Janssen agrees to implement the age and gender distribution observed in SACT despite noting that this introduces an inconsistency with all other efficacy inputs in the model. Janssen maintains, however, that similar differences would be observed between the trial and real-world if we had contemporaneous SACT data available for Bd. Indeed, results from the HMRN and retrospective audit from LRI indicate median survival for standard of care of [redacted] months versus 39.4 months for Bd in CASTOR. As such, while Janssen recognises that the resultant survival extrapolations for DBd and Bd based on the CASTOR trial data may be more favourable than expected in NHS practice, we consider that the relative treatment benefit is expected to hold in the real-world. This view is supported by the exploratory analysis presented in response to the EAG Key Issues 2 above. With the aforementioned issues noted above for SACT in response to EAG Key Issue 1, and no contemporaneous SACT data available for Bd, the phase III CASTOR study comparing DBd against the directly relevant active comparator, Bd, remains the most robust source of evidence to inform cost-effectiveness. This was also recognised in the Managed Access Agreement for TA573, where CASTOR was recognised as the primary source of data collection in the CDF Data Collection Arrangement. While Janssen has performed exploratory analysis to assess whether the relative treatment effect from CASTOR is expected to hold in the real-world, the significant limitations noted above (not only in relation to the simulated Bd OS curve, but also PFS data not collected in SACT), preclude it from being suitable for inclusion in the economic model as a scenario analysis. In conclusion, exploratory analysis has indicated that the relative clinical benefit of DBd versus Bd observed in CASTOR is likely to hold in clinical practice. Rather than introducing unnecessary uncertainty into the economic modelling consequential of scenario analyses based on evidence from the lower end of NICE's hierarchy of evidence, Janssen proposes that it is expected that cost-effectiveness based on CASTOR will translate into cost-effectiveness in the real world, particularly since DBd has a simple discount patients access scheme for daratumumab.

<table>
<tr>
<td>EAG Key Issue 5
Extrapolation of OS in the Bd arm</td>
<td>No</td>
<td>Table 5 below presents a summary of the different methods employed to select the optimal curves across this submission and technical engagement. The Weibull and Gompertz curves present good visual fit and best statistical fit respectively and are also favoured by other investigations. Hence, Janssen considers that these are the only curves that should be considered relevant for decision making.

Table 5: Summary of Curve Selection Approach for Bd in CASTOR

<table>
<tr><td>Method</td><td>Optimal curve selection</td><td>Second-best</td></tr>
<tr><td>Visual fit</td><td>Gompertz</td><td>Weibull</td></tr>
<tr><td>Statistical goodness-of-fit (AiC/BiC)</td><td>Gompertz</td><td>Weibull</td></tr>
<tr><td>Observed (smoothed) hazard function (new information presented below)</td><td>Gompertz</td><td>Gamma/Weibull</td></tr>
<tr><td>Clinical plausibility (expert feedback)</td><td>Gompertz</td><td>Weibull</td></tr>
<tr><td>Clinical plausibility (external validity)</td><td>Gompertz/Weibull</td><td>Gompertz/Weibull</td></tr>
</table>

As observed for DBd comparing CASTOR with SACT, Janssen would expect a similar difference in absolute survival outcomes comparing trial versus real-world for Bd. In real-world clinical practice, no Bd patients are expected to survive beyond 10-years from the start of second-line therapy. This estimate was based on expert feedback received by Janssen following a clinical advisory board meeting held in June and July 2022 involving five UK clinicians and is supported by the HONEUR and HMRN real-world evidence results presented in our response to Key Issue 2 above. Specifically, the 10-year estimate was based on a structured elicitation process that followed an adaptation of the Sheffield Elicitation Framework[6] (SHELF) methodology. SHELF is a formal process of quantifying the beliefs of experts and is considered the most robust approach for characterising uncertainty associated with those beliefs[6]. Further</td>
</tr>
</table>

		details of the clinical advisory board meeting and the SHELF method are provided in the original CS, Appendix O. It is important to recognise that this 10-year estimate for Bd is from the start of second-line therapy, not 10-years from diagnosis. In CASTOR, the median time from diagnosis to randomisation was [redacted] years for the second-line Bd subgroup, implying no patients are expected to be alive approximately [redacted]-years after diagnosis. Despite Gompertz representing the statistically best-fitting curve, Janssen acknowledges that a small minority of patients may be expected to be alive at 10-years in a clinical trial setting. To investigate this issue further, Janssen explored the empirical hazard function for Bd observed in CASTOR (Figure 6. The bandwidth range for the analysis was manually set to ensure a minimum number at risk of at least 15 patients). [redacted]

		 Although the smoothed hazard curve needs to be interpreted with caution beyond month 42 due to low remaining number of patients at risk, there is a monotonically increasing upward trend, consistent with the shape of the Gompertz, Weibull and Gamma distributions. The increasing risk of death with longer follow-up observed for the second-line Bd subgroup is consistent with clinical evidence from CASTOR which demonstrated that very few patients on the control arm achieved MRD-negativity, equivalent to no residual disease (for DBd;). It is therefore intuitive that, over time, the risk of death would increase as there are very few super responders within the cohort. Contrary to the EAG assertion, the Weibull distribution (not exponential) has the second-best statistical fit with the lowest Akaike information criterion (AIC) and Bayesian information criterion (BIC) statistics after Gompertz, predicting a survival rate of % at 10-years (or % 10-

		years after diagnosis). Assuming a baseline patient age of [redacted] per SACT, this implies a small minority of patients treated with Bd would survive beyond 80 years of age. By contrast, the exponential distribution preferred by the EAG has poor visual fit and third-best statistical fit. It is also a poor candidate for curve selection based on the empirical (observed) hazard and clinical evidence from CASTOR. The exponential curve predicts a survival rate of [redacted]% at 10-years (or [redacted]% 10-years after diagnosis). Assuming a baseline patient age of [redacted] years per SACT, this implies a significant minority of patients treated with Bd would survive beyond 80 years of age which is considered clinically improbable. On the basis that the Weibull has both good statistical and visual fit, retains a shape consistent with the observed hazard function, and predicts a non-zero value at 10-years acknowledging the clinical trial setting, Janssen has revised its base case model selection for Bd from Gompertz to Weibull. Janssen also notes that Weibull was the preferred distribution of the EAG from the original appraisal in 2019 and the Committee preferred distribution for Bd in TA457 giving comparable life-year gained estimates of [redacted] based on the updated cost-effectiveness model, and 3.34 in the appraisal of carfilzomib. Please refer to Table 6 below for a summary of the impact of this change to the Company's cost-effectiveness estimates.

Additional issues

All: Please use the table below to respond to additional issues in the EAR that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this evaluation (for example, at the clarification stage) Additional issues from the EAR

Issue from the EAR	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response

Additional issue 1: Collection of HRQoL data in CASTOR	3.2.3.2 HRQoL outcomes	**No**	The EAG, while agreeing with our initial approach to use the same utility values that were accepted by the committee in the original appraisal, also acknowledged that further data would be helpful to assess whether an updated HRQoL analysis would affect the cost-effectiveness results. We agree with the EAG that additional data to base utility values on the same source as the efficacy inputs would be desirable, following the examination of the compliance rate of completing the HRQoL questionnaire we concluded that due to the sudden drop in the rate starting at around treatment cycle 40 in case of DBd there is no additional value of performing further analysis. Details of compliance with the EQ-5D-5L questionnaire are presented below with reference to the intention-to-treat population. In the 1 prior line subgroup similar rates are expected, with a smaller cohort providing the inputs, as the compliance results exclude anyone who died during the study. [redacted]

			[redacted]
Additional issue 2: Source of drug acquisition costs	4.2.8 Resources and costs	**No**	The EAG highlighted that NICE recommends the use of eMIT prices for drugs to improve transparency and subsequently updated drug costs in their further scenario analysis. We agree with this approach.

Summary of changes to the company's cost-effectiveness estimate(s)

Company only: If you have made changes to the base-case cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes. Please also provide sensitivity analyses around the revised base case. If there are sensitivity analyses around the original base case which remain relevant, please re-run these around the revised base case.

Table 6 Changes to the company's cost-effectiveness estimate (discounts for medicines other than DBD not included)

Key issue(s) in the EAR that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case incremental cost-effectiveness ratio (ICER)
Key issue 1. Uncertainty about overall survival in the Systemic Anticancer Therapy (SACT) dataset	• Baseline characteristics (age and gender distribution) as per original company's base case from the CASTOR trial: • Age: [redacted] year • Males: [redacted] %	• Baseline characteristics (age and gender distribution) as per the EAG preferred scenario from SACT • Based on SACT • Age: [redacted] years • Males: [redacted]	Revised base-case ICER with PAS = [redacted] (ICER increased [redacted] versus original base case)
Key issue 5. Extrapolation of OS in the Bd arm	The company used the Gompertz parametric function to extrapolate OS in the Bd arm	The company uses the Weibull parametric function to extrapolate OS in the Bd arm	Revised base-case ICER with PAS = [redacted] (ICER increased [redacted] versus original base case)
Other issue: Costs and resource use	Drug costs based on Monthly Index of Medical Specialities (MIMS)	Drug costs based on Drugs and pharmaceutical electronic market information tool (eMIT) as recommended by NICE	Revised base-case ICER with PAS = [redacted] (ICER increased [redacted] versus original base case)

Cumulative change: Key 1+ Key issue 5+ other issue related to costs	All of the above	All of the above	Revised base-case ICER with PAS = [redacted] (ICER increased [redacted] versus company base case following corrections based on the clarification questions)

Updated analyses around revised base case

Table 7 Updated base-case cost-effectiveness analysis results

Health Outcomes	DBd	Bd	Cd
LY accrued	[redacted]	[redacted]	[redacted]
LYs accrued: Progression Free Survival	[redacted]	[redacted]	[redacted]
LYs accrued: Post Progression Survival	[redacted]	[redacted]	[redacted]
QALY accrued	[redacted]	[redacted]	[redacted]
QALYs accrued: Progression Free Survival	[redacted]	[redacted]	[redacted]
QALYs accrued: Post progression Survival	[redacted]	[redacted]	[redacted]
QALYs accrued: Adverse Events	[redacted]	[redacted]	[redacted]
PFS Drug Cost	[redacted]	[redacted]	[redacted]
PFS Administration Cost	[redacted]	[redacted]	[redacted]
PFS Co-medication Cost	[redacted]	[redacted]	[redacted]
PFS Medical Resource Use	[redacted]	[redacted]	[redacted]
PPS Subsequent Treatment Drug Cost	[redacted]	[redacted]	[redacted]
PPS Medical Resource Use	[redacted]	[redacted]	[redacted]
Adverse Event Cost	[redacted]	[redacted]	[redacted]
Terminal Cost	[redacted]	[redacted]	[redacted]
Total Cost	[redacted]	[redacted]	[redacted]

Bd = bortezomib and dexamethasone; Cd = carfilzomib and dexamethasone; DBd = daratumumab, bortezomib and dexamethasone; LY = life year; PFS = progression-free survival; PPS = post-progression survival; QALY = quality-adjusted life year.

Technical engagement response form

Table 8 Updated Incremental cost-effectiveness results

Incremental results	Bd	Cd
Incremental costs	[redacted]	[redacted]
Incremental QALYs	[redacted]	[redacted]
Incremental LY	[redacted]	[redacted]
Cost per QALY gained	£35,196	Cd is dominated
Cost per LY gained	£24,828	Cd is dominated

Bd = bortezomib and dexamethasone; Cd = carfilzomib and dexamethasone; LY = life year; QALY = quality-adjusted life year.

[redacted]

[redacted]

Technical engagement response form

Daratumumab with bortezomib and dexamethasone for previously treated multiple myeloma (Managed Access Review of TA573) [ID4057]

Table 9 Updated probabilistic analysis results

Comparator	Mean LYs	Mean QALYs	Mean Total cost	ICER
Bd	[redacted]	[redacted]	[redacted]	£35,916
Cd	[redacted]	[redacted]	[redacted]	Cd is dominated
DBd	[redacted]	[redacted]	[redacted]	N/A

Bd = bortezomib and dexamethasone; Cd = carfilzomib and dexamethasone; DBd = daratumumab, bortezomib and dexamethasone; ICER = incremental cost-effectiveness ratio; LY = life year; QALY = quality-adjusted life year.

[redacted]

Bd = bortezomib and dexamethasone (BOR-DEX); Cd = carfilzomib and dexamethasone (CAR-DEX); DBd = daratumumab, bortezomib and dexamethasone (DARA-BOR-DEX); QALY = quality-adjusted life year.

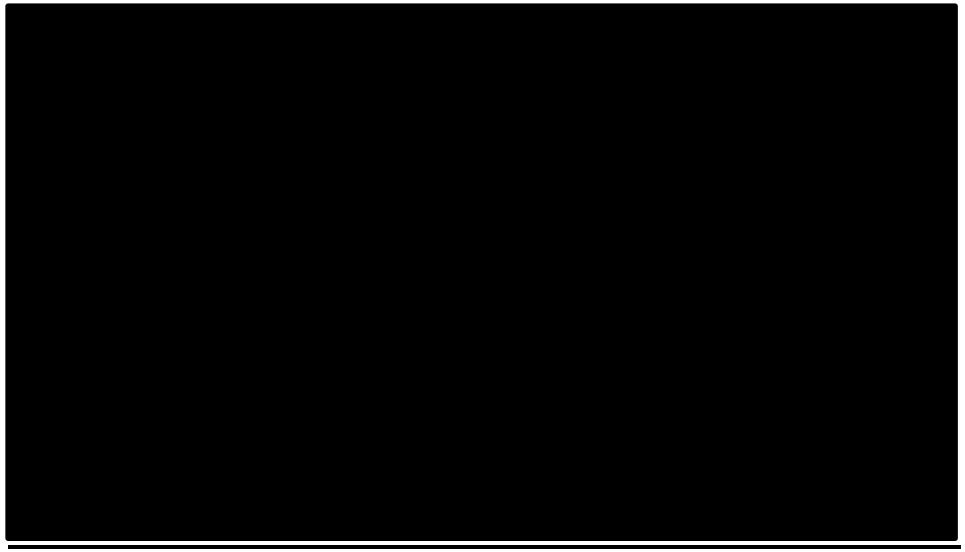
[redacted]

Bd = bortezomib and dexamethasone (BOR-DEX); Cd = carfilzomib and dexamethasone (CAR-DEX); DBd = daratumumab, bortezomib and dexamethasone (DARA-BOR-DEX); QALY = quality-adjusted life year.

[redacted]

Bd = bortezomib and dexamethasone (BOR-DEX); DBd = daratumumab, bortezomib and dexamethasone (DARA-BOR-DEX); OS = overall survival; PFS = progression-free survival; Pts = patients; Subs = subsequent; TTD = time to treatment discontinuation; Tx = treatment.

[redacted]



Cd = carfilzomib and dexamethasone (BOR-DEX); DBd = daratumumab, bortezomib and dexamethasone (DARA-BOR-DEX); OS = overall survival; PFS = progression-free survival; Pts = patients; Subs = subsequent; TTD = time to treatment discontinuation; Tx = treatment.

Table 10 Updated results of unadjusted OS scenario

	DBd	Bd	Cd

Life-years (LY) accrued	[redacted]	[redacted]	[redacted]
LYs accrued: Progression Free Survival	[redacted]	[redacted]	[redacted]
LYs accrued: Post Progression Survival	[redacted]	[redacted]	[redacted]
Quality adjusted life-years (QALY) accrued	[redacted]	[redacted]	[redacted]
QALYs accrued: Progression Free Survival	[redacted]	[redacted]	[redacted]
QALYs accrued: Post progression Survival	[redacted]	[redacted]	[redacted]
Total Cost	[redacted]	[redacted]	[redacted]
Incremental costs		[redacted]	[redacted]
Incremental QALYs		[redacted]	[redacted]
Incremental LY		[redacted]	[redacted]
Cost per QALY gained		£45,938	Cd is dominated

Bd = bortezomib and dexamethasone; Cd = carfilzomib and dexamethasone; DBd = daratumumab, bortezomib and dexamethasone; LY = life years; OS = overall survival; QALY = quality-adjusted life year.

Table 11 Updated summary results of scenario analyses - cost per QALY gained

	Scenario		**ICER (£) DBd vs Bd**	**ICER (£) DBd vs Cd**
0	Base case		£35,196	DBd dominated Cd
1	Different survival curves	Unadjusted OS	£45,938	DBd dominated Cd
2		PFS Weibull	£36,356	DBd dominated Cd
3		Bd OS Gompertz	£32,791	DBd dominated Cd
4		DBd OS exponential	£36,147	DBd dominated Cd

	Scenario		ICER (£) DBd vs Bd	ICER (£) DBd vs Cd
5	Longer subsequent treatment duration	13 months	£37,669	DBd dominated Cd
6		15 months	£38,955	DBd dominated Cd
7	Different time horizons	5 years	£96,462	DBd dominated Cd
8		10 years	£54,239	DBd dominated Cd
9		20 years	£37,112	DBd dominated Cd
10	Allow vial sharing		£35,160	DBd dominated Cd
11	Dose intensity option off		£36,787	DBd dominated Cd

Bd = bortezomib and dexamethasone; B = bortezomib; Cd = carfilzomib and dexamethasone; DBd = daratumumab, bortezomib and dexamethasone; ICER = incremental cost-effectiveness ratio; LY = life years; OS = overall survival; PFS = progression-free survival; TTD = time to treatment discontinuation; QALY = quality-adjusted life year.

Table 12 Updated summary results of scenario analyses for discount rates

Scenario 12						
Health benefit discount	**0%**		**1.5%**		**6.0%**	
Cost discount	ICER (£) DBd vs Bd	ICER (£) DBd vs Cd	ICER (£) DBd vs Bd	ICER (£) DBd vs Cd	ICER (£) DBd vs Bd	ICER (£) DBd vs Cd
0%	£28,963	DBd dominated Cd	£33,895	DBd dominated Cd	£51,248	DBd dominated Cd
1.5%	£26,986	DBd dominated Cd	£31,583	DBd dominated Cd	£47,751	DBd dominated Cd

6%	£22,527	DBd dominated Cd	£26,364	DBd dominated Cd	£39,861	DBd dominated Cd

Bd = bortezomib and dexamethasone; Cd = carfilzomib and dexamethasone; DBd = daratumumab, bortezomib and dexamethasone; ICER = incremental cost-effectiveness ratio.

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Evidence Review Group Report commissioned by the
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Daratumumab in combination with bortezomib and dexamethasone for treating relapsed or refractory multiple myeloma (Review of TA573)

Evidence Review Group's summary and critique of the company's response to technical engagement

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LIST OF ABBREVIATIONS

1PL	One prior line
AIC	Akaike information criterion
ASCT	Autologous stem cell transplant
Bd	Bortezomib and dexamethasone
Cd	Carfilzomib in combination with dexamethasone
CS	Company submission
DBd	Daratumumab in combination with bortezomib and dexamethasone
DCA	Data collection arrangement
EAG	External Assessment Group
EAR	External assessment report
EQ-5D-5L	EuroQol Five Dimensions Questionnaire
HMRN	Haematological Malignancy Research Network
HR	Hazard ratio
HRQoL	Health-related quality of life
ICER	Incremental cost effectiveness ratio
ILd	Ixazomib with lenalidomide and dexamethasone
IPCW	Inverse probability of censoring weights
KM	Kaplan-Meier
LRI	Leicester Royal Infirmary
MM	Multiple myeloma
NDMM	Newly diagnosed multiple myeloma
NHS	National Health Service
NICE	National Institute for Health and Clinical Excellence
NIHR	National Institute for Health Research
OS	Overall survival
PAS	Patient Access Scheme
PFS	Progression-free survival
QALY	Quality-adjusted life year
SACT	Systemic Anticancer Therapy
SHTAC	Southampton Health Technology Assessments Centre
TE	Technical engagement
UK	United Kingdom

1. Introduction

This document is the External Assessment Group's (EAG) summary and critique of the response by the company, Janssen-Cilag Ltd, to the key issues for technical engagement (TE) proposed in the EAG report for this appraisal (submitted to NICE on 20/10/2022). The EAG received the company's response on 22/12/22.

The company's TE response form contains the following information:

- A written response to each of the five key issues, one of which includes new evidence and analyses (see Table 1).
- A written response to two additional issues, neither of which includes new evidence or analyses (see Table 1)
- A set of updated cost-effectiveness results, incorporating three changes to their base case model assumptions.
- A set of sensitivity- and scenario analyses conducted on their updated base case model.
- An updated version of the company's economic model accompanying the response form.

In this report we present the following:

- Our critique of the company's response to each of the five issues for technical engagement (Section 2)
- A validation of the results of the company's updated cost-effectiveness analysis (Section 3)

Table 1 Summary of key issues for technical engagement

Issue number	Summary of issue	Does this response contain new evidence, data or analyses?
1	Uncertainty about overall survival in the Systemic Anticancer Therapy (SACT) dataset	No
2	Absence of real-world data for second-line patients receiving bortezomib plus dexamethasone (Bd)	Yes
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])	No
4	Difference in the OS estimates for DBd obtained from the real-world evidence-SACT database and the company's trial CASTOR	No
5	Extrapolation of OS in the Bd arm	No
Additional issue 1[a]	Collection of HRQoL data in CASTOR	No
Additional issue 2[a]	Source of drug acquisition costs	No

[a] The additional issues have been numbered by the company, they are not numbered in the external assessment report (EAR). In the EAR, additional issue 1 is noted in sections 1.6 and 3.2.3.2 and additional issue 2 in section 4.2.8.

2. Critique of the company's response to key issues for technical engagement

2.1 Issue 1 – Uncertainty about overall survival in the Systemic Anticancer Therapy (SACT) dataset

Summary of the issue

The SACT dataset provides evidence from [redacted] NHS patients treated with DBd in England but i) the median follow-up for OS [redacted] and median OS has not been reached for the SACT cohort, ii) Only three baseline patient characteristics are reported for the SACT dataset and the extent to which differences in population characteristics between

SACT and CASTOR have influenced OS is uncertain, iii) Some patients in the SACT dataset could have received [redacted] which may have had an impact on OS in the SACT database.

Critique of the company's response

The company reiterates that the primary source of data, as per the Data Collection Arrangement (DCA) for TA573, is the phase III CASTOR study and that the SACT dataset is a secondary data source whose results should be interpreted with caution due to the issues raised and noted above (in the 'Summary of the issue'). The company provides a helpful reminder of data provided in their response to clarification questions which gives some information about [redacted]. Two sources of market share data that the company cite (Ipsos Healthcare Cancer Therapy Monitor – UK) and HARMONY market research data) show that ILd use exceeded [redacted] from 2020 in the one prior line (1PL) setting and peaked at approximately [redacted] in Q1 of 2021. It is not clear to the EAG if this data is specifically for the 1PL setting in patients with multiple myeloma (MM) specifically or any cancer more generally, but nevertheless it provides some indication of the level of ILd use [redacted]

2.2 Issue 2 – Absence of real-world data for second-line patients receiving bortezomib plus dexamethasone (Bd)

Summary of the issue

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 carfilzomib in combination with dexamethasone (Cd). The company submission (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.

Critique of the company's response

The company has explored what plausible real-world Bd curves might look like by investigating two alternative real-word evidence sources for standard of care and by

simulating a Bd OS curve using the inverse probability of censoring weights (IPCW) adjusted hazard ratio from CASTOR.

The key features of the two real-world evidence data sources are summarised in Table 2. The company points out that neither data source is fully representative of English MM patients because in both datasets approximately 80% of patients were ineligible for autologous stem cell transplant (ASCT) at diagnosis compared with ~66% for England as a whole and compared with the SACT dataset where [redacted]. That a greater proportion were ineligible for ASCT, suggests that the populations in both the real-world evidence sources are likely to be older and less fit than the population in England as a whole. This is supported by baseline data reported in the company's TE response Table 1 for the Leicester Royal Infirmary (LRI) HONEUR Federated Data Network population which has a [redacted].

Table 2 Features of two real-world evidence sources for standard of care

Data source and Geographical coverage	Haematological Malignancy Research Network (HMRN) cohort study. Established in the UK in 2004, the region covers the area formerly served by the Yorkshire and the Humber and Yorkshire Coast Cancer Networks, a region comprising a total population of 3.8 million	Retrospective audit of second-line (non-DBd) outcomes from Leicester Royal Infirmary (LRI, part of the HONEUR Federated Data Network)
Data analysed	OS among second-line adult patients diagnosed with MM between 01/01/2008 and 31/08/3015 and receiving treatment with bortezomib based therapy	OS among all non-DBd second-line patients (due to the low number of Bd patients), covering the period from [redacted] to [redacted]
Proportion with no prior ASCT	80%	[redacted]
Sample size	N = 348	N = 216
Median follow-up	Not stated	[redacted] months
Median OS	19.2 months from the start of second-line treatment	[redacted] months for second-line (non-DBd) patients

Source: Compiled by the EAG from information provided in the company response to technical engagement issue 2

Median OS in the two data sources (Table 1, 19.2 months for bortezomib based therapy in the HMRN cohort and [redacted] months for non-DBd therapy in the LRI (HONEUR Federated Data Network) population) is much lower than median OS in IPL patients in the CASTOR trial who received Bd (47.0 months, 95% CI 32.6 to 58.7) which is the population of relevance to this appraisal. We note that the company's technical engagement response makes a comparison with the CASTOR trial giving a value of 39.5 months which we cannot identify, unless the company are making a comparison with median OS in the CASTOR ITT population (Bd arm 38.5 months) and have made a typographical error.

The company present the Kaplan-Meier (KM) plots for OS in their TE response Figures 1 and 2. The trajectories of these KM plots indicate no patients are expected to be alive after 10 years.

The final part of the company's response to Issue 2 is to conduct an exploratory analysis simulating a Bd arm for the SACT dataset using the relative treatment effect observed in CASTOR. Both we and the company are aware that there are significant methodological issues with this approach, which the company summarises in their response, but nevertheless we felt this 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, and we are glad the company has taken the opportunity to conduct this analysis.

The first step in simulating a Bd arm for the SACT dataset was for the company to extrapolate the DBd SACT OS KM curve (because there is only median OS has not been reached for the SACT cohort and median follow-up for OS is only [redacted]. Details are provided in the company's TE response to issue 2, but in brief the DBd SACT curve was digitised, simulated patient level data was generated using the Guyot algorithm and then standard parametric distributions were fitted. After considering model fits by visual comparison to original KM curve, statistical goodness-of-fit (Akaike information criterion (AIC) statistics and Bayesian information criterion (BIC) statistics) and clinical validity at key milestones (proportion of patients alive at 5-year intervals from 5 years to 30 years and clinical expert feedback) the company selected the Weibull distribution. We agree with the company that the Weibull distribution is an appropriate choice.

The second step in simulating the Bd arm for the SACT dataset was to apply the IPCW-adjusted hazard ratio for OS from CASTOR (HR = [redacted]) to the SACT DBd reference curve generated in the first step above (as described in the original CS and EAG report, the IPCW-adjustment of OS data was conducted to reduce bias in the treatment effect related to the use of post-progression therapies unavailable in England and the greater proportion of these therapies used in the Bd arm of the CASTOR trial). The company present their results in a figure which we reproduce below (Figure 1). The EAG agrees with the company that this exploratory analysis should be interpreted with caution given that it relies on i) extrapolation of SACT DBd data (blue curve), ii) simulated Bd data (grey curve) and iii) makes a naïve comparison with two different real-world data sources (Bd green line with red tail, non-DBd black line). However, despite the caveats, we find this exploratory analysis useful because it suggests that there is clinical plausibility to the company's assertion that the relative treatment effect observed in CASTOR will hold in the real world.

Source: Reproduction of company figure 5

Figure 1 Simulated Bd OS vs DBd SACT extrapolation OS

2.3 Issue 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])

Summary of the issue

The EAG believes that the 24-month survival in a population containing a mix of ASCT-negative and ASCT-positive patients who had not received daratumumab would be higher than 24-month survival among first-line ASCT-negative patients from the NDMM standing cohort who had not received daratumumab (because of the greater OS rate for ASCT-positive patients).

Critique of the company's response

The company clarify the purpose of their naïve comparison of OS rates for DBd patients in the SACT dataset and newly diagnosed patients in the NDMM standing cohort who did not receive an ASCT and did not receive daratumumab as a subsequent treatment was to put into context the SACT OS outcome against a similar real-world evidence source. The company then reiterate their point that the proportion of patients treated with DBd second - line and alive at 24-months in the SACT dataset ([redacted]%) compares favourably with the [redacted]% OS rate at 24 months for first-line for transplant-ineligible patients in the NDMM standing cohort who did not receive daratumumab during their course of treatment. The company point out that the 24-month survival rate for SACT is for the period from the initiation of second-line therapy and that the survival rate from diagnosis for patients treated with DBd at second-line would be higher.

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

Summary of the issue

Data from the SACT dataset shows that 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 from CASTOR used in the company's base case are likely to be more favourable than would be expected in routine NHS practice.

Critique of the company's response

The company has implemented the age and gender distribution observed in SACT in their model, but they note that this introduces an inconsistency with all the other efficacy inputs in the model (which for DBd and Bd are based on the CASTOR trial). The company also maintains that whilst the CASTOR trial data extrapolations may be more favourable than

expected in NHS practice, the relative treatment effect is likely to hold in the real-world (as discussed under 2.2 Issue 2 above).

We had suggested that the company could conduct an exploratory scenario analysis using OS extrapolation for DBd from SACT and the simulated Bd curve (the SACT DBd extrapolation and simulated Bd curve have been provided in the company's TE response as discussed under 2.2 Issue 2 above). The company believe a such a scenario, based on evidence from the lower end of NICE's hierarchy of evidence, would introduce unnecessary uncertainty into the economic modelling and given the limitations of the analyses presented in section 2.2 these data are not suitable for inclusion in the economic model. Instead, the company propose that it is expected that cost-effectiveness based on CASTOR data will translate into cost-effectiveness in the real-world, particularly taking into account the simple discount PAS for daratumumab. We have noted the company's concerns and acknowledge the uncertainties about estimating the real-world comparative effectiveness of DBd versus Bd (as discussed within Issue 2 above). However, despite the caveats, we view that conducting an **exploratory** cost-effectiveness scenario, using the additional information provided within Issue 2, although speculative would illustrate the degree of impact on the cost-effectiveness ratio and might aid the company's assertion that the relative treatment effect observed in CASTOR will translate in the real world.

2.5 Issue 5 – Extrapolation of OS in the Bd arm

Summary of the issue

The company's base case Bd OS extrapolation (Gompertz distribution) predicts a survival rate of 0% at 10 years. This is inconsistent with estimates from other cost-effectiveness studies and EAG expert advice where which estimates survival lies between 8-20% at 10 years.

Critique of the company's response

In their response to the technical engagement, the company revised their base-case model selection from Gompertz to Weibull distribution. They cited several reasons for their selection, including: i) good visual and statistical fit; ii) a small proportion of patients likely to be alive at 10 years; and iii) retaining a shape consistent with the observed hazard function (company TE response Figure 6). Furthermore, the company point out that Weibull was the Committee preferred distribution for Bd in TA457 giving comparable life-year gained estimates of [redacted] based on the updated cost-effectiveness model, and 3.34 in the appraisal of carfilzomib. We accept the company's arguments and agree that it is appropriate to extrapolate Bd using the Weibull distribution.

2.6 Additional Issue – Collection of HRQoL data in CASTOR

We were aware that the company was assessing additional EQ-5D-5L data from CASTOR and believed it would be helpful to assess whether the additional data were consistent with the values used in the model and if they were not, what impact different values would have on the overall cost-effectiveness results. The company have advised that there is no additional value of performing further analysis because of a sudden drop in the rate of compliance in completing the questionnaire starting at about treatment cycle 40 (Company TE response Figure 7 and reproduced below as Figure 2). The company do not provide any further information on the reasons behind the drop in compliance.

Overall, we agree with the company's initial approach to use the same utility values that were accepted by the committee in the original appraisal.

Source: Figure 7 from the company's response to the technical engagement document

Figure 2 Compliance with EQ-5D-5L Assessment over tie (ITT population): final data cut, pre-progression

2.7 Additional Issue – Source of drug acquisition costs

The company confirms that they agree with the use of eMIT prices for drugs and the EAG notes that the company have used eMIT prices for drug costs when generating the cost-effectiveness estimates they present in their TE response.

3. Updated cost-effectiveness results – EAG summary and critique

3.1 Company's revised base case cost-effectiveness results

In response to the technical engagement the company made three changes to their base case model assumptions as stated in Table 6 of the company's TE response document. These are:

- Using baseline characteristics of age and gender from the SACT population
- Using Weibull distribution to extrapolate the Bd OS arm
- Using eMIT prices for drug costs

All these changes cumulatively resulted in an ICER of [redacted] per QALY for DBd versus Bd; this is an increase of [redacted] versus the company base case following corrections based on the EAG clarification questions.

Critique of the company's response:

The EAG agree with the company's revised assumptions for their base case. We replicated the company's revised base case results as well as those for all the scenarios, except for the following shown in Table 3 below.

Table 3 Inconsistency in the cost-effectiveness results – cost per QALY gained

Scenario	Company's result **ICER DBd vd Bd**	EAG result **ICER DBd vd Bd**
PFS Weibull distribution	[redacted]	[redacted]

3.2 EAG's revised preferred assumptions

The EAG agree with the company's revised base case assumptions (as discussed above). For clarity, we provide a summary of the preferred model assumptions on the cost-effectiveness model before and in response to technical engagement in Table 4 below.

Table 4 Summary of the preferred model assumptions on the cost-effectiveness model

Model features	Before technical engagement		Changes made in response to technical engagement	
	Company's base case assumptions	EAG preferred assumptions	Company's revised base case assumptions	EAG preferred assumptions
Baseline characteristics	Based on CASTOR	Based on SACT	Same as EAG preferred assumption before technical engagement	Agree with all three of the company's revised base case assumptions in response to the technical engagement
Bd OS extrapolation	Gompertz	Exponential	Weibull	
Drug costs	Based on MIMS	Based on eMIT	Same as EAG preferred assumption before technical engagement	