SMC2891

daratumumab solution for injection (Darzalex®)

Johnson & Johnson

09 October 2026

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHSScotland. The advice is summarised as follows:

ADVICE: following a full submission assessed under the orphan medicine process

daratumumab (Darzalex ®) is accepted for restricted use within NHSScotland.

Indication under review: in combination with bortezomib, lenalidomide and dexamethasone for the treatment of adult patients with newly diagnosed multiple myeloma.

SMC restriction: for use in patients who are ineligible for autologous stem cell transplant (ASCT).

An open-label, phase III study demonstrated that daratumumab plus bortezomib, lenalidomide and dexamethasone had a significantly higher minimal residual disease (MRD)-negativity rate and improved progression free survival (PFS) compared with bortezomib, lenalidomide and dexamethasone in patients with newly diagnosed multiple myeloma. Results from a transplant ineligible subpopulation were consistent with the intention to treat (ITT) population. Indirect evidence suggested improved PFS versus daratumumab, lenalidomide and dexamethasone but no evidence of a difference for overall survival.

This advice takes account of the views from a Patient and Clinician Engagement (PACE) meeting.

This advice applies only in the context of an approved NHSScotland Patient Access Scheme (PAS) arrangement delivering the cost-effectiveness results upon which the decision was based, or a PAS/ list price that is equivalent or lower.

Co Vice Chair
Scottish Medicines Consortium

1. Clinical Context

1.1. Medicine background

Daratumumab is an immunoglobulin G1 kappa (IgG1K) human monoclonal antibody. It binds to and inhibits CD38, a protein expressed at a high level on the surface of multiple myeloma tumour cells, which leads to immune mediated tumour cell death.[1]

The recommended dose of daratumumab in combination with bortezomib, lenalidomide and dexamethasone is 1,800 mg by subcutaneous injection. Further information including the dosing schedule is included in the summary of product characteristics (SPC).[1] For dosing information relating to bortezomib, lenalidomide and dexamethasone consult the individual SPCs.

1.2. Disease background

Multiple myeloma is an incurable haematological cancer characterised by the proliferation of clonal plasma cells in the bone marrow. This can result in complications such as hypercalcaemia, bone disease, renal failure, anaemia, and infections; the most common presenting symptoms are bone pain and anaemia. Multiple myeloma predominantly affects older people and the median age at diagnosis is approximately 70 years. In all patients with multiple myeloma, the overall survival rate is 61% at 5 years.[2, 3]

1.3. Company proposed position

The submitting company has requested that daratumumab in combination with bortezomib, lenalidomide and dexamethasone is restricted for use in patients who are ineligible for autologous stem cell transplant (ASCT).

Daratumumab in combination with bortezomib, lenalidomide and dexamethasone is undergoing a separate review when positioned for use in patients who are eligible for ASCT (SMC2913).

1.4. Treatment pathway and relevant comparators

The choice of first line treatment for multiple myeloma is patient specific and dependent on various factors including age, frailty, co-morbidities, and eligibility to receive high-dose induction chemotherapy with ASCT. Generally, ASCT are recommended for younger fitter patients however selected patients over 70 years with a low mortality risk may also be considered.[3]

Cancer Medicines Outcome Programme Public Health Scotland (CMOP-PHS) data indicate that most patients with multiple myeloma who were ineligible for ASCT receive daratumumab, lenalidomide and dexamethasone. Small proportions received lenalidomide and dexamethasone; daratumumab and lenalidomide; bortezomib and dexamethasone; and lenalidomide monotherapy.[4] Since the publication of this report, isatuximab plus bortezomib, lenalidomide and dexamethasone has been accepted by SMC (SMC2804) and most clinical experts indicated this is the predominant treatment for fitter patients who are ineligible for ASCT. However, as this advice was recently published, the submitting company were not required to include isatuximab plus bortezomib, lenalidomide and dexamethasone as a comparator. Therefore, the most relevant comparator for this submission is daratumumab, lenalidomide and dexamethasone.

1.5. Category for decision-making process

Eligibility for a PACE meeting

Daratumumab meets SMC orphan criteria.

2. Summary of Clinical Evidence

2.1. Evidence for the licensed indication under review

Evidence to support the efficacy and safety of daratumumab plus bortezomib, lenalidomide and dexamethasone is from the CEPHEUS study as detailed in Table 2.1.

Table 2.1. Overview of relevant study

Criteria	CEPHEUS [5, 6]
Study design	a multicentre, randomised, open-label, parallel group, phase III study

Eligible patients	• Adult patients aged ≥18 years.
	• Newly diagnosed multiple myeloma (as per IMWG criteria) with evidence of measurable disease.
	• Not considered a candidate for high-dose chemotherapy with ASCT as:
	  ○ Aged ≥65 years or
	  ○ Aged 18 to 65 years with comorbid condition(s) likely to have a negative impact on tolerability of high-dose chemotherapy with stem cell transplant; or who refuse high-dose chemotherapy with stem cell transplant as initial treatment
	• ECOG performance status score of 0 to 2

Treatments	Patients were randomised to receive bortezomib, lenalidomide and dexamethasone with or without daratumumab 1,800 mg by SC injection once weekly in cycles 1 and 2, every 3 weeks in cycles 3 to 8 and every 4 weeks from cycle 9 onwards. Bortezomib, lenalidomide and dexamethasone were dosed and administered per the CEPHEUS study protocol. Cycles 1 to 8 were 21 days and cycles 9 onwards were 28 days. After cycle 8, patients continued lenalidomide and dexamethasone with or without daratumumab until disease progression or unacceptable toxicity.
Randomisation	Randomisation was equal and stratification was according to international staging system (Stage I, II, or III, based on β-2 microglobulin and albumin by central laboratory), and age/transplant eligibility (<70 years ineligible, or age <70 years and refusal to transplant, or age ≥70 years).
Primary outcome	Overall MRD negativity rate: proportion of patients who achieve MRD negativity (at 10^{-5}) by NGS on bone marrow aspirate and achieved CR or better response.
Secondary outcomes	Key secondary outcomes were investigator assessed and tested in the following hierarchical order: • CR or better rate: proportion of patients who achieve CR or sCR per IMWG 2011 criteria during or after the study treatment. • PFS: time from the date of randomisation to disease progression per IMWG 2011 criteria or death due to any cause. • Durable MRD negativity rate: proportion of patients who achieved CR or better response and achieved MRD negative status (at 10^{-5}) at two bone marrow examinations that are a minimum of one year apart, without any examination showing MRD positive status in between.
Statistical analysis	A hierarchical statistical testing strategy was applied in the study with no formal testing of outcomes after the first non-significant outcome in the hierarchy. The primary and selected secondary outcomes including, CR or better rate, PFS and durable MRD negativity rate were sequentially tested.

Abbreviations: ASCT = autologous stem cell transplant; CR = complete response; ECOG = Eastern Cooperative Oncology Group; IMWG = IMWG = International Myeloma Working Group; NGS = next generation sequencing; OS = overall survival; PFS = progression free survival; MRD = minimal residual disease; SC = subcutaneous; sCR = stringent complete response

At the primary analysis for the primary outcome (data cut: 08 April 2021; median follow-up 22.3 months) daratumumab plus bortezomib, lenalidomide and dexamethasone (hereafter referred to as the daratumumab group) was associated with a significantly higher overall MRD negativity rate (at 10^{-5}) compared with the lenalidomide, bortezomib and dexamethasone (hereafter referred to as the control group). There were also significant improvements at pre-specified boundaries in hierarchically tested secondary outcomes including progression free survival (PFS), sustained MRD negativity rate and complete response or better rate in the daratumumab group compared with the control group. The beneficial effects in the daratumumab group compared with the control group were maintained at the 07 May 2024 data cut (final PFS analysis; median follow-up 58.7 months). The overall survival data remain immature. Results from the most recent data cut have been detailed in Table 2.2.[5, 6]

Table 2.2. Key efficacy results for CEPHEUS study in ITT population (data cut: 07 May 2024).[5-7]

	Daratumumab group (n=197)	Control group (n=198)
Median follow-up	58.7 months	
Primary outcome: Overall MRD negativity rate (at 10^{-5}) in bone marrow[a]		
Rate, n (%)	120 (61%)	78 (39%)
Odds ratio, 95% CI	2.37 (1.58 to 3.55)	
Secondary outcome: Sustained MRD negativity[a]		
Rate, n (%)	96 (49%)	52 (26%)
Odds ratio, 95% CI	2.63 (1.73 to 4.00)	
Secondary outcome: Complete response or better per IMWG 2011 criteria[a]		
Rate, n (%)	160 (81%)	122 (62%)
Odds ratio, 95% CI	2.73 (1.71 to 4.34)	
Secondary outcome: Progression free survival per IMWG 2011 criteria[a]		
Events, n	63	91
Median PFS	NR	53 months
Hazard ratio, 95% CI	0.57 (0.41 to 0.79)	
PFS rate 54 months	68%	50%

Abbreviations: CI = confidence interval; IMWG = International Myeloma Working Group; ITT = intention to treat; MRD = minimal residual disease; NR = not reached; PFS = progression free survival. [a]The primary and secondary outcomes were assessed by the investigator.

*Other data were also assessed but remain confidential.**

The submitting company also conducted two post hoc sensitivity analysis that adjusted for the impact of COVID-19 on OS. The first censored any death caused by COVID-19 and the second censored any death in which COVID-19 was considered a competing risk. At the 07 May 2024 data cut, there were more deaths caused by COVID-19 in the daratumumab group (n=15) compared with the control group (n=9) and the results of the two sensitivity analyses indicated a more pronounced OS benefit for daratumumab compared with the control group (hazard ratio [HR] 0.69, 95% confidence interval [CI]: 0.45 to 1.05 and HR 0.67, 95% CI: 0.44 to 1.03).[5]

2.2. Evidence to support the positioning proposed by the submitting company

To support the proposed positioning, the submitting company presented evidence from a post-hoc subgroup analysis of patients that were transplant ineligible (referred to as the transplant ineligible population) which included patients aged <70 years and ineligible for ASCT, and patients aged ≥70 years. This included 73% (289/395) of the ITT population. Patients aged <70 years who refused transplant were excluded from the analysis as they were considered to be transplant deferred or refused transplant and were deemed not relevant to this submission. Results from the transplant ineligible population from the most recent data cut have been detailed in Table 2.3.

Table 2.3. Key efficacy results for CEPHEUS study in the transplant ineligible population (data cut: 07 May 2024).[8, 9]

	Daratumumab group (n=144)	Control group (n=145)
Median follow-up	58.7 months	
Primary outcome: Overall MRD negativity rate in bone marrow[a]		
Rate (10^{-5}), n(%)	87 (60%)	57 (39%)
Odds ratio, 95% CI	2.37 (1.47 to 3.80)	
Secondary outcome: Progression free survival per IMWG 2011 criteria [a]		
Follow-up	58.7 months	
Events	-	-
Median PFS	NR	49.6 months
Hazard ratio (95% CI)	0.51 (0.35 to 0.74)	
PFS rate at 54 months	69%	48%

Abbreviations: CI = confidence interval; ITT = intention to treat; MRD = minimal residual disease; NR = not reached; PFS = progression free survival. [a] Investigator assessed.

Additional post hoc PFS and OS analyses were conducted in the transplant ineligible population which censored deaths due to COVID-19. There were more deaths caused by COVID-19 in the daratumumab group compared with the control group. The results, similar to the ITT population, also indicated a more pronounced PFS and OS benefit compared with the full transplant ineligible population results (and OS HR 0.55; 95% CI: 0.34 to 0.90).[8, 9]

*Other data were also assessed but remain confidential.**

2.3. Health-related quality of life outcomes

Health Related Quality of Life (HRQoL) was assessed using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 (EORTC QLQ-C30), European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire Multiple Myeloma Module 20 (EORTC QLQ-MY20) and EuroQol 5-Dimension 5-Level (EQ-5D-5L). Compliance rates were high at baseline and remained so at all timepoints. In the ITT population, the improvements in HRQoL and physical functioning, and reductions in symptoms (pain, fatigue and overall disease symptoms) were similar in both treatment groups throughout the study. The submitting company reported similar results in the transplant ineligible population.[7, 10]

*Other data were also assessed but remain confidential.**

2.4. Indirect evidence to support clinical and cost-effectiveness comparisons

In the absence of direct evidence versus daratumumab, lenalidomide and dexamethasone, the submitting company conducted an indirect treatment comparison. The results have been detailed in Table 2.4.

Table 2.4: Summary of indirect treatment comparison

<table>
<tr><th>Criteria</th><th>Overview</th></tr>
<tr><td>Design</td><td>Inverse probability of treatment weighting (IPTW)</td></tr>
<tr><td>Population</td><td>Adult patients with newly diagnosed multiple myeloma (NDMM) who are ineligible for autologous stem cell transplant (ASCT)</td></tr>
<tr><td>Comparator</td><td>Daratumumab, lenalidomide and dexamethasone</td></tr>
<tr><td>Studies included</td><td>CEPHEUS[5, 7, 8] (transplant ineligible population) and MAIA[11, 12]</td></tr>
<tr><td>Outcomes</td><td>Minimal residual disease (MRD)-negative CR (complete response) rate, progression free survival (PFS) and overall survival (OS)</td></tr>
<tr><td>Results</td><td>The base case results of the IPTW indirect treatment comparison (ITC) suggest that daratumumab plus bortezomib, lenalidomide and dexamethasone is superior to daratumumab, lenalidomide and dexamethasone for MRD-negative CR rate, PFS and OS. In sensitivity analysis for PFS and OS unadjusted for COVID-19 deaths in the daratumumab plus bortezomib, lenalidomide and dexamethasone group, the quadruplet therapy remained superior for PFS but there was no evidence of a difference between groups for OS.

Table 2.3.1 Results of the indirect treatment comparison
<table>
<tr><th></th><th>Base case</th><th>Sensitivity analysis (unadjusted for COVID-19 deaths)</th></tr>
<tr><td>MRD-negative CR rate odds ratio (95% CI)</td><td>3.04 (2.01 to 4.61)</td><td>-</td></tr>
<tr><td>PFS hazard ratio (95% CI)</td><td>0.55 (0.38 to 0.79)</td><td>0.62 (0.44 to 0.88)</td></tr>
<tr><td>OS hazard ratio (95% CI)</td><td>0.63 (0.41 to 0.98)</td><td>0.80 (0.53 to 1.19)</td></tr>
</table>
As part of the ITC, the submitting company provided an unadjusted comparison of Grade 3 or 4 AEs with an incidence of ≥ 5% from the CEPHEUS and MAIA studies. In general, the frequency of most reported grade 3 or 4 AEs was lower or similar in the daratumumab plus bortezomib, lenalidomide and dexamethasone versus daratumumab, lenalidomide and dexamethasone except for thrombocytopenia, diarrhoea (12% versus 9%) and peripheral sensory neuropathy which were higher.</td></tr>
</table>

3. Summary of Safety Evidence

Evidence from the CEPHEUS study supports the relative safety of daratumumab in combination with bortezomib, lenalidomide and dexamethasone compared with bortezomib, lenalidomide and dexamethasone for the treatment of patients with newly diagnosed multiple myeloma who are ineligible for ASCT. However, triplet therapy with bortezomib, lenalidomide and dexamethasone is not considered a relevant comparator in this submission.

In the CEPHEUS study, at the May 2024 data cut, the median duration of study treatment was 56 months in the daratumumab group and 34 months in the control group. In the daratumumab and control groups respectively, all patients experienced a treatment-emergent adverse event (TEAE) and these were considered treatment related in 99% (195/197) and 97% (190/195). Serious TEAEs were reported by 72% and 67%, any grade 3 or 4 adverse event was reported by 92% versus 86%

and patients discontinuing treatment due to a TEAE were 7.6% versus 16%. The number of fatal adverse events was higher in the daratumumab group compared with the control group (37 deaths versus 25 deaths); the regulator noted that longer treatment exposure in the daratumumab group, particularly during the COVID-19 pandemic may have contributed to the difference.[5, 6]

The most common grade 3 or 4 TEAE with an incidence of ≥ 10% in either treatment group were: neutropenia (44% versus 30%), infection (40% versus 32%), thrombocytopenia (28% versus 20%), pneumonia (14% versus 13%), anaemia (13% versus 12%), lymphopenia (12% versus 10%), diarrhoea (12% versus 9.2%), hypokalaemia (12% versus 6.2%), COVID-19 (11% versus 4.6%). The safety profile in the transplant ineligible population was broadly consistent with the ITT population.[5, 6] The safety results from the daratumumab group from the transplant ineligible population have been used in the economic analysis.

The regulator considered that the safety profile of daratumumab in combination with bortezomib, lenalidomide and dexamethasone was as expected based on the patient population, backbone therapy and known safety profile of subcutaneous daratumumab. See the SPC for further safety information.[1, 6]

4. Summary of Clinical Effectiveness Considerations

4.1. Key strengths

- In the ITT population of the CEPHEUS study, daratumumab plus bortezomib, lenalidomide and dexamethasone was associated with a significantly higher MRD negativity rate in patients achieving a complete response or better compared with bortezomib, lenalidomide and dexamethasone alone. This was supported by a statistically significant improvement in PFS and other hierarchically tested outcomes including CR rate or better and sustained MRD negativity rate. The results of the primary and secondary outcomes were considered clinically meaningful by regulators.[5, 6]
- In the transplant ineligible subgroup, the population relevant to the proposed positioning, there were improvements in MRD negativity rate and PFS in the daratumumab group compared with the control group which were consistent with the ITT population.[8]

4.2. Key uncertainties

- There is no direct evidence versus daratumumab, lenalidomide and dexamethasone which is the most relevant comparator for this submission, therefore the submitting company conducted an indirect treatment comparison which was associated with a number of limitations which increase the uncertainty of the results. These included methodological issues with an unanchored design and assumptions associated with the IPTW approach, differences between studies in terms of follow-up and assessment of survival outcomes, and immaturity of survival data. Furthermore, data for daratumumab plus bortezomib, lenalidomide and dexamethasone base case is from a subgroup which has then been adjusted further for COVID-19 deaths.

- As the CEPHEUS study was conducted during the COVID-19 pandemic, the submitting company presented additional analyses for PFS and OS with deaths due to COVID-19 censored. There were more deaths caused by COVID-19 in the daratumumab group compared with the control group. After censoring for COVID-19 deaths, the PFS and OS improved in favour of the daratumumab group in both the ITT population and transplant ineligible population. However, these results are associated with additional uncertainty and should be interpreted with caution as the analysis was conducted post hoc, and the numbers were low which makes it difficult to draw conclusions on patient characteristics that may have affected outcomes on study treatment. These results have been used to inform the economic analysis.[5, 8]
- At the most recent May 2024 data cut, OS data remained immature as most patients on the study remained alive (72% of the ITT population and 72% of the transplant ineligible population). Furthermore, OS was not included in the hierarchical testing procedure and therefore results are descriptive only. Survival data will be collected in the follow-up phase until the end of the study. The regulator noted that there did not appear to be any obvious detriment to OS by adding daratumumab to bortezomib, lenalidomide and dexamethasone in patients ineligible for treatment with ASCT.[6]
- The ITT population of the CEPHEUS study was broader than the population of relevance for this submission as it included patients who were eligible for ASCT but refused a transplant as initial therapy. The submitting company presented a subgroup analysis in the transplant ineligible patients.[8] Although the results were consistent with the ITT population, this subgroup analysis was unplanned and results are descriptive only.
- CEPHEUS was an open-label study in which outcomes were assessed by the investigator. This may introduce potential bias as both patients and the investigators were aware of treatment allocations and were also responsible for the assessment of subjective efficacy, quality of life and safety outcomes.[6]

4.3. Clinical expert input

Most clinical experts consulted by SMC considered that daratumumab plus bortezomib, lenalidomide and dexamethasone would be used as a first line quadruplet treatment option in patients with multiple myeloma who are ineligible for ASCT.

4.4. Service implications

Clinical experts consulted by SMC indicated the impact on the patient and service would be minimal.

5. Patient and clinician engagement (PACE)

A patient and clinician engagement (PACE) meeting with patient group representatives and clinical specialists was held to consider the added value of **daratumumab**, as an **orphan** medicine, in the context of treatments currently available in NHSScotland.

The key points expressed by the group were:

- Multiple myeloma is an incurable, relapsing and remitting blood cancer. The symptoms and complications include severe bone pain, fractures, kidney damage, fatigue and a depleted immune system that can lead to increased infections. Patients who are ineligible for autologous stem cell transplant (ASCT) are more likely to be older or frailer and experience a heavy disease burden and high rate of treatment side effects. The continuous treatment courses and relapsing nature of the condition have a substantial impact on the quality of life of patients and carers.
- PACE clinicians highlighted that isatuximab quadruplet therapy is the most likely comparator in current practice (recently approved by SMC and therefore was not considered a comparator in this submission). Until recently, isatuximab has only been available as an intravenous infusion. It is now available as a subcutaneous injection, although this requires administration via an on-body injector or manual syringe by a healthcare professional. PACE participants agreed there is an unmet need for efficacious treatments with more convenient dosing and administration regimens.
- PACE clinicians noted that isatuximab quadruplet therapy and daratumumab quadruplet therapy have broadly similar efficacy and outcomes. However, the overall dosing of daratumumab is less frequent and it is given as a subcutaneous injection. This would reduce the frequency and duration of hospital visits, which would be advantageous for patients and their carers. The route of administration also eliminates the risk of first dose infusion reactions and thrombosis. In the longer-term patients may be able to self-administer daratumumab at home. There could also be benefits for the clinical service by increasing capacity in haematology day units, easing the workload pressure on clinical teams and reducing the cost of overall service delivery.
- This daratumumab quadruplet therapy is already used for transplant eligible patients and therefore haematology teams are familiar with the monitoring and management of common adverse events.
- The most appropriate place in the treatment pathway is as per the license and company proposed positioning.

Additional Patient and Carer Involvement

We received a patient group submission from Myeloma UK, which is a registered charity. Myeloma UK has received 2.03% pharmaceutical company funding in the past two years, including from the submitting company. A representative from the patient group participated in the PACE meeting. The key points of their submission have been included in the full PACE statement considered by SMC.

6. Summary of Comparative Health Economic Evidence

6.1. Economic case

Table 6.1 Description of economic analysis

Criteria	Overview
Analysis type	Cost-utility analysis
Time horizon	Lifetime
Population	Adult patients with NDMM.
Comparators	Daratumumab plus lenalidomide and dexamethasone (Ld).
Model description	The analysis is based on a partitioned survival model. Parametric distributions determine OS, PFS, and time to treatment discontinuation (TTD), but are constrained in a number of ways. OS hazards are maintained to be at least at general population levels; PFS is not permitted to exceed OS, and TTD to not cross PFS. Survival distributions are 'attenuated' to comply with clinical opinion as to possible long-term outcomes as modelled functions could not produce plausible outcomes.
Clinical data	Clinical data from CEPHEUS and MAIA were analysed in an indirect comparison using IPTW with an average treatment effect weighting approach, making use of individual participant data available for both studies. In addition to weighting adjustments, COVID-19 adjudicated deaths in CEPHEUS were censored. The analysis indicated statistically significant reductions in hazards for both PFS and OS with daratumumab plus bortezomib, lenalidomide and dexamethasone (BLd).
Extrapolation	Outcomes are modelled based on parametric functions up to five years for daratumumab plus BLd, and seven years for daratumumab plus Ld, reflecting greater follow-up availability in MAIA. Beyond this point the model is driven by setting event hazards such that the model complies with landmark point estimates for survival for each endpoint, according to expert clinical opinion.
Quality of life	The submitting company considered that as the only difference between the intervention (daratumumab plus BLd) and comparator (daratumumab plus Ld) is short, upfront, fixed duration bortezomib, treatment-independent health state utility values (HSUVs) are appropriate. Utility values from CEPHEUS are used in the base case with estimates from MAIA used in a scenario analysis. EQ-5D-5L scores from CEPHEUS were mapped to the EQ-5D-3L UK value set using the mapping function developed by Hernández Alava *et al*. (2017). There was better (higher) utility at later points in the progression free health state: HSUVs in cycles 9+ were higher than in Cycles 0–8. Therefore time-dependent progression free utilities were applied separately for cycles 0–8 and cycles 9+. Progressed disease was valued as being similar (marginally lower) in terms of utility to PFS. For adverse events one-off decrements were applied for the proportion of patients who experienced AEs.
Costs and resource use	In the model bortezomib is administered once weekly with the SPC-recommended dose delivered more conveniently than under the SPC-recommended twice-weekly schedule. Cost per administration for bortezomib is calculated using the mean BSA of ASCT-ineligible NDMM patients in CEPHEUS, with an assumption of no vial sharing for any treatment. Relative dosing intensity is applied based on CEPHEUS data. Costs for monitoring visits and tests are applied dependent on whether patients are on treatment. Concomitant treatment is applied as a single cost in the first cycle of the model as are adverse event costs based on the proportion of patients experiencing each event. An end of life cost is also applied. Costs of subsequent therapies were included calculated as weighted averages applied in all cycles for patients with progressed disease. Common estimates for uptake of subsequent therapies were applied in each arm other than after 1st line. According to the submitting company, based on CEPHEUS and MAIA, fewer patients who progressed received subsequent

	treatment following daratumumab plus BLd than after daratumumab plus Ld. This is attributed by the submitting company to PFS benefits associated with daratumumab plus BLd resulting in patients tending to be older at disease progression, and therefore less likely to receive subsequent treatments.
PAS/contract price	A Patient Access Scheme (PAS) was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHSScotland. Under the PAS, a discount was offered on the list price of daratumumab in DBLd. Contract prices are in place for bortezomib and lenalidomide and these were included in the results used for decision-making.

6.2. Results

The base case results are shown in table 6.2. SMC considered results for decision-making that took into account all relevant discounts. SMC is unable to present these results due to competition law issues.

Table 6.2 Base Case Results (with PAS)

	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
Daratumumab plus BLd	CIC	8.49	CIC	CIC	1.06	CIC	CIC
Daratumumab plus Ld	CIC	7.43	CIC				

Abbreviations: Bld = bortezomib, lenalidomide and dexamethasone; CIC = commercial in confidence; Incr. = incremental; ICER = incremental cost-effectiveness ratio; Ld = lenalidomide and dexamethasone; LYG= life years gained; QALYs =quality-adjusted life years.

6.3. Sensitivity analyses

A range of sensitivity and scenario analyses were considered and descriptions of these key scenarios are provided in Table 6.3 below. SMC considered results for decision-making that took into account all relevant PAS.

	Parameter	Base case	Scenario
1	Utilities	CEPHEUS time-dependent PFS	CEPHEUS, time-independent
2			CEPHEUS, time-dependent PFS & PD
3			MAIA
4	Bortezomib dosing	Once weekly	Twice weekly (aligns SmPC)
5	TTD	DBLd TTD: Gompertz DLd TTD: Weibull	DBLd TTD: attenuated exponential DLd TTD: attenuated Gompertz
6	Discounting	3.5% (costs & QALYS)	1.5%
7	Impact of COVID-19	Censored	Not censored
8	Subsequent treatment distributions	Clinician supplied; arm specific	DLd 2nd & 3rd line distributions applied per DBLd
9	DBLd TTD	Gompertz	Weibull
10	Subsequent therapy use	Lower probability for DBLd	Equal probability
11	9 & 10 in combination		

12	OS & PFS; adjusted attenuation point MAIA; proportion subsequent treatment	Exponential 7 years, 65%	Gen gamma 5 years, equal
13			Additional 10% reduction applied to all landmark survival assumptions
14	OS benefit	As base case	Remove OS benefit. HR = 1; landmark assumptions equalised
15	Attenuation long term OS and PFS hazards	From 5-7 years to match company assumptions	No attenuation. Equal hazards both arms after 5 years
16	Time horizon	Lifetime	5 years
17			10 years

Abbreviations: Bld = bortezomib, lenalidomide and dexamethasone; Ld = lenalidomide and dexamethasone; PD = progressed disease; PFS = progression-free survival; TTD = time to discontinuation.

6.4. Key strengths

The analysis is strengthened by the availability of patient data from both CEPHEUS and MAIA to support the ATE weighted indirect treatment comparison. The fitted functions for the various endpoints in both arms appeared to provide good fits to the source data. Data and assumptions around resource use and health related quality of life appeared to have been appropriately structured.

6.5. Key uncertainties

- There are limitations regarding the indirect treatment comparison, including the censoring of COVID-19 deaths in CEPHEUS and MAIA, meaning the economic results based on this are uncertain.
- Scenario analysis addressed the censoring of COVID-19 deaths, but there are several other uncertainties regarding modelling of OS and other endpoints. In terms of OS, the underlying data are immature, weakening the basis for modelling long-term outcomes. The rapid decline in modelled OS hazards is such that these must be maintained at general population levels at relatively high remaining estimates of OS. PFS is then also constrained not to exceed overall survival relatively early, with constraints on treatment continuation.
- The unadjusted analysis did not show a statistically significant difference in OS, but the modelled life year gain is substantial, reflecting the combined impact of the adjustment for COVID-19 and replacement of modelled OS estimates with clinician estimates. Clinical expert opinion-based estimates of landmark survival produced erratic relative survival between arms over time, limiting confidence in interpretation of the model outcomes, and leading to tensions within the model both in terms of OS relative to PFS and survival between arms. The company acknowledged that experts had provided opinions on PFS and OS survival, each endpoint independently of the other, had felt it necessary to adjust at least one of these estimates, and found time on treatment estimates to be incompatible with other clinical estimates.
- Given uncertainties around OS due to immaturity of data and Covid adjusted ITC, exploring less favourable outcomes was considered important; whilst not fully addressing all

concerns with the model, scenarios 11 and 14 exploring more conservative treatment benefit assumptions and scenarios 16 and 17 using shorter time horizons, were considered helpful to the Committee as the overall conclusion remained unchanged in these scenarios.

- The base case analysis suggests additional treatment costs associated with daratumumab plus BLd can be entirely offset by cost-savings elsewhere, notably in terms of subsequent therapies. However there is uncertainty around the assumed lower use of subsequent therapies with daratumumab plus BLd following later time to progression. It was suggested by the submitting company that the probability of subsequent therapy use is linked to duration of PFS and older age at time of progression.
- A negligible utility difference was applied for progressed disease compared with PFS. The implications for the analysis if the decrement is underestimated are unclear. While this could probably be considered conservative, the impact will depend on the proportion of incremental life years spent in progressed disease, which is associated with the constraints and uncertainties noted above.

7. Conclusion

The Committee considered the benefits of daratumumab in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios and agreed that as daratumumab is an orphan medicine, SMC can accept greater uncertainty in the economic case.

After considering all the available evidence and the output from the PACE process, the Committee accepted daratumumab for restricted use in NHSScotland.

8. Guidelines and Protocols

The British Society for Haematology and UK Myeloma Forum published guidelines on the diagnosis, investigation and initial treatment of myeloma in March 2021.[13]

The European Haematology Association (EHA) and European Society of Medical Oncology (ESMO) published clinical practice guidelines for diagnosis, treatment and follow-up of multiple myeloma in March 2021.[14]

The National Institute for Health and Care Excellence (NICE) updated its guideline 35 Myeloma: diagnosis and management in October 2018.[15]

9. Additional Information

9.1. Product availability date

22 August 2025

Table 9.1 List price of medicine under review

Medicine	Dose regimen	Cost per year (£)
daratumumab (in combination with bortezomib, lenalidomide, and dexamethasone)	**1,800 mg by subcutaneous injection once weekly for weeks 1 to 6, then once every three weeks for weeks 7 to 24, then once every four weeks thereafter.**	**Year 1 82, 080** **Year 2 onwards 56, 160**

Costs from BNF online on 29/06/26. Costs do not take any patient access schemes into consideration.

10. Company Estimate of Eligible Population and Estimated Budget Impact

SMC is unable to publish the with PAS budget impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget with the PAS. This template does not incorporate any PAS/contract price discounts associated with comparator medicines.

*Other data were also assessed but remain confidential.**

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This assessment is based on data submitted by the applicant company up to and including 14 August 2026.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal:*https://www.scottishmedicines.org.uk/about-us/policies-publications/

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC includes Scottish national contract prices in its decision-making. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document.

Patient Access Schemes (PAS): A PAS is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a medicine and enable patients to receive access to cost-effective innovative medicines. The Patient Access Scheme Assessment Group (PASAG), established under the auspices of Public Services Delivery Scotland, reviews and advises NHS Scotland on the feasibility and acceptability on implementing proposed schemes. PASAG operates separately from SMC to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHS Scotland on the basis of a PAS that has been considered acceptable for implementation by PASAG, a set of guidance notes on the operation of the scheme will be circulated to health boards' Area Drugs and Therapeutics Committees prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.