Healthcare Improvement Scotland | SMC Advice on new medicines

SMC2416

daratumumab 20mg/mL concentrate for solution for infusion and 1,800mg solution for injection (Darzalex®)

Janssen-Cilag Ltd

8 April 2022

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

daratumumab (Darzalex®) is not recommended for use within NHSScotland.

Indication under review: in combination with bortezomib, melphalan and prednisone for the treatment of adult patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant.

In an open-label, phase III study, the addition of daratumumab to bortezomib, melphalan, and prednisone was associated with a significant improvement in progression-free survival.

The submitting company's justification of the treatment's cost in relation to its health benefits was not sufficient and in addition the company did not present a sufficiently robust economic analysis to gain acceptance by SMC.

Chairman
Scottish Medicines Consortium

Indication

Daratumumab in combination with bortezomib, melphalan and prednisone for the treatment of adult patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant.[1,2]

Dosing Information

The recommended dose of daratumumab by intravenous (IV) infusion is 16mg/kg body weight. The dosing schedule is detailed in Table 1. Daratumumab IV infusion should be administered by a healthcare professional, in an environment where resuscitation facilities are available.

The recommended dose of daratumumab solution for subcutaneous (SC) injection is 1,800mg. The dosing schedule is detailed in Table 1. Daratumumab SC formulation should be administered by a healthcare professional, and the first dose should be administered in an environment where resuscitation facilities are available.

Daratumumab SC formulation is not intended for IV administration and should be given by SC injection only. For patients currently receiving daratumumab IV formulation, daratumumab solution for SC injection may be used as an alternative to the IV daratumumab formulation starting at the next scheduled dose.

For more information on infusion rates, recommended concomitant medicines, and management of adverse reactions, please see Summary of Product Characteristics (SPC).[1,2]

Table 1. Dosing schedule of daratumumab in combination with bortezomib, melphalan, and prednisone[1,2]

Weeks	Schedule (total doses)
Weeks 1 to 6	Weekly (total of 6 doses)
Weeks 7 to 54[a]	Every three weeks (total of 16 doses)
Week 55 onwards until disease progression[b]	Every four weeks

a = First dose of the every-3-week dosing schedule is given at week 7
b = First dose of the every-4-week dosing schedule is given at week 55

Product availability date

Daratumumab 20mg/mL concentrate for solution for infusion, July 2018

Daratumumab 1,800mg solution for injection, June 2020

Daratumumab meets SMC orphan criteria for this indication.

Summary of evidence on comparative efficacy

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.[1,2]

ALCYONE is a multicentre, randomised, open-label, parallel group, phase III study which evaluated the efficacy and safety of daratumumab with bortezomib, melphalan and prednisone (BMP) compared with BMP in 706 adult patients with previously untreated multiple myeloma. Study patients were ineligible for high-dose therapy/autologous stem cell transplant (ASCT), due to presence of important comorbid conditions or age ≥65 years. Patients were required to have measurable disease and an Eastern Cooperative Oncology Group (ECOG) score of 0, 1 or 2.[3,4]

Patients were randomised equally to receive BMP with or without daratumumab. All patients received up to nine (42-day) cycles of subcutaneous bortezomib (1.3mg/m^2 twice weekly on weeks 1, 2, 4, and 5 of cycle 1 and once weekly on weeks 1, 2, 4, and 5 of cycles 2 to 9), oral melphalan (9mg/m^2 once daily on days 1 to 4 of each cycle), and oral prednisone (60mg/m^2 once daily on days 1 to 4 of each cycle). Patients randomised to the daratumumab treatment group received daratumumab by IV infusion at a dose of 16mg/kg once weekly in cycle 1 (with concomitant dexamethasone to manage infusion reactions), every 3 weeks in cycles 2 to 9, and every 4 weeks thereafter until disease progression, unacceptable toxic effects, or study end. Randomisation was stratified according to International Staging System (ISS) disease stage (I, II, or III), geographic region (Europe versus other), and age (<75 years versus ≥75 years).[4]

The primary outcome was progression-free survival (PFS), defined as the time from randomisation to either disease progression (according to International Myeloma Working Group [IMWG] response criteria) or death. Efficacy analyses were performed in the intention-to-treat (ITT) population, which included all patients who underwent randomisation. 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 secondary outcomes included in the hierarchical testing were overall response rate (ORR), rate of very good partial response (VGPR) or better, rate of complete response (CR) or better, minimal residual disease (MRD) negativity rate, and overall survival. [3,4]

At an interim analysis of PFS (June 2017), the addition of daratumumab to BMP was associated with a significant improvement in PFS. Since this crossed the pre-specified stopping boundary for PFS, this became the primary PFS analysis.[1,2,4] At an updated interim analysis of PFS (June 2019), the addition of daratumumab to BMP was associated with a significant improvement in overall survival which crossed the pre-specified stopping boundary for overall survival. Median overall survival had not been reached in either group.[5] Other secondary outcomes were supportive. See Table 2 for more details.

Table 2. Efficacy outcomes of ALCYONE (ITT population). [3, 4, 5,6]

	Interim Analysis 2 (June 2017)		Interim Analysis 3 (June 2019)	
	Daratumumab plus BMP (n=350)	**BMP (n=356)**	**Daratumumab plus BMP (n=350)**	**BMP (n=356)**
Median follow-up	16.5 months		40.1 months	
Primary outcome: Progression-free survival (as per IMWG criteria)				
Events	88	143	176	265
Median PFS	NE	18.1 months	36.4 months	19.3 months
Hazard Ratio (95% CI)	0.50 (0.38 to 0.65) p<0.001		0.42 (0.34 to 0.51) p<0.001	
18-month PFS rate	72%	50%	-	-
Secondary outcome: Overall response rate (as per IMWG criteria)				
Proportion with response	91%*	74%	91%	74%
Secondary outcome: Best overall response (as per IMWG criteria)				
Complete response or better	43%*	24%	46%	25%
Partial response	20%	24%	18%	24%
Stable disease	5.7%	21%	5.7%	21%
Secondary outcome: MRD negativity rate				
Proportion with negative status for MRD	22%*	6.2%	28%	7.0%
Sustained negative status for MRD >6 months	-	-	16%	4.5%
Secondary outcome: Overall survival				
Events	45	48	83	126
Median overall survival	NE	NE	NE	NE
Hazard Ratio (95% CI)	0.92 (0.61 to 1.37)		0.60 (0.46 to 0.80)	
36-month survival rate	-	-	78%	68%
Secondary outcome: Progression-free survival on next line of therapy (PFS2)				
Events	44	50	102	152
Median PFS2	NE	NE	NE	42.3 months
Hazard Ratio (95% CI)	0.82 (0.55 to 1.24)		0.55 (0.43 to 0.71)	
36-month PFS2 rate	-	-	73%	55%

* p<0.001 (multiplicity-adjusted secondary outcome).

BMP = bortezomib, melphalan and prednisone; CI = confidence interval; IMWG = International Myeloma Working Group; MRD = minimal residual disease; NE = non-estimable PFS = progression-free survival.

Health Related Quality of Life (HRQoL) was assessed using European Organisation for Research and Treatment of Cancer core quality of life questionnaire (EORTC QLQ-C30) and EuroQol 5 dimension 5 level (EQ-5D-5L). Overall, the results suggest that the addition of daratumumab to BMP had no impact on HRQoL.[3]

The company conducted a propensity score-based adjusted analysis using individual patient data from ALCYONE and the open-label, randomised, phase III study MAIA to compare daratumumab plus BMP with lenalidomide plus dexamethasone. Patient data from MAIA were reweighted using the inverse probability of treatment weighting (IPTW) method to match patient data from ALCYONE. Eight baseline characteristics were adjusted for: age, sex, ECOG performance status, ISS stage, creatinine clearance, cytogenetic risk factors, hepatic function, and multiple myeloma type (IgG/not IgG). Results were statistically significant for daratumumab plus BMP for overall survival and time to discontinuation; PFS results were not as consistent since some weighting approaches failed to achieve statistical significance.

A network meta-analysis (NMA) was conducted to compare the efficacy of daratumumab plus BMP with: lenalidomide plus dexamethasone; BMP; bortezomib plus dexamethasone; bortezomib, cyclophosphamide and dexamethasone; melphalan, prednisone and thalidomide or cyclophosphamide, thalidomide and dexamethasone in newly diagnosed multiple myeloma patients who are ineligible for ASCT. The NMA included nine studies. Outcomes included overall survival, PFS, ORR, and complete response (or better response). Daratumumab plus BMP was likely superior to lenalidomide plus dexamethasone in PFS and complete response; overall survival and ORR favoured daratumumab plus BMP but credible intervals crossed 1. Daratumumab plus BMP was generally likely superior to other comparators in the NMA. Comparisons of BMP with other comparators in the NMA generally had credible intervals that spanned 1, suggesting similar clinical efficacy.

Summary of evidence on comparative safety

In the ALCYONE study at data cut-off June 2019, serious adverse events occurred during cycles one to nine in 38% (132/350) of patients in the daratumumab plus BMP group and in 33% (117/356) of patients in the BMP group. The rate of discontinuation of treatment due to adverse events was lower in the daratumumab plus BMP group than in the BMP group (7% versus 9%).[5]

During cycles 1 to 9, the most common (>15% of patients in either group) grade 3 or 4 treatment-emergent adverse events were neutropenia (40% of patients in the daratumumab plus BMP group and 39% of the BMP group), thrombocytopenia (34% versus 38%), and anaemia (15% versus 20%). During cycles one to nine, the incidence of grade 3 or 4 infections was higher in the daratumumab plus BMP group than in the BMP group (22% versus 15%). Pneumonia was the most common grade 3 or 4 infection (11% versus 4.2%).[5]

The most common (≥10% of patients) adverse events during daratumumab monotherapy after the first nine treatment cycles in patients in the daratumumab plus BMP group were upper respiratory tract infection, bronchitis, viral upper respiratory tract infection, cough, and diarrhoea. The most

common grade 3 or 4 adverse events during this period were anaemia (4.3%), pneumonia (3.6%), hypertension (2.9%), neutropenia (2.2%), and thrombocytopenia (1.8%).[5]

Summary of clinical effectiveness issues

Multiple myeloma is a malignant disorder of plasma cells which leads to dysfunction in the bone marrow, resulting in progressive morbidity and eventual mortality. At diagnosis, patients are broadly categorised into two groups based on whether they are suitable for intensive treatment including ASCT or not. Patients who are ineligible for ASCT commonly receive longer, less intensive treatment regimens.[3] In Scotland, patients with newly diagnosed multiple myeloma who are ineligible for ASCT may receive one of the following:[7]

- melphalan + prednisolone +/- thalidomide or cyclophosphamide
- bortezomib, melphalan and prednisolone if thalidomide is contraindicated or not tolerated
- lenalidomide plus low dose dexamethasone in patients unsuitable for thalidomide containing regimens. Interim advice from the COVID-19 National Cancer Medicines Advisory Group, which allows for greater flexibility in the management of cancer during the pandemic, currently supports use of lenalidomide in combination with dexamethasone within the licensed population, adult patients with previously untreated multiple myeloma who are not eligible for transplant. This includes patients outside of the SMC restriction.[8]

Daratumumab in combination with lenalidomide and dexamethasone is also licensed for the treatment of adult patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant. However, in the absence of a submission, daratumumab plus lenalidomide and dexamethasone is not recommended for use in NHSScotland (SMC 2269).

The primary outcome result of ALCYONE (PFS) was statistically significant and was sufficiently mature. The addition of daratumumab to BMP was associated with a 58% improvement in PFS (data-cut June 2019). All key secondary outcomes were in support of daratumumab, including ORR and overall survival, although overall survival data are still immature. Together, the results can be considered clinically meaningful.[3]

Overall, ALCYONE was a well conducted phase III study with few limitations. One limitation is the open-label study design, which may introduce bias in the evaluation of HRQoL or safety outcomes. A further potential limitation is that clinical management of patients with multiple myeloma has changed in recent years since the inception of ALCYONE. Criteria for patient eligibility for high dose chemotherapy and ASCT have evolved, meaning that some patients in the key study would not be considered transplant ineligible by today's standards. A subgroup analysis for patients considered to be ineligible to high dose chemotherapy/ASCT according to current guidelines was presented, the results of which were consistent with the primary findings. A large majority of the daratumumab plus BMP group (79%) and the BMP group (76%) of the ALCYONE study population were high dose chemotherapy/transplant ineligible according to current guidelines.[3] The full study population can be considered broadly generalisable to the licensed indication.

ALCYONE compared daratumumab plus BMP with BMP, which is a relevant comparator in Scottish practice. However, experts consulted by SMC considered lenalidomide plus dexamethasone to be the most relevant comparator in Scotland, and also noted the availability of other comparators. To address the lack of direct data with relevant comparators, the company conducted a NMA, which had the following limitations: there was methodological and clinical heterogeneity observed across studies, with no measures of inconsistency reported; high to unclear risk of bias across multiple studies; and no assessment of safety or HRQoL, preventing a comprehensive risk/benefit evaluation of different treatments. The propensity score-based adjusted analysis comparing daratumumab plus BMP versus lenalidomide plus dexamethasone was limited by the presence of potentially important differences in baseline characteristics that could not be accounted for. There were also inconsistencies between the magnitudes of treatment differences between the NMA and the propensity score-based adjusted analysis. Despite these limitations, the results appear credible; propensity score-based adjusted analysis using individual patient data can be considered more robust.

Clinical experts consulted by SMC considered that daratumumab plus BMP is a therapeutic advancement due to the improvements in PFS and overall survival. It would likely be used in fitter patients who are ineligible for transplant; not all transplant ineligible patients would be suitable. Daratumumab plus BMP would impact cancer day units as additional resources would be required to deliver daratumumab when compared with lenalidomide plus dexamethasone or BMP. This will also have implications for patients who may have to attend hospital more frequently.

While daratumumab meets SMC orphan criteria in this indication/setting, the company did not request a Patient and Clinician Engagement (PACE) meeting to consider the added value of daratumumab in the context of treatments currently available in NHS Scotland.

Summary of comparative health economic evidence

The company submitted a cost-utility analysis comparing daratumumab plus bortezomib, melphalan and prednisone (DBMP) to bortezomib, melphalan and prednisone (BMP), and lenalidomide plus dexamethasone for the treatment of adult patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant. The submitting company identified lenalidomide plus dexamethasone as the main comparator, due to its high market share and increased usage during the COVID-19 pandemic. SMC clinical experts were consistent that BMP and lenalidomide plus dexamethasone treatments would be displaced by the new regimen. It is noted that lenalidomide plus dexamethasone is currently routinely accessible in this population through a combination of SMC accepted restricted advice (SMC1096/15) and interim advice from the COVID-19 National Cancer Medicines Advisory Group.

The economic analysis incorporated a partitioned survival model with three health states: progression-free (PF), progressed (PD) and dead. Survival outcomes (PFS and overall survival) before the landmark time point (12 months) were based on the observed survival data from the intention to treat (ITT) population of the ALCYONE (for DBMP and BMP) and adjusted MAIA (for lenalidomide plus dexamethasone) studies from the time of randomisation. Post-landmark survival outcomes (PFS and overall survival) were based on the extrapolation of survival data from

the MRD negativity assessment at 12 months and modelled separately for patients who achieved MRD-negative status and those who did not. A 29-year time horizon with a four-week model cycle was adopted, with patients entering the model aged 71 years.

The main sources of clinical data were ALCYONE[11] and MAIA.[13] Direct clinical evidence for DBMP versus BMP in the relevant patient population was taken from ALCYONE. As no direct evidence between DBMP and lenalidomide plus dexamethasone was available, the patient population of the lenalidomide plus dexamethasone arm of MAIA was adjusted to match the patient population of the DBMP arm of the ALCYONE trial using a propensity score weighting approach based on average treatment effect of the treated. This matching was based on patients' clinical characteristics that were prognostic of improved survival outcomes and showed the effect that would have been observed if patients were administered lenalidomide plus dexamethasone in ALCYONE. SMC statistician opinion viewed the approach taken as sensible. Extrapolation of PFS and overall survival was performed in the BMP and lenalidomide plus dexamethasone treatment groups with MRD-positive responses at the landmark assessment point using individual patient level data (IPD) directly from ALCYONE (for BMP) and MAIA (for lenalidomide plus dexamethasone). The company justified this by stating the majority of patients treated with BMP and lenalidomide plus dexamethasone were MRD-positive, and the high number of events for these cohorts provided mature data sources to extrapolate from. Standard survival models were fitted and assessed in terms of goodness-of-fit statistics, visual inspection of the hazard function and survival curves to the observed data from the ALCYONE and MAIA studies, while also considering clinical plausibility of long-term survival predictions in the view of two Scottish clinical experts consulted by the company. In the case of lenalidomide plus dexamethasone MRD-positive extrapolation the generalised gamma was used for both PFS and overall survival. In the case of BMP MRD-positive extrapolation, the log-logistic was used for PFS and Weibull used for overall survival. When modelling PFS and overall survival for DBMP MRD-positive patients, hazard ratios were applied to the BMP MRD-positive survival curves.[11] These were obtained from the ALCYONE post-landmark analysis.[11] Hazard ratios were derived from an updated meta-analysis[12] and were used when modelling PFS and overall survival for MRD-negative patients in the DBMP, BMP and lenalidomide plus dexamethasone arms. This hazard ratio was applied to each arm's respective MRD-positive survival curves.

Utilities were derived from the EQ-5D-5L data from ALCYONE cross-walked to EQ-5D-3L UK value set using Van Hout et al. 2012.[14] Utility values for the progression-free health state were derived using a time-varying approach, increasing from month 0 to month 36, with the month 36 value carried forward. The estimated utility value for the progressed disease state was estimated separately as an average of utility estimates following progression. EQ-5D utility was seen to be similar between the intervention and comparator treatment arms in ALCYONE, hence utility values used in the model were based on pooled EQ-5D data across treatment arms with the same values applied to both model cohorts.[11] One-off decrements in utility were applied in the model for the proportion of patients who experienced grade 3 or 4 adverse events, with the total disutility included in the model being -0.25 for DBMP, -0.25 for BMP and -0.20 for lenalidomide plus dexamethasone. In the model, health state utility values were also age-adjusted over the model time horizon using the UK population norm values for EQ-5D.[15]

In addition to medicine acquisition (including concomitant) and administration costs, other costs included were those for subsequent treatments, monitoring in the on and off treatment state, management of adverse events and end-of-life costs. All patients were modelled as receiving daratumumab with SC injection. Time to treatment discontinuation (TTD) was used to determine the time on treatment (ToT). Extrapolation of TTD used the Kaplan–Meier (KM) data from the overall ITT population in ALCYONE and MAIA trial. As BMP has a fixed treatment duration, there was no extrapolation required and the KM TTD data from the ALCYONE trial was used directly. The model could therefore account for patients who may have discontinued treatment before progression. All patients were assumed to receive 2nd and 3rd line therapies. As ToT was used in the model, application of specific health-state costs could be applied while patients were either on or off treatment, independent of the application of the PF or PD health states. The dosing regimens for daratumumab and lenalidomide were in line with the product SPCs, aside from the BMP regimen which utilised a reduced dosing schedule and was in line with ALCYONE and considered by clinical experts consulted by the submitting company to be reflective of Scottish practice.[1,2, 11, 16, 17]

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.

A PAS discount is also in place for lenalidomide and this was included in the results used for decision-making by using estimates of the comparator PAS price. The results presented do not take account of the PAS for lenalidomide or the PAS for DBMP but these were considered in the results used for decision-making. SMC is unable to present the results provided by the company which used an estimate of the PAS price for lenalidomide due to commercial confidentiality and competition law issues.

The base case results are shown in the table below.

Table 3: Base case results –list price for all medicines

Intervention	ICER
DBMP	-
BMP	£136,168
lenalidomide plus dexamethasone	£126,036

Abbreviations: BMP: bortezomib, melphalan and prednisone; DBMP: daratumumab, bortezomib, melphalan and prednisone; ICER: incremental cost-effectiveness ratio; LY: life years; QALY: quality-adjusted life year.

The most substantial incremental cost-effectiveness ratio (ICER) increases from the presented scenarios in the table below were associated with assumptions around BMP MRD-positive extrapolations, DBMP MRD-positive/negative extrapolations, including 4th line treatments, and DBMP and lenalidomide plus dexamethasone ToT determined by PFS data from ALCYONE as opposed to TTD.

The submitting company viewed scenario 1 as clinically implausible, based on input from an advisory board meeting involving two Scottish clinicians comparing long term survival estimates.

Table 4. Scenario analyses

			DBMP List price ICER (£ per QALY)	
#	Base Case	Scenario	Versus BMP	Versus lenalidomide plus dexamethasone
0	Base Case	-	£136,168	£126,036
1	BMP MRD-positive extrapolation (PFS = log logistic, OS = Weibull)	BMP MRD-positive extrapolation based on statistical goodness-of-fit (PFS = lognormal, OS = Gompertz)	£207,748	-£922,405 (Negative QALYs, Positive Costs)
2	lenalidomide plus dexamethasone MRD-positive extrapolation (PFS = Generalised Gamma, OS = Generalised Gamma)	lenalidomide plus dexamethasone MRD-positive extrapolation based on statistical goodness-of-fit (PFS = exponential, OS = Weibull)	£136,168	£115,100
3	DBMP MRD- negative extrapolation based on HR from all included studies in meta-analysis	DBMP MRD- negative extrapolation based on a HR from studies where MRD negativity was measured to 10^-5 only (as per the MRD-negativity measure used in the model to determine the proportion of patients who are MRD-positive or -negative)	£134,961	£124,183
4	DBMP MRD-negative extrapolation based on HR from all included studies in meta-analysis	DBMP MRD-negative extrapolation for PFS based on a treatment effect HR derived from ALCYONE (applied to the BMP MRD- arm) and assuming a HR of 1 (i.e., no treatment effect) for OS	£143,675	£134,217
5	DBMP MRD-positive extrapolation based on HR from ALCYONE landmark analysis.	DBMP MRD-positive extrapolation based on independent extrapolation. PFS= log logistic distribution. OS= exponential.	£142,519	£136,622
6	DBMP ToT based on TTD Extrapolations from ALCYONE lenalidomide plus dexamethasone ToT based on TTD Extrapolations from MAIA	DBMP and lenalidomide plus dexamethasone ToT determined by PFS data from ALCYONE as opposed to TTD	£169,662	£133,483
7	Utility values for PF and PD were based on EQ-5D data from ALCYONE using a time-varying approach for PF.	Utility values from ALCYONE without using a time-varying approach	£154,666	£135,557
8	Subsequent treatments (2nd and 3rd line)	Inclusion of 4th line treatment	£171,097	£170,150

Abbreviations: AE: adverse event; BMP: bortezomib, melphalan and prednisone; DBMP: daratumumab, bortezomib, melphalan and prednisone; HR: hazard ratio; IV: intravenous; ICER: incremental cost-effectiveness ratio; KM: Kaplan-Meier; MRD: minimal residual disease; OS: overall survival; PAS: patient access scheme; PD: progressed disease; PFS: progression-free survival; PF: progression-free; QALY: quality-adjusted life year; SC: subcutaneous; TTD: time to treatment discontinuation; TOT: time on treatment.

Key limitations of the analysis were:

- Proportional hazard assumption: Application of hazard ratios to model survival outcomes required a proportional hazards assumption (relative risk of an event was fixed irrespective of time). As this assumption was required in the model, hazard ratios used in the model (MRD−negative versus MRD-positive; DBMP versus BMP (MRD-positive)) were held constant over the time horizon. From the provided sensitivity analysis, hazard ratios for overall survival and PFS in DBMP vs BMP (MRD-positive) had the potential to create large changes in the ICERs compared to the base case. Furthermore, a scenario analysis of independent extrapolation of the DBMP MRD-positive arm for PFS and overall survival showed an increase in the ICERs compared to the base case. The submitting company assessed the hazard ratios that were used via inspection of log-cumulative hazard plots and their associated Schoenfeld plots. This provided evidence of the proportional hazard assumption not being violated through the non-significant p-values in the Schoenfeld residual plots. However, visual inspection of the log-cumulative hazard plots using both overall survival and PFS DBMP vs BMP (MRD-positive) hazard ratios did show the log-hazard curves crossing (suggesting the hazard in the DBMP group was not proportional to the hazard in the BMP group). The submitting company provided additional analysis using a DBMP MRD-positive time-varying treatment effect, showing a minor decrease to the base ICERs.

- Choice of post-landmark extrapolation distributions: The choice of extrapolation distributions for PFS and overall survival in BMP and lenalidomide plus dexamethasone with a post-landmark MRD-positive response was largely informed by an advisory board with two Scottish clinicians comparing long term survival estimates. When alternate extrapolation distributions were considered, ICERs had the potential to change by a large amount from those in the base case.

- Utilities: Use of time-varying utility values for the PF health state and non-time-varying for the PD health state generated uncertainty in the base case ICERs. The difference in the utility values when moving from the PF to PD health state may have been overstated, compared to when using the non-time-varying approach for the two health states.

- Meta-analysis for MRD: There was potential uncertainty with the MRD-negative versus MRD-positive hazard ratio, as the updated meta-analysis[12] contained studies where MRD negativity was measured differently. Sensitivity analyses were performed, using MRD-negative versus MRD-positive hazard ratios from subgroups of studies from the meta-analysis (grouped by threshold sensitivity, measurement, and eligibility for MRD assessment by response criteria). These showed minimal impact on the ICERs compared to the base case.

The Committee also 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 the criterion for a substantial improvement in life expectancy in the patient population targeted in the submission modifier was satisfied. In addition, as daratumumab is an orphan medicine, SMC can accept greater uncertainty in the economic case.

After considering all the available evidence and after application of the appropriate SMC modifiers, the Committee was unable to accept daratumumab for use in NHSScotland.

Summary of patient and carer involvement

The following information reflects the views of the specified Patient Group.

- We received a patient group submission from Myeloma UK, which is a registered charity.
- Myeloma UK has received 8.6% pharmaceutical company funding in the past two years, including from the submitting company.
- 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.
- The patient population covered in this appraisal make up more than half of all myeloma patients. They are generally older; they can be frailer/less fit and cannot tolerate intensive treatments such as a stem cell transplant. As myeloma is a highly individual, relapsing and remitting cancer which becomes resistant to treatment, patients need and want a range of effective treatment options including treatments with different mechanisms of action, administered in a range of ways, at every stage of the treatment pathway.
- Daratumumab in combination with the current standard treatment of bortezomib, melphalan and dexamethasone (DBMP) improves outcomes whilst not adding much treatment related burden. Patients desire treatments with minimal negative impact on quality of life. The patient group described how in their 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.
- The addition of daratumumab could mean extra hospital visits. Oral treatments are often valued by patients. However, overwhelmingly clinical efficacy and the opportunity of a good remission outweighs any disadvantages in the method of administration.

Additional information: guidelines and protocols

The British Society for Haematology published guidelines in March 2021 titled “Guidelines on the diagnosis, investigation and initial treatment of myeloma: a British Society for Haematology/UK Myeloma Forum Guideline”. The guideline makes the following recommendations for non-transplant eligible patients: non-transplant eligible patients may receive a proteasome inhibitor (PI) (for example, bortezomib) or non-PI-based treatment regimen. Patients with high-risk

cytogenetics should receive a bortezomib/corticosteroid-based regimen if possible. For others, a lenalidomide-based, non-PI containing regimen is also acceptable, and may be preferred for patient-based factors. For non-transplant eligible patients, an alkylating agent (cyclophosphamide or melphalan) or immunomodulatory drugs (thalidomide or lenalidomide) may be added to a bortezomib/corticosteroid-based regimen. Lenalidomide is preferred to thalidomide. Daratumumab is well tolerated and improves response rates and survival. It can be added to combination regimens, as per licence.[9]

The European Haematology Association (EHA)-European Society for Medical Oncology (ESMO) published guidelines in February 2021 titled "Multiple myeloma: EHA-ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up". The guideline makes the following recommendations for non-transplant eligible patients: first options are daratumumab/lenalidomide/dexamethasone, daratumumab plus BMP, and bortezomib/lenalidomide/dexamethasone. If first options are not available then BMP or lenalidomide/dexamethasone should be considered.[10]

Additional information: comparators

Lenalidomide plus dexamethasone. Melphalan plus prednisolone +/- thalidomide or cyclophosphamide. Bortezomib, melphalan and prednisolone.

Additional information: list price of medicine under review

Medicine	Dose Regimen	Cost per course (£)
Daratumumab	In combination with BMP: IV = 16mg/kg SC = 1,800mg Given weekly in weeks 1 to 6, every 3 weeks in weeks 7 to 54, then every 4 weeks in week 55 and beyond (until disease progression).	Week 1 to 6 (total of 6 doses): £25,920 Week 7 to 54 (total of 16 doses): £69,120 Week 55 and beyond: £4,320 every 4 weeks.

Costs from BNF online on 07 January 2022. A patient weight of 70kg was used for these calculations; IV and SC daratumumab cost the same for a patient weighing 70kg. Costs calculated using the full cost of vials/ampoules assuming wastage. Costs do not take patient access schemes into consideration.

Additional information: budget impact

The submitting company estimated there would be an eligible patient population of 300 in Year 1 rising to 303 in Year 5. The estimated uptake rate was 25% in Year 1 and Year 5. This resulted in 75 patients estimated to receive treatment in year 1 to 76 patients in Year 5.

List price

The gross impact on the medicines budget was estimated to be £16.6 milllion in year 1 falling to £8 million in year 5. As other medicines were assumed to be displaced, the net medicines budget impact was estimated to be £12.4 million in year 1 and £5.6 million in year 5. Medicines displaced are BMP and lenalidomide plus dexamethasone.

These estimates do not take account of any patient access schemes applied to displaced medicines.

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This assessment is based on data submitted by the applicant company up to and including 11 February 2022.

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme 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. A Patient Access Scheme Assessment Group (PASAG), established under the auspices of NHS National Services Scotland reviews and advises NHSScotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHSScotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards 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.