SMC2536

daratumumab solution for injection and concentrate for solution for infusion (Darzalex®)

Janssen-Cilag Ltd

04 August 2023

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 use within NHSScotland

Indication under review: in combination with lenalidomide and dexamethasone for the treatment of adult patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant (ASCT).

In a phase III study, daratumumab, in combination with lenalidomide and dexamethasone, improved progression-free survival compared with lenalidomide plus dexamethasone in patients with newly diagnosed multiple myeloma ineligible for ASCT.

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.

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, 2] SMC has previously advised that daratumumab in combination with bortezomib, melphalan and prednisone is not recommended for use within NHSScotland for the treatment of adult patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant (ASCT) (SMC2416).

Daratumumab is available as a weight-based solution for intravenous (IV) infusion (16mg/kg of body weight) or as a fixed-dose subcutaneous (SC) injection (1,800mg), when used in combination with lenalidomide plus dexamethasone for multiple myeloma.[1, 2] The dosing schedule is detailed in Table 1.1. Further details are included in the summary of product characteristics (SPC).[1]

Table 1.1 Dosing schedule of daratumumab in combination with lenalidomide and dexamethasone for multiple myeloma.[1, 2]

Weeks	Schedule
Weeks 1 to 8	Weekly (total of eight doses)
Weeks 9 to 24	Every 2 weeks (total of eight doses)
Week 25 onwards until disease progression	Every 4 weeks

Dexamethasone should be administered at 40mg/week (or a reduced dose of 20 mg/week for patients >75 years or with a body mass index <18.5kg/m^2).[1, 2]

1.2. Disease background

Multiple myeloma is an incurable haematological cancer of plasma cells. This results in the destruction of bone and bone marrow, which can cause bone fractures, anaemia, increased susceptibility to infections, elevated calcium levels in the blood, kidney dysfunction and neurological complications.[3, 4] Multiple myeloma predominantly affects older people and the median age at diagnosis is approximately 70 years.[5] Approximately 47% of patients will be alive 5 years after their diagnosis. The incidence of multiple myeloma in Scotland is estimated to be 8.8 per 100,000 people.[6, 7]

1.3. Treatment pathway and relevant comparators

Upon diagnosing multiple myeloma, patients are assessed for eligibility for intensive treatment (which includes ASCT). Older people are generally not considered eligible for ASCT due to comorbidities. For patients in NHSScotland who are newly diagnosed with multiple myeloma and are ineligible for ASCT, lenalidomide plus dexamethasone is the predominant treatment. Other treatment options include bortezomib-containing regimens, such as bortezomib plus melphalan and prednisolone, and thalidomide-based regimens, such as cyclophosphamide plus thalidomide and dexamethasone.

Lenalidomide plus dexamethasone is accepted for restricted use by SMC in patients with previously untreated multiple myeloma who are not eligible for transplant and unsuitable for thalidomide-containing regimens (SMC 1096/15). In October 2022, the National Cancer Medicines Advisory Group programme issued advice supporting use in adult patients with previously

untreated multiple myeloma who are not eligible for transplant and are suitable for thalidomide-containing regimens, based on the pricing for generic lenalidomide products.[8]

1.4. Category for decision-making process

Eligibility for a PACE meeting
Daratumumab meets SMC orphan criteria for the indication under review.

2. Summary of Clinical Evidence

2.1. Evidence for the licensed indication under review

Evidence to support the efficacy and safety of daratumumab plus lenalidomide and dexamethasone comes from the ongoing MAIA study. Details are summarised in Table 2.1.

Table 2.1. Overview of relevant study.

Criteria	MAIA study[3, 9, 10]
Study design	International, randomised, parallel group, open-label, phase III study.
Eligible patients	• Aged ≥18 years, with an ECOG PS of 0 to 2. • Documented multiple myeloma that satisfies the CRAB (calcium elevation, renal insufficiency, anaemia and bone abnormalities) criteria, monoclonal plasma cells in the bone marrow ≥10% or presence of a biopsy proven plasmacytoma, and measurable disease. • Newly diagnosed multiple myeloma, and not considered a candidate for high-dose chemotherapy with ASCT because they are ≥65 years old; or if <65 years old: they have important comorbid condition(s) that would likely have a negative impact on their tolerability of high-dose chemotherapy with stem cell transplantation.
Treatments	As part of a 28-day cycle, both treatment groups received: • **Oral lenalidomide** 25mg once daily on days 1 to 21 of each cycle (10mg once daily if creatinine clearance was between 30 to 50 mL/min) • **Oral dexamethasone** 40mg once daily on days 1, 8, 15 and 22 of each cycle (patients >75 years old or with a BMI <18.5kg/m^2 could receive 20mg weekly) In addition, patients randomised to the daratumumab group received **IV daratumumab** 16mg/kg weekly for eight doses (cycles 1 to 2), every two weeks for eight doses (cycles 3 to 6), then every four weeks thereafter (cycle 7 onwards). Following a protocol amendment (03 April 2020), patients could switch from IV daratumumab to SC daratumumab on day 1 of any cycle (at the discretion of the investigator). All treatments continued until disease progression or unacceptable toxicity. All patients on daratumumab treatment received premedication with corticosteroids, antihistamines and analgesia.
Randomisation	Patients were randomised equally and stratified according to ISS staging (I versus II versus III), geographic region (North America versus other) and age (<75 years versus ≥75 years).
Primary outcome	PFS assessed in all randomised patients was defined as the duration from the date of randomisation to either progressive disease (independently assessed according to IMWG response criteria) or death. Patients were censored at the date of last disease assessment before subsequent anti-myeloma therapy or withdrawal of consent to study participation, whichever occurred first.
Secondary outcomes	These included but were not limited to the rate of CR or better[a]; rate of VGPR or better; MRD negativity rate; ORR; and overall survival.

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 order of the hierarchical statistical testing analysis was PFS, then the secondary outcomes as outlined above.

[a]this outcome comprised of a stringent complete response (that is complete response plus a normal free light-chain ratio and absence of clonal plasma cells, as assessed by immunofluorescence or immunohistochemical analysis or by two-colour to four-colour flow cytometry) and a complete response. ASCT = autologous stem cell transplant; BMI = body mass index; CR = complete response; ECOG PS = Eastern Cooperative Oncology Group Performance Status; IgM M-protein = immunoglobulin M monoclonal-paraprotein; IMWG = International Myeloma Working Group; ISS = International Staging System; IV = intravenous; MRD = minimal residual disease; ORR = overall response rate; PFS = progression-free survival; VGPR = very good partial response.

At the primary analysis of progression-free survival (PFS) (data cut-off September 2018), patients who received daratumumab plus lenalidomide and dexamethasone (hereafter referred to as the daratumumab group) had a statistically significant improvement in PFS, compared with patients who received lenalidomide plus dexamethasone (hereafter referred to as the control group). At a subsequent interim analysis of overall survival (data cut-off February 2021), there was a statistically significant increase in overall survival in the daratumumab group, compared with the control group.[10] Detailed results are presented in Table 2.2.

Table 2.2. Primary and selected secondary outcomes from the MAIA study.

Data cut-off date	September 2018[3, 9]		February 2021[10]	
	Daratumumab + lenalidomide + dexamethasone (n=368)	**Lenalidomide + dexamethasone (n=369)**	**Daratumumab + lenalidomide + dexamethasone (n=368)**	**Lenalidomide + dexamethasone (n=369)**
Median follow-up	28.0 months		56.2 months	
Primary outcome: progression-free survival (assessed per IMWG criteria)				
Events, n	97	143	160	217
Median PFS (months)	NE	31.9	NE	34.4
HR (95% CI), p-value	0.56 (0.43 to 0.73), p<0.001		0.53 (0.43 to 0.66)	
KM estimated PFS at 24 months	76%	62%	-	-
KM estimated PFS at 60 months	-	-	53%	29%
Secondary outcome: overall survival				
Deaths, n	62	76	117	156
Median overall survival	NE	NE	NE	NE
HR (95% CI), p-value	0.78 (0.56 to 1.10), NSS		0.68 (0.53 to 0.86)[b], p=0.0013	
KM estimated overall survival at 24 months	84%	84%	-	-
KM estimated overall survival at 60 months	-	-	66%	53%

[a] statistically significant at prespecified stopping boundary of p=0.0244.

[b] statistically significant at prespecified stopping boundary of p=0.0414.

Abbreviations: CI = confidence interval; CR = complete response; HR = hazard ratio; IMWG = International Myeloma Working Group; KM = Kaplan-Meier; MRD = minimal residual disease; NE = not estimable; NSS = not statistically significant; PFS = progression-free survival; VGPR = very good partial response.

The submitting company provided updated data for PFS (data cut October 2021; median follow-up of 64.5 months). In the daratumumab and control groups respectively, the median PFS (61.9 months and 34.4 months), Kaplan-Meier (KM) estimated PFS at 60 months, and hazard ratio 0.55 (95% confidence interval [CI]: 0.45 to 0.67) were consistent with the PFS data from the earlier data cuts.[1, 2, 12] The submitting company also provided updated data for overall survival (data cut October 2022; median follow-up 73.6 months). In the daratumumab and control groups respectively, the median overall survival (not estimable and 64.1 months), KM estimated overall survival at 60 months (67% and 54%) and hazard ratio 0.65 (95% CI: 0.52 to 0.80) were consistent with the overall survival data from the earlier data cuts.[13] These updated PFS and overall survival results were used to inform the base case for the cost-effectiveness analysis.

2.2. Health-related quality of life outcomes

Health-Related Quality of Life (HRQoL) was assessed using the EuroQol-5 Dimensions-5 Levels (EQ-5D-5L) and the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ-C30). At the updated PFS analysis (data cut-off October 2021), the results suggest that overall, the addition of daratumumab to lenalidomide plus dexamethasone had no notable impact on HRQoL.[11]

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

In the absence of direct evidence comparing daratumumab plus lenalidomide and dexamethasone with bortezomib-containing regimens, including bortezomib plus melphalan and prednisolone, the submitting company provided an indirect treatment comparison (ITC) based on adjusted individual patient data (IPD). This was used to inform the overall survival and PFS estimates for bortezomib plus melphalan and prednisolone in the economic analysis, as described in Table 2.3. The submitting company consider this comparison a proxy for all bortezomib-containing regimens.

Table 2.3: Summary of indirect treatment comparison based on adjusted individual patient data.

Criteria	Overview
Design	Unanchored ITC with propensity score analysis. IPD from the ALCYONE study were reweighted (using the IPW ATT method) to match IPD from the MAIA study.
Population	Adult patients with newly diagnosed multiple myeloma who were ineligible for ASCT.
Comparators	BMP.
Studies included	MAIA (for daratumumab plus lenalidomide and dexamethasone) and ALCYONE (for BMP).
Outcomes	Overall survival and PFS.
Results	In the indirect comparisons, before and after adjustment, HRs for overall survival and PFS did not cross 1, suggesting a potential difference between treatments that favours daratumumab plus lenalidomide and dexamethasone.

ASCT = autologous stem cell transplant; ATT = Average Treatment effect on the Treated; BMP = bortezomib plus melphalan and prednisolone; CI = confidence interval; HR = hazard ratio; IPD = individual patient data; IPW = inverse probability weighting; ITC = indirect treatment comparison; PFS = progression-free survival.

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

3. Summary of Safety Evidence

The overall safety profile of daratumumab plus lenalidomide and dexamethasone was deemed to be consistent with the known safety profiles of these medicines, and was considered to be manageable with dosing modifications and reasonably tolerated based on the relatively low number of discontinuations due to adverse events (AEs).[3]

In the MAIA study (data cut September 2018), the median duration of treatment in the daratumumab group was 25.3 months and in the control group was 21.3 months. In the daratumumab (n=364) and control (n=365) groups respectively, patients reporting a grade 3 or higher AE were 90% versus 83%, patients with a reported serious AE was 63% in both groups and patients discontinuing treatment due to an AE was 7.1% versus 16%.[3, 9]

The most frequently reported grade 3 or 4 AEs with an incidence >5% in the daratumumab group versus the control group were: neutropenia (50% versus 35%), lymphopenia (15% versus 11%), pneumonia (14% versus 7.9%), anaemia (12% versus 20%), leukopenia (11% versus 4.9%), hypokalaemia (8.8% in both groups), fatigue (8.0% versus 3.8%), thrombocytopenia (7.4% versus 8.8%), hyperglycaemia (7.1% versus 3.8%), cataract (7.1% versus 7.9%), diarrhoea (6.6% versus 4.1%), hypertension (6.6% versus 3.6%) and pulmonary embolism (5.2% in both groups).[3, 9] After longer follow-up (data cut October 2021), no new safety concerns were identified for daratumumab compared to the previously reported safety analyses.[11]

Based on pooled data, the safety profiles of the SC and IV formulations of daratumumab appear to be similar.[1]

4. Summary of Clinical Effectiveness Considerations

4.1. Key strengths

- In the MAIA study, the addition of daratumumab to lenalidomide plus dexamethasone (the main comparator used in Scottish clinical practice) resulted in a statistically significant improvement in PFS and overall survival; this was considered clinically meaningful.[3, 9, 10]
- The daratumumab group also had a statistically significant improvement in some other secondary outcomes, including the MRD negativity rate and the rate of CR or better, when compared with the control group.[3, 9]

4.2. Key uncertainties

- Despite a median follow-up of 73.6 months (data cut October 2022), the overall survival data still appear to be relatively immature, with the median only just reached in the control group (64.1 months) and not yet reached in the daratumumab group.[13]
- At the February 2021 data cut, in the daratumumab and control groups respectively, 31% (114/364) and 51% (186/365) of patients had received subsequent treatments.[10] It is unclear if the subsequent treatments used reflect the proportions and types of subsequent treatments used for multiple myeloma patients in Scottish practice. Additionally, the imbalances in the proportions of the subsequent treatments may confound the assessment of overall survival.[10]

- The open-label design of MAIA may have biased patient-reported outcome including safety outcomes and health-related quality of life, and may have resulted in early patient withdrawals in the control group. This could also have influenced the investigator's assessment of PFS events, despite the study team being blinded to the initial treatment allocation (which was carried out by a central interactive web response system).[3, 10, 11]
- Despite direct evidence against the most relevant comparator, lenalidomide and dexamethasone, there was no direct evidence against the other comparators. There were some limitations with the company's ITC, which provides data for the comparison with bortezomib plus melphalan and prednisolone. The unanchored ITC, which provides data for the economic base case, is limited since it inherently breaks randomisation and any unknown or unobserved prognostic factors that were not adjusted for in the propensity score analysis may have biased the results. Despite these factors, statistician feedback advised that the IPD analysis approach was still reasonable. Safety and HRQoL were not assessed in the analyses. However, despite these limitations, the results of the ITC seem credible.

4.3. Clinical expert input

Clinical experts consulted by SMC considered that the addition of daratumumab, to the most widely used treatment (lenalidomide and dexamethasone) in NHSScotland, to be a therapeutic advancement and fills an unmet need in this therapeutic area as it prolongs PFS and overall survival. They considered that the place of therapy would be as per the indication under review.

4.4. Service implications

Clinical experts consulted by SMC highlighted that use of the IV daratumumab formulation would result in significant service implications, but use of the SC daratumumab formulation would reduce these pressures; they highlighted the SC formulation of daratumumab is already in use for other indications.

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

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 (Darzalex®),** as an **orphan** medicine, in the context of treatments currently available in NHSScotland.

The key points expressed by the group were:

- Multiple myeloma is a chronic, life-limiting blood cancer that can have significant complications that are debilitating and painful, and can drastically affect quality of life. Multiple myeloma is incurable and the majority of newly diagnosed patients are over the age of 65 and not eligible for a stem cell transplant. Multiple myeloma is characterised by periods of remission and relapse, eventually becoming resistant to treatment.
- Many patients (who are not eligible for a stem cell transplant) initially respond to current first-line treatments, commonly lenalidomide plus dexamethasone. The first remission is usually the longest and preserves function. However, not all patients respond to first-line therapy and

these patients require second-line treatments. Each additional line of treatment is associated with worse outcomes, reduced remission times, and increased side effects. Almost half of patients who are transplant ineligible do not go on to receive treatments beyond the first-line setting. Therefore, there is a need to optimise first-line therapy with well-tolerated and more effective treatments.

- The addition of daratumumab to the well-established first-line treatment lenalidomide plus dexamethasone was associated with statistically and clinically significant improvements in overall and progression-free survival; there were no prominent negative impacts on health-related quality of life outcomes. This could lead to improvements in psychological wellbeing, reductions in symptomatic disease and disability (for example pain, fatigue, and ability to function), reduced hospitalisations, and a delay in subsequent treatments that are associated with more side effects. Based on these clinical benefits, patients, families and carers would welcome a treatment that could keep the patient alive and well for longer.
- Despite the addition of daratumumab to two other medicines, the adverse effects profile appears manageable. Daratumumab is a generally well-tolerated treatment that can now be given subcutaneously as well as intravenously, which has significantly reduced administration time and the risk of infusion related side effects.
- Use of daratumumab as a first-line therapy could have considerable service implications. Patients would require an additional parenteral medicine as well as their current oral treatments (usually lenalidomide plus dexamethasone). The use of daratumumab would initially require additional weekly visits to a haematology clinic to administer the medicine, which could also impact patients and their family/carers. However, after 6 months daratumumab only requires monthly administration, which coincides with the existing lenalidomide, dexamethasone and supportive care schedule. Daratumumab is already in use as a second-line treatment option for these patients, so no new training would be required for hospital staff.

Additional Patient and Carer Involvement

We received a patient group submission from Myeloma UK, which is a registered charity. Myeloma UK has received 9.5% pharmaceutical company funding in the past two years, including from the submitting company. A representative from Myeloma UK 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

The submitting company provided an economic case, as described in Table 6.1

Table 6.1 Description of economic analysis

Criteria	Overview
Analysis type	Cost-utility analysis
Time horizon	Lifetime (26 years)
Population	Adults with newly diagnosed multiple myeloma who are ineligible for ASCT
Comparators	Lenalidomide and dexamethasone (Ld) as the most relevant comparator; Bortezomib in combination with melphalan and prednisone (BMP) as a second comparator. BMP was used as a proxy for any alternative bortezomib-based regimens.
Model description	The economic analysis used a partitioned survival model with three health states (progression free, progressed, and death), applying a four-week cycle length, with patients entering the model at a median age of 74.1 years. The model adopts an NHS Scotland and social care perspective.
Clinical data	The primary source of clinical data for daratumumab with lenalidomide and dexamethasone (DLd) in the economic model was the MAIA study, based on results from the October 2021 (representing 64.5 months of follow-up for PFS),[12] and October 2022 data cut (representing 73.6 months follow-up for overall survival).[13] In the absence of direct evidence, efficacy data for BMP was obtained from the ALCYONE study.[14]
Extrapolation	To estimate long-term efficacy of the intervention, data from the MAIA study were extrapolated by fitting parametric curves for overall survival (OS), PFS and for time to treatment discontinuation (TTD). The best fitting curve was selected based on statistical fit, visual fit and clinical expert validation. For PFS - the exponential, exponential and Weibull extrapolations were utilised in the base case for DLd, Ld and BMP, respectively. For OS - the exponential, Gompertz and Gompertz extrapolations were utilised in the base case for DLd, Ld and BMP, respectively. For TTD - generalised gamma and exponential extrapolations were selected in the base case for DLd and Ld, respectively.
Quality of life	Utility values were based on EQ5D-5L data from the MAIA study, which were mapped onto the 3L UK value set. Alternative values from the ALCYONE study were tested in scenario analysis.
Costs and resource use	The economic analysis included costs associated with medicine acquisition, administration, health-state monitoring, subsequent treatments, adverse events and terminal care. The cost of subsequent treatments across second and third lines of therapy was included as a single, per-cycle cost, based on a weighted average, which was applied in all cycles for patients in the PD health state. Market share estimates for subsequent treatments were based on feedback from an advisory board of nine clinical experts and on subsequent treatment proportions used in a previous daratumumab submission in this indication (SMC2416)
PAS	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 simple discount is offered on the list price. A PAS discount is in place for branded lenalidomide (Revlimid®). Generic versions of lenalidomide are also available on the market. However, the price of branded lenalidomide (including PAS) is used in the analysis since it costs less than the list prices of any generic alternatives. Discounts on generic lenalidomide may be available at local level but are not included within SMC decision making. PAS discounts are also in place for subsequent treatments (carfilzomib pomalidomide and panobinostat) which were included in the results for decision-making.

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

6.2. Results

The results presented do not take account of the PAS for lenalidomide or subsequent treatments 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 comparator medicines due to commercial confidentiality and competition law issues.

The base case analysis presented by the submitting company including the PAS for daratumumab and list prices for comparators produced an ICER of £31,143 versus Ld and £46,919 versus BMP. This results from an estimated QALY gain of 1.60 and 2.32 versus Ld and BMP respectively.

6.3. Sensitivity analyses

In deterministic one-way sensitivity analysis, the parameters with greatest impact on ICER were the DLd OS and Ld TTD exponential curve intercepts. A range of scenario analyses were performed and presented in Table 6.3.

Table 6.3 Scenario analyses results (with daratumumab PAS, list prices for all other medicines)

	Scenario	ICER vs Ld (£/QALY)	ICER vs BMP (£/QALY)
	Base case	£31,143	£46,919
1	DLd TTD Extrapolations: Gompertz	£39,744	£52,856
2a	DLd OS extrapolation: Weibull	£30,481	£46,350
2b	DLd OS extrapolation: Gompertz	£37,017	£51,907
3	BMP OS extrapolation: Generalised Gamma	£31,143	£54,182
4a	DLd PFS extrapolation: Weibull	£33,528	£48,515
4b	DLd PFS extrapolation: Generalised Gamma	£29,634	£45,925
5	BMP PFS extrapolation: Generalised Gamma	£31,143	£47,481
6	Ld PFS extrapolation: Weibull	£32,077	£46,919
7	Ld OS extrapolation: Generalised Gamma	£32,644	£46,919
8	Utility values: ALCYONE	£32,874	£49,619
9	Daratumumab medicinal forms: combination of 98% SC and 2% IV	£31,246	£46,932
10	Vial sharing	£32,507	£49,235
11	Time on Treatment: BMP KM, 100% patients discontinue at fixed-duration	£31,143	£47,491
12	NMA as source for BMP PFS, OS	£31,143	£53,629
13	Combined Scenario: 1 + 2b + 4b	£44,210	£56,761

Abbreviations: BMP: bortezomib, melphalan and prednisone; DLd: daratumumab, lenalidomide and dexamethasone ICER: incremental cost-effectiveness ratio; Ld: lenalidomide and dexamethasone; NMA: network meta-analyses; OS: overall survival; PFS: progression free survival; QALY: quality adjusted life year; SC: Subcutaneous; IV: Intravenous

6.4. Key strengths

The economic model was comprehensive and structurally sound. Appropriate sources were selected to inform the model parameters and reasonable methods were used for the indirect treatment comparisons. Results were based on the latest available data-cut from the MAIA trial.

6.5. Key uncertainties

The main weaknesses of the economic analysis were:

- To inform the comparison with BMP, the company used individual patient data to adjust the BMP arm in the ALCYONE study to the DLd arm in the MAIA study. It used a propensity score based inverse probability weighting approach. This approach relies on the assumption that all prognostic factors and effect modifiers have been accounted/adjusted for. However this might not be true and could potentially bias results. An alternative approach is to use a NMA that does not break randomisation. Using the NMA increases the ICER versus BMP (scenario 12 in Table 6.3). Feedback from SMC statisticians suggests that whilst the IPW approach would be preferable to NMA in this instance, a better understanding of the structural uncertainty associated with different approaches is needed.
- Long-term survival outcomes and total medicine costs vary depending on subsequent treatments, and there is some uncertainty about the subsequent treatments in MAIA being reflective of clinical practice. Although the company has employed the best possible approach to estimate usage, the distribution of patients receiving various third line therapies in particular, might be quite different to those applied in the base case. Furthermore, the model did not include any fourth line therapies. Varying treatment distributions and adding lines of therapy are both likely to have an upward impact on costs, albeit the probabilistic sensitivity analysis suggests that these are unlikely to be key drivers of cost effectiveness.
- TTD data has been used to estimate treatment duration in the model. There remains some uncertainty about the choice of curve used to extrapolate time on treatment. The generalised gamma curve for DLd TTD was chosen in the base case as it has the best visual and statistical fit, however alternate curves are equally plausible options. Applying the second best fitting curve, Gompertz, results in a notable increase in ICER (scenario 1 in Table 6.3).
- The predicted overall survival in the base case might be too optimistic. Despite a median follow-up of 73.6 months (data cut-off October 2022), the overall survival data still appear to be relatively immature, with the median only just reached in the control group (64.1 months) and not yet reached in the daratumumab group. Scenario analysis showed that applying a more pessimistic yet plausible Gompertz model to DLd OS extrapolation leads to a large increase in ICER (scenario 2b in Table 6.3). Combined with alternate, yet plausible models for PFS and TTD results in an even larger uplift in ICER (scenario 13 in Table 6.3)

7. Conclusion

The Committee considered the benefits of daratumumb 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 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 the output from the PACE process, and after application of the appropriate SMC modifiers, the Committee accepted daratumumab for use in NHSScotland.

8. Guidelines and Protocols

The British Society for Haematology (BSH) published "Guidelines on the diagnosis, investigation and initial treatment of myeloma: a British Society for Haematology/UK Myeloma Forum Guideline" in March 2021.[15]

The European Society for Medical Oncology (ESMO) and the European Haematology Association (EHA) published "Multiple myeloma: EHA-ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up" in February 2021.[16]

The National Institute for Health and Care Excellence (NICE) published "Myeloma: diagnosis and management" (NG35) in February 2016, which was updated in October 2018.[17]

9. Additional Information

9.1. Product availability date

19 November 2021.

Table 9.1 List price of medicine under review.

Medicine	Dose regimen	Cost per course (£)
Daratumumab	**In combination with lenalidomide and dexamethasone:** **SC = 1,800mg** **IV = 16mg/kg** **Given weekly in weeks 1 to 8, given every 2 weeks in weeks 9 to 24, then given every 4 weeks from week 25 onwards (until disease progression).**	**Weeks 1 to 8 (total of eight doses):** **£34,560** **Weeks 9 to 24 (total of eight doses):** **£34,560** **Week 25 onwards:** **£4,320 every 4 weeks**

Costs from BNF online on 03 April 2023. 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 assuming wastage. Costs do not take any patient access schemes into consideration.

10. Company Estimate of Eligible Population and Estimated Budget Impact

The submitting company estimated there would be 302 patients eligible for treatment with daratumumab in year 1 rising to 304 patients in year 5, to which confidential uptake rates were applied.

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 discounts associated with comparator medicines.

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

References

1. Janssen-Cilag Ltd. Daratumumab 1,800 mg solution for injection (Darzalex®). Summary of product charateristics. Electronic Medicines Compendium www.medicines.org.uk/emc/ Last updated 04 Nov 2022.
2. Janssen-Cilag Ltd. Daratumumab 20mg/mL concentrate for solution for injection (Darzalex®). Summary of product charateristics. Electronic Medicines Compendium www.medicines.org.uk/emc/ Last updated 25 Oct 2022.
3. European Medicines Agency (EMA). European Public Assessment Report. Daratumumab (Darzalex®). EMEA/H/C/004077/II/0029. Published: 17 October 2019. Available at: https://www.ema.europa.eu/en/documents/variation-report/darzalex-h-c-4077-ii-0029-epar-assessment-report-variation_en.pdf [Accessed: 27 March 2023].
4. Cowan AJ, Green DJ, Kwok M, Lee S, Coffey DG, Holmberg LA, et al. Diagnosis and Management of Multiple Myeloma: A Review. JAMA. 2022;327(5):464-477.
5. Cancer Research UK. Myeloma statistics: Myeloma Incidence. Available at: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/myeloma#heading-Zero. [Accessed: 03 April 2023].
6. Public Health Scotland. Cancer incidence and prevalence in Scotland to December 2019. Published: 2021. Available at: https://beta.isdscotland.org/find-publications-and-data/conditions-and-diseases/cancer/cancer-incidence-in-scotland/. [Accessed: 03 April 2023].
7. Cancer Research UK. Myeloma statistics: Myeloma survival. Available at: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/myeloma#heading-Two. [Accessed: 03 April 2023].
8. National Cancer Medicines Advisory Group (NCMAG) Programme. NCMAG103 Lenalidomide: Advice Document v1.0. Published October 2022. Available at: https://www.healthcareimprovementscotland.org/our_work/technologies_and_medicines/ncmag_programme/ncmag_advice.aspx [Accessed: 03 April 2023].
9. Facon T, Kumar S, Plesner T, Orlowski RZ, Moreau P, Bahlis N, et al. Daratumumab plus Lenalidomide and Dexamethasone for Untreated Myeloma. N Engl J Med. 2019 May 30; 380(22):2104-2115.
10. Facon T, Kumar SK, Plesner T, Orlowski RZ, Moreau P, Bahlis N, et al. Daratumumab, lenalidomide, and dexamethasone versus lenalidomide and dexamethasone alone in newly diagnosed multiple myeloma (MAIA): overall survival results from a randomised, open-label, phase 3 trial. Lancet Oncol. 2021 Nov; 22(11):1582-1596. .
11. Janssen-Cilag Ltd. Data on file: MMY3008 (MAIA) Abbreviated Clinical Study Report (October 2021 data-cut). 2022.
12. Kumar SK, Moreau P, Bahlis NJ, Facon T, Plesner T, Orlowski RZ, et al. Daratumumab Plus Lenalidomide and Dexamethasone (D-Rd) Versus Lenalidomide and Dexamethasone (Rd) Alone in Transplant-Ineligible Patients with Newly Diagnosed Multiple Myeloma (NDMM): Updated Analysis of the Phase 3 Maia Study. Blood 2022; 140 (Supplement 1): 10150–10153.
13. Kumar SK, Moreau P, Bahlis N, Facon T, Plesner T, Orlowski RZ, et al. Daratumumab Plus Lenalidomide and Dexamethasone (D-Rd) Versus Lenalidomide and Dexamethasone (Rd) Alone in Transplant-ineligible Patients With Newly Diagnosed Multiple Myeloma (NDMM): Updated Analysis of the Phase 3 MAIA Study [Conference abstract]. Presented at the 64th American Society of Hematology (ASH) Annual Meeting & Exposition; December 10-13, 2022; New Orleans, LA, USA. Abstract Number: 4559. .
14. Mateos MV, Cavo M, Blade J, Dimopoulos MA, Suzuki K, Jakubowiak A, et al. Overall survival with daratumumab, bortezomib, melphalan, and prednisone in newly diagnosed multiple myeloma (ALCYONE): a randomised, open-label, phase 3 trial. The Lancet. 2020; 395:132-141.

15. Sive J, Cuthill K, Hunter H, Kazmi M, Pratt G, Smith D; British Society of Haematology. Guidelines on the diagnosis, investigation and initial treatment of myeloma: a British Society for Haematology/UK Myeloma Forum Guideline. Br J Haematol. 2021 Apr;193(2):245-268.
16. Dimopoulos MA, Moreau P, Terpos E, Mateos MV, Zweegman S, Cook G, et al. Multiple myeloma: EHA-ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of oncology: official journal of the European Society for Medical Oncology. 2021; 32(3):309-322.
17. National Institute for Health and Care Excellence (NICE). Myeloma: diagnosis and management. NICE Guideline [NG35]. Published: February 2016. Lasy updated: October 2018. Available at: https://www.nice.org.uk/guidance/ng35.

This assessment is based on data submitted by the applicant company up to and including 16 May 2023.

**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 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.