Healthcare Improvement Scotland | SMC Advice on new medicines

SMC2180

daratumumab 20mg/mL concentrate for solution for infusion (Darzalex®)

Janssen-Cilag Ltd

7 June 2019

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 considered under the orphan assessment process.

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

Indication under review: In combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone, for the treatment of adult patients with multiple myeloma who have received at least one prior therapy.

SMC restriction: in combination with bortezomib and dexamethasone, for the treatment of adult patients with multiple myeloma who have received one prior therapy only.

Progression-free survival was significantly longer in patients who received daratumumab in combination with bortezomib and dexamethasone compared with those who received bortezomib and dexamethasone in a phase III study in patients with multiple myeloma who had received at least one prior therapy.

This SMC advice takes account of the benefits of a Patient Access Scheme (PAS) that improves the cost-effectiveness of daratumumab. This advice is contingent upon the continuing availability of the PAS in NHSScotland or a list price that is equivalent or lower. This advice takes account of the views from a Patient and Clinician Engagement (PACE) meeting.

Chairman,
Scottish Medicines Consortium

Indication

In combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone, for the treatment of adult patients with multiple myeloma who have received at least one prior therapy.[1]

Dosing Information

Dosing schedule of daratumumab when used in combination with bortezomib (3-week cycle regimen):

16mg/kg body weight administered as an intravenous infusion according to the following dosing schedule:

Weeks	**Schedule**
Weeks 1 to 9	weekly (total of 9 doses)
Weeks 10 to 24	every three weeks (total of 5 doses)
Week 25 onwards until disease progression	every four weeks

For dose and schedule of medicinal products administered with daratumumab see the corresponding Summary of Product Characteristics (SPC).

Following dilution the daratumumab infusion should be intravenously administered at the initial infusion rate detailed in the SPC. Incremental escalation of the infusion rate should be considered only in the absence of infusion reactions.

Daratumumab should be administered by a healthcare professional, in an environment where resuscitation facilities are available. Pre- and post-infusion medications should be administered to reduce the risk of infusion-related reactions (IRRs) with daratumumab. For IRRs of any grade/severity, immediately interrupt the infusion and manage symptoms. Management of IRRs may further require reduction in the rate of infusion, or treatment discontinuation.

If a dose is missed, the dose should be administered as soon as possible and the dosing schedule should be adjusted accordingly, maintaining the treatment interval. No dose reductions are recommended. Dose delay may be required to allow recovery of blood cell counts in the event of haematological toxicity.

Anti-viral prophylaxis should be considered for the prevention of herpes zoster virus reactivation.

Further details are included in the SPC.[1]

Product availability date

April 2017
Daratumumab meets SMC orphan criteria.

Summary of evidence on comparative efficacy

Daratumumab is an immunoglobulin G1 kappa ($IgG1_K$) 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 submitting company has requested that SMC considers daratumumab when positioned for use in combination with bortezomib and dexamethasone, for the treatment of adult patients with multiple myeloma who have received one prior therapy only. Daratumumab monotherapy has previously been accepted for restricted use by SMC as a fourth line treatment option for this indication (SMC 1205/17).

Key evidence for this indication is from CASTOR, a multi-centre, randomised, active-controlled, open-label phase III study in patients with multiple myeloma with at least one previous line of therapy. Recruited patients were required to have at least a partial response to one or more of their previous treatments and have progressive disease according to International Myeloma Working Group (IMWG) criteria during or after completion of their last treatment. Patients had measurable disease in accordance with IMWG criteria, based on assessment of serum, urine or both or assessed by the serum light-chain assay.[2] Patients were required to have an Eastern Cooperative Oncology Group (ECOG) Performance Status score of 0 to 2. Patients were excluded if their disease was refractory to, or had unacceptable toxicity with bortezomib, or refractory to another proteasome inhibitor. Refractory was defined as no response while on therapy or progression within 60 days of stopping therapy in patients who have achieved minimal response or better. [2, 3]

Patients were randomised equally to receive daratumumab in combination with bortezomib and dexamethasone (n=251) or bortezomib and dexamethasone (n=247), stratified according to International Staging System (ISS) disease state at screening (stage I, II or III) where increasing stage indicates increasing severity of disease, number of previous lines of therapy (1 versus 2 or 3 versus >3) and previously received bortezomib (no versus yes).[2] In 21 day cycles, daratumumab intravenous infusion 16mg/kg was given weekly during cycles 1 to 3, every 3 weeks for cycles 4 to 8 then every 4 weeks. All patients received up to 8 cycles (21 days per cycle) of bortezomib and dexamethasone. Bortezomib 1.3mg/m^2 was administered subcutaneously on days 1, 4, 8, and 11 of cycles 1 to 8, and dexamethasone 20mg was administered orally or intravenously on days 1, 2, 4, 5, 8, 9, 11, and 12. The dose of dexamethasone could be reduced to 20mg once weekly for patients who were older than 75 years of age, had poorly controlled diabetes, had a body-mass index (BMI) of <18.5, or for patients who had previous unacceptable adverse effects associated with glucocorticoid therapy. Treatment continued until the patient withdrew consent, the disease progressed, or unacceptable toxicity occurred. Patients in the daratumumab group received medications before or after their infusions of daratumumab as needed to manage infusion related reactions.[2, 3]

The primary outcome was progression-free survival, assessed in all randomised patients.[2] A validated computerised algorithm using laboratory results and imaging assessed by investigators

was used to assess disease progression according to IMWG criteria. After a median follow-up of 7.4 months, a progression-free survival event (progression or death) had occurred in 67 patients (27%) in the daratumumab group and 122 patients (49%) in the control group.[2, 3] Median progression-free survival had not been reached in the daratumumab group and was 7.2 months in the control group (hazard ratio [HR] 0.39, 95% confidence interval [CI]: 0.28 to 0.53, p<0.001, this crossed the pre-specified stopping boundary).[2] The primary outcome and selected secondary outcomes are included in Table 1 below.

Table 1. Primary and selected secondary outcomes from CASTOR.

	Median follow-up 7.4 months[2, 4]		**Median follow-up 26.9 months[5]**		**Median follow-up 40 months[6, 7]**	
	daratumumab	control	daratumumab	control	daratumumab	control
Progression-free survival (months)	NR	7.2	16.7	7.1	16.7	7.1
Time to progression (months)	NR	7.3				
Overall response rate	83%	63%	85%	63%	85%	63%
Complete response or better	19%	9.0%	30%	9.8%	30%	9.8%
Duration of response (months)	NR	7.9				
Overall survival	NR	NR	NR	31.2		
Minimal residual disease rate (10^{-4})	14%	2.8%				

NR: Not reached, p ≤0.001 for differences apart from overall survival at 26.9 month cut-off (p=0.088)

Pre-specified subgroup analyses generally favoured the daratumumab group for the primary outcome. In the subgroup of patients who had previously received one prior line of therapy, representative of the proposed positioning (n=122 in the daratumumab group and n=113 in the and control group), median progression-free survival was not reached in the daratumumab group and was 7.5 months in the control group (HR 0.31, 95% CI 0.18 to 0.52, p<0.001).[2] At a median follow-up of 40 months, in the subgroup of patients who received one prior line of therapy, median PFS was 27 months in the daratumumab group compared with 7.9 months in the control group (HR 0.22, 95% CI: 0.15 to 0.32, p<0.0001). Overall response rate, complete response or

better and minimal residual disease rate (sensitivity threshold 10^{-5}) were significantly higher in the daratumumab group compared with the control group.[6, 7]

Patient reported outcomes were assessed using the European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire EORTC-QLQ-C30 and the EuroQol EQ-5D-5L questionnaire. Baseline scores were comparable between groups and the results indicated that there were no statistically significant differences between groups at most time points.[3]

Other data were also assessed but remain confidential.*

Summary of evidence on comparative safety

At the data cut-off at a median follow-up of 26.9 months, most patients had at least one treatment emergent adverse event (TEAE), 99% in the daratumumab group and 95% in the control group. Grade 3 or 4 TEAEs were reported in 81% and 63% of the respective groups. TEAE leading to discontinuation was similar in both groups (9.5% and 9.3%). The most frequent TEAEs were thrombocytopenia (60% and 44%), peripheral sensory neuropathy (50% and 38%), diarrhoea (35% and 22%), upper respiratory tract infection (33% and 18%), anaemia (28% and 32%), cough (28% and 13%), constipation (22% and 16%), fatigue (22% and 24%), back pain (20% and 10%) and dyspnoea (19% and 8.9%).[5]

Daratumumab can cause serious infusion related reactions (IRRs), including anaphylactic reactions. It is noted in the SPC that IRRs were reported in approximately half of all patients treated with daratumumab in clinical studies. All patients should be monitored throughout the infusion for IRRs.[1]

The EMA notes that daratumumab may increase the rate of thrombocytopenia known to be associated with bortezomib. However, this seemed to be manageable by supportive care and dose modifications, and did not result in an increase in discontinuation of study treatment or deaths. Neutropenia and thrombocytopenia have been classified as important identified risks in the Risk Management Plan.[3]

Summary of clinical effectiveness issues

Multiple myeloma is an incurable haematological malignancy accounting for 1% of all cancers.[3, 8] Treatment options for patients with multiple myeloma include combination chemotherapy, proteasome inhibitors (bortezomib and carfilzomib), immunomodulatory agents (thalidomide, lenalidomide, and pomalidomide), histone deacetylase inhibitors (panobinostat), monoclonal antibodies (daratumumab), high-dose chemotherapy, and autologous stem cell transplantation (ASCT).[3] Thalidomide in combination with an alkylating agent and a corticosteroid is an option for

the first-line treatment of multiple myeloma in patients for whom high-dose chemotherapy with ASCT is considered inappropriate. Regimens including bortezomib or lenalidomide are recommended for patients unsuitable for thalidomide-containing regimens. Subsequent treatment options for relapsed or refractory multiple myeloma include carfilzomib and dexamethasone, bortezomib, usually in combination with dexamethasone, lenalidomide and dexamethasone (in patients with 1 prior regimen with bortezomib or at least 2 prior regimens), panobinostat, bortezomib and dexamethasone and pomalidomide and dexamethasone (both in patients with at least 2 prior regimens).

Clinical experts consulted by SMC considered that daratumumab fills an unmet need in this therapeutic area, namely treatment of patients with relapsed multiple myeloma as this is an incurable disease and patients are likely to require long-term treatment. Daratumumab meets SMC orphan criteria for this indication. The submitting company has requested that SMC considers daratumumab when positioned for use in combination with bortezomib and dexamethasone, for the treatment of adult patients with multiple myeloma who have received one prior therapy only.

In the key CASTOR study, in patients with multiple myeloma who have received at least one prior therapy, progression-free survival was significantly longer in the daratumumab plus bortezomib and dexamethasone group compared with the bortezomib and dexamethasone group.[2, 5, 6] The EMA considered that the HR of 0.39 indicated that adding daratumumab to the standard regimen of bortezomib and dexamethasone provided a significant clinical benefit and can be considered clinically relevant.[3] Overall survival data were immature in the daratumumab group at the latest analysis (median follow-up 40 months) and are likely to be confounded by treatment crossover and patients receiving subsequent lines of therapy.[6]

The study population represents the licensed indication. However, it is wider than the proposed positioning; patients who have received one prior therapy only. The study was not powered for the subgroup analysis in patients who have received one prior therapy only, but the result for this subgroup was consistent with the primary outcome for the full population. Overall, 66% of patients in CASTOR had previously received bortezomib and progression-free survival results in this subgroup were consistent with the ITT population.[2] Patients were required to have had at least a partial response to previous treatment. This is not specified in the licensed indication.

The control arm in the key study was bortezomib plus dexamethasone which is a relevant comparator. However, other relevant comparators include lenalidomide and carfilzomib, both plus dexamethasone. The submitting company presented a Bayesian network meta-analysis (NMA) of two studies comparing daratumumab, bortezomib plus dexamethasone with bortezomib plus dexamethasone and carfilzomib plus dexamethasone. Outcomes measured were progression free survival, overall survival, overall response rate, complete response, very good partial response and safety. An additional NMA was carried out in the subgroup of patients who had received only one prior therapy. The submitting company also presented an indirect treatment comparison of two studies consisting of a Cox adjusted regression model using individual patient data (IPD) and a propensity score nearest-neighbour matched indirect comparison which was used as a sensitivity

analysis of the IPD of daratumumab, bortezomib plus dexamethasone compared with lenalidomide plus dexamethasone. Outcomes assessed were progression free survival, overall survival and safety.

Results of the NMA, in patients with one prior treatment only, indicated that daratumumab, bortezomib plus dexamethasone was superior to carfilzomib plus dexamethasone for progression-free survival. For the overall survival outcome, the results suggested no difference between daratumumab, bortezomib plus dexamethasone and carfilzomib plus dexamethasone. The safety analyses suggested increased risk of Grade 3+ TEAEs, particularly diarrhoea, neutropenia and thrombocytopenia associated with daratumumab, bortezomib plus dexamethasone.

Results of the Cox adjusted regression model base case indicated that, in patients with one prior treatment only who were not refractory to bortezomib or lenalidomide, daratumumab, bortezomib plus dexamethasone was superior to lenalidomide plus dexamethasone for overall survival, however this was not supported by a sensitivity analysis which matched patients from each treatment group. The p value for the hazard ratio for progression-free survival was not significant. Safety analyses identified that patients treated with daratumumab, bortezomib and dexamethasone were less likely to discontinue treatment due to adverse events than those who received lenalidomide plus dexamethasone.

There were some limitations affecting the indirect evidence evaluations. Only one study was included for each comparison. There were differences in the bortezomib regimens, assessment times and follow-up in the studies included in the NMA and overall survival data were immature. The Cox adjusted regression model was only adjusted for International Staging System (ISS) stage and cytogenetic risk. Although these are considered as significant prognostic factors, residual confounding due to unobserved and unadjusted risk factors cannot be excluded. No quality of life outcomes were included in the NMA or Cox adjusted regression model. Despite the limitations, it may be reasonable to accept the results of the indirect treatment comparisons.

Clinical experts consulted by SMC considered that daratumumab in combination with bortezomib and dexamethasone is a therapeutic advancement due to significant improvement in progression-free survival and they considered that the place in therapy would be as second-line treatment for patients with multiple myeloma. Clinical experts considered that the introduction of this medicine may impact on the patient and service delivery as it would require day ward time due to the method of administration and monitoring required.

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 (in combination with bortezomib and dexamethasone), as an orphan medicine, in the context of treatments currently available in NHSScotland.

The key points expressed by the group were:

- Myeloma remains a rare, incurable cancer that is associated with relapses and complications that impact significantly on the quality of life for patients and their family and carers.
- Currently there are no triplet therapies available for use earlier in the myeloma treatment pathway.
- Daratumumab in combination with bortezomib and dexamethasone has been shown to be highly efficacious for patients with myeloma who have previously received one line of therapy providing the opportunity for a deep response early in the treatment pathway.
- This innovative triplet combination is more tolerable in the earlier stages of disease progression when patients are fitter and so it can be made available to a larger proportion of patients with myeloma.
- By prolonging time until progression, daratumumab reduces the risk of myeloma complications, allowing patients to live healthier lives for longer. This also has a positive impact on the patient's family and carers.

Additional Patient and Carer Involvement

We received a patient group submission from Myeloma UK, which is a registered charity. Myeloma UK has received 20.6% pharmaceutical company funding in the past two years, including from the submitting company. A representative from Myeloma UK also participated in the PACE meeting. The key points of their submission have been included in the full PACE statement considered by SMC.

Summary of comparative health economic evidence

The submitting company presented a cost-utility analysis comparing daratumumab plus bortezomib and dexamethasone to bortezomib plus dexamethasone, carfilzomib plus dexamethasone, and lenalidomide plus dexamethasone for the treatment of adult patients with multiple myeloma who had received one prior therapy only, in line with the selective positioning for the medicine. All these comparators were mentioned by SMC clinical experts as potentially being displaced by the daratumumab regimen, although the responses were less clear as to which regimen constituted current second line practice for the treatment of multiple myeloma.

The economic analysis used a partitioned survival model with three health states: pre-progression, post-progression and death, with pre and post-progression divided into time on and time off treatment to account for some patients discontinuing initial second-line treatment prior to

progression or subsequent therapies prior to death. A 30-year time horizon with a one-week model cycle was adopted, with patients entering the model aged 63 years.

The clinical data for daratumumab plus bortezomib and dexamethasone and for bortezomib plus dexamethasone used in the economic analyses were from the subgroup of patients in the CASTOR study who had received one prior therapy only. [2] Clinical data for the comparison with carfilzomib plus dexamethasone and with lenalidomide plus dexamethasone in the one prior therapy only subgroup were from the indirect treatment comparisons described in the summary of clinical effectiveness section above. Clinical data for carfilzomib plus dexamethasone were from the ENDEAVOUR study with bortezomib plus dexamethasone as the reference comparator for the comparison with daratumumab plus bortezomib and dexamethasone. [9] For the comparison with lenalidomide plus dexamethasone multivariate regression analysis was performed to analyse the one-prior subgroup individual patient data (IPD) from CASTOR and POLLUX studies respectively. [2,10] These analyses provided estimates of relative PFS, overall survival (OS) and time to treatment discontinuation (TTD) for use in the economic analysis.

The data cut relating to a median 40 months follow-up from the CASTOR study was used for PFS, OS and TTD extrapolation for daratumumab plus bortezomib and dexamethasone versus bortezomib plus dexamethasone. In the base case the Gompertz function was fitted to the one prior therapy subgroup data for both regimens for PFS. For OS extrapolation the Gompertz function was used for bortezomib plus dexamethasone, and the log logistic function for daratumumab plus bortezomib and dexamethasone, on the grounds that these were estimated to produce the most clinically plausible long run survival projections (6% 10-year survival for bortezomib and 29% for 20-year survival for daratumumab). PFS and OS extrapolation for carfilzomib plus dexamethasone and lenalidomide plus dexamethasone were based on hazard ratios for each therapy relative to bortezomib plus dexamethasone estimated from the NMA and IPD regression analysis respectively. The Gompertz function was used to extrapolate TTD data for daratumumab plus bortezomib and dexamethasone, bortezomib plus dexamethasone (capped at 24 weeks in line with CASTOR dosing schedule), and lenalidomide plus dexamethasone on the grounds this aligned best with PFS extrapolation for each regimen and capped so as not to exceed PFS (in that each therapy is intended to be used to treat to progression). For carfilzomib plus dexamethasone a proportional hazard between PFS and TTD was assumed based on data from a NICE technology appraisal.[11] Account was also taken of death during PFS with a constant probability of 14.6% applied based on analysis of CASTOR data and applied for all comparators.

Utilities for pre and post progression health states were derived from EQ 5D-5L data from the CASTOR study mapped to the EQ 5D-3L value set, with estimates of 0.73 pre-progression and 0.70 post-progression. Disutilities for selected treatment specific adverse events were also included based on published estimates.

Medicine costs included acquisition costs, medicine administration costs, treatment of adverse events, concomitant and prophylactic medicines, and subsequent therapies. Account was taken of relative dose intensity. Resource use costs for routine follow-up care were estimated based on

previous NICE appraisals in multiple myeloma, and verified by Scottish clinical expert opinion. The costs of subsequent multiple myeloma therapies post second-line treatment discontinuation were included in the model, based on those received in the CASTOR study and assumed to be received by 78-81% of patients based on the CASTER and POLLUX studies, with a treatment duration of 9 months based on published evidence, and a constant discontinuation rate assumed. [12] OS associated with subsequent therapies was adjusted using statistical methods to account for treatments not available in Scottish clinical practice.

A patient access scheme was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHSScotland. A PAS is in place for carfilzomib and lenalidomide and these were included in the results used for decision-making by including an estimate of the comparator PAS prices. Bortezomib has a PAS in place but only when used as a monotherapy, hence no discount was included within the analysis. Bortezomib is expected to be available in generic form from March 2019 so an indicative lower price for bortezomib was explored in scenario analysis.

The base case incremental cost-effectiveness ratios (ICERs) for each comparison for the patient population who have received one prior therapy are presented in Table 2. Life years and quality-adjusted life-years (QALY) gained were driven by estimated survival benefits in the post progression state for the comparisons with bortezomib or carfilzomib with dexamethasone. The results presented do not take account of the PASs for daratumumab, carfilzomib or lenalidomide 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 prices for carflizomib and lenalidomide due to commercial confidentiality and competition law issues.

Table 2: Base case results (list prices)

Daratumumab regimen vs.	**ICER (cost per QALY)**
Bortezomib plus dexamethasone	£51,522
Carfilzomib plus dexamethasone	£13,842
Lenalidomide plus dexamethasone	£32,704

ICER = incremental cost-effectiveness ratio, QALY = quality-adjusted life-year

In one way sensitivity analysis the results were particularly sensitive to variation in the OS parameters for bortezomib plus dexamethasone. The ICERs associated with selected scenario analyses are presented in Table 3, showing there is sensitivity to OS extrapolation, but low sensitivity to a shorter time horizon, subsequent therapy duration, and applying an assumed generic price for bortezomib.

Table 3: Selected scenario analyses at list price for all treatments

	ICER (cost per QALY) for daratumumab regimen vs		
Scenario analysis	**bortezomib plus dexamethasone**	**carfilzomib plus dexamethasone**	**lenalidomide plus dexamethasone**
OS extrapolation for bortezomib plus dexamethasone using Weibull function	£53,948	£15,064	£34,298
OS extrapolation for daratumumab combination using exponential function	£62,707	£17,242	£39,982
Longer subsequent treatment duration of 15 months	£54,507	£18,131	£36,643
Time horizon 25 years	£53,898	£14,466	£34,208
Assumed generic price bortezomib (50% discount)	£52,343	£13,842	£32,704
Utility of 0.64 for post progression health state	£54,360	£14,772	£35,359

ICER = incremental cost-effectiveness ratio, QALY = quality-adjusted life-year

The main limitations and uncertainties with the economic analysis were as follows:

- There is uncertainty over the survival benefit associated with daratumumab for patients with multiple myeloma who have received one prior therapy only, due to immature OS data from the CASTOR study (28.7% of patients having died at median 40 month follow up) extrapolated over a 30-year time horizon. The cost-effectiveness results are sensitive to the parametric functions adopted to extrapolate OS for daratumumab and bortezomib regimens, which impact on the ICERs for each comparison, in particular the function used for OS extrapolation for the daratumumab regimen. The estimate of 29% patient survival at 20 years for the daratumumab combination may be optimistic. Applying an exponential function (which had a good statistical/visual fit to the data and potential clinical plausibility) is associated with 20 year survival estimate of 17% and a higher ICER than in the base case (see table 3).
- There are limitations with the indirect treatment comparisons performed, as noted in the summary of clinical effectiveness section above, which mean there are uncertainties over the results, in particular for the estimated survival benefit for daratumumab plus bortezomib and dexamethasone versus carfilzomib plus dexamethasone estimated in the economic analysis. From the NMA the overall survival HR is estimated as 0.71 (95% CI 0.42, 1.21), so there is an estimated survival benefit for daratumumab but as the credible interval crosses one this is uncertain.
- The utility estimation for post-progression survival is high at 0.70 (relative to 0.73 for pre-progression) in order to be representative of all patients in the post progression state, which may be related to limited completion of the EQ 5D shortly after progression in the CASTOR study. Further scenario analysis was requested using a lower utility for post progression that has potentially greater face validity (i.e. a value of 0.64 from a published study, which resulted in a modest increase in the ICER (Table 3). [13] However, if pre-

progression utility were higher than 0.73 this would offset the impact on the ICER of lower utility post progression.

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.

Additional information: guidelines and protocols

For the indication under review the most up to date guidance for diagnosis and management of multiple myeloma is the European Society for Medical Oncology (ESMO) 'Multiple Myeloma: ESMO clinical practice guidelines for diagnosis, treatment and follow-up', published in 2017. [8]For patients with relapsed or refractory disease the choice of therapy depends on several factors such as age, performance status, comorbidities, the type, efficacy and tolerance of previous treatment, the number of prior treatment lines, the available remaining treatment options, the interval since the last therapy and the type of relapse. The guideline notes that the EMA has approved, at the time of first relapse and beyond, lenalidomide in combination with dexamethasone and bortezomib, either alone as single-agent or in combination with pegylated doxorubicin. They state that in the relapsed setting, bortezomib is mostly used in combination with dexamethasone. For patients who have received at least one prior therapy, carfilzomib, in combination with lenalidomide and dexamethasone, carfilzomib in combination with dexamethasone, elotuzumab, in combination with lenalidomide and dexamethasone, and ixazomib, in combination with lenalidomide and dexamethasone are also recommended. Daratumumab was also recently approved for the treatment of adults with relapsed/refractory multiple myeloma whose previous treatment included a proteasome inhibitor and an immunomodulatory agent and whose disease worsened after treatment. The guideline also notes that daratumumab has shown significant efficacy at earlier stages of the disease, first relapse and beyond in combination with bortezomib and dexamethasone or lenalidomide and dexamethasone in two randomised phase III clinical trials. Lastly, the ESMO guideline recommends that a second ASCT can be considered in young patients who responded well to previous transplant and had a progression free survival of more than 24 months.[8]

The National Institute for Health and Care Excellence (NICE) published guidelines "Myeloma: diagnosis and management" in 2016. For the management of relapsed myeloma it is noted that NICE has a number of technology appraisal guidance on myeloma either published or in development. These guidelines recommend bortezomib monotherapy as an option for the treatment of progressive multiple myeloma in people who are at first relapse having received one prior therapy and who have undergone, or are unsuitable for, bone marrow transplantation, when the response to bortezomib is measured using serum M protein after a maximum of 4 cycles of treatment, and treatment is continued only in people who have a complete or partial response; and when the manufacturer rebates the full cost of bortezomib for people who, after a maximum of 4 cycles of treatment, have less than a partial response.[14] The guideline recommends that a

second ASCT should be offered to people with relapsed myeloma who are suitable and who have: completed re-induction therapy without disease progression and had a response duration of more than 24 months after their first ASCT. It should also be considered for people with relapsed myeloma who are suitable and who have: completed re-induction therapy without disease progression and had a response duration of between 12 and 24 months after their first ASCT.[14]

The British Council on Standards in Haematology (BCSH) "Guidelines for the diagnosis and management of multiple myeloma 2014" which were published in February 2014, were archived in 2016.[15]

Additional information: comparators

Bortezomib plus dexamethasone, lenalidomide plus dexamethasone, or carfilzomib plus dexamethasone.

Cost of relevant comparators

Medicine	Dose Regimen	Cost per cycle (£)
daratumumab in combination with bortezomib and dexamethasone	**3 week cycle.** **Daratumumab: 16mg/kg IV infusion weekly for weeks 1 to 9, every 3 weeks for weeks 10 to 24 and every 4 weeks for week 25 onwards.** **Bortezomib: 1.3mg/m^2 body surface area twice weekly for two weeks on days 1, 4, 8, and 11.** **Dexamethasone: 20mg orally on days 1, 2, 4, 5, 8, 9, 11, and 12.**	**Initially: 16,022** **Cycle 4 onwards: 5,095**
carfilzomib plus dexamethasone	4 week cycle. Carfilzomib: IV infusion on two consecutive days, each week for three weeks (days 1, 2, 8, 9, 15, and 16). Starting dose 20mg/m^2 (maximum dose 44mg) in cycle 1 on days 1 and 2. If tolerated, the dose should be increased on day 8 of cycle 1 to 56 mg/m^2 (maximum dose 123 mg). Dexamethasone: 20 mg orally or IV on days 1, 2, 8, 9, 15, 16, 22, and 23.	Initially: 8,461 Cycle 2 onwards: 10,573
lenalidomide plus dexamethasone	4 week cycle.	Initially: 4,407 Cycle 5 onwards: 4,381

	Lenalidomide: 25mg orally once daily on days 1 to 21. Dexamethasone: 40mg orally once daily on days 1 to 4, 9 to 12, and 17 to 20 for the first 4 cycles of therapy and then 40mg once daily on days 1 to 4.	
bortezomib plus dexamethasone	3 week cycle. Bortezomib: 1.3mg/m^2 body surface area IV or SC twice weekly for two weeks on days 1, 4, 8, and 11. Dexamethasone: 20mg orally on days 1, 2, 4, 5, 8, 9, 11, and 12.	3,062

IV = intravenous, SC = subcutaneous. Doses are for general comparison and do not imply therapeutic equivalence. Costs from BNF online on 01 March 2019. Costs calculated using the full cost of vials/ampoules assuming wastage. Costs calculated for weight 70kg or BSA 1.8m^2. Costs do not take any patient access schemes into consideration.

Additional information: 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.

Other data were also assessed but remain confidential.*

References

1. Janssen Cilag Ltd. Darzalex 20mg/ml concentrate for solution for infusion. Summary of product characteristics. Electronic Medicines Compendium www.medicines.org.uk/emc/ Last updated 02.01.19. 2017 [cited; Available from: https://www.medicines.org.uk/emc/medicine/32088.
2. Palumbo A, Chanan-Khan A, Weisel K, Nooka AK, Masszi T, Beksac M*, et al.* Daratumumab, Bortezomib, and Dexamethasone for Multiple Myeloma. The New England journal of medicine. 2016;375(8):754-66.
3. The European Medicines Agency. European Public Assessment Report (EPAR), Darzalex (Daratumumab). 2016.
4. Janssen. MMY3004 Clinical Study Report. 2016.
5. Janssen. [Data on File] MMY 3004, IA2 Analysis. 2018.
6. Mateos M. [Data on File] Efficacy and Safety of Daratumumab, Bortezomib, and Dexamethasone (D-Vd) Verus Bortezomib and Dexamethasone (Vd) in First Relapse Patients With Multiple Myeloma: Update of CASTOR. Poster presentation at ASH December 2018: 2018.
7. Janssen. [Data on File] MMY 3004, ASH 2018. 2018.
8. Moreau P, San Miguel J, Sonneveld P, Mateos MV, Zamagni E, Avet-Loiseau H*, et al.* Multiple myeloma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2017;28(suppl_4):iv52-iv61. Epub 2017/04/30.
9. Dimopoulos MA, Moreau P, Palumbo A, Joshua D, Pour L, Hájek R*, et al.* Carfilzomib and dexamethasone versus bortezomib and dexamethasone for patients with relapsed or refractory multiple myeloma (ENDEAVOR): a randomised, phase 3, open-label, multicentre study. The Lancet Oncology. 2016;17(1):27-38.
10. Janssen. [Data on File] MMY 3003(POLLUX) Efficacy and Safety Update: ASH 2018 Data Cut. 2018.
11. National institute for Health and Care Excellence (NICE). NICE Technology appraisal guidance 457: Carfilzomib for previously treated multiple myeloma 2017. 2017 [cited; Available from: https://www.nice.org.uk/guidance/ta457.
12. Yong K, Delforge M, Driessen C, Fink L, Flinois A, Gonzalez-McQuire S*, et al.* Multiple myeloma: patient outcomes in real-world practice. British journal of haematology. 2016;175(2):252-64.
13. van Agthoven M, Segeren CM, Buijt I, Uyl-de Groot CA, van der Holt B, Lokhorst HM*, et al.* A cost-utility analysis comparing intensive chemotherapy alone to intensive chemotherapy followed by myeloablative chemotherapy with autologous stem-cell rescue in newly diagnosed patients with stage II/III multiple myeloma; a prospective randomised phase III study. Eur J Cancer. 2004;40(8):1159-69. Epub 2004/04/28.
14. National Institute of Health and Care Excellence. Myeloma: diagnosis and management. 2016 [cited; Available from: https://www.nice.org.uk/guidance/ng35.
15. BCSH. British Council for Standards in Haematology (BCSH). Guidelines for the diagnosis and management of multiple myeloma 2014, February 2014.

This assessment is based on data submitted by the applicant company up to and including 12 April 2019.

**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: http://www.scottishmedicines.org.uk/About_SMC/Policy*

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.