Healthcare Improvement Scotland | SMC Advice on new medicines

SMC2302

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

Janssen-Cilag Ltd

4 December 2020

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 NHS Scotland. 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 bortezomib, thalidomide and dexamethasone, for the treatment of adult patients with newly diagnosed multiple myeloma who are eligible for autologous stem cell transplant.

The addition of daratumumab to bortezomib, thalidomide and dexamethasone was associated with a significant improvement in stringent complete response rates in patients with newly diagnosed multiple myeloma who were eligible for autologous stem cell transplant. 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.

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

Chairman
Scottish Medicines Consortium

Indication

In combination with bortezomib, thalidomide and dexamethasone for the treatment of adult patients with newly diagnosed multiple myeloma who are eligible for autologous stem cell transplant (ASCT).[1]

Dosing Information

The recommended dose of daratumumab is 16mg/kg body weight administered as an intravenous infusion according to the following dosing schedule:

Treatment Phase	**Weeks**	**Schedule**
Induction	Weeks 1 to 8	Weekly (total of 8 doses)
	Weeks 9 to 16	Every two weeks (total of 4 doses)
Stop for high dose chemotherapy and ASCT		
Consolidation	Weeks 1-8	Every two weeks (total of 4 doses)

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 require further reduction in the rate of infusion, or treatment discontinuation.

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 can be found in the SPC.[1]

Product availability date

20 January 2020

Daratumumab has been designated as an orphan medicine by the European Medicines Agency and meets SMC orphan criteria.

Summary of evidence on comparative efficacy

Daratumumab is an immunoglobulin G1 kappa ($IgG1_K$) human monoclonal antibody. It binds to CD38, a protein expressed at a high level on the surface of multiple myeloma cells which inhibits growth of CD38-expressing tumour cells resulting in immune-mediated tumour cell death.[1]

Key evidence for this indication is from CASSIOPEIA, a European, multicentre, randomised, open-label, parallel group, phase III study in patients with newly diagnosed multiple myeloma who were eligible for ASCT. The study recruited adult patients aged between 18 and 65 years with a documented new diagnosis of multiple myeloma who were eligible for high-dose therapy and ASCT. Eligible patients had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2 and laboratory values within acceptable parameters.[2, 3]

Patients were randomised equally to receive daratumumab in combination with bortezomib, thalidomide and dexamethasone (n=543) or bortezomib, thalidomide and dexamethasone (n=542) for up to four 28-day, pre-transplant induction cycles and two 28-day, post-transplant consolidation cycles (part 1). Randomisation was stratified according to site affiliation (Intergroupe Francophone du Myélome or Dutch-Belgian Cooperative Trial Group for Hematology Oncology), International Staging System (ISS) disease stage (I, II or III) and cytogenic risk status (presence [high risk] or absence [standard risk] of del17p or t[4;14] cytogenetic abnormalities confirmed by centralised analysis during screening). Daratumumab 16mg/kg intravenous infusion was administered once weekly for induction cycles 1 and 2 and once every 2 weeks for induction cycles 3 and 4 and consolidation. All patients received subcutaneous bortezomib 1.3mg/m^2 twice weekly for week 1 and 2 (days 1, 4, 8 and 11) of each cycle, oral thalidomide 100mg daily for each cycle and oral or intravenous dexamethasone 40mg on days 1, 2, 8, 9, 15, 16, 22, and 23 of induction cycles 1 and 2 and days 1 and 2 of induction cycles 3 and 4 and 20 mg on days 8, 9, 15, and 16 of induction cycles 3 and 4 and days 1, 2, 8, 9, 15, and 16 of both consolidation cycles. Pre- and post-infusion medications were administered to patients who received daratumumab to prevent or manage infusion reactions. Patients who achieved at least a partial response by day 100 post-transplant were re-randomised to receive daratumumab maintenance or observation only until progressive disease up to a maximum of 2 years (part 2).[2, 3] The indication relating to this submission does not include part 2 of the CASSIOPIEA study.

The primary outcome was the proportion of patients who achieved a stringent complete response (sCR) after consolidation, systematically assessed at 100 days after ASCT (or immediately after consolidation if >100 days) in accordance with IMWG criteria. Stringent complete response was defined as achieving a complete response (CR) in addition to having a normal serum free light chain (FLC) ratio and absence of clonal cells in bone marrow.[4] This analysis was performed in all randomised patients. At the pre-specified data cut-off date on 19 June 2018 (median duration of follow-up of 18.8 months), a statistically significant improvement was demonstrated in the sCR rate post-consolidation (100 days post-ASCT) for the daratumumab group compared with the control group. A hierarchical statistical testing strategy was applied to key secondary outcomes following the prioritised order listed in table 1 with no formal testing of outcomes after the first non-significant outcome in the hierarchy. Updated results for the primary outcome and survival

outcomes were provided from a second, later data-cut off on 1 May 2019 (median duration of follow-up of 29.2 months) in support of the primary analyses. See Table 1 for details.[2, 3]

Table 1: Primary and key secondary outcomes from the CASSIOPIEA study.[2, 3, 5]

	Daratumumab group (n=543)	Control group (n=542)	Daratumumab group (n=543)	Control group (n=542)
Data cut-off date	**19 June 2018**		**1 May 2019**	
Primary outcome				
sCR, n(%)	157 (29%)	110 (20%)	295 (54%)	228 (42%)
OR (95% CI)	1.60 (1.21 to 2.12)		1.64 (1.29 to 2.09)	
p-value	0.001		<0.001	
Key secondary outcomes				
Post consolidation MRD-negative rate (10^{-5})[a]	64%	44%	NR	NR
OR (95% CI), p-value	2.27 (1.78 to 2.90), p<0.001			
Post consolidation CR or better rate[b]	39%	26%	62%	48%
OR (95% CI), p-value	1.82 (1.40 to 2.36), p<0.001		1.80 (1.41 to 2.30), p<0.001	
PFS events (n)	45	91	83	151
Median duration of PFS (days)	NE	NE	NE	NE
HR (95% CI), p-value	0.47 (0.33 to 0.67), p<0.001		0.50 (0.38 to 0.65), p<0.001	
KM estimated PFS rate at 12 months	96%	92%	95%	93%
KM estimated PFS rate at 24 months	89%	77%	88%	77%
Deaths (n)	14	32	26	48
Median duration of overall survival (days)	NE	NE	NE	NE
HR (95% CI), p-value	0.43 (0.23 to 0.80), p<0.001		0.52 (0.33 to 0.85), p<0.001	

sCR= stringent complete response, MRD=minimal residual disease, OR=odds ratio, CI= confidence interval, CR=complete response, PFS=progression-free survival, NE=not estimable, HR=hazard ratio, KM= Kaplan-Meier, [a]at a threshold of 1 tumour cell per 10^{-5} white cells as assessed by multiparametric flow cytometry, [b]includes stringent complete response and complete response.

Pre-specified subgroup analyses of the primary outcome were supportive of the primary analyses with the exception of patients with a high-risk cytogenic profile (OR 0.83, [95% CI 0.42 to 1.66]) and ISS disease stage III (OR 1.07 [95% CI 0.54 to 2.12]). However, at the later data-cut on 1 May 2019 results for these subgroups were consistent with the ITT population.[3]

Health Related Quality of Life (HRQoL) was assessed using the European Organisation for Research and Treatment of Cancer-Quality of life Questionnaire-Core (EORTC-QLQ-C30) and EuroQol 5-dimension (EQ-5D-5L) questionnaires. The EORTC-QLQ-C30 indicated a reduction in pain

symptoms, less deterioration in cognitive functioning and an improvement in emotional functioning in the daratumumab group compared with the control group. No significant between group differences were noted using the EQ-5D-5L questionnaire.[3]

The submitting company presented unanchored matching adjusted indirect comparisons (MAICs) of daratumumab plus bortezomib, thalidomide and dexamethasone (DBTd)[2] and bortezomib, thalidomide and dexamethasone (BTd) versus bortezomib, cyclophosphamide and dexamethasone (BCd)[6]and bortezomib and dexamethasone (Bd)[7] in patients with newly diagnosed multiple myeloma who were eligible for ASCT. These comparators were not included in the economic case presented to SMC.

Summary of evidence on comparative safety

The EMA concluded that the addition of daratumumab to bortezomib, thalidomide and dexamethasone did not seem to significantly increase toxicity and overall the combination is relatively well tolerated. At data cut-off 19 June 2018, the median duration of treatment in the daratumumab group was 8.9 months and in the control group was 8.7 months. Any treatment-emergent adverse event (AE) was reported by 99.8% (535/536) of patients in the daratumumab group and 99.6% (536/538) in the control group and these were considered treatment-related in 98% and 96% respectively. In the daratumumab and control groups respectively, patients reporting a grade 3 or higher AEs were 54% versus 55%, patients with a reported serious AE were 47% in both groups and patients discontinuing therapy due to an AE was 7.5% versus 8.4%.[3]

The most frequently reported treatment-emergent AEs of any grade with an incidence >20% in the daratumumab group versus the control group were: peripheral sensory neuropathy (59% versus 63%), constipation (51% versus 49%), asthenia (32% versus 29%), peripheral oedema (30% versus 28%), nausea (30% versus 24%), neutropenia (29% versus 16%), pyrexia (26% versus 21%), paraesthesia (22% versus 20%), thrombocytopenia (20% versus 14%), stomatitis (16% versus 19%).[3]

Daratumumab can cause serious infusion-related reactions (IRR)s and the SPC recommends pre- and post-infusion medications to minimise this risk. In CASSIOPIEA, approximately a third of patients experienced IRRs and most (90%) of these were grade 1 or 2.[1, 2]

The incidence of neutropenia-related events was higher in the daratumumab group (35%) compared with the control group (24%). However, patients experiencing neutropenic fever was similar between treatment groups (6.9% and 5.2%) and there were no neutropenia events that lead to the discontinuation of study treatment in either group.[3]

Summary of clinical effectiveness issues

Multiple myeloma is an incurable haematological cancer, characterised by uncontrolled and progressive proliferation of plasma cells in the bone marrow. It causes displacement of the normal bone marrow leading to dysfunction in normal haematopoietic tissue and destruction of normal bone marrow architecture, resulting in progressive morbidity and mortality. Multiple myeloma accounts for approximately 1% of cancers and 10% of all haematological malignancies.[3, 8]

For patients deemed fit, standard front-line treatment of multiple myeloma consists of induction treatment followed by high-dose therapy and ASCT.[9] SMC has accepted bortezomib, dexamethasone and thalidomide for use as induction treatment. Off-label combinations of cyclophosphamide and dexamethasone with either thalidomide or bortezomib may also be used. Daratumumab meets SMC orphan criteria.

In the CASSIOPIEA study, at the pre-specified data cut-off on 19 June 2018, patients with newly diagnosed multiple myeloma who were eligible for ASCT treatment showed a statistically significant improvement in the sCR rate post-consolidation (100 days post-ASCT) in the daratumumab in combination with bortezomib, thalidomide and dexamethasone group compared with the bortezomib, thalidomide and dexamethasone group. This was supported by results from a later data-cut-off on 1 May 2019 that were consistent with the primary analysis for the ITT and across all pre-specified subgroups. The EMA concluded the addition of daratumumab to standard induction therapy of bortezomib, thalidomide and dexamethasone resulted in a deeper response at day 100 post ASCT in terms of sCR and MRD negativity and this was of high clinical relevance.[2, 3] Overall survival and PFS data appear favourable but were still immature at the latest analysis (median follow-up 29.2 months). Updated results for PFS (including an analysis censoring patients in each arm who were randomised to daratumumab maintenance in the second randomisation) and overall survival are expected in 2021.[3]

In CASSIOPIEA, limited study follow-up meant it was not possible to establish a quantitative correlation between sCR and PFS. which could have informed a positive conclusion for the first part of the study (induction, ASCT and consolidation). The study design did not permit isolation of the impact of the induction and consolidation regimen on PFS as only those patients who had at least a partial response in part 1 of the study were eligible for randomisation to part 2 (maintenance therapy). However, a sensitivity analysis for PFS was conducted with patients who received maintenance therapy at the second randomisation censored, these results were consistent with the primary analysis (HR 0.50, [95% CI: 0.34 to 0.75]).

Not all patients who were MRD negative achieved a sCR or CR and an analysis was performed to ascertain why this may have been the case. This showed the main reasons for not having sCR or CR was that a negative immunofixation on the serum or urine could not be established, either due to missing confirmation of the clearance of paraprotein from serum or urine, or due to remaining traces of the paraprotein, further sampling error in patients not in CR could not be ruled out.

Daratumumab in combination with bortezomib, thalidomide and dexamethasone is licensed for four induction cycles followed by ASCT and a further two consolidation cycles. In Scotland,

patients do not routinely receive consolidation therapy and a more relevant comparison may have included induction with bortezomib, thalidomide and dexamethasone and ASCT only. Therefore, the comparator used in CASSIOPIEA may underestimate the relative treatment benefit. Thalidomide was administered at a dose of 100mg daily in CASSIOPIEA. The dosing schedule of thalidomide in combination with bortezomib and dexamethasone is a gradual increase from 50mg to 200mg however, in practice due to tolerability, patients may not reach the higher dose.

Clinical experts consulted by SMC considered that daratumumab in combination with bortezomib, thalidomide and dexamethasone is a therapeutic advancement due to a deeper response shown by sCR and MRD outcomes in the CASSIOPIEA study and they consider it would be used as first-line treatment. They indicated that the introduction of this medicine would require additional nursing, pharmacy and day unit time because of the additional two consolidation cycles required and significant length of infusion. A licensed subcutaneous formulation of daratumumab is available for this indication but is out with the scope of this submission.

Patient and clinician engagement (PACE)

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

The key points expressed by the group were:

- Multiple myeloma is a life limiting haematological cancer associated with progressive kidney failure, recurrent infections and spontaneous fractures of long bones and of the spine which can lead to spinal cord compression. The disease is associated with periods of remission and relapse. Patients and their families can experience negative psychological stress and anxiety about the future. Myeloma can be associated with significant morbidity affecting patients' quality of life including their ability to perform daily activities, work, socialise and participate in family life.
- There is currently no cure and a high unmet need exists in this patient group for effective upfront treatment options. PACE clinicians highlighted that first remission is the best opportunity to gain the deepest and longest response. The addition of daratumumab to current first line triplet therapy (bortezomib, thalidomide and dexamethasone) was associated with a deeper response and therefore could provide patients with the best opportunity to achieve longer periods of remission.
- In patients who respond, improved disease control and fewer disease-related symptoms would allow patients to feel well for longer. This is important at this early stage of disease when patients are likely to be younger and fitter. This could mean patients were able to participate in family activities, go on holiday, return to work and rely less on family or carers, overall improving their quality of life.
- Daratumumab in combination with bortezomib, thalidomide and dexamethasone is generally well tolerated with no significant increase in overall toxicity. Patients considered adverse events to be clinically manageable. Additional hospital visits may be required to

administer daratumumab as an intravenous infusion however, patients considered clinical efficacy and the opportunity of a good remission to outweigh any disadvantages in the method of administration.

Additional Patient and Carer Involvement

We received a patient group submission from Myeloma UK, which is a registered charity. Myeloma UK has received 8% 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.

Summary of comparative health economic evidence

The submitting company presented a cost-utility analysis of DBTd versus BTd for the treatment of adult patients with newly diagnosed multiple myeloma who are eligible for ASCT. It was assumed that patients in the comparator arm would receive two consolidation cycles as described in the CASSIOPEIA study protocol. The cost-utility analysis utilised a hybrid model structure with two discrete phases; a decision tree phase followed by a Markov model phase. The decision tree phase represented first line therapy and therefore included induction therapy, ASCT and consolidation therapy health states while the Markov model phase included progression free survival, subsequent treatment lines (2^{nd}/3^{rd} and 4^{th} line therapies) and progressed disease. A lifetime time horizon (43 years) was used with a cycle length of 28 days. It was assumed death could occur from any health state.

Overall survival (OS) and time to progression (TTP) were estimated using a combination of data from the CASSIOPEIA study and further analyses of a meta-analysis of the prognostic value of minimal residual disease (MRD) status in patients with newly diagnosed transplant- eligible multiple myeloma.[10]A parametric survival curve was fitted to data from the CASSIOPEIA study for MRD positive patients who received BTd as induction and consolidation therapy to allow extrapolation of OS and TTP over the model time horizon. This survival curve was used to derive transition probabilities for MRD positive patients who received BTd. Parallel probabilities for MRD negative patients and those receiving DBTd were calculated via the application of hazard ratios, estimated from the meta-analysis and the CASSIOPEIA study, to these original curves. Other transitions were modelled using median figures for TTP used in previously published health technology assessments.

Utility estimates for health states included in the decision tree phase were derived from EQ-5D-5L data collected in the CASSIOPEIA study and subsequently 'cross-walked' to EQ-5D-3L index scores prior to applying the UK value set. Other health states used utility estimates from a published cost-utility analysis by van Agthoven et al (2004) however the precise instrument used to elicit the health-related quality-of-life information for these health states and the value set applied is unclear.[11] Furthermore, the range of utilities from this paper (prior to age adjustment) is relatively high and narrow given the indication (from second line therapy: 0.69, to progressed disease: 0.64).

An alternative approach using utility estimates from a publication by Uyl de Groot (2005) was tested in a scenario analysis.[12]

The submission considered a comprehensive range of costs including medicines acquisition costs, adverse event management, costs of subsequent treatment, and scheduled medical resource use. The dose and duration of treatment with DBTd and BTd were assumed to be equal to the protocols of the CASSIOPEIA study and were adjusted for any discontinuation observed during the study. Costs were applied for each administration of medicines that are required to be administered either intravenously or by subcutaneous injection. Initial administrations were associated with a higher cost than subsequent administrations. Sources for assigning costs were generally appropriate and relevant to NHSScotland.

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. Under the PAS, a discount is offered on the list price of the medicine. The with-PAS results are summarised in Table 2.

Table 2: Base-case results (PAS price)

Intervention	Total LYs	Inc. LYs	ICER (Cost per QALY)
DBTd	13.61		
BTd	10.61	3.00	£5,973
BTd: bortezomib, thalidomide and dexamethasone; DBTd: daratumumab, bortezomib, thalidomide and dexamethasone; ICER: incremental cost-effectiveness ratio; LY: life year; QALY: quality-adjusted life year.			

The base-case cost-effectiveness results for DBTd versus BTd shown in Table 2**Error! Reference source not found.** indicate that treatment with DBTd is associated with an increased number of life years and quality-adjusted life years (QALYs) but also higher total costs. Disaggregated results provided by the company demonstrate that the majority of the incremental costs associated with DBTd occur between the 1st line therapy and the progression free post consolidation health states and consist primarily of medicine acquisition costs and administration costs. The majority of incremental QALYs are also accrued in these health states.

A number of scenario analyses were included in the company's submission and others were obtained through correspondence with the company – a selection of these are shown in Table 3. These scenario analyses indicated that the cost-effectiveness results were upwardly sensitive to the inclusion of a treatment effect for DBTd, above that for MRD status, on TTP for MRD negative patients, (see difference in results between scenarios 1 and 2), the distribution of patient time spent in post progression survival health states (scenario 3) and the curve used to extrapolate TTP in the analysis (scenario 4).

Table 3: Scenario analyses

Scenario	Description	ICER
	Base case	£5,973
1	No additional treatment effect for DBTd where statistical significance has not been demonstrated above that for MRD status	Dominant
2	No additional treatment effect for DBTd above that for MRD status	£88,478
3	Proportion of patient time spent in post progression survival health states reweighted	£11,270
4	Gompertz curve used to extrapolate TTP	£25,594
5	10 year time horizon	Dominant
6	20 year time horizon	£2,337
7	Generic price of bortezomib used	£6,201
8	Scenarios 1 and 4 combined	£38,915
9	Scenarios 3 and 4 combined	£95,685
10	Scenarios 1, 3 and 4 combined	£39,055
DBTd: daratumumab, bortezomib, thalidomide and dexamethasone; ICER: incremental cost-effectiveness ratio; Inc.: incremental; MRD: minimal residual disease; PAS: Patient Access Scheme; QALY: quality-adjusted life year; TTP: time to progression		

There are a number of important limitations to the analysis including:

- A number of DBTd treatment effects for improvement in TTP and OS, above the impact of MRD status, included in the model are not statistically significant. The impact of removing treatment effects where statistical significance has not been demonstrated is shown in scenario 1 where DBTd is estimated to be a dominant strategy. The impact of removing the remaining treatment effect of DBTd, above that of MRD status, on TTP for MRD negative patients is shown in scenario 2. The difference in results between these scenarios indicates the sensitivity of the model to the inclusion of this treatment effect but scenario 2 should be considered a very conservative estimate given it requires removal of a statistically significant effect.
- The TTP and OS data available from the CASSIOPEIA study is relatively immature and requires extrapolation over the model time horizon. Results appear particularly sensitive to the choice of curve used to extrapolate TTP within the model as demonstrated by scenario 4.The impact of extrapolation on results was further explored via scenario analyses that used shorter time horizons (see scenarios 5 and 6). The decrease in the ICERs observed relative to the base-case in these scenarios is expected to reflect a higher proportion of patient time being spent in the

progressed disease health state versus the base-case where patients incur smaller costs.

- The base-case model estimates an implausibly long average time spent in the progressed disease health state. This finding may underestimate the costs associated with both treatment strategies if patients would typically spend a longer time receiving anti-cancer therapies at prior lines of treatment. The impact of assuming a different distribution of patient time in post progression survival health states was investigated in scenario 3.
- The application of the treatment effects used in the analysis does not account for any waning of treatment effects over time. While the company have tested this assumption over the current follow-up period and this appears reasonable, it is unclear if these treatment effects will continue for the duration of the model time horizon. The submitting company provided some additional exploratory analysis in which the hazard ratios for DBTd versus BTd were set to include no treatment effect at 5 or 10 years. In all scenarios provided, the maximum cost per QALY was £26,441
- The branded list price for bortezomib was used in the base-case analysis while cheaper generic versions of this medicine are now available. The impact on results of using the cheapest generic price of bortezomib available is shown in scenario 7.
- The use of consolidation therapies in the study does not reflect current practice in Scotland and therefore as noted above the relative treatment benefit of DBTd may be underestimated. However, the impact of this on results in unclear as the inclusion of consolidation cycles for BTd may over-estimate costs in the model.

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,the output from the PACE process, the Committee accepted daratumuab for use in NHSScotland.

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

Additional information: guidelines and protocols

The National Institute for Health and Care Excellence (NICE) published the myeloma: diagnosis and management guideline (NICE guideline NG35) in February 2016 and updated in October 2018. In patients with newly diagnosed myeloma who are eligible for ASCT, the guideline recommends the use of bortezomib in combination with either dexamethasone or with dexamethasone and thalidomide.[13]

The European Society for medical oncology published clinical practice guidelines for the diagnosis, treatment and follow-up of multiple myeloma in August 2017 and they make the following recommendations: in patients <70 and in good clinical condition induction therapy followed by

high dose therapy with ASCT is recommended. In Europe, the use of bortezomib and dexamethasone (Bd) is common practice, more recently the results of phase II trials suggest the addition of a third agent, thalidomide (BTd) may demonstrate higher response rates.[9]

Additional information: comparators

Bortezomib with thalidomide and dexamethasone
Bortezomib or thalidomide with cyclophosphamide and dexamethasone (off-label)

Additional information: list price of medicine under review

Medicine	Dose Regimen	Cost per 28-day cycle (£)
Daratumumab, bortezomib, thalidomide and dexamethasone	Daratumumab IV: 16mg/kg weekly for cycles 1 and 2 and every 2 weeks for cycles 3 and 4 and both consolidation cycles Bortezomib SC: 1.3mg/m^2 twice weekly for week 1 and 2 of each cycle (days 1, 4, 8 and 11) Thalidomide oral: 100mg daily Dexamethasone oral: 40mg on days 1, 2, 8, 9, 15, 16, 22, and 23 of induction cycles 1 and 2, 40mg on days 1 and 2 of induction cycles 3 and 4, and 20mg on days 8, 9, 15, and 16 of induction cycles 3 and 4 and days 1, 2, 8, 9, 15, and 16 of both consolidation cycles.	19,600 for cycles 1 and 2 11,187 for cycles 3 and 4 11,194 for consolidation cycles

Costs from BNF online on 31 August 2020. Costs based on body weight of 70kg and body surface area of 1.8m^2 and are 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 the population eligible for treatment to be 161 patients. This was estimated using a combination of data from Public Health Scotland regarding the incidence of multiple myeloma, company information on the proportion of patients eligible for treatment under the daratumumab license and market share estimates provided by the company.

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.

It should also be noted that within the medicines costs presented, both for the daratumumab regimen and the comparator regimen, the company has included the costs associated with treatment administration and the costs associated with SCT.

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

References

1. Janssen-Cilag Ltd. daratumumab (Darzalex) 20mg/ml concentrate for solution for infusion: Summary of Product Characteristics. Electronic Medicines Compendium (EMC) 2020. Available from: https://www.medicines.org.uk/emc/product/7250/smpc.
2. Moreau P, Attal M, Hulin C, Arnulf B, Belhadj K, Benboubker L*, et al.* Bortezomib, thalidomide, and dexamethasone with or without daratumumab before and after autologous stem-cell transplantation for newly diagnosed multiple myeloma (CASSIOPEIA): a randomised, open-label, phase 3 study. Lancet (London, England). 2019;394(10192):29-38. Epub 2019/06/07.
3. European Medicines Agency (EMA). European Public Assessment Report Variation. daratumumab (Darzalez). Available at: https://www.ema.europa.eu/en/documents/variation-report/darzalex-h-c-4077-ii-0030-epar-assessment-report-variation_.pdf.
4. U.S. National Library of Medicine. A Study to Evaluate Daratumumab in Transplant Eligible Participants With Previously Untreated Multiple Myeloma (Cassiopeia). Available at: https://clinicaltrials.gov/ct2/show/NCT02541383 Last updated: 29 October 2019.
5. Janssen. [Data on File] MMY3006. Post-hoc Interim Analysis. May 1, 2019.
6. Harousseau JL, Attal M, Avet-Loiseau H, Marit G, Caillot D, Mohty M*, et al.* Bortezomib plus dexamethasone is superior to vincristine plus doxorubicin plus dexamethasone as induction treatment prior to autologous stem-cell transplantation in newly diagnosed multiple myeloma: results of the IFM 2005-01 phase III trial. J Clin Oncol. 2010;28(30):4621-9.
7. Mai EK, Bertsch U, Durig J, Kunz C, Haenel M, Blau IW*, et al.* Phase III trial of bortezomib, cyclophosphamide and dexamethasone (VCD) versus bortezomib, doxorubicin and dexamethasone (PAd) in newly diagnosed myeloma. Leukemia. 2015;29(8):1721-9.
8. BMJ Best Practice. Multiple myeloma. Available at: https://bestpractice.bmj.com/topics/en-gb/179 Last updated: December 2018
9. 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. Annals of oncology : official journal of the European Society for Medical Oncology. 2017;28(suppl_4):iv52-iv61. Epub 2017/04/30.
10. Munshi, N. et al. Expanded Meta-Analysis Confirms the Association Between MRD and Long-term Survival Outcomes in Multiple Myeloma (MM). Poster no.4742. Presented at American Society of Hematology (ASH). 7-10 December 2019, Orlando Florida.
11. 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. European journal of cancer (Oxford, England : 1990). 2004;40(8):1159-69. Epub 2004/04/28.
12. Uyl-de Groot, CA, Buijt, I, Gloudemans, IJM, et al. Health related quality of life in patients with multiple myeloma undergoing a double transplantation. European Journal of Haematology. 2005;74:136-143.
13. National Institute for Health and Care Excellence. Myeloma: diagnosis and management NICE guideline [NG35]. Available at: https://www.nice.org.uk/guidance/ng35 Last updated: 25 October 2018.

This assessment is based on data submitted by the applicant company up to and including 16 October 2020.

**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.