Healthcare Improvement Scotland | SMC Advice on new medicines

SMC2447

daratumumab 1,800mg solution for injection (Darzalex®)

Janssen-Cilag Ltd

08 July 2022

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

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

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

Indication under review: In combination with cyclophosphamide, bortezomib and dexamethasone for the treatment of adult patients with newly diagnosed systemic light chain (AL) amyloidosis.

In a phase III study in patients with newly diagnosed AL amyloidosis with at least one affected organ, the addition of daratumumab to bortezomib, cyclophosphamide and dexamethasone was associated with a significant improvement in complete haematologic response rate.

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 cyclophosphamide, bortezomib and dexamethasone for the treatment of adult patients with newly diagnosed systemic light chain (AL) amyloidosis.[1]

Dosing Information

The recommended dose is 1,800mg of daratumumab solution for subcutaneous injection administered over approximately 3 to 5 minutes. The dosing schedule is detailed in Table 1.

Table 1: Dosing schedule of daratumumab in combination with bortezomib, cyclophosphamide and dexamethasone for AL amyloidosis (4-week cycle dosing regimen)[a]

Weeks	Schedule
Weeks 1 to 8	weekly (total of 8 doses)
Weeks 9 to 24[b]	every two weeks (total of 8 doses)
Week 25 onwards until disease progression[c]	every four weeks

[a]In the clinical study, daratumumab was given until disease progression or a maximum of 24 cycles (approximately 2 years) from the first dose of study treatment.
[b] First dose of the every-2-week dosing schedule is given at Week 9
[c] First dose of the every-4-week dosing schedule is given at Week 25

Daratumumab subcutaneous formulation is not intended for intravenous administration and should be given by subcutaneous injection only, using the doses specified. For further information on recommended concomitant medicines, method of administration and management of adverse reactions, please see Summary of Product Characteristics (SPC). Daratumumab should be administered by a healthcare professional, and the first dose should be administered in an environment where resuscitation facilities are available.[1]

Product availability date

21 June 2021

Daratumumab meets SMC orphan criteria.

Summary of evidence on comparative efficacy

Daratumumab is an immunoglobulin G1 kappa human monoclonal antibody. It binds to and inhibits CD38, a protein expressed on clonal plasma cells in AL amyloidosis, which leads to immune mediated tumour cell death.[1]

Evidence for this indication is from ANDROMEDA, a multicentre, randomised, open-label phase III study that recruited adult patients (≥18 years) with a histopathological diagnosis of systemic AL amyloidosis and measurable haematologic disease. Eligible patients had one or more organs impacted by the disease, an Eastern Co-operative Oncology Group (ECOG) performance status of ≤2 and an estimated glomerular filtration rate of ≥20mL/min/1.73 m^2. Patients were excluded if they had received previous treatment for AL amyloidosis or had significant cardiovascular disease

including New York Heart Association (NYHA) classification stage IIIB or IV heart failure. Patients were randomised equally to receive once weekly: subcutaneous bortezomib 1.3mg/m^2; oral or intravenous cyclophosphamide 300mg/m^2 (maximum weekly dose of 500mg); and oral or intravenous dexamethasone 40mg (reduced to 20mg in patients older than 70 years, underweight [BMI <18.5], had hypervolaemia, poorly controlled diabetes mellitus, or a prior intolerance to steroid therapy); for six 28-day cycles, with (n=195) or without (n=193) subcutaneous daratumumab. Daratumumab was administered at a dose of 1,800mg once weekly for cycles 1 and 2, once every 2 weeks for cycles 3 to 6, and then once every 4 weeks from cycle 7 onwards until disease progression, the start of subsequent therapy, or a maximum of 24 cycles from the first dose of study treatment. Randomisation was stratified according to cardiac stage based on the European modification of the Mayo Clinic Cardiac Staging System (I or II or IIIa), availability of transplantation in the local country (countries that do or do not typically offer transplantation for patients with AL amyloidosis) and renal function (creatinine clearance ≥60mL/min or <60mL/min). Any patient that achieved a best response of partial response or had worsening organ function on cycle 4 day 1 was permitted to switch to a second line treatment.[2, 3]

The primary endpoint was a complete haematologic response (CHR) based on independent review committee (IRC) assessment. A CHR was defined as an involved free light chain level less than the upper limit of the normal range with negative serum and urine immunofixation. 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. Secondary outcomes were tested in the following order: major organ deterioration progression-free survival (MOD-PFS) (a composite outcome defined as time from randomisation to any of the following events, whichever came first: clinical manifestation of cardiac or renal failure, haematologic progressive disease [IRC assessed] or death) then overall survival. As very few MOD-PFS and overall survival events were expected at the time of the primary analysis (conducted after at least 180 patients have been treated for at least 6 cycles), formal testing of these outcomes was conducted at the primary analysis with further analysis planned after approximately 200 MOD-PFS events. Efficacy analyses were performed in the intention to treat population, which included all patients who underwent randomisation.[2, 3]

At the primary analysis (data cut-off: 14 February 2020), after a median follow-up of 11.4 months the addition of daratumumab to bortezomib, cyclophosphamide and dexamethasone (DBCd) resulted in a statistically significant improvement in CHR rate. Results from a subsequent November 2020 data cut-off (described as a 12 month landmark analysis by the company but was not pre-specified) with 20.3 months follow-up were supportive of the primary analysis. At the primary analysis there was no significant difference between groups for MOD-PFS (results were not available for the November 2020 data cut-off). Both MOD-PFS and overall survival data are immature. Results for the primary and hierarchically tested secondary outcomes are presented in Table 1.[2, 3]

Table 1: Primary and selected secondary outcomes from the ANDROMEDA study in the ITT population.[2, 3]

	Daratumumab + BCd (N=195)	BCd (N=193)	Daratumumab + BCd (N=195)	BCd (N=193)
Data cut-off date	14 February 2020		13 November 2020	
Median follow-up	11.4 months		20.3 months	
Primary outcome: complete haematologic response assessed by IRC				
CHR rate % (n)	53% (104)	18% (35)	59% (115)	19% (37)
Odds ratio (95% CI)	5.13 (3.22 to 8.16) p<0.001		5.90 (3.72 to 9.37)	
VGPR	25%	31%	20%	31%
Partial response	13%	28%	13%	26%
No response	4.1%	20%	4.1%	20%
CHR rate at 6 months	50%	14%	50%	14%
Secondary outcome: MOD-PFS[A] assessed by IRC				
MOD-PFS events (n)	34	53	-	
Median MOD-PFS	NR	NR		
HR (95% CI)	0.58 (0.36 to 0.93), p=0.02			
Secondary outcome: overall survival				
Deaths	27	29	-	
Median overall survival	NR	NR		
HR (95% CI)	0.90 (0.53 to 1.53)			
KM estimated survival at 18 months	86%	77%		

BCd=bortezomib, cyclophosphamide and dexamethasone, CHR=complete haematologic response, CI=confidence interval, ITT=intention to treat, HR=hazard ratio, KM=Kaplan-Meier, MOD-PFS=major organ deterioration progression-free survival, NR=not reached, VGPR=very good partial response. [A]Analysed with the use of an inverse-probability-of-censoring weighting method to adjust estimates of the treatment in the presence of subsequent non-cross resistant anti-plasma cell therapy.

Pre-specified subgroup analyses were generally consistent with the primary analysis for the primary outcome including subgroups based on stratification factors.[2]

Health Related Quality of Life (HRQoL) was assessed using the Short Form 36 Health Survey Questionnaire (SF-36) Version 2, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Version 3.0 (EORTC QLQ-C30) and EuroQol-5 Dimensions-5 Level (EQ-5D-5L) questionnaire. No statistically significant difference was observed between DBCd and BCd for change from baseline or median time to improvement or worsening.[2, 3]

As overall survival data from the ANDROMEDA study were immature, the submitting company used data from the EMN23 study to inform long-term survival in the economic model. EMN23 is an ongoing, retrospective, observational, multicentre study that recruited adult patients with systemic AL amyloidosis who started first-line treatment between 2004 and 2018. The study enrolled 3,064 European patients (including 38% from the UK) who initiated first-line treatment

between 2011 and 2018. The majority were male (59%), median age was 66 years, the most commonly involved organs were the heart (70%) and kidneys (66%), and 17%, 35%, 28%, and 16% of patients had Mayo cardiac stage I, II, IIIa, and IIIb disease, respectively. The most common first line treatments were bortezomib (75%) and chemotherapy based regimens (9%). Autologous stem cell transplant (ASCT) was used in 10% of patients <65 years and in 2% >65 years with earlier cardiac stage disease. Second line treatment was received by 984 patients, approximately half (48%) of first-line bortezomib-based therapy patients received immunomodulatory-based therapy at second line, 12% received chemotherapy, 12% ASCT, and 14% were re-treated with bortezomib-based therapy. Median overall survival was 67 months, 31 months, and 4 months for patients of stages II, IIIa, and IIIb, and not reached for stage I patients.[4]

Summary of evidence on comparative safety

The regulator concluded that no new safety findings, adverse drug reactions or major concerns were identified for subcutaneous daratumumab in combination with BCd and the safety profile was as observed when used in the indication for multiple myeloma.[2]

In the ANDROMEDA study at data cut-off 14 February 2020, the median duration of treatment was 9.6 months in the DBCd group and 5.3 months in the BCd group; the treatment duration was expected to be longer with DBCd as daratumumab monotherapy continued after the initial 6 treatment cycles. Any treatment-emergent adverse event (AE) was reported by 98% (189/193) of patients in the DBCd group and 98% (185/188) in the BCd group and these were considered treatment-related in 90% for both groups. In the DBCd and BCd groups respectively, patients reporting a grade 3 or higher AE were 62% versus 61%, patients with a reported serious AE were 43% versus 36% and patients discontinuing therapy due to an AE was 4.1% versus 4.3%. The most frequently reported treatment-emergent AEs of any grade with an incidence >25% in the DBCd group versus the BCd group were: diarrhoea (36% versus 30%), peripheral oedema (36% in both groups), constipation (34% versus 29%), peripheral sensory neuropathy (31% versus 20%), fatigue (27% versus 28%), nausea (27% versus 28%) and upper respiratory tract infection (26% versus 11%).[2, 3]

Daratumumab can cause serious infusion-related reactions (IRR), including anaphylactic reactions. In the ANDROMEDA study the incidence, severity and onset of IRRs was consistent with those previously reported for subcutaneous daratumumab. The SPC notes that all patients should be monitored and counselled regarding IRRs especially during the first and second injection. Treatment-emergent cardiac disorders were more common in the daratumumab group (33% versus 22%), however, the incidence of these events at grade 3 and 4 was similar in both treatment groups (11% versus 9.6%) and most serious cardiac treatment-emergent AEs occurred in patients with baseline cardiac involvement. Data suggest that most of the cardiac-related deaths are attributable to underlying AL amyloidosis-related cardiomyopathy. A prospective study of daratumumab-based therapy in patients with newly diagnosed AL amyloidosis will be conducted in the post marketing setting in order to further characterise cardiac adverse events.[1, 2, 5]

Summary of clinical effectiveness issues

Systemic AL amyloidosis is a rare malignant disease characterised by the abnormal growth of clonal plasma cells in the bone marrow which secrete light chain proteins that misfold into insoluble amyloid fibrils. The amyloid deposits can accumulate in vital organs, for example the heart and kidneys and can cause significant life-threatening morbidities such as congestive heart failure and renal failure which can lead to death. Prognosis depends on early diagnosis, treatment and extent of organ involvement. Symptomatic multiple myeloma is simultaneously diagnosed in approximately 10% of patients with AL amyloidosis. The aim of treatment is to achieve a rapid, deep and durable haematological response. The depth of response is associated with organ improvement and better survival outcomes. There is no treatment licensed for AL amyloidosis and therapy is based on regimens used for multiple myeloma; choice is based on patient characteristics such as age, comorbidities, organ involvement and preferences. In Scotland, treatment is guided by the National Amyloidosis Centre (NAC) and combination chemotherapy is recommended for most patients. The NAC and British Society for Haematology recommend off-label treatment with cyclophosphamide in combination with bortezomib and dexamethasone as a first line regimen for newly diagnosed patients, thalidomide in combination with cyclophosphamide and dexamethasone may also be used. Selected patients may be suitable for high dose melphalan and ASCT however its use is limited by cardiac and renal toxicities and a high mortality rate. In all lines of treatment, clinical trials should be considered.[2, 6, 7] Clinical experts consulted by SMC considered that daratumumab fills an unmet need for the treatment of newly diagnosed patients with AL amyloidosis. Daratumumab meets SMC orphan criteria for this indication.

In the ANDROMEDA study, the addition of daratumumab to bortezomib, cyclophosphamide and dexamethasone was associated with a significant improvement in CHR rate (53% versus 18% at the February 2020 data cut-off) in newly diagnosed AL amyloidosis patients with organ involvement and was considered clinically relevant and meaningful by the regulator. Pre-specified subgroup analyses were consistent with the primary analysis, and results from a subsequent November 2020 data cut were supportive.[2, 3] Overall survival data are immature; final overall survival analyses will be provided to the regulator as a post-authorisation efficacy study although results may be confounded by subsequent treatments (9.8% and 42% of patients received subsequent non-cross resistant therapy in the DBCd and BCd groups respectively).[3]

There were some limitations with the evidence presented. ANDROMEDA had an open-label study design because of differences in administration of study treatments which may have introduced potential bias for subjective efficacy, quality of life and safety outcomes. This risk was minimised for the primary and secondary outcomes which were assessed by a blinded IRC. MOD-PFS is not a standard outcome in AL amyloidosis studies, although it may be clinically informative.[2] The IPCW statistical method (used to adjust estimates of a treatment effect in the presence of subsequent anti-plasma therapy) was regarded as hypothetical by the regulator and the results considered exploratory. Major organ deterioration event-free survival (MOD-EFS) was a supplementary

sensitivity analysis to MOD-PFS and incorporated patient switching to alternative treatment following a suboptimal response or worsening organ function as an event. At the primary analysis, the median time to MOD-EFS was not reached in the DBCd group and was 8.8 months in the BCd group (hazard ratio 0.39 [95% CI: 0.27 to 0.56]).[2, 3]

Patients with NYHA class IIIb and IV heart failure or Mayo Clinic Cardiac Stage IIIb disease were excluded from the ANDROMEDA study and therefore there is limited evidence for the efficacy and safety of DBCd in this patient population.[3] Clinical experts consulted by SMC estimated that patients with NYHA class IIIb and IV heart failure could include approximately 20% of patients with newly diagnosed AL amyloidosis in Scotland, they indicated that although these patients would be considered for treatment with DBCd many would be deemed unsuitable due to fitness. Data from a subgroup of patients from the EMN23 study with Mayo Clinic cardiac stage IIIb disease was used to inform a scenario analysis in the economic assessment.

In the ANDROMEDA study the addition of daratumumab to BCd was compared to BCd alone. This is considered the most relevant comparator as SMC clinical experts indicated that BCd is the most frequently used first line treatment in patients with AL amyloidosis in Scottish clinical practice. In the study, daratumumab was continued until disease progression or up to 24 treatment cycles (approximately 2 years), therefore there is limited evidence beyond this treatment period for patients with AL amyloidosis.

Clinical experts consulted by SMC considered that the addition of daratumumab to BCd is a therapeutic advancement due to the favourable results of the ANDROMEDA study. They indicated that the place in therapy would be in addition to BCd in eligible patients but noted that advice on treatment is guided by the NAC. Clinical experts considered that additional capacity in day units may be required although this would not be significant as the medicine is given via subcutaneous injection and patient numbers are expected to be low.

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:

- Systemic light chain (AL) amyloidosis is a rare complex disease. Patients often present late with significant frailty which can make the condition difficult to treat. There is a high symptom burden and the build-up of amyloid deposits in the body can cause progressive organ dysfunction affecting the kidneys, heart and nerves.

- There is a significant unmet need in this patient population as there are currently no licensed treatments approved for the treatment of AL amyloidosis in Scotland. Standard therapies such as bortezomib, cyclophosphamide and dexamethasone (BCd) are based on

treatment for myeloma and are used off-label. The haematological response rates and depth of response with these treatments are suboptimal.

- The addition of daratumumab to BCd (DBCd) demonstrated a deep and durable haematological response rate, which is expected to reduce the disease and symptom burden. This could have a sustained improvement on quality of life for the patient, reduce the anticipated caring responsibilities for family and carers and decrease the reliance on supportive services to manage the clinical manifestations of organ damage.

- DBCd is generally well tolerated with comparable toxicities to BCd. The introduction of DBCd is expected to have minimal impact on haematology services, as the patient numbers will be low.

- PACE participants considered that DBCd would be used first line in newly diagnosed patients with AL amyloidosis.

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.

Summary of comparative health economic evidence

The submitting company provided a cost-utility analysis assessing daratumumab in combination with BCd for the treatment of adult patients with newly diagnosed systemic AL amyloidosis. A subgroup analysis for patients with cardiac stage IIIb involvement was also provided.
The comparator used in the base case was current practice, defined as treatment with BCd.

A model with a paired decision-tree and Markov model structure was used, whereby within the decision-tree component patients are followed up for a maximum of six cycles (cycle length is 28 days). Following this, they enter the Markov component of the model where their longer-term health states are governed by their haematologic response at the end of the decision tree component. In the base case, the timepoint at which patients were modelled to exit the decision tree and enter into the Markov component of the model was Cycle 6, and this was reduced to Cycle 3 in a scenario analysis.

Within the Markov component of the model, patients achieving CHR or VGPR could remain "on treatment", be "off-treatment/on a fixed treatment dose", be on "second line treatment" or in "organ failure". Patients whose haematologic response was partial response or no response (PR/NR) at the decision tree exit timepoint moved directly to second line treatment in the model. The MOD-PFS data from ANDROMEDA were used to inform transitions to the deteriorating states (second line treatment and organ failure). Overall survival data were taken from the EMN23 study,

a retrospective observational study of adult patients with systemic AL amyloidosis[4], as overall survival data from the ANDROMEDA study were immature. The Weibull distribution was used in the base case to extrapolate data for all three response categories but this was tested in scenario analysis upon request.

Observed deaths in the ANDROMEDA study informed the data for deaths in the decision-tree part of the model only. Notably, even for the EMN23 study median overall survival for stage I patients has not been reached. The time horizon of the model was 35 years. This was reduced to 15 and 25 years in requested scenario analysis.

Utility data for the model came predominantly from EQ-5D-5L data collected in the ANDROMEDA study cross walked to the EQ-5D-3L using the method by van Hout et al (2012). Mean utility values were given for each of the response categories. Progression to the second-line treatment and end-stage organ failure health states used utility decrements applied for each cycle spent in those states. Utility values were tested in scenario analysis based on estimates provided by a panel of clinicians. Upon request, the submitting company also provided results for scenarios using health state utilities data previously used in health technology assessments for a similar condition; first line treatment of multiple myeloma patients (the HOVON-24 study).[8]

Costs included first-line medicine acquisition costs, administration costs, and co-medications, the cost of subsequent therapies, treatment of first-line adverse events, disease monitoring costs, health state-specific healthcare resource use costs, end-stage organ failure management costs, and end of life costs. Daratumumab can be provided for up to 24 months, which is longer than the maximum possible duration of BCd treatment (six months). Mean treatment durations from the ANDROMEDA study were used in the base case, but maximum treatment durations were used in scenario analysis. For disease monitoring and healthcare resource use the economic analysis used results from a modified Delphi panel of seven UK-based experts.[9] Subsequent therapies were informed by the ALchemy trial; this was due to no information being available from either the ANDROMEDA or EMN23 studies.

A Patient Access Scheme (PAS) was proposed by the submitting company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHSScotland. Under the PAS, a simple discount was offered on the list price of daratumumab.

The main economic results are shown in Table 6 below. A subgroup analysis for patients with cardiac stage IIIb involvement was undertaken by the submitting company, informed by EMN23 as stage IIIb patients were excluded from the key ANDROMEDA trial.

Table 6: Scenario analyses (with PAS) results

Scenario	Description	ICER vs BCd £/QALY
Base case	Main analysis	29,991
Subgroup	Subgroup analysis for cardiac Stage IIIb cohort	37,986
1.	Use of next best fitting extrapolations as per AIC and BIC statistics (CR: log-normal; VGPR: log-logistic; and PR/NR: generalised gamma)	27,574
2.	Maximum possible treatment duration assumed for patients in the DBCd and BCd arms (24 and 6 cycles respectively)	35,529
3.	Three-month exit from decision tree	36,670
4.	Exclusion of third-line therapies	32,669
5.	HSUV as per clinician estimations at the UK advisory board	24,053

Abbreviations: BCd: bortezomib, cyclophosphamide and dexamethasone; DBCd: daratumumab, bortezomib, cyclophosphamide and dexamethasone; ICER: incremental cost-effectiveness ratio; CHR: complete haematologic response; NR: no response; OS: overall survival; PR: partial response; VGPR: very good partial response; AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion; HSUV: health state utility values.

The main limitations of the economic case were as follows:

- Stratifying patients by haematologic response following the decision tree component of the model makes it harder to compare the model data with the available comparative ANDROMEDA study data directly comparing DBCd and BCd. This issue is confounded by the immaturity of the overall survival data (and median MOD-PFS also not being reached). Notably, at the end of the decision-tree part of the model (at six cycles in the base case reduced to three in scenario analysis), observed deaths did not favour the DBCd arm, but it was at this time point that overall survival data from the observational EMN23 study were used to estimate the overall survival gain based on haematologic response, and so considerable uncertainty exists regarding the longer-term survival benefit associated with daratumumab.
- A subgroup analysis has been provided for stage IIIb patients who were excluded from the key clinical study (ANDROMEDA) meaning there is even greater uncertainty regarding the assumptions underpinning this analysis. An unpowered analysis of the ANDROMEDA study suggested that daratumumab may be a useful treatment for people with higher baseline cardiac staging (up to stage IIIa patients who met the ANDROMEDA study inclusion criteria). Data for the stage IIIb subgroup analysis were informed by the EMN23 study, as for the extrapolated overall survival in the base case Markov component of 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 and the output from the PACE process, the Committee accepted daratumumab for use in NHSScotland.

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

Additional information: guidelines and protocols

The NAC provide advice for newly diagnosed patients with AL amyloidosis in Scotland. The NAC website[6] provides the following guidance for the treatment of AL amyloidosis:

Chemotherapy for AL amyloidosis can be broadly divided up as follows:

- Intermediate dose combination chemotherapy is recommended as first-line treatment for most patients. This involves several drugs given together over 1 to 4 days, usually for up to 6 courses, 3 to 4 weeks apart. Commonly used drug combinations include the 'CVD' (cyclophosphamide, velcade (bortezomib) and dexamethasone) protocol and the 'CTD' (cyclophosphamide, thalidomide and dexamethasone) protocol. Other protocols include 'MD' (melphalan [either orally or intravenously] and dexamethasone, 'VD' (velcade and dexamethasone) and 'VMP' (velcade, melphalan and prednisolone). Other drugs that are sometimes recommended include lenalidomide, pomalidomide and carfilzomib.

- Low dose: Low dose tablet chemotherapy is recommended for fewer than 10% of the patients. This is usually melphalan with prednisolone (steroids). This is normally taken for 5 to 7 days each month, in cycles that are repeated every 4 to 6 weeks. This type of chemotherapy may need to be continued for up to 18 months.

- High dose: About one fifth of newly diagnosed patients with AL amyloidosis may be suitable for consideration of high dose intravenous chemotherapy as first-line treatment. It may also be suitable for some patients with relapsed or refractory disease. This is usually a high dose of intravenous melphalan, requiring 'stem cell rescue' - a single treatment lasting about one month. This might be the only treatment required, but it can, if necessary, be augmented by additional intravenous or low dose chemotherapy. This procedure is commonly referred to as autografting or autologous stem cell transplantation; the stem cells are collected from the patient prior to the high dose chemotherapy, and returned to the patient after chemotherapy in order to form a new bone marrow.

The British Society for Haematology published guidelines on the management of AL amyloidosis in 2014.[7] These guidelines include the following recommendations for the treatment of newly diagnosed AL amyloidosis:

- Where possible patients should be treated in the context of clinical trials and treatment must be undertaken in selected centres experienced in treating such patients.
- Treatment is based on anti-myeloma therapy but there is no standard of care with key considerations being given to frailty in older adults, comorbidities, the extent of organ involvement and patient preferences.
- The treatment goal of first-line therapy is to achieve a very good partial response or better if possible.

- First-line treatment is recommended with combination chemotherapy regimens using dexamethasone. Proteasome inhibitor-based regimens are the preferred choice due to better response rates and outcomes in phase II studies. A bortezomib-alkylator-steroid combination is preferred where a rapid response is required i.e. where there is cardiac involvement, renal impairment, severe hypoalbuminaemia or fluid retention.
- Further recommendations include thalidomide in combination with cyclophosphamide and dexamethasone.
- There is currently no standard treatment at relapse, however, lenalidomide at reduced dose and pomalidomide can be considered.

Additional information: comparators

Bortezomib in combination with cyclophosphamide and dexamethasone (off-label).

Additional information: list price of medicine under review

Medicine	Dose Regimen	Cost per 28 day cycle (£)
Daratumumab, bortezomib, cyclophosphamide and dexamethasone	Daratumumab: 1,800mg subcutaneously weekly for cycles 1 and 2, every 2 weeks for cycles 3 to 6 and every 4 weeks for cycle 7 onwards. Bortezomib: 1.3mg/m^2 subcutaneously once weekly for 6 cycles. Cyclophosphamide: 300mg/m^2 (maximum 500mg weekly) orally once weekly for 6 cycles. Dexamethasone: 40mg orally once weekly once weekly for 6 cycles.	Cycle 1 and 2 19,325 Cycles 3 to 6 10,685 Cycle 7 onwards 4,320

Costs from BNF online on 1st April 2022. Costs calculated using the full cost of vials assuming wastage. Costs calculated for BSA 1.8m^2. Costs do not take patient access schemes into consideration.

Additional information: budget impact

The submitting company estimated there would be 38 patients eligible for treatment with daratumumab in each year.

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 or PAS associated with medicines used in a combination regimen.

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

References

1. Janssen-Cilag Ltd. Daratumumab solution for injection (Darzalex®) Summary of product characteristics. Electronic Medicines Compendium https://www.medicines.org.uk/emc/product/11488/smpc Last updated: 09 March 2022.
2. European Medicines Agency (EMA). European Public Assessment Report. Daratumumab (Darzalex®). 20/05/2021, EMEA H-C-004077-II-0043. www.ema.europa.eu.
3. Kastritis E, Palladini G, Minnema MC, Wechalekar AD, Jaccard A, Lee HC*, et al.* Daratumumab-based treatment for immunoglobulin light-chain amyloidosis. New England Journal of Medicine. 2021;385(1):46-58.
4. G P, Schönland S, Merlini G, Milani P, Jaccard A, Bridoux F*, et al.*, editors. Real-world Data on Patient Characteristics and Treatment Patterns for 3000 Patients with Systemic AL Amyloidosis in Europe between 2011 and 2018: A Retrospective Study by the European Myeloma Network. European Hematology Association. June 9-17. 2021.
5. U.S. National Library of Medicine. ClinicalTrials.gov A Study of Daratumumab-Based Therapies in Participants With Amyloid Light Chain (AL) Amyloidosis (NCT05250973). Last updated 22 April 2022. Available at: https://clinicaltrials.gov/ct2/show/NCT05250973
6. National Amyloidosis Centre. Amyloidosis Overview. Available at: https://www.ucl.ac.uk/amyloidosis/national-amyloidosis-centre/amyloidosis-overview#AL%20amyloidosis
7. Wechalekar AD, Gillmore JD, Bird J, Cavenagh J, Hawkins S, Kazmi M*, et al.* Guidelines on the management of AL amyloidosis. Br J Haematol. 2015;168(2):186-206. Epub 2014/10/11.
8. van Agthoven M, Segeren CM, Buijt I, Uyl-de Groot CA, van der Holt B, Lokhorst HM, Sonneveld P. 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 May;40(8):1159-69. .
9. Janssen. [Data on File]. HCRU in AL Amyloidosis UK Delphi Panel Report. 2021.

This assessment is based on data submitted by the applicant company up to and including 16 May 2022.

**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.