NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Appraisal consultation document

Daratumumab in combination for treating newly diagnosed systemic amyloid light-chain amyloidosis

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using daratumumab in combination in the NHS in England. The appraisal committee has considered the evidence submitted by the company and the views of non-company consultees and commentators, clinical experts and patient experts.

This document has been prepared for consultation with the consultees. It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from the consultees and commentators for this appraisal and the public. This document should be read along with the evidence (see the committee papers).

The appraisal committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Issue date: January 2022

Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.

After consultation:

- The appraisal committee will meet again to consider the evidence, this appraisal consultation document and comments from the consultees.
- At that meeting, the committee will also consider comments made by people who are not consultees.
- After considering these comments, the committee will prepare the final appraisal document.
- Subject to any appeal by consultees, the final appraisal document may be used as the basis for NICE's guidance on using daratumumab in combination in the NHS in England.

For further details, see NICE's guide to the processes of technology appraisal.

The key dates for this appraisal are:

Closing date for comments: 7th February 2022

Second appraisal committee meeting: 17th March 2022

Details of membership of the appraisal committee are given in section 5.

1 Recommendations

1.1 Daratumumab plus bortezomib, cyclophosphamide and dexamethasone is not recommended, within its marketing authorisation, for treating newly diagnosed systemic amyloid light-chain (AL) amyloidosis in adults.

1.2 This recommendation is not intended to affect treatment with daratumumab plus bortezomib, cyclophosphamide and dexamethasone that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop.

Why the committee made these recommendations

Systemic AL amyloidosis is currently treated with medicines that are licensed for multiple myeloma. These include bortezomib plus cyclophosphamide and dexamethasone. Daratumumab plus bortezomib, cyclophosphamide and dexamethasone (daratumumab in combination) is the first treatment licensed for AL amyloidosis. If the disease responds to daratumumab in combination after 6 cycles, daratumumab alone is offered.

Clinical evidence suggests that daratumumab in combination increases the time until systemic AL amyloidosis gets worse compared with bortezomib plus cyclophosphamide and dexamethasone. However, the treatment has not been shown to increase how long people live.

All the cost-effectiveness estimates for daratumumab are in a range higher than what NICE considers an effective use of NHS resources. Therefore, daratumumab in combination is not recommended.

2 Information about daratumumab

Marketing authorisation indication

2.1 Daratumumab (Darzalex, Janssen-Cilag) is 'indicated in combination with bortezomib, cyclophosphamide and dexamethasone for the treatment of adults with newly diagnosed systemic light chain (AL) amyloidosis'.

Dosage in the marketing authorisation

2.2 The dosage schedule is available in the summary of product characteristics.

Price

2.3 The list price of daratumumab is £4,320 for a 1,800 mg per 15 ml vial (excluding VAT; BNF online accessed December 2021). Costs may vary in different settings because of negotiated procurement discounts. The company has a commercial arrangement. This makes daratumumab available to the NHS with a discount, and it would have also applied to this indication if the technology had been recommended. The size of the discount is commercial in confidence. It is the company's responsibility to let relevant NHS organisations know details of the discount.

3 Committee discussion

The appraisal committee considered evidence submitted by Janssen-Cilag, a review of this submission by the evidence review group (ERG), and responses from stakeholders. See the committee papers for full details of the evidence.

Experience of people with the condition

Systemic amyloid light-chain (AL) amyloidosis is incurable, and its mental and physical effects can be overwhelming

3.1 Amyloidosis occurs when amyloid, an abnormal protein, builds up in the organs affecting normal function. Systemic AL amyloidosis is the most severe form of amyloidosis and is incurable. The clinical experts explained

that it is a heterogenous condition that affects several organs, commonly the heart and kidneys, as well as nerves, among other complications. Some people may also have multiple myeloma. They explained that people with AL amyloidosis have care in the NHS in multidisciplinary clinics, and may have input from haematology, nephrology and cardiology specialities. The most severe forms of systemic AL amyloidosis present with heart failure and renal failure. If the condition is advanced causing heart failure (cardiac stage 3b disease), the median survival is about 4.5 months. The patient experts highlighted feelings of hopelessness at diagnosis. They explained that people with systemic AL amyloidosis well enough to have treatment have hope of improvement. But the treatment could cause adverse effects that may affect quality of life, for example, autologous stem cell transplant. They stated that they would like treatment options that are easy to have, with tolerable adverse effects, and which everyone has access to regardless of how severe their condition is. The committee concluded that systemic AL amyloidosis is a serious, incurable condition, and that people with the condition would welcome new treatment options.

Clinical management

There is an unmet need for licensed treatments for systemic AL amyloidosis

3.2 The clinical experts explained that there are currently no licensed treatment options for systemic AL amyloidosis in the NHS. They and the Cancer Drugs Fund lead explained that clinicians instead offer treatments for multiple myeloma and that the treatment pathways are similar. For newly diagnosed AL amyloidosis, first-line treatment is usually bortezomib plus cyclophosphamide and dexamethasone (from now, bortezomib in combination). If bortezomib is contraindicated or not tolerated, for example, because of neuropathy, lenalidomide plus dexamethasone or melphalan plus dexamethasone may be offered. For people with relapsed

or refractory systemic AL amyloidosis, various options are available. These include:

- second-line options such as:
  - lenalidomide plus dexamethasone
  - melphalan plus dexamethasone
  - carfilzomib plus dexamethasone
  - bortezomib plus dexamethasone with or without cyclophosphamide
  - an autologous stem cell transplant
- third-line options such as:
  - lenalidomide plus dexamethasone
  - panobinostat plus bortezomib and dexamethasone
  - pomalidomide plus dexamethasone.

The committee agreed that, for people newly diagnosed with systemic AL amyloidosis, standard care in the NHS is bortezomib in combination. It concluded that this was the relevant comparator for this appraisal. It further concluded that there is an unmet need for effective treatment for systemic AL amyloidosis.

Positioning of daratumumab in the treatment pathway

The licence for daratumumab includes combination treatment followed by daratumumab alone

3.3 The marketing authorisation for daratumumab in combination includes adults with newly diagnosed systemic AL amyloidosis. Daratumumab is first used with bortezomib (limited to 6 cycles), cyclophosphamide (limited to 6 cycles) and dexamethasone. Thereafter, but before disease progression, daratumumab can be offered as monotherapy for a maximum of 18 cycles, so 24 cycles in total. The Cancer Drugs Fund lead highlighted that treatments used in multiple myeloma commonly have induction and maintenance phases, as does daratumumab in the key trial for AL amyloidosis (see section 3.5). They suggested that the NHS could

follow a similar approach. The clinical experts explained that some people, particularly those at low risk for disease progression and depending on haematological response (see section 3.9), would not need to continue onto maintenance daratumumab alone.

Daratumumab in combination is a first-line treatment for newly diagnosed systemic AL amyloidosis

3.4 The company has positioned daratumumab in combination followed by daratumumab alone as first-line treatment for people with newly diagnosed systemic AL amyloidosis irrespective of disease severity. The company excluded people with more severe AL amyloidosis from its trial, citing ethical reasons and issues with recruitment (see section 3.5). The committee considered whether people with severe AL amyloidosis should also be excluded from any NICE recommendation on daratumumab in combination. Both the patient and clinical experts supported including people with heart failure (cardiac stage 3b disease) and people who need renal replacement therapy (stage 5 chronic kidney disease). The patient experts explained that people with heart failure and renal failure would find it difficult to accept being excluded from a licensed treatment available on the NHS for systemic AL amyloidosis, especially because the condition is progressive and incurable. The clinical experts acknowledged that people with end-stage cardiac and renal disease may need lower dosages of bortezomib, but would otherwise benefit from the treatment. They highlighted that although cardiovascular toxicity from daratumumab is minimal, it is only licensed for use with bortezomib, which has more cardiovascular adverse effects. The committee agreed with the company's positioning of daratumumab as a first-line option for newly diagnosed systemic AL amyloidosis, regardless of severity. The committee concluded that it would consider daratumumab in combination within its full licensed indication. It also concluded that the most relevant comparator is bortezomib in combination.

Clinical evidence

The ongoing ANDROMEDA trial is generalisable to NHS practice

3.5 ANDROMEDA is an ongoing, phase 3, multinational, multicentre, open-label, parallel group, randomised controlled trial comparing daratumumab in combination followed by daratumumab alone with bortezomib in combination. The primary end point was haematological response (see section 3.6). People in either trial arm can switch to another treatment after 3 cycles if their organ function worsens or their condition shows a suboptimal response (that is, a partial or no response and worsening organ function). There are 388 adults enrolled in the trial. They all have newly diagnosed systemic AL amyloidosis involving at least 1 organ, with measurable haematological disease, and with an Eastern Cooperative Oncology Group Performance Status score of 0, 1 or 2. The trial has excluded people who are severely ill, for example, with cardiac stage 3b disease. The company explained that it excluded people with cardiac stage 3b disease because these people cannot take the standard dose regimen for bortezomib and excluded people on dialysis in agreement with regulators. The committee was aware of its remit to look at technologies across their marketing authorisations. The clinical experts considered that the baseline characteristics of the people in ANDROMEDA, other than having excluded people with severe complications, reflect people in the NHS who are likely to have daratumumab in combination. They noted a longer delay in time to diagnosis at baseline in people randomised to daratumumab in combination compared with those randomised to standard care. They explained that this suggests that people randomised to daratumumab in combination might have more organ damage and worse prognosis. The committee considered that if this were true, and if people with more severe complications respond less well to treatment, then this would bias the results in favour of standard care. The committee concluded that

ANDROMEDA had excluded people with severe complications, but that the population is likely to be broadly generalisable to the NHS.

ANDROMEDA's primary end point of haematological response is a surrogate end point for overall survival and is usually assessed at 3 months

3.6 The primary end point of ANDROMEDA is overall complete haematological response. This is defined as a negative serum and urine immunofixation and normalised free light-chain (FLC) levels and ratios. If the level of involved FLC is lower than the upper limit of normal, uninvolved FLC needs to be normalised. The committee was aware that, if not complete, haematological response is categorised as 'very good partial response', 'partial response', or 'no response'. The clinical experts agreed that the criteria for response are in line with those used in NHS clinical practice. They explained that an early and very good haematological response is important, particularly for severe AL amyloidosis. They also noted that the category of response is associated with risk of progression and overall survival. They explained that factors which increase or decrease the probability of haematological response (apart from treatment itself) are cardiac involvement, renal disease and autonomic function. The clinical experts highlighted that guidance from the National Amyloidosis Centre recommends assessing people for a haematological response at 3 months and guides NHS practice. But, in practice, assessment can happen from monthly to 6 monthly. They explained that assessment at 3 months allows clinicians to offer people other therapies if the current treatment is not effective. The committee was aware that the company used haematological response categorised as 'complete', 'very good partial', 'partial and no' response as a surrogate end point for overall survival in its model of cost effectiveness and discussed whether this was appropriate (see section 3.9). It concluded that haematological response measured at either 3 or 6 months reflected a clinically important outcome.

Daratumumab in combination improves haematological response, but the effect on overall survival is uncertain

3.7 The company submitted analyses from a planned interim analysis with a median follow up of 11.4 months, and an unplanned 12-month 'landmark analysis' with a median follow up of 20.3 months. The committee noted that more people randomised to daratumumab in combination had an overall complete haematological response compared with people on standard care (53% in the daratumumab arm compared with 18% in the standard care arm in the prespecified interim analysis, and 59% and 19% respectively in the unplanned 12-month landmark analysis). The committee noted that ANDROMEDA is an ongoing trial and that the data on overall survival presented by the company, a secondary outcome in the trial, is immature. Fewer than 20% of people have died in both arms. Among other secondary endpoints, people randomised to daratumumab in combination had longer times to major organ deterioration progression-free survival (MOD-PFS) compared with standard care (results are academic in confidence so cannot be presented here). The clinical experts noted that delaying or preventing major organ deterioration are important outcomes, as are keeping people out of hospital or going on to dialysis. The committee concluded that daratumumab in combination is an effective treatment for improving haematological response and reducing major organ deterioration in people with newly diagnosed systemic AL amyloidosis. However, it concluded that whether it improves overall survival has not been shown.

Daratumumab has tolerable adverse effects

3.8 The patient and clinical experts explained that they value having treatments with tolerable adverse effects. The committee noted from the interim analysis from ANDROMEDA that adverse events happened in the same frequency in both treatment arms. It was aware that the trial excluded people with advanced cardiac and renal disease who are more likely to experience treatment-related adverse events. It was also aware

that the company used grade 3 or 4 treatment-emergent adverse events reported by at least 5% of the people in its economic model (see section 3.9). The committee discussed whether it would be appropriate to include adverse events that occurred less frequently. The Cancer Drugs Fund lead explained that it is common practice to include these adverse events in economic models for cancer drugs. The committee concluded that adverse events associated with adding daratumumab to standard care were tolerable. It also concluded that the company's approach of including adverse events in its economic model was acceptable.

Economic model

The company used a decision tree and Markov model to extrapolate overall survival based on haematological response

3.9 In its submission, the company made the case that daratumumab in combination compared with standard care prolongs life and improves health-related quality of life. Neither of these results have been shown in ANDROMEDA's interim analyses. The company developed a model to show that people who have better haematological responses live longer than those who have poorer responses. They are also less likely to develop end-organ complications, which are associated with a poorer quality of life. The company used a hybrid cohort model that included a decision-tree treatment component. After this, people were put into 1 of 3 response categories: 'complete response'; 'very good partial response'; or combined 'partial or no response'. The decision tree was followed by a Markov component with 5 health states:

- remaining on first-line treatment
- off first-line treatment (if previously on standard care, bortezomib in combination) or on fixed daratumumab alone treatment (if previously on daratumumab in combination)
- second-line treatment
- end-stage organ failure

- death.

People in the combined category of partial or no response, and those who progressed, moved to second-line treatment. People on standard care were on first-line treatment for a maximum of 6 cycles (see section 5.1 of the summary of product characteristics). Each cycle lasted 28 days. People on daratumumab in combination who had at least a partial response and stable or improved major organ failure after 6 cycles continued to have maintenance daratumumab monotherapy until their condition progressed, until they started a subsequent treatment or until a maximum of 24 cycles from the first dose. The clinical experts explained that, in practice, people whose condition partially responds to treatment would have different management than those whose condition had not responded at all. The committee concluded that the partial and no response groups should be separate in the model to reflect clinical practice.

Observational studies of standard care

ALchemy is more representative of UK clinical practice than EMN23

3.10 The company positioned daratumumab in combination for the full licensed population, although ANDROMEDA excluded people with cardiac stage 3b disease and renal failure. To model the full licensed population, the ERG used data collected between 2010 and 2019 from a prospective observational UK-based study, ALchemy. This study included 1,194 people treated first-line with bortezomib-based regimens. The ERG used the ALchemy study for 2 main purposes: to characterise people in the NHS likely to be offered daratumumab in combination, and to model the survival of people by haematological response. The company agreed with using observational data, but preferred to use a different source, the post-2010 data from a European-based retrospective observational study, EMN23. This study included 1,156 people based in the UK, about 40% of the overall study population. The ERG considered that EMN23 was less

generalisable to NHS practice than ALchemy. This was because approximately 25% of people in EMN23 did not have first-line bortezomib-based regimens, and because some European countries define haematological response differently. In addition, the ERG highlighted that it was unable to fully critique the ENM23 study because of the limited data submitted by the company, and because the only published data are abstracts or posters. The company explained that ANDROMEDA and EMN23 used the same criteria to define haematological response. The committee noted the overlap with people based in the UK in ALchemy and EMN23. The clinical experts agreed with the ERG that ALchemy better reflects NHS practice. The committee considered the size and composition of the cohorts and concluded that ALchemy was the best source of data to reflect NHS clinical practice.

Population modelling and assessing haematological response

Data from ALchemy best represents NHS clinical practice, but the choice of when to assess haematological response is uncertain

3.11 In its original base case, the company used data from ANDROMEDA in the decision-tree component of its model to estimate and model the distribution of haematological response among people assessed at 6 months (6 cycles). To model the full licensed population (see section 3.10), the ERG instead used the distribution of haematological response from ALchemy for people having standard care, bortezomib in combination. To derive the distribution for people having daratumumab in combination, the ERG applied a value reflecting the relative effectiveness of daratumumab in combination over standard care from ANDROMEDA. It preferred to use an assessment time point of 3 months (3 cycles) to reflect NHS clinical practice. In response to NICE technical engagement, and before the first committee meeting, the company provided 2 base cases. The first followed the ERG's approach but used post-2010 data from EMN23 (base case a). The second used data from ANDROMEDA (base case b). The committee considered that the preferred choice of when to

assess haematological response, 3 or 6 months, was unclear. While the 6-month time point may represent a better proxy for overall survival, the 3-month time point may better represent NHS clinical practice. For the 6-month time point, the committee was concerned that how the company categorised response in its analysis of ANDROMEDA data was not consistent with that used in ALchemy, and subsequent concerns about the linking of these data to estimate overall survival. In ANDROMEDA, patients could switch treatment after 3 cycles (see section 3.5). In its analysis of ANDROMEDA, the company categorised any patients who switched treatments before 6 months as non-response at the 6-month time point. However, in ALchemy, response status at 6 months was reported irrespective of previous treatment changes – for instance, a person who switched treatments after 3 months and whose condition subsequently responded would be reported as having a response. This suggests that the response categorisation at 6 months in ANDROMEDA does not match the response categorisation from ALchemy. The ERG explained that in ANDROMEDA, no one had switched treatments at 3 months, and in ALchemy, almost no one had switched treatments at 3 months. Therefore, it considered the response categorisation at this 3-month time point should be consistent between the 2 studies. The committee recalled that data from the 3-month assessment time point was more specific and reflects NHS practice. It concluded that this data should have been used in the base case, and that the company should explore using a time point of 6 months ensuring consistency between the response categorisation used in the analysis of ANDROMEDA and ALchemy.

Modelling overall survival

Survival curves extrapolated from ALchemy better predict life expectancy at 15 years but are still highly uncertain

3.12 The committee was aware that ANDROMEDA has not shown a survival benefit for daratumumab in combination compared with standard care

based on interim analyses. But the company made a case for a survival benefit by using haematological response as a surrogate end point for survival. The company did a 'landmark' analysis; the survival curves were based on people reaching the landmark of a specific haematological response at a specified time point (3 or 6 months). These survival curves informed the survival of the patient cohort in the economic model, stratified by haematological response. The committee discussed informative censoring related to people who die before being tested for a haematological response and understood that this was less than 10% of people in ANDROMEDA. It discussed the possibility of confounding, that is, whether people who had a better haematological response had other characteristics beyond haematological response that increased their likelihood of living longer. The committee was not presented with (observational) analyses from ANDROMEDA that identified risk factors for having a haematological response and for living longer for which the model might be adjusted. Apart from treatment itself, the clinical experts identified cardiac and renal disease as risk factors for having a haematological response and for mortality. They explained that the association between cardiac and renal disease to haematological response may partly relate to lower treatment doses to avoid adverse effects. The committee then discussed the potential biases associated with moving to second-line treatments between 3 and 6 months, and the implications to the model of being in a progressed disease state. To model long-term survival for both treatments, the company used haematological response from EMN23 to extrapolate overall survival beyond 6 cycles. The ERG preferred to use data from ALchemy to extrapolate overall survival curves beyond 3 cycles. It highlighted that the 15-year survival predicted by ALchemy more closely matched the predictions of the ERG clinical advisers than the predictions from EMN23. The main difference was in predictions for a very good partial response. EMN23 predicted lower survival than ALchemy, while the curves for complete response predicted slightly higher survival using EMN23 than

ALchemy. The ERG stated that it did not have any concerns about the choice of parametric models used to extrapolate, but that the overall survival data from ANDROMEDA are not mature, and the company assumed that overall survival depends only on haematological response. The committee agreed there was high uncertainty in the modelling. It recognised that neither the ERG nor the company directly compared the available data from ANDROMEDA on overall survival with the extrapolated curves from ALchemy and EMN23. The ERG explained that it did not do this because the company had not adjusted ANDROMEDA's overall survival curves for people who had switched treatment after 3 cycles. The committee was aware that the company's statistical analysis plan called for using inverse probability of censoring weighting to adjust for MOD-PFS and overall survival. But the company did not present these results. The committee concluded that, because the company used haematological response as a surrogate for overall survival, the committee would prefer to see analyses that show whether the extrapolations are sensitive to potential confounders of the relationship between haematological response and death. It concluded that it would prefer to see life-expectancy estimates using haematological response from trial data compared with those using haematological response from observational data sets. The committee further concluded that it preferred the survival extrapolations from ALchemy, but considered that they were highly uncertain.

Utility values in the economic model

Some utilities derived from ANDROMEDA EQ-5D-5L data lack face validity and comparison with utilities from ALchemy is preferred

3.13 The company derived utility values using EQ-5D-5L data from ANDROMEDA collected in the first 6 cycles for people on daratumumab in combination or on standard care. The ERG identified that utility values from the group with a very good partial response were lower than utility values from the combined partial and no response group. It suggested the

company should have used SF36v2 data from ALchemy to validate the data from ANDROMEDA. One clinical expert explained that, because of end-stage organ failure, disutility is likely to be higher than the value presented by the company. The Cancer Drugs Fund lead considered the utilities plausible, but unlikely to be maintained throughout second-line treatment and end-stage organ failure. The committee concluded that the company should have used SF36v2 data from ALchemy to validate its utility set derived from ANDROMEDA.

Stopping rule

Daratumumab in combination followed by daratumumab monotherapy will apply for up to 24 cycles only

3.14 In line with ANDROMEDA, the company modelled a maximum duration of up to 24 cycles of daratumumab (6 cycles of daratumumab in combination and 18 cycles of daratumumab monotherapy as maintenance therapy). The summary of product characteristics does not explicitly state a 24-cycle stopping rule but highlights that, 'In the clinical trial, DARZALEX was given until disease progression or a maximum of 24 cycles (approximately2 years) from the first dose of study treatment'. The clinical experts explained that the NHS could implement this stopping rule. This is despite noting that, for people whose condition responds well to treatment and does not progress, clinicians would likely prefer to continue treatment, rather than risk progression. The Cancer Drugs Fund lead explained that should daratumumab in combination receive a positive recommendation, NHS England would commission it in line with its marketing authorisation and modelling, based on the clinical trial, that is, for up to 24 cycles. The committee concluded that it was acceptable to model a maximum of 24 cycles.

Modelling of subsequent treatments

The administration cost of £99 for bortezomib plus daratumumab underestimates the true cost

3.15 Before the first committee meeting, the company increased its value for administration cost for bortezomib plus daratumumab to £99. This was based on specialist nursing costs and is in line with another ongoing NICE technology appraisal on daratumumab in combination for untreated multiple myeloma when stem cell transplant is suitable. The ERG noted this cost is much lower than the codes for Healthcare Resource Group (HRG) to procure bortezomib-based chemotherapy regimens for an average cycle. These costs ranged from £241 to £2,110. The Cancer Drugs Fund lead considered that £99 underestimated the true administration cost and considered that it would likely be £332 (HRG code for SB15Z for delivery of subsequent elements of chemotherapy in the same cycle). The committee was aware that its decision differed from that of the other ongoing appraisal. It concluded that the company's choice of administration costs underestimated the true costs and should instead be £332.

The cost of an autologous stem cell transplant should be included in the model

3.16 In its original base case, the company excluded the cost of an autologous stem cell transplant, despite some people in ANDROMEDA having transplants. The clinical experts explained that some people with systemic AL amyloidosis have autologous stem cell transplants in the NHS. The company provided a scenario using ALchemy data to estimate the distribution of people by second- and third-line therapy who had an autologous stem cell transplant at a unit cost of £15,065. Before the first committee meeting, the company provided a scenario using data from EMN23 reflecting the proportion of people who had an autologous stem cell transplant as a second-line therapy. The company assumed that this

affected only costs; it did not consider in its scenario that an autologous stem cell transplant improves health outcomes. The clinical experts considered that autologous stem cell transplant should have been included in the model. The committee concluded that it was appropriate for the cost of an autologous stem cell transplant to be included in the model.

Estimates on the number of people having second- and third-line treatment from a UK clinical advisory board have face validity

3.17 In its original base case, the company used the views of a UK clinical expert advisory board to model the types of treatment and related distributions of people having these treatments at second- and third-line in the treatment pathway. Before the first committee meeting, the company provided a scenario using distributions from ALchemy. The ERG used data from ALchemy in its base case because it considered it more relevant than the UK clinical expert advisory board data. The clinical experts explained that access to chemotherapy varies across the UK and thought that the estimates from the company's UK advisory board better reflected NHS practice than ALchemy, particularly for second-line treatments. However, they noted that the UK advisory board excluded some third-line treatment options, notably, panobinostat. The Cancer Drugs Fund lead considered that the UK advisory board estimates had better face validity than ALchemy. The committee concluded that the model should include the company's estimates.

End of life criteria

Daratumumab does not meet end of life criteria

3.18 According to NICE, end of life criteria are met if the technology under appraisal is indicated for people:

- with a short life expectancy, normally less than 24 months, and

- there is sufficient evidence to show that the treatment extends life, normally for at least an additional 3 months, compared with current NHS treatment.

  The company considered that daratumumab meets the end of life criteria for the population with cardiac stage 3b disease. However, the ERG and committee noted that the company did not propose that daratumumab in combination be limited exclusively to this population. In addition, the committee did not see evidence that the life expectancy for people who have standard care is less than an average of 24 months. The committee concluded that daratumumab in combination treatment for systemic AL amyloidosis does not meet end of life criteria.

Innovation

Daratumumab in combination is innovative

3.19 The clinical experts considered daratumumab in combination to be a step-change in managing newly diagnosed systemic AL amyloidosis. The committee considered that there may be benefits with daratumumab in combination that were not captured in the modelling, such as benefits for people with concomitant multiple myeloma. The committee concluded that daratumumab in combination is innovative.

The uncertainty means an acceptable incremental cost-effectiveness ratio (ICER) is £20,000 per quality-adjusted years (QALY) gained

3.20 NICE's guide to the methods of technology appraisal notes that above a most plausible ICER of £20,000 per QALY gained, judgements about the acceptability of a technology as an effective use of NHS resources will take into account the degree of certainty around the ICER. This means a committee will be more cautious about recommending a technology if it is less certain about the ICERs presented. The committee noted the high level of uncertainty, specifically:

- The company presented no trial evidence for people with more severe complications (see section 3.5).
- ANDROMEDA is ongoing, and the committee was not presented with final analyses for overall survival. Data for overall survival are immature and at the latest interim data cut, no difference between daratumumab and standard care was seen (see section 3.7).
- Modelling of overall survival used a surrogate end point of haematological response. The company did not address the possibility of confounding. The company extrapolated overall survival by haematological response from 6 months, but NHS practice would assess people at 3 months. The company used observational studies that used standard care regimens (see sections 3.9, 3.10 and 3.12).
- The effects of treatment switching after 3 cycles on the modelling distribution of haematological response were uncertain (see section 3.11).
- Some utility values lack face validity (see section 3.13).
- The base case did not incorporate the stopping rule as from the trial, the marketing authorisation or what would be used in the NHS if commissioned (see section 3.14).
- The company underestimated the administration costs for bortezomib and daratumumab (see section 3.15).

When taking the confidential discounts into account, the committee agreed that the cost-effectiveness estimates ranged from £34,000 to £62,000.

None of the analyses presented include the committee's preferred assumptions

3.21 The committee's preferred assumptions were:

- model partial and no response groups separately (see section 3.9)
- include people with end-stage cardiac and renal disease in the population (see section 3.4)

- use data from ALchemy for the distribution of haematological response for standard care and use relative effectiveness from ANDROMEDA for the daratumumab in combination arm (see section 3.11)
- provide estimates of the association between haematological response and overall survival accounting for potential confounders (see section 3.12)
- assess haematological response at 3 months in the base case but explore a scenario using 6 months, adjusting analyses to ensure consistency in response categorisation between the 2 data sources, ANDROMEDA and ALchemy (see section 3.11)
- use ALchemy to extrapolate overall survival, but explore fit compared with overall survival from ANDROMEDA (see section 3.12)
- use SF36v2 data from ALchemy to validate the company's utility set (see section 3.13)
- apply a stopping rule for daratumumab monotherapy of a maximum of 24 cycles (see section 3.14)
- increase chemotherapy administration costs from £99 to £332 (see section 3.15)
- include autologous stem cell transplant in the model (see section 3.18)
- use estimates from the UK expert advisory board for second- and third-line treatments use (see section 3.17).

The committee considered that none of the analyses presented reflected their preferred assumptions. It concluded that, on balance, when taken together, the changes would likely lead to an increase in the ICER.

Daratumumab in combination cannot be recommended for routine commissioning

3.22 None of the ICERs reflected the committee's preferred assumptions. Also, the company's own base case using the company's price for daratumumab was not within the range considered to be a cost-effective use of NHS resources; the committee's preferred assumptions would

likely increase the ICER. So, daratumumab in combination could not be recommended for routine commissioning for newly diagnosed systemic AL amyloidosis in adults.

Cancer Drugs Fund

Daratumumab in combination is not eligible for the Cancer Drugs Fund because plausible potential for cost effectiveness is not shown

3.23 The committee discussed the arrangements for the Cancer Drugs Fund agreed by NICE and NHS England in 2016, noting NICE's Cancer Drugs Fund methods guide (addendum). It was aware that ANDROMEDA is ongoing, and that the company anticipates that there will be final analyses related to overall survival. However, at the price that the company has chosen to charge the NHS for daratumumab, the committee deemed that treatment was not plausibly cost effective. The committee concluded that daratumumab did not meet the criteria to be considered for inclusion in the Cancer Drugs Fund. However, a period of further data collection may address some of the uncertainties highlighted by the committee.

4 Proposed date for review of guidance

4.1 NICE proposes that the guidance on this technology is considered for review by the guidance executive 3 years after publication of the guidance. NICE welcomes comment on this proposed date. The guidance executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Amanda Adler
Chair, Appraisal Committee
January 2022

5 Appraisal committee members and NICE project team

Appraisal committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee B.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each appraisal committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Sharlene Ting
Technical lead

Carl Prescott
Technical adviser

Shonagh D'Sylva
Project manager

ISBN: [to be added at publication]