

# NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

## Final appraisal document

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

## 1 Recommendations

1.1 Daratumumab plus bortezomib, cyclophosphamide and dexamethasone is recommended as an option for treating newly diagnosed systemic amyloid light-chain (AL) amyloidosis in adults. It is recommended only if:

- daratumumab is stopped after 24 cycles of treatment, or earlier if the condition progresses, and
- the company provides daratumumab according to the commercial arrangement (see [section 2](#)).

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 usually 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 condition responds to daratumumab in combination after 6 cycles, daratumumab alone is offered for up to 18 cycles, for a total of 24 cycles.

Clinical evidence suggests that daratumumab in combination increases the time until systemic AL amyloidosis gets worse compared with bortezomib plus cyclophosphamide and dexamethasone. People whose condition responds to daratumumab in combination may live longer, but this is uncertain.

The cost-effectiveness estimates for daratumumab are within the range NICE considers an acceptable use of NHS resources. So, daratumumab in combination is 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 for daratumumab](#).

### **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 February 2024). The company has a commercial arrangement (commercial access agreement). This makes daratumumab available to the NHS with a discount. 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 AL amyloidosis is rare, incurable and life limiting with a serious effect on physical and mental health**

3.1 Amyloidosis happens when amyloid, an abnormal protein, builds up in the organs affecting normal function. Systemic amyloid light-chain (AL) amyloidosis is the most severe form of amyloidosis. It is rare and 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 need care in the NHS in multidisciplinary clinics, and are primarily treated by haematologists. They may also have input from nephrology and cardiology specialties. 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 treatments such as autologous stem cell transplant could cause adverse effects that may affect quality of life. 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 rare, 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
- fourth-line option such as:
  - pomalidomide plus dexamethasone.

At the third committee meeting, the clinical and patient experts explained that systemic AL amyloidosis is challenging to treat. They explained that rapid and deep haematological response, which often is followed by organ response, greatly improves all aspects of a person's life. 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

### 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 maintenance 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 with low risk of disease progression, would not need to continue onto maintenance daratumumab alone, depending on haematological response (see [section 3.9](#)).

### 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 in combination 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 have the standard dosing regimen for bortezomib and excluded people having 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 used haematological response as a surrogate end point for overall survival and it 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 does not need to be normalised ([Palladini et al. 2021](#)). 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 used in ANDROMEDA 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 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 other treatments 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 evidence on overall survival from ANDROMEDA is immature**

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 have daratumumab in combination had an overall complete haematological response compared with people having 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). For the second committee meeting, the company presented a post hoc analysis from its 18-month landmark data cut (median 25.8 months follow up), which showed a sustained response at 24 months in people with complete haematological response on daratumumab in combination compared with standard care. The committee noted that ANDROMEDA is an ongoing trial and that overall survival data presented by the company, a secondary outcome in the trial, is immature at the planned interim and 12-month landmark analyses. Evidence from ANDROMEDA has not shown a statistically significant improvement in overall survival with daratumumab

in combination compared with standard care at the 12-month landmark analysis. No further data on overall survival was available at the 18-month landmark analysis. Less than 20% of people have died in both arms. Among other secondary end points, people randomised to have 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 reducing the need to have 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. It noted that the survival data from ANDROMEDA is immature and to date, has not shown a statistically significant improvement with daratumumab in combination compared with standard care. The committee took this into account in its decision making.

### **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 ANDROMEDA interim analysis 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 happened 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-stage organ complications, which are associated with a poorer quality of life. During the first committee meeting, the company presented 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 monotherapy (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 whose condition progressed, moved to second-line treatment. People having standard care were on first-line treatment for a maximum of 6 cycles (see [section 5.1 of the summary of product characteristics for](#)

[daratumumab](#)). Each cycle lasted 28 days. People having 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 considered that the partial and no response groups should be separate in the model to reflect clinical practice. In response to the appraisal consultation document, at the second committee meeting, the company revised its model structure to include separate response categories for partial and no response. The committee concluded that the company's revised model structure is appropriate for decision making.

## **Observational studies of standard care**

### **ALchemy and EMN23-UK are representative of people likely to have daratumumab in combination in the NHS**

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 who had first-line treatment with bortezomib-based regimens. The ERG used ALchemy for 2 main purposes: to characterise people in the NHS likely to be offered daratumumab in combination, and to model survival by haematological response. The company agreed with using observational data, but preferred to use 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. During the first committee meeting, the ERG considered that

EMN23 was less generalisable to NHS practice than ALchemy. This was because about 25% of people in EMN23 did not have first-line bortezomib-based regimens, and because some European countries define haematological response differently. Also, the ERG highlighted that it was unable to fully critique the EMN23 study because of the limited data submitted by the company, and because the only published data are abstracts or posters. The committee noted the size and composition of the 2 cohorts, and 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 agreed that ALchemy may be a better source of data. In response to the appraisal consultation document and at the second committee meeting, the company explained that it did not have access to patient-level data for ALchemy. So, it used data from the UK sub-population of EMN23 (from now referred to as EMN23-UK) in its revised base case to address the committee's concerns. These included treatment switching at 3 and 6 months, and inconsistency of response categorisation between ANDROMEDA and ALchemy (see [section 3.11](#)). The committee noted the 95% overlap of people in ALchemy and EMN23-UK. At the third committee meeting, the clinical expert confirmed that ALchemy and EMN23-UK included the same patient population but that the data cuts for overall survival were at different time points (see [section 3.12](#)). The clinical expert explained that EMN23-UK data had been updated more recently and so had a longer follow up period than in ALchemy. The committee concluded that both ALchemy and EMN23-UK are representative of people likely to have daratumumab in combination in the NHS.

## **Population modelling and assessing haematological response**

### **Haematological response should be assessed at 3 months and EMN23-UK is preferred for modelling, but there are uncertainties**

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. The second used data from ANDROMEDA. At the first meeting, 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 response to the appraisal consultation document, the company instead used patient-level data from EMN23-UK and ANDROMEDA to identify people who had switched treatments and attempt to ensure consistency in how haematological response had been defined. This was because the company did not have access to patient-level data for ALchemy and because of the 95% overlap of UK patients between ALchemy and EMN23 (see [section 3.10](#)). The company removed people who had switched treatments from its EMN23-UK dataset. This represented a small proportion of people overall, less than 3% at either 3 or 6 months. In aligning the response criteria definitions between ANDROMEDA and EMN23-UK, the company excluded 18% of people at 3 months and 22% of people at 6 months because of missing data. At the third committee

meeting, the company provided details of the missing data. It also presented Kaplan–Meier overall survival curves at 3 and 6 months for the unadjusted EMN23-UK dataset before re-categorisation compared with the unadjusted EMN23-UK dataset with cases removed because of missing data during the re-categorisation. The ERG noted that the overall survival curves showed substantial similarity and overlap. It considered that the impact of missing data resulting from re-classification is likely to be negligible in the EMN23-UK dataset. The clinical expert explained that the haematological response criteria used in ALchemy was outdated and that the criteria used in ANDROMEDA and EMN23-UK are the updated version, which are widely used in NHS practice. They also explained that there was a more recent update on the survival data in EMN23-UK compared with ALchemy, so the EMN23-UK dataset is likely to be more representative of NHS practice. The committee recalled that the 3-month assessment time point better reflected NHS practice. It concluded that the 3-month timepoint should be used in the base case. The committee acknowledged that the censored and re-categorised EMN23-UK dataset used the updated haematological response classification and had more recent overall survival data. It concluded that it is likely more appropriate to use the EMN23-UK dataset to model the full licensed population, but that some uncertainties exist (see [section 3.13](#)).

## Modelling overall survival

### Improvement in haematological response may be correlated with improved survival, but there are uncertainties in the evidence

3.12 The committee was aware that evidence from the ANDROMEDA interim analysis has not shown a statistically significant survival benefit for daratumumab in combination compared with standard care, and the company did not provide any updated analyses on overall survival at the second committee meeting (see section 3.7). But the company made a case for a survival benefit by using haematological response as a surrogate end point for survival. At the third committee meeting, the

company presented a meta-analysis ([Kastritis et al. 2023](#)) based on 9 observational studies (including ALchemy, but not EMN23) that showed a relationship between haematological response (complete and very good partial response) and overall survival in people with newly diagnosed AL amyloidosis. The committee noted the different definitions for complete response and the heterogeneous studies included in the meta-analysis. The clinical experts explained that, among the factors that impact overall survival, complete response plays a dominant role. An early, rapid and deep haematological response is directly related to overall survival. They explained that complete response is usually followed by organ response resulting in less organ damage. So, for most people, a complete haematological response would improve survival. One clinical expert also explained that, being a monoclonal antibody, daratumumab can attach to the abnormal white blood cells in amyloidosis and kill them by activating the immune system. This addresses the underlying causes of amyloidosis and could potentially improve survival. They also explained that the benefits of treatment can be seen as early as 1 to 3 months in people with systemic AL amyloidosis with cardiac involvement compared with about 4 years in people with the condition but with no cardiac involvement. The committee noted that the meta-analysis presented by the company showed that haematological response may be correlated with overall survival, but that there is uncertainty about the strength of this correlation between the 2 end points (see [section 3.13](#)). The committee concluded that improvement in complete haematological response is likely correlated with improved survival, but there is uncertainty in the evidence.

### **The company's analysis on the potential confounding factors between haematological response and overall survival is not informative**

- 3.13 The committee noted the possibility of confounding in the relationship between haematological response and overall survival at the first committee meeting. That is, whether people who had a better haematological response had other characteristics beyond haematological response that increased their likelihood of living longer. The clinical

experts also noted that cardiac and renal disease may be risk factors for not having a haematological response, and for mortality. To address the committee's concern and in response to the appraisal consultation document, at the second committee meeting, the company provided the results from a series of multivariate analyses. These assessed the impact of baseline patient characteristics on overall survival in people with complete response at 3 and 6 months for the whole population and per treatment using the safety data from ANDROMEDA's planned interim analysis. The company explained that because of the limited number of events (31 deaths in the daratumumab arm and 40 in the standard care arm), many of the models failed to converge and the results are numerically unstable but there was no indication of confounding. The ERG considered the analyses and results unreliable because all hazard ratios were estimated at 0 and many had extremely wide 95% confidence intervals. At the third committee meeting, the company explained that it had not provided any updated analyses on potential confounding factors because there were no new data cuts. The clinical experts explained that timing, speed and depth of haematological response may be important confounding factors, particularly when the condition entails more severe cardiac involvement. However, the clinical experts noted that cardiac response itself may not be a confounding factor in the relationship between haematological response and overall survival. This is because organ response may only happen when complete response occurs. The company confirmed that the meta-analysis done by [Kastritis et al. \(2023\)](#) had not reported on potential confounding factors. The committee recalled its discussion on the correlation between haematological response and overall survival (see section 3.12). Considering the lack of evidence and analysis presented by the company on confounding factors in this surrogate relationship, the committee concluded that the company's analysis on the confounding factors was not informative for decision making.

### The extrapolations for overall survival are highly uncertain

3.14 In its original submission, 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 from the ERG's clinical advisers than the predictions from EMN23. In response to the appraisal consultation document, the company presented extrapolated survival curves using the adjusted EMN23-UK dataset which was censored and re-categorised. The ERG highlighted that a large proportion of data was missing because of the re-categorisation of EMN23-UK dataset (see [section 3.11](#)). It highlighted that the extrapolated survival curve for complete response is higher in the censored and re-categorised EMN23-UK dataset at 3 months, while the relative difference in extrapolated overall survival between complete response and the other response categories was greater in the re-categorised EMN23-UK dataset compared with ALchemy. Also, the extrapolated overall survival for complete response in the re-categorised EMN23-UK dataset crossed the general population overall survival sooner than in 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 is not mature, and the company assumed that overall survival depends only on haematological response. The ERG explained that in principle, the EMN23-UK dataset would be a suitable alternative to ALchemy given the 95% overlap in patient population. It considered that outcomes should be near equivalent. At the third committee meeting, the company presented the Kaplan–Meier overall survival curves at 3 and 6 months for all haematological response categories for the original EMN23, unadjusted EMN23-UK before censoring and re-categorisation, and ALchemy datasets. The ERG noted the differences in the overall survival curves between the unadjusted EMN23-UK and ALchemy datasets were greater

than might be expected. It was concerned that the 2 datasets were likely not equivalent. The clinical expert explained that the overall survival data in the EMN23-UK dataset had been recently updated by about 1.5 to 2 years. They considered that the EMN23-UK dataset may provide a more realistic reflection of overall survival because of the more recent update on survival data. The committee questioned why the overall survival curves were longer in the Kaplan–Meier graphs for ALchemy compared with the EMN23-UK dataset when ALchemy had a shorter follow-up period. It noted that these observational studies were retrospective in nature. The clinical expert explained that for ALchemy, overall survival data is updated using the Office for National Statistics every 3 to 12 months. So, some people may have longer follow up, and some with missing data may not have been included in the EMN23-UK dataset. The committee considered that it would have been useful to see the censoring points on the graphs. It noted that the extrapolated overall survival associated with the re-categorised EMN23-UK dataset was higher compared with ALchemy at both 3 and 6 months. It concluded that although the censored and re-categorised EMN23-UK dataset is preferred to inform the model, there was uncertainty in the extrapolations for overall survival in the longer term using either the adjusted EMN23-UK or ALchemy datasets.

### **Expected survival benefit for daratumumab maintenance therapy may be overestimated and is uncertain**

3.15 At the second committee meeting, the company assumed a survival benefit because of an observed sustained response in people whose condition showed a complete response and who had daratumumab maintenance monotherapy, at the 18-month landmark analysis (see [section 3.7](#)). Because of this, the company applied an increased survival benefit to all response states in the daratumumab maintenance arm by a factor of 1.044 from cycle 7 onwards, based on the observed survival ratio (1.066) between daratumumab and standard care at the 12-month

ANDROMEDA landmark analysis and the equivalent ratio from EMN23-

UK (1.021). The company explained that this expected benefit was calculated using the 12-month landmark analysis because there was no other available outcome data at the post hoc 18-month landmark analysis. The ERG was concerned that the company applied this 4.4% uplift of survival benefit to all haematological response states including no response. At the third committee meeting, the company applied this uplift of survival benefit to complete and very good partial response categories for only the daratumumab arm in its revised base case. It also provided a scenario in which this uplift was not included. The committee noted that this increased benefit continued over the person's lifetime even after daratumumab maintenance monotherapy stopped in the model. The clinical experts explained that when the condition shows a complete response to any treatment, the clone that is producing the abnormal light chain proteins is deactivated. They explained that there is no direct effect on the proteins already in situ, rather, these deposits of amyloid are cleared by the body over time. They considered that if there is no relapse, the effects on overall survival may continue even after daratumumab monotherapy is stopped. The patient expert also explained that organ response, which occurs after complete haematological response, would also benefit survival even after stopping treatment. The committee considered that modelling an expected survival benefit for daratumumab maintenance treatment is reasonable. But, a 4.4% uplift over a lifetime time horizon may have overestimated the survival benefit that may be associated with daratumumab maintenance therapy. Given the uncertainty of the duration of sustained benefit, the committee concluded that it would consider a range of no sustained benefit and a sustained benefit over a lifetime.

## 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**

3.16 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. At the second committee meeting, the company explained that it did not have access to patient-level data for ALchemy but expect that data should be published in due course. The committee concluded that the company should have used SF36v2 data from ALchemy to validate its utility set derived from ANDROMEDA but understood that this was not possible because of lack of published data from ALchemy.

## Stopping rule

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

3.17 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 for daratumumab](#) 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 (approximately 2 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

3.18 Before the first committee meeting, the company used an administration cost for bortezomib plus daratumumab of £99. This was based on specialist nursing costs and is in line with another [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 administration of subsequent elements of chemotherapy in the same cycle). The committee was aware that its decision differed from that of the other appraisal. It considered that the company's choice of administration costs underestimated the true costs and should instead be £332. In response to the appraisal consultation document, the company maintained its use of £99 in its revised base case and presented scenario analyses using costs of £123 based on a micro-costing exercise it had done and £332. The Cancer Drugs Fund lead explained that the cost for administering daratumumab and bortezomib will only incur 1 cost and this

would be the same for both the daratumumab in combination and standard care arms. They explained that for daratumumab in combination, per 28-day cycle, the HRG code 12Z at £161 should be used for day 1 and for subsequent days 8, 15 and 22, the HRG code 15Z at £322 should be used (total of £1,127 per cycle). For cycles 3 to 6 when daratumumab in combination is administered every 2 weeks, the cost is £1,127 per cycle. For daratumumab maintenance monotherapy from cycle 7 onwards, only HRG 12Z at £161 should be used per cycle. For the standard care arm, the cost is £1,127 per cycle. At the third committee meeting, the company applied the administrative costs as outlined. The ERG noted that the company had not included the cost of £161 for cycle 1 and £322 for subsequent cycles for treatments at second line. But, it explained that the impact was very minor and decreased the company's revised base case incremental cost-effectiveness ratio (ICER). The committee concluded that the administration cost for daratumumab in combination and standard care should be the same for cycles 1 to 6. When daratumumab maintenance monotherapy starts at cycle 7 onwards, a lower cost should be applied to reflect the subcutaneous administration. It concluded that these costs should be applied at all lines of therapy.

## **End of life criteria**

### **Daratumumab does not meet the end of life criteria**

3.19 The committee considered the advice about life-extending treatments for people with a short life expectancy in [NICE's guide to the methods of technology appraisal 2013](#). To meet NICE's end of life criteria, the technology should be indicated for people with a short life expectancy, normally less than 24 months, and there should be sufficient evidence that the treatment extends life, normally for at least an additional 3 months, compared with current NHS treatment. The company did not consider that daratumumab met the end of life criteria for the full population. The ERG agreed, and the committee concluded that the end of life criteria were not met in the indicated population. The company submitted a case that the

end of life criteria were met in the subgroup with cardiac stage 3b disease. The committee recalled earlier comments from the clinical experts that people with cardiac or renal failure had more severe disease, and that if the condition causes heart failure (cardiac stage 3b disease), the median survival is about 4.5 months. The ERG noted that the company had not proposed that daratumumab in combination be limited to this population and had not presented clinical or cost-effectiveness evidence for this subgroup. The committee noted that it had not seen evidence that the life expectancy of the whole indicated population having standard care was on average less than 24 months. The committee concluded that daratumumab in combination for treating systemic AL amyloidosis regardless of severity did not meet end of life criteria.

## **Innovation**

### **Daratumumab in combination is innovative**

3.20 The clinical experts considered daratumumab in combination to be a step-change in managing newly diagnosed systemic AL amyloidosis. The committee was aware that there were no licensed treatment options for systemic AL amyloidosis in the NHS. It considered that there may be benefits with daratumumab in combination that were not fully captured in the modelling, such as benefits for people with concomitant multiple myeloma. The clinical experts explained that people who have an early and deep complete response without cardiac involvement may be eligible for kidney transplant. The committee concluded that daratumumab in combination is innovative and would take this into consideration in its decision making.

## Cost-effectiveness estimates

### An acceptable ICER is towards the middle of £20,000 to £30,000 per QALY gained range

3.21 [NICE's guide to the methods of technology appraisal 2013](#) notes that above a most plausible ICER of £20,000 per quality-adjusted life year (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 planned 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's analysis on confounding factors is not informative. The company used observational studies that used standard care regimens (see [section 3.6](#), [section 3.10](#) and [section 3.12](#)).
- The censored and re-categorised EMN23-UK dataset is preferred to inform the model but there are uncertainties (see [section 3.10](#) and [section 3.11](#)).
- The company's application of an expected survival benefit of 4.4% for daratumumab maintenance monotherapy only from cycle 7 onwards over a lifetime may have been overestimated and is uncertain (see [section 3.15](#)).
- Some utility values lack face validity (see [section 3.16](#)).

Considering the rarity of the condition, unmet need, innovativeness of the technology and uncertainties in the modelling, the committee concluded that an acceptable ICER would be towards the middle of the £20,000 to £30,000 per QALY gained range.

### The committee's preferred assumptions

3.22 The committee's preferred assumptions were:

- to include people with end-stage cardiac and renal disease in the population (see [section 3.4](#))
- to use the censored and re-categorised EMN23-UK data to inform the distribution of haematological response for standard care (see [section 3.10](#) and [section 3.11](#))
- that there may be confounding factors in the relationship between haematological response and overall survival (see [section 3.12](#))
- to assess haematological response at 3 months (see [section 3.11](#))
- to use the censored and re-categorised EMN23-UK data for the extrapolated overall survival in the longer term (see [section 3.12](#))
- that the company's application of an expected increased survival benefit for daratumumab maintenance monotherapy may lie between no expected benefit and over a lifetime horizon (see [section 3.15](#))
- that some utility data lack face validity (see [section 3.16](#))
- to apply a stopping rule for daratumumab of a maximum of 24 cycles (see [section 3.17](#))
- to increase chemotherapy administration costs to £1,127 per cycle applied to both daratumumab in combination and standard care arms for cycles 1 to 6, then £161 per cycle for daratumumab maintenance monotherapy from cycle 7 onwards, and at all lines of therapy (see [section 3.18](#)).

At the third committee meeting, the company revised its base case in line with the committee's preferred assumptions. The company's and ERG's ICERs were within the range that NICE considers an acceptable use of

NHS resources (see [section 3.21](#)). To maintain the confidentiality of the medicine prices included in the model, the actual cost-effectiveness estimates cannot be published here.

## **Daratumumab in combination is recommended for routine commissioning**

3.23 When taking all confidential discounts into account, the ICERs presented were within the range considered to be a cost-effective use of NHS resources. So, daratumumab in combination is recommended for routine commissioning for treating newly diagnosed systemic AL amyloidosis in adults.

## **4 Implementation**

- 4.1 [Section 7 of the National Institute for Health and Care Excellence \(Constitution and Functions\) and the Health and Social Care Information Centre \(Functions\) Regulations 2013](#) requires integrated care boards, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.
- 4.2 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final appraisal document.
- 4.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has newly diagnosed systemic amyloid light-chain amyloidosis and the doctor responsible for their care thinks that daratumumab plus bortezomib, cyclophosphamide and dexamethasone is

the right treatment, it should be available for use, in line with NICE's recommendations.

## **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.

#### **Chair**

Charles Crawley

Chair, technology appraisal committee B

#### **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

#### **Yelan Guo and Carl Prescott**

Technical advisers

**Jeremy Powell and Shonagh D'Sylva**

Project managers

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