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 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 condition 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

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cyclophosphamide and dexamethasone. But, 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 November 2022). 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 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 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 need 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 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 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 maintenance 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 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 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 dose 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'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 (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 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 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 the data on overall survival presented by the company, a secondary outcome in the trial, is immature at the planned interim and 12-month landmark analyses, and only data on haematological response was available at the 18-month landmark analysis. Fewer 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 needing 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. But, it concluded that it had not been shown if daratumumab in combination improves overall survival.

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 analy4sis 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 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-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 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 having 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 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 may be representative of UK clinical practice

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. 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, the company explained that because it did not have access to patient-level data for ALchemy, 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. It concluded that both ALchemy and EMN23-UK may be representative of UK clinical practice.

Population modelling and assessing haematological response

Haematological response should be assessed at 3 months, but whether to use data from EMN23-UK or ALchemy 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). 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, 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 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. 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. The ERG noted that the company did not provide details of the missing data or analyses using the original EMN23-UK dataset and the censored and re-categorised EMN23-UK dataset. Given the lack of data presented, the committee considered that there was uncertainty around the EMN23-UK dataset, in particular, whether the missing data were truly random. 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 but the choice of dataset, that is, EMN23-UK or ALchemy is uncertain (see section 3.10).

Modelling overall survival

Potential confounding factors between haematological response and overall survival are not appropriately explored

3.12 The committee was aware that ANDROMEDA has not shown a survival benefit for daratumumab in combination compared with standard care based on the interim analysis and the company did not provide any updated analyses at the second committee meeting. But the company made a case for a survival benefit by using haematological response as a surrogate end point for survival. The company 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. In response to the appraisal consultation document, at the second committee meeting, the company provided the results from a series of multivariate analyses assessing the impact of baseline patient characteristics on overall survival in people with complete response at 3 and 6 months, respectively 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 that 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. The committee considered that the analyses were not appropriately conducted and uncertainty about the potential confounding factors for having a haematological response and for living longer remained. Apart from treatment itself, the clinical experts noted that cardiac and renal disease as risk factors for having a haematological response and for mortality. The committee concluded that the issue of possible confounding between haematological response and overall survival remained.

The extrapolations for overall survival in the longer term is still highly uncertain

3.13 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 of the ERG clinical advisers than the predictions from EMN23. In response to the appraisal consultation document, the company presented extrapolated survival curves using the censored and re-categorised EMN23-UK dataset. 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 are not mature, and the company assumed that overall survival depends only on haematological response. The committee 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 noted the high level of missing data in the re-categorised EMN23-UK dataset. It concluded that there was high uncertainty in extrapolations for overall survival in the longer term using either the re-categorised EMN23-UK or ALchemy datasets.

The company's modelling of an expected survival benefit for daratumumab maintenance therapy is not appropriate

3.14 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 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 explained that the company applied this 4.4% uplift of survival benefit to all haematological response states including no response. The committee also noted that this increased benefit continued even after daratumumab maintenance monotherapy stopped in the model. The committee considered that modelling an expected survival benefit for daratumumab maintenance treatment may be reasonable in principle. But there was considerable uncertainty in the company's approach to calculating the expected survival benefit, and applying this benefit independent of haematological response categories was unlikely to be appropriate. It was also highly uncertain whether this benefit should continue to apply after daratumumab has been stopped. The committee concluded that the company's approach to modelling sustained benefit was not appropriate for decision making.

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

3.15 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

3.16 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 (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

3.17 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 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 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. 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.

End of life criteria

Daratumumab does not meet the end of life criteria

3.18 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

3.19 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 committee concluded that daratumumab in combination is innovative and would take this into consideration in its decision making.

The uncertainty means an acceptable ICER is £20,000 per QALY gained

3.20 NICE's guide to the methods of technology appraisal 2013 notes that above a most plausible incremental cost-effectiveness ratio (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 did not adequately address the possibility of confounding. The company used observational studies that used standard care regimens (see 3.6, section 3.10 and section 3.12).

- The effects of censored and re-categorised EMN23-UK data were uncertain (see section 3.11 and section 3.12).
- The company's approach and application of an expected survival benefit for daratumumab maintenance monotherapy from cycle 7 onwards is uncertain (see section 3.13).
- Some utility values lack face validity (see section 3.14).
- The company underestimated the administration costs for bortezomib and daratumumab (see section 3.16).

The committee concluded that because of the high uncertainty in the modelling, that an acceptable ICER would be well below £30,000 per QALY gained.

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

3.21 The committee's preferred assumptions were:

- to include people with end-stage cardiac and renal disease in the population (see section 3.4)
- that the distribution of haematological response for standard care may lie between ALchemy and the censored and re-categorised EMN23-UK (see 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 in the base case but explore a scenario using 6 months (see section 3.11)
- that the extrapolated overall survival in the longer term may lie between the ALchemy data and the censored and re-categorised EMN23-UK data (see section 3.12)
- that the company's approach of applying an expected increased survival benefit for daratumumab maintenance monotherapy is not appropriate for decision making (see section 3.14)
- that some utility data lack face validity (see section 3.15)

- to apply a stopping rule for daratumumab monotherapy of a maximum of 24 cycles (see section 3.16)
- 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 (see section 3.17).

The committee considered that none of the analyses presented reflected its preferred assumptions. But on balance, when taken together, these changes would increase the ICER. Given that the company's and ERG's ICERs were above the range that NICE considers an acceptable use of NHS resources, using the committee's assumptions would therefore not bring the ICERs into the acceptable range. NICE has considered if it could publish the range of ICERs for transparency. But to maintain the confidentiality of the medicine prices included in the model, the actual cost-effectiveness estimates cannot be published here. The committee agreed that, if its preferred assumptions were used, the ICERs would be above the range that NICE considers an acceptable use of NHS resources.

Daratumumab in combination cannot be recommended for routine commissioning

3.22 When taking all confidential discounts into account, none of the ICERs presented, including the company's own base-case ICER, were within the range considered to be a cost-effective use of NHS resources. If the committee's preferred assumptions were used, the ICERs would be above the range that NICE considers an acceptable use of NHS resources. The committee recalled that it would take into account benefits that had not been captured in the model (see section 3.19). But on balance, the ICERs were still higher that the range considered to be a cost-effective use of NHS resources. 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 has not been shown

3.23 Having concluded that daratumumab in combination could not be recommended for routine use, the committee then considered if it could be recommended for treating newly diagnosed systemic AL amyloidosis in adults within the Cancer Drugs Fund. 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). The committee recalled the uncertainty in the estimates of overall survival and was aware that ANDROMEDA is ongoing. The company anticipates that there will be final analyses related to overall survival. The committee acknowledged that further data collection may help resolve the uncertainty, and considered the other criteria for suitability and entry to the Cancer Drugs Fund. It recalled that at the price the company had chosen to charge the NHS for daratumumab, none of the plausible cost-effectiveness estimates were within the range considered a cost-effective use of NHS resources. So the committee concluded that daratumumab was not plausibly cost effective, and that so far it did not meet the criteria to be considered for inclusion in the Cancer Drugs Fund.

Charles Crawley
Chair, Appraisal Committee
November 2022

4 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

Yelan Guo and Carl Prescott
Technical advisers

Jeremy Powell and Shonagh D'Sylva
Project managers

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