NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Appraisal consultation document

Daratumumab in combination for untreated multiple myeloma when a stem cell transplant is suitable

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

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

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

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

Issue date: May 2021

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

After consultation:

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

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

The key dates for this appraisal are:

Closing date for comments: Friday 18 June 2021

Second appraisal committee meeting: Wednesday 7 July 2021

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

1 Recommendations

1.1 Daratumumab plus bortezomib, thalidomide and dexamethasone is not recommended, within its marketing authorisation, as induction and consolidation treatment for untreated multiple myeloma in adults, when an autologous stem cell transplant is suitable.

1.2 This recommendation is not intended to affect treatment with daratumumab plus bortezomib, thalidomide 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

Most people with untreated multiple myeloma who have an autologous stem cell transplant have bortezomib plus thalidomide and dexamethasone induction therapy before their transplant. As an alternative, daratumumab would be added (daratumumab in combination), but this treatment would also be continued for a short period after transplant (consolidation).

Clinical trial results show that, compared with bortezomib plus thalidomide and dexamethasone, adding daratumumab increases how long people live and extends the time before the condition gets worse.

But assumptions in the economic model around how long the effect of daratumumab lasts and how long people live are uncertain. Also, the model does not reflect what happens in the NHS in England.

The cost-effectiveness estimates are likely to be higher than what NICE considers acceptable. So, daratumumab plus bortezomib, thalidomide and dexamethasone cannot be recommended for use in the NHS.

2 Information about daratumumab

Marketing authorisation indication

2.1 Daratumumab (Darzalex, Janssen-Cilag) in combination with bortezomib, thalidomide and dexamethasone, is indicated 'for the treatment of adult patients with newly diagnosed multiple myeloma who are eligible for autologous stem cell transplant'.

Dosage in the marketing authorisation

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

Price

2.3 The list price for daratumumab is £4,320 per 1,800 mg vial of solution for injection intended for a fixed-dose subcutaneous administration (excluding VAT; BNF online, accessed May 2021). It is also available as a concentrate for solution for intravenous infusion with a list price of £360 per 100 mg vial, and £1,440 per 400 mg vial (excluding VAT; BNF online, accessed May 2021). The company has a commercial arrangement. This makes daratumumab available to the NHS with a discount, which would have 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.

2.4 The list price for bortezomib is £762.38 per 3.5 mg vial (excluding VAT; BNF online, accessed May 2021). There is a price reduction for bortezomib agreed with the Commercial Medicines Unit. The prices agreed through the framework are commercial in confidence.

2.5 The list price for thalidomide is £298.48 per 28-pack of 50-mg capsules (excluding VAT; BNF online, accessed May 2021).

2.6 There is a nationally available price reduction for dexamethasone with the Commercial Medicines Unit. The prices agreed through the framework are commercial in confidence.

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.

The committee recognised that there were remaining areas of uncertainty associated with the analyses presented, and took these into account in its decision making. It discussed the following issues, which were outstanding after the technical engagement stage:

- the uncertainty in the hazard ratios from the company's meta-analysis on the relationship between minimal residual disease status and survival outcomes (issue 1, see ERG report page 14)
- the most appropriate definition of minimal residual disease negativity (issue 2, see ERG report page 15)
- the most plausible long-term survival extrapolations for people having bortezomib plus thalidomide and dexamethasone (issue 4, see ERG report page 17)
- uncertainty around the treatment effect of daratumumab on progression-free survival and overall survival, based on the company's landmark analysis (issue 5, see ERG report page 18)
- how long the treatment effect of daratumumab lasts (issue 6, see ERG report page 19).

New treatment option

People with untreated multiple myeloma would welcome a new first-line treatment option

3.1 The patient experts explained that multiple myeloma is a relapsing and remitting disease and can include periods of severe symptoms. The first remission is often the 'best' remission because it is when people with the condition are at their fittest. With each line of new therapy, a substantial proportion of people stop having treatment because they become too ill or have complications. Therefore, the most effective treatments should be given as early in the treatment pathway as possible. However, multiple myeloma does not always respond well to current induction treatments. New treatment options are needed which would improve response and offer a longer period of remission, as well as limiting or preventing complications associated with multiple myeloma. The patient experts noted that more people having daratumumab plus bortezomib, thalidomide and dexamethasone have no minimal residual disease (a measure of the residual tumour cells in bone marrow) than those having other treatments. This signifies a 'deep' response. They also considered that daratumumab is well-tolerated. The committee concluded that people with untreated multiple myeloma would welcome a new treatment option that gives a longer period of remission and improves survival.

Treatment pathway

Bortezomib plus thalidomide and dexamethasone is a relevant comparator, but bortezomib plus dexamethasone should be included

3.2 The committee was aware that the following comparators were included in the NICE scope: bortezomib plus dexamethasone, or plus dexamethasone and thalidomide; bortezomib plus cyclophosphamide and dexamethasone; and cyclophosphamide plus thalidomide and dexamethasone. The committee understood that the company had only included bortezomib plus dexamethasone and thalidomide as a

comparator in its economic model. The clinical experts advised that most people with untreated multiple myeloma for whom an autologous stem cell transplant is suitable would have an induction regimen of bortezomib plus thalidomide and dexamethasone. When thalidomide is not tolerated or is contraindicated, bortezomib plus dexamethasone with or without cyclophosphamide can be offered. Cyclophosphamide plus thalidomide and dexamethasone is rarely used. The clinical experts noted that bortezomib plus thalidomide and dexamethasone has comparable efficacy to bortezomib plus cyclophosphamide and dexamethasone. They also explained that both triple regimens induce a 'deeper' response than the double regimen of bortezomib plus dexamethasone. The committee understood that the company had omitted bortezomib plus cyclophosphamide and dexamethasone as a comparator in its economic model. This was because the company believed that it had similar efficacy and costs to bortezomib plus thalidomide and dexamethasone. However, the committee considered that there was uncertainty in the company's matching-adjusted indirect comparison (see section 3.9). The company also omitted bortezomib plus dexamethasone as a comparator in its model. This was because the company believed that it had similar costs to bortezomib plus thalidomide and dexamethasone, but lower efficacy. However, the committee noted that bortezomib plus dexamethasone is cheaper than bortezomib plus thalidomide and dexamethasone. As such, it does not necessarily follow that showing cost effectiveness against bortezomib plus thalidomide and dexamethasone would also show cost effectiveness against bortezomib plus dexamethasone. The committee concluded that bortezomib plus thalidomide and dexamethasone was a relevant comparator, but it would have preferred bortezomib plus dexamethasone to be included as a comparator in the model.

Daratumumab consolidation treatment can be incorporated into NHS clinical practice

3.3 In the company's clinical trial (see section 3.5), treatment with daratumumab involved 4 cycles of induction treatment followed by high-

dose chemotherapy, followed by an autologous stem cell transplant, and then 2 cycles of 'consolidation' treatment, in line with the marketing authorisation. Consolidation aims to improve depth of response and achieve long-term disease control, but the clinical experts explained that it was not standard clinical practice in the NHS. Instead, 6 rather than 4 cycles of induction treatment were usually offered. However, the clinical experts stated they would be keen to offer consolidation if the evidence supported it. They considered that consolidation could be incorporated into NHS clinical practice and implemented with few challenges. The committee concluded that consolidation treatment with daratumumab could be incorporated into NHS clinical practice.

Lenalidomide maintenance is widely used in clinical practice, and should be incorporated into the economic model

3.4 The company did not include maintenance treatment with lenalidomide after an autologous stem cell transplantation in its economic model as a subsequent treatment. This was because at the time of the company submission, NICE was still appraising lenalidomide maintenance and it was not standard clinical practice. However, after NICE's technology appraisal guidance on lenalidomide maintenance treatment after an autologous stem cell transplant for newly diagnosed multiple myeloma, the clinical experts explained that lenalidomide maintenance was now widely used in clinical practice and this was likely to increase in future. The clinical lead for the Cancer Drugs Fund stated that adding daratumumab to induction (and consolidation) treatment would likely increase the duration of lenalidomide maintenance. The effect of including lenalidomide maintenance on the cost effectiveness of daratumumab plus bortezomib, thalidomide and dexamethasone was therefore unclear. The committee concluded that a scenario analysis incorporating lenalidomide maintenance as a subsequent treatment should be provided to represent current NHS clinical practice.

Clinical evidence

Adding daratumumab to bortezomib plus thalidomide and dexamethasone improves progression-free and overall survival

3.5 The main clinical evidence for daratumumab plus bortezomib, thalidomide and dexamethasone for untreated multiple myeloma when a stem cell transplant is suitable came from the CASSIOPEIA trial. This was a phase 3, open-label, randomised trial based in 111 European sites. A total of 1,085 adults aged up to 65 with untreated multiple myeloma eligible for an autologous stem cell transplant were randomised 1:1 to either daratumumab plus bortezomib, thalidomide and dexamethasone (experimental arm) or bortezomib plus thalidomide and dexamethasone (control arm). People in both arms had 4 cycles of induction treatment with the above regimens, followed by an autologous stem cell transplant and 2 cycles of consolidation treatment. The primary outcome was the proportion of people having a stringent complete response within 100 days after an autologous stem cell transplant. The committee was aware that the company chose not to model this primary outcome in its cost-effectiveness analyses (see section 3.10). Secondary outcomes included overall survival, progression-free survival, and the rate of minimal residual disease negativity. At the primary data cut (and final analysis for the primary outcome) after a median follow up of 18.8 months, 28.9% of patients in the experimental arm and 20.3% of patients in the control arm had a stringent complete response after consolidation (odds ratio [OR] 1.60, 95% confidence interval [CI] 1.21 to 2.12). The company also presented survival results from 2 later data cuts with a median follow up of 29.2 months and 44.5 months, respectively. At the earlier of the 2, the hazard ratios for progression-free survival and overall survival were 0.50 (95% CI 0.38 to 0.65) and 0.52 (95% CI 0.33 to 0.85) respectively, favouring the experimental arm. The results of the latest data cut are confidential. CASSIOPEIA also has an ongoing second part, in which people whose disease at least partially responded after consolidation are

eligible to participate. These people are re-randomised to either daratumumab monotherapy maintenance treatment or observation until progression. However, daratumumab maintenance treatment is not currently included in the marketing authorisation and does not represent NHS clinical practice. The committee recognised that the CASSIOPEIA results would not reflect NHS clinical practice. The company adjusted for people switching to daratumumab maintenance using a pre-specified inverse probability weighting method, which produced similar results to the unadjusted analysis. The committee was aware that the ERG was unable to validate the inverse probability weighting results because the company could not provide the individual patient data from the second part of CASSIOPEIA. However, the committee concluded that adding daratumumab to bortezomib plus thalidomide and dexamethasone improved progression-free survival and overall survival.

The company's censored landmark analysis is likely biased, though the direction of the bias is unclear

3.6 The company presented an exploratory landmark analysis to explore the relationship between minimal residual disease status and survival. Minimal residual disease negativity in the bone marrow was assessed at 2 timepoints in CASSIOPEIA. The first was after the completion of induction therapy, and the second was after the completion of consolidation therapy (around 100 days after an autologous stem cell transplant). The company used only the data from people alive at the post-consolidation assessment (the 'landmark' timepoint). It split these people by their minimal residual disease status (negative or positive), and calculated hazard ratios for progression-free survival and overall survival for people having daratumumab plus bortezomib, thalidomide and dexamethasone compared with those having bortezomib plus thalidomide and dexamethasone. The company calculated these hazard ratios separately for people with and without minimal residual disease and used them to extrapolate long-term survival in the economic model (see section 3.10). At technical engagement, the company updated the landmark analysis to

use the latest data cut from CASSIOPEIA (median follow up of 44.5 months). The company could not use inverse probability weighting to adjust the updated landmark analysis results for the re-randomisation to daratumumab maintenance (see section 3.5). It noted that the landmark analysis was not pre-specified, and that it did not have access to the individual patient data from the second part of CASSIOPEIA because it remains blinded. At technical engagement, the company instead adjusted the landmark analysis by censoring the data from all people re-randomised to daratumumab maintenance. The results of this censored analysis showed that adding daratumumab improved progression-free survival and overall survival, regardless of minimal residual disease status. The ERG noted that the results of the landmark analysis were inconsistent with those from the intention-to-treat (ITT) data adjusted using inverse probability weighting. The ERG considered that this was likely because of bias introduced by the company's censoring approach. The ERG also noted that the treatment effect of daratumumab on overall survival in the landmark analysis was highly uncertain. The committee agreed that the results of the landmark analysis were likely biased because of informative censoring. However, it deemed that the direction of the bias was unclear because it affected both treatment arms. The committee concluded that the company's censoring approach had limitations, and that its effect on the results of the landmark analysis was uncertain.

Minimal residual disease negativity is likely to better predict survival outcomes than conventional response, and can be used in the model

3.7 The committee was aware that the company had based the progression-free survival and overall survival extrapolations in its economic model on minimal residual disease status at the landmark timepoint (see section 3.6). The clinical experts stated that, although minimal residual disease is not routinely measured in clinical practice, minimal residual disease negativity is associated with better progression-free survival and overall survival than minimal residual disease positivity. The committee queried

why the company had chosen to split the patients in the model by minimal residual disease (a secondary outcome in CASSIOPEIA) rather than stringent complete response (the primary outcome in CASSIOPEIA). The company explained that when it designed CASSIOPEIA, stringent complete response was considered the most informative outcome. However, according to the company, minimal residual disease has since been identified as superior to stringent complete response in assessing depth of response. But the company acknowledged that minimal residual was yet to be accepted by regulators as a primary outcome in multiple myeloma trials not designed to show superiority in terms of progression-free survival. The ERG agreed that having no minimal residual disease is likely to better predict survival outcomes than a stringent complete response. The committee was aware that in NICE's technology appraisal guidance on daratumumab with bortezomib and dexamethasone for previously treated multiple myeloma, the committee had concluded that the relationship between minimal residual disease and long-term overall survival was not well established and could not inform the economic model. However, it understood that there was now greater clinical support for the link between minimal residual disease negativity and survival outcomes. The committee would have preferred to see further evidence to support the company's assertion that minimal residual disease status better predicts progression-free survival and overall survival than does stringent complete response. Based on the clinical input, the committee concluded that in the company's approach to modelling long-term survival (see section 3.10), it was reasonable to split patients into those with and without minimal residual disease.

Adverse events

The adverse event profile of daratumumab plus bortezomib, thalidomide and dexamethasone is acceptable

3.8 The company considered that overall, the adverse event profile of treatments was similar between groups in CASSIOPEIA. However, the

committee noted the higher frequency of nausea, neutropenia, thrombocytopenia, lymphopenia and cough reported in the experimental arm. According to the company, the increased rate of neutropenia in people having daratumumab was not associated with an increased risk of neutropenic fever. The company noted that, at a median follow up of 18.8 months, infusion-related reactions of any grade associated with daratumumab were seen in around 35% of patients. These were manageable, with a low frequency of severe (grade 3 or 4) events (3.5%), low rates of stopping treatment (0.6%) and no fatal events. The company added that it anticipated that the subcutaneous formulation of daratumumab would have a lower incidence of infusion-related reactions. The clinical experts noted that overall, daratumumab has limited and manageable adverse effects. The committee concluded that the adverse event profile of daratumumab plus bortezomib, thalidomide and dexamethasone was acceptable.

Indirect treatment comparisons

The results of the company's matching-adjusted indirect comparisons are uncertain

3.9 There are no trials directly comparing daratumumab plus bortezomib, thalidomide and dexamethasone with bortezomib plus dexamethasone, with or without cyclophosphamide. Therefore, the company did matching-adjusted indirect comparisons and used these to estimate the relative efficacy of the 2 regimens. The company also estimated the relative efficacy of bortezomib plus thalidomide and dexamethasone compared with bortezomib plus dexamethasone, with or without cyclophosphamide. For bortezomib plus cyclophosphamide and dexamethasone the company used the data from GMMG-MM5, a randomised trial comparing this regimen with doxorubicin plus dexamethasone. For bortezomib plus dexamethasone, the company used the data from IFM 2005-01, a randomised trial comparing this regimen with vincristine plus doxorubicin and dexamethasone. The company adjusted the patient-level data from

CASSIOPEIA to match the study-level baseline patient characteristics from GMMG-MM5 and IFM 2005-01. The comparisons were unanchored because there was no common comparator between the studies. The company did not use the results of the indirect comparisons to inform the economic model directly, but rather to support the omission of some comparators from the model (see section 3.2). The ERG could not verify that the company had correctly implemented the matching-adjusted indirect comparisons, nor check the results because the company could not provide the ERG with individual patient data from CASSIOPEIA. The ERG added that it would have preferred to see a scenario analysis using a simulated treatment comparison. The committee understood that there were large reductions in effective sample size for the comparison with bortezomib plus cyclophosphamide and dexamethasone, and that adjusting for more covariates would further reduce the effective sample size. The committee also noted that the comparison of bortezomib plus thalidomide and dexamethasone compared with bortezomib plus cyclophosphamide and dexamethasone had wide confidence intervals. It concluded that there was uncertainty around whether the indirect comparisons supported the clinical expert opinion on the relative efficacy of the different comparators (see section 3.2).

The company's economic model

It is unclear if the company's approach to long-term survival modelling reduces uncertainty

3.10 The company presented a partitioned survival model comprising 3 health states (pre-progression, progressive disease and death) to estimate the cost effectiveness of daratumumab plus bortezomib, thalidomide and dexamethasone compared with bortezomib plus thalidomide and dexamethasone. The company developed survival models to predict survival beyond the end of the CASSIOPEIA trial over a lifetime time horizon. The company explored a conventional approach of fitting parametric models to the ITT data from CASSIOPEIA, but considered that

there was wide variation in the overall survival predicted by the different distributions. The company chose not to provide cost-effectiveness results based on these analyses because it believed that they would have been very uncertain. Instead, the company used the Kaplan–Meier curves from CASSIOPEIA up to the landmark timepoint (see section 3.6). The company split the people still alive at this timepoint into those with and without minimal residual disease. The company then took a 5-step approach to modelling long-term progression-free survival and overall survival:

1. For people with minimal residual disease who had bortezomib plus thalidomide and dexamethasone, the company fitted separate parametric distributions to the post-landmark data from CASSIOPEIA to model progression-free survival and overall survival (see section 3.13).

2. The company did a meta-analysis to estimate the relationship between minimal residual disease and survival for people for whom a stem cell transplant is suitable having standard care (see section 3.11). From this, it calculated 2 hazard ratios. The first reflected the association between minimal residual disease status and overall survival, and the second the association between minimal residual status and progression-free survival.

3. The company applied the hazard ratios from step 2 to the parametric curves for people with minimal residual disease who had bortezomib plus thalidomide and dexamethasone (from step 1), to calculate progression-free survival and overall survival curves for people without minimal residual disease having the same treatment.

4. The company applied the hazard ratios from the landmark analysis (see section 3.6) to the survival curves for people having bortezomib plus thalidomide and dexamethasone (from steps 1 and 3) to

calculate the curves for people having daratumumab, split by minimal residual disease status.

5. Finally, the company weighted the survival curves for all patients in each arm split by minimal residual disease status based on the proportion of people with and without minimal residual disease at the landmark timepoint.

The ERG agreed with the company that the overall survival data from CASSIOPEIA was too immature for parametric distributions fitted to the ITT data to be robust. The committee noted the uncertainties associated with the different elements of the company's approach; these included the choice of extrapolations for people with minimal residual disease having bortezomib plus thalidomide and dexamethasone (see section 3.13), and the results of the meta-analysis (see section 3.11) and landmark analysis (see section 3.6). The committee was unsure if the company's approach to the long-term survival modelling reduced the uncertainty. It would have preferred that a scenario be provided using a conventional approach of fitting models directly to the ITT data from CASSIOPEIA.

The meta-analysis on the relationship between minimal residual disease status and survival is uncertain, but has minimal effect on results

3.11 To inform the survival curves for people without minimal residual disease having bortezomib plus thalidomide and dexamethasone, the company did a meta-analysis exploring the relationship between minimal residual disease and survival for people having any treatment representing standard care. The results showed improved progression-free survival and overall survival in people without minimal residual disease compared with those with minimal residual disease. The company modelled this using hazard ratios, which needed the proportional hazards assumption (that is, the relative risk of an event was fixed irrespective of time) to be met. The ERG considered that there was some uncertainty with the hazard ratios from the meta-analysis. This was because the included

studies differed with respect to baseline International Staging System scores (which signify prognosis), as well as the treatments representing standard care. The ERG also observed that the assessments of progression-free survival and overall survival started at different timepoints across the studies. However, the company commented that no events were reported across the studies before the start of assessment, so this should not have affected the results. The committee was uncertain if the effect of minimal residual disease on survival outcomes would stay constant over time, as was needed for the proportional hazards assumption. However, it understood that the hazard ratios for people with and without minimal residual disease were not a key driver of the cost-effectiveness results.

People without minimal residual disease would have a complete response over time and the company's definition is appropriate

3.12 The ERG found that the definition of minimal residual disease varied across the studies the company included in its meta-analysis. According to the criteria of the International Myeloma Working Group (IMWG), minimal residual disease status should be determined only in people with a conventional complete response. This was the definition used in some studies included in the meta-analysis. However, in CASSIOPEIA, minimal residual disease was assessed regardless of conventional complete response. The ERG noted that there were more people in CASSIOPEIA without minimal residual disease than there were with a conventional complete response. The clinical experts explained that this may have been because there was a delay in the clearance of paraprotein in the serum, which is needed for conventional complete response. At technical engagement, the company updated its meta-analysis to include only studies in which minimal residual disease had been defined regardless of conventional complete response. This had broadly similar results to the company's original meta-analysis. The ERG would have preferred that the company also provide a scenario in which it applied a consistent definition of minimal residual disease according to the IMWG criteria (that is,

needing a conventional complete response). The ERG also noted that in CASSIOPEIA the absolute rates of minimal residual disease negativity were much lower when using the IMWG definition. This would affect the survival extrapolations in the model, changing the weight attributed to the curves for people with and without minimal residual disease in each treatment arm. The committee noted that a scenario provided by the ERG with post-consolidation minimal residual negativity rates defined according to the IMWG definition considerably impacted the cost-effectiveness results. The clinical experts explained that all people without minimal residual disease would eventually have a conventional complete response, but agreed that there was sometimes a delay between the 2 outcomes. The committee agreed that people without minimal residual disease would have a conventional complete response over time. As such, the definition used in the company's economic model (regardless of conventional complete response) was likely to be appropriate.

Modelling survival

The company's model likely underestimates survival for people having bortezomib plus thalidomide and dexamethasone

3.13 The company extrapolated progression-free survival and overall survival for people with minimal residual disease having bortezomib plus thalidomide and dexamethasone using parametric distributions fitted to the post-landmark data from CASSIOPEIA. The company used this patient group because it had the highest number of events and therefore the most mature data. It selected an exponential distribution for both progression-free survival and overall survival because it had a good statistical and visual fit to the data, and provided clinically plausible predictions. To validate the survival curves predicted by the model for all people having bortezomib plus thalidomide and dexamethasone (regardless of minimal residual disease status), the company compared them with external data sources. It found that the overall survival rates up to 10 years were broadly comparable with the GIMEMA study, which

compared bortezomib plus thalidomide and dexamethasone with thalidomide plus dexamethasone in people with newly diagnosed multiple myeloma. The ERG considered the exponential distribution for overall survival to be reasonable. For progression-free survival, the committee noted that the company's choice of exponential distribution underestimated survival during the first 3 years after the landmark timepoint, when there was more data. The ERG noted that the Weibull and Gompertz distributions gave a better overall fit to the trial data. The ERG was also concerned that the censoring of people re-randomised to daratumumab maintenance in the company's landmark analysis would bias the overall survival results (see section 3.6). This was because people who had maintenance therapy in CASSIOPEIA had to have disease with at least a partial response after consolidation, and therefore a better prognosis. The clinical experts predicted that around 70% of people having bortezomib plus thalidomide and dexamethasone would be alive after 5 years, and between 50% and 60% of people would be alive after 10 years. The committee agreed with the ERG that the company's censoring approach would likely underestimate survival for patients having bortezomib plus thalidomide and dexamethasone. The committee concluded that the company's extrapolations likely underestimated survival for patients having bortezomib plus thalidomide and dexamethasone.

Treatment effect waning should be included in the model, but the duration of the daratumumab treatment effect is highly uncertain

3.14 Treatment effect waning refers to whether the relative treatment effect of daratumumab is likely to reduce over time after people stop taking it. The company's base case included a lifetime treatment effect with daratumumab. The company believed that there was no evidence to suggest if, or when, the treatment effect of daratumumab would wane over time. It noted that the latest data cut from CASSIOPEIA, with a median follow up of almost 4 years, continued to show a relative benefit for daratumumab. The company also presented evidence that people

having daratumumab had deeper responses, which correlated with improved survival outcomes. Also, after 10 years median follow up in GIMEMA (see section 3.13), there was no evidence to suggest a waning in the relative effect of bortezomib plus thalidomide and dexamethasone over thalidomide plus dexamethasone. The ERG felt that there was not enough evidence to support a lifetime treatment effect with daratumumab, and that this was an optimistic assumption. It was reluctant to draw conclusions from the updated CASSIOPEIA landmark analysis because of the potential bias from censoring (see section 3.6). The ERG preferred a scenario with a treatment effect lasting 5 years after consolidation therapy. This was modelled by setting the disease progression and mortality rates as equal to that of the comparator from this timepoint onwards. The clinical experts considered that the GIMEMA results suggested that the daratumumab treatment effect would last longer than 5 years after consolidation therapy. The clinical lead for the Cancer Drugs Fund stated that because people had daratumumab for fixed, short treatment duration, it was likely that the treatment effect would wane over time. The committee understood that including treatment effect waning in the model considerably affected the cost-effectiveness results. It considered that the daratumumab treatment effect was likely to decline gradually over time, but the timepoints at which this decline would start and finish were highly uncertain. The committee concluded that treatment effect waning should be included in the model, but that the duration of the daratumumab treatment effect was highly uncertain. The committee considered it reasonable to consider scenarios with a treatment effect lasting 5 and 10 years after consolidation therapy.

Age at the start of induction

The age of the patient at the start of induction should be based on epidemiological evidence

3.15 The company used a mean age of 56.6 years at the start of induction in its economic model, taken from CASSIOPEIA. The ERG considered that this

did not reflect NHS clinical practice, because CASSIOPEIA excluded patients aged over 65. Real-world evidence from Public Health England suggested that many people with newly diagnosed multiple myeloma who are eligible for transplant are aged over 65. As such, the ERG preferred to use the mean age at diagnosis from the Public Health England data, which was higher than the company's estimate. The committee agreed that the mean age from the Public Health England data better reflected NHS clinical practice and should be used in the economic model.

Costs of subsequent treatments

Panobinostat plus bortezomib and dexamethasone should not be included as a subsequent treatment at third or fourth line

3.16 The company's model included the costs of second-, third- and fourth-line treatments given after consolidation therapy. The NICE Cancer Drugs Fund position statement specifies that companies should not include treatments recommended for use in the Cancer Drugs Fund as treatment sequence products in their economic modelling because they do not yet reflect routine NHS practice. To reflect this, the company omitted treatments recommended for use in the Cancer Drugs Fund as subsequent treatments in its base case. It assumed that around 45% of people would have panobinostat plus bortezomib and dexamethasone as their third-line treatment. However, the ERG understood that this regimen is rarely used in third or fourth line because of its poor tolerability, and is mainly used in later lines. The clinical experts agreed, stating that they tended to avoid offering panobinostat. The committee concluded that panobinostat plus bortezomib and dexamethasone should not be included as a third- or fourth-line treatment in the model.

Cost-effectiveness results

The most plausible cost-effectiveness estimate is above the range usually considered a cost-effective use of NHS resources

3.17 The committee recalled that its preferred assumptions were:

- using an approach less subject to bias than simple censoring to adjust the landmark analysis for re-randomisation to daratumumab maintenance (see section 3.6)
- a treatment effect lasting 5 to 10 years after consolidation therapy (see section 3.14)
- a mean age at the start of induction based on the real-world evidence from Public Health England (see section 3.15)
- omitting panobinostat plus bortezomib and dexamethasone as a subsequent treatment at third or fourth line (see section 3.16).

The cost-effectiveness results are commercial in confidence because they included confidential discounts for daratumumab, bortezomib, dexamethasone and some of the follow-on treatments in the model. The committee noted the uncertainties in the modelling, specifically:

- the duration of the daratumumab treatment effect
- the potential effect of lenalidomide maintenance, which was now widely used in the NHS
- if minimal residual disease negativity better predicts long-term survival outcomes than stringent complete response, the primary outcome in CASSIOPEIA
- the possible bias introduced into the landmark analysis by censoring to adjust for re-randomisation to daratumumab maintenance
- if showing cost effectiveness compared with bortezomib plus thalidomide and dexamethasone would necessarily mean that cost

effectiveness is shown compared with bortezomib plus dexamethasone.

The committee considered that it would have liked to see cost-effectiveness results based on the following scenarios, to reduce the uncertainty:

- a scenario incorporating lenalidomide maintenance as a subsequent treatment to reflect current NHS clinical practice (see section 3.4)
- a scenario using a conventional approach of fitting progression-free and overall survival models directly to the ITT data from CASSIOPEIA (see section 3.10).

It concluded that, based on the current evidence, the incremental cost-effectiveness ratio (ICER) was likely to be closer to the ERG's estimate. This was above the upper end of the range normally considered a cost-effective use of NHS resources (£30,000 per quality-adjusted life year [QALY] gained). The committee concluded that the cost-effectiveness estimate for daratumumab plus bortezomib, thalidomide and dexamethasone was higher than what NICE normally considers a cost-effective use of NHS resources.

Other factors

3.18 The ERG raised 2 potential equalities issues. The first was that daratumumab plus bortezomib, thalidomide and dexamethasone should not be restricted to people aged up to 65 (which would reflect the inclusion criteria in CASSIOPEIA). The second was that multiple myeloma is more common in men than women, and it also has a higher incidence in people of African American family origin. The population considered by the committee was not restricted to people aged up to 65. Issues related to differences in prevalence or incidence of a disease cannot be addressed in a technology appraisal.

3.19 The company stated the daratumumab was innovative because it has a different mechanism of action from other available treatments for multiple myeloma. The committee agreed that there were likely to be improvements in survival with daratumumab plus bortezomib, thalidomide and dexamethasone. However, it concluded that there were no additional gains in health-related quality of life over those already included in the QALY calculations.

Conclusion

Daratumumab plus bortezomib, thalidomide and dexamethasone is not recommended for routine use in the NHS

3.20 Daratumumab plus bortezomib, thalidomide and dexamethasone is more clinically effective than standard care for untreated multiple myeloma when a stem cell transplant is suitable. However, there are several uncertainties in the economic modelling. The committee agreed that the most plausible ICER for daratumumab plus bortezomib, thalidomide and dexamethasone compared with bortezomib plus thalidomide and dexamethasone was above the range normally considered to be a cost-effective use of NHS resources. Therefore, it concluded that daratumumab plus bortezomib, thalidomide and dexamethasone could not be recommended for routine use as an option for untreated multiple myeloma when a stem cell transplant is suitable.

Daratumumab plus bortezomib, thalidomide and dexamethasone is not recommended for use in the Cancer Drugs Fund

3.21 Having concluded that daratumumab plus bortezomib, thalidomide and dexamethasone could not be recommended for routine use, the committee then considered if it could be recommended for untreated multiple myeloma when a stem cell transplant is suitable 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

was aware that the company had not expressed an interest in the treatment being considered for funding through the Cancer Drugs Fund. It recalled that the key clinical uncertainty was the duration of the daratumumab treatment effect. The committee was aware that the final analysis of the CASSIOPEIA trial will be available in 2023, after 5 years of follow up. It noted that length of follow up would therefore not be enough to inform the treatment waning assumption with greater certainty. It also recalled that some people in CASSIOPEIA were re-randomised to daratumumab maintenance (see section 3.5), limiting the relevance of the data to NHS clinical practice. It concluded that daratumumab plus bortezomib, thalidomide and dexamethasone did not meet the criteria to be considered for inclusion in the Cancer Drugs Fund.

4 Proposed date for review of guidance

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

Amanda Adler
Chair, appraisal committee
May 2021

5 Appraisal committee members and NICE project team

Appraisal committee members

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

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

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

NICE project team

Each technology appraisal is assigned to a team consisting of technical staff and a project manager.

Iordanis Sidiropoulos
Senior Scientific Adviser

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Technical adviser

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Project manager

ISBN: [to be added at publication]