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: August 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 17 September 2021

Third appraisal committee meeting: Thursday 4 November 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

Before having an autologous stem cell transplant, most people with untreated multiple myeloma have bortezomib plus thalidomide and dexamethasone as the first (induction) treatment. This appraisal looks at adding daratumumab (daratumumab in combination). This treatment would also continue for a short time 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.

The company's economic model made assumptions around how long the effect of daratumumab lasts and how long people live which are uncertain. Also, there is some uncertainty around how the company modelled treatment after daratumumab.

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 fixed-dose subcutaneous administration (excluding VAT; BNF online, accessed July 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 July 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 July 2021). There is a discount 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 July 2021).

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

3 Committee discussion

The appraisal committee met twice to consider 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).

In its second meeting, the committee discussed how lenalidomide maintenance should be included as a subsequent treatment in the modelling, having raised this as an issue in the first meeting.

New treatment option

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

3.1 The patient experts explained that multiple myeloma is a relapsing and remitting disease and can include severe symptoms. The first remission is often the 'best' remission because people are at their fittest. With each line of new treatment, some people stop treatment because they become too ill or have complications. Therefore, the patient experts believed that the most effective treatments should be given as early as possible in the treatment pathway. Multiple myeloma does not always respond well to current induction treatments (see section 3.2). Patients need new treatment options which improve response and offer a longer period of remission, as well as limiting or delaying 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 new treatment options that give a longer period of remission and improve survival.

Treatment pathway

People for whom a stem cell transplant is suitable usually have induction treatment followed by high-dose chemotherapy before transplant

3.2 Around 1 in 3 people newly diagnosed with multiple myeloma in the UK will be eligible for an autologous stem cell transplant based on overall fitness. For this population, first-line treatment consists of induction treatment to stabilise the disease, high-dose chemotherapy (usually melphalan) followed by an autologous stem cell transplant to improve

depth of response and progression-free survival. Consolidation treatment, which also aims to improve depth of response and involves offering the treatment used at induction again for a short period, is not currently part of NHS practice. NICE recommend lenalidomide as maintenance treatment after an autologous stem cell transplant for newly diagnosed multiple myeloma in adults, with the aim of increasing the length of remission. After relapse, people will progress onto subsequent lines of treatment. The committee concluded that people for whom an autologous stem cell transplant is suitable usually have induction treatment followed by high-dose chemotherapy before their transplant.

Bortezomib plus thalidomide and dexamethasone is the most relevant comparator reflecting NHS practice, and has similar efficacy and costs to bortezomib plus cyclophosphamide and dexamethasone

3.3 The committee was aware that the NICE scope included the following comparators to reflect NHS practice: bortezomib plus dexamethasone; bortezomib plus dexamethasone and thalidomide; bortezomib plus cyclophosphamide and dexamethasone; and cyclophosphamide plus thalidomide and dexamethasone. The committee understood that the company had included only bortezomib plus dexamethasone and thalidomide as a comparator in its original economic model, but had added bortezomib plus dexamethasone in response to consultation after the first committee meeting. The clinical experts advised that most people with untreated multiple myeloma for whom an autologous stem cell transplant is suitable would have an induction (first treatment) regimen of bortezomib plus thalidomide and dexamethasone. When thalidomide is not tolerated or is contraindicated, clinicians usually offer bortezomib plus dexamethasone and cyclophosphamide. Cyclophosphamide plus thalidomide and dexamethasone is rarely offered. The clinical experts noted that bortezomib plus thalidomide and dexamethasone has comparable efficacy to bortezomib plus cyclophosphamide and dexamethasone. They explained that both triple regimens (3 drugs)

induce a 'deeper' response than the double regimen (2 drugs) of bortezomib plus dexamethasone. The clinical experts explained that they may offer bortezomib plus dexamethasone to patients who do not tolerate a triple regimen, but these patients would be unlikely to be offered an autologous stem cell transplant. Consequently, bortezomib plus dexamethasone is rarely offered to people for whom a stem cell transplant is suitable. The committee understood that the company omitted bortezomib plus cyclophosphamide and dexamethasone as a comparator in its economic model. It heard that the company assumed that bortezomib plus cyclophosphamide and dexamethasone had similar efficacy and costs to bortezomib plus thalidomide and dexamethasone. The committee considered that there was some uncertainty in the company's matching-adjusted indirect comparison comparing bortezomib plus cyclophosphamide and dexamethasone to bortezomib plus thalidomide and dexamethasone (see section 3.10). The committee concluded that bortezomib plus thalidomide and dexamethasone was the most relevant comparator, with similar efficacy and costs to bortezomib plus cyclophosphamide and dexamethasone.

Daratumumab consolidation treatment can be incorporated into NHS practice

3.4 Consolidation treatment follows induction treatment and autologous stem cell transplant and is not currently part of NHS practice (see section 3.2). In the company's clinical trial (see section 3.6), 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. The marketing authorisation reflects using the treatment before and after transplant, but the clinical experts reiterated that it was not standard clinical practice in the NHS. Instead, 6 rather than 4 cycles of induction treatment are usually offered before transplant. 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 practice and implemented

with few challenges. The committee concluded that consolidation treatment with daratumumab could be incorporated into NHS practice.

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

3.5 In its original submission, the company's economic model did not include maintenance treatment with lenalidomide after an autologous stem cell transplant. This was because at the time of the company's 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 is now widely used in practice and this was likely to increase further. Because the company had not included it in is original model, the committee could not assess the effect of including lenalidomide maintenance on the cost effectiveness of daratumumab plus bortezomib, thalidomide and dexamethasone. The clinical experts noted that there is no clinical evidence evaluating the efficacy of lenalidomide maintenance after daratumumab. They noted that induction and maintenance regimens are tested separately in clinical trials. The committee acknowledged that the lack of clinical evidence exploring the use of lenalidomide maintenance following daratumumab plus bortezomib, thalidomide and dexamethasone made incorporating it into the model challenging, but not impossible. It considered that the model should reflect current NHS practice, and was aware that practice changes over time. At the second meeting, the company including lenalidomide maintenance in their model, but only included the costs and did not consider any clinical benefits (see section 3.16). The committee concluded that both the costs and benefits of lenalidomide maintenance should be incorporated as a subsequent treatment in the model to represent current NHS practice.

Clinical evidence

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

3.6 The clinical evidence for daratumumab plus bortezomib, thalidomide and dexamethasone for untreated multiple myeloma when an autologous stem cell transplant is suitable comes from the CASSIOPEIA trial. This was a phase 3, open-label, randomised trial based in 111 European sites. Patients included 1,085 adults aged up to 65 with untreated multiple myeloma eligible for an autologous stem cell transplant randomised 1:1 to either daratumumab plus bortezomib, thalidomide and dexamethasone (experimental arm) or bortezomib plus thalidomide and dexamethasone (control arm). The protocol stipulated that people in both arms have 4 cycles of induction treatment with the above regimens, followed by an autologous stem cell transplant and a further 2 cycles of consolidation treatment. The primary outcome was the proportion of people with a 'stringent complete disease 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 3.11). Secondary outcomes included overall survival, progression-free survival, and the proportion of patients without minimal residual disease. 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 maintenance treatment or observation until progression. However, daratumumab maintenance treatment is not currently included in the marketing authorisation and does not represent NHS practice. The committee recognised that the CASSIOPEIA results do not reflect NHS 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, at the time of the first committee meeting, could not provide the individual patient data from the second part of CASSIOPEIA. The committee concluded that adding daratumumab to bortezomib plus thalidomide and dexamethasone improved progression-free survival and overall survival.

The inverse probability of censoring weighting (IPCW)-adjusted landmark analysis is likely less biased than the censoring-adjusted landmark analysis

3.7 The company presented a landmark analysis to explore the relationship between minimal residual disease status and survival. Minimal residual disease negativity in the bone marrow (determined by bone marrow aspiration) was assessed at 2 timepoints in CASSIOPEIA. The first was after patients completed induction treatment, and the second after they completed consolidation treatment (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 the data by a patient's minimal residual disease status (negative or positive), and for each group 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. Taking these calculated hazard

ratios for people with and without minimal residual disease, the company then used them to extrapolate long-term progression-free and overall survival in the economic model (see section 3.11). At technical engagement, the company updated the landmark analysis using the latest data cut from CASSIOPEIA but could not use inverse probability weighting to adjust the updated landmark analysis results for re-randomising patients to daratumumab maintenance (see section 3.6). The company justified this, noting that the landmark analysis was not pre-specified in the trial protocol and that it could not yet access the individual patient data from the second part of CASSIOPEIA because the trial was still blinded. Instead, the company 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 to bortezomib plus thalidomide and dexamethasone improved progression-free survival and overall survival, independent 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 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. After the first committee meeting, the company was able to access the individual patient data it needed to adjust the results of the landmark analysis for re-randomisation to daratumumab maintenance using an IPCW approach. The results of the IPCW-adjusted landmark analysis were broadly comparable with the censoring-adjusted landmark analysis for progression-free survival. However, the hazard ratio for overall survival compared with bortezomib plus thalidomide and dexamethasone improved slightly for people with minimal residual disease and worsened for people without minimal residual disease. The ERG commented that although it could not fully

validate the analysis, the IPCW-adjusted landmark analysis appeared appropriate and the results reasonable. The ERG noted that uncertainty remained because some relevant prognostic factors were not measured or included. The committee concluded that the company's IPCW-adjusted landmark analysis was likely less biased than the censoring-adjusted landmark analysis and more appropriate for decision making, but that residual confounding may remain.

Minimal residual disease negativity is likely to predict survival outcomes better than stringent complete response

3.8 The committee was aware that the company had based the extrapolations of progression-free survival and overall survival in its economic model on minimal residual disease status at the landmark timepoint (see section 3.7). The clinical experts stated that, although minimal residual disease is not routinely measured in clinical practice and so does not guide treatment choices, minimal residual disease negativity compared with minimal residual disease positivity is associated with better progression-free survival and overall survival. The committee queried why the company chose 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 by the oncology community to be the most informative outcome. However, according to the company, minimal residual disease is now considered better than stringent complete response in assessing depth of response. The company acknowledged that minimal residual disease status was yet to be accepted by regulators as a primary outcome in multiple myeloma trials not designed to show superiority for 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 experts' input, the committee concluded that in the company's approach to modelling long-term survival (see section 3.11), 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

3.9 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

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

3.10 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 data from GMMG-MM5, a randomised trial comparing this regimen with doxorubicin plus dexamethasone. For bortezomib plus dexamethasone, the company used 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 3.3). The ERG could not verify that the company had correctly implemented the matching-adjusted indirect comparisons, nor check the results because the company did 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 comparing bortezomib plus

thalidomide and dexamethasone with bortezomib plus cyclophosphamide and dexamethasone generated 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 3.3).

The company's economic model

The company's approach to modelling long-term survival, using a landmark analysis, is acceptable for decision making

3.11 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. It explored a conventional approach of fitting parametric models to the ITT (whole trial population) data from CASSIOPEIA but considered the predicted overall survival varied widely by the different distributions. In its original submission, 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 3.7). The company split the people still alive at this timepoint into those with and without minimal residual disease. It 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 3.14).

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 3.12). 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 disease 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 3.7) 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. In the first meeting, 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 3.14), and the results of the meta-analysis (see section 3.12) and landmark analysis (see section 3.7). In its first meeting, 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. In response to consultation, the company updated its economic model to include a scenario with standard parametric models fitted directly to the IPCW-adjusted ITT data from the first part of CASSIOPEIA. The company selected a Weibull model for progression-free survival and overall survival for both treatment arms. The committee considered that both the company's approaches to survival modelling had uncertainty, but noted that the cost-effectiveness results were similar between the 2. It concluded that the company's original approach of using a landmark analysis split by minimal residual disease status was acceptable to model long-term survival.

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

3.12 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 hazard's 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

3.13 The ERG found that the definition of minimal residual disease varied across the studies the company included in its meta-analysis. Some studies included the criteria of the International Myeloma Working Group (IMWG), which states people must have a conventional complete disease response. However, in CASSIOPEIA, minimal residual disease was assessed regardless of conventional complete response. The ERG noted that there were more people without minimal residual disease in CASSIOPEIA than there were with a conventional complete disease 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 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, and change 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 accepted that people without minimal residual disease would have a conventional complete response over time, and that the definition used in the company's economic model (regardless of conventional complete response) was likely to be appropriate.

Modelling survival

Survival for people having bortezomib plus thalidomide and dexamethasone should be modelled based on the IPCW-adjusted landmark analysis

3.14 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. The committee discussed if limiting the analysis to people who had survived to the landmark time would bias the results, but the company explained that very few patients in CASSIOPEIA had died before this point. The company adjusted the survival extrapolations to account for people switching to daratumumab maintenance in CASSIOPEIA using a censoring approach and an IPCW approach (see section 3.7). In the model presented at the first committee meeting, the company fitted the parametric distributions to the censoring-adjusted landmark analysis data. However, the ERG was concerned that the censoring of people re-randomised to daratumumab maintenance would bias the overall survival results (see section 3.7). This was because people who had maintenance treatment in CASSIOPEIA had to have disease with at least a partial response after consolidation, and therefore a better prognosis. The committee agreed with the ERG that the company's censoring approach would likely underestimate survival for patients having bortezomib plus thalidomide and dexamethasone. In

response to consultation, the company provided a revised base case analysis that used the data from the updated IPCW-adjusted landmark analysis (see section 3.7). In its revised base case, the company extrapolated survival for people with minimal residual disease having bortezomib plus thalidomide and dexamethasone using a Gompertz distribution for progression-free and an exponential distribution for overall survival. The company considered that its revised analysis likely overestimated overall survival for people having bortezomib plus thalidomide and dexamethasone. It suggested that this was because people in CASSIOPEIA had consolidation treatment, which was not currently part of NHS practice (see section 3.4). Consolidation treatment could have produced a deeper response than induction treatment alone, and therefore longer survival. The ERG considered that the extrapolations used by the company in its revised base case reasonably fit the CASSIOPEIA trial data. However, the ERG agreed with the company that the predictions of overall survival exceeded those from clinical experts. The ERG suggested that this could be due to the nature of the population and interventions in the trial, and the use of a constant hazard ratio to estimate overall survival for people without minimal residual disease. The committee recalled that the company's revised IPCW-adjusted landmark analysis was likely less subject to bias than the censoring-adjusted landmark analysis (see section 3.7). It concluded that survival for people having bortezomib plus thalidomide and dexamethasone should be modelled using curves fitted to the IPCW-adjusted data from the landmark analysis.

Waning of treatment effect should be included in the model, and the duration of the daratumumab treatment effect is highly uncertain

3.15 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 original 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 the GIMEMA trial, 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 the company's assumption was optimistic. It preferred a scenario with a treatment effect lasting 5 years after consolidation treatment. This was modelled by setting the disease progression and mortality rates as equal to that of the comparator from this timepoint onwards. At the first committee meeting, the clinical experts noted that the GIMEMA results suggested that the daratumumab treatment effect would last longer than 5 years after consolidation treatment. 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 felt that it was reasonable to consider scenarios with a treatment effect lasting 5 and 10 years after consolidation treatment. In response to consultation, the company presented 2 new treatment waning scenarios at the second committee meeting. The first scenario assumed a gradual waning effect between 5 and 10 years after consolidation, while the second assumed a treatment effect lasting 7.5 years after consolidation. However, the company continued to assume a lifetime treatment effect for daratumumab in its base case. The ERG considered that the scenario with a gradual waning effect between 5 and 10 years after consolidation fairly reflected the committee's preference from the first committee meeting. It highlighted that evidence of a long-term survival benefit for daratumumab from CASSIOPEIA remained uncertain, particularly in

people without minimal residual disease. At the second committee meeting, the clinical lead for the Cancer Drugs Fund noted that recently published results from CASSIOPEIA part 2 showed that only people who had bortezomib plus thalidomide and dexamethasone as induction and consolidation treatment benefited from daratumumab maintenance. This suggested that the effect of adding daratumumab to bortezomib plus thalidomide and dexamethasone had not waned during CASSIOPEIA part 2, because no extra relative benefit from daratumumab maintenance was seen in people who had daratumumab induction and consolidation treatment. The committee considered the possibility that because people have first-line daratumumab for a fixed, short treatment duration, its treatment effect may be less likely to wane than if they had it for longer. This is because the entire benefit of first-line daratumumab would have been delivered, with no opportunity for a gradual loss of effect over time. This difference in prescribing compared with NICE appraisals of daratumumab monotherapy for treating relapsed and refractory multiple myeloma and daratumumab with bortezomib and dexamethasone for previously treated multiple myeloma mean that it may be more reasonable to consider a scenario with no treatment effect waning. However, the committee considered that the treatment effect of daratumumab was likely to wane at some point, and that when this would happen remained uncertain. It decided that it had not seen enough evidence to support changing its original conclusion that the treatment effect of daratumumab would likely last 10 years or less after consolidation.

Lenalidomide maintenance

A scenario including maintenance with lenalidomide should include both its costs and benefits

3.16 In response to the committee's request after the first committee meeting (see section 3.5), the company provided 2 scenarios which included lenalidomide maintenance treatment after consolidation with or without

daratumumab for the second committee meeting. The company included the costs of lenalidomide maintenance, but did not include any benefit of lenalidomide maintenance, stating it was unaware of any clinical evidence evaluating the efficacy of lenalidomide maintenance after daratumumab. In its first scenario, the company assumed that regardless of whether they had daratumumab induction and consolidation treatment, people would have lenalidomide maintenance for the same length of time. In this scenario, the company based the duration of lenalidomide maintenance treatment on the median time to discontinuation from the transplant-eligible subgroup of the Myeloma XI trial. Myeloma XI was a phase 3 trial that aimed to answer several questions, including if lenalidomide maintenance treatment improved progression-free and overall survival compared with observation. In its second scenario, the company assumed that people who have daratumumab induction and consolidation treatment would have lenalidomide maintenance for longer than those who do not. To calculate the duration of lenalidomide treatment for this scenario, the company took the ratio of the median time to discontinuation and progression-free survival from the transplant-eligible subgroup of Myeloma XI. It then applied this ratio to the progression-free survival results from CASSIOPEIA to produce different durations of lenalidomide maintenance treatment for each arm. The company suggested that both its scenarios were likely to be conservative because they did not account for potentially fewer people having lenalidomide maintenance after having daratumumab first line, and also because they did not consider the benefits of lenalidomide maintenance. The company believed that lenalidomide maintenance was likely to have greater efficacy in people having daratumumab induction and consolidation treatment. It also suggested that the ratio modelled between time to discontinuation and progression-free survival in its second scenario may be conservative. 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, and considered that the duration of

lenalidomide maintenance modelled in the company's scenarios was not plausible. In the company's second scenario it was unclear why people having bortezomib plus thalidomide and dexamethasone had lenalidomide maintenance for less time than the median time to -discontinuation from the transplant-eligible subgroup of Myeloma XI. The ERG considered that because the company's scenarios included the costs of lenalidomide maintenance, but not the benefits, they were biased. It also agreed with the company that the scenarios may be conservative because they assumed equal or longer lenalidomide maintenance after daratumumab induction and consolidation. The committee noted that there was considerable uncertainty around the duration of lenalidomide maintenance in each arm and the associated efficacy. It also noted that while there is no direct evidence of daratumumab followed by lenalidomide maintenance, this would be the likely treatment pathway for people having daratumumab at first line. Therefore, the committee concluded that it would have preferred to see a scenario that includes both the costs and benefits of lenalidomide maintenance. This scenario should include a longer duration of lenalidomide maintenance for people having daratumumab at first line compared with those who have not had it.

Age at the start of induction treatment

The age of patients at the start of induction treatment should reflect UK epidemiological evidence

3.17 The company used a mean age of 56.6 years at the start of induction treatment 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. Evidence from Public Health England suggests that many people with newly diagnosed multiple myeloma eligible for transplant are aged over 65. The ERG considered that the mean age at diagnosis from the Public Health England data, which was higher than the company's estimate, better reflected NHS practice. The committee concluded in its first committee meeting that the

mean age from the Public Health England data better reflected NHS practice and should be used in the economic model. The company revised its base case for the second committee meeting to include a mean age at the start of induction from the Public Health England data.

Costs of subsequent treatments

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

3.18 The company's model included the costs of second-, third- and fourth-line treatments given after first-line induction and consolidation treatment. The NICE Cancer Drugs Fund position statement specifies that companies should not include treatments recommended for use in the Cancer Drugs Fund 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. 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 it is poorly tolerated 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. The company revised its base case at consultation to omit panobinostat plus bortezomib and dexamethasone as a third- or fourth-line treatment.

Cost-effectiveness results

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

3.19 The committee recalled that its preferred assumptions were:

- including lenalidomide maintenance as a subsequent treatment, to reflect current NHS practice (see section 3.5 and section 3.16).
- a landmark analysis adjusted for re-randomisation to daratumumab maintenance using the company's IPCW approach (see section 3.7).
- basing the long-term survival modelling on the company's landmark analysis approach, split by minimal residual disease status (see section 3.11).
- using the IPCW-adjusted landmark analysis to model survival for people having bortezomib plus thalidomide and dexamethasone (see section 3.14).
- a daratumumab treatment effect lasting up to 10 years after consolidation treatment (see section 3.15).
- a mean age at the start of induction treatment based on evidence from Public Health England (see section 3.17).
- omitting panobinostat plus bortezomib and dexamethasone as a treatment at third or fourth line (see section 3.18).

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
- how the duration and benefits of lenalidomide maintenance may differ for people having daratumumab plus bortezomib, thalidomide and dexamethasone compared with people having bortezomib, thalidomide and dexamethasone without daratumumab.

The committee considered that it would have liked to see cost-effectiveness results based on a scenario incorporating both the costs and benefits of lenalidomide maintenance (see section 3.16). It noted that the

incremental cost-effectiveness ratios (ICERs) compared with bortezomib plus thalidomide and dexamethasone were 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) in all scenarios in which the daratumumab treatment effect after consolidation was limited to 10 years or less. This was regardless of whether lenalidomide maintenance was included as a subsequent treatment, based on the 2 scenarios provided by the company. The committee also noted that the ICERs compared with bortezomib plus thalidomide and dexamethasone were above £30,000 per QALY gained in both the company's lenalidomide maintenance scenarios, regardless of whether the daratumumab treatment effect after consolidation was limited to 10 years or less. The committee concluded that the cost-effectiveness estimates for daratumumab plus bortezomib, thalidomide and dexamethasone was higher than what NICE normally considers a cost-effective use of NHS resources.

Other factors

3.20 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 are not equality issues if they do not affect access to a technology, if recommended.

3.21 The company stated the daratumumab was innovative because it has a different mechanism of action from other available treatments. The committee agreed that while the technology would likely improve survival, 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

3.22 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 and biases 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. 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

3.23 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 if placed in the Cancer Drug Fund would not be enough to inform the treatment waning assumption

with greater certainty. It recalled that some people in CASSIOPEIA were re-randomised to daratumumab maintenance (see section 3.6), limiting the relevance of the data to NHS practice. It concluded that daratumumab plus bortezomib, thalidomide and dexamethasone did not meet the criteria to be included 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
August 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.

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