NICE National Institute for Health and Care Excellence

NICE guidance

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

Technology appraisal guidance

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Your responsibility

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Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

Contents

1 Recommendations

1.1 Daratumumab plus bortezomib, thalidomide and dexamethasone is recommended, within its marketing authorisation, as induction and consolidation treatment for untreated multiple myeloma in adults, when an autologous stem cell transplant is suitable. It is recommended only if the company provides daratumumab according to the commercial arrangement.

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 treatment. This appraisal looks at adding daratumumab to bortezomib plus thalidomide and dexamethasone (daratumumab in combination) before transplant (induction) and for a short time after transplant (consolidation).

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

The cost-effectiveness estimates are within what NICE considers acceptable. So, daratumumab in combination is recommended.

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 for daratumumab.

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 November 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 November 2021). The company has a commercial arrangement. This makes daratumumab available to the NHS with a discount. The size of the discount is commercial in confidence. It is the company's responsibility to let relevant NHS organisations know details of the discount.

2.4 The list price for bortezomib is £762.38 per 3.5-mg vial (excluding VAT; BNF online, accessed November 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 November 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 3 times 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 that preceded the first committee meeting:

- 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 extrapolations of long-term survival for people having bortezomib plus thalidomide and dexamethasone (issue 4, see ERG report, page 17)
- the uncertainty around the treatment effect of daratumumab plus bortezomib, thalidomide and dexamethasone (daratumumab in combination) 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 in combination lasts (issue 6, see ERG report, page 19).

The committee also considered that maintenance with lenalidomide should be included as a subsequent treatment in the modelling.

New treatment option

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

3.1 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 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. Patients need new treatment options that improve response and offer a longer remission, as well as limit or delay complications associated with multiple myeloma. The patient experts noted that more people having daratumumab in combination have no minimal residual disease (a measure of residual tumour cells in bone marrow) than those having other treatments. This signifies a deep response. They considered that daratumumab in combination is well tolerated. The committee concluded that people with untreated multiple myeloma would welcome well-tolerated new treatment options that give a longer period of remission and improve survival.

Treatment pathway

When an autologous stem cell transplant is suitable, people 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. 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 deepen response and prolong 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 standard 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 when an autologous stem cell transplant is suitable, people will 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 4 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. Clinical experts advised that when an autologous stem cell transplant is suitable, most people with untreated multiple myeloma 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 would be suitable, a requirement of this appraisal. The committee understood that the company did not include bortezomib plus cyclophosphamide and dexamethasone as a comparator in its economic model. The company discussed that its rationale for not including bortezomib plus cyclophosphamide and dexamethasone was because they thought it had similar efficacy and costs to bortezomib plus thalidomide and dexamethasone. The committee considered that there was uncertainty in the company's matching-adjusted indirect comparison comparing bortezomib plus cyclophosphamide and dexamethasone to bortezomib plus thalidomide and dexamethasone (see section 3.11). 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.

Consolidation treatment including daratumumab can be

incorporated into NHS practice

3.4 Consolidation treatment follows induction treatment and autologous stem cell transplant and is not standard NHS practice (see section 3.2) but was included in the company's clinical trial (see section 3.6). Specifically, treatment with daratumumab in combination 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, and none after 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 in combination could be incorporated into NHS practice.

Maintenance with lenalidomide 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. The clinical experts noted that there is no clinical evidence evaluating the efficacy of lenalidomide maintenance after daratumumab in combination. They noted that clinical trials separately test induction and maintenance regimens. The committee acknowledged that the lack of clinical evidence exploring using lenalidomide maintenance after daratumumab in combination made incorporating it into the model challenging, but not impossible. It concluded that the model should reflect NHS practice and include both costs and benefits of lenalidomide maintenance.

Adding daratumumab to bortezomib plus thalidomide and

dexamethasone improves progression-free and overall survival

3.6 The CASSIOPEIA trial provides the clinical evidence for daratumumab in combination for untreated multiple myeloma when an autologous stem cell transplant is suitable. 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 in combination (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 3.12). 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 data cuts, 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 company submitted the results of the latest data cut as confidential.

3.7 CASSIOPEIA also has an ongoing second part, in which people whose disease at least partially responded after consolidation are eligible to take part. These people are re-randomised to maintenance treatment either with daratumumab monotherapy or observation until disease progression. However, maintenance treatment with daratumumab monotherapy 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 the results of progression-free survival and overall survival from CASSIOPEIA for people switching to maintenance treatment with daratumumab monotherapy using a pre-specified inverse probability weighting

method, which produced similar results to the unadjusted analysis. 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 appropriate to adjust for daratumumab monotherapy

3.8 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 in combination 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 3.12). At technical engagement before the committee's first meeting, the company updated the landmark analysis using the latest data cut from CASSIOPEIA, but could not use inverse probability weighting to adjust the results of the updated landmark analysis for re-randomising patients to daratumumab maintenance (which would not happen in practice; 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 may be biased because of informative censoring. However, it deemed that the direction of the bias was unclear and affected both treatment arms. After the first committee meeting, the company accessed the individual patient data it needed to adjust the results of its landmark analysis for re-randomisation to daratumumab maintenance using an inverse probability of censoring weighting (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 improved slightly for overall survival for daratumumab in combination compared with bortezomib plus thalidomide and dexamethasone for people with minimal residual disease and worsened for people without minimal residual disease. The ERG commented that although it could not validate the analysis, the IPCW-adjusted landmark analysis appeared reasonable. At the third committee meeting, the company explained that it considered residual confounding unlikely because people in phase 2 of the trial were re-randomised before having maintenance treatment or observation. The committee concluded that the company's IPCW-adjusted landmark analysis is likely to be less biased than the censoring-adjusted landmark analysis and more appropriate for decision making.

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

3.9 The committee was aware that the company extrapolated progression-free survival and overall survival in its economic model based on the presence (positivity) or absence (negativity) of minimal residual disease at the landmark timepoint (see section 3.8). The clinical experts stated that, although minimal residual disease is not routinely measured in clinical practice and 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. The ERG agreed that having no minimal residual disease is likely to predict survival outcomes better 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 3.12), it was reasonable to split patients into those with and without minimal residual disease.

Adverse events

The adverse event profile of daratumumab in combination is acceptable

3.10 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 in combination 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 in combination happened in around 35% of patients. The adverse events were manageable, with a frequency of severe (grade 3 or 4) events (3.5%), 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 in combination was acceptable.

Indirect comparisons

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

3.11 There are no trials directly comparing daratumumab in combination with bortezomib plus dexamethasone, with or without cyclophosphamide. Therefore, the company did matching-adjusted indirect comparisons and used these to estimate the relative effectiveness of the 2 regimens. The company also estimated the relative effectiveness 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 for the comparison with bortezomib plus cyclophosphamide and dexamethasone, the sample size was smaller, 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 experts' 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

3.12 The company presented a partitioned survival model comprising 3 health states (pre-progression, progressive disease and death) to estimate the cost effectiveness of daratumumab in combination 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 3.8). 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:

- **Step 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 3.15).
- **Step 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 and who have standard care (see section 3.13). 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.
- **Step 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.

- Step 4: The company applied the hazard ratios from the landmark analysis (see section 3.8) 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 in combination, split by minimal residual disease status.

- Step 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 who had bortezomib plus thalidomide and dexamethasone (see section 3.15), and the results of the meta-analysis (see section 3.13) and landmark analysis (see section 3.8). 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 of 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 minimally affects results

3.13 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, that 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.

It is likely people without residual disease would have a complete response over time and the company's definition of minimal residual disease is appropriate

3.14 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

Modelled survival for people who have bortezomib plus thalidomide and dexamethasone should be based on IPCW-adjusted landmark analyses

3.15 The company extrapolated progression-free survival and overall survival for people with minimal residual disease who have 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 extrapolations of survival to account for people switching to maintenance with daratumumab monotherapy in CASSIOPEIA using a censoring approach and an IPCW approach (see section 3.8). 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 maintenance with daratumumab monotherapy would bias the overall survival results (see section 3.8). 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 3.8). 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 survival 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 because of 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 3.8). The committee also appreciated in its third meeting that the re-randomisation in the CASSIOPEIA trial would minimise residual confounding in adjusted analyses because of the randomisation. 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.

The estimate of long-term survival for people who have bortezomib plus thalidomide and dexamethasone reflects clinical practice

3.16 At the third committee meeting, the company reiterated its belief that the model overestimates survival for people who have bortezomib plus thalidomide and dexamethasone so any cost-effectiveness results underestimate cost effectiveness. The company noted that the revised base case now included lenalidomide maintenance (see section 3.5) and that the predicted survival rate at 5 years in the model exceeded that seen in the Myeloma XI trial. The ERG explained that validating modelled extrapolations with clinical opinion and data from external sources does not entirely resolve uncertainty. The committee considered the results from: the company's revised base case, CASSIOPEIA, the GIMEMA study and Myeloma XI. It noted that the differences between the survival estimates in the company's revised base case and those seen in the

Myeloma XI trial were relatively small. The committee concluded that estimates for long-term survival for people who have bortezomib plus thalidomide and dexamethasone are likely to reflect clinical practice.

The duration of the treatment effect for daratumumab in combination is unknown, but it is reasonable to assume it will be maintained long term

3.17 Treatment effect waning refers to if 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 presented evidence that people who have daratumumab have deeper responses, which is associated with improved survival outcomes. The company presented evidence from the GIMEMA-MMY-3006 trial, which investigated the efficacy of bortezomib plus dexamethasone compared with bortezomib plus dexamethasone and thalidomide in people with previously untreated symptomatic and measurable myeloma. The company explained that the results support maintaining a treatment effect driven by deeper responses. Clinical experts explained that they expect a similar effect for daratumumab in combination. The ERG noted that there was limited evidence to support a lifetime treatment effect with daratumumab in combination, and that the company's assumption was optimistic. It presented scenarios where the treatment effect lasted only 5 years, and a scenario where the treatment effect declined between 5 and 10 years and stopped at 10 years. The ERG modelled this by setting the disease progression and mortality rates of daratumumab in combination as equal to that of bortezomib plus dexamethasone and thalidomide from the set timepoint, for example, 5 years, onwards. The committee understood that including a treatment effect that wanes in the model considerably affects the cost-effectiveness results. At the first committee meeting, the committee agreed that it was reasonable to consider scenarios in which the treatment effect declined between 5 and 10 years. In response to consultation, the company presented scenarios for treatment waning but continued to assume a lifetime treatment effect for daratumumab in combination in its base case. At the second committee meeting, the clinical lead

for the Cancer Drugs Fund noted that results from CASSIOPEIA part 2 suggested the effect of adding daratumumab to bortezomib plus thalidomide and dexamethasone had not waned. The committee considered the possibility that because people have first-line daratumumab in combination 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 in combination would have been delivered, followed by high-dose chemotherapy, and there would be no opportunity for a gradual loss of effect over time. At the third committee meeting, the company presented a revised base case that assumed a lifetime treatment effect for daratumumab in combination but included treatment waning for subsequent lenalidomide maintenance therapy (as per the preferred assumptions from NICE's technology appraisal guidance on lenalidomide maintenance treatment after an autologous stem cell transplant for newly diagnosed multiple myeloma; see section 3.5). The company reiterated that the long-term outcomes for people who had daratumumab in combination were driven by a deeper post-consolidation response and not a conventional treatment effect. The ERG explained that the model structure 'hard wires' a treatment effect and that the evidence from CASSIOPEIA for additional survival benefits within the minimal residual disease groups are uncertain with wide confidence intervals. The clinical lead for the Cancer Drugs Fund explained that having daratumumab in combination could deliver a long or even lifetime treatment effect. He explained that people who have daratumumab in combination are more likely to achieve minimal residual disease negative status after induction and that evidence suggests these people are likely to experience better long-term outcomes after chemotherapy and autologous stem cell transplant. The committee acknowledged that it was clinically plausible that people who had daratumumab in combination would have a different natural history of disease after treatment, but recalled the uncertainty around the additional survival benefits within the minimal residual disease groups. The committee considered that the scenarios exploring treatment waning showed different survival outcomes for people who had daratumumab in combination and which showed the range of possible cost-effectiveness estimates. However, the committee concluded that, based on the evidence presented to it, it was reasonable to assume that the effect of deepening a response would be maintained over a lifetime for daratumumab in combination.

Lenalidomide maintenance

Previous treatment with daratumumab in combination is likely to extend maintenance therapy with lenalidomide and extend survival

3.18 The committee requested that the company include lenalidomide maintenance treatment after consolidation with or without daratumumab in the company's economic modelling (see section 3.5). At the second committee meeting, the company included the costs of lenalidomide maintenance but did not include any benefit of lenalidomide maintenance. At the third committee meeting, the company presented its revised base-case and scenario analyses, which included both costs and benefits of lenalidomide maintenance. The company based the duration of lenalidomide maintenance treatment on the median time to stopping lenalidomide seen in the subgroup of the Myeloma XI trial for whom a transplant was suitable. Myeloma XI was a phase 3 trial and the key clinical evidence was from NICE's technology appraisal guidance on lenalidomide maintenance treatment after an autologous stem cell transplant for newly diagnosed multiple myeloma, which compared lenalidomide maintenance treatment with observation. The company modelled an 'uplift' (improvement) in progression-free survival for this appraisal using the observed hazard ratio by minimal residual disease status in the Myeloma XI trial. The company assumed no survival benefits associated with lenalidomide maintenance in its revised base case; the costs and survival benefits of lenalidomide maintenance were equal for both arms. The company also provided a scenario analysis that included a longer treatment duration on lenalidomide maintenance for the subgroup who were minimal residual disease negative in the daratumumab in combination arm. In a scenario analysis, this subgroup had 18 additional cycles of lenalidomide maintenance and a survival benefit for both progression-free and overall survival. The company modelled this by improving the hazard ratios by 20% in the minimal residual disease negative subgroup in the daratumumab in combination arm. The clinical lead for the Cancer Drugs Fund explained that adding daratumumab to induction and consolidation treatment would likely increase the duration of lenalidomide maintenance and so it was reasonable to assume it prolonged overall survival. The committee considered that the company's scenario analysis was more likely to reflect clinical practice. The ERG noted that the duration of additional treatment and any associated benefits were uncertain because of limited evidence. The ERG provided additional

scenario analyses that tested the sensitivity of results to the duration and associated benefits of lenalidomide maintenance after daratumumab in combination. The committee noted that amending the duration or additional benefit of lenalidomide maintenance after daratumumab in combination modestly affected the incremental cost-effectiveness ratio (ICER), and concluded that the company scenario that included a 20% improvement in the hazard ratios for overall and progression-free survival was reasonable for decision making.

Age at the start of induction treatment

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

3.19 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 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 fourth line

3.20 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 or may not be commissioned in future. To reflect this, the company omitted treatments recommended for use in the Cancer Drugs Fund. It further 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 avoid offering panobinostat plus bortezomib and dexamethasone. 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

Daratumumab in combination is cost effective when compared with bortezomib, thalidomide and dexamethasone

3.21 The committee recalled that its preferred assumptions were:

- including lenalidomide maintenance to reflect NHS practice (see section 3.5 and section 3.18)
- using a landmark analysis adjusted for re-randomisation to daratumumab maintenance using the company's IPCW approach (see section 3.8)
- basing the long-term survival modelling on the company's approach using a landmark analysis, split by minimal residual disease status (see section 3.12)
- using the IPCW-adjusted landmark analysis to model survival for people having bortezomib plus thalidomide and dexamethasone (see section 3.15)
- modelling a daratumumab lifetime treatment effect (see section 3.17)
- using a mean age at the start of induction treatment based on evidence from Public Health England (see section 3.19)

- omitting panobinostat plus bortezomib and dexamethasone as a treatment at third or fourth line (see section 3.20).

The committee agreed that the most plausible ICER was within the range NICE normally considers an acceptable use of NHS resources, that is £20,000 to £30,000 per quality-adjusted life year (QALY) gained. The figure cannot be reported because it includes confidential discounts for daratumumab, bortezomib, dexamethasone and some of the treatments offered second line and beyond. The committee concluded that daratumumab in combination is a cost-effective use of NHS resources compared with bortezomib plus thalidomide and dexamethasone.

Equalities and innovation

3.22 The ERG raised 2 potential equalities issues. The first was that daratumumab in combination should not be restricted to people aged up to 65, which reflects 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 or Caribbean family background. The committee did not restrict its discussion to an age-restricted population. Issues related to differences in prevalence or incidence of a disease are not equality issues if they do not affect access to a technology.

3.23 The company stated that daratumumab in combination was innovative because it has a different mechanism of action from other available treatments. The committee agreed that although the technology would likely improve survival, there were no additional gains in health-related quality of life over those already included. In response to consultation, patient experts explained that they believed daratumumab was innovative. They suggested that people having daratumumab in combination may benefit psychologically from knowing they have a higher chance of achieving minimal residual disease negative status. However, the committee concluded that it had not been presented with evidence to change its view that there were no additional gains in health-related quality of life over those already included in the QALY calculations.

Conclusion

Daratumumab in combination is recommended for routine use in the NHS

3.24 Daratumumab in combination is more clinically effective than standard care, bortezomib plus thalidomide and dexamethasone for untreated multiple myeloma when a stem cell transplant is suitable. The committee agreed that the most plausible ICER for daratumumab in combination compared with bortezomib plus thalidomide and dexamethasone was within the range considered to be a cost-effective use of NHS resources. It concluded that daratumumab in combination should be recommended for routine use as an option for untreated multiple myeloma when a stem cell transplant is suitable.

4 Implementation

4.1 Section 7 of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.

4.2 Chapter 2 of Appraisal and funding of cancer drugs from July 2016 (including the new Cancer Drugs Fund) – a new deal for patients, taxpayers and industry states that for those drugs with a draft recommendation for routine commissioning, interim funding will be available (from the overall Cancer Drugs Fund budget) from the point of marketing authorisation, or from release of positive draft guidance, whichever is later. Interim funding will end 90 days after positive final guidance is published (or 30 days in the case of drugs with an Early Access to Medicines Scheme designation or fast track appraisal), at which point funding will switch to routine commissioning budgets. The NHS England and NHS Improvement Cancer Drugs Fund list provides up-to-date information on all cancer treatments recommended by NICE since 2016. This includes whether they have received a marketing authorisation and been launched in the UK.

4.3 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final appraisal document.

4.4 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has untreated multiple myeloma and the doctor responsible for their care thinks that daratumumab plus bortezomib, thalidomide and dexamethasone, is the right treatment, it should be available for use, in line with NICE's recommendations.

5 Appraisal committee members and NICE project team

Appraisal committee members

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

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

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

NICE project team

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

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Accreditation