NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Draft guidance consultation

Daratumumab with lenalidomide and dexamethasone for untreated multiple myeloma when stem cell transplant is unsuitable

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

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

The evaluation 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 age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Issue date: February 2023

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- After considering these comments, the committee will prepare the final draft guidance.
- Subject to any appeal by stakeholders, the final draft guidance may be used as the basis for NICE's guidance on using daratumumab with lenalidomide and dexamethasone in the NHS in England.

For further details, see NICE's manual on health technology evaluation.

The key dates for this evaluation are:

- Closing date for comments: 14 March 2023
- Second evaluation committee meeting: 7 June 2023
- Details of membership of the evaluation committee are given in section 4.

1 Recommendations

1.1 Daratumumab with lenalidomide and dexamethasone is not recommended, within its marketing authorisation, for untreated multiple myeloma in adults, when an autologous stem cell transplant is unsuitable.

1.2 This recommendation is not intended to affect treatment with daratumumab plus lenalidomide 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

Adults with multiple myeloma usually have lenalidomide plus dexamethasone as a first treatment when an autologous stem cell transplant is unsuitable. But, sometimes bortezomib plus an alkylating agent (cyclophosphamide or melphalan) and a corticosteroid (dexamethasone or prednisolone) might be more suitable. Daratumumab plus lenalidomide and dexamethasone could be an alternative first treatment when an autologous stem cell transplant is unsuitable.

Clinical trial evidence shows that daratumumab plus lenalidomide and dexamethasone increases the amount of time people have before their condition gets worse and how long they live for compared with lenalidomide plus dexamethasone. But based on the clinical trial evidence it is uncertain by how much daratumumab plus lenalidomide and dexamethasone increases how long people live for. There is no direct evidence comparing daratumumab plus lenalidomide and dexamethasone with bortezomib plus an alkylating agent and a corticosteroid, but indirect comparisons suggests that it is more effective.

The most likely cost-effectiveness estimates for daratumumab plus lenalidomide and dexamethasone are uncertain and substantially above what NICE considers to be an acceptable use of NHS resources. So, it is not recommended.

2 Information about daratumumab

Marketing authorisation indication

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

Dosage in the marketing authorisation

2.2 The dosage schedule for both injection and infusion formulations are available in the summary of product characteristics for daratumumab.

Price

2.4 The list prices for daratumumab (excluding VAT; BNF online, accessed January 2023) are:

- £4,320 per 1,800 mg/15 ml solution for injection vial
- £360 per 100 mg/5 ml concentrate for solution for infusion vial
- £1,440 per 400 mg/20 ml concentrate for solution for infusion vial.

2.5 The company has a commercial arrangement. This makes daratumumab available to the NHS with a discount and it would have also applied to this indication if the technology had been recommended. The size of the discount is commercial in confidence. It is the company's responsibility to let relevant NHS organisations know details of the discount.

2.6 The list price for lenalidomide is £3,057.60 per 21-pack of 25 mg capsules (excluding VAT; BNF online, accessed January 2023). List prices for different doses are available on the BNF webpage for medicinal forms of lenolidomide. There is a discount for lenalidomide agreed with the Commercial Medicines Unit. The prices agreed through the framework are commercial in confidence.

2.7 The list price of dexamethasone is £19.62 per 50-pack of 4 mg capsules (excluding VAT; electronic market information tool (eMIT) online, accessed January 2023). List prices for different doses are available on the BNF webpage for medicinal forms of dexamethasone. Costs may vary in different settings because of negotiated procurement discounts.

3 Committee discussion

The evaluation committee considered evidence submitted by Janssen, a review of this submission by the external assessment group (EAG), and responses from stakeholders. See the committee papers for full details of the evidence.

The condition

A new treatment option

3.1 Multiple myeloma is a chronic condition that affects how long people live and quality of life. Patient experts explained that multiple myeloma is a relapsing and remitting disease and can include severe symptoms. They also explained that because multiple myeloma becomes resistant to treatment the most effective treatment should be given as early as possible in the treatment pathway to achieve the deepest response and prolong remission. Treatment options for people with multiple myeloma depend on if a stem cell transplant is suitable, how many previous lines of treatment a person has had, the type of treatments they have had, the response to these treatments, and patient preferences. For someone with a new diagnosis of multiple myeloma, if a stem cell transplant is unsuitable, available options are:

- lenalidomide plus dexamethasone if the person is unable to tolerate or has contraindications to thalidomide (NICE's technology appraisal guidance on lenalidomide plus dexamethasone for previously untreated multiple myeloma)
- bortezomib in combination with an alkylating agent and a corticosteroid if the person is unable to tolerate or has contraindications to

thalidomide (NICE's technology appraisal guidance on bortezomib and thalidomide for the first-line treatment of multiple myeloma)

- thalidomide in combination with an alkylating agent and a corticosteroid (NICE's technology appraisal guidance on bortezomib and thalidomide for the first-line treatment of multiple myeloma).

The clinical experts noted that daratumumab has already shown benefits in terms of survival when used at later stages in the treatment pathway, so its use in previously untreated multiple myeloma would be welcome. The committee concluded that daratumumab with lenalidomide and dexamethasone would be a welcomed treatment option by clinicians and people with multiple myeloma.

Clinical management

Comparators

3.2 NICE's final scope for this appraisal lists all currently available treatment options as comparators (see section 3.1). In its submission the company provided evidence for the treatment effectiveness of daratumumab plus lenalidomide and dexamethasone compared with:

- lenalidomide plus dexamethasone
- 2 bortezomib combination treatments (bortezomib plus cyclophosphamide and dexamethasone [BCD] and bortezomib plus melphalan and prednisone [BMP])
- 2 thalidomide combination treatments (thalidomide plus cyclophosphamide and dexamethasone and thalidomide plus melphalan and prednisone).

The company explained that thalidomide combination treatments are rarely used within the NHS because of their toxicity profiles. Because of this, thalidomide combination treatments were only included in its submission for completeness. The company noted that only lenalidomide plus dexamethasone and bortezomib combination treatments were the

main comparators considered in its submission. However, the company suggested that lenalidomide plus dexamethasone is currently the preferred treatment for standard care and should be considered the most relevant comparator. The clinical experts agreed that thalidomide combination treatments are very rarely used. In addition, they explained that lenalidomide plus dexamethasone is the most widely used treatment option in clinical practice and accounts for about 70% of first-line treatment. Clinical experts estimated that less than 30% of people have bortezomib combination treatments. But it was noted that there are many regional variations in use of treatment options. The committee concluded that lenalidomide plus dexamethasone is the main comparator for this appraisal. But that bortezomib combination treatments should also be considered.

Clinical evidence

Data sources

3.3 Clinical evidence for daratumumab plus lenalidomide and dexamethasone compared with lenalidomide plus dexamethasone came from the MAIA trial. MAIA is an ongoing, randomised, open-label, multicentre, phase 3 trial. The population included adults with previously untreated multiple myeloma who were not eligible for autologous stem cell transplant. The company reported data from the trial's primary data cut (September 2018, median follow up 28 months) and subsequent data cut (October 2021, median follow up 64.5 months). The primary outcome of the MAIA trial was progression-free survival. At the later data cut, daratumumab plus lenalidomide and dexamethasone reduced the risk of disease progression and death by 45% (hazard ratio [HR] 0.55, 95% confidence interval [CI] 0.45 to 0.67) compared with lenalidomide plus dexamethasone. Median progression-free survival was 61.9 months in the daratumumab plus lenalidomide and dexamethasone group and 34.4 months in the lenalidomide plus dexamethasone group. The EAG considered that the data for progression-free survival was mature and showed a clear benefit

for daratumumab plus lenalidomide and dexamethasone. The company also provided data for other secondary endpoints including overall survival. At the later data cut, daratumumab plus lenalidomide and dexamethasone reduced the risk of death by 34% (HR 0.66, 95% CI 0.53 to 0.83) compared with lenalidomide plus dexamethasone. Median overall survival was not reached in the daratumumab plus lenalidomide and dexamethasone group and was 65.5 months in the lenalidomide plus dexamethasone group. The EAG considered that the overall survival data was relatively immature (see section 3.5). The company explained that a more recent data cut was completed in October 2022. But, because of timings, this could not be included within the appraisal and considered by the committee at this time. The committee concluded that the MAIA trial has shown that daratumumab plus lenalidomide and dexamethasone is a clinically effective treatment, but that longer-term overall survival is uncertain.

Generalisability

3.4 The MAIA trial included people from the United Kingdom and 13 other countries, which meant some people had subsequent treatments not routinely commissioned by the NHS. Treatments not routinely commissioned by the NHS included treatments recommended for use in the Cancer Drugs Fund and treatments not recommended in NICE technology appraisal guidance. The company did an inverse probability of censoring weights (IPCW) analysis to adjust the overall survival estimates to account for subsequent treatments not routinely commissioned by the NHS. The company stated that the results of the IPCW analysis showed an even greater overall survival benefit for daratumumab plus lenalidomide and dexamethasone compared with lenalidomide plus dexamethasone. The actual numbers are considered confidential by the company and cannot be reported here. However, the company used the unadjusted overall survival extrapolations in its base-case economic model. It said that this could be conservative and may underestimate the relative treatment efficacy of daratumumab plus lenalidomide and

dexamethasone compared with lenalidomide plus dexamethasone. The EAG explained that the IPCW analysis made strong assumptions that could not be validated and that it preferred the unadjusted overall survival extrapolations. The EAG noted that in the MAIA trial, the proportion of people having treatments not routinely commissioned was similar across arms at second line but differed at third line. It agreed with the company that the results from the MAIA trial may be conservative. The EAG considered that the characteristics of people in the trial were broadly comparable to those of people seen in NHS clinical practice. The committee agreed that the population in MAIA is generalisable to NHS clinical practice. However, it also noted that the subsequent treatments used in MAIA were likely to differ from those offered in NHS clinical practice. The committee considered that this would impact generalisability and lead to uncertainty in the long-term treatment effect of daratumumab plus lenalidomide and dexamethasone (see section 3.10). Despite the uncertainty, the committee considered that the MAIA trial represented the best available evidence.

Long-term effectiveness

3.5 The MAIA trial is ongoing. At the October 2021 data cut, median overall survival had only just been met for the lenalidomide plus dexamethasone arm (65.5 months) and had not been met for the daratumumab plus lenalidomide and dexamethasone arm. The EAG considered that the overall survival data is relatively immature. The EAG noted that overall survival is a key outcome and that daratumumab plus lenalidomide and dexamethasone is very likely to show a long-term overall survival benefit. But it is uncertain how the hazard ratio for daratumumab plus lenalidomide and dexamethasone compared with lenalidomide and dexamethasone changes after the follow up in the most recent data cut. The EAG suggested that longer follow-up data from MAIA may help to resolve the uncertainty. The company considered the available data to be sufficiently mature and that additional follow-up data would not resolve the uncertainty. It highlighted how multiple models produced similar long-term

estimates of overall survival. It also noted that the follow up from MAIA was similar to the follow up in the FIRST trial, which was the main source of clinical evidence in NICE's technology appraisal guidance on lenalidomide plus dexamethasone for previously untreated multiple myeloma.The EAG explained that the estimates produced by the models could change with additional follow-up data. It also thought that because daratumumab plus lenalidomide and dexamethasone has longer survival than lenalidomide plus dexamethasone, longer follow up is needed. The clinical experts explained that from a clinical perspective MAIA showed clear evidence of a survival benefit. The committee accepted that from the current follow up MAIA showed a survival benefit. But it noted that with the current data cut, median overall survival was only just being reached in the lenalidomide plus dexamethasone arm. Because of this, the overall survival modelling was uncertain and would benefit from longer follow-up data from MAIA. It recalled that further data that could be incorporated into the appraisal is now available and that this may reduce uncertainty (see section 3.3).

Indirect treatment comparison

Indirect comparison with BMP

3.6 The company did not identify any direct evidence comparing the efficacy of daratumumab plus lenalidomide with BMP. So, it used a propensity score based inverse probability weight approach using data from MAIA and the ALCYONE trial. ALCYONE is a phase 3 study comparing daratumumab plus BMP with BMP alone in people with newly diagnosed multiple myeloma ineligible for autologous stem cell transplant. Individual person data was used to adjust the BMP alone population from ALCYONE to the daratumumab plus lenalidomide and dexamethasone population from MAIA. The company considers the results from the analysis to be confidential. The EAG noted that the inverse probability weight approach relies on the assumption that all prognostic factors and effect modifiers have been correctly adjusted for. It explained that this is a

strong assumption, particularly given that not all prognostic factors might have been reported in both trials. Because of this, the EAG preferred a parametric network meta-analysis (NMA) approach, which used randomised evidence. In response to technical engagement, the company maintained that the inverse probability weight approach was the most robust approach. It suggested that the parametric NMA was associated with uncertainty because of the long chain of evidence. But it revised its base case to use the parametric NMA in line with the EAGs preferred approach. The committee concluded that the parametric NMA approach was appropriate for decision making.

Indirect comparison with BCD

3.7 The company did not identify any direct evidence comparing the efficacy of daratumumab plus lenalidomide and dexamethasone with BCD or any evidence that could be used to include BCD in the NMA. So, the company did a matching-adjusted indirect treatment comparison (MAIC) of BMP compared with BCD. In the MAIC, the BMP alone arm of ALCYONE was weighted to match the population in an observational study of BCD in people with newly diagnosed multiple myeloma ineligible for autologous stem cell transplant. The company considered the results of the MAIC to be inconclusive with progression-free survival and overall survival hazard ratios close to 1 and wide 95% confidence intervals crossing 1. The actual numbers are considered confidential by the company and cannot be reported here. Based on the results of the MAIC, naive comparisons from observation studies and clinical expert opinion, the company assumed clinical equivalence of BCD to BMP. The EAG considered that the observational studies did not provide evidence of equivalence and noted that the clinical expert opinion was not elicited using a formal process. The EAG stated that a non-inferiority approach should have been used to assess equivalence. It noted the wide confidence intervals and acknowledged that the MAIC may be associated with bias. This was because of difficulties in adjusting for important prognostic factors or effect modifiers and one of the studies included was found to be at critical risk of

bias. However, it preferred to use the hazard ratios from the MAIC to assess the efficacy of BCD. Clinical experts explained that BCD is generally more tolerable so has a higher relative dose intensity (RDI) compared with BMP. But they considered that, in essence, BMP and BCD are equivalent. The EAG considered that the higher RDI of BCD supports the assumption of greater relative treatment efficacy compared with BMP. The committee concluded that the company had not demonstrated equivalence. It recognised the uncertainty but was satisfied that the decision did not materially impact the fully incremental analysis cost-effectiveness results.

Economic model

Company's modelling approach

3.8 The company chose a partitioned survival model to estimate the cost effectiveness of daratumumab plus lenalidomide and dexamethasone. The model included 3 health states: progression free, progressed disease and death. The probability of being in a given health state was calculated using the overall survival and progression-free survival curves. The model cycle length was 4 weeks and the time horizon was 26 years. The company said that the model structure allowed intuitive incorporation of the progression-free survival and overall survival data that was collected from the key trials. The EAG agreed that using a partitioned survival model was appropriate. The committee concluded that the model structure is acceptable and is similar to previous models used for multiple myeloma.

Time on treatment

3.9 People may stop taking daratumumab plus lenalidomide and dexamethasone for reasons other than disease progression. To account for this, the company used time to treatment discontinuation data to estimate treatment duration in the model. For daratumumab plus lenalidomide and dexamethasone, time to treatment discontinuation was

extrapolated using data from MAIA. The company used a Gompertz parametric curve in its base case. The company explained that it preferred a Gompertz curve based on statistical fit and its validity compared with progression-free survival. It also explained that the Gompertz curve sat within the clinically plausible range and between the generalised gamma (lowest Akaike information criterion [AIC]) and exponential (lowest Bayesian information criteria [BIC]) curves. The EAG explained that it had done scenario analysis and the results were sensitive to the choice of curve used to extrapolate. It used an exponential curve in its base case because it had the best statistical fit (lowest BIC). In response to technical engagement the company presented the results of a piecewise Cox model analysing the relationship between progression-free survival and time to treatment discontinuation. It noted that the hazard ratio point estimates decreased over the trial follow-up period. The company believed that the difference between progression-free survival and time to treatment discontinuation would continue to widen overtime and may be even larger in the real-world setting. The EAG stated that both the Gompertz and exponential curves showed a reducing hazard ratio over time. It noted that there was a high level of overlap of the confidence intervals from the piecewise Cox model. The EAG considered that how the hazard ratio changed beyond the follow-up period was uncertain and that longer follow up from MAIA could help reduce the uncertainty. The clinical experts stated that they expected the proportion of people who stopped taking daratumumab plus lenalidomide and dexamethasone before progression after the follow-up period in MAIA to be small. They explained that those still having treatment would be those who find the treatment most tolerable. The company suggested that the most recent MAIA data cut (October 2022) supports the use of the Gompertz curve based on statistical fit. The committee recalled that this data cut was not currently included within this appraisal. Based on the appraised evidence, the committee concluded that the exponential curve was most appropriate for decision making. But it said that it would reconsider its decision if

evaluation of the most recent data cut suggested another extrapolation is more appropriate.

Long-term extrapolation

3.10 The company's model used independently fitted parametric curves to estimate overall survival in the daratumumab plus lenalidomide and daratumumab plus lenalidomide and dexamethasone arms. These curves diverged from each other over time, suggesting that the survival benefit with which daratumumab plus lenalidomide and dexamethasone is associated increases over time. The committee noted that beyond 12 years of follow up, the mortality rate in the daratumumab plus lenalidomide and dexamethasone population needed a cap to ensure it did not fall below the general population mortality rate. The company explained that the results from MAIA showed that deeper and longer sustained responses were achieved after daratumumab plus lenalidomide and dexamethasone and that the treatment effect improved at subsequent data-cuts. The NICE manual states that when extrapolating treatment effects beyond observed data, 'alternative scenarios should also be routinely considered to compare the implications of different methods for extrapolation of the results.' Also, scenarios 'where treatment effect stops or diminishes gradually over time' should be considered. The committee noted that the company had only presented 1 scenario, which assumed that the survival benefit for daratumumab plus lenalidomide and dexamethasone continued to improve throughout the time horizon. The EAG explored this issue through a series of analyses, including:

- Scenarios with the benefit of daratumumab plus lenalidomide and dexamethasone declining linearly over a further period until the risk of death was equivalent to the lenalidomide plus dexamethasone population.
- In response to a request from the committee, a scenario in which the treatment effect remained constant after the point of the most recent MAIA data cut, by modelling a fixed hazard ratio.

In its base case, the EAG applied waning of the treatment effect linearly starting at 12 years for a duration of 7 years. This meant that an improvement in treatment effect was assumed up until 12 years. After this the hazard ratio for daratumumab plus lenalidomide and dexamethasone compared with lenalidomide plus dexamethasone waned towards 1 over 7 years (with mortality rates of both arms being equivalent at this point). The company suggested there was no evidence for waning of the treatment effect from the MAIA study or that would be expected from the mechanism of action of daratumumab. Also, the company explained that data for daratumumab in later lines of multiple myeloma did not show waning of the treatment effect. The company also noted that waning of the treatment effect was not included in previous technology appraisals of daratumumab and other multiple myeloma treatments (for example NICE's technology appraisal guidance on daratumumab in combination for untreated multiple myeloma when a stem cell transplant is suitable). The clinical experts considered that there was no evidence or biological justification to support waning of the treatment effect. The EAG accepted that daratumumab plus lenalidomide and dexamethasone had shown a survival benefit in MAIA and that depth of response is a plausible mechanism driving this survival benefit. However, it also noted the uncertainty of the long-term treatment effect and suggested that data from using daratumumab in later lines of treatment showed some attenuation of treatment effect towards the end of the follow-up period. The committee considered each of the scenarios available and noted that:

- The company base-case was not outside the range of plausible outcomes, but it was the most optimistic assumption possible.
- The EAG base-case survival curves had an obvious drop at the point at which attenuation of treatment effect began. It agreed that this is unlikely to represent experiences in clinical practice. However, it noted that the EAG's scenarios enabled it to explore results with a more conservative extrapolated treatment effect, compared with the optimistic company base case.

- The scenario with constant treatment effect was supported by the company's piecewise Cox model, which showed that overall survival hazard ratios remained stable over the 4- to 6-year period, indicating a constant survival benefit.

The committee noted that, although the term 'waning' had been used within the appraisal materials, its concern was not that it expected the effectiveness of daratumumab plus lenalidomide and dexamethasone to get worse over time. Instead, it was not convinced that there is evidence to support the company's assumption of a constantly improving treatment effect throughout the time horizon. It recalled that in the fixed hazard ratio scenario it requested that the treatment effectiveness remained constant at the maximum level supported by empirical data. The committee also considered it possible that there could be an attenuation of the treatment effect where the relative treatment effect reduced overtime but where the hazard ratio for daratumumab plus lenalidomide and dexamethasone compared lenalidomide plus dexamethasone did not reach 1. The committee also noted that long-term survival outcomes are impacted by subsequent treatments. It recalled that there was uncertainty about whether subsequent treatment used in MAIA reflected what is likely to happen in clinical practice. It was not convinced that this had been reflected in the model. For these reasons, the committee concluded that the company's base case could potentially be plausible, but it is highly optimistic and associated with high uncertainty. It noted that the most recent MAIA data cut (October 2022) could provide a small amount of additional evidence to help inform the extrapolation, but recalled this data cut was not currently included within this appraisal.

Costs of subsequent treatments

3.11 The company's model included the costs of second- and third-line treatments given after first-line treatment. Subsequent treatment costs were included in the progressed disease health state as a single cost applied in all cycles. The costs were calculated using costs and average

time on treatments weighted by the estimated market share of each of the subsequent treatments. The market share estimates used were the average of values elicited from clinical experts. The EAG noted that in clinical practice there is a wide variation in the treatments given after first-line treatment and that the market share estimates provided by the clinical experts differed. It provided scenario analyses using the market shares elicited from each clinical expert separately. The EAG considered that the company's approach was acceptable but that the market share of subsequent treatments was a key unresolved uncertainty. The committee acknowledged the uncertainty but concluded that using the company's estimates of the market share of treatments used at second and third line were acceptable for decision making.

Inclusion of treatments only available through the Cancer Drugs Fund

3.12 The company's model included the functionality to include and exclude treatments recommended for use in the Cancer Drugs Fund. The company noted that subsequent treatments recommended in the Cancer Drugs Fund included daratumumab plus bortezomib and dexamethasone used at second line and ixazomib plus lenalidomide and dexamethasone used at third line. The NHS England Cancer Drugs Fund clinical lead explained that treatments recommended for use in the Cancer Drugs Fund are routinely used by clinicians. He stated that most people who have lenalidomide plus dexamethasone at first line will go on to have daratumumab plus bortezomib and dexamethasone at second line. The committee recalled that the NICE Cancer Drugs Fund position statement specifies that treatments recommended for use in the Cancer Drugs Fund cannot be considered established practice and therefore should not be included in a treatment sequence. But the committee was also aware that there are ongoing reviews looking at NICE's technology appraisal guidance on daratumumab with bortezomib and dexamethasone for previously treated multiple myeloma and NICE's technology appraisal guidance on ixazomib with lenalidomide and dexamethasone for treating relapsed or refractory multiple myeloma. The committee concluded that

treatments recommended for use in the Cancer Drugs Fund should not be considered as subsequent treatments. But it said that if treatments currently included within the Cancer Drugs Fund are recommended for routine practice after their respective ongoing reviews and are considered established clinical practice, the modelling could be updated to incorporate these as subsequent treatments.

Cost-effectiveness estimates

Acceptable ICER

3.13 NICE's manual on health technology evaluation notes that above a most plausible incremental cost-effectiveness ratio (ICER) of £20,000 per quality-adjusted life year (QALY) gained, decisions about the acceptability of a technology as an effective use of NHS resources will take into account the degree of certainty around the ICER. The committee will be more cautious about recommending a technology if it is less certain about the ICERs presented. Because of confidential commercial arrangements for daratumumab, lenalidomide, melphalan and post-progression treatments, the ICERs are confidential and cannot be reported here.

The committee noted a number of uncertainties, specifically:

- the relative immaturity of the overall survival data for daratumumab plus lenalidomide and dexamethasone (see section 3.5)
- the relative effectiveness of bortezomib combination treatments (see section 3.7)
- the appropriate parametric curve for time to treatment discontinuation for daratumumab plus lenalidomide and dexamethasone (see section 3.9)
- the attenuation of the treatment effect (see section 3.10)
- the market share of second- and third-line treatments (see section 3.11).

The committee also took into account that MAIA has shown that daratumumab plus lenalidomide and dexamethasone is a clinically effective treatment. It also heard from patient and clinical experts about the importance of having the most effective treatment possible at first line and that people have fewer treatment options when stem cell transplant is unsuitable. The committee considered the uncertainty, particularly relating to the long-term treatment attenuation. It concluded that the ICER would have to be substantially below £30,000 per QALY gained to be considered a cost-effective use of NHS resources and accepted for routine commissioning.

Company and EAG cost-effectiveness estimates

3.14 Because of confidential commercial arrangements for daratumumab, lenalidomide, melphalan and post-progression treatments, the exact cost-effectiveness results are confidential and cannot be reported here. The committee's preferred assumptions were:

- including lenalidomide plus dexamethasone as the main comparator but also considering bortezomib combination treatments (see section 3.2)
- using the parametric NMA approach to inform the comparison with BMP (see section 3.6)
- using the hazard ratios from the MAIC to inform the comparison with BCD (see section 3.7)
- using an exponential curve to model time to treatment discontinuation for daratumumab plus lenalidomide and dexamethasone based on currently available evidence (see section 3.9)
- using the company's estimates of the market share of treatments used at second and third line (see section 3.11)
- omitting treatments currently recommended for use in the Cancer Drugs Fund as subsequent treatments (see section 3.12).

It recalled that none of the scenarios on treatment attenuation were likely to be a true reflection of the expected long-term treatment effect. Fully incremental analyses were considered for both the company's and EAG's base cases. In each of these scenarios, BMP and BCD were dominated by lenalidomide plus dexamethasone (this means they were more costly and less effective). Therefore, both BMP and BCD were removed from the analysis. Also, the company's and EAG's base cases comparing daratumumab plus lenalidomide and dexamethasone with lenalidomide plus dexamethasone resulted in deterministic and probabilistic ICERs that were substantially above the range normally considered a cost-effective use of NHS resources.

Other factors

Equality issues

3.15 The committee considered a potential equality issue raised by the company and patient organisations. It was suggested that there is an inequity in access to effective treatments for adults with previously untreated multiple myeloma who are ineligible for autologous stem cell transplant compared with those who are eligible for autologous stem cell transplant. It was noted that since NICE's technology appraisal guidance on daratumumab in combination for untreated multiple myeloma when a stem cell transplant is suitable, adults who are eligible for autologous stem cell transplant can have daratumumab at first line. The EAG explained that its clinical experts noted that adults who are ineligible for autologous stem cell transplantation are often frailer, have more comorbidities and are older than those who are eligible for autologous stem cell transplantation. The committee agreed that people who are ineligible for a transplant have a high unmet need (see section 3.1). Also, the committee discussed equality issues and agreed that its recommendations do not have a different impact on people protected by the equality legislation than on the wider population.

3.16 NICE's advice about conditions with a high degree of severity did not apply.

Innovation

3.17 The committee considered if daratumumab plus lenalidomide and dexamethasone was innovative. It heard from the company that it considered daratumumab plus lenalidomide and dexamethasone to be innovative. This is because of its mechanism of action and because it provides improved outcomes compared with existing treatments available within the NHS. The committee noted that patient and clinical experts considered daratumumab plus lenalidomide and dexamethasone to be innovative. The company considered that there were additional benefits of daratumumab plus lenalidomide and dexamethasone that were not captured within the model. It believed that the EQ-5D-derived utility values used in the model did not capture benefits of daratumumab plus lenalidomide and dexamethasone that would be captured using the cancer-specific EORTC QLQ-C30. These benefits include shorter time to improvement, longer time to worsening, improvement on the pain sub-scale and other improvements in wellbeing. It also suggested that daratumumab plus lenalidomide and dexamethasone may have a positive impact on carer's health-related quality of life. The committee accepted that daratumumab plus lenalidomide and dexamethasone would likely improve outcomes and address unmet need in people with previously untreated multiple myeloma when a stem cell transplant is unsuitable. But the committee concluded that it was uncertain if there were any additional benefits that had not been captured in the QALY calculations because it had not been provided with evidence.

Conclusion

3.18 The committee concluded that daratumumab plus lenalidomide and dexamethasone is not recommended for treating previously untreated multiple myeloma in adults, when an autologous stem cell transplant is unsuitable. The committee considered the uncertainty and the cost-

effectiveness estimates. It noted that all ICERs were substantially above the range considered to be a cost-effective use of NHS resources.

4 Evaluation committee members and NICE project team

Evaluation 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 being evaluated. If it is considered there is a conflict of interest, the member is excluded from participating further in that evaluation.

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

Chair

Charles Crawley

Chair, technology appraisal committee B

NICE project team

Each evaluation is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the evaluation), a technical adviser and a project manager.

Ross Wilkinson

Technical lead

Fatima Chunara

Technical adviser

Jeremy Powell

Project manager

ISBN: [to be added at publication]