NICE National Institute for Health and Care Excellence

NICE guidance

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

Technology appraisal guidance
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# Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card Scheme.

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

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 with lenalidomide and dexamethasone is recommended, within its marketing authorisation, as an option for untreated multiple myeloma in adults, when an autologous stem cell transplant is unsuitable. It is only recommended if the company provides it according to the commercial arrangement.

**Why the committee made this recommendation**

Multiple myeloma is usually first treated with lenalidomide plus dexamethasone when an autologous stem cell transplant is unsuitable. But sometimes bortezomib plus an alkylating agent (cyclophosphamide or melphalan) and a corticosteroid (dexamethasone or prednisone) might be more suitable. Daratumumab plus lenalidomide and dexamethasone is 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 compared with lenalidomide plus dexamethasone. Clinical trial evidence also shows it increases how long people live compared with lenalidomide plus dexamethasone, but by how much is uncertain. There is no direct evidence comparing daratumumab plus lenalidomide and dexamethasone with bortezomib plus an alkylating agent and a corticosteroid, but indirect comparisons suggest that it is more effective.

The most likely cost-effectiveness estimates for daratumumab plus lenalidomide and dexamethasone are within the range that NICE normally considers an acceptable use of NHS resources, so it is 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

2.3 The list prices for daratumumab (excluding VAT; BNF online, accessed August 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.

2.4 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.

2.5 The list price for lenalidomide is £3,057.60 per 21-pack of 25-mg capsules (excluding VAT; BNF online, accessed August 2023). List prices for different doses are available on the BNF webpage for medicinal forms of lenalidomide.

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

2.6 The list price of dexamethasone is £30.73 per 50-pack of 4-mg capsules (excluding VAT; electronic market information tool [eMIT] online, accessed August 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 the quality of their lives. Patient experts explained that multiple myeloma is a relapsing and remitting disease that can have 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 to prolong remission. Treatment options for people with multiple myeloma depend on:

- whether or not a stem cell transplant is suitable
- how many previous lines of treatment a person has had
- the type of treatments they have had and the response to those treatments, and
- the person's preferences.

For someone with a new diagnosis of multiple myeloma, if a stem cell transplant is unsuitable, available options are:

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

guidance on lenalidomide plus dexamethasone for previously untreated multiple myeloma) or

— bortezomib in combination with an alkylating agent and a corticosteroid (see 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 welcomed. 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 listed all currently available treatment options as comparators (see section 3.1). In its submission the company provided evidence for the 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 when an autologous stem cell transplant is unsuitable, 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 so should be considered the most relevant comparator. The clinical experts agreed that thalidomide combination treatments are very rarely used when an autologous stem cell transplant is unsuitable. 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 fewer than 30% of people have bortezomib combination treatments. But it was noted that there are many regional variations in the 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

## Clinical trial results

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 could not have an autologous stem cell transplant. The company initially 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 October 2021 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 October 2021 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 3.6). In response to the draft guidance consultation document the company reported data from a more recent data cut (October 2022, median follow up 73.6 months). At the October 2022 data cut, daratumumab plus lenalidomide and dexamethasone reduced the risk of death by 35% (HR 0.65, 95% CI 0.52 to 0.80) compared with lenalidomide plus dexamethasone. Median overall survival had still not been reached in the daratumumab plus lenalidomide and dexamethasone group. The committee concluded that the MAIA trial showed 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 UK and 13 other countries, which meant that 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 agreed with the company that the unadjusted results from the MAIA trial may be conservative. However, 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. 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.

## Treatment switching

3.5 In response to the draft guidance consultation document, the company updated the IPCW analysis to include treatments that have moved into routine commissioning since the first committee meeting (from here, referred to as the first meeting; see section 3.16). The company stated that the updated results continue to show a greater overall-survival benefit than the unadjusted results used in its base case. The actual numbers are considered confidential by the company and cannot be reported here. The EAG stated that the unadjusted results remain conservative. The EAG explained that the IPCW analysis did not adjust the overall-survival estimates to account for the proportion of people who are expected to have daratumumab plus bortezomib and dexamethasone at second line in current NHS clinical practice. The company considered the subsequent treatments used in MAIA to be generalisable to NHS clinical practice. It stated that most treatments after daratumumab plus lenalidomide and dexamethasone were bortezomib based. Also, the most common treatment after lenalidomide plus dexamethasone was daratumumab plus bortezomib and dexamethasone. The company suggested that in MAIA after lenalidomide plus dexamethasone, some people had experimental treatments that could improve overall survival. It also stated that the observed outcomes from the lenalidomide plus dexamethasone arm in the UK are better than from other comparable studies. The committee noted that the company did not provide evidence to support its suggestion that the outcomes from the lenalidomide plus dexamethasone arm in the UK are better than from other comparable studies. The committee stated that the studies the company referenced were also unlikely to be generalisable to current NHS clinical practice. The committee recalled the NHS England Cancer Drugs Fund clinical lead's comments at the first meeting. They had stated that most people who have lenalidomide plus dexamethasone at

first line would go on to have daratumumab plus bortezomib and dexamethasone at second line. The committee further recalled that based on clinical expert opinion, the company's model assumed that after lenalidomide plus dexamethasone 90% of people go on to have daratumumab plus bortezomib and dexamethasone. The committee noted that the proportion who went on to have daratumumab plus bortezomib and dexamethasone after lenalidomide plus dexamethasone in MAIA was much lower. The committee considered that this would affect generalisability and lead to uncertainty in the long-term treatment effect of daratumumab plus lenalidomide and dexamethasone (see section 3.12). The committee considered that the MAIA trial provided the best available evidence but there was uncertainty about the generalisability of the overall-survival data to NHS clinical practice.

## Long-term effectiveness

3.6 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 was uncertain how the hazard ratio for daratumumab plus lenalidomide and dexamethasone compared with lenalidomide and dexamethasone would change after the follow up in the October 2021 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 have 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 October 2021 data cut, MAIA showed a survival benefit. But it noted that with the October 2021 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. At the first meeting, the committee noted that further data that could be incorporated into the appraisal was available and could reduce uncertainty. In response to the draft guidance consultation document the company reported data from the most recent MAIA data cut (October 2022; see section 3.3). The company and EAG agreed that data from the October 2022 data cut shows that the overall-survival treatment benefit of daratumumab plus lenalidomide and dexamethasone is maintained at the 73.6 months median follow-up time point. However, the EAG did not believe that the data supported a trend for a continuously improving treatment effect. The committee agreed that the treatment effect was maintained at the October 2022 data cut, although it recalled its concerns about the generalisability of the overall-survival data (see section 3.5). The committed concluded that the data from the October 2022 data cut did not resolve the uncertainty in the overall-survival modelling.

# Indirect treatment comparison

## Indirect comparison with BMP

3.7 The company did not identify any direct evidence comparing the efficacy of daratumumab plus lenalidomide and dexamethasone 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 who cannot have an 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 EAG's preferred approach. The committee concluded that the parametric NMA approach was appropriate for decision making.

## Indirect comparison with BCD

3.8 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 who could not have autologous stem cell transplants. 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 1 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

3.9 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

3.10 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 stopping data to estimate treatment duration in the model. For daratumumab plus lenalidomide and dexamethasone, time to treatment stopping 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 analyses 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 stopping. 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 stopping would continue to widen over time 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 it was uncertain how the hazard ratio changed beyond the follow-up period, and that longer follow-up data 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. At the first meeting, 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 October 2022 data cut suggested another extrapolation is more appropriate. In response to the draft guidance consultation document the company revised its base case and used a generalised gamma curve to extrapolate time to treatment stopping for daratumumab plus lenalidomide and dexamethasone and lenalidomide plus dexamethasone. It explained that, based on the October 2022 data cut, the generalised gamma curve had the best statistical fit (lowest AIC and BIC). It further explained that visual inspection of the extrapolations supported the use of the generalised gamma curve. The EAG accepted that the October 2022 data cut supported the use of the generalised gamma curve, and updated its base case. However, it considered that there was still uncertainty in the extrapolation of time to treatment stopping for daratumumab plus lenalidomide and dexamethasone. The EAG explained the generalised gamma curve assumes that there are no people still having daratumumab plus lenalidomide and dexamethasone at 10 years. It further explained that this may have implications for the plausibility of some treatment effect extrapolations (see section 3.12). The company noted that visual inspection also supported the Gompertz curve and that the Gompertz curve was ranked second based on statistical fit. The EAG

agreed that the Gompertz curve may also be plausible. The clinical experts explained that they thought it very likely some people would continue having daratumumab plus lenalidomide and dexamethasone beyond 10 years. The committee accepted that data from the October 2022 data cut no longer supported the use of the exponential curve. The committee considered that the clinical experts' comments supported using the Gompertz curve. The committee concluded that it would consider scenarios using generalised gamma and Gompertz curves in its decision making because they were both clinically plausible.

## Overall survival

3.11 At technical engagement the company stated that the exponential and Gompertz curves resulted in similar plausible long-term survival estimates. It revised its base case to use the Gompertz curve in line with the EAG's preferred approach. In response to the draft guidance consultation document the company retained the Gompertz curve in its base case. But it explained that based on data from the October 2022 MAIA data cut, there was increased divergence between the 2 curves. The company further explained that the exponential curve has the best statistical fit (lowest AIC and BIC) for daratumumab plus lenalidomide and dexamethasone and resulted in a higher long-term survival estimate than the Gompertz curve. The company stated that it considered the Gompertz curve to be a conservative estimate of long-term survival. The EAG commented that a scenario using the exponential curve for daratumumab plus lenalidomide and dexamethasone was clinically plausible. It explained that the exponential was preferred based on BIC but that there was little difference between the exponential and other curves, including the Gompertz, based on AIC. The EAG further explained that it preferred to use the same curve for both treatment groups, as recommended in NICE's technical support document 14. The EAG retained the Gompertz curve in its base case. The committee recalled that the average age of people in the model was 74.1 years. It considered that the long-term survival estimates from the exponential and Gompertz curves appeared implausible. The committee concluded that, of the curves presented, the generalised gamma appeared to be the most plausible.

## Long-term treatment effect extrapolation

3.12 The company's model used independently fitted parametric curves to estimate overall survival in the lenalidomide plus dexamethasone and daratumumab plus lenalidomide and dexamethasone arms (see section 3.11). These curves diverged from each other over time, suggesting that the survival benefit associated with daratumumab plus lenalidomide and dexamethasone increases over time. At the first meeting 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. NICE's health technology evaluations 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 in which 'treatment effect stops or diminishes gradually over time' should be considered. The committee noted that ahead of the first meeting 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 October 2021 MAIA data cut, by modelling a fixed hazard ratio.

  In its base case, the EAG applied treatment effect waning 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 treatment effect waning 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 treatment effect waning. The company also noted that treatment effect waning 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 treatment effect waning. 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 at the first meeting 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 treatment effect waning 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.

## Treatment effect waning

3.13 At the first meeting, 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 was 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, whereby the relative treatment effect reduced over time, but whereby the hazard ratio for daratumumab plus lenalidomide and dexamethasone compared with lenalidomide plus dexamethasone did not reach 1. The committee also noted that long-term survival outcomes are affected 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 included in the appraisal at the first meeting.

## Alternative overall-survival hazard ratio scenarios

3.14 In response to the draft guidance consultation document, the company did not revise its approach to estimating long-term overall survival. It continued to use independently fitted parametric curves that resulted in an assumption that the survival benefit for daratumumab plus lenalidomide and dexamethasone continues to improve throughout the time horizon. The company suggested that results from a piecewise Cox analysis of MAIA overall-survival data using data from the most recent data cut (October 2022) suggested that the cumulative overall-survival hazard ratio continued to improve with each successive data cut. The company maintained that the deep and durable response associated with daratumumab plus lenalidomide and dexamethasone in MAIA supports a constantly improving treatment effect. However, the company stated that it understood the inherent uncertainty when modelling a lifetime time horizon. Therefore, it provided a range of scenarios when the hazard ratio was fixed or increased after a certain point but did not reach 1. The EAG considered scenario 1, which fixed the modelled hazard ratio at the end of the observed period from

the most recent MAIA data cut (October 2022) to be most plausible. It suggested that the results from the company's piecewise Cox analysis show the hazard ratios are stable beyond 60 months. The committee noted that the company's piecewise Cox analysis produced cumulative hazard ratios and that the scenarios the company presented related to the instantaneous hazard ratios in each model cycle. It also noted that even in the EAG's base case where the instantaneous hazards are fixed, the cumulative hazards will continue to improve. The committee noted that clinical experts considered that daratumumab plus lenalidomide and dexamethasone may be associated with a long-term treatment benefit. The committee considered that a fixed hazard ratio from the point of the most recent data cut (October 2022) was not inconsistent with a long-term treatment benefit. The committee recalled that its concerns about the generalisability of the subsequent treatment in MAIA had not been resolved (see section 3.4 and section 3.5), and its comments from the first meeting that this had not been reflected in the model. The committee acknowledged that the extrapolation of the long-term treatment effect is highly uncertain. It concluded that it preferred scenario 1, which fixed the modelled hazard ratio at the end of the observed period from the most recent MAIA data cut, October 2022.

## Costs of subsequent treatments

3.15 The company's model included the costs of second- and third-line treatments offered 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 given by 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. At the second committee meeting the committee considered that the

uncertainty about the market share of subsequent treatments had been reduced, after some treatments previously only available through the Cancer Drugs Fund were recommended for routine commissioning (see section 3.16).

## Including Cancer Drugs Fund treatments

3.16 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 so should not be included in a treatment sequence. But the committee was also aware that there were ongoing appraisals reviewing daratumumab with bortezomib and dexamethasone for previously treated multiple myeloma and ixazomib with lenalidomide and dexamethasone for treating relapsed or refractory multiple myeloma. At the first meeting 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 were recommended for routine use after their respective ongoing reviews and are considered established clinical practice, the modelling could be updated to incorporate these as subsequent treatments. Ahead of the second meeting, final guidance was published for 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, which recommended the treatments for routine commissioning. Both the company and EAG updated their base case to include daratumumab plus bortezomib and dexamethasone and ixazomib plus lenalidomide and dexamethasone as subsequent treatments. The committee concluded that for this appraisal both

treatments should be incorporated into the modelling as subsequent treatments as an accurate reflection of current NHS clinical practice.

# Cost-effectiveness estimates

## Acceptable ICER

3.17 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:

- generalisability of overall-survival data from MAIA to NHS clinical practice (see section 3.4)
- long-term effectiveness of daratumumab plus lenalidomide and dexamethasone (see section 3.6 and section 3.11)
- appropriate parametric curve for time to treatment stopping for daratumumab plus lenalidomide and dexamethasone (see section 3.10)
- extrapolation of the long-term treatment effect (see sections 3.12 to 3.14).

When considering the ICER range, the committee also considered that MAIA has a long follow up and has shown that daratumumab plus lenalidomide and dexamethasone is a clinically effective treatment. It also considered that there were potential benefits of daratumumab plus lenalidomide and dexamethasone that were not completely captured in the model. The committee heard from clinical experts about the benefits of increased progression-free survival, the importance of a quality first remission and that people have fewer treatment options when stem cell transplant is unsuitable. The committee also heard from patient experts about the reduced anxiety

and psychological benefits of a sustained remission. The committee noted its preferences (see section 3.18), the potential uncaptured benefits and the need for uncertainty to be taken into account, in its decision. It concluded that the uncertainties would have to be reflected in the maximum ICER it would be willing to accept, which would need to be below £30,000 per QALY gained.

## Committee's preferred assumptions

3.18 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 3.7)
- using the hazard ratios from the MAIC to inform the comparison with BCD (see section 3.8)
- using a Gompertz or generalised gamma curve to model time to treatment stopping for daratumumab plus lenalidomide and dexamethasone (see section 3.10)
- using the scenario that fixed the modelled hazard ratio at the end of the observed period from the October 2022 MAIA data cut to model the long-term treatment effect extrapolation (see section 3.14)
- using the company's estimates of the market share of treatments used at second and third line to calculate the costs of subsequent treatments (see section 3.15)
- including treatments that have moved into routine commissioning since the first meeting (see section 3.16).

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 expensive and less effective). Therefore, both BMP and BCD were removed from the analysis. The committee noted that using its preferred assumptions comparing daratumumab plus lenalidomide and dexamethasone with lenalidomide plus dexamethasone resulted in deterministic and probabilistic ICERs lower than the maximum ICER it was willing to accept (see section 3.17).

# Other factors

## Equality

3.19 The committee considered a potential equality issue raised by the company and patient organisations. They suggested that there is an inequity in access to effective treatments for people with previously untreated multiple myeloma who cannot have an autologous stem cell transplant compared with those who can. 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 can have an autologous stem cell transplant can have daratumumab at first line. The EAG explained that its clinical experts noted that adults who cannot have an autologous stem cell transplant are often frailer, have more comorbidities and are older than those who can have an autologous stem cell transplant. The committee agreed that people who cannot have a transplant have a high unmet need (see section 3.1). The committee discussed equality issues and agreed that its recommendations do not affect people protected by the equality legislation differently to the wider population.

## Severity

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

## Innovation

3.21 The committee considered if daratumumab plus lenalidomide and dexamethasone was innovative. The company explained that it considered daratumumab plus lenalidomide and dexamethasone to be innovative. This is because of its mechanism of action and that it provides improved outcomes compared with existing treatments available in 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 quality-of-life measure, 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 reduce anxiety associated with relapse and reduce carer burden. It also may allow people to access potential innovative treatments in the future. The committee noted it was uncertain if daratumumab plus lenalidomide and dexamethasone was associated with these proposed benefits because it had not been provided with evidence. 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. The committee noted that the company had pooled the utility data from both groups in MAIA. The committee concluded that it is possible that there were uncaptured benefits relating to how health-related quality of life was measured and captured in the model. It also concluded that it would take this into account when determining an acceptable ICER range.

# Conclusion

3.22 The committee concluded that, using its preferred assumptions, the ICERs for daratumumab plus lenalidomide and dexamethasone were within the range that NICE considers a cost-effective use of NHS resources. Therefore, the committee recommended daratumumab plus lenalidomide and dexamethasone for treating previously untreated multiple myeloma in adults, when an autologous stem cell transplant is unsuitable.

# 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 integrated care boards, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this evaluation 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 cost comparison evaluation), at which point funding will switch to routine commissioning budgets. The NHS England 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 guidance 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 draft guidance.

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 lenalidomide and dexamethasone is the right treatment, it should be available for use, in line with NICE's recommendations.

# 5 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 and Rufaro Kausi**
Technical advisers

**Jeremy Powell**
Project manager

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