NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Draft guidance consultation

Belantamab mafodotin for treating relapsed or refractory multiple myeloma after 4 or more treatments [ID2701]

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using belantamab mafodotin 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: April 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- After considering these comments, the committee will prepare the final draft guidance.
- Subject to any appeal by stakeholders, the final draft guidance may be used as the basis for NICE's guidance on using belantamab mafodotin in the NHS in England.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: 31 May 2023
- Second evaluation committee meeting: 14 June 2023
- Details of membership of the evaluation committee are given in section 4

1 Recommendations

1.1 Belantamab mafodotin is not recommended, within its marketing authorisation, for treating multiple myeloma in adults who:

- have had 4 or more previous treatments and
- whose cancer is refractory to at least:
  - 1 proteasome inhibitor
  - 1 immunomodulatory drug, and
  - 1 anti-CD38 monoclonal antibody, and
- whose cancer progressed on the last treatment.

1.2 This recommendation is not intended to affect treatment with belantamab mafodotin 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

There is no standard treatment for multiple myeloma after 4 or more treatments, when those treatments include at least 1 proteasome inhibitor, 1 immunomodulatory drug and 1 anti-CD38 monoclonal antibody. Most people have pomalidomide plus dexamethasone.

It is not clear from the clinical evidence how well belantamab mafodotin works compared with pomalidomide plus dexamethasone. This means that it is not possible to reliably estimate the cost effectiveness of belantamab mafodotin. So, it is not recommended.

2 Information about belantamab mafodotin

Conditional marketing authorisation indication

2.1 Belantamab mafodotin (Blenrep, GlaxoSmithKline) is indicated 'as monotherapy for the treatment of multiple myeloma in adult patients, who have received at least four prior therapies and whose disease is refractory to at least one proteasome inhibitor, one immunomodulatory agent, and an anti-CD38 monoclonal antibody, and who have demonstrated disease progression on the last therapy'.

Dosage in the marketing authorisation

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

Price

2.3 The list price of belantamab mafodotin is £5,707.83 per 100-mg vial (excluding VAT; BNF online, accessed April 2023).

2.4 The company has a commercial arrangement, which would have applied if belantamab mafodotin had been recommended.

3 Committee discussion

The evaluation committee considered evidence submitted by GlaxoSmithKline, 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.

Clinical management

Clinical need

3.1 Multiple myeloma is a type of blood cancer that develops from plasma cells in the bone marrow. It is usually diagnosed in older people. The committee noted stakeholder submissions from a patient group and 2

clinical experts. It understood that people with relapsed or refractory multiple myeloma may experience a greater disease burden which can significantly affect the quality of life of people with the condition, and their families and carers. The patient expert explained how they had received 8 previous lines of treatment for multiple myeloma, and that they were currently having belantamab mafodotin (from now, referred to as belantamab). They described how their life had changed since being diagnosed with multiple myeloma and how the condition impacts their ability to carry out usual activities. The committee discussed the population relevant to the decision problem for this evaluation: adults with relapsed or refractory multiple myeloma who have had 4 or more previous treatments and whose disease is refractory to at least 1 proteasome inhibitor, 1 immunomodulatory agent and 1 anti-CD38 monoclonal antibody (also known as triple-class refractory disease). It noted that there were no NICE-recommended treatments for this population. The stakeholder submissions highlighted that current treatment options for people who have had 4 or more previous treatments are limited, with little evidence to support use. The committee understood that multiple myeloma evolves over time and becomes resistant to different classes of treatment as it progresses. The clinical experts highlighted that because of this, treatments with new targets and mechanisms of action are needed for people whose disease is triple-class refractory. The committee understood that belantamab is the only antibody drug conjugate to be licensed for multiple myeloma that targets the B-cell maturation antigen protein. It recognised that there is an unmet need for people with relapsed or refractory multiple myeloma after 4 or more treatments whose disease is triple-class refractory. The committee also recognised that people with the condition and their clinicians would welcome belantamab as a treatment option for multiple myeloma.

Comparators

3.2 The committee discussed the company's positioning of belantamab as a treatment option for triple-class refractory multiple myeloma after 4 or

more previous treatments. The final scope for the appraisal included established clinical management without belantamab as a comparator. This included pomalidomide plus dexamethasone, panobinostat plus bortezomib and dexamethasone, and chemotherapy (with or without a steroid and with or without thalidomide). The company considered that use of panobinostat plus bortezomib and dexamethasone in the population under consideration was limited, and likely driven by desperation. It stated that chemotherapy combinations were also not relevant comparators, because they are likely used palliatively rather than as active treatment. The company considered pomalidomide plus dexamethasone to be the most relevant comparator, and that this was supported by the National Cancer Registration and Analysis Service (NCRAS) dataset in the relevant population. The EAG considered that pomalidomide plus dexamethasone is rarely used in this population because it will usually have been used with isatuximab as a fourth-line treatment in line with NICE's technology appraisal guidance on isatuximab with pomalidomide and dexamethasone for treating relapsed and refractory multiple myeloma (TA658). The clinical experts confirmed that pomalidomide plus dexamethasone was the most appropriate comparator. The committee understood that there was no established standard care for people whose disease relapses after fifth-line treatment. The clinical experts estimated that around 25% of such people would have sixth-line treatment. This could include treatment in a clinical trial or palliative therapy (such as dexamethasone) depending on a person's fitness. They highlighted that panobinostat plus bortezomib and dexamethasone is rarely used and not appropriate when the disease is refractory to a proteosome inhibitor. The committee concluded that pomalidomide plus dexamethasone was the most appropriate comparator for belantamab as a fifth-line treatment, and that clinical practice varied in subsequent lines.

Clinical effectiveness

DREAMM-2 trial

3.3 The company presented evidence for belantamab from DREAMM-2. This was a phase 2, open-label, randomised study of belantamab at 2 doses (2.5 mg/kg and 3.4 mg/kg) in people with triple-class refractory multiple myeloma who experienced disease progression after 3 or more previous treatments. The study included 58 centres, 7 of which included a small number of people from the UK (the company considers the actual figure confidential and so it cannot be reported here). The company only presented results for the licensed dose of belantamab (2.5 mg/kg). The intention-to-treat (ITT) population (n=97) included a very small number of people who had 3 previous treatments. This meant that the subgroup that had 4 or more previous treatments, which is in line with the marketing authorisation indication, included most people from the ITT population. The company therefore considered that the ITT population was closely aligned with the subgroup who had 4 or more previous treatments. So, it used the results from the ITT population to inform the appraisal and economic model. The committee considered outcomes from the final data cut (May 2022) with a maximum follow up of 40 months. The primary outcome was the overall response rate with belantamab (based on independent review committee assessment of response), which was reported as 32% (97.5% confidence interval of 21.7 to 43.6). Secondary outcomes included a median overall survival of 15.3 months and median progression-free survival of 2.8 months. The median time to treatment discontinuation (TTD) and median time to next treatment (TTNT) were calculated by the company in post-hoc analyses. The committee concluded that DREAMM-2 did not provide evidence of the relative efficacy of belantamab compared with the relevant comparator for this evaluation, pomalidomide plus dexamethasone.

Eye-related adverse events in DREAMM-2

3.4 The most frequent adverse event reported in DREAMM-2 was keratopathy, a condition involving changes to the cornea (the company considers the actual figure to be confidential and so it cannot be reported here). Recovery and resolution of keratopathy and best corrected visual acuity occurred for most people in DREAMM-2 with no reports of permanent loss of vision. The clinical expert submission highlighted that eye-related adverse events are frequent with belantamab and are likely to need management by an eye-care professional. The clinical experts considered that blurring of vision with belantamab would likely be intermittent and reversible. The patient expert described how they usually notice visual changes around 2 weeks after having belantamab. They explained that this can affect their ability to carry out some usual activities, but that their eyesight does correct itself over time. The committee recognised that some people may experience eye-related adverse events with belantamab. It noted stakeholder comments that such adverse effects could usually be managed with either a dose delay or reduction so that belantamab treatment can be continued.

Efficacy evidence for pomalidomide plus dexamethasone

3.5 The company's systematic literature review did not identify any head-to-head evidence comparing belantamab with pomalidomide plus dexamethasone in people with triple-class refractory multiple myeloma who have had 4 or more previous treatments. It also did not identify any clinical trial evidence for pomalidomide plus dexamethasone in the relevant population to use in an indirect treatment comparison. Because of this, the company used its NCRAS study to inform efficacy data for pomalidomide plus dexamethasone. The NCRAS study was a descriptive, retrospective, non-interventional study which used routine patient-level health data from England available through the NCRAS dataset. The study identified a population that the company considered to be closely aligned with the decision problem and which had pomalidomide plus

dexamethasone at a dose in line with its licensed indication (n=65). Outcomes for this population included a median overall survival of 10.2 months, a median TTNT of 6.0 months and median TTD of 4.1 months. Because progression-free survival was not reported in the NCRAS dataset, the company used the TTNT from NCRAS as a proxy to inform progression-free survival in the economic model. The committee acknowledged that data from the NCRAS study was likely to be generalisable to the NHS setting, but noted that the selected population was small. It considered that this introduced uncertainty around estimates of efficacy for pomalidomide plus dexamethasone.

Indirect treatment comparisons using DREAMM-2 data

3.6 The company initially did an unanchored matched adjusted indirect comparison (MAIC) using individual patient data from DREAMM-2 (ITT population) and aggregate data from the NCRAS dataset. Outcomes used in the MAIC included overall survival, progression-free survival (TTNT used as proxy measure in both arms) and TTD. The company calculated the TTNT from DREAMM-2 data to allow a comparison with the TTNT data from the NCRAS study. The company considers the results of the MAIC to be confidential, so they cannot be reported here. The company stated that it was not possible to adjust for all imbalances in the important prognostic factors and treatment effect modifiers because of limitations in the data reported in the NCRAS dataset. Because of this and the small effective sample size of DREAMM-2 after matching, the company considered the MAIC results to be too uncertain. The EAG agreed that these estimates were implausible. Instead, the company used a naive unadjusted comparison of belantamab with pomalidomide plus dexamethasone to inform its base case, for the same outcomes used in the MAIC. The company considered that the results of the naive comparison were less uncertain than those from the MAIC, because it had used all the available evidence from DREAMM-2 and NCRAS, resulting in a larger sample size. The EAG noted that outcomes from both datasets lacked a control, and the populations were likely to differ in their

prognostic factors. Because of this, it considered that it was not possible to determine the true treatment effect of belantamab and that the results of the naive comparison were likely to be biased. The committee noted the results from the naive comparison were counterintuitive because they suggested a longer overall survival for belantamab but a shorter proxy progression-free survival and TTD when compared with pomalidomide plus dexamethasone. It considered that it was unclear whether the overall survival gain suggested by the naive comparison was because of the treatment effect of belantamab or a consequence of differences in subsequent treatments after disease progression. So, the committee considered that it would be helpful for the company to provide analyses showing the length of overall survival, progression-free survival and TTD for each participant in DREAMM-2, along with the duration of each individual subsequent line of therapy. It concluded that the results of the company's indirect treatment comparisons comparing belantamab with pomalidomide plus dexamethasone were highly uncertain and considered this in its decision making.

Naive comparison using Named Patient Program data

3.7 In response to technical engagement, the company presented new efficacy evidence for belantamab from its Named Patient Program (NPP). The NPP study (n=56) was a non-interventional retrospective evaluation of belantamab in the UK used in line with its licensed indication. Outcomes in the NPP dataset included overall survival, progression-free survival and TTD (the company considers the actual figures to be confidential and so they cannot be reported here). The company explored the feasibility of an unanchored MAIC for belantamab (using data from the NPP) compared with pomalidomide plus dexamethasone (using data from NCRAS). It stated that some baseline characteristics were incomplete or missing in both datasets, and that adjusting for key prognostic factors while maintaining a sufficiently effective sample size was unfeasible. Despite this, the company considered the baseline characteristics to be broadly comparable across the 2 datasets. So, it selected a naive

unadjusted comparison of belantamab compared with pomalidomide plus dexamethasone to inform its revised base-case analysis. Outcomes in the naive unadjusted comparison included overall survival, progression-free survival (TTNT used as a proxy measure in the pomalidomide plus dexamethasone arm only) and TTD. The unadjusted comparison favoured belantamab compared with pomalidomide plus dexamethasone for all outcomes. The committee discussed whether the people having belantamab in the NPP were likely to be different to those having pomalidomide plus dexamethasone in the NCRAS study. The clinical experts explained that belantamab was not restricted to tertiary centres in the NPP, because it can be easily given by intravenous infusion and the only additional care needed would be from an eye-care professional. The clinical experts considered that any differences between the populations would likely be minor. The EAG considered that the company had not provided a valid reason for changing the efficacy source for belantamab from DREAMM-2 to NPP. The company explained that the NPP and NCRAS data sets were more comparable because they both included populations from the UK relevant to the decision problem. It explained that any bias would likely be introduced into the pomalidomide plus dexamethasone group because progression-free survival would probably be overestimated by using a proxy measure (TTNT). The committee noted the EAG's critique that the feasibility of a MAIC was not improved by using NPP, and that the data source introduced additional uncertainty because it was less mature and included a smaller sample size than DREAMM-2. It noted that the median progression-free survival was much longer in the NPP study than in DREAMM-2. The committee considered that this suggested that the population in NPP may be less likely to experience disease progression and that this may favour belantamab in the company's updated naive unadjusted comparison. The committee agreed that the magnitude and direction of the potential bias was unclear in the company's naive comparison. It concluded that the company's updated naive comparison lacked validity and added further uncertainty around the

efficacy of belantamab compared with pomalidomide plus dexamethasone.

DREAMM-3 trial

3.8 In response to technical engagement, the company presented newly available results from the DREAMM-3 trial. The DREAMM-3 trial (n=325, ITT population) is an ongoing, phase 3, open-label, randomised study comparing belantamab (2.5 mg/kg) with pomalidomide plus dexamethasone in people with relapsed or refractory multiple myeloma who had 2 or more previous treatments (including lenalidomide and a proteasome inhibitor). In the ITT population, belantamab did not significantly improve progression-free survival (the primary outcome of trial) or overall survival compared with pomalidomide plus dexamethasone (the primary analysis results). The committee recognised that the ITT population included belantamab being used earlier in the treatment pathway, meaning it is a broader population than that under consideration in this appraisal. But it considered that the results still provided evidence of comparative efficacy for belantamab in people with relapsed refractory multiple myeloma. The committee concluded that the DREAMM-3 ITT population results were relevant to its decision making.

DREAMM-3 subgroup results

3.9 The company also presented results for a subgroup from DREAMM-3 in line with the licensed indication for belantamab (people with triple-class refractory multiple myeloma who had had 4 or more previous treatments). The estimated hazard ratio for progression-free survival in the subgroup favoured pomalidomide plus dexamethasone rather than belantamab (the company considers the subgroup results to be confidential and so they cannot be reported here). The company considered that because the subgroup is very small (the company considers the exact figure to be confidential and so it cannot be reported here), that no interpretations can be made about the efficacy of belantamab compared with pomalidomide plus dexamethasone. The company explained that the subgroup was not

pre-specified and that randomisation may not be balanced in the post-hoc subgroup analysis. The committee acknowledged the limitations of the DREAMM-3 subgroup analysis, and the uncertainty around the results evidenced by wide confidence intervals. Despite these limitations, it agreed with the EAG that the randomised subgroup data from DREAMM-3 may be less biased than the single-arm, non-randomised evidence presented by the company (see sections 3.3 to 3.7). It discussed how the effectiveness data was likely to be more comparable in DREAMM-3 because it came from a single study rather than 2 independent studies. The committee also discussed that DREAMM-3 provided progression-free survival results for both treatment arms, so there is no need to use a proxy measure. The clinical experts considered that progression-free survival from the DREAMM-3 subgroup analysis was largely overestimated for pomalidomide plus dexamethasone in people who had had 4 or more previous treatments. They considered that this may be because in the DREAMM-3 subgroup analysis randomisation was broken, resulting in a selected population that may not represent people who would have pomalidomide plus dexamethasone as a fifth-line treatment. The committee considered that the uncertainty associated with the outcomes from the DREAMM-3 subgroup did not seem to be greater than that associated with the naive unadjusted comparisons presented by the company. It discussed how the results from DREAMM-3 were contrary to those in the company's naive unadjusted comparisons, which added to further uncertainty about the comparative efficacy of belantamab. The clinical experts explained that in people whose disease responds to belantamab, it responds quickly with a long duration of response. They considered that this was evidenced in the DREAMM-3 dataset, with the depth and duration of response being higher with belantamab than with pomalidomide plus dexamethasone. The patient expert described how belantamab had been effective in controlling their myeloma for quite some time but that they had to stop treatment with pomalidomide plus dexamethasone after a few months because of adverse events. The

committee recognised that belantamab may offer significant benefits to some people, but that it was not possible to define this group. It concluded that it had not been presented with sufficient evidence to confirm that belantamab is more clinically effective than pomalidomide plus dexamethasone at a population level. It agreed with the EAG that, despite the limitations, the randomised subgroup data from DREAMM-3 was preferable to the non-randomised evidence presented by the company. The committee discussed that it would like to see additional data from DREAMM-3 to further explore the effectiveness of belantamab compared with pomalidomide plus dexamethasone. It considered that it would be helpful for the company to present the baseline characteristics and results for different subgroups from DREAMM-3 based on the number of previous treatments and by triple-class refractory disease status.

Economic model

Company's modelling approach

3.10 The company presented a partitioned survival model with 4 mutually exclusive health states: progression-free: on treatment, progression-free: off treatment, progressed disease and death. The progression-free: off treatment health state was applied to people who had withdrawn from treatment before disease progression. Different utility values were applied in the model based on whether a person was on or off treatment for the progression-free health states. The model included a cycle length of 1 week with no half-cycle correction over a lifetime time horizon. The EAG considered that the model structure was appropriate for modelling the decision problem and consistent with previous NICE technology appraisals for multiple myeloma. The committee concluded that the company's model was acceptable for decision making.

Utility values

3.11 The company's model used health-state utility values from the DREAMM-2 trial. Since DREAMM-2 did not report EQ-5D data, the company

mapped patient-reported outcomes from the general cancer health-related quality of life questionnaire (EORTC-QLQ-C30) and the myeloma-specific instrument (EORTC-QLQ-MY20) to the EQ-5D-3L to generate health-state utility values. The company initially used utility data in the model from the 13-month follow-up analysis of DREAMM-2. The EAG considered that the modelled progression-free utility values were optimistic for people with multiple myeloma who had had 4 or more previous treatments. It preferred a scenario that capped the progression-free: on treatment utility in line with the quality of life of people whose condition has relapsed after or is refractory to 1 previous treatment (utility sourced from the literature). In response to technical engagement, the company stated that the EAG's utility scenario implied a higher utility for the progressed disease health state than for the progression-free: on treatment health state. It considered this to be unrealistic and that the EAG's scenario lacked face validity. The company's revised base-case analysis used utility analyses from the final data cut of DREAMM-2 (40 months maximum follow up). The committee noted that the company's utility adjustments resulted in lower utilities for the progression-free health states. It noted that the EAG considered the company's new utilities to be more reasonable for informing the model. The committee concluded that the company's updated utility values were appropriate for decision making.

Time to next treatment

3.12 Progression-free survival was not reported in the NCRAS dataset, so the company used TTNT from NCRAS as a proxy measure for progression-free survival in the model (see section 3.5). In its initial naive comparison, the company also calculated TTNT in a post-hoc analysis of DREAMM-2 data to allow a comparison with TTNT from NCRAS (see section 3.6). The EAG considered that using a proxy progression-free survival measure introduced uncertainty into the cost-effectiveness estimates. This was because it considered that TTNT was unlikely to be comparable across treatment arms because healthcare systems are likely to differ between

DREAMM-2 trial centres and the NCRAS dataset. The EAG also noted that using a proxy progression-free survival measure will tend to accumulate more quality-adjusted life years (QALYs) than using progression-free survival. In response to technical engagement, the company explained that differences in healthcare systems may exist between the DREAMM-2 trial centres and the NCRAS NHS setting but it was unlikely to affect the comparability of outcomes such as TTNT. The company noted that the use of a proxy progression-free survival measure had been accepted in previous NICE appraisals for multiple myeloma. It considered that this issue was largely resolved because its updated naive comparison used data from both NPP and NCRAS, which were both UK datasets and so access to next treatment would likely be equitable. The EAG considered that TTNT is not an appropriate proxy measure for progression-free survival, but that no alternative was available. The committee concluded that using a proxy progression-free survival measure was associated with uncertainty and that the impact on the cost-effectiveness estimates was unclear. It recalled its preference for clinical-effectiveness data from DREAMM-3 which provided progression-free survival results for both treatment arms (see section 3.9). It further concluded that using the DREAMM-3 data resolved the need to use a proxy progression-free survival measure in the model.

Severity

Data used in the company's QALY shortfall analysis

3.13 In its submission, the company provided evidence that relapsed or refractory multiple myeloma after 4 or more treatments in people whose disease is triple-class refractory is a severe condition. The committee considered the severity of the condition (the future health lost by people living with the condition and having standard care in the NHS). The committee may apply a greater weight (a severity modifier) to QALYs if technologies are indicated for conditions with a high degree of severity. The company provided absolute and proportional QALY shortfall

estimates as outlined in NICE's health technology evaluations manual. The company used a weighted average of comparators (pomalidomide plus dexamethasone and panobinostat plus bortezomib and dexamethasone) for estimating the remaining QALYs for people with the condition on current treatment. This was based on real-world use of each treatment in the NCRAS dataset. In response to technical engagement, the company updated the data inputs for the mean age and sex distributions based on the NPP dataset (they were originally from DREAMM-2) and used the utility values from the final data cut of DREAMM-2 with 40 months maximum follow up (these were originally from the 13-month follow-up analysis). The committee noted that the company's updated data inputs had a minimal impact on the absolute and proportional QALY shortfall estimates. The committee considered that because pomalidomide plus dexamethasone was the most relevant comparator (see section 3.2), the most relevant shortfall estimates would be for people with the condition on pomalidomide plus dexamethasone alone. It noted that the EAG preferred to use NCRAS as the data source for the mean age and sex distributions because this dataset was used by the company to initially derive evidence on the real-world use of potential comparators. The committee discussed how the mean age of people on pomalidomide plus dexamethasone in the NCRAS dataset was higher than that from the NPP dataset. The clinical experts explained that the population having fifth-line treatment were likely to be younger and fitter than the overall population with multiple myeloma. They explained that people having fifth-line treatment would usually be around the age of 65 years. The committee noted that the population in NCRAS were slightly older than the estimate provided by the clinical expert. It considered that the dataset likely reflected the average age for people in the UK with triple-class refractory disease having pomalidomide plus dexamethasone after 4 or more previous treatments. The committee concluded that the EAG's approach of using NCRAS data was more appropriate than the

company's for informing the baseline characteristics in the QALY shortfall calculations.

QALY weighting for severity

3.14 The company's QALY shortfall estimates after technical engagement resulted in a proportional shortfall above 0.85 but below 0.95 (the company considers the exact figure to confidential and so it cannot be reported here). The company stated that a QALY weighting of 1.7 should apply because the 95% confidence interval around the proportional shortfall point estimate included both the 1.2 and 1.7 multiplier. The committee discussed that using the 95% confidence interval may reward uncertainty around QALY shortfall estimates, with greater uncertainty increasing the likelihood of overlapping the severity weighting thresholds. Because of this, it preferred to use the point estimates in its decision making. The committee noted that NICE's health technology evaluations manual did not specify whether deterministic or probabilistic QALYs should be used for shortfall calculations. The company considered that the NICE methods guide was more likely to imply a probabilistic approach to severity. The company presented results for what it termed 'a probabilistic analysis' which explored the proportion of people for whom the 1.7 weighting would apply by varying age at treatment start (using the same values as in the company's probabilistic base-case analysis). The results of the analysis suggested that a QALY weighting of 1.7 would apply to a minority of the population, which the company considered provided further support for applying the highest severity weighting. The committee agreed with the EAG's critique that if a probabilistic analysis was to be chosen, then the mean QALYs for current treatment (used to derive absolute and proportional QALY shortfalls) should have been based on the company's main probabilistic sensitivity analysis. This mean QALY value would incorporate uncertainty around all key parameters including age at which treatment is started. The EAG estimated the proportional QALY shortfall for people with the condition on pomalidomide plus dexamethasone based on the company's main probabilistic

sensitivity analysis (using the NCRAS dataset for age and sex distributions). The results suggested a proportional shortfall of above 0.85 but below 0.95 (the company considers the exact figure to be confidential and so it cannot be reported here). Based on this, the EAG preferred a QALY weighting of 1.2, which it considered to be in line with the NICE QALY weightings for severity. The committee noted that even if a deterministic approach was taken to estimate the QALY shortfalls, the proportional QALY shortfall would still fall below 0.95. It recalled the patient expert comments describing the substantial impact of multiple myeloma on their quality of life (see section 3.1). It recognised that this was a severe disease for the population under consideration. The committee concluded that, based on the evidence provided, a severity weight of 1.2 applied to the QALYs would likely be appropriate. But it further considered that, to reflect the totality of the available clinical evidence, it would be helpful for the company to provide QALY shortfall estimates using data from DREAMM-3.

Cost-effectiveness estimates

Uncertainty in cost-effectiveness estimates and further analyses needed

3.15 NICE's health technology evaluations manual notes that judgements about the acceptability of a technology as an effective use of NHS resources will take into account the degree of certainty around the incremental cost-effectiveness ratio (ICER). The committee will be more cautious about recommending a technology if it is less certain about the ICERs presented. Including the severity weighting of 1.2 (see section 3.14), the company's revised base-case ICERs for belantamab compared with pomalidomide plus dexamethasone were above £30,000 per QALY gained. The exact ICERs are confidential and cannot be reported here because they include the confidential patient access scheme for belantamab and confidential comparator discounts. The committee discussed how the company's revised base-case results were informed by its updated naive comparison which suggested that belantamab was more

efficacious than pomalidomide plus dexamethasone (see section 3.7). It recalled that the unadjusted comparisons were too uncertain for informing the model, and so the EAG had not presented a preferred ICER. Instead, the committee preferred the results from the DREAMM-3 subgroup, in which the estimated hazard ratio for progression-free survival favoured pomalidomide plus dexamethasone rather than belantamab (see section 3.9). The committee acknowledged that there were limitations associated with the subgroup data from the trial. It noted that the EAG's analysis, which explored the DREAMM-3 subgroup data to estimate the cost effectiveness of belantamab compared with pomalidomide plus dexamethasone, suggested a large impact on the ICER. It also considered that the DREAMM-3 ITT population results were relevant to the evaluation, recalling that belantamab did not significantly improve progression-free survival or overall survival compared with pomalidomide plus dexamethasone (see section 3.8). The committee took into consideration all of the evidence presented to it and agreed that there was significant uncertainty around the effectiveness of belantamab compared with pomalidomide plus dexamethasone. Because of this, it concluded that it had not been presented with a plausible, reliable cost-effectiveness estimate for decision making. So, it could not recommend belantamab for treating triple-class refractory multiple myeloma after 4 or more previous treatments. The committee indicated that it would welcome further data from the company that would confirm the superiority of belantamab compared with a relevant comparator. Relevant analyses could include:

- overall survival, progression-free survival and TTD for each participant in DREAMM-2, along with the duration of each individual subsequent line of therapy (see section 3.6)
- baseline characteristics and results for different subgroups from DREAMM-3 based on the number of previous treatments and by triple-class refractory disease status (see section 3.9).

Managed access

Recommendation with managed access

3.16 Having concluded that belantamab could not be recommended for routine use, the committee considered if it could be recommended with managed access. The committee recalled that the limitations in the clinical evidence meant that it had not been presented with a plausible, reliable cost-effectiveness estimate (see section 3.15). It also discussed that additional data collection would be unlikely to resolve the uncertainty around the efficacy of belantamab compared with pomalidomide plus dexamethasone. So, the committee concluded that managed access was not a feasible option.

Other factors

Equality issues

3.17 No equality or social value judgement issues were identified.

Innovation

3.18 The committee considered if belantamab was innovative. It did not identify any additional benefits of belantamab not captured in the economic modelling. So, the committee concluded that all additional benefits of belantamab had already been taken into account.

Conclusion

Recommendation

3.19 The committee concluded that it had not been presented with a cost-effectiveness estimate that was suitable for decision making, and so it could not recommend belantamab as 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 D.

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

Stephen Smith

Vice Chair, technology appraisal committee D

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), and a project manager.

Anita Sangha

Technical lead

Kate Moore

Project manager

ISBN: [to be added at publication]