NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Draft guidance consultation

Belantamab mafodotin with pomalidomide and dexamethasone for previously treated multiple myeloma

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 with pomalidomide and dexamethasone in the NHS in England. The evaluation committee has considered the evidence submitted by the company and the views of non-company stakeholders, clinical experts and patient experts.

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

The evaluation committee is interested in receiving comments on the following:

- In the treatment pathway for multiple myeloma, are the following technologies still used in the NHS:
  - bortezomib monotherapy for relapsed multiple myeloma (TA129)
  - bortezomib and thalidomide for the first-line treatment of multiple myeloma (TA228)
  - lenalidomide plus dexamethasone for previously untreated multiple myeloma (TA587)?
- 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?

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Note that this document is not NICE's final guidance on belantamab mafodotin with pomalidomide and dexamethasone. 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- After considering these comments, the committee will prepare the final draft guidance.
- Subject to any appeal by stakeholders, the final draft guidance may be used as the basis for NICE's guidance on using belantamab mafodotin with pomalidomide and dexamethasone in the NHS in England.

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

The key dates for this evaluation are:

- Closing date for comments: **Thursday 17 July 2025**.
- Second evaluation committee meeting: TBC
- Details of the evaluation committee are given in section 4.

1 Recommendations

1.1 Belantamab mafodotin plus pomalidomide and dexamethasone should not be used to treat multiple myeloma in adults who have had at least 1 treatment including lenalidomide.

1.2 This recommendation is not intended to affect treatment with belantamab mafodotin plus pomalidomide and dexamethasone that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS healthcare professional consider it appropriate to stop.

What this means in practice

Belantamab mafodotin plus pomalidomide and dexamethasone is not required to be funded in the NHS in England to treat multiple myeloma in adults who have had at least 1 treatment including lenalidomide. It should not be used routinely in the NHS in England.

This is because the available evidence does not suggest that belantamab mafodotin plus pomalidomide and dexamethasone offers value for money in this population.

Why the committee made these recommendations

Belantamab mafodotin plus pomalidomide and dexamethasone is licensed for use at second line and beyond. But for this evaluation, the company asked for it to be considered as a treatment at second line only.

Usual treatment for multiple myeloma after 1 line of treatment that includes lenalidomide is:

- carfilzomib plus dexamethasone
- daratumumab plus bortezomib and dexamethasone
- selinexor plus bortezomib and dexamethasone, if the multiple myeloma has not responded to both daratumumab and lenalidomide.

Clinical trial evidence shows that belantamab mafodotin plus pomalidomide and dexamethasone increases how long people have before their condition gets worse compared with pomalidomide plus bortezomib and dexamethasone. But pomalidomide plus bortezomib and dexamethasone is not used in the NHS.

There have been no other direct comparisons. Indirect comparisons suggest that belantamab mafodotin plus pomalidomide and dexamethasone increases how long people have before their condition gets worse compared with:

- carfilzomib plus dexamethasone
- selinexor plus bortezomib and dexamethasone.

They do not show that it increases how long people live compared with usual treatment. And these indirect comparison results are highly uncertain.

There are uncertainties in the economic model, largely related to the assumptions about how long people live after having belantamab mafodotin plus pomalidomide and dexamethasone compared with other second-line treatments. This is mainly because of the way the indirect comparisons were done.

Because of the uncertainties in the economic model and clinical evidence, it is not possible to determine the most likely cost-effectiveness estimates for belantamab

mafodotin plus pomalidomide and dexamethasone. And all the cost-effectiveness estimates are substantially above the range that NICE considers an acceptable use of NHS resources. So, it should not be used.

2 Information about belantamab mafodotin, pomalidomide and dexamethasone

Marketing authorisation indication

2.1 Belantamab mafodotin (BlenRep, GlaxoSmithKline) is indicated 'in combination with pomalidomide and dexamethasone for the treatment of adults with multiple myeloma who have had at least one prior therapy including lenalidomide'.

Dosage in the marketing authorisation

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

Price

2.3 The list price for belantamab mafodotin is £16,848 per 100-mg vial and £11,784 per 70-mg vial (excluding VAT, company correspondence). The list price for pomalidomide is £7,995.60 per 21-pack of 1-mg, 2-mg, 3-mg or 4-mg tablets (excluding VAT; BNF online accessed June 2025).

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

2.5 There are nationally available price reductions for pomalidomide with the Medicines Procurement and Supply Chain. The prices agreed through the framework are commercial in confidence.

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.

The condition

Multiple myeloma

3.1 Multiple myeloma is an incurable, relapsing and remitting cancer of plasma cells. Relapsed multiple myeloma refers to previously treated myeloma that has progressed. Refractory refers to multiple myeloma that shows no response to treatment or that has progressed on or within 60 days of the last treatment. The patient experts emphasised that multiple myeloma is a highly individual and complex cancer with a wide range of symptoms and variation in severity. They explained that the condition has a large psychological impact because of the constant possibility of relapse and the knowledge that with each relapse, the condition is more difficult to treat and options become more limited. The patient experts explained that the condition can have a large impact on quality of life, affecting all aspects of life for both the individual and their carers. The committee acknowledged that multiple myeloma is a chronic, incurable, highly individual condition, that can have a negative impact on quality of life for people with the condition and their families and carers.

Treatment pathway

3.2 First-line treatment options for people with multiple myeloma depend on whether a stem cell transplant may be suitable. NICE recommends the following treatments as first-line options when a stem cell transplant is suitable:

- bortezomib plus dexamethasone, or bortezomib plus dexamethasone and thalidomide (NICE technology appraisal guidance TA311)

- daratumumab plus bortezomib, thalidomide and dexamethasone (from now, Dar-Bor-Tha-Dex; NICE technology appraisal guidance TA763)
- lenalidomide maintenance treatment after stem cell transplant (NICE technology appraisal guidance TA680).

NICE recommends the following treatments as first-line options when a stem cell transplant is not suitable:

- thalidomide plus an alkylating agent and a corticosteroid (NICE technology appraisal guidance TA228)
- bortezomib plus an alkylating agent and a corticosteroid (TA228)
- lenalidomide plus dexamethasone, only if thalidomide is contraindicated or not tolerated (NICE technology appraisal guidance TA587)
- daratumumab plus lenalidomide and dexamethasone (from now, Dar-Len-Dex; NICE technology appraisal guidance TA917).

At second line, NICE recommends the following treatments as options:

- bortezomib monotherapy (NICE technology appraisal guidance TA129), although this treatment is rarely used in NHS clinical practice
- lenalidomide plus dexamethasone (from now, Len-Dex), if the person has only had 1 previous line of treatment containing bortezomib (NICE technology appraisal guidance TA586)
- carfilzomib plus dexamethasone (from now, Car-Dex; NICE technology appraisal guidance TA657)
- carfilzomib plus lenalidomide and dexamethasone, if the person has only had 1 previous line of treatment containing bortezomib (NICE technology appraisal guidance TA695)
- daratumumab plus bortezomib and dexamethasone (from now, Dar-Bor-Dex), if the person has only had 1 previous line of treatment that included lenalidomide or if lenalidomide is unsuitable at second line (NICE technology appraisal guidance TA897)

- selinexor plus bortezomib and dexamethasone (from now, Sel-Bor-Dex), if the person has only had 1 previous line of treatment, and their condition is refractory to both daratumumab and lenalidomide (NICE technology appraisal guidance TA974).

  At third line, NICE also recommends Sel-Bor-Dex if the person has only had 2 previous lines of treatment, and their condition is refractory to lenalidomide (TA974).

  At third and fourth line, NICE recommends the following treatments as options:

- lenalidomide plus dexamethasone (NICE technology appraisal guidance TA171)
- panobinostat plus bortezomib and dexamethasone (from now, Pan-Bor-Dex; NICE technology appraisal guidance TA380)
- ixazomib plus lenalidomide and dexamethasone (NICE technology appraisal guidance TA870).

  At fourth line, NICE also recommends daratumumab monotherapy (NICE technology appraisal guidance TA783).

  At fourth and fifth line, NICE recommends the following treatments as options:

- pomalidomide plus low-dose dexamethasone (from now, Pom-Dex; NICE technology appraisal guidance TA427)
- teclistamab after 3 or more lines of treatment only (including an immunomodulatory drug, a proteasome inhibitor and an anti-CD38 antibody) and when the myeloma has progressed on the last treatment (NICE technology appraisal guidance TA1015).

At fifth line, NICE also recommends the following treatments as options:

- Pan-Bor-Dex (TA380)
- selinexor plus dexamethasone if the person has had 4 or more previous lines of treatment, and their condition is refractory to at least 2 proteasome inhibitors, 2 immunomodulatory agents and an anti-CD38 monoclonal antibody (penta-refractory), and it has progressed on the last treatment (NICE technology appraisal guidance TA970).

Evolving treatment pathway

3.3 The clinical experts agreed with the EAG's clinical advisers that:

- the treatment pathway, although representative of current NHS practice, is evolving
- most people would have a daratumumab-containing regimen at first line, which is proving to be effective. But the impact of previous daratumumab treatment on overall survival in subsequent lines of treatment is not known.

The clinical experts disagreed with the EAG's clinical advisers that about 30% of people eligible for stem cell transplant may choose not to have lenalidomide maintenance treatment at first line. The NHS England Cancer Drugs Fund clinical lead (from now, Cancer Drugs Fund lead) provided statistics that supported the EAG's clinical advisers' view. The Cancer Drugs Fund lead explained that of the 1,500 people having daratumumab annually for transplant induction, only 1,000 start lenalidomide maintenance after transplant. So, there may be a growing population of people having transplants who do not have lenalidomide. One clinical expert suggested several reasons for the low uptake of lenalidomide maintenance treatment. They suggested that for some people starting Dar-Bor-Tha-Dex for transplant induction, their multiple myeloma may not adequately respond to enable them to have the transplant and then lenalidomide maintenance treatment. They also

suggested that some people whose multiple myeloma responds well to daratumumab transplant induction treatment may be recruited to the RADAR trial. RADAR is investigating the clinical effectiveness of treatment regimens in people with different genetic profiles that may affect how well their multiple myeloma responds to treatment. These people would not go on to have maintenance treatment with lenalidomide. The committee noted that people are recruited to RADAR at diagnosis rather than after transplant, so this is unlikely to explain the low uptake of lenalidomide maintenance treatment. The clinical expert also suggested that over the next few years, transplant numbers will likely decrease because people who are borderline candidates for transplant may be offered Dar-Len-Dex, which provides an overall survival of about 7 years. They explained that while Dar-Len-Dex is normally recommended when a transplant is unsuitable, NHS England has been allowing this switch for people starting transplant induction therapy who cannot tolerate Dar-Bor-Tha-Dex for transplant induction.

The Cancer Drugs Fund lead explained that, according to Blueteq data, of the most recent 2,000 people having Dar-Bor-Dex at second line, their clinicians indicated that 48% had previously had lenalidomide ('lenalidomide-exposed'). In the other 52%, people either had no previous treatment with lenalidomide ('lenalidomide-naive') or their condition was considered 'unsuitable' for second-line treatment with lenalidomide. They explained that since October 2023 when TA917 was published, 2,200 people have had Dar-Len-Dex, with 400 having Len-Dex at second line. So, the proportion of people who have had lenalidomide is likely to change.

The committee questioned the impact on subsequent treatments if most people have a daratumumab-containing regimen at earlier lines. The company acknowledged the need for treatment options at third line. It suggested that it is unlikely daratumumab monotherapy would be used at

fourth line. Instead, it suggested that other B-cell maturation antigen (BCMA) agents such as elranatamab (recommended with managed access in elranatamab for treating relapsed and refractory multiple myeloma after 3 or more treatments [TA1023]) and teclistamab may be used at fourth or fifth line. The committee noted that teclistamab and elranatamab are recommended after an anti-CD38 treatment, so people should have had daratumumab at first, second or fourth line. For people who have not had an anti-CD38 treatment, the committee noted that isatuximab plus pomalidomide and dexamethasone is recommended with managed access in isatuximab with pomalidomide and dexamethasone for treating relapsed and refractory multiple myeloma (TA658). The clinical experts explained that there is limited data on the impact of using a BCMA agent such as belantamab mafodotin early in the treatment pathway on the clinical effectiveness of other BCMA agents at fourth line and beyond. But they explained that there is some evidence that there may be a reduction of about 10% in response rates at fourth line in people who had prior belantamab mafodotin. They explained that if the period between BCMA agents is sufficiently long, for example 6 months based on real-world data, there is a greater chance of the BCMA agent at later lines being clinically effective.

The company highlighted that a large proportion of people with newly diagnosed multiple myeloma are 75 years and over. So, factors such as frailty and comorbidities are important considerations when offering treatment. The patient experts explained that, because of the highly individual nature of the condition and its response to treatment, a range of treatment options with different mechanisms of action are needed. The committee acknowledged the complex and evolving treatment pathway for multiple myeloma, and the high unmet need for effective and safe treatments, especially at later lines.

Positioning of belantamab mafodotin plus pomalidomide and dexamethasone

3.4 For this evaluation, the company initially positioned belantamab mafodotin plus pomalidomide and dexamethasone (from now, Bel-Pom-Dex) as a second-line treatment option when lenalidomide is unsuitable. It explained that reasons for lenalidomide unsuitability include refractoriness, contraindications, intolerance and individual preference. The company clarified that in line with its marketing authorisation, use of Bel-Pom-Dex will be restricted to people who have had lenalidomide. The committee recalled that some people may not have lenalidomide maintenance treatment at first line (see section 3.2), so there will likely be people at second line who have not had lenalidomide and who would not be eligible for treatment with Bel-Pom-Dex, but may become eligible at later lines of treatment. It noted that in the company's pivotal trial, DREAMM-8, everyone had prior lenalidomide, of which 53% had 1 previous line of treatment (Bel-Pom-Dex at second line) while the remaining 47% had 2 or more treatments (Bel-Pom-Dex at third line and beyond; see section 3.5). The clinical and patient experts reiterated the need for options at later lines in the treatment pathway. At second line in a lenalidomide-exposed population, the company explained that the relevant comparators are Car-Dex, Dar-Bor-Dex and Sel-Bor-Dex. Sel-Bor-Dex is only available if the condition is also refractory to daratumumab. The committee queried whether multiple myeloma would become refractory to both lenalidomide and daratumumab at the same time. The clinical experts explained that more people are likely to have multiple myeloma that is refractory to daratumumab only than to both daratumumab and lenalidomide. For some people having Dar-Len-Dex, lenalidomide may be stopped while they continue to have daratumumab.

The committee noted the ongoing NICE evaluation of belantamab mafodotin plus bortezomib and dexamethasone (from now, Bel-Bor-Dex) for treating relapsed or refractory multiple myeloma after 1 or more

treatments (ID6212). It queried the clinical rationale for choosing to combine belantamab mafodotin with either pomalidomide (ID6211; this evaluation) or bortezomib (ID6212). The clinical experts explained that in a situation of equally effective regimens for the same indication, the choice will usually be based on the person's clinical history. For example, some people may prefer a tablet (pomalidomide) than a subcutaneous treatment (bortezomib) because having a tablet needs less time in hospital. The Cancer Drugs Fund lead highlighted that belantamab mafodotin has different administration frequency when combined with pomalidomide (once every 4 weeks) than with bortezomib (once every 3 weeks). The clinical experts explained that with dose modifications to address the eye-related adverse events of belantamab mafodotin (see section 3.8), the interval between doses may be increased to every 8 to 12 weeks in practice. The committee noted that should the indication and positioning be similar across both evaluations (ID6211 and ID6212), the 2 treatment regimens are, in practice, comparators to each other, and should ideally have been considered in a single evaluation.

The committee acknowledged that the marketing authorisation for Bel-Pom-Dex restricts the population to people who have previously had lenalidomide. It noted that the company's positioning at second line only is narrower than the marketing authorisation. It considered that additional positioning at later lines is also clinically relevant and this flexibility would be welcomed by people with the condition and clinicians. It agreed that for a lenalidomide-exposed population, the company's choice of second-line comparators was appropriate.

Clinical evidence

Key clinical trial: DREAMM-8

3.5 The clinical-effectiveness evidence for Bel-Pom-Dex came from DREAMM-8, an ongoing, phase 3, international, randomised, open-label trial. It was stratified by prior bortezomib, prior anti-CD38 therapy (such as

daratumumab) and line of treatment. It included people 18 years or over with relapsed or refractory multiple myeloma, who had 1 or more lines of treatment including a lenalidomide-containing regimen. People in the trial were randomised to have Bel-Pom-Dex (n=155) or pomalidomide plus bortezomib and dexamethasone (from now, Pom-Bor-Dex; n=147). There was no treatment crossover. The company used data from the full intention-to-treat (ITT) population, who had treatment at second line (53%), third or fourth line (35%) and beyond (12%). The primary outcome was progression-free survival as assessed by an independent review committee that was blind to treatment group allocation.

The committee noted that the average age of people in DREAMM-8 was about 66 years. This was younger than people seen in the NHS, where the average age on diagnosis is usually around 75 years (see section 3.2). The committee noted that about half the population had treatment at later lines than the company's second-line positioning of Bel-Pom-Dex. It noted that only about 25% of the population had previously had daratumumab and there were no people of Black African or Caribbean ethnicity. In terms of generalisability of the results, the clinical experts mainly had concerns about the lower proportion having had daratumumab in DREAMM-8 compared with about 50% who would have it in the NHS. The committee questioned the impact of refractoriness to daratumumab on the clinical effectiveness of Bel-Pom-Dex. The clinical experts explained that there is no data, but generally, if the condition is refractory, outcomes are worse, but that this would apply to Bel-Pom-Dex and any comparator. The committee recalled that the clinical experts suggested that prior belantamab mafodotin treatment would likely not affect the clinical effectiveness of other BCMA agents at later lines of treatment (see section 3.3). This was inconsistent with the clinical experts' suggestion that prior daratumumab would affect the clinical effectiveness of Bel-Pom-Dex and other treatments at later lines. The company explained that progression-free survival was consistent for daratumumab-exposed

and refractory subgroups compared with the ITT population (see section 3.7).

Indirect treatment comparisons

3.6 The company did Bayesian network meta-analyses using Markov chain Monte Carlo simulations to estimate the effectiveness of Bel-Pom-Dex compared with the following second-line options in a lenalidomide-exposed population:

- Car-Dex
- Dar-Bor-Dex
- Sel-Bor-Dex (when the condition was also refractory to daratumumab).

The company used fixed-effects models in its base case because results were similar across the fixed- and random-effects models. The committee noted that although the point estimates may have been similar, the confidence intervals may have been wider with the random-effects models. The EAG considered that the company's network meta-analyses were at high risk of bias because:

- The populations of the included trials were variable, including different lines of treatment and levels of exposure to lenalidomide and daratumumab.
- The DREAMM-8 data, particularly for overall survival, was immature (see section 3.7).
- There was limited reporting of the trials' baseline characteristics, which made it difficult to assess between-study heterogeneity and the assumptions of transitivity and inconsistency.
- For some comparator trials, the proportional hazards assumption for progression-free and overall survival may not have held.
- The analyses had not been adjusted for treatment-effect modifiers, specifically prior line of treatment, Eastern Cooperative Oncology Group Performance Status, and International Scoring System stage.

- The analyses had not accounted for the impact of subsequent treatments on overall survival, including whether subsequent treatments in the trials represented NHS practice.
- The company's hazard ratio (HR) for overall survival (HR 0.76; 95% CI 0.62 to 0.93) from the OPTIMISMM trial – the common comparator trial investigating Pom-Bor-Dex compared with bortezomib plus dexamethasone (from now, Bor-Dex) that linked DREAMM-8 to the rest of the network – lacked credibility.

  The company explained that it had used the HR of 0.76 because the analysis that generated this result had been adjusted for subsequent treatments. The company explained that the adjustment was methodologically necessary and appropriate, because it accounted for the high rates of unintended crossover of people between the trial groups. The company explained that 79% in the Bor-Dex group and 68% in the Pom-Bor-Dex group had subsequent treatments. More than 66% of people in the Bor-Dex group had pomalidomide as a subsequent treatment. It explained that this pomalidomide crossover was unique to OPTIMISMM and that adjusting for subsequent treatments may not be appropriate for other trials in the network. The committee noted that OPTIMISMM's publication states that adjustments were made for any subsequent treatments, not only for pomalidomide crossover.

  The EAG highlighted that the company's preferred HR was sourced from an unpublished conference presentation. The EAG explained that the HR had been generated from a pre-planned exploratory overall-survival analysis using a Cox proportional hazards model with subsequent treatment as a time-dependent covariate and adjusting for stratification factors. The committee noted that the approach used to adjust for subsequent treatment is not preferred because it is associated with a high risk of bias (Morden et al. 2011). The EAG

highlighted that there was a final ITT analysis in a published conference abstract, which reported an unadjusted HR of 0.94 (95% CI 0.77 to 1.15). It highlighted that the company provided limited information about the adjustment applied in OPTIMISMM and its impact on other trials in the network. It explained that the effect of subsequent treatments on overall survival was likely important as shown by the adjusted results being statistically significant, whereas the ITT results were not. It explained that using the unadjusted HR of 0.94 would likely have led to all the HRs in the network meta-analysis being closer to 1, altering the results of the network meta-analysis.

The company could not provide details about the adjustment method used in OPTIMISMM and confirmed that it had not provided a network meta-analysis using the unadjusted HR. It highlighted that adjusted HRs were only used in trials in which there was unintended crossover and explained that there were 2 trials affected, OPTIMISMM and CANDOR (which compared Car-Dex with daratumumab plus carfilzomib and dexamethasone).

The committee queried whether the group in OPTIMISMM having Bor-Dex and then pomalidomide represented NHS clinical practice. The clinical experts thought it did. The committee recalled that in the CASTOR trial which compared Dar-Bor-Dex with Bor-Dex, most people had pomalidomide as subsequent treatment, but this had not been adjusted for in its analyses.

The committee noted that subsequent treatments are important in understanding overall survival. It considered that the same approach to subsequent treatments should be applied to all the trials in the network where possible. It acknowledged the importance of OPTIMISMM given that it includes the common treatment linking Bel-Pom-Dex with all the comparators in the decision problem. It noted the limited details

provided by the company about the adjustment method used in the OPTIMISMM analysis. It would have preferred to see detailed information about the adjustment method used in OPTIMISMM, and where relevant, approaches to subsequent treatment for all other trials in the network. It considered that the unadjusted HR of 0.94 represented NHS clinical practice, and it would prefer to have seen a scenario analysis using this HR. The committee acknowledged the other methodological limitations of the network meta-analyses and noted that the uncertainty of the results would be considered in its decision making.

Clinical-effectiveness results

3.7 From DREAMM-8 (see section 3.5), Bel-Pom-Dex showed:

- for the full ITT population, a statistically significant improvement in progression-free survival (HR 0.52; 95% CI 0.37 to 0.73; n=302), but no statistically significant difference in overall survival (HR 0.77; 95% CI 0.53 to 1.14; n=302) compared with Pom-Bor-Dex
- for the following subgroups, compared with Pom-Bor-Dex:
  - 1 prior line of treatment (second line): a statistically significant improvement in progression-free survival (HR 0.52; 95% CI 0.31 to 0.88; n=159)
  - daratumumab exposed: no statistically significant difference in progression-free survival (HR 0.69; 95% CI 0.39 to 1.21; n=80)
  - daratumumab refractory: no statistically significant difference in progression-free survival (HR 0.65; 95% CI 0.36 to 1.18; n=71).

From the indirect treatment comparisons (see section 3.6), Bel-Pom-Dex showed:

- a statistically significant improvement in progression-free survival compared with Car-Dex and Sel-Bor-Dex only (the company considers the exact data to be confidential and so it cannot be reported here)

- no statistically significant differences in overall survival compared with any of the comparators (the company considers the exact data to be confidential and so it cannot be reported here).

The company explained that in DREAMM-8, the primary endpoint of median progression-free survival had been met only in the Pom-Bor-Dex group. It acknowledged that the overall-survival data was immature. The committee noted that there was better progression-free survival with Bel-Pom-Dex than Car-Dex and Sel-Bor-Dex only. It recalled the methodological limitations of the indirect treatment comparisons (see section 3.6). It acknowledged the limitations of the available data, but agreed that it would also like to have seen network meta-analyses using data specific to the company's target second-line population. It concluded that there was uncertainty in the results from the overall-survival network meta-analysis.

Eye-related adverse events

3.8 In DREAMM-8 (see section 3.5), Bel-Pom-Dex showed higher rates of:

- all eye-related adverse events: 91% compared with 37% for Pom-Bor-Dex
- Grade 3 or higher eye-related adverse events: 48% compared with 6% for Pom-Bor-Dex.

The company explained that eye-related adverse events can occur in 1 or both eyes and may reoccur. It suggested that the endpoint relevant to eye-related events is best corrected visual acuity, that is, the best vision when wearing corrective lenses. Normal vision is 6/6 (20/20), 6/15 (20/50) represents significant blurring of vision and visual impairment is 6/60 (20/200). The company thought blurred vision was a clinically important threshold because it can affect activities of daily living. The committee noted that the DVLA (Driver and Vehicle

Licensing Agency) driving threshold eyesight is 6/12 (20/40). In DREAMM-8:

- blurred vision affected 34% of people having belantamab mafodotin (the first event started at a median of 112 days with about 92% resolved, that is, not having blurred vision)
- visual impairment affected about 1% of people having belantamab mafodotin (the first event started at a median of 351 days with all resolved).

The company explained that most eye-related adverse events were reversible and were managed with changes to the belantamab mafodotin dose based on the keratopathy and visual acuity scale. These changes included dose reductions (the company considers the exact proportion to be confidential and so it cannot be reported here), interruptions or delays (86%) and stopping belantamab mafodotin (9%). The company stated that the clinical effectiveness of Bel-Pom-Dex was maintained even with the dose changes which resulted in a lower relative dose intensity (RDI) for belantamab mafodotin compared with all other treatment components for Pom-Bor-Dex.

The summary of product characteristics for belantamab mafodotin suggests that the dose is reduced after cycle 1. The committee recalled that the clinical experts stated that the interval between belantamab mafodotin doses may be increased from the recommended 4 weeks to 8 to 12 weeks to manage eye-related adverse events (see section 3.4). The patient expert explained that they have Bel-Pom-Dex every 8 weeks because of eye-related adverse events. The committee noted that the RDI for belantamab mafodotin in DREAMM-8 was low and queried the evidence supporting no change in its clinical effectiveness. The company explained that at the most recent data cut, in line with the analysis presented in its submission (see section 3.7), Bel-Pom-Dex showed improved progression-free survival compared with

Pom-Bor-Dex. The committee queried what the longest delay was likely to be before a loss in clinical effectiveness was seen. The clinical experts explained that a decrease in clinical effectiveness is typically seen at 100 days. Generally, dose delays of less than 3 months do not cause a loss in clinical effectiveness. But they explained that this varies, and some people have had dose delays of 6 months with no loss of clinical effectiveness. The committee had not been presented with evidence about the impact on clinical effectiveness of dose modifications of belantamab mafodotin. It concluded that it would like to have seen analyses including Kaplan–Meier plots comparing progression-free survival in people having 8 and 12 weekly treatment of belantamab mafodotin.

Health-related quality of life and eye-related adverse events

3.9 The EAG clinical advisers suggested that the high number of eye-related adverse events with belantamab mafodotin may affect health-related quality of life. They highlighted that eye-related effects can continue even after treatment is stopped. They noted that as part of the marketing authorisation, people would need ophthalmic examinations (such as visual acuity, slit lamp) before each of the first 4 belantamab mafodotin doses (once every 4 weeks), and be continually monitored during treatment as clinically indicated. They considered that this level of monitoring could be burdensome to people with the condition and their carers, and could be a substantial burden on NHS resources. The company explained that despite a higher incidence of eye-related adverse events in the Bel-Pom-Dex group, there was no difference in overall health-related quality of life as measured by the EQ-5D-3L between the treatment groups over time in DREAMM-8. The EAG highlighted that the generic EQ-5D-3L may not adequately capture health-related quality-of-life changes. It highlighted that there is a vision ‘bolt-on’, the EQ-5D-V, which the company had not used (see section 3.19). The clinical experts explained that across belantamab mafodotin clinical trials, the EQ-5D had not shown a detriment to health-related quality of life because of eye-

related adverse events. But they explained that with a more sensitive tool such as the Ocular Surface Disease Index, some variation in health-related quality of life may be seen.

The patient expert explained that eye-related adverse events had affected their ability to read and the distance at which they could watch television. But they explained that they are still able to drive according to DVLA standards. They explained that these eye-related adverse events do not cause pain, anxiety or depression, or affect their mobility. They said that the eye-related adverse events are more of an inconvenience, because their lens prescription does not match their spectacles. They explained that their ophthalmologist does not recommend renewing the spectacles while on treatment as there would likely be more changes to their vision. The clinical experts explained that dose changes to reduce eye-related adverse events can help to maintain health-related quality of life.

The committee noted that almost half of the people having belantamab mafodotin in DREAMM-8 had eye-related adverse events (see section 3.8), but that the impact varied. It concluded that eye-related adverse events and their impact should be appropriately captured in the economic model.

Economic model

Company's modelling approach

3.10 The company provided a cohort-based partitioned survival model to estimate the cost effectiveness of Bel-Pom-Dex compared with Car-Dex, Dar-Bor-Dex and Sel-Bor-Dex. The model included 4 health states: progression free on treatment, progression free off treatment, progressed disease, and death. The probability of being in each health state was calculated using extrapolated progression-free survival, overall survival and time-to-treatment-discontinuation curves, using standard parametric distributions fitted to DREAMM-8 Kaplan–Meier data. People started in

the progression-free on-treatment health state at second line. The model included a cycle length of 1 week with no half-cycle correction over a lifetime horizon of 33.9 years. The starting age of 66.1 years in the model was based on DREAMM-8. The committee was aware of the Systemic Anti-Cancer Therapy (SACT) dataset that had collected data on overall survival and treatment duration from clinical practices in England since 2019 for 1 of the comparators, Dar-Bor-Dex (see TA897). It considered that the starting age in the model should reflect NHS practice and should be based on the SACT dataset. It concluded that the company's model structure was acceptable for decision making.

Overall-survival benefit

3.11 In its base case, the company modelled differences in overall survival between treatments based on extrapolated data from DREAMM-8 Kaplan–Meier curves and the indirect treatment comparisons. In the EAG's base case, it assumed no overall-survival differences between treatments and used the company's overall-survival extrapolation for Bel-Pom-Dex from DREAMM-8 for all the comparators. The EAG thought that this was justified because the overall-survival data from DREAMM-8 was immature and uncertain. And there were no statistically significant overall-survival differences for Bel-Pom-Dex compared with any of the comparators from the network meta-analysis (see section 3.6). The EAG noted that an overall-survival benefit would likely include the varying effects of subsequent treatments on overall survival after disease progression.

The company argued that an overall-survival benefit was plausible. This was because of the improvement seen in the surrogate measures of progression-free survival and minimal residual disease negativity, which was 5 times higher in the Bel-Pom-Dex group compared with the Pom-Bor-Dex group in DREAMM-8. It explained that a similar trend was seen with Bel-Bor-Dex (ID6212), which showed statistically significant differences in overall survival after improvements in progression-free

survival and minimal residual disease negativity compared with Dar-Bor-Dex. The clinical experts agreed that there is a strong correlation between minimal residual disease negativity and overall-survival benefit but noted that an overall-survival benefit from DREAMM-8 had not yet been shown. One clinical expert noted that OPTIMISMM did not show overall-survival benefit in a lenalidomide-refractory population and emphasised that mature data is needed to ensure that there is a difference in overall survival.

The company explained that it had provided a scenario analysis in its submission in which overall survival was extrapolated assuming a surrogacy between progression-free survival and overall-survival outcomes. HRs (reflecting the surrogacy between progression-free survival and overall survival) for each comparator were applied to the progression-free survival curve of each comparator to estimate overall survival for each comparator. A Bel-Pom-Dex progression-free survival curve was used as the baseline treatment curve. The EAG noted that the overall-survival estimates for both Bel-Pom-Dex and Pom-Bor-Dex were above the estimates from DREAMM-8 at 12 and 24 months, and so lacked face validity. The EAG reiterated the additional issue of the methodological limitations of the network meta-analysis (see section 3.6), which would not be resolved with more mature overall-survival data from DREAMM-8.

The committee considered that the company's scenario analysis did not reduce the uncertainty about the overall-survival benefit. It agreed with the EAG that there would likely still be uncertainties in the relative estimates of Bel-Pom-Dex compared with the relevant comparators because of the methodological limitations of the network meta-analysis. It acknowledged the strong correlation between minimal residual disease negativity and overall survival, but agreed that a strong correlation alone is not sufficient to assume surrogacy. It considered that there was high uncertainty about

the size and direction of the overall-survival benefit of Bel-Pom-Dex compared with Car-Dex, Dar-Bor-Dex and Sel-Bor-Dex. To address the uncertainty in the relative estimates of overall survival, it would also have preferred to see scenario analyses using matching-adjusted indirect comparisons (MAIC) for all the comparators. And it reiterated that it would have preferred to see a scenario analysis using estimates from the network meta-analysis that included the published HR of 0.94 from OPTIMISMM (see section 3.6).

The committee recalled the issue of generalisability of the population of DREAMM-8 to the company's target population in the NHS, in terms of being younger and only 53% having treatment at second line (see section 3.5). For the base case, it would have preferred to see an analysis in which the overall-survival data from SACT for Dar-Bor-Dex was used to estimate the absolute baseline curve, with the relative effects of the comparators applied from the network meta-analysis. The committee considered that neither the company's modelling of overall survival nor the EAG's assumption of no differential overall-survival benefit were aligned with its preferred assumptions. It had serious concerns about the credibility of the company's estimates of long-term overall survival and recalled that no overall-survival benefit for Bel-Pom-Dex over its comparators had been shown (see section 3.7). So, in the absence of evidence of differential overall survival and concerns about the company's overall-survival modelling, it preferred to apply the EAG's base case that assumed no difference in overall survival among the treatments.

Dose interruption of belantamab mafodotin

3.12 The summary of product characteristics states that belantamab mafodotin should be given in a 4-week cycle, starting at 2.5 mg/kg once in cycle 1 and then decreased to 1.9 mg/kg once every 4 weeks from cycle 2 until progression or unacceptable toxicity. Clinicians may increase the time between doses from 8 weeks up to 6 months to reduce eye-related adverse events. It was aware that there are restrictions on funding for

breaks in treatment. The Cancer Drugs Fund lead confirmed that the treatment break policy for adverse events is normally 6 weeks, but may extend to up to 3 months for immunotherapy. They explained that should Bel-Pom-Dex be recommended, a treatment-interruption break of up to 6 months would be allowed. The clinical experts explained that in the compassionate-use programme for belantamab mafodotin, most treatment interruptions were less than 6 months. They agreed a threshold of 6 months would be adequate. The committee concluded that a 6-month treatment interruption should be allowed for eye-related adverse events with belantamab mafodotin.

Acquisition cost of generic alternatives of pomalidomide

3.13 In its base case, the company assumed the acquisition cost of pomalidomide would be reduced because of the availability of generic alternatives. The company considers that the assumed percentage reduction is confidential and so it cannot be reported here. The Cancer Drugs Fund lead advised that it is likely that the cost of pomalidomide would be higher than that assumed by the company. They explained that the price should be available before the marketing authorisation for Bel-Pom-Dex has been granted. After the committee meeting, the price of pomalidomide through the Medicines Procurement and Supply Chain framework became available. These prices are commercial in confidence and cannot be reported here. The EAG provided revised confidential cost-effectiveness estimates using the updated price for pomalidomide. The committee acknowledged that there may be variation in the acquisition price of generic pomalidomide. It concluded that the price of pomalidomide should reflect prices that are available to the NHS at the time of writing, and preferred to use the revised cost-effectiveness estimates provided by the EAG.

Medication use and drug costs

3.14 In its base case, the company used different approaches to estimate medication use for belantamab mafodotin compared with the other

treatment options. It used individual patient data (IPD) from DREAMM-8 to estimate doses of belantamab mafodotin. For all other medicines including pomalidomide and dexamethasone, the company based medication use on the summary of product characteristics and a constant RDI to capture dose modifications, sourced from the publications of key trials. The company explained that it had used the IPD data for belantamab mafodotin to account for its unique time-varying dose delays. It explained that this was not done for other medicines because their RDIs were high (ranging from 92% to almost 100%) compared with belantamab mafodotin, the RDI of which was much lower. The EAG agreed that using IPD provided a more accurate estimate of costs for belantamab mafodotin and would be the preferred approach for all treatments. But it considered a consistent approach should have been adopted across all treatments. So, it provided a scenario analysis in which RDI-based costs were used for all treatments. This analysis showed that the total cost of belantamab mafodotin increased considerably (the company considers the exact figure to be confidential and so it cannot be reported here). The committee acknowledged the company's concerns about using the RDI for belantamab mafodotin and understood its rationale for preferring the IPD. It noted that the company had access to IPD for pomalidomide, bortezomib and dexamethasone from DREAMM-8, and also Dar-Bor-Dex from ID6212. The committee would have preferred to see a scenario analysis in which all available IPD was used to estimate medication use and costs to provide reassurance on the consistency of the RDI-based costs for the comparators.

Costs of subsequent treatments

3.15 In its base case, the company included a one-off cost for up to 2 lines of subsequent treatments following disease progression after second-line treatment. It assumed that people would stay on subsequent treatments for a median of 9 months, in line with the median overall survival for multiple myeloma at third line and beyond shown in Kumar et al. (2012). It assumed that the same proportion of people would start third-line (81%)

and fourth-line (34%) treatment based on Raab et al. (2019). The committee questioned the validity of these studies, given their age and that the treatment pathway for multiple myeloma has progressed with many more options now being available. The company used the average proportions of subsequent treatment options provided by 3 clinical experts to inform the distribution of subsequent treatments. At third line, included options were Sel-Bor-Dex (63.3% to 66.7%) and Pan-Bor-Dex (33.3% to 100%). At fourth line, included options in order of preference were Pom-Dex (81.1% to 83.3%), daratumumab monotherapy (16.7%) and Pan-Bor-Dex (2.1% to 2.2%). The EAG thought that the company's approach to modelling subsequent treatments was acceptable. The committee recalled that the company had stated that it was unlikely daratumumab monotherapy would be used at fourth line, and that other BCMA agents such as teclistamab may be used (see section 3.2). It had concerns about the old studies used to inform the modelling of subsequent treatments. It considered that data collected from SACT may better reflect subsequent treatments used in the NHS. It would have preferred to see scenario analyses in which SACT data was used to inform the modelling of subsequent treatments and teclistamab was included as a fourth-line option.

Monitoring costs for belantamab mafodotin

3.16 In its base case, the company assumed that people having Bel-Pom-Dex would be seen by an ophthalmologist for only the first 4 treatment cycles as per the summary of product characteristics, at a resource use per model cycle of 0.33. The company thought that this was likely to be an overestimate given that dose delays are common and so people would likely see an ophthalmologist fewer than 4 times over the first 4 treatment cycles (see section 3.7). The Cancer Drugs Fund lead explained that the ophthalmic monitoring needed for belantamab mafodotin would likely be burdensome for ophthalmology departments in the NHS, which have long waiting lists. They explained that delays in implementation would be likely. They highlighted that everyone must have an ophthalmic eye exam before

each of the first 4 doses of belantamab mafodotin, and subsequent monitoring in the event of eye-related adverse events. They explained that the mechanism of delivery of this monitoring service and method of communication between ophthalmology departments or community services and oncologists were unclear. The clinical experts highlighted that about 30 to 40 hospitals took part in the compassionate-use scheme for belantamab mafodotin, and so hospitals have a pathway in place for eye examinations. The company explained that between 2018 and 2024, over 100 NHS sites administered belantamab mafodotin in different settings. It is exploring the option of supporting people through access to community-based ophthalmology at the point of recommendation.

The committee recalled that about 50% of people in DREAMM-8 experienced eye-related adverse events (see section 3.8). It was aware that the company had included a one-off cost for keratopathy, blurred vision and dry eyes using incidence rates from DREAMM-8. The EAG highlighted that the proportion of people having grade 3 eye-related adverse events in the model was lower than that reported in DREAMM-8. It noted that the cost for the eye-related adverse event included 1 hospitalisation. It considered this cost to be plausible given that a change in treatment for eye-related adverse events would be to stop or reduce the dose of belantamab mafodotin and allow the adverse event to resolve, possibly with some ointments. The committee considered that there was uncertainty about whether the cost of eye-related adverse events had been adequately accounted for in the model because it had not included continued monitoring until resolution of eye-related adverse events. So, the cost of monitoring with belantamab mafodotin was likely to be underestimated. It concluded that the base case should include the cost of monitoring eye-related adverse events using hospital-based ophthalmology services, with a scenario analysis using the community-based ophthalmology services proposed by the company.

Wastage of tablets and vial sharing

3.17 In its base case, the company assumed wastage on 100% of administrations including tablets, and no vial sharing. In its base case, the EAG considered that wastage of tablets (pomalidomide, selinexor and dexamethasone) should be excluded. This is because these medicines come in tablet sizes that allow reductions from the recommended dose; so doses can be lowered without wastage. The company agreed that it was plausible that there may be no wastage of tablets. The EAG explained that its clinical advisers suggested that there would likely be some vial sharing, although the extent of sharing is unknown. The clinical experts explained that while measures are taken to give treatment to people having the same medicines on the same day to maximise vial sharing, there is still some wastage. The committee concluded that no vial sharing should be included in the base case given the lack of information on its extent in clinical practice. It concluded that wastage of tablets should be excluded because they will likely be re-used in future cycles. The committee noted that the EAG's base case included both these assumptions.

Health-state utility values

3.18 In its base case, the company used EQ-5D-3L data from DREAMM-8 to derive health-state utilities. It assumed that health-related quality of life in the 'progression-free on-treatment' health state varied by treatment. For all comparators, it assumed that the utility value for the 'progression-free on-treatment' health state was the same as the utility value from the Pom-Bor-Dex group in DREAMM-8. The company used a higher utility value for the Bel-Pom-Dex group than the comparators for the 'progression-free on-treatment' health state. For the 'progression-free off-treatment' health state, the company used the pooled 'progression-free on-treatment' utility value and applied it to all treatments. For the 'progressed-disease' health state, the company used the pooled utility value from the Pom-Bor-Dex group and Bel-Pom-Dex group in DREAMM-8 and applied it to all treatments. The company considers the values to be confidential and so they cannot be reported here.

The EAG thought it implausible for belantamab mafodotin to have a higher 'progression-free on-treatment' utility value than its comparators given the eye-related adverse events, likely not captured by the generic EQ-5D-3L (see section 3.8). It also thought that the pooled 'progression-free off-treatment' and 'progressed-disease' utility values were not appropriate because they included data from the Pom-Bor-Dex group, which was not a relevant comparator. The EAG noted that the DREAMM-8 data comprised a population in which only 53% had treatment at second line. So, the EAG preferred to use the company's scenario that applied utility values from one of the comparators, Dar-Bor-Dex (see TA897). The EAG noted that these utility values were derived from a fully second-line population, and applied them to all treatments. For the 'progression-free on and off-treatment' health states it applied a utility value of 0.737, and for the 'progressed-disease' health state it applied a value of 0.665, which it noted was similar to the value derived from DREAMM-8.

The company had explained that despite a higher incidence of eye-related adverse events in the Bel-Pom-Dex group, there was no difference in overall health-related quality of life as measured by the EQ-5D-3L between the treatment groups over time in DREAMM-8 (see section 3.8). The company explained that it modelled a treatment-specific progression-free on-treatment utility because of a statistically significant coefficient in the linear regression utility model. The committee acknowledged this but highlighted that there was no interaction term between Bel-Pom-Dex and the progression-free health state. It explained that the interaction term would be necessary to claim that quality of life is different with a given treatment in a given state. It noted that the company had also fitted a simpler model that did not assume a difference by treatment, and this had an objectively better fit to the data (judged by quasi-likelihood under the independence model criterion). The committee queried whether it would be plausible to have a better health-related quality of life by only having

Bel-Pom-Dex compared with other treatments, before experiencing longer progression-free survival. The clinical experts explained that based on DREAMM-8, people had a deeper response on Bel-Pom-Dex given every 10 to 12 weeks compared with Pom-Bor-Dex that was given more frequently, and so a better health-related quality of life was plausible. But, they acknowledged that although belantamab mafodotin has limited side effects, issues of eye-related adverse events may affect health-related quality of life. The committee was aware that the company had also presented a scenario using DREAMM-8 pooled values in which no differential effect of treatment on health-state utilities was applied. It considered that there was not strong evidence to justify applying a higher 'progression-free on-treatment' health-state utility value for belantamab mafodotin than its comparators. It concluded that it preferred the EAG's approach that used the same utilities derived from a wholly second-line population, regardless of treatment.

Disutility of eye-related adverse events

3.19 In its base case, the company included grade 3+ treatment-emergent adverse events that occurred in at least 5% of people in DREAMM-8 and respective trials for the comparators. For non-eye-related adverse events, it applied a one-off disutility in the first cycle of the model. For eye-related adverse events, the company included keratopathy, blurred vision and dry eyes event rates per model cycle. These eye-related adverse events only affected people having belantamab mafodotin and the company assumed that any disutility was already captured in the generic EQ-5D-3L (see section 3.8). The committee noted that the company had applied a disutility for eye-related adverse events for the evaluation of Bel-Bor-Dex (ID6212). The committee recalled the discussion around the responsiveness of the EQ-5D-3L in assessing the impact of eye-related adverse events on health-related quality of life, and the availability of the vision bolt-on, EQ-5D-V. The vision bolt-on asks respondents to describe their vision on a scale of 'no problems', 'some problems' or 'extreme problems'. Based on feedback from the patient expert, the committee

considered that the EQ-5D-3L in DREAMM-8 would have likely captured the impact of eye-related adverse events on health-related quality of life, given the frequency of assessments. But, it recalled the clinical experts' suggestion that other vision-specific assessment tools may better capture changes in health-related quality of life (see section 3.9). It considered that the extent to which the EQ-5D-3L captures the impact of vision loss on quality of life is uncertain. The committee preferred to use the same health-state utility values irrespective of treatment (see section 3.18). It noted that disutility was applied to non-eye-related adverse events. It would have preferred to see a scenario in which the disutility of eye-related adverse events had also been applied.

Cost-effectiveness estimates

Committee's preferred assumptions

3.20 The committee noted that neither the company's nor the EAG's base case included all its preferred assumptions, which were:

- to use the starting age based on the SACT dataset (see section 3.10)
- for overall-survival benefit, to use the overall-survival data from SACT for Dar-Bor-Dex to estimate the absolute baseline curve, with the relative effects of the comparators applied from an updated network meta-analysis that addresses the methodological issues highlighted (in particular, the approach used for subsequent treatments; see sections 3.6 and 3.11)
- to model a maximum dose interruption interval of 6 months for belantamab mafodotin (see section 3.12)
- to use the acquisition cost of pomalidomide from the Medicines Procurement and Supply Chain framework (see section 3.13)
- to include the cost of monitoring eye-related adverse events using hospital-based ophthalmology services (see section 3.16)
- to assume no vial sharing (see section 3.17)
- to exclude wastage of tablets (see section 3.17)

- to apply the EAG's approach that used the same utilities derived from a wholly second-line population, regardless of treatment (see section 3.18).

Acceptable ICER

3.21 NICE's manual on health technology evaluations notes that, above a most plausible incremental cost-effectiveness ratio (ICER) of £20,000 per quality-adjusted life year (QALY) gained, judgements 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. But it will also take into account other aspects including uncaptured health benefits. The committee noted the high level of uncertainty, specifically related to the:

- generalisability of the population of DREAMM-8 to the company's target population in the NHS, in terms of:
  - the trial population being younger
  - there being no one of Black African or Caribbean ethnicity
  - only 53% of people having treatment at second line
  - only 25% of people having daratumumab-refractory multiple myeloma (see section 3.5)
- indirect treatment comparisons and their methodological limitations (see section 3.6)
- clinical effectiveness of belantamab mafodotin (see sections 3.7 and 3.8)
- credibility of HRs derived from the network meta-analyses, particularly for overall survival and its impact on assumptions of overall-survival benefit (see sections 3.6 and 3.11)
- estimation of medication use and related drug costs for all treatments (see section 3.14)
- modelling of subsequent treatments (see section 3.15)

- cost of monitoring eye-related adverse events for belantamab mafodotin (see section 3.16).

So, the committee concluded that an acceptable ICER would be around £20,000 per QALY.

Areas needing clarification

3.22 The committee recalled that people with multiple myeloma and clinicians would welcome the option of having Bel-Pom-Dex at later lines (see section 3.4). It noted that there were many areas of uncertainty (see section 3.21) and would like to see clarification on:

- the adjustment method undertaken in OPTIMISMM and where relevant, approaches to subsequent treatment for all other trials in the network (see section 3.6)
- the evidence of clinical effectiveness of Bel-Pom-Dex in the company's target second-line population (see section 3.7)
- the impact of dose modifications (reductions, delays or interruptions because of eye-related adverse events) of belantamab mafodotin on its clinical effectiveness (see sections 3.7 and 3.8)
- the company's statement that it is exploring the option of supporting people with access to community-based ophthalmology at the point of recommendation (see section 3.16).

The committee also requested the following analyses:

- network meta-analyses using data specific to the company's target second-line population (see section 3.7)
- analyses including Kaplan–Meier plots comparing progression-free survival in people having Bel-Pom-Dex treatment at 8 and 12 weekly intervals, to assess the impact of dose interruptions (see section 3.8)
- a base-case analysis using overall-survival data from SACT for Dar-Bor-Dex to estimate the absolute baseline curve, with the relative

effects of the comparators applied from an updated network meta-analysis that addresses the methodological issues highlighted; in particular, the approach used for subsequent treatments (see sections 3.6 and 3.11)

- a scenario analysis using the unadjusted overall-survival HR of 0.94 from OPTIMISMM in the network meta-analysis (see sections 3.6 and 3.11)
- a scenario analysis in which all available IPD is used to estimate medication use and costs for all treatments (see section 3.14)
- a scenario analysis in which SACT data is used to inform the modelling of subsequent treatments (see section 3.15)
- scenario analyses in which teclistamab is included as a fourth-line option for subsequent treatments (see section 3.15)
- a base-case analysis that includes the cost of monitoring eye-related adverse events using hospital-based ophthalmology services (see section 3.16)
- a scenario analysis in which the cost of monitoring eye-related adverse events is provided using the community-based ophthalmology services as proposed by the company (see section 3.16)
- a scenario analysis in which the disutility of eye-related adverse events is applied (see section 3.19).

Company and EAG cost-effectiveness estimates

3.23 The committee considered the cost effectiveness of Bel-Pom-Dex compared with Car-Dex, Dar-Bor-Dex and Sel-Bor-Dex at second line. It concluded that because of the uncertainties in the economic model and clinical evidence, it was not possible to determine the most likely cost-effectiveness estimates for Bel-Pom-Dex.

Managed access

3.24 Having concluded that Bel-Pom-Dex could not be recommended for routine use (see section 3.28), the committee then considered if it could

be recommended with managed access for treating multiple myeloma in adults who have had at least 1 treatment including lenalidomide. The committee noted that the key uncertainties were related to the methodological limitations of the overall-survival network meta-analysis that used OPTIMISMM to connect Bel-Pom-Dex to all the comparators, and the immature overall-survival data from the ongoing DREAMM-8 trial. The company explained that it was not sure when the final endpoint for overall-survival events at 60% would occur. The committee considered that even with more mature overall-survival data, the methodological issues of the network meta-analyses and related uncertainties would persist. It noted that the company had not submitted a managed access proposal and so the feasibility of data collection and analysis could not be assessed. Nevertheless, it considered whether a recommendation with managed access could be made and noted that there were no plausibly cost-effective ICERs, so Bel-Pom-Dex could not be recommended through managed access.

Other factors

Equality

3.25 The recommendations apply equally to all people with relapsed or refractory multiple myeloma. The clinical experts noted that multiple myeloma is common in men, elderly people, and people from Black African and Caribbean ethnic groups. The committee noted that its recommendations apply equally, regardless of sex, age or ethnicity. It concluded that the difference in prevalence did not represent an equality issue in this evaluation.

Uncaptured benefits

3.26 The committee considered whether there were any uncaptured benefits of Bel-Pom-Dex. It acknowledged that Bel-Pom-Dex provided a different mechanism of action earlier in the treatment pathway and has longer dose intervals, which may be more convenient for people. But, it noted that the

eye-related adverse events and the related monitoring may reduce this benefit. And it considered that these benefits were captured in the economic model. So, the committee concluded that all additional benefits of Bel-Pom-Dex had already been taken into account.

Severity

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

Conclusion

Recommendation

3.28 Because of the uncertainties in the economic model and clinical evidence, it was not possible to determine the most likely cost-effectiveness estimates for Bel-Pom-Dex. So, it could not be recommended for routine commissioning in the NHS for treating multiple myeloma in adults who have had at least 1 treatment including lenalidomide.

4 Evaluation committee members and NICE project team

Evaluation committee members

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

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, a project manager and an associate director.

Sharlene Ting
Technical lead

Eleanor Donegan
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Vonda Murray
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Richard Diaz
Associate director

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