NICE National Institute for Health and Care Excellence

NICE guidance

Belantamab mafodotin with pomalidomide and dexamethasone for previously treated multiple myeloma

Technology appraisal guidance
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Your responsibility

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

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

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

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1 Recommendations

1.1 Belantamab mafodotin plus pomalidomide and dexamethasone can be used as an option to treat multiple myeloma in adults, if:

- they have only had 1 line of treatment and that contained lenalidomide, and
- lenalidomide is not tolerated or the condition is refractory to it.

Belantamab mafodotin can only be used if the company provides it according to the commercial arrangement.

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 must be funded in the NHS in England for the condition and population in the recommendations. It must be funded in England within 90 days of final publication of this guidance.

There is enough evidence to show that belantamab mafodotin plus pomalidomide and dexamethasone provides benefits and value for money, so it can be used routinely across the NHS in this population.

NICE has produced tools and resources to support the implementation of this guidance.

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 only as a treatment at second line. It provided evidence for multiple myeloma when lenalidomide is not tolerated or the condition is refractory to it.

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 is refractory 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
- daratumumab plus bortezomib and dexamethasone
- selinexor plus bortezomib and dexamethasone.

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

There are also uncertainties in the economic model. But the cost-effectiveness estimates for belantamab mafodotin plus pomalidomide and dexamethasone are within the range that NICE considers an acceptable use of NHS resources. So, it can 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 is 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 ranges from £7,995.60 to £8,884 per 21-pack of 1-mg, 2-mg, 3-mg or 4-mg tablets (excluding VAT; BNF online accessed December 2025).

2.4 GlaxoSmithKline has a commercial arrangement for belantamab mafodotin. This makes it available to the NHS with a discount. The size of the discount is commercial in confidence.

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.

Sustainability

2.6 For information, the Carbon Reduction Plan for UK carbon emissions is available on GlaxoSmithKline's UK webpage.

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. This is 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 them 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 (from now, Bor-Dex), or bortezomib plus dexamethasone and thalidomide (see NICE's technology appraisal guidance

on bortezomib for induction therapy in multiple myeloma before high-dose chemotherapy and autologous stem cell transplantation)

- daratumumab plus bortezomib, thalidomide and dexamethasone (from now, Dar-Bor-Tha-Dex; see NICE's technology appraisal guidance on daratumumab in combination for untreated multiple myeloma when a stem cell transplant is suitable)
- lenalidomide maintenance treatment after a stem cell transplant (see NICE's technology appraisal guidance on lenalidomide maintenance treatment after an autologous stem cell transplant for newly diagnosed multiple myeloma).

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 (see NICE's technology appraisal guidance on bortezomib and thalidomide for the first-line treatment of multiple myeloma, from now TA228)
- bortezomib plus an alkylating agent and a corticosteroid (TA228)
- lenalidomide plus dexamethasone (from now, Len-Dex), only if thalidomide is contraindicated or not tolerated (see NICE's technology appraisal guidance on lenalidomide plus dexamethasone for previously untreated multiple myeloma)
- daratumumab plus lenalidomide and dexamethasone (from now, Dar-Len-Dex; see NICE's technology appraisal guidance on daratumumab with lenalidomide and dexamethasone for untreated multiple myeloma when a stem cell transplant is unsuitable, from now TA917)
- isatuximab plus bortezomib, lenalidomide and dexamethasone (see NICE's technology appraisal guidance on isatuximab in combination for untreated multiple myeloma when a stem cell transplant is unsuitable).

The clinical experts explained that thalidomide or bortezomib plus an alkylating agent and a corticosteroid, and lenalidomide plus dexamethasone are rarely used in NHS clinical practice. At second line, NICE recommends the following treatments as options:

- bortezomib monotherapy (see NICE's technology appraisal guidance on bortezomib monotherapy for relapsed multiple myeloma), although this treatment is rarely used in NHS clinical practice
- Len-Dex if the person has only had 1 previous line of treatment containing bortezomib (see NICE's technology appraisal guidance on lenalidomide plus dexamethasone for multiple myeloma after 1 treatment with bortezomib)
- carfilzomib plus dexamethasone (from now, Car-Dex; see NICE's technology appraisal guidance on carfilzomib for previously treated multiple myeloma)
- carfilzomib plus lenalidomide and dexamethasone, if the person has only had 1 previous line of treatment containing bortezomib (see NICE's technology appraisal guidance on carfilzomib with dexamethasone and lenalidomide for previously treated multiple myeloma)
- 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 (see NICE's technology appraisal guidance on daratumumab with bortezomib and dexamethasone for previously treated multiple myeloma, from now 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 (see NICE's technology appraisal guidance on selinexor with bortezomib and dexamethasone for previously treated multiple myeloma, from now 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:

- Len-Dex (see NICE's technology appraisal guidance on lenalidomide for the treatment of multiple myeloma in people who have received at least 2 prior therapies)

- panobinostat plus bortezomib and dexamethasone (from now, Pan-Bor-Dex; see NICE's technology appraisal guidance on panobinostat for treating multiple myeloma after at least 2 previous treatments, from now TA380)
- ixazomib plus lenalidomide and dexamethasone (see NICE's technology appraisal guidance on ixazomib with lenalidomide and dexamethasone for treating relapsed or refractory multiple myeloma).

At fourth line, NICE also recommends daratumumab monotherapy (see NICE's technology appraisal guidance on daratumumab monotherapy for treating relapsed and refractory multiple myeloma).

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

- pomalidomide plus low-dose dexamethasone (from now, Pom-Dex; see NICE's technology appraisal guidance on pomalidomide for multiple myeloma previously treated with lenalidomide and bortezomib)
- 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 (see NICE's technology appraisal guidance on teclistamab for treating relapsed and refractory multiple myeloma after 3 or more treatments).

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 (see NICE's technology appraisal guidance on selinexor with dexamethasone for treating relapsed or refractory multiple myeloma after 4 or more treatments).

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 with newly diagnosed multiple myeloma 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 (OS) 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 a stem cell transplant may choose not to have lenalidomide maintenance treatment at first line. The NHS England Cancer Drugs Fund clinical lead (from now, the 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 a 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 a transplant, so this is unlikely to explain the low uptake of lenalidomide maintenance treatment. The clinical expert suggested that, over the next few years, transplant numbers will likely decrease. This is because people who are borderline candidates for a transplant may be offered Dar-Len-Dex, which provides an OS of about 7 years. They explained that Dar-Len-Dex is normally recommended when a transplant is unsuitable. But 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 healthcare professionals indicated that 48% had previously had lenalidomide ('lenalidomide-exposed'). In the other 52%, people had 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 of them 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 NICE's technology appraisal guidance on elranatamab for treating relapsed and refractory multiple myeloma after 3 or more treatments) 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 NICE's technology appraisal guidance on isatuximab with pomalidomide and dexamethasone for treating relapsed and refractory multiple myeloma. 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 have 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 patient 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 having second-line treatment 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, but:

- 53% had 1 previous line of treatment (Bel-Pom-Dex at second line)
- 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 the second committee meeting, the patient expert reiterated their disappointment that the company had chosen not to extend the target population beyond second line, despite the available clinical evidence. 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. For a population for whom lenalidomide is suitable but choose not to have it, the company did not present comparisons with second-line lenalidomide-containing regimens. The committee noted the evolving treatment landscape (see section 3.3) and the expected increased use of daratumumab at first line (see section 3.5). It suggested that Dar-Bor-Dex will likely become a less relevant comparator in the future. The clinical experts agreed that this was a reasonable assessment. 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 (from now, ID6212). It queried the clinical rationale for choosing to combine belantamab mafodotin with either pomalidomide (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 means less time in hospital. The Cancer Drugs Fund lead highlighted that belantamab mafodotin has a different administration frequency when combined with pomalidomide (once every 4 weeks) than with bortezomib (once every 3 weeks). The clinical experts explained that there can be dose modifications to address the eye-related adverse events of belantamab mafodotin (see section 3.8). This can mean the interval between doses may be increased to every 8 to 12 weeks in practice. The committee noted that the indication and positioning might be similar across both evaluations (this evaluation and ID6212). If this is the case, 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 recalled that the patient expert thought that the company's decision to limit the use of Bel-Pom-Dex to second line was too restrictive. The committee thought that additional positioning at later lines is also clinically relevant and this flexibility would be welcomed by people with the condition and healthcare professionals. But it noted that it could make recommendations only for second-line positioning because the company had not submitted evidence for later lines in the treatment pathway. It thought that the company's choice of second-line comparators excluding lenalidomide-containing regimens was appropriate specifically for people with multiple myeloma that is refractory, intolerant of, or contraindicated to lenalidomide. The committee concluded that any recommendation should specify these conditions to provide clear guidance to healthcare professionals in the NHS on the appropriate population.

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 (PFS) 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, in which the average age at diagnosis is usually around 75 years (see section 3.2). The committee noted that about half of the DREAMM-8 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 that it did not include any people of Black African or Caribbean ethnicity. In terms of generalisability of the results, at the first committee meeting, 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.

At the second committee meeting, the clinical experts clarified that the proportion of people currently having daratumumab at first line in the NHS is likely to be similar to that seen in DREAMM-8 (around 25%). But they noted that this proportion is expected to increase over time. 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 they thought 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 PFS was consistent for daratumumab-exposed and refractory subgroups compared with the ITT population (see section 3.7). The committee noted that there were no statistically significant differences in PFS between Bel-Pom-Dex and Pom-Bor-Dex in the daratumumab-exposed and refractory subgroups. But it noted that the hazard ratios for PFS were higher compared with the ITT population. So, it concluded that there was uncertainty about whether prior daratumumab was a treatment-effect modifier.

Indirect treatment comparisons

3.6 The company did Bayesian network meta-analyses (NMAs) 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 thought that the company's NMAs were at high risk of bias because:

- The populations of the trials in the NMAs were variable, including that they had different lines of treatment and levels of exposure to lenalidomide and daratumumab.
- The DREAMM-8 data, particularly for OS, 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 consistency.
- For some comparator trials, the proportional hazards assumption for PFS and OS 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 revised International Scoring System stage.
- The analyses had not accounted for the impact of subsequent treatments on OS, including whether subsequent treatments in the trials represented NHS practice.
- There was uncertainty around using the company's hazard ratio of 0.76 for OS (95% confidence intervals [CI] 0.62 to 0.93) from OPTIMISMM, the common comparator trial investigating Pom-Bor-Dex compared with Bor-Dex that linked DREAMM-8 to the rest of the network.

The company explained that it had used the hazard ratio of 0.76 because the analysis that generated this result had been adjusted for subsequent

treatments. It also 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% of people 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 hazard ratio was sourced from an unpublished conference presentation. The EAG explained that the hazard ratio had been generated from a preplanned exploratory OS analysis. This analysis used a Cox proportional hazards model with subsequent treatment as a time-dependent covariate and adjusted 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 hazard ratio 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 OS was likely important as shown by the adjusted results being statistically significant, whereas the ITT results were not. It explained that using the unadjusted hazard ratio of 0.94 would likely have led to all the hazard ratios in the NMA being closer to 1, altering the results of the NMA.

The company could not provide details about the adjustment method used in OPTIMISMM and confirmed that it had not provided a NMA using the unadjusted hazard ratio. It highlighted that adjusted hazard ratios were only used in trials in which there was unintended crossover. It 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 it noted that this had not been adjusted for in its analyses.

The committee also noted that subsequent treatments are important in understanding OS. It thought that the same approach to subsequent treatments should have been applied to all the trials in the network when 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 thought that the unadjusted hazard ratio of 0.94 represented NHS clinical practice, and it would have preferred to see a scenario analysis using this hazard ratio.

In response to the draft guidance consultation, the company reiterated that it did not have access to information on OPTIMISMM's adjustment methods. It maintained that the adjusted hazard ratio of 0.74 remained the most appropriate estimate. But it provided an alternative analysis using individual patient data (IPD) and inverse-probability-of-treatment weighting (IPTW) to connect Bel-Pom-Dex from DREAMM-8 to Dar-Bor-Dex from DREAMM-7. The resulting relative survival estimates were then integrated into a fixed-effects NMA to derive PFS and OS outcomes. The EAG explained that the IPTW analysis provided a more direct connection to relevant comparators, but it thought that the methodological limitations of the original NMA remained. This was particularly so for the issue of adjusting for subsequent treatments across trials and the centrality of OPTIMISMM in linking Bel-Pom-Dex to Sel-Bor-Dex. The company thought that the new IPTW analysis was methodologically robust and statistically balanced. This was because it used available IPD and provided an independent validation of the original NMA results in terms of the direction of treatment effect (see section 3.7).

The committee acknowledged the company's attempt to mitigate the issue of linking Bel-Pom-Dex to the network. But it agreed with the EAG that the methodological limitations of the original NMA remained. It acknowledged the similarity in the PFS and OS results between the original and IPTW-integrated NMAs. But it noted the very wide confidence intervals for OS. The committee appreciated the company's additional analysis and the consistency between the 2 approaches to estimating relative effects. It agreed that the IPTW analysis helped with some of the uncertainty related to the Dar-Bor-Dex comparison. But it thought that the IPTW-integrated NMA did not effectively provide new data or resolve the limitations of the original NMA. It concluded that the IPTW-integrated NMA did not materially change the uncertainty related with the relative OS estimates.

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 PFS (hazard ratio [HR] 0.52; 95% CI 0.37 to 0.73; n=302), but no statistically significant difference in OS (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:
  - at second line and lenalidomide refractory: a statistically significant improvement in PFS (HR 0.43; 95% CI 0.25 to 0.75) but no difference in OS (HR 0.72; 95% CI 0.37 to 1.41)
  - at second line: a statistically significant improvement in PFS (HR 0.52; 95% CI 0.31 to 0.88; n=159)
  - daratumumab exposed: no statistically significant difference in PFS (HR 0.69; 95% CI 0.39 to 1.21; n=80)
  - daratumumab refractory: no statistically significant difference in PFS (HR 0.65; 95% CI 0.36 to 1.18; n=71).

From the indirect treatment comparisons including the original and IPTW-integrated NMAs (see section 3.6), Bel-Pom-Dex showed:

- a statistically significant improvement in PFS compared with Car-Dex, Dar-Bor-Dex and Sel-Bor-Dex (the company considers the exact data to be confidential, so it cannot be reported here)
- no statistically significant differences in OS compared with any of the comparators (the company considers the exact data to be confidential, so it cannot be reported here).

At the first committee meeting, the company explained that, in DREAMM-8, the primary endpoint of median PFS had been met only in the Pom-Bor-Dex group. It acknowledged that the OS data was immature. In response to the draft guidance consultation, the company reported that the median PFS had been met at the latest data cut up to October 2024 for Bel-Pom-Dex (median 32.6 months compared with 12.5 months with Pom-Bor-Dex; HR 0.49; 95% CI 0.35 to 0.68). The committee noted that there was better PFS with Bel-Pom-Dex than with all 3 comparators. It recalled the methodological limitations of the indirect treatment comparisons (see section 3.6). It concluded that there was uncertainty in the results from the OS NMAs.

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, no blurred vision, in a median of 29 days)
- visual impairment affected about 1% of people having belantamab mafodotin (the first event started at a median of 351 days with all resolved, in a median of 25.5 days).

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, so it cannot be reported here), interruptions or delays (86%) and stopping belantamab mafodotin (9%). The company highlighted that the clinical effectiveness of Bel-Pom-Dex was maintained even with the dose changes. This 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 noted 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). One 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 PFS 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.

In response to the draft guidance consultation, the company submitted analyses exploring the impact of dose interruptions of belantamab mafodotin on first-quartile PFS and progression or death in the overall ITT population compared with subgroups that had dose delays of at least 8, 12 or 24 weeks. It highlighted that, in people having Bel-Pom-Dex, 99% had 1 dose delay lasting a median of 53 days, while 74% had 3 dose delays. It provided Kaplan–Meier plots comparing PFS in people having belantamab mafodotin dose delays of at least 8 or 12 weeks after at least 6 months of Bel-Pom-Dex treatment. The company suggested that dose interruptions of belantamab mafodotin did not appear to affect the clinical effectiveness of Bel-Pom-Dex. This was because the delayed-dose subgroups had similar survival outcomes to the overall population. The company considers the exact data to be confidential, so it cannot be reported here. The clinical experts noted that dose delays typically occurred in people whose condition was responding to Bel-Pom-Dex. They explained that some delays were for managing eye-related adverse effects of belantamab mafodotin. But some dose delays in DREAMM-8 during the COVID-19 period may have reflected concerns that BCMA-targeted treatments could reduce the effectiveness of COVID-19 vaccines. They also highlighted that, although belantamab mafodotin dosing was interrupted, people generally continued effective treatments of pomalidomide and dexamethasone. The committee noted the inherent risk of time-related (immortal time) bias. It recognised that people must survive long enough to experience a dose delay, which could create an apparent lower risk of progression in the delayed-dose subgroups. It thought that the company's exploratory analyses provided useful contextual information. But it thought that they were limited by selection and time-related biases and did not robustly show an effect of belantamab mafodotin dose delays on clinical outcomes. The committee concluded that uncertainty remained about the impact of belantamab mafodotin dose delays on its clinical effectiveness.

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 and slit lamp) before each of the first 4 belantamab mafodotin doses (once every 4 weeks). They would then need to be continually monitored during treatment as clinically indicated. They thought that this level of monitoring could be burdensome to people with the condition and their carers. It could be a substantial burden on NHS resources. The company agreed that there were a higher incidence of eye-related adverse events in the Bel-Pom-Dex group in DREAMM-8. But they explained that there was no difference in overall health-related quality of life as measured by the EQ-5D-3L between the treatment groups over time. 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.

One 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 because there would likely be more changes to their vision. The committee noted that belantamab mafodotin-related deterioration in visual acuity is not correctable by spectacles. 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 most people having belantamab mafodotin in

DREAMM-8 had eye-related adverse events (see section 3.8), but that the impact can vary. 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 PFS, OS 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 OS and treatment duration from clinical practices in England since 2019 for 1 of the comparators, Dar-Bor-Dex (see TA897). It thought that the starting age in the model should reflect NHS practice and should be based on the SACT dataset. In response to the draft guidance consultation, the company updated its base case to include the starting age of 70 years derived from the SACT dataset. The committee concluded that the company's model was acceptable for decision making.

OS benefit

3.11 In its original base case, the company modelled differences in OS 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 OS differences between treatments and used the company's OS extrapolation for Bel-Pom-Dex from DREAMM-8 for all the comparators. The EAG thought that this

was justified because the OS data from DREAMM-8 was immature and uncertain. Also, there were no statistically significant OS differences for Bel-Pom-Dex compared with any of the comparators from the NMA (see section 3.6).The EAG noted that an OS benefit would likely include the varying effects of subsequent treatments on OS after disease progression.

The company argued that an OS benefit was plausible. This was because of the improvement seen in the surrogate measures of PFS 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). In that evaluation, there were statistically significant differences in OS after improvements in PFS 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 OS benefit. But they noted that an OS benefit from DREAMM-8 had not yet been shown. One clinical expert noted that OPTIMISMM did not show OS benefit in a lenalidomide-refractory population. They emphasised that mature data is needed to ensure that there is a difference in OS.

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

The committee thought that the company's scenario analysis did not reduce the uncertainty about the OS 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 NMAs. It acknowledged the strong correlation between minimal residual disease negativity and OS. But it agreed that a strong correlation alone is not sufficient to assume surrogacy. It noted that, in line with sections 4.6.6 to 4.6.9 in NICE's technology

appraisal and highly specialised technologies guidance: the manual, the company had not provided evidence of surrogacy from a randomised controlled trial for minimal residual disease negativity or PFS. The committee also noted that the company had not submitted any evidence that subsequent treatment was not an effect modifier for OS.

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 OS 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 NMA. In response to the draft guidance consultation, the company updated its base case:

- using OS data from SACT for Dar-Bor-Dex to estimate the absolute baseline curve
- applying the relative effects of the comparators from the IPTW analyses (see section 3.6).

The committee acknowledged that it is plausible that an OS benefit may become apparent with longer follow up of DREAMM-8. But it had serious concerns about the credibility of the company's estimates of long-term OS. It recalled that no statistically significant OS benefit for Bel-Pom-Dex over its comparators had been shown (see section 3.7). It thought that there was high uncertainty about the size and direction of the OS benefit of Bel-Pom-Dex compared with Car-Dex, Dar-Bor-Dex and Sel-Bor-Dex. The committee noted the absence of convincing evidence of OS benefit and the concerns about the company's OS modelling. It concluded that the EAG's assumption of no difference in OS between treatments to be appropriate for decision making.

Dose interruption of belantamab mafodotin

3.12 Belantamab mafodotin's summary of product characteristics states that it should be given in a 4-week cycle. Treatment starts at a dose of 2.5 mg/kg once in cycle 1 and is then decreased to a dose of 1.9 mg/kg once every 4 weeks from

cycle 2 until progression or unacceptable toxicity. Healthcare professionals may increase the time between doses from 8 weeks up to 6 months to reduce eye-related adverse events. The committee 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. But 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. In response to the draft guidance consultation, the company suggested that applying a maximum threshold of 6 months for dose interruptions could create inequity. So, it did not include this in its model. The committee noted that treatment-break policies are determined by NHS England and that there are mechanisms to accommodate longer treatment breaks (see the document from NHS England on continuation of funding for systemic anti-cancer therapy following a break in treatment). It also noted that the 6-month threshold would allow treatment to continue without completion of a treatment-break request form. It concluded that a 6-month treatment interruption should be modelled for eye-related adverse events with belantamab mafodotin.

Medication use and drug costs

3.13 In its base case, the company used different approaches to estimate medication use for belantamab mafodotin compared with the other treatment options. It used 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 of these medicines and a constant RDI. This was 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. But it thought that the same approach should be applied to all treatments. So, in the absence of IPD data for all medicines, 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, 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 for 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. It thought this would have provided reassurance on the consistency of the RDI-based costs for the comparators.

In response to the draft guidance consultation, the company provided graphs comparing RDI and IPD average doses for pomalidomide from DREAMM-8 and daratumumab from DREAMM-7 in the ITT populations. This was to show that time-varying trends do not impact their dosing. So, it did not provide a scenario analysis using the IPD data for pomalidomide and daratumumab. The company considers the data to be confidential, so it cannot be reported here. The committee noted the uncertainty of using different metrics to inform dosing for belantamab mafodotin and other medicines. But it was reassured that the data provided by the company showed that the RDI and IPD average doses were consistent for pomalidomide and daratumumab. So, it concluded that using IPD from DREAMM-8 to inform the dosing of belantamab mafodotin, and RDI to inform the dosing of the other drugs was likely appropriate for decision making.

Costs of subsequent treatments

3.14 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 OS 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 evolved, 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 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 said that:

- it was unlikely daratumumab monotherapy would be used at fourth line
- 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 thought 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. In response to the draft guidance consultation, the company explained that it could not access SACT data to inform modelling of subsequent treatments. It provided 2 scenarios:

- scenario 1, in which the proportion of people starting subsequent treatment was informed by clinical opinion (75% start third line and 50% start fourth line)
- scenario 2, in which teclistamab was included as a third-line subsequent treatment with a distribution of 40% teclistamab, 40% Sel-Bor-Dex and 20% Pan-Bor-Dex.

The committee noted that, although DREAMM-8 permitted teclistamab post-progression, uptake was low (6 of 155 in the Bel-Pom-Dex arm and 16 of 147 in the Pom-Bor-Dex arm). It was concerned that assuming substantially higher use would increase costs without modelling associated benefits. It noted that all the evidence informing subsequent treatment distributions was based on historical data, so did not reflect future treatment pathways for people with multiple myeloma that relapses after Bel-Pom-Dex. Given this uncertainty, the committee agreed to take a pragmatic approach. It noted

that cost of subsequent treatment was not a driver of cost-effectiveness estimates. So it concluded that it would take all scenarios into consideration in its decision making.

Monitoring costs for belantamab mafodotin

3.15 In its original 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 belantamab mafodotin's 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. So, people would likely see an ophthalmologist fewer than 4 times over the first 4 treatment cycles (see section 3.8). 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. 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 most people in DREAMM-8 had 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 thought that this cost was plausible because a change in treatment for eye-related adverse events would mean:

- stopping or reducing the dose of belantamab mafodotin
- allowing the adverse event to resolve, possibly with some ointment use.

The committee thought that there was uncertainty about whether the cost of eye-related adverse events had been adequately accounted for in the model. This was 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 have been underestimated. It thought 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.

In response to the draft guidance consultation, the company updated its base case to include ophthalmology monitoring costs. It based these on the median time to treatment discontinuation from DREAMM-8. The company considered the number of ophthalmology visits to be confidential, so it cannot be reported here. These visits were assumed to be divided between hospital (20%) and community settings (80%). This was informed by the views of an advisory board comprising consultant haematologists, ophthalmologists and optometrists with direct experience managing treatment for people having belantamab mafodotin.

The EAG noted that, even if all ophthalmology visits were hospital-based, the total cost of Bel-Pom-Dex would only increase by about 1%. This suggests it would have a minimal impact on cost-effectiveness results. The clinical experts explained that ophthalmology visits are typically needed to assess eye toxicity and determine when treatment can safely restart after interruption. They noted that people having belantamab mafodotin are usually seen in secondary care, with no involvement of primary care services. They suggested that the frequency of eye examinations would likely reduce over time as healthcare professionals gain more experience in managing eye-related adverse events. The committee noted that there may be variability in clinical practice and in the number of tests done, which could differ across treatment centres. The committee noted that there is some uncertainty about the future organisation of monitoring services and that the company's estimate of eye examinations may be an underestimate. But it noted the small

impact of this on total costs. It concluded that the company's approach to modelling ophthalmology monitoring costs for belantamab mafodotin was acceptable for decision making. But it acknowledged the potential impact this may have on ophthalmology services.

Wastage of tablets and vial sharing

3.16 In its original base case, the company assumed wastage on 100% of administrations including tablets, and no vial sharing. In its base case, the EAG thought that tablet wastage (pomalidomide, selinexor and dexamethasone) should be excluded. This was 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 tablet wastage. 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 measures are taken to make sure people having the same medicines have them on the same day to maximise vial sharing. But they said 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 tablet wastage should be excluded because the tablets will likely be re-used in future cycles. The committee noted that the EAG's base case included both these assumptions. In response to the draft guidance consultation, the company updated its base case to reflect the committee's preferred assumptions.

Health-state utility values

3.17 In its original 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. For the 'progression free on-treatment' health state, the company used a higher utility value for the Bel-Pom-Dex group than the

comparators. 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, so they cannot be reported here.

The EAG thought that it was implausible for belantamab mafodotin to have a higher 'progression free on-treatment' utility value than its comparators. This was because of the eye-related adverse events, likely not captured by the generic EQ-5D-3L (see section 3.9). It also thought that the pooled 'progression free off-treatment' and 'progressed-disease' utility values were not appropriate. This was 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, it 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. 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 noted a higher incidence of eye-related adverse events in the Bel-Pom-Dex group. But it explained 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 3.9). 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 it 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. 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 having longer PFS. The clinical experts explained that people whose condition continues to respond and has had a deep enough response on Bel-Pom-Dex to allow treatment intervals to be extended to every 10 to 12 weeks may have a better health-related quality of life. This is because treatment is less frequent than with Pom-Bor-Dex that is given more frequently. 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 thought that there was no strong evidence to justify applying a higher 'progression free on-treatment' health-state utility value for belantamab mafodotin than its comparators. It preferred the EAG's approach that used the same utilities derived from a wholly second-line population, regardless of treatment.

In response to the draft guidance consultation, the company updated its base case to apply treatment-independent utility values for the progression free health state, informed directly by data from DREAMM-8. A utility decrement on progression, based on Hatswell et al. (2019), was applied to derive the progressed-disease health-state utility value. The committee concluded that the company's updated approach to modelling health-state utility values was appropriate for decision making.

Disutility of eye-related adverse events

3.18 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 3.9). 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. It also noted the availability of the vision bolt-on, EQ-5D-V, which asks respondents to describe their vision on a scale of 'no problems', 'some problems' or 'extreme problems'. Based on feedback from 1 patient expert and the frequency of assessments in DREAMM-8, the committee thought that the EQ-5D-3L would have likely captured the impact of eye-related adverse events on health-related quality of life. 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 thought 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 3.17). 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.

In response to the draft guidance consultation, the company provided a scenario that included the disutility associated with eye-related adverse events. The company explained that incorporating this disutility had a negligible impact on the overall quality-adjusted life years (QALYs) for Bel-Pom-Dex. The exact figure is considered confidential, so cannot be reported here. The company also noted that some double counting might have occurred because the EQ-5D elicitation may have already captured the impact of eye-related adverse events. The committee acknowledged the uncertainty about the extent to which EQ-5D captured these events. It concluded that the disutility of eye-related adverse events should be included in the model.

Cost-effectiveness estimates

Committee's preferred assumptions

3.19 The committee noted that neither the company's nor the EAG's base cases or scenarios included all its preferred assumptions, which were:

- to use the starting age based on the SACT dataset (see section 3.10)
- to assume no OS benefit (see section 3.7 and section 3.11)
- to model a maximum dose interruption interval of 6 months for belantamab mafodotin (see section 3.12)
- to include the cost of monitoring eye-related adverse events using hospital-based ophthalmology services (see section 3.15)
- to assume no vial sharing (see section 3.16)
- to exclude tablet wastage (see section 3.16)
- to apply the company's updated approach to model health-state utilities (see section 3.17)
- to apply a disutility for eye-related adverse events (see section 3.18).

Acceptable ICER

3.20 NICE technology appraisal and highly specialised technologies guidance: the manual notes that, above a most plausible incremental cost-effectiveness ratio (ICER) of £20,000 per 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 section 3.7 and section 3.8)
- appropriateness of hazard ratios derived from the NMAs, particularly for OS and its impact on assumptions of OS benefit (see section 3.6 and section 3.11)
- modelling of subsequent treatments (see section 3.14)
- cost of monitoring eye-related adverse events for belantamab mafodotin (see section 3.15).

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

Company and EAG cost-effectiveness estimates

3.21 The committee considered the cost effectiveness of Bel-Pom-Dex compared with Car-Dex, Dar-Bor-Dex and Sel-Bor-Dex at second line. After the second committee meeting, the cost-effectiveness estimates using all the committee's preferred assumptions were provided. The exact figures cannot be reported because of confidential discounts for carfilzomib, daratumumab, pomalidomide and selinexor. All the cost-effectiveness estimates were within a range that the committee considered to be an acceptable use of NHS resources.

Other factors

Equality

3.22 The clinical experts noted that multiple myeloma is common in men, older 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

3.23 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. It also thought 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

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

Conclusion

Recommendation

3.25 The committee acknowledged the unmet need for effective and tolerable treatments for multiple myeloma, particularly for later lines of treatment. It noted that Bel-Pom-Dex improved PFS relative to its comparators. But it recalled the immature OS data from DREAMM-8 and the uncertainty around Bel-Pom-Dex's OS benefit relative to its comparators. It noted the added uncertainty of the impact of dose delays on Bel-Pom-Dex's clinical effectiveness and the need for ongoing monitoring of eye-related adverse events. But the most likely cost-effectiveness estimates were within a range considered to be a cost-effective use of NHS resources. So, Bel-Pom-Dex can be used in the NHS as an option for

treating multiple myeloma in adults if:

- they have only had 1 line of treatment and that contained lenalidomide, and
- if lenalidomide is not tolerated or the condition is refractory to it.

4 Implementation

4.1 Section 7 of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires integrated care boards, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this evaluation within 90 days of its date of publication.

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

4.3 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal guidance recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 60 days of the first publication of the final draft guidance.

4.4 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has previously treated multiple myeloma and the healthcare professional responsible for their care thinks that belantamab mafodotin with pomalidomide and dexamethasone is the right treatment, it should be available for use, in line with NICE's recommendations.

5 Evaluation committee members and NICE project team

Evaluation committee members

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

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
Technical adviser

Jennifer Upton and Vonda Murray
Project managers

Ian Watson and Richard Diaz
Associate directors

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