NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Final draft guidance

Belantamab mafodotin with bortezomib and dexamethasone for previously treated multiple myeloma

1 Recommendations

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

- they have only had 1 previous line of treatment, and
- the company provides it according to the commercial arrangement (see section 2).

1.2 This recommendation is not intended to affect treatment with belantamab mafodotin plus bortezomib 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 bortezomib and dexamethasone must be funded in the NHS in England for the condition and population in the recommendations, if it is considered the most suitable treatment option. It must be funded in England within 90 days of final publication of this guidance.

Issue date: April 2026

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

Why the committee made these recommendations

Belantamab mafodotin plus bortezomib 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 at second line includes:

- carfilzomib plus lenalidomide and dexamethasone
- daratumumab plus bortezomib and dexamethasone, when lenalidomide is not an option.

Evidence from a clinical trial shows that belantamab mafodotin plus bortezomib and dexamethasone increases how long people have before their condition gets worse compared with daratumumab plus bortezomib and dexamethasone. The evidence also suggests that people live longer. But the trial is ongoing, so this is uncertain.

Belantamab mafodotin plus bortezomib and dexamethasone has not been directly compared in a clinical trial with carfilzomib plus lenalidomide and dexamethasone. An indirect comparison suggests that it is likely to work as well as carfilzomib plus lenalidomide and dexamethasone, but this is uncertain.

The cost-effectiveness estimates for belantamab mafodotin plus bortezomib and dexamethasone compared with usual treatment are within the range that NICE considers an acceptable use of NHS resources. So, it can be used at second line.

2 Information about belantamab mafodotin with bortezomib and dexamethasone

Marketing authorisation indication

2.1 Belantamab mafodotin (Blenrep, GlaxoSmithKline) 'in combination with bortezomib and dexamethasone is indicated for the treatment of adult patients with multiple myeloma who have received at least one prior therapy'.

Dosage in the marketing authorisation

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

Price

2.3 The list price for belantamab mafodotin is £16,848 per 100-mg vial and £11,784 per 70-mg vial (excluding VAT; company submission).

2.4 The company has a commercial arrangement (commercial access agreement). This makes belantamab mafodotin available to the NHS with a discount. The size of the discount is commercial in confidence.

Sustainability

2.5 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 a chronic, incurable relapsing and remitting cancer of the plasma cells. Relapsing and remitting means that there can be episodes in which the symptoms worsen, and treatment is needed to bring them back under control. Refractory means that the multiple myeloma has shown no response to treatment or has progressed on or within 60 days of the last treatment. Patient experts told the committee that complications from multiple myeloma can be debilitating and can have a severe impact on quality of life. The constant possibility of relapse has a huge psychological impact. Patient organisations said that there is a clear need for innovative treatments at second line and beyond that deliver deep, durable responses for people with relapsed and refractory multiple myeloma. The committee recognised the substantial impact multiple myeloma has on survival and quality of life. It acknowledged the unmet need for effective treatments for people with multiple myeloma who have had 1 or more previous treatments.

Treatment pathway

Positioning of belantamab mafodotin plus bortezomib and dexamethasone

3.2 The treatment pathway for multiple myeloma is complex and evolving. Clinical experts said that relapsing–remitting multiple myeloma is challenging to treat because people with the condition are often impacted by side effects from previous treatments and the effects of disease relapse or treatment refractoriness. They said that there is a clear unmet need for treatments that provide longer, more durable remission and manage complications of multiple myeloma.

In its original submission, the company proposed belantamab mafodotin plus bortezomib and dexamethasone (Bel-Bor-Dex) as a treatment for adults with multiple myeloma who have had only 1 previous line of treatment (that is, at second line only) and when lenalidomide is unsuitable. This is narrower than the marketing authorisation. The

company explained that although there are currently 6 treatment options available at second line, the choice of treatment depends on which treatments people have had at first line. The company said that the number of people having treatment at second line for whom lenalidomide would be suitable would be small. So, the company suggested that the second-line positioning for people for whom lenalidomide is unsuitable is where Bel-Bor-Dex would address the highest unmet need.

The Cancer Drugs Fund lead noted that after publication of NICE's technology appraisal guidance on daratumumab with lenalidomide and dexamethasone (Dar-Len-Dex) for untreated multiple myeloma when a stem cell transplant is unsuitable (TA917), more people would have lenalidomide at first line. So over time, fewer people would be eligible for lenalidomide as a second-line treatment because they were unable to tolerate it or their condition was refractory to it. The committee acknowledged that the treatment pathway was rapidly evolving but said that this evaluation should be based on the current NHS population. It agreed that there is an unmet need for treatment at second line when the person cannot tolerate or their condition is refractory to lenalidomide. But the committee noted that there is also an unmet need in the wider population covered by the marketing authorisation. This includes people who did not have lenalidomide at first line because it was not available at the time. The clinical and patient experts suggested that Bel-Bor-Dex would also be beneficial as an option at third line.

The committee asked the company to provide analyses to evaluate Bel-Bor-Dex within its full marketing authorisation. But if this was not possible, the committee said that it would prefer to evaluate Bel-Bor-Dex in adults with multiple myeloma who have had either:

- only 1 previous treatment (that is, second line only), or
- 1 or 2 previous treatments, with previous exposure to lenalidomide.

In response, the company updated its positioning of Bel-Bor-Dex to include people who have not had previous exposure to lenalidomide as a new subpopulation. The committee concluded that the updated positioning, for the full second-line population, was acceptable. But it said that it would have expected the company to provide cost-effectiveness analyses for Bel-Bor-Dex within its full marketing-authorisation population, which includes third-line use.

Use of the term 'unsuitable'

3.3 When considering subgroups within the second-line population, the committee discussed which criteria would make lenalidomide 'unsuitable' and whether the term 'unsuitable' was appropriate and reflected NHS practice. The company said that using 'unsuitable' would support making consistent and equitable recommendations across the multiple myeloma treatment pathways. It noted that previous appraisals had used the term 'unsuitable' to describe lenalidomide (see NICE's technology appraisal guidance on daratumumab with bortezomib and dexamethasone [Dar-Bor-Dex] for previously treated multiple myeloma [TA897]). It said that the main reasons for lenalidomide unsuitability are when the multiple myeloma is refractory to lenalidomide, or when lenalidomide cannot be tolerated because of toxicity. The company also noted that there would be some cases in which healthcare professionals would prefer to offer a non-lenalidomide treatment. The clinical experts agreed that refractoriness and intolerance would be the main reasons for lenalidomide unsuitability. But they said that there would also be cases when lenalidomide was contraindicated, for example, in pregnancy. The committee understood that, in TA897, lenalidomide was described as 'unsuitable' to mean that people could not tolerate lenalidomide or it was contraindicated or their myeloma was refractory to it. The NHS England Cancer Drugs Fund clinical lead (from here, the Cancer Drugs Fund lead) said that the term 'unsuitable' was used differently in practice. They reported that for approximately half of the people who have had Dar-Bor-Dex at second line and not had lenalidomide, the healthcare professional had determined

that lenalidomide would be unsuitable for other reasons. The committee noted that the recommendations in the more recently published NICE technology appraisal guidance on selinexor with bortezomib and dexamethasone for previously treated multiple myeloma include the term 'refractory to… lenalidomide'. The committee concluded that the terms 'refractory to lenalidomide' and 'cannot tolerate lenalidomide' would provide much clearer guidance to healthcare professionals in the NHS than the term 'unsuitable'.

Comparators

3.4 Treatment options for newly diagnosed multiple myeloma depend on whether a stem cell transplant is considered appropriate. When the multiple myeloma progresses, treatment options at second line depend on which treatments people have had before and the response to those treatments (whether they were effective or tolerated).

For someone who has had 1 previous line of treatment, currently available options at second line are:

- selinexor plus bortezomib and dexamethasone (see NICE's technology appraisal guidance on selinexor with bortezomib and dexamethasone for previously treated multiple myeloma [TA974])
- Dar-Bor-Dex (see NICE's technology appraisal guidance on daratumumab plus bortezomib and dexamethasone for previously treated multiple myeloma [TA897])
- carfilzomib plus lenalidomide and dexamethasone (see NICE's technology appraisal guidance on carfilzomib with dexamethasone and lenalidomide for previously treated multiple myeloma [TA695])
- carfilzomib plus dexamethasone (see NICE's technology appraisal guidance on carfilzomib for previously treated multiple myeloma [TA657])

- lenalidomide plus dexamethasone (see NICE's technology appraisal guidance on lenalidomide with dexamethasone for multiple myeloma after 1 treatment with bortezomib [TA586])
- bortezomib (see NICE's technology appraisal guidance on bortezomib monotherapy for relapsed multiple myeloma [TA129]).

The company provided comparisons with the following regimens at second line only:

- Dar-Bor-Dex
- selinexor plus bortezomib and dexamethasone (Sel-Bor-Dex)
- carfilzomib plus dexamethasone (Car-Dex)
- carfilzomib plus lenalidomide and dexamethasone (Car-Len-Dex).

The company did not include bortezomib monotherapy as a comparator because clinical expert advice suggested that this treatment was rarely used in clinical practice. And it did not include lenalidomide plus dexamethasone. The EAG agreed, based on clinical advice it had received, that bortezomib monotherapy was not a relevant comparator. It also agreed that Car-Len-Dex was likely to supersede lenalidomide plus dexamethasone. The Cancer Drugs Fund lead provided data on the use of different treatments at second line in the NHS. The data suggested that:

- most people have Dar-Bor-Dex
- the second-most used option is Car-Len-Dex
- only a small proportion of people have Car-Dex or Sel-Bor-Dex.

The company did not explore further populations covered by the marketing authorisation for Bel-Bor-Dex by providing comparisons with treatments used at third line or later. The committee thought that the analyses provided by the company for second line only included the most relevant comparators. The committee concluded that for people

whose multiple myeloma is refractory to, or who cannot tolerate lenalidomide, Dar-Bor-Dex is the most appropriate comparator. For the new population in the company's updated positioning (people who have not had previous exposure to lenalidomide) the committee concluded that Car-Len-Dex is the most appropriate comparator.

Clinical effectiveness

Evidence comparing Bel-Bor-Dex with Dar-Bor-Dex

3.5 Clinical evidence for Bel-Bor-Dex compared with Dar-Bor-Dex came from the DREAMM-7 trial. DREAMM-7 is an ongoing, phase 3, open-label, multicentre, randomised controlled trial. The population includes adults with multiple myeloma who have had at least 1 previous treatment. The company presented data from the intention-to-treat (ITT) population of the trial, which aligns with the proposed population for the marketing authorisation, that is, treatment at second line onwards. But, it used this data to inform the treatment effect for people having Bel-Bor-Dex at second line whose multiple myeloma is refractory to, or who cannot tolerate lenalidomide (see section 3.2). The company explained that using the ITT data to inform clinical effectiveness for the narrower population was the best approach because the data was more robust than the subgroup data. The company explained that using subgroup data would introduce more uncertainty and would limit the indirect treatment comparisons that could be made with Sel-Bor-Dex and Car-Dex. The EAG acknowledged the company's justification for using the ITT population but noted that the company-proposed restriction limits the generalisability of the evidence.

The committee noted that the ITT population in DREAMM-7 was younger and fitter than the NHS population. So, the results may not have fully represented the population eligible for Bel-Bor-Dex in the NHS. The committee also said that using the results from the DREAMM-7 ITT population to inform analyses in a narrower population (second line and when a person is unable to tolerate lenalidomide or their condition is

refractory to it) assumed that the number of previous lines of treatment and previous exposure to lenalidomide does not affect treatment outcomes. It said this assumption has not been substantiated and so is a potential source of bias for the estimated treatment effect of Bel-Bor-Dex.. But it said that, taking these uncertainties into account, analyses based on the broader ITT population would be acceptable for decision making.

Network meta-analysis

3.6 There was no evidence directly comparing Bel-Bor-Dex with Car-Dex or Sel-Bor-Dex. So, the company presented a Bayesian network meta-analysis (NMA) comparing Bel-Bor-Dex with Car-Dex and Sel-Bor-Dex, as well as with comparators that were not relevant to NHS clinical practice. The networks that included the relevant treatments did not include any loops. This meant that the comparisons could not be informed by both direct and indirect evidence, and consistency in the indirect evidence could not be checked. In addition, the committee noted that because the network did not include a single common node, some comparators could only be assessed through intermediary nodes. The EAG reported that the methods used by the company were appropriate but poorly described, and the dataset provided by the company had unexplained differences. It noted that the company's results were not reproducible. Additionally, the EAG identified published evidence describing a later data cut-off for one of the trials than was used in the company submission (LEPUS, which compared Dar-Bor-Dex with Bor-Dex). The EAG updated the analyses with the later data cut-off but noted that this did not dramatically change the results. The company agreed with using the EAG-updated analyses. The committee concluded that the company's NMA was uncertain but was suitable for decision making and should include the most recent data cut-off from LEPUS.

Matching-adjusted indirect comparison

3.7 It was not possible to include Car-Len-Dex in the NMA (see section 3.6) because there was no available network of indirect evidence. So, for the

comparison of Bel-Bor-Dex with Car-Len-Dex, the company presented an unanchored matching-adjusted indirect comparison (MAIC). The company used data from DREAMM-7 for Bel-Bor-Dex and from ASPIRE for Car-Len-Dex. ASPIRE was a phase 3, open-label, multicentre, randomised controlled study. The company explored heterogeneity across the studies by comparing study designs, prognostic factors, treatment-effect modifiers, treatment arms and outcomes. Key treatment-effect modifiers and prognostic factors for people in the DREAMM-7 Bel-Bor-Dex arm were matched to those for people in the ASPIRE Car-Len-Dex arm. The reweighted outcomes of the DREAMM-7 Bel-Bor-Dex arm were then compared with those from the ASPIRE Car-Len-Dex arm. The EAG had several concerns with the MAIC. It noted that unanchored MAICs are inherently uncertain. The EAG also said that the ASPIRE trial population, on which the MAIC was based, may not be generalisable to NHS practice. It gave the example that ASPIRE included some people who had not previously had bortezomib and some people who had previously had lenalidomide. These people would not be eligible for Car-Len-Dex in the NHS (see TA695). The EAG also noted that it was not possible to adjust for all key prognostic factors and treatment-effect modifiers with the available data (see section 3.8). It noted that this leads to considerable uncertainty in the results. The committee acknowledged that the MAIC was associated with high uncertainty. But, in the absence of any other evidence, the committee concluded that it was suitable for decision making. It further concluded that it would consider in its decision making the uncertainty associated with the MAIC.

R-ISS adjustment

3.8 When doing the MAIC, the company aimed to adjust for all key prognostic factors and treatment-effect modifiers (see section 3.7). It identified the Revised International Staging System (R-ISS) as an important prognostic factor and treatment-effect modifier. But 31.1% of people in the Car-Len-Dex arm of ASPIRE had an unknown R-ISS stage. Also, the ASPIRE trial included a higher proportion of stage-3 R-ISS patients than DREAMM-7.

Because of the large amount of missing data and inadequate balancing, the company excluded R-ISS from the matching process. The company provided a sensitivity analysis that used serum beta2-microglobulin as a proxy for R-ISS staging. The company explained that serum beta2-microglobin is a key component of the R-ISS staging system and its clinical experts thought that it was a suitable substitute for R-ISS staging. The company said that a statistically significant treatment effect for Bel-Bor-Dex compared with Car-Len-Dex was maintained when this adjustment was included, which gave confidence in the results of the MAIC. The clinical expert at the committee meeting said that they would not expect R-ISS staging to alter the effectiveness of either Bel-Bor-Dex or Car-Len-Dex and so did not consider it to be a treatment-effect modifier. The EAG said that excluding R-ISS from the matching process may be appropriate given the level of missing data, but that excluding it may introduce bias favouring Bel-Bor-Dex. The committee noted that NICE Decision Support Unit's technical support document 18 states that for an unanchored indirect comparison, population adjustment methods should adjust for all effect modifiers and prognostic variables. The committee also noted that the R-ISS staging system is an important prognostic factor for this population. It said that this is because people with R-ISS stage 3 are expected to have poorer outcomes compared to people with R-ISS stages 1 to 2. The committee discussed the scenario analysis, presented by the company, that used serum beta2-microglobulin as a proxy for R-ISS staging. The committee noted that beta2-microglobulin is only one of several components of the R-ISS tool. So, they said there is prognostic value in the R-ISS staging system that is not captured in the company's scenario analysis. The committee noted the level of missing R-ISS data in ASPIRE. The committee thought that excluding R-ISS from the analyses may exclude an important prognostic variable. But, including it may introduce bias to the results if the data for R-ISS is not 'missing at random'. On balance, the committee concluded that R-ISS staging should be adjusted for in the MAIC.

Clinical-effectiveness results

3.9 From the DREAMM-7 full ITT population (see section 3.5), Bel-Bor-Dex showed a statistically significant improvement in overall survival (HR 0.57; 95% CI 0.40 to 0.80) and progression-free survival (PFS; HR 0.41; 95% CI 0.31 to 0.53) compared with Dar-Bor-Dex. The full ITT population is people who have had 1 or more prior lines of treatment (including or not including lenalidomide), and people whose condition is lenalidomide-refractory.

From the NMA (see section 3.6), Bel-Bor-Dex showed a statistically significant improvement in:

- PFS compared with Dar-Bor-Dex, Car-Dex and Sel-Bor-Dex (the company considers the exact data to be confidential and so it cannot be reported here)
- overall survival compared with Dar-Bor-Dex, Car-Dex and Sel-Bor-Dex (the company considers the exact data to be confidential and so it cannot be reported here).

From the MAIC analysis adjusting for R-ISS (see section 3.8) Bel-Bor-Dex showed a:

- statistically significant improvement in PFS compared with Car-Len-Dex (the company considers the exact data to be confidential and so it cannot be reported here)
- numerical improvement in overall survival compared with Car-Len-Dex, but the difference was not statistically significant (the company considers the exact data to be confidential and so it cannot be reported here).

The committee concluded that Bel-Bor-Dex is an effective treatment for multiple myeloma which provides benefits to people with the condition. But it concluded that the size of the benefits in the proposed population

compared with specific comparators is uncertain because of limitations with the available data.

Exposure to belantamab mafodotin

3.10 The summary of product characteristics (SmPC) for belantamab mafodotin (see section 2.2) lists the starting dose as 2.5 mg/kg once every 3 weeks. In cases of moderate or severe ocular side effects, the SmPC states that belantamab mafodotin should be withheld until there is observed improvement in both corneal examination findings and best corrected visual acuity to 'mild severity or better'. Belantamab mafodotin can then be resumed at a reduced dose of 1.9 mg/kg once every 3 weeks. In the DREAMM-7 safety population, the mean dose was lower than the SmPC-recommended reduced dose (the company considers the actual dose to be confidential, so it cannot be reported here). The company analyses included dose reductions and delays based on DREAMM-7 individual patient data to inform costs of belantamab mafodotin in the model. The EAG said that while this approach was reasonable, EAG clinical experts noted that healthcare professionals are likely to be cautious with dosing because of potential side effects and would consider starting treatment on a lower dose. The clinical experts at the committee meeting explained that they would start most people on the 2.5 mg/kg dose. Clinical advice to the company at clarification also suggested that healthcare professionals may choose to start with a dosing window of every 4 weeks, extending to every 8 weeks and then every 12 weeks. So, exposure to belantamab mafodotin may be lower in NHS clinical practice, which is not accounted for in the company submission. The EAG noted that costs for belantamab mafodotin were sensitive to whether delays were captured or not. But it also noted that the impact on effectiveness was unknown and so could not be explored in the model. The clinical experts gave their experience of using belantamab mafodotin in practice, in which some people had delays to dosing of up to 6 months with no loss of response. The committee noted that subgroup data for people who had belantamab mafodotin at 8 to 12-week intervals was not included in the

company submission. In response the company explained that based on data from 15 months after the first dose in DREAMM-7, people in the trial had a median of 9 to 12 weeks between doses. It also explained that modified PFS in the ITT population of DREAMM-7 was similar to people with a dosing schedule extended to 12 weeks or more. The EAG noted that the assumption of no change in efficacy with 8 to 12-week dosing intervals is likely to be reasonable but the evidence was limited. The committee recalled that the company used individual patient data to inform belantamab mafodotin costs but did not use individual patient data for the comparators and instead used relative dose intensity (RDI). The company explained that RDI for comparators remained high and individual patient data was not available for some comparators. So, it did not think that using RDI for comparators instead of individual patient data would make a difference to the results. The EAG agreed that daratumumab dosing is likely to be constant and less variable than belantamab mafodotin. The EAG noted that RDI is likely appropriate to model dosing of daratumumab, and individual patient data would have a small impact on the cost-effectiveness results. The committee agreed that using individual patient data from DREAMM-7 to inform dosing of belantamab mafodotin and RDI to inform dosing for other comparators may be appropriate. But it noted the uncertainty of using different metrics to inform dosing for belantamab mafodotin and its comparators.

Cost effectiveness

Company's modelling approach

3.11 The company provided a cohort-based partitioned survival model to estimate the cost effectiveness of Bel-Bor-Dex compared with Dar-Bor-Dex, Car-Dex, Sel-Bor-Dex and Car-Len-Dex. The model included 4 health states: progression free on treatment, progression free off treatment, progressed disease, and death. Progression free was split into the on-treatment and off-treatment health states because some people in DREAMM-7 withdrew from active treatment before disease progression,

which resulted in different costs and consequences. The probability of being in each health state was calculated using extrapolated PFS, overall survival and time to treatment discontinuation (TTD). The model used a cycle length of 1 week over a lifetime horizon. The committee noted that the starting age used in the model, based on the age in DREAMM-7, was younger than would be expected in clinical practice. The company updated its model to include a starting age that reflects the NHS population based on Dar-Len-Dex data from the Systemic Anti-Cancer Therapy (SACT) dataset. For the population for whom lenalidomide is an option, the company included the mean age based on the weighted Bel-Bor-Dex arm from the MAIC (see section 3.7). It stated that including a starting age from a different source to the MAIC could introduce bias into the analysis. The committee concluded that the company's updated modelling approaches were acceptable for decision making.

Overall-survival predictions for regimens that do not contain lenalidomide

3.12 Because DREAMM-7 is still ongoing, clinical data on long-term outcomes is unknown. So, the company extrapolated overall-survival data by fitting independent parametric models to the observed data. For Dar-Bor-Dex, a Weibull parametric fit was applied, informed by the more mature data available from the Dar-Bor-Dex arm of the CASTOR trial. To justify fitting independent models to the overall-survival data, the company said that there was inconclusive evidence about the appropriateness of assuming proportional hazards in the DREAMM-7 data. There appeared to be timepoints when the cumulative hazards for the 2 treatments cross, which would usually be a reason to reject proportional hazards assumptions. But a formal test for nonproportionality was not significant and the Schoenfeld residuals did not deviate from an expected pattern, which is when proportional hazards would apply. The committee noted that the timepoints when the cumulative hazards crossed were in the first few months of follow-up, when few events had occurred. The committee said that this should not rule out the use of an approach that assumes

proportional hazards. Overall-survival curves for comparators were calculated by applying hazard ratios from the NMA to the extrapolated Dar-Bor-Dex curve. The EAG considered this approach to be appropriate. The committee recalled that data from DREAMM-7 was based on the ITT population, which may not be reflective of the subgroup proposed by the company (see section 3.5). So, it concluded that the overall-survival extrapolations may not be representative of overall survival in the population proposed by the company. The committee suggested that it would be possible to use alternative models. These could provide more accurate overall-survival estimates in the relevant population and reduce the uncertainty between the immature survival data and long-term predictions. The committee said that it would prefer to see updated analyses applying the relative effects of DREAMM-7 to SACT data for Dar-Bor-Dex to generate overall survival for Bel-Bor-Dex and its comparators in the most relevant population. It noted that such data had been collected and reported recently in a conference abstract (see Lawton et al. 2024). The company updated its analyses to include SACT data as a reference for the Dar-Bor-Dex arm (baseline curve) with relative treatment effects being informed by DREAMM-7 and applied to the SACT baseline curve. The committee concluded that the company-updated approach using SACT data was appropriate.

Survival predictions for comparison with Car-Len-Dex

3.13 In response to consultation, the company said that real-world evidence for Car-Len-Dex in the relevant population was not available to them. So, it said that the committee's preferred approach for modelling overall survival in the population for whom lenalidomide is not an option (see section 3.12) could not be replicated for the comparison with Car-Len-Dex. Instead, the company fitted independent models to the weighted Bel-Bor-Dex arm (see section 3.7) and the Car-Len-Dex arm. The company stated that the log-cumulative hazards, Schoenfeld residual plot, and quantile-quantile plot suggested that relative hazards varied over time, which suggested that the proportional hazard assumption did not hold. It

also said that assuming proportional hazards underestimated the long-term benefit of Bel-Bor-Dex. The EAG said that analyses applying the hazard ratio from the MAIC to the unweighted Bel-Bor-Dex curve should be considered. It noted that this analysis assumed proportional hazards. The EAG explained that the observed hazard rates for Bel-Bor-Dex and Car-Len-Dex were uncertain, particularly at the beginning and towards the end of the observed follow-up periods. So, the diagnostic plots did not rule out the use of an approach that assumes proportional hazards. The committee noted that the company's preferred approach assumed an increasing relative treatment effect over time. It considered that it had not been provided with sufficient evidence to support such an optimistic assumption.

The EAG explained that fitting independent models and using the MAIC (excluding the R-ISS adjustment) resulted in extrapolations that assumed that most of the overall-survival benefit associated with Bel-Bor-Dex occurred post progression. The clinical expert at the meeting noted that ASPIRE is a much older study than DREAMM-7. They explained that improvements in the treatments available at subsequent lines, since ASPIRE was done, have led to improvements in overall survival. The committee considered that the MAIC analyses were not able to account for these differences and likely produced a biased estimate of relative efficacy in favour of Bel-Bor-Dex.

The EAG modelled Car-Len-Dex survival by applying the hazard ratio from the MAIC (including the R-ISS adjustment) to the unweighted Bel-Bor-Dex curve. The committee noted that, when this was done, most of the survival benefit occurred in the pre-progression health state, and the modelling also assumed a constant relative treatment effect. It considered these assumptions to be more plausible than the alternative approaches. The committee concluded that modelling Car-Len-Dex overall survival by applying the hazard ratio from the MAIC (including the R-ISS adjustment)

to the Bel-Bor-Dex curve should be used for decision making. The committee considered that a consistent approach to extrapolating treatment effect over time should be followed. So, the committee said that the same approach should be used to model PFS.

Time-on-treatment predictions

3.14 The company stated that Car-Len-Dex TTD data, which could inform a MAIC, was not available. So, the company suggested 3 approaches for modelling Car-Len-Dex TTD:

- using DREAMM-7 data to estimate the TTD-to-PFS hazard ratio for Dar-Bor-Dex and applying this hazard ratio to the Car-Len-Dex PFS curve
- using median lenalidomide treatment duration and median PFS from ASPIRE to estimate the TTD-to-PFS hazard ratio for Car-Len-Dex and applying this hazard ratio to the Car-Len-Dex PFS curve
- assuming TTD is equal to PFS.

In line with TA695, a stopping rule of 18 cycles was included for carfilzomib in all approaches. Both the company and the EAG agreed that setting TTD to be equal to PFS was conservative and lacked clinical plausibility. In its base case the company used the hazard ratio derived from the DREAMM-7 data. It stated that this approach replicated the method used to derive TTD for Car-Dex and Sel-Bor-Dex. The EAG explained that the DREAMM-7 data used to derive the TTD-to-PFS hazard ratio was inconsistent with the data source used to estimate overall survival and PFS, because it had not been adjusted for the characteristics in ASPIRE (see section 3.7). The EAG said that the company-preferred approach may overestimate the costs associated with Car-Len-Dex. It also assumed longer TTD than was assumed in TA695. So, the EAG preferred to use the hazard ratio derived from the ASPIRE data. It explained that using ASPIRE data ensured consistency between evidence sources in the model. The company

considered this approach overly conservative, because data from TA695 indicated that people may discontinue lenalidomide before carfilzomib. The committee noted that the choice of approach used to model Car-Len-Dex TTD had a small impact on the cost-effectiveness results. It considered that the TTD-to-PFS hazard ratio used to derive Car-Len-Dex TTD should be based on lenalidomide (rather than Dar-Bor-Dex). And it preferred to use the same data source for efficacy and treatment duration (ASPIRE). So, the committee concluded that the approach using ASPIRE data to model TTD for Car-Len-Dex should be used for decision making.

Utility values

3.15 In the company submission, progression-free utilities were informed by EQ-5D-3L data from DREAMM-7. The company used a higher utility value for Bel-Bor-Dex than the comparators for the progression-free health states. The EAG noted that the approach to apply treatment-dependent utility values, rather than based on the line of treatment, was appropriate and an approach taken in previous NICE evaluations. But it said that the company had not provided empirical evidence to support the assumption that Bel-Bor-Dex would have a higher utility than its comparators. It considered that an alternative assumption that the same progression-free health-state utility as the comparators would be just as plausible. The EAG explored this in a scenario analysis and reported that it did not have a material impact on the cost-effectiveness results. The committee acknowledged this but highlighted that there is no interaction term between Bel-Bor-Dex and the progression-free health state. It explained that the interaction term is an important factor in assessing improved health-related quality of life. It said that this is because a higher quality-adjusted life year (QALY) is expected the more time is spent in the progression-free health state. It noted that a simpler model that does not assume a difference by treatment may be a better fit.

For the comparator treatments, the company modelled a higher utility

value for the progressed-disease than progression-free health state. (The company considers the exact values to be confidential, so they cannot be reported here). This meant that people with progressed disease had a better quality of life. The EAG highlighted that the higher utility value for progressed disease was not clinically plausible. It also said that the utilities provided by the company did not take into account line of treatment. It proposed applying a utility decrement to the progressed-disease health state for the comparators, calculated from Hatswell et al. (2019). At the committee meeting, the company agreed that the utilities in the company submission lacked validity and there was no difference in EQ-5D between the comparators. The committee noted that the utility values were generally higher than expected. It suggested that this may have been caused by the DREAMM-7 population being younger and fitter than the NHS population (see section 3.5). The committee agreed that higher utility values for the progressed-disease than progression-free health state was implausible. The committee recalled that the company had not provided sufficient evidence to suggest a treatment-specific utility benefit for Bel-Bor-Dex. The committee concluded that it preferred to apply utility values independent of treatment arm based on the health state only (progressed disease and progression free). The company updated its base case to apply treatment-independent utility values that were informed directly by DREAMM-7 for the progression-free health state. It then applied a utility decrement upon progression, based on Hatswell et al. to the progression-free health state to derive the progressed-disease health-state utility value. The committee concluded that the company's updated approach was appropriate.

Ocular adverse events and health-related quality of life

3.16 In DREAMM-7, EQ-5D-3L scores at last follow-up were the same across the Bel-Bor-Dex and Dar-Bor-Dex arms, and there was no significant difference between baseline and final follow-up. The EAG's clinical adviser noted that quality of life is likely to be negatively affected for some people in the Bel-Bor-Dex arm who experience adverse events. Corneal

adverse events relating to study treatment were more common with Bel-Bor-Dex than Dar-Bor-Dex (the data was considered confidential by the company so cannot be reported here). The model included treatment-specific ocular adverse events of grade 3 and above, including keratopathy, blurred vision and dry eyes. These adverse events were only applied to the Bel-Bor-Dex arm. The EAG noted that the incidence of keratopathy applied in the model was much lower than the incidence in DREAMM-7. In addition, the adverse events were applied as a one-off quality-of-life decrement to the first cycle in the model, using disutilities sourced from NICE's technology appraisal guidance on ciclosporin for treating dry eye disease that has not improved despite treatment with artificial tears. The EAG said that applying the adverse events as a one-off may not be appropriate to capture adverse events that occur later or are experienced for a longer length of time. It also noted that time to onset and duration of events of grade 3 and above were not reported.

The committee discussed whether EQ-5D-3L was sensitive enough to capture the impact on quality of life of ocular side effects and visual impairment with Bel-Bor-Dex. The clinical experts, along with the patient and expert submissions, advised that belantamab mafodotin is well tolerated, and that people are prepared to tolerate the ocular side effects. But advice to the EAG noted that, in clinical practice, other treatments may be preferred over Bel-Bor-Dex at second line because of the risk of ocular adverse events with Bel-Bor-Dex. The clinical experts in the committee meeting thought that EQ-5D-3L is a reasonable tool to capture the impact of ocular side effects on quality of life. In addition, the committee noted that patient experts said that the EQ-5D-3L in the trial would have likely captured the impact of ocular adverse events on health-related quality of life, given the frequency of assessments.

The committee noted that although EQ-5D-3L is not disease-specific, it allows for consistent evaluations across disease areas and the concern

about sensitivity could apply to many conditions. But it acknowledged that the extent to which EQ-5D-3L captures the impact of vision loss on quality of life is uncertain. So, the committee concluded that a disutility for ocular adverse events should be included in the base case with scenarios exploring the impact of excluding a disutility for ocular adverse events.

Cost of subsequent treatments

3.17 The company applied different costs for the subsequent treatments in the model, as a one-off cost to each cycle, which was proportional to the number of people entering the progressed-disease health state. Subsequent costs were the same for Bel-Bor-Dex, Car-Dex, Sel-Bor-Dex and Car-Len-Dex, but differed for Dar-Bor-Dex. The company considered 3 distributions, which were aligned to either the:

- NICE treatment pathway
- current treatment pathway in NHS practice, or
- likely future treatment pathway.

It said that the most appropriate distribution to use was to align treatments with the current pathway in NHS practice. The EAG said that the key driver affecting costs of subsequent treatments was the delay to disease progression rather than the actual distribution of treatments. So, the EAG preferred to apply the same distribution of treatments after disease progression, across all comparators. But it noted that the subsequent treatment teclistamab was not included in the company submission. The company said that this was because teclistamab was still under NICE evaluation at the time of submission. (see NICE's technology appraisal guidance on teclistamab for treating relapsed and refractory multiple myeloma after 3 or more treatments). The committee acknowledged that the multiple myeloma treatment pathway is rapidly evolving (see section 3.2), but agreed that because teclistamab has had a positive recommendation from NICE it was now part of standard practice. The company updated its base case to

include teclistamab as a subsequent treatment. It also applied the same distribution of treatments after disease progression, across all comparators. The committee considered that the company's updated approach appropriately captured the cost of subsequent treatments. But it noted that it would have preferred for both the costs and benefits of teclistamab to be modelled. But the benefits of teclistamab were not available to the committee. In the absence of these, the committee concluded that the company's updated approach should be used for decision making. It further concluded that it would consider in its decision making the uncertainty around the benefits of subsequent treatments.

Monitoring and ocular adverse-event costs

3.18 In its base case, the company assumed that people having Bel-Bor-Dex would be seen by an ophthalmologist for only the first 4 treatment cycles as per the draft SmPC. It assumed that this would be at a resource use per model cycle of 0.33. The company thought that the assumed number of ophthalmology visits 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. The EAG noted that the SmPC also states that further visits can occur if clinically indicated. But it said that this could potentially be captured by the adverse-events costs. The company suggested that including additional ophthalmologist visits in addition to adverse-events costs could result in double counting. On this basis, the EAG suggested the company's assumptions for resource use and costs were reasonable.

At the first committee meeting, the Cancer Drugs Fund clinical 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. At the second committee meeting, the company explained that an independent screening service, provided by community optometrists, was now in place for NHS patients having

belantamab mafodotin. But the company acknowledged that if people have grade-3 adverse events they will be referred to NHS hospital-based ophthalmology departments. The clinical experts highlighted that about 30 to 40 hospitals took part in the compassionate-use scheme for belantamab mafodotin, and so those hospitals have a pathway in place for this population. The company explained that between 2018 and 2024, over 100 NHS sites administered belantamab mafodotin in different settings. The committee recalled that the incidence and costs of ocular adverse events were applied as a one-off in the model, and the incidence of keratopathy applied in the model was lower than was observed in DREAMM-7 (see section 3.16). It also recalled that time to onset and duration of adverse events of grade 3 and above was not reported. The committee said that there was uncertainty around whether the cost of ocular adverse events had been adequately accounted for in the model. It said that this was because the model had not included continued monitoring until resolution of ocular adverse events. So, the cost of ocular adverse events was likely to have been underestimated. The committee concluded that the base case should include the continued cost of ocular adverse events using hospital-based ophthalmology services. It further concluded that it would consider in its decision making the uncertainty around the cost of ocular adverse events.

Severity

3.19 NICE's methods about conditions with a high degree of severity did not apply.

Cost-effectiveness estimates

The committee's preferred assumptions

3.20 For the comparison with Dar-Bor-Dex, Sel-Bor-Dex and Car-Dex, when lenalidomide is not an option, the committee concluded that its preferred modelling assumptions were:

- using a later data cut-off from the LEPUS study (see section 3.6)

- using individual patient data for Bel-Bor-Dex and RDI for other comparators (see section 3.10)
- using a baseline age that is reflective of the NHS population, from the SACT dataset (see section 3.11)
- using Dar-Bor-Dex SACT data to inform the baseline overall-survival curve with relative effects applied for Bel-Bor-Dex and other comparators (see section 3.12)
- using treatment-independent utility values (see section 3.15)
- including disutilities from ocular adverse events for Bel-Bor-Dex (see section 3.16)
- including teclistamab as fourth-line treatment (see section 3.17).

Additionally, for the comparison with Car-Len-Dex, when lenalidomide is an option, the committee concluded that its preferred modelling assumptions were:

- including adjustment for R-ISS staging in the MAIC (see section 3.8)
- using a baseline age that is based on the mean age of the weighted Bel-Bor-Dex arm in the MAIC (see section 3.11)
- modelling Car-Len-Dex survival using the hazard ratio from the MAIC applied to the unweighted Bel-Bor-Dex curve (see section 3.13)
- using the data from ASPIRE to estimate TTD for Car-Len-Dex (see section 3.14).

Acceptable ICER

3.21 NICE's manual on technology appraisal and highly specialised technologies guidance notes that, above a most plausible incremental cost-effectiveness ratio (ICER) of £25,000 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 that:

- the indirect treatment comparison with Car-Len-Dex was based on an unanchored MAIC (see section 3.7)
- exposure to belantamab mafodotin may be lower in clinical practice and the impact on clinical and cost effectiveness is uncertain (see section 3.10)
- the long-term predictions of overall survival for belantamab mafodotin are uncertain (see section 3.12)
- the long-term predictions of clinical effectiveness do not take into account recently approved subsequent treatments (see section 3.17)
- the cost of monitoring ocular adverse events with belantamab mafodotin was likely to have been underestimated (see section 3.18).

The committee noted that its preferred assumption to include adjustment for R-ISS in the MAIC may underestimate the benefit of Bel-Bor-Dex. Taking this into account, along with the other uncertainties identified and the unmet need, the committee concluded that an acceptable ICER would be around the middle of the range NICE considers a cost-effective use of NHS resources (£25,000 to £35,000 per QALY gained; see section 3.22).

Cost-effectiveness results

3.22 The committee considered the cost effectiveness of Bel-Bor-Dex in the relevant populations at second line only, incorporating all of its preferred assumptions (see section 3.20). The committee recalled that Dar-Bor-Dex and Car-Len-Dex are the most appropriate comparators because only a small proportion of people have Car-Dex or Sel-Bor-Dex (see section 3.4). The exact ICERs cannot be reported here because the prices of some of the comparators are confidential. For the comparison with Dar-Bor-Dex

(when lenalidomide is not an option), the deterministic and probabilistic ICERs for Bel-Bor-Dex were within the range NICE considers a cost-effective use of NHS resources. The committee recalled that when lenalidomide is an option at second line, Car-Len-Dex is the most appropriate comparator (see section 3.4). For the comparison with Car-Len-Dex, the deterministic and probabilistic ICERs for Bel-Bor-Dex were within the range NICE considers a cost-effective use of NHS resources.

Other factors

Equality

3.23 The committee noted that the company's proposed restrictions may create inequalities in treatment access. The committee reiterated its preference to evaluate Bel-Bor-Dex within its full marketing authorisation, that is second line onwards. It thought that restricting a recommendation to second line only may disadvantage people with multiple myeloma at third line and later. But it did not consider this to be a formal equality issue because the potential disadvantage does not relate to any of the protected characteristics under the Equality Act 2010.

The committee also considered that the prevalence of multiple myeloma is higher in people from Black ethnic backgrounds. But the Cancer Drugs Fund clinical lead confirmed that 4.5% of people diagnosed with multiple myeloma in England are Black and there is a similar proportion of Black people in England and Wales. So, the committee did not think that an optimised recommendation would increase or reduce any health inequalities.

Uncaptured benefits

3.24 The committee considered whether there were any uncaptured benefits of Bel-Bor-Dex. It did not identify additional benefits of Bel-Bor-Dex not captured in the economic modelling. So, the committee concluded that all additional benefits of Bel-Bor-Dex had already been taken into account.

Conclusion

Recommendation

3.25 The committee noted that the ICERs for Bel-Bor-Dex compared with Dar-Bor-Dex and compared with Car-Len-Dex were within the range NICE considers a cost-effective use of NHS resources. So, Bel-Bor-Dex can be used for adults with multiple myeloma if they have had 1 previous line of treatment only.

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

5 Evaluation committee members and NICE project team

Evaluation committee members

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

Committee members are asked to declare any interests in the technologies being evaluated. If it is considered there is a conflict of interest, the member is excluded from participating further in that evaluation.

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

Chair

Charles Crawley

Chair, technology appraisal committee B

NICE project team

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

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