# NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

## Draft guidance consultation

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

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using daratumumab plus bortezomib, lenalidomide and dexamethasone in the NHS in England. The evaluation committee has considered the evidence submitted by the company and the views of non-company stakeholders, clinical experts and patient experts.

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

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

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

**Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.**

After consultation:

- The evaluation committee will meet again to consider the evidence, this evaluation consultation document and comments from the stakeholders.
- At that meeting, the committee will also consider comments made by people who are not stakeholders.
- After considering these comments, the committee will prepare the final draft guidance.
- Subject to any appeal by stakeholders, the final draft guidance may be used as the basis for NICE's guidance on using daratumumab plus bortezomib, lenalidomide and dexamethasone in the NHS in England.

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

The key dates for this evaluation are:

- Closing date for comments: 4 June 2026
- Third evaluation committee meeting: 17 June 2026
- Details of membership of the evaluation committee are given in section 4.

# 1 Recommendations

1.1 Daratumumab plus bortezomib, lenalidomide and dexamethasone followed by daratumumab plus lenalidomide maintenance should not be used as an option for untreated multiple myeloma in adults when an autologous stem cell transplant is suitable.

1.2 This recommendation is not intended to affect treatment with daratumumab plus bortezomib, lenalidomide 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

These are NICE's draft recommendations. If these recommendations become final, daratumumab plus bortezomib, lenalidomide and dexamethasone followed by daratumumab plus lenalidomide maintenance would not be required to be funded and should not be used routinely in the NHS in England for the condition and population in the recommendations.

This is because there is not enough evidence to determine whether daratumumab plus bortezomib, lenalidomide and dexamethasone followed daratumumab plus lenalidomide maintenance is value for money in this population.

## Why the committee made these recommendations

NICE is separately evaluating daratumumab with bortezomib, lenalidomide and dexamethasone for untreated multiple myeloma when a stem cell transplant is unsuitable.

Usual treatment for untreated multiple myeloma when an autologous stem cell transplant is suitable is:

- daratumumab plus bortezomib, thalidomide and dexamethasone as induction and consolidation treatment, then
- lenalidomide alone as maintenance treatment.

This evaluation looks at:

- daratumumab plus bortezomib, lenalidomide and dexamethasone as induction and consolidation treatment, then
- daratumumab plus lenalidomide as maintenance treatment.

Daratumumab plus bortezomib, lenalidomide and dexamethasone as induction and consolidation treatment, then daratumumab plus lenalidomide as maintenance treatment, has not been directly compared with daratumumab plus bortezomib, thalidomide and dexamethasone induction and consolidation treatment followed by lenalidomide alone as maintenance treatment. The results of indirect comparisons suggest that the new combination may have similar effectiveness to usual treatment during induction and consolidation, but there is considerable uncertainty around its long-term benefits. Comparisons of daratumumab plus lenalidomide maintenance treatment with lenalidomide alone as maintenance treatment, suggest daratumumab plus lenalidomide increases how long people live and how long they have before their condition gets worse. But this is uncertain because comparisons of the full treatment sequence (including induction, consolidation and maintenance) were not conducted in the same trials.

There are uncertainties in the economic model. These include how it models subsequent treatments and how long people had treatment for.

Because of the considerable uncertainty around the long-term benefits of the new combination, it is not possible to determine the most likely cost-effectiveness estimates. But, they are likely to be higher than the range that NICE considers an acceptable use of NHS resources. So, daratumumab plus bortezomib, lenalidomide, and dexamethasone, followed by daratumumab plus lenalidomide, should not be used.

# 2 Information about daratumumab

## Marketing authorisation indication

2.1 Daratumumab (Darzalex, Janssen-Cilag) is indicated 'in combination with bortezomib, lenalidomide and dexamethasone for the treatment of adult patients with newly diagnosed multiple myeloma'.

## Dosage in the marketing authorisation

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

## Price

2.3 The list price of daratumumab is £4,320.00 per 1,800 mg/15 ml vial (excluding VAT; BNF online accessed December 2025).

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

## Carbon Reduction Plan

2.5 Information on the Carbon Reduction Plan for UK carbon emissions for Janssen-Cilag will be included here when guidance is published.

# 3 Committee discussion

The evaluation committee considered evidence submitted by Janssen-Cilag, 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 the plasma cells. It is a chronic condition that affects how long people live and their quality of life. People whose myeloma is in complete remission after initial treatment may still have residual myeloma cells present at levels that are only detectible using sensitive molecular techniques. This is known as minimal residual disease (MRD). The committee recognised that detectible MRD (referred to as MRD-positive disease) is associated with worse outcomes, but that relapses also occur without MRD (referred to as MRD-negative disease). The patient experts emphasised that multiple myeloma is a highly individual and complex cancer that has significant and varied symptoms. They explained that the condition has a large psychological impact because of the constant possibility of relapse. The patient experts added that each additional line of treatment is associated with worse outcomes and that myeloma can evolve over time and become more resistant to treatment. They emphasised that the condition can have a large impact on quality of life, affecting all aspects of life. They added that people who are eligible for an autologous stem cell transplant (ASCT) tend to be younger, more likely to be working and often have caring responsibilities. So, they said that multiple myeloma can have a wider impact on their families and carers. The committee acknowledged that multiple myeloma is a chronic, incurable and 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 ASCT is suitable. NICE recommends the following treatments as options at first line when a ASCT is suitable:

- bortezomib plus dexamethasone with or without thalidomide induction treatment (Bor-Dex, or Bor-Dex-Tha; see NICE's technology appraisal guidance on induction therapy in multiple myeloma before high-dose chemotherapy and autologous stem cell transplantation)
- daratumumab plus bortezomib, thalidomide and dexamethasone
- induction and consolidation treatment (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, from here referred to as TA763)
- lenalidomide maintenance treatment (Len; see NICE's technology appraisal guidance on lenalidomide maintenance treatment after an autologous stem cell transplant for newly diagnosed multiple myeloma).

The clinical experts explained that multiple myeloma can become resistant to treatment over time. This means that the most effective treatment should be given as early as possible in the treatment pathway to gain the deepest response and longest remission. The company explained that Dar-Bor-Tha-Dex induction and consolidation treatment then Len maintenance treatment is standard care in the NHS for newly diagnosed multiple myeloma when an ASCT is suitable. The clinical experts and EAG agreed that a very small percentage of people who have renal impairment may have bortezomib plus cyclophosphamide and dexamethasone induction treatment because of concerns around

thalidomide toxicity. The clinical experts explained that Len is the only comparator for maintenance treatment. The committee noted that some people are offered a combination other than Dar-Bor-Tha-Dex induction and consolidation treatment in the NHS. It concluded that Dar-Bor-Tha-Dex induction and consolidation treatment followed by Len maintenance treatment was the most relevant comparator for most people.

## Clinical effectiveness

### Key clinical trial: PERSEUS

3.3 The clinical-effectiveness evidence for Dar-Bor-Len-Dex came from PERSEUS, a phase 3, multicentre, international, randomised, open-label study. It compared Dar-Bor-Len-Dex (n=345) with Bor plus Len and Dex (Bor-Len-Dex) at the induction and consolidation phases (n=345). PERSEUS had an induction phase comprising 4 cycles of 28 days of treatment. This was followed by high-dose chemotherapy and an ASCT (HDT-ASCT). This was followed by a consolidation phase comprising 2 cycles of 28 days. People then had a maintenance phase of numerous 28-day treatment cycles. People randomised to the Dar-Bor-Len-Dex arm had Dar-Len maintenance and people randomised to Bor-Len-Dex had Len alone as maintenance. People in the Dar-Bor-Len-Dex arm could stop taking daratumumab maintenance if their disease had progressed or if they had been having it for 2 years and had sustained MRD negativity for 12 months.

The primary endpoint was progression-free survival (PFS) assessed according to the International Myeloma Working Group criteria. The EAG noted that the company had presented results using data from the 1 August 2023 data cut with a median follow up of 47.5 months. It explained that this data was immature because neither median overall survival (OS) nor median PFS had been reached in either arm. The EAG added that the

PERSEUS trial was also not done in England or Wales. The company stated that people in the trial had similar demographic and disease characteristics to people seen in the NHS. It added that data from the National Cancer Registration and Analysis Service suggested that people diagnosed with multiple myeloma in the NHS are a similar age to the Dar-Bor-Len-Dex arm in PERSEUS. A clinical expert stated that the median age of 61 years in the Dar-Bor-Len-Dex arm might be slightly younger than what is expected in the NHS. Another clinical expert noted Eastern Cooperative Oncology Group (ECOG) performance status scores in PERSEUS differed slightly from UK clinical practice but they thought the trial population was broadly generalisable. The EAG felt that the PERSEUS trial was sufficiently generalisable to the NHS. The committee concluded that although the data was immature and that this added uncertainty to the survival analysis, the results from the trial were suitable for decision making.

## Direct and indirect treatment comparisons

3.4 The company explored different options for comparing Dar-Bor-Len-Dex induction and consolidation followed by Dar-Len maintenance with the relevant comparator. The company had not identified any randomised controlled trials (RCT) that included the full treatment sequence of Dar-Bor-Tha-Dex induction and consolidation followed by Len maintenance. So, the company split its comparative analysis into 2 steps; a comparison of clinical effectiveness in induction and consolidation phases, and separate comparison of efficacy of maintenance treatment. The EAG agreed that, in the absence of direct evidence of the full treatment sequence, the approach was appropriate. The committee discussed whether the intervention should be modelled as the full treatment sequence of induction, consolidation, HDT-ASCT and maintenance phases or split with separate cost-effectiveness analysis done for each

phase. It discussed how Dar-Bor-Len-Dex followed by Dar-Len maintenance would be used in clinical practice (in line with the summary of product characteristics). It concluded that although there is no evidence for the full sequence of Dar-Bor-Tha-Dex induction and consolidation followed by Len maintenance, the intervention and comparator should be modelled as the full treatment sequence.

The company did an indirect treatment comparison (ITC) using patient-level data of the induction and consolidation phases only of Dar-Bor-Len-Dex (from PERSEUS) compared with Dar-Bor-Tha-Dex (from the phase 3 randomised open-label CASSIOPEIA trial). The company used an inverse probability of treatment weighting (IPTW) approach with people in both arms being censored at the start of maintenance treatment. The EAG agreed that the approach to the ITC was appropriate. But, it noted that 3 covariates in the company base case IPTW had standardised mean differences above 0.2, which could indicate poor balance after matching. But it added that the results in the company base case IPTW were consistent with the results using other ITC adjustment methods presented by the company. Based on the IPTW, the company assumed equal efficacy during the induction and consolidation phases between Dar-Bor-Len-Dex and Dar-Bor-Tha-Dex (see section 3.6). The committee noted the uncertainty in the IPTW analysis. But, it was reassured by similar results using other ITC adjustment methods and concluded the simplifying assumption of equal efficacy was appropriate.

For the maintenance phase, the company estimated the effectiveness of Dar-Len compared with Len directly without adjustments. This comparison was informed using data from PERSEUS and the AURIGA trial. AURIGA is an ongoing phase 3 RCT that compares Dar-Len with Len maintenance after an HDT-SCT. People in the trial had a range of different induction regimens and then were randomised to have Dar-Len or Len

maintenance. The median follow up in AURIGA was 32.3 months and neither median OS nor PFS was reached in either arm. The EAG highlighted that the population in AURIGA differed from PERSEUS because everyone in AURIGA had MRD-positive disease that had achieved a very good partial response or better after induction treatment and HDT-ASCT. It added that very few people in AURIGA had consolidation therapy, and no one had either Dar-Bor-Len-Dex, Dar-Bor-Tha-Dex or any other regimen including daratumumab as induction or consolidation treatment. At clarification, the company explored using an ITC to isolate the maintenance phase of PERSEUS. In the ITC, people randomised to the Dar-Bor-Len-Dex arm had Dar-Len maintenance, and people randomised to Bor-Len-Dex had Len maintenance alone. The company used an IPTW approach for the comparison of Dar-Len and Len maintenance using patient level data from PERSEUS. This approach reweighted the baseline characteristics and post-consolidation MRD-status of the people starting Len maintenance, so that they resembled people starting Dar-Len maintenance in the trial.

The company argued that the lack of randomisation after the consolidation phase in PERSEUS makes it difficult to isolate the effects in the maintenance phase. It added that AURIGA provided the best unbiased estimate of the treatment effect of Dar-Len compared with Len alone. The EAG agreed that using PERSEUS for direct comparisons in the maintenance phase could overestimate the relative effectiveness of Dar-Len maintenance. This was because people in the Len maintenance arm had a different induction and consolidation regimen (they had Bor-Len-Dex instead of Dar-Bor-Tha-Dex). The EAG added that adjusting PERSEUS using the IPTW approach could reduce bias. A clinical expert stated that the people in AURIGA had worse disease status compared with people in PERSEUS. This means the benefits of Dar-Len could be biased. The committee noted some generalisability issues with the

AURIGA trial. It queried whether the low proportion of people who had subsequent anti-CD38 treatments (daratumumab or isatuximab) after Len maintenance in AURIGA would be representative of what would happen in the NHS. A clinical expert stated that it is likely people would have treatment with daratumumab if they had not already had it. So, AURIGA might not be representative of NHS practice. Another clinical expert thought PERSEUS was more relevant to clinical practice, because more people who had not had daratumumab at first line went on to have it at subsequent lines. The committee expressed its concern that neither Dar-Bor-Len-Dex or Dar-Bor-Tha-Dex was used for induction or consolidation in AURIGA. It was particularly concerned that AURIGA might not be representative of what would be seen in the NHS because many people did not have subsequent daratumumab. The committee noted that people having Len maintenance in PERSEUS also did not have Dar-Bor-Tha-Dex induction and consolidation. It acknowledged that people who had Len maintenance in PERSEUS would not have had daratumumab for induction and consolidation. Without analysis using AURIGA to adjust for the low proportions having subsequent anti-CD38 treatment (including daratumumab) in the Len maintenance arm, the committee preferred to use PERSEUS. This was because some people in PERSEUS were randomised to have the full intervention sequence of Dar-Bor-Len-Dex followed by Dar-Len maintenance. The committee concluded that reweighted IPTW analysis from the PERSEUS trial should be used for the relative effectiveness to inform the cost-effectiveness estimates. But, it added that it would value further evidence on the effectiveness of Dar-Bor-Tha-Dex followed by Len, including real world evidence.

During consultation, NICE provided real-world data from the National Disease Registration Service's Systemic Anti-Cancer Therapy (SACT) dataset. The SACT data (n=759) reported age, sex, OS and time on treatment. The cohort included adults in the NHS diagnosed with multiple

myeloma between February 2022 and December 2023. Participants all had first-line Len maintenance after an ASCT and an induction or consolidation regimen that included daratumumab. The data had a median follow up of 22.7 months, and median survival was not reached by the data cut off (October 2025). The company considered the SACT data to be more relevant for validating the generalisability of the PERSUES trial instead of informing the efficacy of Dar-Bor-Tha-Dex followed by Len. It noted that the cohort definition used to identify the population likely includes people who do not belong to the relevant indication. For example, people with myelomatosis, plasma cell myeloma and myeloma (not otherwise specified) or plasmacytic leukemia. It also noted that the SACT data does not capture important prognostic factors for myeloma and felt that PFS cannot be robustly estimated using SACT data. The company also noted that a target trial emulation approach recommended in the NICE real-world evidence framework was not applied. For these reasons it considered the SACT data to be inappropriate for informing the effectiveness of Dar-Bor-Tha-Dex followed by Len. The company considered the reweighted IPTW analysis from the PERSEUS trial to be more appropriate to inform relative effectiveness in the model. It noted that the mean age and proportion of males were similar between the SACT data and PERSEUS. An overlay of the OS Kaplan–Meier curve from SACT and the IPTW reweighted Bor-Len-Dex arm of PERSEUS also showed Len maintenance outcomes were aligned. After fitting extrapolations to the SACT data, 10-year OS rates for the best fitting extrapolations were also broadly aligned with estimates using the PERSEUS data. The EAG acknowledged the concerns about the SACT data and agreed with the company's approach. A clinical expert stated that the comparability of age and sex is reassuring and another agreed that the data suggests PERSEUS is generalisable. The committee noted the concerns raised by the company about using the SACT data to inform

the effectiveness of Dar-Bor-Tha-Dex followed by Len. It acknowledged that the PERSEUS data was also immature and that people having Len maintenance in PERSEUS did not have Dar-Bor-Tha-Dex induction and consolidation. It concluded that the comparisons with the SACT data suggest the PERSEUS data is likely broadly aligned with NHS practice and the most appropriate data source for modelling relative effectiveness of standard care compared with Dar-Len maintenance.

In response to the draft guidance consultation, the company provided additional details of the reweighted IPTW analysis from PERSEUS. It presented IPTW analysis adjusting for post-consolidation MRD status and a set of base-case variables, which included:

- age
- sex
- ECOG performance status,
- international staging system stage
- baseline cytogenic risk
- type of multiple myeloma, and
- haemoglobin levels.

This was used to inform the relative effectiveness of Dar-Len versus Len in the model. The company provided scenario analysis of the IPTW adjustment using the following additional variables:

- lactate dehydrogenase
- creatinine clearance
- multiple myeloma diagnostic criteria
- presence of extramedullary plasmacytomas
- serum calcium
- bone lesions and

- platelet levels.

It also presented analysis using doubly robust and multivariate regression adjustment methods to isolate the treatment effect of Dar-Len compared with Len. The company stated that the results of the scenario analyses were broadly consistent with the IPTW analysis using the base case variable set. The committee queried whether the additional variables should be included in the IPTW adjustment. A clinical expert stated that the base case and additional variables are clinically relevant. Another added that some of the additional variables are adverse prognostic factors, so it is reassuring the results of the IPTW do not change too much when including the additional variables. The EAG stated that, because of the randomised design of PERSEUS, most covariates were already balanced before reweighting and agreed that the IPTW adjustment with base case variables is appropriate. The committee considered the input from the clinical experts and the EAG. It noted the inclusion of the additional variables had a small impact on the results of the IPTW adjustment. It concluded that the relative effectiveness of Dar-Len compared with Len maintenance used to inform the cost-effectiveness estimates, should be calculated using:

- the reweighted IPTW analysis adjusting for post-consolidation status and
- the base case variable set from the PERSEUS trial.

## Economic model

### Company's modelling approach

3.5 The company provided a partitioned survival model to estimate the cost-effectiveness of Dar-Bor-Len-Dex followed by Dar-Len compared with Dar-Bor-Tha-Dex followed by Len. The model included 3 health states: progression free, progressed disease and death. The probability of being

in each health state was calculated using extrapolated PFS and OS curves (see section 3.6). The model used a cycle length of 28 days with a half cycle correction over a lifetime of 40 years. The OS rate was capped by the age and sex-matched general population mortality rate. In each cycle, the PFS rate was capped by the OS rate for the same time period to ensure that OS was always greater than PFS. The committee noted that a single health state (and utility value) for progressed disease might not reflect the patient journey as they progress through subsequent lines of treatment. But it concluded that the model choice was appropriate for decision making.

## Modelling PFS and OS

3.6 During the induction and consolidation phases of treatment, the company assumed equal efficacy in OS and PFS between Dar-Bor-Len-Dex and Dar-Bor-Tha-Dex (see section 3.4). PFS and OS for both arms were taken from Kaplan–Meier curves of the Dar-Bor-Len-Dex arm of PERSEUS. The EAG noted that assuming equal efficacy during induction and consolidation meant that modelled differences in OS and PFS between treatments are caused by differences in PFS and OS from the maintenance phase only. The committee acknowledged that although there was uncertainty in the relative OS and PFS because of the short follow up, this data showed a benefit for Dar-Bor-Len-Dex. It concluded that, overall, assuming equal efficacy between Dar-Bor-Len-Dex and Dar-Bor-Tha-Dex for OS and PFS during the induction and consolidation phases is acceptable. But it noted that this was a simplifying assumption.

At the first committee meeting the company modelled PFS and OS using extrapolated data from PERSEUS Kaplan–Meier curves and data from AURIGA. To provide survival estimates for people having Dar-Bor-Tha-Dex followed by Len maintenance, the company:

- fitted distributions to PFS and OS for the Dar-Bor-Len-Dex followed by Dar-Len arm of PERSEUS and
- applied hazard ratios for PFS and OS from AURIGA.

It fitted a generalised gamma distribution for PFS. The EAG agreed that the generalised gamma for PFS had the best fit to clinical expert estimates for the Dar-Bor-Len-Dex followed by Dar-Len arm. But it noted that after applying the hazard ratio from AURIGA, PFS estimates for the comparator arm were above clinical expert estimates at 10, 15 and 25 years. The company fitted an exponential distribution for OS and the EAG agreed this was the most appropriate distribution. But it noted that immature survival data in both PERSEUS and AURIGA make the extrapolations very uncertain. The committee recalled its preference for using the PERSEUS data alone to model the maintenance phase of treatment (see section 3.4). It also preferred to apply the hazard ratios generated from the IPTW of the PERSEUS trial to model PFS and OS for the Dar-Bor-Tha-Dex followed by Len maintenance arm. It noted long-term OS and PFS estimates after applying the hazard ratios from PERSEUS had not been presented. So, the clinical experts could not comment on whether the long-term estimates of OS and PFS for the comparator arm were similar to what would be expected in the NHS. The committee was therefore not able to conclude on the most appropriate OS and PFS parametric distributions.

In response to the draft guidance consultation, the company provided additional analysis using the hazard ratios from the reweighted IPTW of the PERSEUS trial (see section 3.4). It maintained the generalised gamma to extrapolate PFS in the Dar-Bor-Len-Dex followed by Dar-Len arm. The company applied the PFS hazard ratio from the IPTW of the PERSEUS trial to get a proxy extrapolation for Dar-Bor-Tha-Dex followed by Len maintenance arm. After doing this, the PFS estimates were

aligned with its clinical expert estimates at 10 and 25 years. The EAG commented that all distributions except for the Gompertz provided higher PFS estimates. But the Gompertz appeared to overestimate survival for the Dar-Bor-Tha-Dex followed by Len arm at 10 years. It added that applying the Gompertz had little impact on cost effectiveness and that the generalised gamma was suitable to extrapolate PFS for both arms. A clinical expert stated that either extrapolation of PFS was plausible. The committee considered the input from the clinical experts and the EAG. It concluded that the generalised gamma was appropriate to extrapolate PFS in the Dar-Bor-Len-Dex followed by Dar-Len arm.

The company maintained an exponential distribution to extrapolate OS in the Dar-Bor-Len-Dex followed by Dar-Len arm. It applied the OS hazard ratio from the IPTW of the PERSEUS trial. This produced OS estimates from the proxy extrapolation for Dar-Bor-Tha-Dex followed by Len arm that were in line with clinical expert estimates at 15 and 25 years. The EAG added that although the exponential assumes constant hazards, which is inconsistent with the observed hazards for Dar-Bor-Len-Dex followed by Dar-Len, alternative OS extrapolations do not provide a better fit. The committee concluded that the exponential was appropriate to extrapolate OS for Dar-Bor-Len-Dex followed by Dar-Len. The committee noted that because people had different induction and consolidation treatments in PERSEUS, the outcomes may not fully reflect what would be expected in NHS clinical practice. The committee concluded it would take this uncertainty into account in its decision making.

## MRD-negativity stopping rule

3.7 The company modelled a stopping rule in which people who had been having maintenance treatment for 2 years could stop daratumumab if they had sustained MRD-negativity for 12 months. This was in line with the summary of product characteristics for daratumumab. In the company

base case, daratumumab maintenance discontinuation for people who met the stopping rule criteria was informed by a mature time to treatment discontinuation (TTD) Kaplan–Meier curve from PERSEUS. People who did not meet the criteria were assumed to continue having daratumumab maintenance treatment until progression. The company fitted an exponential distribution to a TTD Kaplan–Meier curve using data from PERSEUS to estimate daratumumab discontinuation for this group. It explained that this distribution had the best fit to the observed data and to clinical expert estimates. The company added that two thirds of people having Dar-Len maintenance in PERSEUS stopped daratumumab maintenance treatment. The EAG stated that assuming everyone continue daratumumab maintenance treatment until disease progression has a large impact on cost effectiveness.

At the first committee meeting the NHS England Cancer Drugs Fund clinical lead (from here, Cancer Drugs Fund lead) explained that MRD testing might be done as part of clinical trials. But they added that currently it is it is not done routinely in NHS clinical practice for multiple myeloma and MRD testing is only done in 2 centres in England. The clinical experts explained that MRD testing is routine in other conditions and new clinical trials in multiple myeloma include MRD-guided treatment. The clinical experts were concerned if MRD testing is not done, multiple myeloma would be treated differently to other diseases. The Cancer Drugs Fund lead had concerns about the number of MRD tests that would be needed to guide daratumumab discontinuation and if further MRD testing would be necessary after discontinuation. The company stated that most people would need 2 MRD tests and that if people had not reached MRD-negativity they would be unlikely to ever reach it. So, 3 MRD tests would likely be the maximum needed. A patient expert stated that MRD testing is invasive and requires a bone marrow biopsy, so it is unlikely that people would want more testing than needed. Another patient expert

added that although a bone marrow biopsy for MRD testing is unpleasant, it would be acceptable to people with myeloma if it enabled them to stop treatment. A clinical expert explained that there is value in MRD testing because it could allow people to stop having daratumumab before their condition becomes refractory to it. The committee acknowledged that there would be clinical benefits to MRD-guided treatment but that it was unclear whether MRD testing would be feasible in the NHS. It had concerns around how many MRD tests would be needed to allow daratumumab to be stopped and if some people would decline testing in clinical practice. The committee was unclear on if it was feasible for all treatment centres to do MRD testing and in which centres the tests would be processed. It also had concerns on if delays to MRD testing would result in people stopping daratumumab later than the 2-year time point. So, the committee could not conclude whether an MRD stopping rule was appropriate in the model, and this led to uncertainty in the cost-effectiveness estimates.

In response to the draft guidance consultation, the company provided new evidence from a UK Clinical Advisory Board on the feasibility of MRD-testing to guide daratumumab discontinuation in clinical practice. It maintained the stopping rule for daratumumab in the model assuming next generation flow (NGF) MRD testing would be used. It stated that Leeds and The Royal Marsden NHS trusts currently do NGF MRD testing. It added that these trusts have the capacity to do the volume of testing needed for the stopping rule if daratumumab was recommended in this indication. It added that MRD testing is already routine in other diseases, such as chronic lymphocytic leukaemia. For these diseases it is common for bone marrow samples to be taken locally then transferred to specialist labs. The company explained that this means there are established sampling, packaging and transport pathways. It added that Leeds and The Royal Marsden NHS trusts confirmed that they regularly receive samples

from other NHS sites. The company also provided additional scenarios assuming daratumumab maintenance for a fixed 2 years as an alternative to the MRD-informed stopping rule. One of these scenarios assumed people with 'high risk' myeloma would have daratumumab and Len maintenance treatment to progression. Here, the modelled proportion of people with high-risk disease was based on if people had a cytogenetic abnormality in the PERSEUS trial, including the presence of del[17p], t[4;14] or t[4;16].

At the second committee meeting, a clinical expert confirmed that Leeds NHS Trust regularly does NGF MRD tests in the NHS and as part of clinical trials. They explained that other centres want to adopt MRD testing but have not because the results cannot currently be used for clinical decisions. The Cancer Drugs Fund lead stated that MRD testing is not widely or routinely available in the NHS. They added that MRD-testing in other diseases is mostly a single diagnostic test rather than continuous testing. A clinical expert argued that staff in NHS trusts are already being upskilled to do MRD testing for this indication. The company added that it is committed to supporting education and training across trusts to allow MRD testing in line with the stopping rule. The committee queried which type of MRD testing would be done to inform the stopping rule in the NHS. It also queried if the type of test would change the specificity used to define MRD negativity. The Cancer Drugs Fund lead stated that NGF is the most logical choice initially. This is because it is already available in some NHS labs, it was used in the PERSEUS trial, and other options could be very expensive. They explained that next generation sequencing (NGS) MRD testing is in very early stages in the NHS. The Cancer Drugs Fund lead stated that NGS has a higher sensitivity of approximately 1 in 1 million cells compared with NGF at approximately 1 in 100,000 cells. So, some people may test negative with NGF but test positive with NGS. The company argued that a sensitivity of 1 in 1 million cells is not required for

the stopping rule and 1 in 100,000 cells would be used. The company stated that a scenario assuming NGS MRD testing through the NHS Genomic Medicines Service instead of NGF testing had little impact on cost effectiveness. The committee queried how many tests would be required to stop daratumumab. The company maintained that when using NGF testing, 2 tests would be required. The first MRD test would be done 12 months into maintenance treatment and the second around 24 months. A clinical expert agreed. They noted that if the first test at 12 months was MRD positive but the second test at 24 months was MRD negative, a third test could be done at around 36 months to assess if MRD negativity was sustained and then daratumumab could be stopped. So, 3 tests would likely be the maximum. The committee asked if some people would decline testing. A patient expert explained that there will always be some people who do not want testing. But they added that most people would do it to reduce their number of treatments and hospital visits. Another patient expert added that very few people would decline testing and that this percentage is likely less than 5%. A clinical expert commented that some people do not have the molecular marker that would allow MRD testing. The committee discussed what treatment should be offered in clinical practice to people who either cannot get MRD testing or decline testing. It recalled the additional scenarios presented by the company assuming people would have daratumumab for a fixed period of 2 years and queried if this would be reasonable. A clinical expert agreed that daratumumab for a fixed 2 years sounds reasonable. Another added that because people with high-risk disease likely have worse outcomes it would be reasonable for this group to continue daratumumab and Len maintenance until progression. The committee considered stopping rules based on MRD negativity to be a key uncertainty. The committee requested additional analysis following the second committee that assumed 95% of people have MRD testing in the base case. This was to

account for people who cannot have or refuse MRD testing. It also requested scenarios for the remaining 5% who are assumed not to have MRD testing. These included assuming 5% of people have daratumumab maintenance:

- until progression
- for a fixed 2 years or
- for a fixed 2 years unless they have 'high-risk' disease, when they can continue until progression.

## Modelling TTD

3.8 The company used TTD to determine the time on treatment. It explained that this allowed specific costs to be applied while people were having treatment independently of the health state they were in. Treatment duration for the induction and consolidation phase of Dar-Bor-Len-Dex was informed by TTD in PERSEUS and Dar-Bor-Tha-Dex used TTD from CASSIOPEIA. TTD in the maintenance phase of the Dar-Bor-Len-Dex followed by Dar-Len arm was modelled separately to reflect the MRD-negativity stopping rule (see section 3.7). At the first committee meeting, the company fitted an exponential distribution to a TTD Kaplan–Meier curve using data from PERSEUS to model Len maintenance discontinuation in the intervention arm. For the Dar-Bor-Tha-Dex followed by Len arm, the company also modelled Len maintenance fitting an exponential distribution to a TTD Kaplan–Meier curve from PERSEUS. The EAG was unclear why the company had used PERSEUS to inform Len discontinuation when AURIGA was used to inform effectiveness (see section 3.4). The EAG stated that this implied that having daratumumab for induction and consolidation does not impact Len discontinuation. The EAG recalled that people having Len maintenance in PERSEUS had Bor-Len-Dex induction and consolidation and not Dar-Bor-Tha-Dex. So, using PERSEUS to inform TTD in the comparator arm assumes that having

either induction and consolidation regimen does not impact Len discontinuation. The EAG had concerns because thalidomide is not well tolerated. So it is likely that having thalidomide for induction and consolidation would have an impact on Len discontinuation. At clarification, the company acknowledged that there is limited evidence on the impact of adding daratumumab for induction and consolidation on Len discontinuation. It added that most people in AURIGA received Bor-Len-Dex induction therapy. The committee discussed which data should be used to inform Len maintenance TTD. It acknowledged that people having Len maintenance in both AURIGA and PERSEUS did not have Dar-Bor-Tha-Dex induction and consolidation. The committee concluded that the same source should be used to model treatment discontinuation and clinical effectiveness. It recalled its preference for using hazard ratios using the PERSEUS data to estimate the effectiveness of Len maintenance. So, the committee concluded that the TTD Kaplan–Meier from PERSEUS should be used to inform Len discontinuation in the Dar-Bor-Tha-Dex followed by Len arm. The committee noted that because people had different induction and consolidation treatments in PERSEUS, the outcomes may not fully reflect what would be expected in NHS clinical practice. The committee concluded it would take this uncertainty into account in its decision making.

In response to the draft guidance consultation, the company updated its base case to reflect the committee's preferred assumptions. It maintained an exponential distribution to extrapolate the TTD Kaplan–Meier from PERSEUS to inform Len discontinuation for Dar-Bor-Tha-Dex followed by Len. The company also fitted an exponential distribution to extrapolate Len maintenance in the Dar-Bor-Len-Dex followed by Dar-Len arm. The EAG agreed the approach was appropriate and noted alternative extrapolations did not provide a better fit. To extrapolate the daratumumab maintenance TTD Kaplan–Meier for people who did not meet the stopping

rule criteria (see section 3.7) in the Dar-Bor-Len-Dex followed by Dar-Len arm, the company used an exponential distribution. It argued this distribution was the best statistical fit and aligned with observed hazards and clinical expert estimates at 5, 8, and 10 years. The EAG highlighted that costs in the model were very sensitive to stopping daratumumab maintenance treatment in the intervention arm. It explained that this was mainly because of the stopping rule and the extrapolation fitted to the daratumumab maintenance TTD Kaplan–Meier for people who did not meet the stopping rule criteria. The committee noted that the chosen extrapolations for Len and daratumumab maintenance discontinuation in the Dar-Bor-Len-Dex followed by Dar-Len maintenance arm estimated that more people would stay on Len maintenance longer than daratumumab maintenance. It queried whether this was reflective of clinical practice. The company stated that people who had Len toxicity in the PERSEUS trial also stopped daratumumab. A clinical expert argued that because Len has many side effects, people would be more likely to stop Len first and continue daratumumab. The committee discussed whether the modelled extrapolations were appropriate. It thought the distributions fitted to extrapolate Len maintenance in both arms produced plausible estimates. The committee concluded that the exponential was suitable to extrapolate Len maintenance discontinuation in both the Dar-Bor-Tha-Dex followed by Len and Dar-Bor-Len-Dex followed by Dar-Len arms. It had concerns that the daratumumab maintenance TTD Kaplan–Meier for people who did not meet the stopping rule criteria in PERSEUS might underestimate daratumumab discontinuation in clinical practice. It concluded that an alternative extrapolation might better reflect outcomes in the NHS. The committee noted that both the log normal and log logistic TTD had good face validity. It requested additional analysis using the log-normal and log-logistic to extrapolate daratumumab maintenance TTD for

people without sustained MRD-negativity from PERSEUS in the Dar-Bor-Len-Dex followed by Dar-Len arm.

## Subsequent treatment costs

3.9 The company estimated the proportion of people having the various subsequent lines of treatment based on clinical expert opinion. The duration of each treatment was based on TTD and PFS from clinical trials. The same proportions of second-line treatments were used for both arms with 80% of people having belantamab mafodotin, bortezomib and dexamethasone combination treatment (Bel-Bor-Dex). The uptake of subsequent treatments was based on the treatment had at the previous line. At the first committee meeting a clinical expert disagreed with some of the company estimates. They explained that some people who have Len maintenance would also have daratumumab with Dar-Bor-Dex at second line and people would not have Len retreatment at subsequent lines. Another clinical expert noted that because Bel-Bor-Dex is newly recommended (see NICE's technology appraisal guidance on belantamab mafodotin with pomalidomide and dexamethasone for previously treated multiple myeloma), its use may not be as high as 80%. They added that more people would likely have teclistamab at fourth line than the modelled 50% to 60%. The EAG highlighted that subsequent treatment costs are a key driver in the model because of high prices for some of the treatments. It noted that it had not consulted its own clinical expert to validate the proportions modelled to have each treatment. The committee acknowledged that there was significant uncertainty around how well the proportions modelled to have subsequent treatments reflected NHS practice. It was particularly concerned about the proportion modelled to have Bel-Bor-Dex at second line. It also had concerns about how many people in each arm were modelled to progress to each line of treatment. It noted that some of the subsequent treatments in the model were very

expensive, which had a large impact on cost-effectiveness. The committee requested further information on whether the distribution of subsequent treatments and the proportion of people having subsequent treatments reflected NHS clinical practice.

In response to the draft guidance consultation, the company provided new evidence in the form of real-world data from the VSTx dataset. The data showed the proportion of second-, third- and fourth-line treatments prescribed in the NHS between October 2024 and September 2025. The company used this data (September 2025) alongside clinical opinion to estimate the future use of the subsequent treatments in its updated base case model. Progression to second-line treatments was modelled to depend on PFS in each arm. The uptake of subsequent treatments was assumed to be the same for each arm regardless of previous treatment. The company argued that the treatments prescribed for multiple myeloma change rapidly in the NHS because of new NICE recommendations. It added that the VSTx data showed established treatments had stable use but use of newly approved treatments such as second-line Bel-Bor-Dex increased month on month. The EAG stated that the proportions modelled to have each subsequent treatment should reflect current NHS prescribing and that the company's approach could introduce structural uncertainty in the model.

During consultation, NHS England provided Blueteq data that showed the number of applications for each second-line treatment regimen in the NHS and second-line-treatment trends over 3 years (January 2023 to December 2025). The Cancer Drugs Fund lead confirmed that there was a clear increase in uptake of Bel-Bor-Dex and that it is likely it would continue to increase. A clinical expert added that more people would likely have Bel-Bor-Dex than the proportions in both the VSTx and Blueteq data and that its use will only increase. Another added that it can take time to

build the infrastructure for new treatments so their uptake can be slow initially. They maintained that if someone had previously had Len or daratumumab, they would likely not have it at subsequent lines due to being refractory. So, carfilzomib with Len and dexamethasone (Car-Len-Dex) and Len with dexamethasone (Len-Dex) at second line were likely inappropriate. The committee discussed which data source was the most appropriate to inform subsequent treatment use in the model. It was concerned that some of the proportions in the company base case were highly uncertain. It noted the comments from the clinical experts and NHS England on the uptake of Bel-Bor-Dex. It concluded that the modelled subsequent use should be higher than the proportions in the VSTx and Blueteq data. It acknowledged that it is unlikely that people would have Len or daratumumab again if they had had it at a previous line. It concluded that modelled second-line treatments should not include regimens that contain either of these components.

The committee thought that subsequent-treatment distributions at second and third line were still highly uncertain. It requested analysis after the second meeting that combined real-world evidence from the VSTx dataset and clinical expert opinion. It asked that regimens containing daratumumab and Len (Car-Len-Dex, Len-Dex and Dar-Bor-Dex) should be removed from second line in the VSTx dataset. It also asked that the proportion having Dar-Bor-Dex in VSTx be redistributed to Bel-Bor-Dex. It then requested 2 scenarios, where third- and fourth-line treatments were:

- unchanged from the company base case and
- aligned with those applied in the NICE technology appraisal of daratumumab with bortezomib, lenalidomide and dexamethasone for untreated multiple myeloma when a stem cell transplant is unsuitable (expected publication May 2026).

## Utility values

3.10 The company base case model applied utility values based on the health state and treatment phase (the company considers the values to be confidential and so they cannot be reported here). In the progression-free state, utility values were based on the specific treatment phase (induction, ASCT, consolidation and maintenance). A single utility value was applied in the progressed-disease state regardless of the line of treatment. These values were from EQ-5D-5L data from PERSEUS that had been cross-walked to the EQ-5D-3L value set. The company also applied one-off utility decrements due to adverse events based on utility decrements from TA763 and NICE's technology appraisal guidance on daratumumab with lenalidomide and dexamethasone for untreated multiple myeloma when a stem cell transplant is unsuitable. The company stated that it had applied a higher utility value to people in the progressed-disease health state than to people who were progression free and having induction, ASCT or consolidation. It explained this reflected the psychological impact of diagnosis and treatment. A patient expert agreed that the initial diagnosis has a big impact psychologically and that people's physical condition at diagnosis can vary from person to person. They added that quality of life would be the highest when having maintenance treatment and being progression free. Another patient expert explained that side effects can have a worse impact on quality of life after diagnosis, and that these improve as people come to terms with the diagnosis and start treatment. The committee noted that the impact of multiple myeloma on health-related quality of life can differ from person to person. It considered the utility values used in the progression-free state in the company model to be plausible. But it noted that a single utility value for the progressed-disease state is an oversimplification that would likely overestimate utility in the model. It recognised that people's prognosis and quality of life would likely be worse as they progress on to subsequent lines of

treatment. The company explained that in its base case, the Dar-Bor-Tha-Dex followed by Len maintenance arm accrues more quality-adjusted life years (QALYs) in the progressed-disease health state than the intervention arm. This means that if lower utility values were applied to subsequent lines, this would improve the cost effectiveness of Dar-Bor-Len-Dex followed by Dar-Len maintenance. The committee noted that ideally a different utility value would be applied for each line of treatment in the progressed-disease state. The committee concluded that applying a single utility value post progression was acceptable. But it acknowledged that was a simplifying assumption and that applying a utility value weighted by the line of treatment could be an alternative approach.

## Cost-effectiveness estimates

### Acceptable incremental cost-effectiveness ratio

3.11 NICE's manual on technology appraisal and highly specialised technologies guidance notes that, above a most plausible 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:

- the lack of long-term OS and PFS data for the full sequence of Dar-Bor-Tha-Dex followed by Len maintenance (see section 3.6)
- the availability of MRD testing to guide stopping daratumumab maintenance treatment and whether this would be applied exactly as in the PERSEUS trial (see section 3.7)

- whether the modelled stopping of daratumumab maintenance would be representative of NHS clinical practice (see section 3.8)
- whether the subsequent treatments in the model were representative of what would be seen in NHS clinical practice (see section 3.9).

The committee thought that there was considerable uncertainty remaining after the second committee meeting. But it decided the introduction of real-world evidence on the feasibility of MRD testing and subsequent treatment use in NHS clinical practice had reduced some of this uncertainty. So, 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).

## Committee's preferred assumptions

3.12 The committee considered that neither the company's nor the EAG's base case included all its preferred assumptions. These were:

- assuming equal efficacy in PFS and OS between Dar-Bor-Len-Dex and Dar-Bor-Tha-Dex during the induction and consolidation phase (see section 3.4 and section 3.6)
- applying reweighted hazard ratios using the PERSEUS data for the maintenance phase of Dar-Bor-Tha-Dex followed by Len maintenance (see section 3.4)
- including an MRD stopping rule that assumes 95% of people have MRD testing to stop daratumumab maintenance (see section 3.7)
- using TTD from PERSEUS for stopping maintenance treatment (see section 3.8)
- applying second-line treatment distributions from the VSTx dataset after excluding regimens that include daratumumab or Len (see section 3.9)

- applying a single utility value in the progressed-disease state (see section 3.10).

## Additional analyses requested by committee

3.13 The committee found many areas of uncertainty (see section 3.11) and asked the company to provide the following additional analyses:

- modelling that 95% of people have MRD testing and scenarios where the remaining 5%:
  - continue daratumumab until progression,
  - stop daratumumab at a fixed 2 years, and,
  - stop daratumumab at a fixed 2 years, except for people who have high-risk disease, who are assumed to continue daratumumab until progression.
- scenario analysis including a log-normal and log-logistic distribution to extrapolate daratumumab maintenance TTD for people without sustained MRD-negativity using PERSEUS data.
- second-line subsequent treatment distributions from the VSTx dataset after excluding regimens that include daratumumab or Len, including scenarios assuming third- and fourth-line treatments are aligned with those applied in the company base case and in the NICE technology appraisal of daratumumab with bortezomib, lenalidomide and dexamethasone for untreated multiple myeloma when a stem cell transplant is unsuitable.

## Company and EAG cost-effectiveness estimates

3.14 Because of confidential commercial arrangements for daratumumab, some of the combination treatments, some of the comparators and some of the subsequent treatments, the exact cost-effectiveness results are confidential and cannot be reported here.

# Other factors

## Equality

3.15 The committee did not identify any equality issues.

## Uncaptured benefits

3.16 The committee considered whether there were any uncaptured benefits of daratumumab combination treatment. It acknowledged that a treatment regimen including Len instead of thalidomide is less likely to cause peripheral neuropathy. It noted that the daratumumab stopping rule using MRD status to inform clinical decisions about ongoing treatments represented a step change in the management of multiple myeloma and was therefore innovative. The committee concluded that these additional benefits were not captured in the economic modelling and that it would take these into account in its decision making.

# Conclusion

## Recommendation

3.17 The clinical-effectiveness evidence for Dar-Bor-Len-Dex followed by Dar-Len maintenance is uncertain. This is because there is no clinical data on the full treatment sequence of Dar-Bor-Tha-Dex followed by Len maintenance. There are also uncertainties in the economic model (see section 3.11). The committee thought that the cost-effectiveness estimates presented by the company and the EAG were highly uncertain. It also thought they were likely to be higher than the range that NICE considers an acceptable use of NHS resources. The committee decided that, given its preferred assumptions and based on the analysis it had seen, it could not determine the most likely cost-effectiveness estimates for Dar-Bor-Len-Dex followed by Dar-Len maintenance. Given the uncertainty, the committee would like to see additional analyses (see

section 3.13). So, Dar-Bor-Len-Dex followed by Dar-Len maintenance should not be used.

# 4 Evaluation committee members and NICE project team

## Evaluation committee members

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

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

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

## Chair

**Charles Crawley**

Chair, technology appraisal committee B

## NICE project team

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

**Sally Lewis**

Technical lead

**Eleanor Donegan**

Technical adviser

**Jeremy Powell**

Project manager

**Emily Crowe**

Associate director

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