NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Draft guidance consultation

Daratumumab with bortezomib, lenalidomide and dexamethasone for untreated multiple myeloma when an autologous 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 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- After considering these comments, the committee will prepare the final draft guidance.
- Subject to any appeal by stakeholders, the final draft guidance may be used as the basis for NICE's guidance on using daratumumab in the NHS in England.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: 04 February 2026
- Second evaluation committee meeting: 12 March 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 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 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

Daratumumab plus bortezomib, lenalidomide and dexamethasone followed by daratumumab plus lenalidomide maintenance is not required to be funded and should not be used routinely in the NHS in England for untreated multiple myeloma when an autologous stem cell transplant is suitable.

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

Usual treatment for untreated multiple myeloma when an autologous stem cell transplant is suitable is daratumumab plus bortezomib, thalidomide and dexamethasone induction and consolidation therapy followed by lenalidomide maintenance therapy.

Daratumumab plus bortezomib, lenalidomide and dexamethasone induction and consolidation therapy followed by daratumumab and lenalidomide maintenance has not been directly compared in a clinical trial with daratumumab plus bortezomib, thalidomide and dexamethasone followed by lenalidomide maintenance. The results of indirect comparisons of these combinations suggest the efficacy is similar in induction and consolidation phases of treatment. But the long-term benefits of daratumumab, bortezomib, lenalidomide and dexamethasone induction and consolidation followed by daratumumab and lenalidomide maintenance treatment were uncertain because there was no clinical trial data comparing this with daratumumab plus bortezomib, thalidomide and dexamethasone induction and consolidation followed by lenalidomide maintenance.

There are also uncertainties in the economic model, including the modelling of subsequent treatments and time to stopping treatment.

There is considerable uncertainty in the long-term benefits of daratumumab plus bortezomib, lenalidomide, and dexamethasone combination followed by daratumumab and lenalidomide maintenance. When the long-term benefits are incorporated in the economic model it is not possible to determine the most likely cost-effectiveness estimates. However, the cost-effectiveness estimates are likely to be higher than the range that NICE considers an acceptable use of NHS resources. So, daratumumab plus bortezomib, lenalidomide, and dexamethasone combination followed by daratumumab and lenalidomide maintenance should not be used.

2 Information about daratumumab

Marketing authorisation indication

2.1 Daratumumab (Darzalex, Johnson & Johnson) 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 1800 mg/15 ml vial (excluding VAT; BNF online accessed November 2025)

2.4 The company has a commercial arrangement. This makes daratumumab available to the NHS with a discount. The size of the discount is commercial in confidence.

Carbon Reduction Plan

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

3 Committee discussion

The evaluation committee considered evidence submitted by Johnson & Johnson, 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 the quality of their lives. 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 a stem cell transplant tend to be younger, more likely to be working and often have caring responsibilities so multiple myeloma can have a wider impact on their families and carers. The committee acknowledged that multiple myeloma is a chronic, incurable highly individual condition that can have a negative impact on quality of life for people with the condition, and their families and carers.

Treatment pathway

3.2 First-line treatment options for people with multiple myeloma depend on whether a stem-cell transplant may be suitable. NICE recommends the

following treatments as options at first line when a stem cell transplant is suitable:

- bortezomib plus dexamethasone with or without thalidomide (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 therapy (DAR+BOR+THA+DEX, see NICE's technology appraisal guidance on daratumumab in combination for untreated multiple myeloma when a stem cell transplant is suitable)
- lenalidomide maintenance (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 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 followed by LEN maintenance is standard of care for NHS patients with newly diagnosed multiple myeloma when an autologous stem cell transplant (ASCT) is suitable. The clinical experts and external assessment group (EAG) were in agreement that a very small percentage of people who have renal impairment may receive bortezomib plus cyclophosphamide and dexamethasone because of concerns around thalidomide toxicity. Clinical experts explained that LEN maintenance is the only comparator for maintenance treatment. The committee noted that a few people are offered combinations other than DAR+BOR+THA+DEX for induction and consolidation in the NHS and

concluded that DAR+BOR+THA+DEX for induction and consolidation followed by LEN maintenance was the most relevant comparator for most people.

Key clinical trial: PERSEUS

3.3 The clinical-effectiveness evidence for daratumumab plus bortezomib, lenalidomide and dexamethasone came from PERSEUS, a phase 3, multicentre, international, randomised, open-label, 2-arm study. It compared DAR+BOR+LEN+DEX (n=345) induction and consolidation with bortezomib plus lenalidomide and dexamethasone (BOR+LEN+DEX) (n=345). PERSEUS had an induction phase comprising of 4 cycles of 28 days of treatment. This was followed by high dose chemotherapy and an autologous stem cell transplant (HDT-ASCT). A subsequent consolidation phase comprising of 2 cycles of 28 days followed. People then received a maintenance phase of 28-day treatment cycles. People randomised to the DAR+BOR+LEN+DEX arm received DAR+LEN maintenance and people randomised to BOR+LEN+DEX received LEN maintenance alone. People in the DAR+BOR+LEN+DEX arm could stop taking DAR maintenance if they had progressed or if they had been receiving DAR maintenance for 2 years and had achieved MRD negativity that is sustained for 12 months.

The primary endpoint was progression-free survival (PFS) assessed according to the International Myeloma Working Group (IMWG) 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 as neither median overall survival (OS) or median PFS had been reached in either arm. The EAG added that the PERSEUS trial was also not conducted in England or Wales. The company stated that people in the trial had similar demographic and disease characteristics to people seen in the NHS. They added that data from the National Cancer Registration and Analysis Service (NCRAS)

suggested people diagnosed with multiple myeloma in the NHS show similar ages compared 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 considered the trial population to be broadly generalisable. The EAG considered that the PERSEUS trial was sufficiently generalisable to the NHS. The committee concluded that although the data was immature and that this contributed uncertainty to the survival analysis, the results from the trial were suitable for decision making.

Indirect and direct 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. No randomised controlled trials (RCT) were identified that included the full treatment sequence of DAR+BOR+THA+DEX induction and consolidation followed by LEN maintenance. The company therefore split their 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 conducted for each phase. They 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 conducted an indirect treatment comparison (ITC) using patient-level data of the induction and consolidation phases only of DAR+BOR+LEN+DEX (from PERSEUS) compared to 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 censored at the start of maintenance treatment. The EAG agreed that the approach to the ITC was appropriate but noted that three covariates in the company base case IPTW had standardised mean differences over 0.2 which could indicate poor balance after matching. But they added that the results 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 concluded despite the uncertainty in the IPTW analysis, 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 which compares DAR+LEN with LEN maintenance after an HDT-SCT. People in the trial received a range of different induction regimens before they were randomised to receive DAR+LEN or LEN maintenance. The median follow-up in AURIGA was 32.3 months and neither median OS or PFS was reached in either arm. The EAG highlighted that the population in AURIGA differed from PERSEUS as everyone in AURIGA was MRD-positive and had achieved a very good partial response or better after induction and HDT-ASCT treatment. They added that very few people in

AURIGA received consolidation therapy, and no one received 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 where people randomised to the DAR+BOR+LEN+DEX arm received DAR+LEN maintenance, and people randomised to BOR+LEN+DEX received LEN maintenance alone. They used an IPTW approach for comparing of DAR+LEN with 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 they resembled the those 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. They added AURIGA provided the best unbiased estimate of the treatment effect of DAR+LEN compared to LEN alone. The EAG agreed that using PERSEUS for direct comparisons of the maintenance phase could overestimate the relative effectiveness of DAR+LEN maintenance as people in the LEN maintenance arm received a different induction and consolidation regimen (they had BOR+LEN+DEX instead of DAR+BOR+THA+DEX). They 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 to people in PERSEUS which means the benefits of DAR+LEN could be biased. The committee noted some generalisability issues with the AURIGA trial. It queried if the low proportion of people who received 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 be treated with daratumumab if they had not received it previously. So, AURIGA might

not be representative of NHS practice. Another considered PERSEUS to be more relevant to clinical practice as more people who had not received daratumumab at first line went on to receive it at subsequent lines. The committee expressed its concern that neither DAR+BOR+LEN+DEX or DAR+BOR+THA+DEX was received 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 receive subsequent daratumumab. The committee noted that people receiving LEN maintenance in PERSEUS also did not receive DAR+BOR+THA+DEX induction and consolidation. They acknowledged that people who received LEN maintenance in PERSEUS would not have had daratumumab for induction and consolidation. In the absence of analysis using AURIGA that adjusts for the low proportions in the LEN maintenance arm receiving subsequent anti-CD38 treatment (including daratumumab) it had a preference for using PERSEUS. This was because some people in PERSEUS were randomised to receive 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. The committee concluded it would consider the uncertainties with the approach in its decision-making.

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 gender-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. Although 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, it concluded that the choice of model 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 the induction and consolidation phases meant that modelled differences in OS and PFS between the treatments are due to differences in PFS and OS from the maintenance phase of treatment alone. The committee acknowledged that although there was uncertainty in the relative OS and PFS because of the short follow, 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.

The company modelled PFS and OS using extrapolated data from PERSEUS Kaplan-Meier curves and data from AURIGA. For the DAR+BOR+LEN+DEX followed by DAR+LEN arm, the company fitted distributions to PERSEUS OS and PFS Kaplan-Meier data. For the LEN arm, the company estimated hazard ratios for PFS and OS from AURIGA. These hazard ratios were applied to the DAR+BOR+LEN+DEX followed

by DAR+LEN OS and PFS distributions to generate survival estimates for people receiving DAR+BOR+THA+DEX followed by LEN maintenance.

The company fitted a generalised gamma distribution for PFS. It explained that all distributions had a similar statistical fit but generalised gamma produced survival estimates closest to clinician estimates and observed hazards. The EAG agreed that the generalised gamma had the best fit to clinician estimates for the DAR+BOR+LEN+DEX followed by DAR+LEN arm. But that after applying the hazard ratio from AURIGA, PFS estimates for the comparator arm were above clinician estimates at 10, 15 and 25 years. The EAG thought that the Gompertz distribution produced estimates for the DAR+BOR+THA+DEX followed by LEN arm after applying the hazard ratio to the intervention arm that were closer to clinician estimates and had a better statistical fit to the observed data for the DAR+BOR+LEN+DEX followed by DAR+LEN arm. The EAG noted while estimates for the intervention arm using the Gompertz distribution were slightly lower than clinician estimates at 15 years, given that PERSEUS is immature, the Gompertz distribution should be used as a conservative option. The committee concluded that the Gompertz distribution provided the most plausible extrapolations for both arms.

The company fitted an exponential distribution for OS which had the best statistical fit, aligned best with the observed hazards, and had the closest fit to clinician estimates. The EAG agreed that the exponential was the most appropriate distribution for OS. They 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). After the EAG's request, the company presented hazard ratios for OS and PFS for DAR+LEN compared to LEN maintenance using the PERSEUS data. The

ITC used a IPTW adjustment approach (see section 3.4). The EAG noted there is no analysis applying the hazard ratios from PERSEUS to estimate the comparator arm survival outcomes, so it was unable to say which distribution provided the most plausible extrapolation for both arms. The company highlighted that the survival analysis conducted for the DAR+BOR+LEN+DEX followed by DAR+LEN arm in PERSEUS would still be valid and only estimates for the comparator arm would change. The EAG stated that it is also important to consider the estimates for the comparator arm after applying the hazard ratios from PERSEUS. The committee concluded that its preferred method to model PFS and OS for the DAR+BOR+THA+DEX followed by LEN maintenance arm would be to apply the hazard ratios generated from the IPTW of the PERSEUS trial. They noted long term OS and PFS estimates after applying the hazard ratios from PERSEUS had not been presented. As a result, 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. So, the committee was not able to conclude on the most appropriate OS and PFS parametric distributions. The committee discussed that as DAR+BOR+THA+DEX (TA763) and LEN maintenance (TA680) are currently used in the NHS, real-world evidence from the Systemic Anti-Cancer Therapy (SACT) database could be helpful to reduce uncertainty on the long-term estimates (see section 3.13)

MRD-negativity stopping rule

3.7 The company modelled a stopping rule that people who had been receiving maintenance therapy for 2 years could discontinue daratumumab if they had achieved MRD-negativity that is sustained for 12 months (in line with the SmPC). In the company base case, daratumumab maintenance discontinuation for those who met the stopping rule criteria was informed by a mature time to treatment discontinuation (TTD) Kaplan-

Meier curve from PERSEUS. Those who did not meet the criteria were assumed to continue receiving daratumumab maintenance 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. They explained that this distribution had the best fit to the observed data and to clinician estimates. They added that two thirds of people receiving DAR+LEN maintenance in PERSEUS discontinued daratumumab maintenance. The EAG stated that assuming all people continue daratumumab maintenance until progression has a large impact on cost-effectiveness.

The NHSE lead explained that MRD testing might be done as part of clinical trials but currently it is not routinely conducted 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 done in other conditions and new clinical trials in multiple myeloma include MRD guided treatment. The clinical experts were concerned that it would be treating multiple myeloma differently to other diseases if MRD testing is not done. The NHSE lead had concerns about the number of MRD tests that would be required to guide daratumumab discontinuation and if further MRD testing would be necessary after discontinuation. The company stated that most people would require two MRD tests and that if people had not achieved MRD-negativity they would be unlikely to achieve it. So, three MRD tests would likely be the maximum required. A patient expert stated that MRD testing is invasive and requires a bone marrow biopsy, so it is unlikely people would want more testing than necessary. Another added that people would not volunteer to have MRD testing but that if MRD testing could tailor their treatment and enable them to stop treatment, they would be more likely to want the testing done. A clinical expert explained that there is value in MRD testing because it could allow the discontinuation of daratumumab before people become

refractory to daratumumab. 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 required to allow the discontinuation of daratumumab and if some people would decline testing in clinical practice. The committee was unclear on if it was feasible for all treatment centres to undertake MRD testing and where the tests would be processed. They also had concerns on if delays to MRD testing would result in daratumumab discontinuation later than the two year time point. So, the committee was not able to conclude whether an MRD stopping rule was appropriate in the model which leads to uncertainty in the cost effectiveness estimates.

Modelling time to treatment discontinuation

3.8 The company used time to treatment discontinuation (TTD) to determine the time on treatment. They explained that this allowed specific costs to be applied while people are receiving 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 stopping rule. The company fitted an exponential distribution to a TTD Kaplan-Meier curve using data from PERSEUS to model lenalidomide maintenance discontinuation in the intervention arm. For the DAR+BOR+THA+DEX followed by LEN arm, lenalidomide maintenance was also modelled by fitting an exponential distribution to a TTD Kaplan-Meier from PERSEUS. The EAG were unclear why the company had used PERSEUS to inform lenalidomide discontinuation when AURIGA was used to inform effectiveness. They stated that this implies that having daratumumab for

induction and consolidation does not impact lenalidomide discontinuation. The EAG recalled that people receiving LEN maintenance in PERSEUS received BOR+LEN+DEX induction and consolidation and not DAR+BOR+THA+DEX. So, using PERSEUS to inform TTD in the comparator arm assumes that receiving either induction and consolidation regimen does not impact lenalidomide discontinuation. The EAG had concerns because thalidomide is not well tolerated and so it is likely receiving thalidomide for induction and consolidation would have an impact on lenalidomide discontinuation. At clarification, the company acknowledged that there is limited evidence on the impact of adding daratumumab for induction and consolidation on lenalidomide discontinuation. They added that most people in AURIGA received BOR+LEN+DEX induction therapy. The committee discussed which data should be used to inform lenalidomide maintenance TTD. They acknowledged that people receiving lenalidomide maintenance in both AURIGA and PERSEUS did not receive DAR+BOR+THA+DEX induction and consolidation. The committee concluded that the same source should be used to model treatment discontinuation and effectiveness. They recalled their preference for using hazard ratios using the PERSEUS data to estimate the effectiveness of LEN maintenance. So, concluded that the TTD Kaplan-Meier from PERSEUS should be used to inform lenalidomide discontinuation in the DAR+BOR+THA+DEX followed by LEN arm. They noted that as different induction and consolidation treatments were received 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 decision-making.

Subsequent treatment costs

3.9 The company estimated the proportion receiving the various subsequent lines of treatment based on clinical opinion. The duration on 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% people modelled to receive belantamab mafodotin, bortezomib and dexamethasone combination treatment. The uptake of subsequent treatments was based on the treatment received at the previous line. A clinical expert disagreed with some of the companies estimates. They explained that some people receiving LEN maintenance would receive DAR+BOR+DEX at second line and people would not be retreated with lenalidomide again at subsequent lines. Another clinical expert noted that as belantamab mafodotin is newly recommended, its use may not be as high as 80%. They added that teclistamab at fourth line would likely be used in more people than the modelled 50% to 60%. The EAG highlighted that subsequent treatment costs are a key driver in the model due to high prices for some of the treatments. They noted that they had not consulted their own clinician to validate the proportions modelled to receive each treatment. The committee acknowledged that there was significant uncertainty around how well the proportions modelled to receive subsequent treatments reflected NHS practice. It was particularly concerned about the proportion modelled to receive belantamab mafodotin at second line. It also had concerns about how many people in each arm were modelled to progress to each line of therapy. It noted that some of the subsequent treatments in the model were very expensive which had a large impact on cost-effectiveness. So, there was too much uncertainty to conclude if the modelled subsequent treatments were representative of NHS clinical practice.

Utility values

3.10 The company base case model applied utility values based on the health state and treatment phase (which are commercial in confidence and cannot be reported). In the progression free state, utility values were

based on the specific treatment phase (induction, ASCT, consolidation and maintenance) and a single utility value applied in the progressed disease state regardless of the line of treatment being received. 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 for adverse events based on utility decrements from previous NICE appraisals TA763 and TA917. The company stated that it had applied a higher utility value to people in the progressed disease state than to those who were progression free and receiving induction, ASCT or consolidation. They 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 receiving maintenance treatment while being progression free. Another patient expert explained that side effects can have a worse impact on quality of life after diagnosis, which 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 could differ from person to person. It considered the utility values used in the progression free state in the company model to be plausible but noted that a single utility value for the progressed disease state is an oversimplification which 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 EAG noted that applying lower utility values to people receiving 3rd or 4th line treatments had little effect on cost effectiveness. The company explained that in their base case, the DAR+BOR+THA+DEX followed by LEN maintenance arm accrues more quality-adjusted life years (QALYs) in the progressed 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 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 ICER

3.11 NICE's manual on health technology evaluations notes that, above a most plausible ICER of £20,000 per QALY gained, judgements about the acceptability of a technology as an effective use of NHS resources will take into account the degree of certainty around the ICER. The committee will be more cautious about recommending a technology if it is less certain about the ICERs presented. But it will also take into account other aspects including uncaptured health benefits. The committee noted the high level of uncertainty, specifically:

- the lack of long-term OS and PFS data for the full sequence of DAR+BOR+THA+DEX followed by LEN maintenance (section 3.6)
- whether MRD testing would become routine practice in the NHS to guide the discontinuation of daratumumab maintenance treatment and whether this would be applied exactly as in the PERSEUS trial (section 3.7)
- whether the modelled subsequent treatments were representative of what would be seen in NHS clinical practice (section 3.9)

Because of the uncertainties in the clinical-effectiveness and the economic model the committee could not determine the most acceptable ICER or the acceptable ICER threshold.

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, which were:

- equal efficacy in PFS and OS between DAR+BOR+LEN+DEX and DAR+BOR+THA+DEX during the induction and consolidation phase.
- reweighted hazard ratios using the PERSEUS data for the maintenance phase of DAR+BOR+THA+DEX followed by LEN maintenance.
- single utility value in the progressed disease state
- TTD using PERSEUS data for lenalidomide discontinuation in the DAR+BOR+THA+DEX followed by LEN maintenance arm.

Areas needing clarification

3.13 The committee considered that there were many areas of uncertainty (see section 3.11) and would like to see clarification on:

- whether there is further clinical evidence for the full treatment sequence of DAR+BOR+THA+DEX followed by LEN maintenance including if real-world evidence from the SACT dataset is available.
- details of the ITC conducted to generate the hazard ratios using the PERSEUS data and for these hazard ratios to be applied to the

intervention arm survival extrapolations to estimate the comparator outcomes. Also, for alternative ITC adjustment methods to be presented.

- if MRD testing could guide the discontinuation of daratumumab in NHS practice, including if:
  - it is feasible for all centres to undertake MRD testing
  - all patients would accept a minimum of two bone marrow biopsies to facilitate an MRD guided treatment decision
  - it is feasible that the information to make an MRD guided treatment decision would be available at the two year time point
  - delays in MRD testing would cause a lag in the discontinuation of daratumumab
- the distribution of subsequent treatments and the proportion of people having subsequent treatments in the model are what would be expected in NHS clinical practice and are clinically validated using SACT data.

Company and EAG cost-effectiveness estimates

3.14 Because of confidential commercial arrangements for daratumumab, some of the combination treatments and some of the comparators, 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 in combination. It did not identify additional benefits of daratumumab in combination not captured in the economic modelling. So the committee concluded that all additional benefits of daratumumab in combination had already been taken into account.

Conclusion

Recommendation

3.17 The clinical-effectiveness evidence for DAR+BOR+LEN+DEX followed by DAR+LEN maintenance is uncertain 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 considered that the cost-effectiveness estimates presented by the company and the EAG were highly uncertain and 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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