NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Draft guidance consultation

Isatuximab with pomalidomide and dexamethasone for treating relapsed and refractory multiple myeloma [managed access review of TA658]

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

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

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

- 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?

Issue date: February 2024

Note that this document is not NICE's final guidance on isatuximab with pomalidomide and dexamethasone. The recommendations in section 1 may change after consultation.

After consultation:

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- After considering these comments, the committee will prepare the final draft guidance.
- Subject to any appeal by stakeholders, the final draft guidance may be used as the basis for NICE's guidance on using isatuximab with pomalidomide and dexamethasone in the NHS in England.

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

The key dates for this evaluation are:

- Closing date for comments: 28th February 2024
- Second evaluation committee meeting: 14th March 2024
- Details of the evaluation committee are given in section 4

1 Recommendations

1.1 Isatuximab plus pomalidomide and dexamethasone is not recommended, within its marketing authorisation, for treating relapsed and refractory multiple myeloma in adults who have had lenalidomide and a proteasome inhibitor, and whose disease has progressed on their last treatment.

1.2 This recommendation is not intended to affect treatment with isatuximab plus pomalidomide and dexamethasone that was funded with managed access before final guidance is published. If this applies, NHS England and the company have an arrangement to make sure people who started treatment during the period of managed access will continue to have isatuximab plus pomalidomide and dexamethasone until they and their NHS clinician consider it appropriate to stop.

Why the committee made these recommendations

This evaluation reviews the evidence for isatuximab plus pomalidomide and dexamethasone for treating relapsed and refractory multiple myeloma (NICE technology appraisal guidance 658). It also reviews new data collected as part of the managed access agreement.

After 3 lines of treatment, people with multiple myeloma usually have pomalidomide plus dexamethasone, or daratumumab by itself.

Clinical trial evidence shows that people on isatuximab plus pomalidomide and dexamethasone have longer before their cancer gets worse and live longer compared with people on pomalidomide plus dexamethasone. Other evidence suggests that people on isatuximab plus pomalidomide and dexamethasone also have longer before their cancer gets worse and live longer compared with people on daratumumab alone. But this evidence is uncertain because it is from a comparison of people having treatment in the NHS without the controls of a clinical trial.

The economic evidence for isatuximab plus pomalidomide and dexamethasone is also uncertain. This is because there are uncertainties around how well it works in the long-term and some of the assumptions used to estimate its cost effectiveness.

The most likely cost-effectiveness estimates are higher than what NICE considers an acceptable use of NHS resources, even when considering the condition's severity and effect on quality and length of life. So isatuximab plus pomalidomide and dexamethasone is not recommended.

2 Information about isatuximab

Marketing authorisation indication/anticipated marketing authorisation indication

2.1 Isatuximab (Sarclisa, Sanofi) is indicated 'in combination with pomalidomide and dexamethasone, for the treatment of adult patients with relapsed and refractory multiple myeloma who have received at least 2 prior therapies including lenalidomide and a proteasome inhibitor and have demonstrated disease progression on the last therapy'.

Dosage in the marketing authorisation

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

Price

2.3 The list prices for isatuximab per 500-mg vial (excluding VAT; BNF online, accessed January 2024) are:

- £506.94 per 100 mg/5 ml solution for infusion vial
- £2,534.69 per 500 mg/25 ml solution for infusion vial

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

3 Committee discussion

The evaluation committee considered evidence submitted by Sanofi, 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

Details of condition

3.1 Multiple myeloma is a progressive and incurable condition that affects survival and quality of life. It arises from plasma cells in the bone marrow and is characterised by periods of disease remission and relapse. Symptoms include fatigue and shortness of breath, bone pain and fractures, infections, hypercalcaemia and kidney damage. The patient experts explained that people's experience of multiple myeloma varies considerably because they can have different side effects and outcomes following treatment. They also explained that after a relapse people often experience a more significant disease burden and face a worse prognosis. They highlighted the substantial psychological and emotional impact for people approaching the end of the treatment pathway. Therefore, having a range of treatment options is very important to provide hope for the future. One of the patient experts also highlighted his positive experience of taking isatuximab plus pomalidomide and dexamethasone as a fourth-line treatment over the last 2 years. He explained that he was able to lead a full life with few adverse effects. The committee recognised the need for effective treatments for relapsed and refractory multiple myeloma. It concluded that people would welcome the continued availability of isatuximab plus pomalidomide and dexamethasone to prolong survival and maintain quality of life.

Decision problem

Comparators

3.2 In the original NICE technology appraisal guidance on isatuximab with pomalidomide and dexamethasone for treating relapsed and refractory multiple myeloma (from here referred to as TA658) the company positioned isatuximab plus pomalidomide and dexamethasone after 3 previous lines of treatment. The clinical experts at the TA658 meeting explained that pomalidomide plus dexamethasone and daratumumab monotherapy were the most commonly used options after 3 previous lines of treatment. The committee concluded that pomalidomide plus dexamethasone was the relevant comparator. Daratumumab was not included because it was in the Cancer Drugs Fund and was not considered by NICE to be established practice at that time. Since then, final guidance has been published for NICE's technology appraisal guidance on daratumumab monotherapy for treating relapsed and refractory multiple myeloma (from here referred to as TA783), which recommended daratumumab monotherapy for routine commissioning. For the current review, the company provided analyses using pomalidomide plus dexamethasone and daratumumab monotherapy as comparators. But, the company's base case focused on pomalidomide plus dexamethasone because it believed that this is more commonly used. The clinical experts agreed that pomalidomide plus dexamethasone is widely used after 3 lines of treatment. They explained that these are oral drugs and very convenient. But the clinical experts also explained that some people have daratumumab at fourth line so that pomalidomide and dexamethasone can be offered at fifth line. This allows people to benefit from both treatments because daratumumab is not available as a fifth-line treatment. The NHS England Cancer Drugs Fund clinical lead also commented that most people having isatuximab plus pomalidomide and dexamethasone in the Cancer Drugs Fund have not had prior CD38 targeted therapy. So, if isatuximab plus pomalidomide and dexamethasone was not available, daratumumab would be an option. The committee concluded that both pomalidomide plus dexamethasone and daratumumab monotherapy were relevant comparators.

Clinical effectiveness

Updated clinical trial data

3.3 ICARIA-MM is an open-label randomised trial, comparing isatuximab plus pomalidomide and dexamethasone with pomalidomide plus dexamethasone. It included people with relapsed and refractory multiple myeloma who have had at least 2 previous lines of treatment, including lenalidomide and a proteasome inhibitor. In TA658 the committee accepted clinical evidence from a subgroup of people from ICARIA-MM who had 3 previous lines of treatment. But it concluded that median follow up was short, the subgroup was small and the data was immature. For this review, the company provided data from the final analysis of ICARIA-MM for the same subgroup of people who had 3 previous lines of treatment. Median progression-free survival (PFS) in the isatuximab plus pomalidomide and dexamethasone arm was 12.39 months and 6.54 months in the pomalidomide plus dexamethasone arm (hazard ratio [HR] 0.536, 95% confidence interval [CI] 0.343 to 0.840). Median overall survival (OS) had been achieved in both arms. Median OS was 33.28 months in the isatuximab plus pomalidomide and dexamethasone arm and 17.71 months in the pomalidomide plus dexamethasone arm (HR 0.657, 95% CI 0.409 to 1.055). The committee concluded that isatuximab plus pomalidomide and dexamethasone had been shown to improve overall survival and PFS compared with pomalidomide plus dexamethasone.

SACT data

3.4 In TA658 the committee noted that data collection through the Systemic Anti-Cancer Therapy (SACT) dataset could be used to collect evidence on clinical outcomes. For this review, the company presented real-world SACT data for isatuximab plus pomalidomide and dexamethasone, pomalidomide plus dexamethasone and daratumumab monotherapy. Median OS was 18.8 months for isatuximab plus pomalidomide and dexamethasone, 6.3 months for pomalidomide and dexamethasone, and

15.5 months for daratumumab. The company considered treatment duration a proxy for PFS. Median treatment duration was 8.9 months for isatuximab plus pomalidomide and dexamethasone, 3.2 months for pomalidomide and dexamethasone, and 4.5 months for daratumumab. The committee concluded that the SACT data provided further evidence on clinical outcomes and real-world evidence relevant to UK clinical practice.

Comparison with pomalidomide plus dexamethasone

3.5 The company proposed that a naive comparison of the SACT data sets be used to compare isatuximab plus pomalidomide and dexamethasone with pomalidomide plus dexamethasone. The company said that data from the ICARIA-MM trial (see section 3.3) was confounded by the use of post-study treatments that are not available in the NHS, whereas the SACT data reflects clinical practice. The company acknowledged that a limitation of naive comparisons is that differences in outcomes could be due to differences in patient characteristics. But it stated that where data was available, patient characteristics were similar across the SACT data sets. The EAG disagreed with the use of a naive comparison to inform the comparison with pomalidomide and dexamethasone. It explained that naive comparisons have considerable potential for bias because there is no adjustment for potential confounders. The EAG believed that the SACT datasets were not directly comparable because they collected data from different sources and over different time periods. It explained that there may be important differences in the populations, which could favour isatuximab. The EAG noted that the population in the pomalidomide and dexamethasone data set may be frailer or less healthy than the population in the isatuximab data set because of the different ways of administering the drugs (pomalidomide and dexamethasone taken orally and isatuximab by intravenous infusion in hospital). Also, the pomalidomide and dexamethasone data set excluded people who had had drugs in the Cancer Drugs Fund, whom the EAG said were generally younger and healthier. The EAG was also concerned about missing data in the

pomalidomide plus dexamethasone data set and its generalisability to clinical practice. Also, the dataset included people at fourth line or subsequent line treatment and it was unclear if the people having fourth-line treatment had been correctly identified. The committee agreed with the EAG's concerns about the naive comparison. It noted that the separation of the Kaplan–Meier curves in the SACT data suggested a survival benefit for isatuximab plus pomalidomide and dexamethasone within 2 months, which it considered implausible. The clinical experts agreed that a survival benefit would not be expected within 2 months. The committee concluded that the data from ICARIA-MM was more appropriate. It also concluded that OS data should be adjusted to account for the use of subsequent treatments, such as daratumumab and carfilzomib, which are not available in the NHS.

Comparison with daratumumab

3.6 The company stated that no data was identified that would allow a direct or anchored indirect treatment comparison of isatuximab plus pomalidomide and dexamethasone with daratumumab monotherapy. It explained that it had attempted an unanchored matching adjusted indirect treatment comparison (MAIC) analysis, but it was not possible to match on prognostic factors and keep an effective sample size. The company proposed that a naive comparison of the SACT data sets be used to compare isatuximab plus pomalidomide and dexamethasone with daratumumab monotherapy. The EAG noted the limitations associated with the use of a naive comparison and how they are prone to bias (see section 3.5). But it agreed that, given the available data, there was no better method for comparing isatuximab plus pomalidomide and dexamethasone with daratumumab monotherapy. The committee concluded that in the absence of additional data a naive comparison provided the best estimates of relative effectiveness. But it considered that the result from a naive comparison would be associated with a high level of uncertainty.

Economic model

Model structure

3.7 The company presented a partitioned survival model to estimate the cost effectiveness of isatuximab plus pomalidomide and dexamethasone after 3 lines of treatment. The model included the following health states:

- progression-free on or off treatment
- post-progression on or off treatment, and
- death.

The model was accepted by the committee as part of TA658 and was updated with the mature ICARIA-MM trial data and SACT data. The committee concluded that the model was appropriate for decision making.

Efficacy data in the model

3.8 In the model, efficacy data for the comparison with daratumumab came from the naïve comparison of the SACT datasets because this was the best available data (see section 3.6). For the comparison with pomalidomide plus dexamethasone, the committee preferred to use data from ICARIA-MM for estimating relative effects (see section 3.5). However, the committee appreciated the relevance of the SACT data to the UK setting. It considered that using randomised data to estimate absolute event rates could mean that the results may not reflect NHS practice. It also thought that using SACT data to estimate relative effects ran the risk of biased effects because of unadjusted confounding variables. The committee noted that section 4.6.16 of NICE's health technology evaluations manual states that quantifying the baseline risk of health outcomes can be informed by observational studies and that relative treatment effects seen in randomised trials may then be applied to data on the baseline risk of health outcomes. The committee therefore requested analyses that use OS data from the real-world SACT evidence to estimate the absolute event rates for isatuximab plus pomalidomide and dexamethasone. It requested that the relative efficacy from ICARIA-

MM then be applied to the isatuximab OS SACT data to estimate the OS for pomalidomide plus dexamethasone. The committee considered that it would be better to subtract benefit from the isatuximab plus pomalidomide and dexamethasone data than to add it to the pomalidomide plus dexamethasone data. This was because the committee was concerned that the real-world evidence for pomalidomide plus dexamethasone would include people who didn't get isatuximab because they were too frail, and such people were not relevant to the decision problem. However, the committee considered that adding benefit to the pomalidomide plus dexamethasone data would provide useful validation. The committee also agreed that the relative effect from ICARIA-MM should be adjusted to account for non-NHS subsequent treatments, such as daratumumab and carfilzomib. This should be done using a variety of adjustment methods and a rationale should be given for the preferred method. The committee also requested scenario analyses that explore waning of relative effect (see section 3.9). For PFS, the committee noted that absolute data from SACT are not available. However, it considered that time on treatment provides a reasonable proxy. The committee concluded that the OS analyses outlined above applying the relative effect from ICARIA-MM to the absolute efficacy of isatuximab plus pomalidomide and dexamethasone from the real-world SACT evidence should also be done for PFS using time on treatment.

Modelling OS for isatuximab plus pomalidomide and dexamethasone compared with pomalidomide plus dexamethasone using ICARIA-MM

3.9 The company selected a restricted log-normal distribution to extrapolate the OS data from both arms of the trial. The company said that this distribution produced reasonable OS projections, had the best statistical fit and was a good visual fit to the observed trial data. The EAG noted that the company's model assumed that the treatment effect was constant over time. It also noted that a large proportion of patients in the isatuximab arm of the model had disease that had progressed at 5 years (about 80%). The EAG considered that maintaining an OS benefit many years

after progression was unlikely to be plausible. So, the EAG selected independent log-normal distributions. These were adjusted so the risk of death for people who had isatuximab plus pomalidomide and dexamethasone was never higher than for pomalidomide and dexamethasone. Both the company and EAG received clinical advice that the exponential distribution provided the best long-term extrapolation of OS. But the company said that an exponential distribution implies a constant hazard rate, which is not supported by the trial data. It explained that the hazard rate observed in the trial period showed an initial increase and then declines over time, because people with aggressive disease or those who do not respond to treatment tend to progress quickly compared with those who respond to treatment. The EAG agreed that the exponential distribution had a poor fit to the trial data. The clinical experts estimated that, after 3 previous lines of treatment, up to 10% of people on isatuximab plus pomalidomide and dexamethasone would be expected to survive for 10 years or more. By comparison, very few people on pomalidomide plus dexamethasone would be expected to survive for that length of time. The committee noted that the exponential distribution provided the OS prediction closest to those estimates. But it agreed with the company and the EAG that there was a poor fit to the trial data. The committee preferred the distributions chosen by the company and the EAG because they had a better fit to the trial data. But it considered that both models gave optimistic OS predictions for isatuximab plus pomalidomide and dexamethasone. The committee also considered whether the company's assumption of a constant treatment effect was plausible. It noted the clinical experts' comments that they would expect to see an ongoing survival benefit after progression and had not seen evidence of treatment effect waning. But the committee was not persuaded that the evidence supported a constant treatment effect because it was uncertain how long the relative benefit would last after stopping treatment. It recalled that it had requested additional analyses that explore waning of treatment effect (see section 3.8). The committee

concluded that, using ICARIA-MM data, the EAG's extrapolation of the survival curves was the most appropriate.

Modelling PFS for isatuximab plus pomalidomide and dexamethasone compared with pomalidomide plus dexamethasone using ICARIA-MM

3.10 The company selected a restricted cubic spline (RCS) Weibull distribution to extrapolate the PFS data from both arms of the trial. The company said that the RCS Weibull distribution was selected based on statistical goodness of fit, visual fit, treatment effect diagnostics supporting the proportional hazard assumption and clinical plausibility. The EAG noted that the company's chosen distribution assumed that the treatment effect is constant over time. The EAG accepted that it may be plausible for there to be an ongoing advantage for isatuximab plus pomalidomide and dexamethasone for PFS, unlike for OS (see section 3.9). But the EAG preferred to use the independently fitted log-normal distributions that did not assume a constant treatment effect. The EAG stated that, compared with the RCS Weibull distributions, the independently fitted log-normal distributions had better statistical goodness of fit and equally good visual fit and produced plausible long-term PFS predictions. The committee noted that the company's and EAG's extrapolation approaches produced similar estimates of the long-term PFS outcomes. It concluded that both approaches were plausible.

Modelling OS for isatuximab plus pomalidomide and dexamethasone using SACT data

3.11 The company selected a log-normal distribution to extrapolate OS using the SACT data for the isatuximab plus pomalidomide and dexamethasone arm. The company said that the log-normal distribution was selected based on visual and statistical goodness of fit. It also said that the log-normal distribution produced an OS projection that was in the middle of the range of projections from the other distributions that were considered. The EAG selected the RCS Weibull 3-knot distribution. It said that the RCS Weibull 3-knot provided the best fit to the observed data and had

similar statistical fit. The committee considered that both the company's and EAG's approaches could be plausible. But it noted that the company's approach appeared to overestimate the tail end of the Kaplan–Meier curve from the SACT data. So the committee concluded that the EAG's extrapolation approach was most appropriate.

Modelling OS for daratumumab using SACT data

3.12 The company selected a Weibull distribution to extrapolate OS using the SACT data for the daratumumab arm. It noted that in TA783 the Weibull distribution was used to model OS from the SACT data. It also noted that the EAG for TA783 had described the Weibull curve as being a conservative long-term extrapolation of survival. The EAG explained that in TA783 daratumumab was being appraised, so it was reasonable to use a conservative distribution because there was a risk of recommending a treatment that was not cost effective. It considered that in this appraisal, where daratumumab is a comparator, the best fitting distribution should be used. So the EAG selected the RCS log-normal 2-knot distribution. The committee agreed with the EAG's comments. It also noted that the company's approach appeared to underestimate the tail end of the Kaplan–Meier curve from the SACT data. So the committee concluded that the EAG's extrapolation approach was most appropriate.

Utility values

3.13 ICARIA-MM included the EQ-5D-5L health questionnaire to measure health-related quality of life. The company mapped the EQ-5D-5L data to the EQ-5D-3L to estimate mean utility for the pre-progressed and progressed disease health states. In TA658 the committee accepted the company's use of utility values for the progression-free health state that differed by treatment arm. The utility value for the isatuximab plus pomalidomide and dexamethasone arm (0.719) was slightly higher than for the pomalidomide and dexamethasone arm (0.717). For this review, the company used the same approach but the differences between the treatment arms were larger. The values are considered confidential by the

company and cannot be reported here. In the absence of trial data for daratumumab, the company assumed the same utility values for daratumumab as for pomalidomide and dexamethasone. The EAG noted that a simpler model using the same utility values regardless of treatment produced a better statistical fit to the data. The EAG also said that data from ICARIA-MM on utility change from baseline provides no clear indication that isatuximab plus pomalidomide and dexamethasone produced more of a benefit than pomalidomide plus dexamethasone. The committee discussed whether a better depth of remission reflected by a complete response would result in a greater reduction in symptoms. The patient experts explained how a deeper response could have a positive psychological impact. The committee recognised the psychological benefit to patients of knowing they have had a deeper response. But it was not convinced that a complete response would lead to better control of symptoms. Also, it considered that there were other factors that may lead to negative utility with isatuximab. For example, it was likely that there would be more adverse effects of treatment overall with the triplet combination therapy, as had been shown in the trial. Also, pomalidomide and dexamethasone are oral drugs and convenient to use, whereas isatuximab involves a visit to hospital every 2 weeks for an intravenous infusion. For these reasons, the committee was not convinced that people who are progression-free and on isatuximab plus pomalidomide and dexamethasone would have a higher utility than people on pomalidomide and dexamethasone.

Costs

Subsequent therapies

3.14 The company used the SACT data set for isatuximab plus pomalidomide and dexamethasone to calculate the cost of subsequent therapies after isatuximab plus pomalidomide and dexamethasone and after pomalidomide and dexamethasone. For daratumumab, the company used the SACT data from TA783. The EAG believed that the costs of

subsequent treatment should be aligned with the source of the clinical evidence. Because the EAG used data from ICARIA-MM to estimate relative efficacy compared with pomalidomide and dexamethasone (see section 3.5) it also used data from the trial to calculate the cost of subsequent therapies for that comparison. The committee agreed with the EAG that the cost of subsequent treatments should be aligned with the source of the clinical evidence. But it also recalled that it preferred to see analyses that adjusted the efficacy data from ICARIA-MM for the use of subsequent treatments that are not available in the NHS (see section 3.5) and therefore that the cost of subsequent treatments from the trial should also be adjusted.

Administration cost of daratumumab

3.15 The company assumed that the cost per administration of daratumumab was £281.11. The EAG said that this cost appeared high and they had assumed that patients would self-administer at home. So, in its base case the cost was applied for the first dose only. The clinical experts explained that daratumumab is administered by a healthcare professional and this usually takes place in a hospital setting. The NHS England Cancer Drugs Fund clinical lead also said that daratumumab is administered in a day case setting and not self-administered at home. He also explained that there is a specific tariff cost for every subcutaneous chemotherapy injection and that the cost used by the company was close to the cost incurred by the NHS. The committee concluded that the company's administration cost assumptions were broadly appropriate.

Severity

3.16 The committee considered the severity of the condition (the future health lost by people living with the condition and having standard care in the NHS). The committee may apply a greater weight to the quality adjusted life years (QALYs) if technologies are indicated for conditions with a high degree of severity. This is called a severity modifier. The company provided absolute and proportional QALY shortfall estimates in line with

NICE's health technology evaluations manual. The estimates are considered confidential by the company and cannot be reported here. The committee noted that, using the ICARIA-MM trial data, the absolute and proportional QALY shortfall estimates presented by both the company and the EAG for the comparison with pomalidomide plus dexamethasone were not high enough for a severity weight to be applied. But when using SACT data, the estimates of proportional QALY shortfall qualified for a QALY weighting of 1.2. The committee recalled its conclusion that the data from ICARIA-MM was more appropriate (see section 3.5). It concluded that the severity weight of 1 applied to the QALYs was appropriate but that it would review the weightings for both comparators after it had considered the additional analyses that it had requested (see section 3.20).

Additional benefits

3.17 The company considered that there are additional benefits of isatuximab plus pomalidomide and dexamethasone not captured in the economic modelling. It said that hope was increasingly relevant at later lines of therapy but was not explicitly captured in the utilities used in the modelling. Both the company and patient experts explained how knowing there is an effective treatment available after a third relapse provides a substantial psychological benefit. The company also suggested that isatuximab plus pomalidomide and dexamethasone could act as bridge therapy to effective future fifth-line treatments. The committee noted that the clinical experts had stated in their written submissions that they believed that the health-related benefits were mostly captured in the QALY calculation. It also recalled that the in TA658 the EAG had noted the possibility that hope was captured by the anxiety and depression domain of the EQ-5D. The committee recognised the high disease burden experienced by people with multiple myeloma (see section 3.1) but concluded that it had not seen any evidence to show that isatuximab plus pomalidomide and dexamethasone provides additional benefits that had not already been taken into account.

Non-reference case analysis

3.18 The company noted that there was a need for flexibility when appraising isatuximab plus pomalidomide and dexamethasone. It said that challenges in demonstrating the cost effectiveness of combination therapies meant isatuximab plus pomalidomide and dexamethasone was unlikely to be cost effective even if it was offered for free. The company considered that pomalidomide plus dexamethasone was unlikely to be considered cost effective if it was appraised using NICE's current methods. It presented a series of analyses, including:

- removing pomalidomide plus dexamethasone's costs from the isatuximab plus pomalidomide and dexamethasone arm
- considering potential generic pomalidomide prices because of the patent expiry expected later in 2024
- attributing value to each of the therapies in the isatuximab plus pomalidomide and dexamethasone combination.

The committee recalled that NICE's methods for economic evaluation state that the committee may consider a non-reference-case analysis with the background care costs removed if the NHS is currently providing care that is expensive or would not be considered cost effective. The committee agreed that it would consider this analysis alongside the reference case analysis. But, it could not make its decision based solely on removing the costs of pomalidomide and dexamethasone. The committee also noted that the price of pomalidomide is expected to fall this year. The NHS England Cancer Drugs Fund lead explained that the price for generic pomalidomide would be agreed in the coming months. The committee acknowledged that this generates another uncertainty for the evaluation at the current time. It noted that the costs used in the analyses should reflect as closely as possible the prices that are paid in the NHS. The committee concluded that it would consider scenarios that include potential discounts for generic pomalidomide.

Cost-effectiveness estimates

3.19 Because of confidential commercial arrangements for isatuximab, pomalidomide, daratumumab and post-progression treatments, the cost-effectiveness results are confidential and cannot be reported here. The company's and EAG's base case cost-effectiveness estimates comparing isatuximab plus pomalidomide and dexamethasone with both pomalidomide plus dexamethasone and daratumumab monotherapy were considerably above what NICE normally considers an acceptable use of NHS resources. This is regardless of whether a 1.2 severity weight was applied.

Summary of additional analyses

3.20 The committee requested the following additional analyses:

- using OS data from the real-world SACT evidence to estimate the absolute efficacy of isatuximab plus pomalidomide and dexamethasone. The relative efficacy from ICARIA-MM should then be applied to the isatuximab OS data to estimate the OS for pomalidomide plus dexamethasone (section 3.8)
- the preferred approach is to subtract the benefit from the absolute event rates in the isatuximab plus pomalidomide and dexamethasone SACT data than to add it to the pomalidomide plus dexamethasone data. But the latter approach would provide useful validation
- the same analyses for PFS, using time on treatment as a proxy (section 3.8)
- adjusting the OS relative effect from ICARIA-MM to account for non-NHS subsequent treatments using a variety of adjustment methods (section 3.8) and adjusting the costs (section 3.14)
- scenario analyses that explore waning of relative effect (section 3.8)
- scenario analyses that include potential discounts for generic pomalidomide (see section 3.18).

Other factors

Equality

3.21 The committee did not identify any equality issues.

Conclusion

3.22 The committee recognised that isatuximab plus pomalidomide and dexamethasone is an effective treatment after 3 previous lines of treatment. But the company's and EAG's cost-effectiveness estimates were considerably above what NICE normally considers an acceptable use of NHS resources. So, isatuximab plus pomalidomide and dexamethasone is not recommended for treating relapsed and refractory multiple myeloma in adults who have had lenalidomide and a proteasome inhibitor, and whose disease has progressed on their last treatment. Had isatuximab plus pomalidomide and dexamethasone been recommended by the committee, it would have been for adults who have had 3 previous lines of treatment.

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 and a project manager.

Ross Wilkinson

Technical lead

Zoe Charles

Technical adviser

Vonda Murray

Project manager

ISBN: [to be added at publication]