NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Final draft guidance

Isatuximab with pomalidomide and dexamethasone for treating relapsed and refractory multiple myeloma

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 this guidance was 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 healthcare professional 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.

In NICE technology appraisal guidance 658, the company asked for isatuximab plus pomalidomide and dexamethasone to be considered only after 3 lines of treatment. This does not include everyone who it is licensed for. After 3 lines of treatment,

Issue date: June 2024

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 than 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 than 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 cost-effectiveness estimates for isatuximab plus pomalidomide and dexamethasone, incorporating a severity weighting of 1.2, are considerably higher than what NICE considers an acceptable use of NHS resources. 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 March 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 after 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. So 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 this 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. 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 through the Cancer Drugs Fund have not had previous CD38-targeted treatment. 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 was 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 had 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 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 had 3 previous lines of treatment. Median progression-free survival (PFS) in the isatuximab plus pomalidomide and dexamethasone arm was 12.4 months, and 6.5 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 33.3 months in the isatuximab plus pomalidomide and dexamethasone arm and 17.7 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 OS 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 that was relevant to UK clinical practice.

Comparison with pomalidomide plus dexamethasone

3.5 The company proposed using a naive comparison of the SACT data sets 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 unmeasured differences in the populations, which could favour isatuximab. For example, clinical advice to the EAG was that people would need to be fitter to have isatuximab. The EAG also had other concerns, including missing data in the pomalidomide plus dexamethasone data set. The committee considered that the naive comparison was associated with high uncertainty. 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. One of the clinical experts also said that the SACT data presented did not reflect clinical experience and that it underestimated survival for pomalidomide plus dexamethasone. The committee concluded that the naive comparison was likely to overestimate the relative treatment effect of isatuximab plus pomalidomide and dexamethasone and that the data from ICARIA-MM provided a more robust estimate of relative effect.

Adjustment for subsequent treatments not available in the NHS

3.6 At the first committee meeting the committee 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. The company used the two-stage estimation (TSE) and inverse probability of censoring weighting (IPCW) methods to adjust the OS outcomes from ICARIA-MM by removing the impact of post-progression daratumumab or post-progression daratumumab or carfilzomib. The company considered that the results using the IPCW method lacked clinical validity but provided scenario analyses using the TSE method. The EAG considered that the results from using the TSE method to adjust for the impact of post-progression daratumumab or carfilzomib also lacked face validity. This was because OS increased when carfilzomib was removed in addition to daratumumab. The EAG explained that the lack of face validity may be caused by limitations of the TSE methods. The committee agreed with the EAG's concerns and concluded that the results from the analysis

adjusting for subsequent treatments not available in the NHS were very uncertain.

Comparison with daratumumab

3.7 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 analysis, but it was not possible to match on prognostic factors and keep an effective sample size. The company proposed using a naive comparison of the SACT data sets to compare isatuximab plus pomalidomide and dexamethasone with daratumumab monotherapy. The EAG noted the limitations associated with naive comparisons 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 clinical experts stated that survival for daratumumab in the SACT data appeared to be higher than in clinical practice. The committee understood that this was because pomalidomide plus dexamethasone may be used as a fifth-line treatment after daratumumab (see section 3.2). The committee acknowledged that there were many limitations in the data. It accepted that in the absence of additional data, a naive comparison provided the best estimates of relative effectiveness. But it considered that the results from a naive comparison would be associated with a high level of uncertainty.

Economic model

Model structure

3.8 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

3.9 In the model, efficacy data for the comparison with daratumumab came from the naive comparison of the SACT datasets because this was the best available data (see section 3.7). For the comparison with pomalidomide plus dexamethasone, the committee preferred to use data from ICARIA-MM for estimating relative effects (see section 3.5). But, 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 considered 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. It also states that relative treatment effects seen in randomised trials may then be applied to data on the baseline risk of health outcomes. So the company provided scenario analyses using the unadjusted HR from ICARIA-MM and TSE-adjusted HRs applied to the isatuximab plus pomalidomide and dexamethasone SACT extrapolation to make simulated pomalidomide plus dexamethasone extrapolations. The company also provided an analysis, requested by the EAG, that used time-varying hazards to make a simulated pomalidomide plus dexamethasone extrapolation. The company stated that the simulated extrapolations made using the unadjusted and TSE-adjusted HRs underestimated the relative treatment effect of isatuximab plus pomalidomide and dexamethasone. And that the simulated pomalidomide plus dexamethasone extrapolation generated

using time-varying hazards was similar to its preferred pomalidomide and dexamethasone SACT extrapolation. It considered that this supported the use of a naive comparison of the SACT data sets. The committee recalled that the clinical experts had said that the SACT data underestimated survival for pomalidomide plus dexamethasone (see section 3.5). It considered that the approach using time-varying hazards also underestimated survival for pomalidomide plus dexamethasone. It further recalled that the TSE-adjusted analyses were very uncertain (see section 3.6). So, the committee concluded that the simulated pomalidomide plus dexamethasone extrapolation made using the unadjusted HR from ICARIA-MM and the isatuximab plus pomalidomide and dexamethasone SACT extrapolation should be used in the model.

Modelling OS for isatuximab plus pomalidomide and dexamethasone using SACT data

3.10 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 company noted that in the ICARIA-MM trial only people in the isatuximab plus pomalidomide and dexamethasone arm had minimal residual disease (MRD)-negative status. It believed this observation would correlate with prolonged OS and so supported its choice of distribution. The EAG stated that the company only provided qualitative discussions on the relationship between achieving MRD-negative status and improved OS outcomes. It added that the data provided by the company was from analyses marked exploratory. The committee agreed with the EAG's comments and noted that only a small proportion of people in the isatuximab plus pomalidomide and dexamethasone arm (about 7%) had MRD-negative status. The EAG selected the restricted cubic spline (RCS) Weibull 3-knot distribution because it said that this 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 were 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

3.11 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. A patient organisation also commented on the need for a consistent approach between appraisals. 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 noted that the RCS log-normal 2-knot distribution was not considered by the company or EAG in TA783. It also noted that in TA783 the EAG and company agreed on the choice of distribution to extrapolate OS, so it was not one of the specific issues considered by the committee. The committee also noted that the company's approach appeared to underestimate the tail end of the Kaplan–Meier curve from the SACT data. It concluded that the EAG's extrapolation approach was the most appropriate.

Utility values

3.12 ICARIA-MM used 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. The company also controlled for differences in the

baseline utility values between arms. 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 company considers the values to be confidential so they 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 utility data from ICARIA-MM. The EAG also said that data from ICARIA-MM on utility change from baseline provided no clear indication that isatuximab plus pomalidomide and dexamethasone improved health-related quality of life more 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. They also explained how myeloma-related anxiety is often cyclical and associated with waiting for tests results, which may not be captured in the trial data. 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 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 who are progression free. The committee also agreed with the EAG that a simpler model that used the same utility regardless of treatment provided a better statistical fit to the utility data from ICARIA-MM. The committee concluded that the same utility values should be used for each treatment arm.

Costs

Subsequent treatments

3.13 The company used the SACT data set for isatuximab plus pomalidomide and dexamethasone to calculate the cost of subsequent treatments after isatuximab plus pomalidomide and dexamethasone and after pomalidomide and dexamethasone. For daratumumab, the company used the SACT data from TA783. The committee agreed with using subsequent treatment costs informed by the SACT data because these would be expected to reflect care in the NHS and meant that the costs were aligned with the clinical data used in the model.

Daratumumab administration cost

3.14 The company assumed that the cost per administration of daratumumab was £281.11. The EAG said that this cost appeared high and it had assumed that people 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 happens 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

3.15 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 company considers the estimates to be confidential so they cannot be reported here. The committee recalled its conclusion that simulated pomalidomide plus dexamethasone extrapolations made using the unadjusted HRs from ICARIA-MM should be used in the model to inform the comparison with pomalidomide plus dexamethasone (see section 3.9). The committee noted that, using the simulated extrapolations and its other preferred assumptions, the proportional QALY shortfall estimates qualified for a QALY weighting of 1.2. It further noted that when using its preferred extrapolation of OS using SACT data for the daratumumab arm (see section 3.11), the absolute and proportional QALY shortfall estimates for the comparison with daratumumab were not high enough for a severity weight to be applied. The committee concluded that a QALY weighting of 1.2 should be applied for the comparison with pomalidomide plus dexamethasone and no additional QALY weighting would be applied for the comparison with daratumumab.

Uncaptured benefits

3.16 The company considered that there were 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 treatment but that this was not explicitly captured in the utilities used in the modelling. The company and patient experts explained how knowing there is an effective treatment available after a third relapse provides a substantial psychological benefit. The patient expert also highlighted the

substantial benefit of having triplet therapy rather than doublet therapy or monotherapy. The company also suggested that isatuximab plus pomalidomide and dexamethasone could act as bridge treatment to effective future fifth-line treatments. The committee noted that the clinical experts' written submissions had stated 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 provided additional benefits that had not already been taken into account. But it acknowledged that isatuximab plus pomalidomide and dexamethasone is the first well-tolerated triplet therapy at this stage of the pathway and could be considered innovative.

Non-reference case analysis

3.17 The company suggested 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 treatments 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 treatments in the isatuximab plus pomalidomide and dexamethasone combination.

The committee recalled that section 4.4.16 of NICE's health technology evaluations manual states 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 could consider this analysis alongside the reference case analysis for context in line with the methods manual. But, it could not make its decision based solely on removing the costs of pomalidomide and dexamethasone. This was because NICE recommends pomalidomide plus dexamethasone and considers it to be cost effective. After consultation, the committee again considered the company's non-reference case scenario removing the background care costs. But having taken into account the specific circumstances of this evaluation, that is, that pomalidomide and dexamethasone has been assessed to be cost effective, it maintained its view that the reference case analysis should be used for decision making.

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. But there is considerable uncertainty about when generic pomalidomide will become available in the NHS in England due to the need to establish programmes for its use. The committee acknowledged that this generated another uncertainty for this evaluation. After consultation, the committee considered scenarios presented by the company that included potential discounts for generic pomalidomide. It concluded that these suggested that introducing generic pomalidomide would not result in cost-effectiveness estimates for isatuximab plus pomalidomide and dexamethasone that would fall within the range that NICE would consider acceptable (see section 3.18), and that it was also uncertain when generic pomalidomide would be available in the NHS in England. The committee also noted that the company had proposed considering value attribution methods in the evaluation. It considered the evidence and found it informative for context. But, without a framework to

consider this approach, the committee concluded that it was unable to consider value attribution in its decision making.

Cost-effectiveness estimates

Acceptable ICER

3.18 NICE's manual on health technology evaluations notes that, above a most plausible incremental cost-effectiveness ratio (ICER) of £20,000 per QALY gained, judgements about the acceptability of a technology as an effective use of NHS resources will take into account the degree of certainty around the ICER. The committee will be more cautious about recommending a technology if it is less certain about the ICERs presented. But it will also take into account other aspects including uncaptured health benefits or whether the treatment is innovative. The committee noted the company's view that an acceptable ICER of £50,000 per QALY should be used to align with NICE's previous methods (that is, before NICE updated its process and methods in 2022) which used the end of life criteria. The company argued that it is inequitable to use a different framework for this evaluation when the comparators were evaluated using NICE's previous methods. But, the managed access and data collection agreement entered into by the company stated that NICE's methods and processes in place at the time of exit from the Cancer Drugs Fund would be used for the review.

3.19 The committee considered that there were other advantages of treatment with isatuximab plus pomalidomide and dexamethasone that could be taken into account:

- it is the first well-tolerated triplet therapy available at this stage of the pathway and could be considered innovative (see section 3.16)
- there is high-quality data on relative treatment effect which reduces uncertainty, including mature clinical trial data, compared with pomalidomide plus dexamethasone

- there is real-world evidence which reduces uncertainty about the absolute benefit likely to be achieved in the NHS.

So, the committee concluded that an acceptable ICER would be towards the upper end of the range NICE considers a cost-effective use of NHS resources (£20,000 to £30,000 per QALY gained).

Committee's preferred assumptions and cost-effectiveness estimates

3.20 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 cost-effectiveness estimates comparing isatuximab plus pomalidomide and dexamethasone with both pomalidomide plus dexamethasone and daratumumab monotherapy were considerably above the acceptable range (see section 3.19) when the committee's preferred assumptions were used, which included using:

- a naive comparison of SACT data for the comparison with daratumumab (see section 3.7)
- a simulated pomalidomide plus dexamethasone extrapolation made using the unadjusted HR from ICARIA-MM for the comparison with pomalidomide plus dexamethasone (see section 3.9)
- the RCS Weibull 3-knot distribution to extrapolate OS using SACT data for isatuximab plus pomalidomide and dexamethasone (see section 3.10)
- the RCS log-normal 2-knot distribution to extrapolate OS using SACT data for daratumumab (see section 3.11)
- the same utility values for each treatment arm (see section 3.12)
- subsequent treatment costs based on the SACT data (see section 3.13)
- a cost per administration of daratumumab of £281.11 (see section 3.14)

- a severity QALY weighting of 1.2 for the comparison with pomalidomide plus dexamethasone and no QALY weighting for the comparison with daratumumab (see section 3.15).

The committee noted that, even using the higher severity weighting (see section 3.18) for both comparisons, the ICERs would still not be considered cost effective.

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, 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]