NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Appraisal consultation document

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

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

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

The appraisal 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 race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Issue date: May 2020

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

For further details, see NICE's guide to the processes of technology appraisal.

The key dates for this appraisal are:

Closing date for comments: 25 June 2020

Second appraisal committee meeting: TBC

Details of membership of the appraisal committee are given in section 5.

1 Recommendations

1.1 Isatuximab plus pomalidomide and dexamethasone is not recommended, within its anticipated marketing authorisation, for treating relapsed and refractory multiple myeloma in adults who have had at least 2 treatments (including lenalidomide and a proteasome inhibitor) and whose disease has progressed on the last treatment.

1.2 This recommendation is not intended to affect treatment with isatuximab plus pomalidomide and dexamethasone that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop.

Why the committee made these recommendations

The company proposes that isatuximab plus pomalidomide and dexamethasone is for treating multiple myeloma only in people who have had at least 3 treatments before. Current treatment at this point is usually pomalidomide plus dexamethasone, or daratumumab alone (in the Cancer Drugs Fund).

Clinical trial evidence in this group suggests that isatuximab plus pomalidomide and dexamethasone delays the disease progressing and increases how long people live compared with pomalidomide plus dexamethasone. But the trial is not yet finished, so it is not certain how much more clinical benefit isatuximab plus pomalidomide and dexamethasone has than pomalidomide plus dexamethasone.

The most likely cost-effectiveness estimates for isatuximab plus pomalidomide and dexamethasone are much higher than what NICE normally considers a cost-effective use of NHS resources. Therefore, it is not recommended.

2 Information about isatuximab

Anticipated marketing authorisation indication

2.1 On 26 March 2020 the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion, recommending the granting of a marketing authorisation for the medicinal product isatuximab (Sarclisa, Sanofi) 'in combination with pomalidomide and dexamethasone, indicated 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 will be available in the summary of product characteristics.

Price

2.3 The list price for isatuximab will be available after the marketing authorisation has been received. The company has a commercial arrangement, which would have applied if the technology had been recommended.

3 Committee discussion

The appraisal committee (section 5) considered evidence submitted by Sanofi, a review of this submission by the evidence review group (ERG), the technical report, and responses from stakeholders. See the committee papers for full details of the evidence.

The appraisal committee was aware that several issues were resolved during the technical engagement stage, and agreed that:

- The model time horizon should be 20 years to capture all benefits and costs of the intervention and the comparators.

- The company's amendment to the probabilistic sampling of health utility data, which ensures the utility value for the progressed disease health state does not exceed the utility value for the progression-free disease health state, is appropriate.
- The company's amendment to its model, which applies drug costs at the start of each cycle, is appropriate.

The committee recognised that there were remaining areas of uncertainty associated with the analyses presented (see technical report, table 4, page 40), and took these into account in its decision making. It discussed the issues which were outstanding after the technical engagement stage.

The condition

People with relapsed and refractory multiple myeloma would welcome a new effective treatment option

3.1 Multiple myeloma is an incurable and progressive condition that affects survival and quality of life. The patient experts explained that it causes severe symptoms, which have a significant impact on patients' quality of life and are also challenging for carers. They highlighted the psychological impact for patients approaching the end of the treatment pathway, where further treatment options are limited. The committee was aware that clinicians value having a range of different treatment options for patients. One patient expert noted that although some treatments are oral and people can take them at home, some people prefer to have their treatment in hospital. He also highlighted that patients value treatments that delay the disease progressing, which outweighs the negative impact of their side effects. The committee recognised the need for effective treatment options for previously treated multiple myeloma, and concluded that people would welcome new treatment options.

Treatment pathway

The treatment pathway for multiple myeloma is rapidly evolving

3.2 Treatment options for multiple myeloma depend on how many previous treatments a person has had, their response to these treatments, and their preferences. If a stem cell transplant is suitable:

- Induction treatment is bortezomib, given before the transplant.
- Second-line treatment may be bortezomib again, along with a second stem cell transplant.

If a stem cell transplant is not suitable:

- First-line treatments include thalidomide or bortezomib plus an alkylating agent, for example, melphalan or chlorambucil, and a corticosteroid, for example, dexamethasone. Lenalidomide plus dexamethasone is also an option when thalidomide is not appropriate.
- Second-line treatments include lenalidomide plus dexamethasone if the person has had bortezomib before or carfilzomib plus dexamethasone if they have not had bortezomib before. Also, daratumumab plus bortezomib and dexamethasone is available in the Cancer Drugs Fund.

After second-line treatment, the options do not depend on whether a stem cell transplant is suitable:

- Third-line treatments include lenalidomide plus dexamethasone or panobinostat plus bortezomib and dexamethasone. Also, ixazomib plus lenalidomide and dexamethasone is available in the Cancer Drugs Fund.
- Fourth-line treatments include pomalidomide plus dexamethasone or panobinostat plus bortezomib and dexamethasone. Daratumumab alone or ixazomib plus lenalidomide and dexamethasone are available in the Cancer Drugs Fund.

Isatuximab plus pomalidomide and dexamethasone can be used whether or not people have had a stem cell transplant. The clinical experts explained that, following recent NICE guidance, the use of lenalidomide plus dexamethasone as first-line treatment and the use of daratumumab plus bortezomib and dexamethasone as second-line treatment is increasing. The committee understood that the multiple myeloma pathway is rapidly evolving.

The company positions isatuximab plus pomalidomide and dexamethasone at fourth line, after 3 previous treatments

3.3 The marketing authorisation for isatuximab plus pomalidomide and dexamethasone states that it must be used after lenalidomide and a proteasome inhibitor, which means as third-line treatment or later. Proteasome inhibitors include bortezomib, carfilzomib and ixazomib. But the marketing authorisation does not specify the position in the treatment pathway. The company chose to position isatuximab plus pomalidomide and dexamethasone after 3 previous treatments, that is, as a fourth-line treatment option. It did this based on unmet clinical need and advice from clinical experts. The committee noted that the company's positioning meant that the population was narrower than defined by both the marketing authorisation and NICE's final scope. The clinical expert explained that to have isatuximab plus pomalidomide and dexamethasone a person must have had previous treatment with lenalidomide, but that currently many clinicians use lenalidomide third line. Lenalidomide is given third line with ixazomib and dexamethasone, in the Cancer Drugs Fund, or with dexamethasone. Therefore, the clinical experts agreed that the fourth-line positioning was appropriate. The committee concluded that it would focus its discussion on people who have had 3 previous treatments.

There is unmet need for new effective third-line treatment options, after 2 previous treatments

3.4 The committee recalled that for isatuximab plus pomalidomide and dexamethasone both the marketing authorisation and NICE's final scope included people who have had at least 2 previous treatments, to include lenalidomide and a proteasome inhibitor. It also recalled that lenalidomide and bortezomib are now options for untreated multiple myeloma and after 1 previous treatment (see section 3.2). The patient expert explained that patients would prefer any NICE recommendation to include the population covered by the marketing authorisation rather than restrict it to those who have had 3 previous treatments. The company did an analysis, using data from people who had had 2 previous treatments, comparing isatuximab plus pomalidomide and dexamethasone with pomalidomide plus dexamethasone. But it was not compared with panobinostat plus bortezomib and dexamethasone, the comparator listed in NICE's final scope after 2 previous treatments. The Cancer Drugs Fund clinical lead explained that the increased use of lenalidomide and a proteasome inhibitor earlier in the treatment pathway has meant that there is an increasing need for new and effective third-line treatment options. The committee concluded that there is unmet need for new effective treatment options for people who have had 2 previous treatments. It would welcome evidence for this population compared with the relevant comparator in NICE's final scope.

Comparators

After 3 previous treatments, pomalidomide plus dexamethasone is the only relevant comparator

3.5 NICE guidance recommends both pomalidomide plus dexamethasone and panobinostat plus bortezomib and dexamethasone as fourth-line treatment options (after 3 previous treatments) for multiple myeloma. NICE's final scope for this appraisal lists these as the comparators. The committee recalled that treatments recommended in the Cancer Drugs

Fund are not considered to be comparators. The company did not consider panobinostat plus bortezomib and dexamethasone to be a relevant comparator to isatuximab plus pomalidomide and dexamethasone after 3 previous treatments. It explained that this was because of toxic adverse effects and the lack of perceived efficacy among clinicians it consulted, which means it is usually used after 4 previous treatments. But to comply with NICE's final scope, the company presented evidence comparing the clinical and cost effectiveness of isatuximab plus pomalidomide and dexamethasone with panobinostat plus bortezomib and dexamethasone. This included an indirect treatment comparison for clinical effectiveness because there was no trial directly comparing the 2 treatments. The ERG noted that 1 of its clinical advisers agreed with the company's position, but 2 stated that panobinostat plus bortezomib and dexamethasone is used after 3 previous treatments and toxicity is managed by adjusting the dose. The clinical experts at the meeting explained that daratumumab, available in the Cancer Drugs Fund, or pomalidomide plus dexamethasone are the most commonly used options after 3 previous treatments. They also stated that panobinostat plus bortezomib and dexamethasone is very rarely used after 3 previous treatments because of toxicity and perceived poor clinical efficacy. The Cancer Drugs Fund clinical lead explained that clinicians can now offer bortezomib again without having to use it with panobinostat and that few clinicians offer panobinostat plus bortezomib and dexamethasone after 3 previous treatments. The committee concluded that after 3 previous treatments, pomalidomide plus dexamethasone is the only relevant comparator.

Clinical evidence

The evidence for people who have had 3 previous treatments is acceptable for decision making

3.6 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 treatments, including lenalidomide and a proteasome inhibitor. The primary outcome was progression-free survival. Because the company positioned isatuximab plus pomalidomide and dexamethasone as a treatment option after 3 previous treatments, it provided clinical effectiveness data from a post hoc subgroup of people from ICARIA-MM who had 3 previous treatments. The committee was aware that this subgroup was not stratified and therefore not a randomised group. The ERG noted there was more uncertainty associated with the subgroup results than with the randomised population results, indicated by wider confidence intervals. The committee understood the limitations of the subgroup analysis, but agreed to accept the analysis for people who have had 3 previous treatments for decision making.

Isatuximab plus pomalidomide and dexamethasone likely extends both progression-free and overall survival, but the data are immature

3.7 ICARIA-MM is ongoing. At the interim data cut (October 2018) median follow up was 11.6 months in the trial for those who had 3 previous treatments. For progression-free survival, the interim subgroup analysis was based on only about half of patients having events. It showed that isatuximab plus pomalidomide and dexamethasone appeared to extend median progression-free survival compared with pomalidomide plus dexamethasone from 7.8 months to 13.3 months (hazard ratio 0.598; 95% confidence interval 0.348 to 1.03, p=0.0611). For time to death, the interim subgroup analysis was based on 11 deaths in the treatment group (which included 52 people) and 23 deaths in the control group (which included 58 people) and heavily censored data. It showed that median overall survival had not yet been reached for the isatuximab plus pomalidomide and dexamethasone arm. The hazard ratio for overall survival compared with pomalidomide plus dexamethasone was 0.494 (95% confidence interval 0.24 to 1.02, p=0.0502). The committee acknowledged the immaturity of the data in this ongoing trial. It concluded that isatuximab

plus pomalidomide and dexamethasone was likely to extend progression-free and overall survival compared with pomalidomide plus dexamethasone after 3 previous treatments, but noted that median follow up was short, the subgroup was small and the data were immature.

No evidence is presented for people who have previously had an anti-CD38 monoclonal antibody

3.8 Isatuximab is an anti-CD38 monoclonal antibody. Daratumumab, another anti-CD38 monoclonal antibody, is an option after 1 previous treatment and 3 previous treatments in the Cancer Drugs Fund. ICARIA-MM included people with multiple myeloma that was not refractory to anti-CD38 antibody treatment, that is, their disease had not progressed on the treatment. But it excluded people whose disease was refractory to previous anti-CD38 antibody treatment, that is, their disease progressed while on treatment. The clinical experts explained that they would consider using isatuximab plus pomalidomide and dexamethasone for people who had previous treatment with an anti-CD38 antibody such as daratumumab, but only if that treatment had stopped for reasons other than disease progression. But they stated that they would not use an anti-CD38 antibody again if the disease had been refractory to one in a previous line of treatment. The company noted that only 1 person in ICARIA-MM had previous anti-CD38 antibody treatment. The clinical experts explained that in NHS practice many people increasingly have daratumumab second line. This means that many people with relapsed and refractory multiple myeloma after 3 previous treatments would have already had an anti-CD38 antibody. The Cancer Drugs Fund clinical lead noted that daratumumab is well tolerated and few people would stop it for reasons other than disease progression. The clinical experts and the Cancer Drugs Fund clinical lead also noted that there was high biological plausibility that daratumumab would reduce any response to isatuximab in people whose disease was refractory to previous daratumumab treatment. The committee acknowledged that evidence of the clinical effect of isatuximab plus pomalidomide and dexamethasone in people who had

previously had anti-CD38 antibody treatment had not been presented. It recalled that the clinical experts explained that using an anti-CD38 antibody treatment again later in the treatment pathway would be appropriate if treatment had been stopped for reasons other than disease progression. The committee concluded that it had not been presented with evidence for people whose disease was refractory to anti-CD38 antibody treatment, and it was not appropriate to generalise the evidence to this group.

Subsequent treatments in ICARIA-MM do not reflect NHS clinical practice

3.9 The subgroup of people in ICARIA-MM who had had 3 previous treatments had a range of subsequent treatments after disease progression. The committee was aware that some of these treatments, such as daratumumab and lenalidomide, were not available at this point in the pathway in the NHS, and may prolong life. The clinical experts explained that there are no standard fifth-line treatments in current NHS clinical practice, and treatments at this point in the pathway would likely be ineffective. They therefore considered that fifth-line and later treatment in ICARIA-MM was unlikely to affect the survival results in the ICARIA-MM subgroup. The committee recognised that these treatment options improve clinical outcomes when used at other points in the treatment pathway, and that it was appropriate to consider this. It also noted that the proportion of people having these treatments varied, with more people having daratumumab in the pomalidomide plus dexamethasone arm and more people having lenalidomide in the isatuximab plus pomalidomide and dexamethasone arm. The committee concluded that the subsequent treatments given in ICARIA-MM did not reflect NHS clinical practice, which made generalising the clinical effectiveness results to NHS practice uncertain.

The company's economic model

The company's model is appropriate for decision making

3.10 The company chose a partitioned survival model to estimate the cost effectiveness of isatuximab plus pomalidomide and dexamethasone. The model included 3 health states: progression-free, progressed, and dead. The probability of being in a given health state was defined by the area under the curves for progression-free survival and overall survival or their difference. The model cycle length was 1 week and the time horizon was 20 years. The committee considered the company's model to be appropriate for decision making.

The clinical data are immature but the Weibull distribution gives the most plausible overall survival estimates

3.11 Follow up for the interim data from ICARIA-MM was short in relation to the modelled time horizon. So the company extrapolated the ICARIA-MM overall survival data for the subgroup who had had 3 previous treatments, choosing an exponential distribution in its base case. The committee understood that the distribution chosen to estimate overall survival affects the incremental cost-effectiveness ratio (ICER). The ERG noted that the exponential distribution provided the best statistical fit to the trial data, but other distributions had similar statistical fits. The committee noted that because there were limited trial data, the statistical fit of a curve is of limited importance when selecting the most appropriate distribution. It heard that 2 of the 3 clinical advisers to the company supported using the Weibull, whereas the other preferred the exponential distribution. The clinical experts at the meeting also stated that the Weibull distribution produced the most plausible long-term overall survival estimates. The company used a jointly fitted lognormal distribution to estimate progression-free survival in its base case, that is, it fitted a curve to data for both treatment arms and included treatment group as a covariate, implying a constant treatment effect over time. The committee was aware that both the ERG and the company used other distributions in sensitivity

analyses to estimate progression-free survival, but that this had little effect on the economic model results. The committee concluded that the clinical data were immature, but the Weibull extrapolation gave the most plausible overall survival estimates.

Adjusting trial data for subsequent treatments not available in clinical practice is appropriate but more information is needed

3.12 The committee was aware that the fifth-line or later treatments given in ICARIA-MM included treatments that would not be available in NHS clinical practice and these might prolong life (see section 3.9). It was also aware that subsequent treatments in the analysis affected total costs in both treatment arms. The company used the inverse probability of censoring weighting method to adjust for the effect of fifth-line treatment with daratumumab and lenalidomide. The company considered these analyses exploratory because they included a small number of people and may not have accounted for all the factors associated with subsequent daratumumab or lenalidomide use. The ERG explained that the company's adjustment methods appeared valid, but the committee was not satisfied that the company had provided enough information about the analyses. The ERG noted that removing treatments reduced the total costs less in the isatuximab plus pomalidomide and dexamethasone arm than in the pomalidomide plus dexamethasone arm. This was because of the higher proportion of people taking pomalidomide plus dexamethasone moving to daratumumab treatment. The committee considered it reasonable to adjust for subsequent treatments not available in the NHS and which may prolong life. But it was concerned about the company's methods and lack of key information needed to judge the analyses. The committee would have liked to see the covariates used in the inverse probability of censoring weighting analyses and the range of weights estimated. It also noted that the company used a hazard ratio to apply the adjustment to only 1 arm of the ICARIA-MM data. The committee would have preferred to see survival models fitted to the weighted survival times, which would adjust both arms of the trial. It noted that although the

company's analyses adjusting for subsequent treatments were exploratory and had limitations, the company's base case ICER was likely to be underestimated. The committee welcomed the company's adjustment but the lack of detail in the company's reporting meant that it could not be satisfied that the adjustment has been done appropriately. The committee concluded that adjusting for subsequent treatments was appropriate but further information was needed from the company.

Utility values in the economic model

Utility estimates in the company's model are appropriate

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. This is in line with the NICE methods guide. The utility value used for the progression-free health state in the isatuximab plus pomalidomide and dexamethasone arm was slightly higher than for the pomalidomide plus dexamethasone arm (0.719 compared with 0.717). The company applied a utility value of 0.611 to both arms for the progressed disease state. More adverse events occurred in the isatuximab plus pomalidomide and dexamethasone arm. The company did not apply utility decrements for adverse events. It explained that health utility data were collected at the beginning of every treatment cycle (every 2 weeks) in the trial and it assumed the EQ-5D would capture any loss in utility from adverse events. The ERG considered this to be reasonable. The patient expert stated that despite the higher rate of adverse events in the isatuximab plus pomalidomide and dexamethasone arm of the trial, fewer people stopped treatment because of adverse events than in the pomalidomide plus dexamethasone arm (7.8% compared with 17.2%). On balance, the committee concluded that the utility estimates used in the company's model were appropriate.

Costs in the economic model

Time on treatment determines cost of treatment, and extrapolated estimates are uncertain

3.14 The committee understood that the cost of treatment was a key driver in the cost effectiveness of isatuximab plus pomalidomide and dexamethasone. It also appreciated that time on treatment and price largely determine the cost of treatment. The company collected time on treatment data in ICARIA-MM. The committee was aware that because the trial is ongoing, some people were on treatment at the time of the interim analysis (27.6% in the pomalidomide plus dexamethasone arm and 45.1% in the isatuximab plus pomalidomide and dexamethasone arm). This added uncertainty to any extrapolation. The company chose an exponential model in its base case to estimate time on treatment. The ERG highlighted that alternative models increased the ICER. The committee considered that there was some uncertainty around the most plausible model to use to estimate time on treatment but concluded that the company's choice was reasonable, given the available data.

Including drug wastage and treatment costs based on relative dose intensities in ICARIA-MM is appropriate

3.15 In its base case, the company assumed drug wastage for isatuximab in line with previous NICE technology appraisal guidance in multiple myeloma. But the company also stated that there is potential for vial sharing, which could reduce drug wastage. The ERG modelled a scenario without drug wastage to highlight the impact on the ICER, while noting this was unlikely in clinical practice. The Cancer Drugs Fund clinical lead confirmed that drug wastage was likely, particularly if treatments are not widely used. The ERG noted that the relative dose intensity, that is the ratio of the given dose to the planned dose, of pomalidomide was lower in the isatuximab plus pomalidomide and dexamethasone arm than in the pomalidomide plus dexamethasone arm in ICARIA-MM. It modelled a scenario which assumed 100% relative dose intensities in both treatment

arms to highlight the impact on the ICER. The company explained that the differences in the relative dose intensities of pomalidomide between trial arms resulted from the trial allowing dose reductions of pomalidomide, but only missed doses of isatuximab. The committee concluded that drug wastage occurs, and the company's base case drug wastage and relative dose intensity assumptions were appropriate.

Waning of treatment effect

The model should include waning of the treatment effect of isatuximab plus pomalidomide and dexamethasone

3.16 The company's model assumed that the relative survival benefit of isatuximab plus pomalidomide and dexamethasone, compared with pomalidomide plus dexamethasone, was maintained at the same level after treatment stopped, for the rest of a person's life. This meant that people who survived long term were assumed to have a much lower risk of death in the isatuximab plus pomalidomide and dexamethasone arm than in the pomalidomide plus dexamethasone arm. The company did not include a treatment waning effect, but tested for proportional hazards, which the trial data supported. However, the proportional hazards assumption was supported only for the observed trial follow up period, with no evidence about what happens after this. The committee was aware that neither the company nor the ERG had modelled scenarios in which the treatment benefit in the extrapolated phase diminishes in the long term. The clinical experts explained that it was plausible for isatuximab plus pomalidomide and dexamethasone to have some treatment benefit that continues after stopping treatment, although it may not be maintained at the same level for the rest of a person's life. The committee heard that the point at which the relative treatment benefit starts to diminish is unknown. It accepted the clinical experts' comments but acknowledged that it had not been presented with evidence to judge the duration of isatuximab's continued and undiminished effect. It acknowledged that the duration of the relative benefit of isatuximab plus

pomalidomide and dexamethasone after stopping treatment was uncertain. But, based on the comments from the clinical experts, isatuximab's survival benefit was unlikely to continue for a person's lifetime. The committee would welcome a scenario that includes equalised hazard ratios for people surviving long term. The committee concluded that the company's model should include waning of the relative treatment effect of isatuximab plus pomalidomide and dexamethasone.

End of life

Isatuximab plus pomalidomide and dexamethasone meets NICE's end-of-life criteria

3.17 The committee considered the advice about life-extending treatments for people with a short life expectancy in NICE's guide to the methods of technology appraisal. Median overall survival in the pomalidomide plus dexamethasone arm of ICARIA-MM fourth-line subgroup was 14.4 months. The ERG noted that the modelled mean survival was higher than the median (these values are commercial in confidence and cannot be reported here). The company referred to epidemiological evidence showing that median overall survival was below 14 months in people with relapsed or refractory multiple myeloma who had 3 previous treatments. The clinical experts stated that life expectancy for people in this group was less than 2 years. Therefore, the committee concluded that the short life expectancy criterion was met. Median overall survival was not reached in the isatuximab plus pomalidomide and dexamethasone arm of ICARIA-MM. But both the Weibull (committee's preferred distribution) and the exponential model (company's base case) estimated that it extended life by more than 3 months compared with pomalidomide plus dexamethasone in the subgroup who had 3 previous treatments. The committee acknowledged the uncertainty in the life-extending benefits of the treatment. But, on balance, it concluded that isatuximab plus pomalidomide and dexamethasone extended mean overall survival by over 3 months compared with pomalidomide plus dexamethasone. The

committee concluded that isatuximab plus pomalidomide and dexamethasone, after 3 previous treatments, met the criteria to be considered a life-extending, end-of-life treatment.

Cost-effectiveness results

No analyses reflect the committee's preferred assumptions

3.18 Because of confidential commercial arrangements for isatuximab, pomalidomide and the comparators, none of the cost-effectiveness results are reported here. However, none of the company's or the ERG's analyses reflected the committee's preferences. The committee would have preferred to see analyses that:

- used a Weibull extrapolation for estimating overall survival (see section 3.11)
- adjusted for subsequent trial treatments not used in NHS clinical practice, with methods fully reported (see sections 3.9 and 3.12)
- applied the drug wastage and relative dose intensity assumptions from the company's base case (see section 3.15)
- included a waning of the relative treatment effect for isatuximab plus pomalidomide and dexamethasone compared with pomalidomide plus dexamethasone (see section 3.16).

Isatuximab plus pomalidomide and dexamethasone is not recommended in the NHS

3.19 The committee considered that the most plausible ICER was above the range NICE normally considers to be a cost-effective use of NHS resources for a life-extending treatment at the end of life. It therefore concluded that it would not recommend isatuximab plus pomalidomide and dexamethasone for relapsed and refractory multiple myeloma.

Cancer Drugs Fund

Isatuximab plus pomalidomide and dexamethasone does not meet the Cancer Drugs Fund criteria

3.20 Having concluded that isatuximab plus pomalidomide and dexamethasone could not be recommended for routine use, the committee then considered if it could be recommended for treating multiple myeloma within the Cancer Drugs Fund. The committee discussed the arrangements for the Cancer Drugs Fund agreed by NICE and NHS England in 2016, noting NICE's Cancer Drugs Fund methods guide (addendum). It recalled:

- The company expressed an interest in isatuximab plus pomalidomide and dexamethasone being considered for the Cancer Drugs Fund.
- Data from ICARIA-MM were immature (data cut was October 2018) and median overall survival was not reached in the isatuximab plus pomalidomide and dexamethasone arm.
- ICARIA-MM is due to finish in March 2021. Further data from this trial could help reduce uncertainties in the long-term progression-free and overall survival and the time on treatment estimates. The committee was aware that overall survival and time on treatment estimates were key drivers of the cost-effectiveness results (see sections 3.11 and 3.14).
- Data collection through the Systemic Anti-Cancer Therapy dataset could be used to collect evidence on clinical outcomes for people with multiple myeloma who have had 3 previous treatments. It may also be able to provide information on the proportion of people having fifth-line treatment after progression and the treatments used. However, there may be not enough time for these data to be collected before ICARIA-MM ends.
- The Cancer Drugs Fund clinical lead stated that because daratumumab, an anti-CD38 monoclonal antibody, is used for second-line treatment, there are fewer people eligible for fourth-line isatuximab,

another anti-CD38 monoclonal antibody treatment. This would limit the amount of data that would be collected for isatuximab in clinical practice.

- It is likely that the cost-effectiveness estimates for isatuximab plus pomalidomide and dexamethasone would worsen if all of the committee's preferences were included.
- The company's price for isatuximab plus pomalidomide and dexamethasone means that it does not have plausible potential to be cost effective at the current price.

The committee concluded that although further data collected in the Cancer Drugs Fund may reduce uncertainties in the evidence, isatuximab plus pomalidomide and dexamethasone did not meet the criteria to be considered for inclusion in the Cancer Drugs Fund.

Innovation

The model adequately captures the benefits of isatuximab plus pomalidomide and dexamethasone

3.21 The company considered isatuximab plus pomalidomide and dexamethasone to be innovative. This is because it is the first treatment option for relapsed and refractory multiple myeloma to combine an anti-CD38 monoclonal antibody and an immunomodulatory agent. The company also highlighted that the treatment shows benefit in a population who have had many previous treatments. The Cancer Drugs Fund clinical lead stated that there are currently no anti-CD38 antibody treatments recommended for NHS routine commissioning to treat multiple myeloma. He also noted that the company supported a recommendation in the Cancer Drugs Fund. But the Cancer Drugs Fund already offers access to anti-CD38 antibody treatment at second line (daratumumab plus bortezomib and dexamethasone) and at fourth line (daratumumab alone). The committee considered that the model captured all health-related quality-of-life benefits. It concluded that it had not been presented with

any evidence of additional benefits from treatment with isatuximab plus pomalidomide and dexamethasone.

Other factors

3.22 No equality or social value judgement issues were identified.

4 Review of guidance

4.1 NICE proposes that the guidance on this technology is considered for review by the guidance executive 3 years after publication of the guidance. NICE welcomes comment on this proposed date. The guidance executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Amanda Adler
Chair, appraisal committee B
May 2020

5 Appraisal committee members and NICE project team

Appraisal 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 to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

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

NICE project team

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

Alan Moore
Technical lead

Emily Eaton Turner
Technical adviser

Jeremy Powell
Project manager

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