NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Draft guidance consultation

Ivosidenib with azacitidine for untreated acute myeloid leukaemia with an IDH1 R132 mutation [ID6198]

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using ivosidenib with azacitidine 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 <u>committee papers</u>).

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?

Draft guidance consultation – ivosidenib with azacitidine for untreated acute myeloid leukaemia with an IDH1 R132 mutation [ID6198]

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

After consultation:

- The evaluation committee will meet again to consider the evidence, this evaluation consultation document and comments from the stakeholders.
- At that meeting, the committee will also consider comments made by people who are not stakeholders.
- After considering these comments, the committee will prepare the final draft guidance.
- Subject to any appeal by stakeholders, the final draft guidance may be used as the basis for NICE's guidance on using ivosidenib in the NHS in England.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: 20 March 2024
- Second evaluation committee meeting: 3 April 2024
- Details of the evaluation committee are given in section 4

Draft guidance consultation – ivosidenib with azacitidine for untreated acute myeloid leukaemia with an IDH1 R132 mutation [ID6198]

Page 2 of 19

1 Recommendations

1.1 Ivosidenib plus azacitidine is not recommended, within its marketing authorisation, for treating newly diagnosed acute myeloid leukaemia (AML) with an IDH1 R132 mutation in adults who cannot have standard intensive induction chemotherapy.

1.2 This recommendation is not intended to affect treatment with ivosidenib plus azacitidine 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

Usual treatment for newly diagnosed AML with an IDH1 R132 mutation in adults who cannot have standard intensive induction chemotherapy is venetoclax plus azacitidine.

Ivosidenib plus azacitidine has not been directly compared in a clinical trial with venetoclax plus azacitidine. It is not certain from an indirect comparison if ivosidenib plus azacitidine increases how long people live and how long they have before their condition gets worse compared with venetoclax plus azacitidine.

There are substantial uncertainties in the economic model, including around the modelling of long-term life expectancy.

Because of the uncertainties in both the economic model and the clinical evidence there is not enough evidence to determine if ivosidenib plus azacitidine is an acceptable use of NHS resources. So, it is not recommended.

Draft guidance consultation – ivosidenib with azacitidine for untreated acute myeloid leukaemia with an IDH1 R132 mutation [ID6198]

Page 3 of 19

2 Information about ivosidenib with azacitidine

Marketing authorisation indication

2.1 Ivosidenib (Tibsovo, Servier Laboratories) in combination with azacitidine is indicated for 'the treatment of adult patients with newly diagnosed acute myeloid leukaemia (AML) with an isocitrate dehydrogenase-1 (IDH1) R132 mutation who are not eligible to receive standard induction chemotherapy'.

Dosage in the marketing authorisation

2.2 The dosage schedule is available in the <u>summary of product</u> <u>characteristics for ivosidenib</u>.

Price

- 2.3 The list price of a 60-tablet pack of 250 mg ivosidenib is £12,500, or £150,000 for a year of treatment (excluding VAT; BNF online accessed January 2024). At the time of evaluation, the average price of azacitidine was £45.16 per 100 mg vial (eMIT accessed September 2023).
- 2.4 The company has a commercial arrangement. This makes ivosidenib available to the NHS with a discount and it would have also applied to this indication if the technology had been recommended. The size of the discount is commercial in confidence. It is the company's responsibility to let relevant NHS organisations know details of the discount.

3 Committee discussion

The <u>evaluation committee</u> considered evidence submitted by Servier Laboratories, a review of this submission by the external assessment group (EAG), and responses from stakeholders. See the <u>committee papers</u> for full details of the evidence.

Draft guidance consultation – ivosidenib with azacitidine for untreated acute myeloid leukaemia with an IDH1 R132 mutation [ID6198]

Page 4 of 19

Acute myeloid leukaemia with an IDH1 R132 mutation

New treatment option

3.1 The patient expert explained that existing treatments for acute myeloid leukaemia (AML) are mainly chemotherapy and stem cell transplant but new options are needed for when these are not suitable. The patient expert described how gruelling intensive induction chemotherapy is, both physically and psychologically, even if you are fit. The clinical expert also emphasised the need for an alternative to intensive induction chemotherapy. They said that up until venetoclax plus azacitidine was recommended, survival rates had been poor if people could not have intensive induction chemotherapy. They added that since venetoclax plus azacitidine became available, survival rates had substantially improved. Ivosidenib plus azacitidine is a treatment option for the 6% to 10% of people with AML who have an IDH1 R132 mutation (from now, IDH1 mutation). Ivosidenib is an oral treatment that can be taken at home, so convenient for people with AML. The clinical expert said that, for people with an IDH1 mutation, they would prefer to offer ivosidenib plus azacitidine over venetoclax plus azacitidine, because haematological toxicity is an issue with venetoclax plus azacitidine. The committee concluded that people with AML with an IDH1 mutation who cannot have intensive induction chemotherapy would welcome a new treatment option.

Clinical management

Treatment pathway

3.2 The first treatment option for AML is intensive induction chemotherapy to bring about remission, then consolidation chemotherapy, followed by maintenance therapy, and then a stem cell transplant. But more than 50% of people with AML cannot have intensive induction chemotherapy and stem cell transplants, for example because of their age or comorbidities. Standard care for AML if someone cannot have intensive induction chemotherapy is venetoclax plus azacitidine (see NICE's technology

Draft guidance consultation – ivosidenib with azacitidine for untreated acute myeloid leukaemia with an IDH1 R132 mutation [ID6198]

Page 5 of 19

<u>appraisal guidance on venetoclax with azacitidine for untreated AML when</u> <u>intensive chemotherapy is unsuitable</u>). Other options are:

- low-dose cytarabine
- azacitidine (for AML with 20% to 30% bone marrow blasts)
- venetoclax plus low-dose cytarabine (for AML with more than 30% bone marrow blasts).

Comparators

3.3 The company said that venetoclax plus azacitidine was the only relevant comparator in this patient group. But the EAG said that it had clinical advice that venetoclax plus azacitidine was only suitable for people who are well enough, and that the other comparators are offered if people cannot tolerate venetoclax plus azacitidine. The clinical expert said that the main treatment for people who could not have intensive induction chemotherapy was venetoclax plus azacitidine. They acknowledged that there were situations in which other treatments could be considered but said that these were unusual because outcomes for them were so poor. The NHS England Cancer Drugs Fund clinical lead (from here, Cancer Drugs Fund lead) said that most people on venetoclax were having it in combination with azacitidine. The committee was satisfied that most people with untreated AML who cannot have intensive induction chemotherapy have venetoclax plus azacitidine in clinical practice. It concluded that the most appropriate comparator for ivosidenib plus azacitidine was venetoclax plus azacitidine.

Clinical effectiveness

Literature searches

3.4 The EAG had concerns that the company had narrowed the population element of the literature searches too much. It said that because the search was narrowed to only include articles specifically mentioning the phrases 'first line', 'treatment-naive' or 'untreated' in the database record,

Draft guidance consultation – ivosidenib with azacitidine for untreated acute myeloid leukaemia with an IDH1 R132 mutation [ID6198]

Page 6 of 19

relevant papers may have been missed. The EAG identified an extra 1,336 potentially relevant documents. It considered that there was a risk that important comparator trials had been missed. The company responded that its search strategy was in line with the target population and was constructed to exclude irrelevant indications. It also said that the approach had been used in previous systematic reviews submitted for NICE appraisals. The clinical expert confirmed that the most important trials had been identified. The committee acknowledged the uncertainty highlighted by the EAG but was reassured that the most important evidence was likely to have been identified.

AGILE trial

3.5 The direct comparative clinical effectiveness evidence for ivosidenib plus azacitidine came from the AGILE trial. This was a phase 3 multicentre, randomised, placebo-controlled trial comparing ivosidenib plus azacitidine (n=72) with azacitidine plus placebo (n=74). The committee noted that azacitidine monotherapy was not considered a relevant comparator treatment by the company. The trial was in people with previously untreated AML with an IDH1 mutation who could not have intensive induction chemotherapy. Median follow up was 28.6 months and the primary outcome was event-free survival. Secondary outcomes were overall survival, complete remission (CR) or CR without haematological recovery (CRi), and objective response rate. In the AGILE trial, event-free survival was significantly better for ivosidenib plus azacitidine than for azacitidine plus placebo, with a hazard ratio of 0.33 (95% confidence interval [CI] 0.16 to 0.69; p=0.0011). Overall survival was also significantly better, with a hazard ratio of 0.42 (95% CI 0.27 to 0.65; p<0.0001). The committee concluded that ivosidenib plus azacitidine improved event-free and overall survival compared with azacitidine plus placebo.

Draft guidance consultation – ivosidenib with azacitidine for untreated acute myeloid leukaemia with an IDH1 R132 mutation [ID6198]

Indirect treatment comparison

Network meta-analysis

3.6 Because there was no direct comparative evidence for ivosidenib plus azacitidine compared with venetoclax plus azacitidine, the company did an indirect treatment comparison using network meta-analysis (NMA). This used data from the VIALE-A trial for venetoclax plus azacitidine. VIALE-A was a randomised controlled trial comparing venetoclax plus azacitidine with azacitidine plus placebo in 433 people with untreated AML who could not have intensive induction chemotherapy. The point estimates in the NMA results for event-free survival, overall survival and complete remission favoured ivosidenib plus azacitidine over venetoclax plus azacitidine. The company considered the exact results confidential and so they cannot be reported here. The committee noted that the credible intervals crossed 1, indicating that there may be no difference in effect between the 2 treatments. The EAG said that, although the company's NMA had been done to a reasonable standard, it had several concerns. Aside from the lack of significance for the treatment effect, there was heterogeneity across some of the studies. And because the company used fixed effect rather than random effects models, the EAG said that the credible intervals did not properly express this uncertainty. The company acknowledged the uncertainties in the NMA results, which it said were because AGILE was a small study, and because each link in the network was only 1 study. It pointed out that all the point estimates in the NMA results consistently favoured ivosidenib plus azacitidine. The EAG also considered that the IDH1 mutation could be an important treatment effect modifier. Results from the VIALE-A trial suggested a stronger treatment effect for venetoclax plus azacitidine in the subgroup of people who had the IDH1 mutation, although the subgroup was small. The company did not submit NMA results for the IDH1 subgroup. It pointed out that this was not possible because, although AGILE only included people who had the IDH1 mutation, the comparator trials did not (they included

Draft guidance consultation – ivosidenib with azacitidine for untreated acute myeloid leukaemia with an IDH1 R132 mutation [ID6198]

Page 8 of 19

around 20% people with the IDH1 mutation). It also said that because venetoclax was not designed to specifically target IDH1, its efficacy is not expected to be different in people who have the mutation and those who do not. The EAG used the VIALE-A results to do an exploratory NMA effect estimate in the IDH1 subgroup for overall survival. This favoured venetoclax plus azacitidine, but the credible intervals crossed 1. The clinical expert said that there is conflicting data on what effect the IDH1 mutation has on outcomes, but that at the moment it is not used for risk stratification in the NHS. The committee acknowledged the uncertainty in the NMA, especially around the lack of significance in the difference in treatment effect and the potential for IDH1 mutation status to affect the overall results. The committee concluded that it had not seen any clear evidence that ivosidenib plus azacitidine improved overall and event-free survival compared with venetoclax plus azacitidine.

Economic model

Company's modelling approach

3.7 The company submitted a partitioned survival model with Markov components. The Markov components were the estimates of the proportion of people with CR or CRi, used to estimate modelled utility values, and the proportion moving to the long-term survival state. The model had a 25-year time horizon. It used the endpoints in the AGILE study to inform the modelled health states: event-free (which contained a long-term survival state), progressed disease or relapse, and death. The EAG noted that model structures for NICE appraisals in this area varied:

NICE's technology appraisal guidance on venetoclax with azacitidine for untreated AML used a Markov model while NICE's technology appraisal guidance on gilteritinib for relapsed or refractory AML used a partitioned survival model. The company explained that it had chosen to vary its approach from that used in the venetoclax guidance because:

Draft guidance consultation – ivosidenib with azacitidine for untreated acute myeloid leukaemia with an IDH1 R132 mutation [ID6198]

Page 9 of 19

- important elements of the model structure had been redacted from the appraisal papers so were not available for reference
- it did not have person-level data to inform the transitions for venetoclax plus azacitidine.

The committee was aware that the company's model structure differed from other models for AML but concluded that it was appropriate for decision making.

Cure assumption

In the company model, anyone who was still event free at 3 years in either treatment arm moved into the long-term survival state (that is, there was a cure assumption). Their risk of death was assumed to be the same as the general population from this point. No medicine acquisition, administration or concomitant medicine costs were applied to people in the long-term survival state. The EAG noted that a higher proportion of people on ivosidenib plus azacitidine enter the long-term survival state than those on venetoclax plus azacitidine. The EAG noted that the long-term survival state produced most of the quality-adjusted life year (QALY) gain for ivosidenib plus azacitidine. The company argued that the remission rates in the AGILE trial showed a link between complete remission and overall survival (41% of people on ivosidenib plus azacitidine were estimated to still be alive at 3 years). It said that the plateau in overall survival in this group implied a potential 'cure'.

The company noted that in previous NICE evaluations in AML, cure assumptions have been considered. In NICE's technology appraisal guidance on venetoclax with low dose cytarabine for untreated AML and on venetoclax with azacitidine for untreated AML the committee considered that the evidence for including a cure state in the model was uncertain but it was plausible that some people may be cured. NICE's technology appraisal guidance on gilteritinib for relapsed or refractory

Draft guidance consultation – ivosidenib with azacitidine for untreated acute myeloid leukaemia with an IDH1 R132 mutation [ID6198]

Page 10 of 19

<u>AML</u> and on <u>gemtuzumab ozogamicin for untreated AML</u> also incorporated a cure assumption (at 2 to 3 years, and 5 years, respectively).

3.9 The clinical expert said that there was not enough long-term data from trials to be able to conclude what proportion of people would be functionally 'cured'. They estimated that, after combination treatment, the chance of relapse was likely to be less than 10% if someone survives to 3 years and is no longer having treatment. The EAG said that, if it was possible for people on ivosidenib plus azacitidine to be cured, they would expect the hazard of death to be equal to the general population. But its calculations did not show this, and the point estimate hazard of death remained higher at the end of the trial than the general population. The company said that it may have overestimated background mortality by assuming that the cohort of patients was homogeneous – that is, it did not separate out by age and by those who had and had not relapsed. It said that it had looked at the effect of increasing the hazard of death above that of the general population by increasing the standardised mortality ratio (SMR) in sensitivity analyses to 1.1, 1.2 and 2. But, because there was no evidence to support increasing the SMR, it had kept an SMR of 1 in its base case. The committee noted that, because the point estimate hazard of death at the end of the trial remained above that of the general population, it would prefer to see scenarios that increased the SMR. The committee also discussed the uncertainty around when people entered the cure state and when people could plausibly become functionally cured. The committee noted that in previous NICE technology appraisals, scenarios with cure points of 2, 3 and 5 years had been considered. The committee concluded that, although there was some evidence supporting a cure assumption in this population, it was uncertain. It said it would like to see scenarios with alternative cure points at 2, 3 and 5 years and scenarios incorporating SMRs of 1.1, 1.2 and 2.

Draft guidance consultation – ivosidenib with azacitidine for untreated acute myeloid leukaemia with an IDH1 R132 mutation [ID6198]

Page 11 of 19

Stopping rule

3.10 The company's model assumed that everyone stopped treatment at 3 years. The EAG had clinical advice that if people's AML responded to treatment, some would continue the treatment beyond 3 years. It estimated from the company's model that a reasonable proportion of people would still be on treatment at 5 years. The summary of product characteristics (SmPC) for ivosidenib says that treatment should be continued until AML progression or until treatment is no longer tolerated. So the EAG removed the 3-year stopping rule from its base case. The clinical expert said that the stopping rule reflected what happened in clinical practice. The committee noted that the stopping rule was only relevant if the cure assumption was removed from the model. This is because if a cure assumption remains at 3 years, treatment stops at that point anyway. The committee concluded that the stopping rule was not relevant when the cure assumption was incorporated in the model.

Overall and event-free survival

3.11 The company used the outputs from the NMA to inform the hazard ratios for overall and event-free survival in the modelling (see section 3.12). The committee recalled that it could not be certain that ivosidenib plus azacitidine improved overall and event-free survival compared with venetoclax plus azacitidine (see section 3.6). The EAG explored this uncertainty using various scenario analyses. It varied the event-free and overall survival hazard ratios for venetoclax plus azacitidine compared with ivosidenib plus azacitidine by 25% either way and by using the upper and lower bound credible intervals. Using the upper bound event-free survival hazard ratio credible intervals increased the incremental costeffectiveness ratio (ICER) substantially. The committee noted that varying the hazard ratios has an impact on the cost-effectiveness results. It noted that it had not been presented with any scenarios that assumed no difference in treatment effect between ivosidenib plus azacitidine and venetoclax plus azacitidine. The committee concluded that ICERs based

Draft guidance consultation – ivosidenib with azacitidine for untreated acute myeloid leukaemia with an IDH1 R132 mutation [ID6198]

Page 12 of 19

on improved overall and event free survival for ivosidenib plus azacitidine compared with venetoclax plus azacitidine were not reliable. It requested a scenario in which the hazard ratio was set at 1 for the comparison of overall and event-free survival (that is, no difference in treatment effect).

Long-term treatment effects

3.12 Treatment effect data for ivosidenib plus azacitidine was only available from the AGILE trial for a median follow up of 28.6 months. So the company modelled long-term overall and event-free survival for ivosidenib plus azacitidine using a log-normal distribution. But the EAG said it had clinical advice that these extrapolations produced estimates of overall and event-free survival that were implausibly high. Also, when the company's cure assumption was applied, it increased the overall survival estimates even higher. The EAG preferred to use a Weibull distribution, which it said produced more plausible estimates. The committee questioned why the company had chosen the log-normal distribution. It noted that 2 out of 3 of the company's own clinical advisers had said they felt the Weibull or exponential distribution (2 of the lowest overall survival estimates) were more plausible. The company responded that it had prioritised statistical goodness of fit when choosing the appropriate extrapolation. The committee noted that at 5 years the percentage of people alive using the company's preferred log-normal curve was 33.2% and using the EAG's preferred Weibull curve it was 28.1%. The clinical expert said that it was difficult to comment on the plausibility of the 5-year survival figures when they had not been adjusted for age and the cure assumption. The committee was concerned that the 5-year survival estimates using both the company's and EAG's preferred curves were overestimating survival, especially because these estimates would increase once the cure assumption was included (see section 3.8). The committee noted that the exponential curve was more conservative and showed survival at 5 years was less than 20% (without the cure assumption applied). It also noted that the company's own clinical advisers had indicated that the

Draft guidance consultation – ivosidenib with azacitidine for untreated acute myeloid leukaemia with an IDH1 R132 mutation [ID6198]

Page 13 of 19

exponential curve was plausible. The committee concluded that there was considerable uncertainty about the most appropriate extrapolations to apply in the modelling. It noted that it had requested alternative assumptions relating to the cure state and that these would affect the overall survival estimates (see section 3.8). The committee considered that the exponential curve may produce more clinically plausible estimates. It requested a scenario using the exponential curve to extrapolate overall and event-free survival.

Cost savings

3.13 The company had claimed that using ivosidenib plus azacitidine to treat AML would lead to cost savings related to healthcare expenditure. The committee was concerned that these claims were not supported by the evidence or explained well enough. The company had suggested that using ivosidenib reduces red blood cell transfusion costs. But the trial evidence showed that blood counts for people on ivosidenib plus azacitidine were comparable with people on venetoclax plus azacitidine. The EAG pointed out that the company had assumed in its model that people on ivosidenib plus azacitidine would need to spend substantially less time in hospital when starting treatment than people on venetoclax plus azacitidine. It noted that the company's choice of modelled hospitalisation days was the main driver of its claim that using ivosidenib would lead to cost savings related to healthcare expenditure. The company calculated hospital stay for ivosidenib plus azacitidine using the AGILE study (it marked this value confidential so it cannot be reported here). It based the venetoclax plus azacitidine stay of 32 days on a US study (Rausch et al. 2021). The EAG said that this assumption likely overestimated the costs for venetoclax and biased the analysis in favour of ivosidenib. It noted that the study was a US-based, retrospective analysis of people with newly diagnosed AML and so lacked generalisability to the UK. The EAG considered that 14 days for the venetoclax plus azacitidine hospital stay was more appropriate, based on

Draft guidance consultation – ivosidenib with azacitidine for untreated acute myeloid leukaemia with an IDH1 R132 mutation [ID6198]

Page 14 of 19

a UK study (Othman et al. 2021). The committee concluded that the EAG's estimates of a 14-day hospital stay for venetoclax plus azacitidine treatment was appropriate. It also concluded that it had not been presented with any evidence to suggest that using ivosidenib results in healthcare expenditure savings.

Modelling complete response with venetoclax plus azacitidine

3.14 The company estimated CR and CRi with venetoclax plus azacitidine using an equation and data from the AGILE study. The EAG preferred to use the data available from the NMA in its base case, and queried why the company had not done the same. The committee concluded that the NMA data should be used to estimate CR and CRi for venetoclax plus azacitidine.

Relative dose intensity

3.15 The company estimated a relative dose intensity (RDI) for ivosidenib of under 100%, using data from AGILE (the company marked the actual value confidential so it cannot be reported here). Because it did not have access to equivalent data for venetoclax, it assumed the same figure for venetoclax. The EAG considered that RDI should be 100% for both treatments because the entire pack is given to the person with AML. So this is a 100% cost to the NHS regardless of the amount the person takes. The committee agreed and concluded that 100% RDI should be modelled for both treatments.

IDH1 mutation testing

3.16 The SmPC for ivosidenib specifies that people must have confirmation of an IDH1 R132 mutation before they are offered it. The scope for this appraisal specified that the economic modelling should include the costs associated with diagnostic testing for an IDH1 mutation in people with AML who would not otherwise have been tested. It also said that a sensitivity analysis should be provided without the cost of the diagnostic

Draft guidance consultation – ivosidenib with azacitidine for untreated acute myeloid leukaemia with an IDH1 R132 mutation [ID6198]

Page 15 of 19

test. The company did not include either of these in its submission. The EAG had clinical expert advice that rapid IDH1 testing would be an implementation challenge if ivosidenib was recommended. The Cancer Drugs Fund lead noted that currently in NHS practice IDH1 testing takes around 3 weeks to return results as part of an array of 20 to 30 mutation tests. So faster testing would be needed, which would have cost and resource implications. The committee concluded that the cost associated with ivosidenib for additional rapid testing for IDH1 mutation should be included in the model.

Cost-effectiveness estimates

- 3.17 The committee considered that a reliable ICER could not be determined because of the following uncertainties it had identified:
 - whether the results from the NMA show that for ivosidenib plus azacitidine improves overall and event-free survival compared with venetoclax plus azacitidine (see <u>section 3.6</u>)
 - the assumption that everyone in the event-free survival state in the model at 3 years is 'cured' (see section 3.8)
 - the most appropriate way to estimate long-term survival (see section 3.12)
 - the assumption that using ivosidenib leads to cost savings (see section 3.13).
- 3.18 NICE's health technology evaluations manual notes that 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. The committee noted the high level of uncertainty in the company's clinical evidence and model assumptions. The committee recalled the statements from the clinical and patient experts about the need for targeted treatments in people for whom intensive induction chemotherapy is unsuitable. It noted that ivosidenib is

Draft guidance consultation – ivosidenib with azacitidine for untreated acute myeloid leukaemia with an IDH1 R132 mutation [ID6198]

Page 16 of 19

the first targeted treatment for AML with an IDH1 mutation, and is administered orally and in an outpatient setting. The committee acknowledged that people with untreated AML who cannot have intensive induction chemotherapy have a poor prognosis. But it also noted the high levels of uncertainty in the evidence. The committee concluded that an acceptable ICER would be below £30,000 per QALY gained.

Further analyses needed

- 3.19 The committee considered that the following further analyses were needed:
 - a scenario analysis exploring the effect on the ICER of setting the hazard ratio at 1 for overall and event-free survival between ivosidenib plus azacitidine and venetoclax plus azacitidine (that is, no difference in treatment effect)
 - scenarios for the cure assumption with alternative cure points at 2,
 3 and 5 years and incorporating SMRs of 1.1, 1.2 and 2
 - a scenario using the exponential curve to extrapolate overall and eventfree survival.

The analyses should be based on the committee's other preferred assumptions, that is:

- including a hospital stay of 14 days for venetoclax plus azacitidine
- using 100% RDI for both interventions
- using the NMA results to inform CR and CRi for venetoclax plus azacitidine
- including the cost of rapid testing for IDH1 mutation.

Other factors

Equality

3.20 The committee did not identify any equality issues.

Draft guidance consultation – ivosidenib with azacitidine for untreated acute myeloid leukaemia with an IDH1 R132 mutation [ID6198]

Page 17 of 19

Innovation

3.21 The committee considered if ivosidenib plus azacitidine was innovative. It did not identify any additional benefits of ivosidenib not captured in the economic modelling.

Severity

3.22 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 severity modifier (a greater weight to QALYs) if technologies are indicated for conditions with a high degree of severity. When taking into account the committee's preferred comparator of venetoclax plus azacitidine, both the absolute and proportional QALY shortfall were not within the range that indicates a severity modifier may be considered. The committee concluded that the severity weighting did not apply.

Conclusion

Recommendation

3.23 The committee concluded that because of the uncertainties in both the economic model and the clinical evidence there is not enough evidence to determine if ivosidenib plus azacitidine is an acceptable use of NHS resources. It requested further evidence and analysis from the company so it could determine if ivosidenib plus azacitidine is an acceptable use of NHS resources. So, ivosidenib plus azacitidine is not recommended for treating newly diagnosed AML with an IDH1 R132 mutation in adults who cannot have standard intensive induction chemotherapy.

Draft guidance consultation – ivosidenib with azacitidine for untreated acute myeloid leukaemia with an IDH1 R132 mutation [ID6198]

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 <u>committee C</u>.

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

Chair

Richard Nicholas

Vice Chair, technology appraisal committee C

NICE project team

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

Emilene Coventry

Technical lead

Victoria Kelly

Technical adviser

Leena Issa

Project manager

ISBN: [to be added at publication]

Draft guidance consultation – ivosidenib with azacitidine for untreated acute myeloid leukaemia with an IDH1 R132 mutation [ID6198]

Page 19 of 19