National Institute for Health and Care Excellence

Health Technology Evaluation

Ivosidenib with azacitidine for untreated IDH1-positive acute myeloid leukaemia [ID6198]

Response to stakeholder organisation comments on the draft remit and draft scope

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment 1: the draft remit and proposed process

Section	Stakeholder	Comments [sic]	Action
Appropriateness of an evaluation and proposed evaluation route	Servier	Servier believe that Ivosidenib fulfils all criteria for the HST route: **The condition is very rare defined by 1:50,000 in England** The incidence of acute myeloid leukaemia (AML) is 3,089 new cases on average of AML each year[1] IDH1 mutations detected in 8% of AML cases[2,] giving an incidence of 247 in the UK. Therefore, using 2020 mid-year England population estimate, 56,550,000 this gives an incidence of 0.2:50,000 **Normally no more than 300 people in England are eligible for the technology in its licensed indication and no more than 500 across all its indications.** Ivosidenib is an isocitrate dehydrogenase-1 (IDH1) inhibitor indicated as targeted therapy for the treatment of adult patients with a susceptible IDH1 mutation with acute myeloid leukaemia (AML) and who are ineligible for intensive chemotherapy Therefore the patient numbers eligible for Ivosidenib are 135 in this indication. • 3089 with AML • 247 with IDH1 mutation (8%) • 55% of these ineligible for intensive chemotherapy[3-5]	Comments noted. The NICE team disagrees that this topic meets the criteria to be routed as a Highly Specialised Technology. The Highly Specialised Technologies Programme is designed to be used in exceptional circumstances. Its purpose is to evaluate technologies for very rare diseases that have:

Section	Stakeholder	Comments [sic]	Action
		Other indications are in relapsed and refractory acute myeloid leukaemia (AML) and as first line monotherapy in AML, although this is only approved in the U.S. There is no intent to pursue a license in these US approved indications outside of the U.S. The only other licensed indication expected in England is for the treatment of adult patients with a susceptible IDH1 mutation with locally advanced or metastatic intrahepatic (icca) cholangiocarcinoma who have been previously treated. The patient numbers eligible for Ivosidenib are expected to be around 107 (IDH1 mutation present in 12.5% of iCCA cases and 90% receive a 1st line treatment[6]) in this indication **The very rare condition significantly shortens life or severely impairs its quality** AML has the worst survival rate of any form of leukaemia, with a 5 year survival rate of 27%[7-10] Fatigue, pain, dyspnoea, insomnia, appetite loss, financial difficulties and anaemia are the most commonly reported events by AML patients. In particular, fatigue (irrespective of treatment status) and appetite loss have been found to have the most detrimental impact on the patients' HRQoL[11]. **There are no other satisfactory treatment options, or the technology is likely to offer significant additional benefit over existing treatment options** Up to 30% of newly diagnosed AML patients fail to achieve complete remission following 1-2 cycles of intensive induction chemotherapy[12] and more than two-thirds of patients receiving non-intensive chemotherapy as frontline therapy are refractory to treatment[13]. The majority of elderly patients receive non-intensive IC as frontline therapy[14] To date, no therapy targeting IDH1 mutation (mIDH1) is available in UK. Ivosidenib is a first-in-class targeted treatment that provides a significant clinical benefit in AML patients with IDH1 mutations, who are ineligible for intensive chemotherapy	• small numbers of patients; • limited or no treatment options • challenges for research and difficulties with collecting evidence, because of the uniqueness of the disease. It is important for NICE to apply appropriate limits on the very rare populations that can potentially be routed to the programme. This is because the Highly Specialised Technologies Programme is a deliberate departure from the standard technology appraisal process.

Section	Stakeholder	Comments [sic]	Action
			For more detail, please refer to section 7 of the NICE health technology evaluation topic selection: the manual.
	Otsuka	No comments	No action required.
	Leukaemia Care	Ivosidenib with azacitidine would be favoured to treat those who are IDH1 mutation positive and unsuitable for chemotherapy as it seems to be less toxic and specifically targeted to the subgroup of patients within the IDH mutation.	Comment noted. No action required.
Wording	Servier	Yes	No action required.
	Otsuka	No comments	No action required.
	Leukaemia Care	No comments	No action required.
Timing issues	Servier	Agree with timings proposed in communication	No action required.
	Otsuka	No comments	No action required.
	Leukaemia Care	No comments	No action required.

Comment 2: the draft scope

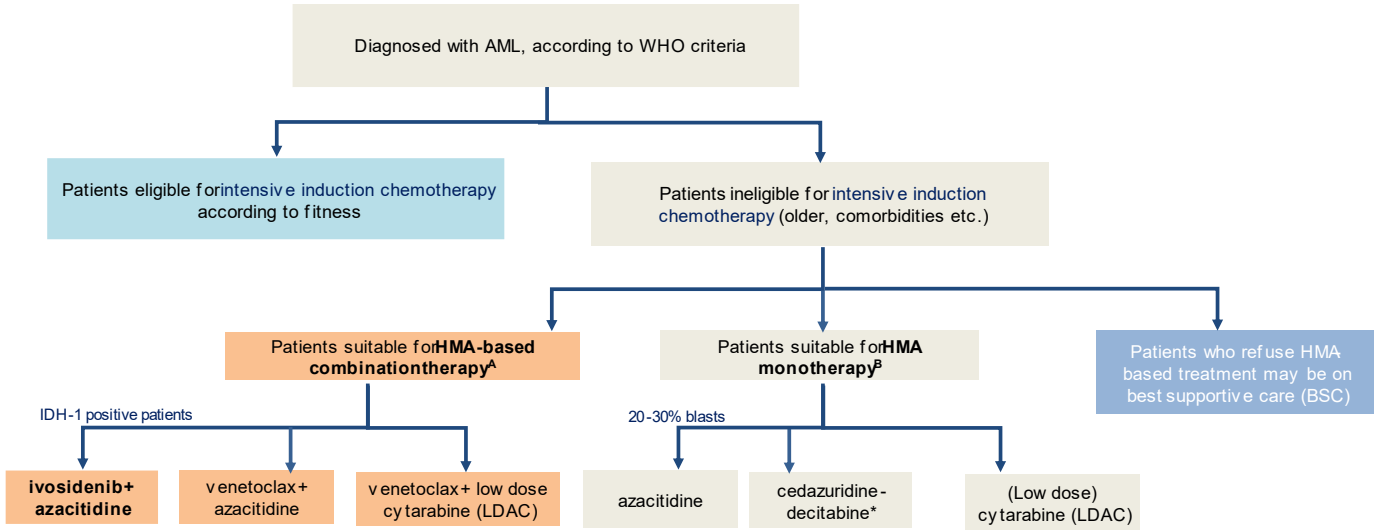
Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Servier	Yes	No action required.
	Otsuka	No comments	No action required.
	Leukaemia Care	No comments	No action required.
Population	Servier	Yes	No action required.
	Otsuka	No comments	No action required.
	Leukaemia Care	No comments	No action required.
Subgroups	Servier	No- appraisal is for the full population	Comment noted. No action required.
	Otsuka	No comments	No action required.
	Leukaemia Care	No comments	No action required.
Comparators	Servier	No, not all. In TA218 (2011) azacitadine was recommended for AML only in those with 20-30% blasts. Therefore low dose cytarabine was used in those with over 30% blasts. However, in TA765 (2022), the committee recommended venetoclax plus azacitidine as an option for untreated acute myeloid leukaemia in adults when intensive chemotherapy is unsuitable. This includes those in the 20% to 30% blast group and the over 30% blast group. Therefore, venetoclax plus azacitadine now supersedes azacitidine as standard of care within the NHS. This is now considered standard of care via clinician feedback and endorsed by ELN 2022 guidelines and BSH 2002 good	Cedazuridine–decitabine removed from the list of comparators in the scope. NICE keeps the comparators list inclusive. In its evidence submission, the company should

Section	Consultee/ Commentator	Comments [sic]	Action
		practice guideline, leaving azacitdine monotherapy as the treatment choice for MDS /AML patients with a blast level below 20% In addition, low dose cytarabine monotherapy is also superseded by venetoclax plus azacitdine for any one with > 30% blasts. As a result of this low dose cytarabine is no longer used in clinical practice. Therefore, Servier believes the following comparators to not be suitable • low dose cytarabine- no longer used in clinical practice • azacitidine alone for adults who are not eligible for HSCT and have AML with 20% to 30% blasts and multilineage dysplasia In addition, the appraisal for cedazuridine–decitabine is listed on the NICE website to begin early June. Under the NICE technology appraisal guidance, it states that a comparator technology is one that is currently used in the NHS. 2 The scope | NICE health technology evaluations: the manual | Guidance | NICE. Therefore, Servier does not believe the below comparator should be included cedazuridine–decitabine (subject to NICE evaluation). Servier believes the population for venetoclax with low dose cytarabine if people have over 30% bone marrow blasts to be very small and therefore questions its suitability as a comparator. According to good practice BSH paper and clinical opinion this combination reserved for very small group of patients who have >30% blast levels and + NPM1 mutation To conclude, Servier believes the only comparator to be venetoclax with azacitadine.	provide a clear rationale for excluding any comparators listed in the final scope.
	Otsuka	It is our understanding based on haemato-oncology clinical guidelines that the sub-population of AML patients who are IDH-1 positive and unsuitable for intensive induction chemotherapy, would be assessed for eligibility for *HMA-based combination therapy* (venetoclax with azacitidine or venetoclax with	Cedazuridine–decitabine removed from the list of

Section	Consultee/ Commentator	Comments [sic]	Action
		low dose cytarabine (LDAC)). *HMA monotherapy* as azacitidine or LDAC would be offered only to patients who are unable to tolerate combination therapy. Furthermore, these combinations have demonstrated superiority versus azacitidine and LDAC alone and are recommended by NICE. Based on the above we believe that **ivosedenib with azacitidine** should be compared to other HMA-based combination therapies and not to HMA monotherapy options. Regarding cedazuridine-decitabine: cedazuridine is a cytidine deaminase inhibitor which allows for the absorption of decitabine (an HMA) when administered orally and has no direct effect on the treatment of AML. On this basis we consider that the fixed-dose single formulation of cedazuridine plus decitabine will be clinically equivalent to *HMA monotherapy* - with the added benefit of an oral route of administration. Therefore, we do not consider it to be a comparator for the HMA-based combination of ivosidenib and azacitidine which has shown superiority versus HMA monotherapy. Instead, we expect cedazuridine-decitabine to be reserved for those IDH1 positive patients who would not be expected to tolerate the combination of ivosidenib and azacitidine but are considered candidates for HMA monotherapy. In order to assist with the above, please see the figure below, *Proposed positioning of HMA-based combination therapy and HMA monotherapy in the AML treatment pathway [NICE draft scope ID6198],* which has also been provided as a MSPowerpoint slide].	comparators in the scope.

Section	Consultee/ Commentator	Comments [sic]	Action

Proposed positioning of *HMA-based combination therapy* and *HMA monotherapy* in the AML treatment pathway [NICE draft scope ID6198].



Notes: A Sub-population of AML patients who are IDH1 positive and unsuitable for intensive induction chemotherapy would be assessed for eligibility for HMA-based combination therapy. B HMA monotherapy as azacitidine or LDAC would be offered only to patients who are unable to tolerate combination therapy. * Subject to NICE evaluation.

Abbreviations: - AML: Acute myeloid leukaemia; HMA: hypomethylating agents (i.e. azacitidine , decitabine, low -dose cytarabine (LDAC)); WHO: World Health Organisation.

Abbreviations:- AML: Acute myeloid leukaemia; HMA : hypomethylating agents (i.e. azacitidine, decitabine, low-dose cytarabine (LDAC))

Section	Consultee/ Commentator	Comments [sic]	Action
	Leukaemia Care	The comparator azacitidine (monotherapy) listed is not normally given as standard in clinical practise anymore, instead many clinicians typically favour venetoclax in combination with azacitidine.	NICE keeps the comparators list inclusive. In its evidence submission, the company should provide a clear rationale for excluding any comparators listed in the final scope.
Outcomes	Servier	Disease free survival is not something that was collected in the relevant study	Comment noted. This outcome is consistent with previous appraisals in this disease area. No action required.
	Otsuka	No comments	No action required.
	Leukaemia Care	No comments	No action required.
Equality	Servier	No equality issues to consider	No action required.
	Otsuka	No comments	No action required.
	Leukaemia Care	No comments	No action required.
	Servier	No comments	No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
Other considerations	Otsuka	No comments	No action required.
	Leukaemia Care	The majority of treatment centres access IDH mutation results through the information that comes from the wider 'Myeloid Next Generation Sequencing (NGS) panel'. The BCSH guidance recommendation is 14 days for this to take place. This means that to initiate treatment including an IDH1 inhibitor, such as ivosidenib with azacitidine, requires a minimum of 2-3 weeks wait before sufficient information is available to indicate that it might be a suitable part of the treatment plan.	Comment noted. No action required.
Questions for consultation	Servier	Servier do not believe best supportive care should be a comparator. Regarding eligibility for HSCT, based on their baseline characteristics (or age and co morbidities) patients who are deemed ineligible to intensive chemotherapy and entering the study / would be treated with Ivo /Aza innately are the same patients not suitable for HSCT based on the same co morbidities and age parameters. IDH1 is routinely tested for in clinical practice, and this is commissioned by NHS England under current practice A mIDH1 prevalence rate of 6% to 10% is assumed in this population (Bullinger L, Döhner K and Döhner H. Genomics of Acute Myeloid Leukemia Diagnosis and Pathways. J Clin Oncol 2017; 35: 934–946) Servier considers that Ivosidenib will fit in to the existing pathway as per the ELN guidelines for newly diagnosed patients with IDH1 mutation (Döhner H. Diagnosis and Management of AML in Adults: 2022 ELN Recommendations from an International Expert Panel. Blood 2022) Servier does not believe ivosidenib with azacitidine to be a candidate for managed access.	Best supportive care has not been included to scope. Stakeholders related to stem cell transplant have been removed from stakeholder list. Other comments noted. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
	Otsuka	No comments	No action required.
	Leukaemia Care	No comments	No action required.
Additional comments on the draft scope	Servier	No comments	No action required.
	Otsuka	Otsuka Pharmaceutical (UK) Ltd would like to thankyou for the opportunity to comment on the draft scope for ivosidenib in combination with azacitadine, for the sub-population of AML patients.	Comment noted. No action required.

The following stakeholders indicated that they had no comments on the draft remit and/or the draft scope

Abbvie

Jazz Pharma