Innovation Observatory

NHS National Institute for Health Research

EVIDENCE BRIEFING
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Ivosidenib for acute myeloid leukaemia with IDH1 mutation

NIHRIO ID	24129	**NICE ID**	10017
Developer/Company	Agios Pharmaceuticals Inc	**UKPS ID**	N/A

Licencing and market availability plans	Ivosidenib is in phase I development

SUMMARY

Ivosidenib is an oral treatment in clinical development for people with acute myeloid leukaemia (AML) with an isocitrate dehydrogenase-1 (IDH1) mutation. AML is a type of cancer that causes the bone marrow to produce excess immature white blood cells. Most patients with AML are treated with standard chemotherapy. AML that is non-responsive to treatment is called refractory while that which returns after response to initial treatment is called relapsed. AML in general, and particularly relapsed or refractory disease, is associated with a poor prognosis. In blood cancers such as AML, certain genetic mutations such IDH1 can occur.

Ivosidenib belongs to a new class of therapies that works by inhibiting the mutated IDH1 enzyme, which in turn reduces the level of d-2-hydroxyglutarate (2-HG), an oncometabolite which impairs myeloid differentiation, increases proliferation of myeloblasts, and blocks cellular differentiation. There are currently no approved treatment options in the EU/UK for those who have relapsed or refractory AML with an IDH1 mutation. If licensed, ivosidenib could be an effective precision medicine for this patient group.

This briefing reflects the evidence available at the time of writing and a limited literature search. It is not intended to be a definitive statement on the safety, efficacy or effectiveness of the health technology covered and should not be used for commercial purposes or commissioning without additional information. A version of the briefing was sent to the company for a factual accuracy check. The company was available to comment.

PROPOSED INDICATION

Ivosidenib monotherapy is intended for the treatment of patients diagnosed with relapsed or refractory acute myeloid leukaemia (AML) harbouring an IDH1 mutation[1]

TECHNOLOGY

DESCRIPTION

Ivosidenib (Tibsovo) is a small molecule inhibitor that targets the mutant isocitrate dehydrogenase-1 (IDH1) enzyme. The most common of such mutations in AML are R132C and R132H substitutions. Ivosidenib was shown to inhibit selected IDH1 R132 mutants at much lower concentrations than wild-type IDH1 in vitro. Inhibition of the mutant IDH1 enzyme by ivosidenib led to decreased 2 HG levels and induced myeloid differentiation in vitro and in vivo in mouse xenograft models of IDH1-mutated AML. In blood samples from patients with AML with mutated IDH1, ivosidenib decreased 2-HG levels ex-vivo, reduced blast counts, and increased percentages of mature myeloid cells.[1]

In the phase I clinical trial (NCT02074839), ivosidenib was administered continuously as an oral dose every day of a 28-day cycle.[2] Prescribing information from the US Food and Drug Administration (FDA) indicates a dosing of 500 mg orally once daily with or without food until disease progression or unacceptable toxicity.[1] The median duration of treatment in patients with relapsed or refractory AML was 3.9 months (range 0.1 to 39.5 months).[1,a]

INNOVATION AND/OR ADVANTAGES

Elevated 2-HG levels are implicated in epigenetic alterations and impaired cellular differentiation, and arise from mutations in the IDH1 enzyme. IDH1 mutations have been described in an array of haematologic malignancies and solid tumours. Ivosidenib is a novel inhibitor of the IDH1 mutant enzyme that exhibits profound 2-HG lowering in tumour models and the ability to effect differentiation of primary patient AML samples ex vivo.[3]

Ivosidenib is a first-in-class, orally available potent inhibitor of mutated IDH1,[4] and if licensed may represent an effective precision medicine for the treatment of relapsed or refractory AML with IDH1 mutations.

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Ivosidenib does not currently have Marketing Authorisation for any indication in the EU.

Ivosidenib is in clinical development for the following indications:

- Glioma[5,6]
- Cholangiocarcinoma[7]
- Intensive chemotherapy ineligible frontline AML (in combination with azacitidine)[8,9]
- Intensive chemotherapy eligible frontline AML (with induction and consolidation therapy)[10]

[a] Company information

PATIENT GROUP

DISEASE BACKGROUND

AML is a group of blood and bone marrow cancers. This disorder is characterized by incomplete maturation of blood cells and reduced production of other normal haematopoietic cells. Haematopoietic stem cells are specialized cells that are formed in the bone marrow, the soft, spongy material found in the centre of long bones. Haematopoietic stem cells develop, or mature, into the three main haematopoietic cells found in blood – red blood cells, white blood cells and platelets.[11]

In AML, a change in the genetic material (DNA) of a myeloblast cell, or blast cell, causes the altered cell to continually reproduce itself. Eventually, these altered cells crowd out normal, healthy cells in the marrow. They also cause damage and scarring in the marrow, further disrupting the production of red cells, white cells, and platelets. These altered blast cells can be released into the bloodstream where they travel to other areas or organs in the body, potentially damaging these organs or interfering with their normal function.[11] Patients die as a consequence of inadequate normal blood cells, infections due to low white blood cells, and fatal bleeding events due to low platelets.

If the disease does not respond to the treatment, this is known as refractory AML and if it returns after response to the initial treatment, it is defined as relapsed AML. Relapsed and refractory AML are associated with a poor prognosis.[12] Without treatment, AML progresses rapidly. AML is the most common acute form of leukaemia in adults.[11] In AML, the majority of patients seek medical attention for symptoms related to anaemia, infection, or bleeding, and require immediate therapeutic intervention.[13] Some of the important risk factors associated with AML are cytogenetics, molecular genetics, the type of AML, performance status and age.[14]

Alterations to genes involved in cellular metabolism and epigenetic regulation are implicated in the pathogenesis of myeloid malignancies. Recurring mutations in IDH genes are detected in approximately 20% of adult patients with AML and 5% of adults with myelodysplastic syndromes (MDS).[15]

CLINICAL NEED AND BURDEN OF DISEASE

In England, in 2016, there were 3,715 registrations of newly diagnosed cases of myeloid leukaemia (ICD-10 code C92).[16] For all types of leukaemias (ICD-10 codes C91-C95), across the UK, the incidence rate is expected to increase from 18.05 per 100,000 European age-standardised rate (EASR) (8,991 cases) in 2014 to 18.92 per 100,000 EASR (13,758 cases) in 2035.[17] AML caused 2,516 deaths in the UK in 2014.[18]

Generally with AML, around 20 out of 100 people (around 20%) will survive their leukaemia for 5 years or more after their diagnosis.[19] Older patients tend to suffer from treatment-related early death and exhibit therapeutic resistance, and therefore are more at risk compared to younger adults.[14] The following 5-year survival statistics have been provided by Cancer Research UK:[19]

- In people aged between 15 and 24, around 60 out of 100 people (around 60%) will survive their leukaemia for 5 years or more after diagnosis.
- In people aged between 25 and 64, almost 40 out of 100 people (almost 40%) will survive their leukaemia for 5 years or more after they are diagnosed.
- In people aged 65 or older, around 5 out of 100 people (around 5%) will survive their leukaemia for 5 years or more after diagnosis.

In 2016/17 there were 47,686 finished consultant episodes (FCEs) and 44,807 hospital admissions with a primary diagnosis of AML (ICD-10 code C92.0), resulting in 118,292 FCE bed days.[20]

A 2015 study in the US estimated that of 4,601 AML patients, 57% were either primary refractory or had a relapse free survival (RFS) of 12 months or less after complete response (CR) achievement.[21] Therefore using the Office of National Statistics estimate above of 3,715 new cases of AML in 2016, approximately 2,117 patients in England have primary refractory or have had a relapse free survival in the past 12 months or less after CR was achieved. As IDH1 mutations occur in approximately 6 to 10% of the patients with AML,[22] using the estimate of 2,117 patients, approximately 130-210 per year could be expected to receive ivosidenib in the UK.[a]

PATIENT TREATMENT PATHWAY

PATIENT PATHWAY

Currently there is no standard treatment for relapsed or refractory AML.[23]

It is generally accepted that enrolling in clinical trials that use novel therapies is best accepted in the relapsed and refractory setting, although treatment efficacy is not well established.[24]

CURRENT TREATMENT OPTIONS

Currently, there are no approved selective mutated IDH1 inhibitor drugs in the EU,[b] and consistent with non-IDH myeloid malignancies, treatment decisions are based on patients' age, performance status, use of prior treatment and other clinico-pathological factors.[25]

PLACE OF TECHNOLOGY

If licensed, ivosidenib will be the first treatment that targets IDH1 mutations in patients who have relapsed or refractory AML.

CLINICAL TRIAL INFORMATION

Trial	NCT02074839, AG120-C-001; Ivosidenib (single experimental arm); phase I
Sponsor	Agios Pharmaceuticals Inc.
Status	Published
Source of Information	Trial registry,[2] publication,[22] company information[a]
Location	France and USA
Design	Open-label, non-randomised, uncontrolled study
Participants	n=258; aged ≥18 years; Eastern Cooperative Oncology Group performance-status score of 0 to 2 (on a scale from 0 to 5, with higher scores indicating greater disability);documented IDH1-mutated hematologic cancer

[b] There are no approved IDH1 inhibitor drugs in the EU

Schedule	Patients receive daily oral ivosidenib at a dose of 500mg in a 28 day cycle
Follow-up	A minimum of 6 months of follow-up
Primary Outcomes	• Safety/tolerability: incidence of adverse events • Maximum tolerated dose and/or the recommended phase II dose of ivosidenib in subjects with advanced hematologic malignancies • Assess clinical activity of ivosidenib in subjects with relapsed or refractory AML who are enrolled in the expansion phase
Secondary Outcomes	• Dose limiting toxicities of ivosidenib in subjects with advanced hematologic malignancies • Pharmacokinetics of ivosidenib in subjects with advanced hematologic malignancies • Pharmacodynamic relationship of ivosidenib and 2-HG • Clinical activity of ivosidenib in advanced hematologic malignancies according to the 2003 revised International Working Group (IWG) criteria for AML or the 2006 modified IWG criteria for MDS or MDS/myeloproliferative neoplasms (MPN)
Key Results	Among patients with relapsed or refractory AML (179 patients), the rate of complete remission or complete remission with partial hematologic recovery was 30.2% (95% confidence interval [CI], 23.5 to 37.5), the rate of complete remission was 21.8% (95% CI, 16.0 to 28.6), and the overall response rate was 39.1% (95% CI, 31.9 to 46.7). The median durations of these responses were 6.5 months (95% CI, 5.5 to 11.1), 9.3 months (95% CI, 5.6 to 12.5), and 6.5 months (95% CI, 4.6 to 9.3), respectively. Acquisition and maintenance of transfusion independence were observed across all response categories, and patients who had a response had fewer infections and febrile neutropenia episodes than those who did not have a response. In the primary efficacy population (125 patients) median overall survival was 8.8 months (95% CI, 6.7 to 10.2) with a median follow-up of 14.8 months. Among 34 patients who had a complete remission or complete remission with partial hematologic recovery, 7 (21%) had no residual detectable IDH1 mutations on digital polymerase-chain-reaction assay. No pre-existing co-occurring single gene mutation predicted clinical response or resistance to treatment.
Adverse effects (AEs)	Among patients with relapsed or refractory AML (179 patients), treatment-related adverse events of grade 3 or higher that occurred in at least 3 patients were prolongation of the QT interval (in 7.8% of the patients), the IDH differentiation syndrome (in 3.9%), anemia (in 2.2%), thrombocytopenia or a decrease in the platelet count (in 3.4%), and leukocytosis (in 1.7%).
Expected reporting date	-

ESTIMATED COST

The cost of ivosidenib is not yet known.

RELEVANT GUIDANCE

NICE GUIDANCE

- None available

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for Cancer: Chemotherapy (Adult). B15/S/a.
- NHS England. 2013/14 NHS Standard Contract for Cancer: Radiotherapy (All Ages). B01/S/a.

OTHER GUIDANCE

- National Comprehensive Cancer Network. Acute Myeloid Leukaemia. 2018[26]

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