National Institute for Health Research

NIHR Innovation Observatory
Evidence Briefing: March 2018

Enasidenib for relapsed or refractory acute myeloid leukaemia (AML) with an isocitrate dehydrogenase 2 (IDH2) mutation

NIHRIO (HSRIC) ID: 11750 NICE ID: 9579

LAY SUMMARY

Acute myeloid leukaemia (AML) is a type of cancer that causes the bone marrow to produce lots of immature white blood cells. It is most common in people aged 60 years and over. Symptoms of AML may include weakness, fatigue, shortness of breath, recurrent infections, prolonged bleeding, loss in appetite and unintended weight loss. 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. Relapsed and refractory AML (rr-AML) are associated with a poor prognosis. Mutations in a gene called isocitrate dehydrogenase 2 (IDH2) is often present in some patients with AML. There are currently no approved targeted therapies specifically for rr-AML with an IDH2 mutation.

Enasidenib is a first-in-class drug specifically being developed for patients with rr-AML with an IDH2 mutation. It is a selective inhibitor of mutant-IDH2 enzymes and acts by blocking the production of chemicals that cause the abnormal (cancerous) white blood cells to grow. Enasidenib is given through the oral route once a day. As there are currently limited treatment options for patients with rr-AML that have an IDH2 mutation, enasidenib, if licensed, has the potential to offer a new treatment option for this area of high unmet medical need.

This briefing presents independent research funded by the National Institute for Health Research (NIHR). The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health.

TARGET GROUP

Acute myeloid leukaemia (IDH2 mutation, relapsed or refractory)

TECHNOLOGY

DESCRIPTION

Enasidenib (AG-221/CC-90007) is an oral, selective small-molecule inhibitor of mutant isocitrate dehydrogenase 2 (IDH2) enzyme.[1] Tumour-associated mutations in the IDH1 and IDH2 genes result in the loss of normal catalytic activity, the production of α-ketoglutarate (α-KG), and gain of a new activity; the production of an oncometabolite, R-2-hydroxylglutarate (R-2-HG). Accumulation of R-2-HG results in tumour growth.[2] Inhibition of the enzyme IDH2, which has been found to be common in acute myeloid leukaemia (AML),[3] leads to decreased levels of 2-hydroxyglutarate (2-HG) and promotion of proper differentiation and clonal proliferation of cells of the myeloid lineage.[1]

In the phase I/II study of patients with advanced haematologic malignancies with an IDH2 Mutation **(**NCT01915498)[4], patients were treated with enasidenib 100 mg daily[a] based on a 28 day cycle over a time frame of 26 weeks.

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

Besides AML, enasidenib is in phase II trials for myelodysplastic syndrome.

INNOVATION and/or ADVANTAGES

Recurrent somatic mutations in the genes encoding for IDH1 and IDH2 are frequently identified in patients with AML.[5] There is an unmet need for new therapies for patients with relapsed or refractory acute myeloid leukaemia (rr-AML). Enasidenib is a first-in-class selective inhibitor of mutant-IDH2 enzymes.[1] If licensed, it has the potential to offer a new treatment option for patients with rr-AML that have an IDH2 mutation.

DEVELOPER

Celgene Ltd

REGULATORY INFORMATION/ MARKETING PLANS

Enasidenib has been given the following designations for relapsed and refractory AML in the USA:[6]

- Orphan designation since June 2014
- Fast track designation since August 2014
- Priority review since March 2017

It was given orphan drug designation in the UK for AML in May 2016.[7]

[a] Information provided by company

PATIENT GROUP

BACKGROUND

Acute myeloid leukaemia (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 stem 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 blood cells – red blood cells, white blood cells and platelets.[8]

In AML, a change in the genetic material (DNA) of a single immature cell, called a blast cell or a myeloblast 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.[8]

If the disease does not respond to the treatment, it is called refractory AML and if it returns after response to the initial treatment, it is called relapsed AML. Relapsed and refractory AML (rr-AML) are associated with a poor prognosis.[9] Without treatment, AML progresses rapidly (acute disease). AML is the most common acute form of leukaemia in adults.[8]

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).[10] Mutation in IDH2 specifically occur in many cancers, including approximately 12% of AML.[11]

Symptoms of AML include weakness, fatigue, shortness of breath (dyspnoea), recurrent infections (which can cause fever, body aches, and night sweats), and prolonged bleeding. Affected individuals may appear pale and they may bruise easily (including with minor injury or without a reason). There may be a loss in appetite and unintended weight loss. Inflammation of tissue in the mouth can cause pain, swollen/bleeding gums and sores.[8]

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).[12] 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.[13] AML caused 2,516 deaths in the UK in 2014.[14]

There are no UK wide statistics available for AML survival. Generally with AML, around 20 out of 100 people (around 20%) will survive their leukaemia for 5 years or more after their diagnosis.[15] Younger people tend to do much better than older people. The following 5-year survival statistics have been provided by Cancer Research UK:

- 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), 44,807 hospital admissions with a primary diagnosis of AML (ICD-10 code C92.0), resulting in 118,292 FCE bed days.[16]

Approximately 20% of adult patients with AML have the IDH gene mutation,[12] while almost 12% of AML patients specifically have the IDH2 mutation.[12]

The population with rr-AML with the IDH2 mutation in the UK, likely to be eligible to receive enasidenib, could not be estimated from available published sources.

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal in development. Leukaemia (acute myeloid, relapsed, refractory) - vosaroxin (GID-TA10070). Expected date of issue to be confirmed.

NHS ENGLAND and POLICY 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

- Alberta Health Services. Clinical Practice Guidelines, Acute Myeloid Leukaemia. 2017.[17]
- Clinical Guidelines for Leukaemia and other Myeloid Disorders – AML. 2016.[18]
- Guidelines on the management of acute myeloid leukaemia in adults. British Society for Haematology. 2006.[19]

CURRENT TREATMENT OPTIONS

Conventional treatment for AML has two phases - induction and consolidation.[20]

- Induction: the aim of induction is to achieve complete remission (CR). The standard induction chemotherapy regimen is the combination of an anthracycline, usually daunorubicin, given for 3 days with continuous infusion of cytarabine for 7 days (3+7).[20]
- Consolidation: consolidation is designed to eliminate residual leukaemia cells that persist after induction. After achievement of CR, all patients will eventually relapse without further treatment, and therefore consolidation treatment is essential provided that patients have adequate organ function.[20]

CR rates of patients given 3+7 are about 70% in patients younger than 60. However, more than half of patients with AML are older than 65 years and about a third are older than 75 years. Generally, older

patients with AML have a very poor outcome—conventional induction treatment results in CR rates of 45–55%, and less than 10% of intensively treated patients survive for 5 years.[20]

According to the guidelines from the British Society for Haematology[19], all eligible patients up to the age of 60 years (or > 60 years able to receive intensive chemotherapy) with de novo or secondary AML should be asked to participate in a clinical trial. Patients not suitable for intensive chemotherapy who are not entered into clinical trials should be offered treatment with low-dose cytarabine.[17] Elderly patients with acute myeloid leukaemia (AML) who are refractory to or relapse following frontline treatment constitute a poor-risk group with a poor long-term outcome.[21] Currently, there are no approved selective mutated IDH inhibitor drugs, 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.[22]

EFFICACY and SAFETY	
Trial	NCT01915498, AG-221-C-001; 18 years and older, relapsed or refractory AML, IDH2 gene mutation; phase I/II
Sponsor	Celgene Ltd
Status	Ongoing
Source of Information	Trial registry[4]
Location	EU (incl UK), USA, Canada and other countries.
Design	Single group assignment, open-label
Participants	n=239 recruited (113 in the dose-escalation phase and 126 in the 4-arm expansion phase); patients aged ≥ 18yrs; mutant-IDH2 advanced myeloid malignancies; relapsed/refractory AML efficacy cohort comprised 176 patients present across both dose-escalation and expansion phases).[d]
Schedule	100 mg enasidenib[b] given orally (PO) once a day (QD) for 28 days over 26 weeks.
Follow-up	Active treatment for 26 weeks, follow-up period not specified.
Primary Outcomes	• Adverse Events (AEs) [Time Frame: Up to 26 weeks] • Maximum Tolerated Dose [Time Frame: Up to 26 weeks] • Clinical Activity of AG-221 for subjects with relapsed or refractory acute myelogenous leukemia (AML) with Isocitrate dehydrogenase protein 2 (IDH2) mutation [Time Frame: Up to 26 weeks]
Secondary Outcomes	• Dose Limiting Toxicities [Time Frame: Up to 26 weeks] • Pharmacokinetic Cmax [Time Frame: Up to 26 weeks] • Pharmacokinetic Tmax [Time Frame: Up to 26 weeks] • Clinical Activity pf AG-221 in subjects with hematologic malignancies [Time Frame: Up to 26 weeks] • Pharmacokinetic AUC [Time Frame: Up to 26 weeks] • Pharmacokinetic Elimination half-life [Time Frame: Up to 26 weeks] • Pharmacodynamics Analyses Plasma [Time Frame: Up to 26 weeks] • Pharmacodynamics Analyses Urine [Time Frame: Up to 26 weeks] • Pharmacodynamics Analyses Bone Marrow (2-HG) [Time Frame: Up to 26 weeks]

[b] Information provided by company

	• Clinical Activity of AG-221 in subjects with Relapse/Refractory AML with an IDH2 mutation [Time Frame: up to 26 weeks]
Key Results	In the dose-escalation phase, an MTD was not reached at doses ranging from 50 to 650 mg per day. Enasidenib 100 mg once daily was selected for the expansion phase on the basis of pharmacokinetic and pharmacodynamic profiles and demonstrated efficacy. Among patients with relapsed or refractory AML, overall response rate was 40.3%, with a median response duration of 5.8 months. Thirty-four patients (19.3%) with relapsed/refractory AML attained complete remission. At a median follow-up of 7.7 months (range, 0.4-26.7 months), median overall survival among patients with relapsed/ refractory AML was 9.3 months (95% CI, 8.2-10.9 months) and estimated 1-year survival was 39%.[1]
Adverse effects (AEs)	Grade 3 to 4 enasidenib-related adverse events included indirect hyperbilirubinemia (12%) and IDH-inhibitor–associated differentiation syndrome (7%).[1]
Expected reporting date	Primary completion date reported as May 2019[c]

ESTIMATED COST and IMPACT

COST

The cost of enasidenib is not yet known.

IMPACT – SPECULATIVE

IMPACT ON PATIENTS AND CARERS

☒ Reduced mortality/increased length of survival

☒ Reduced symptoms or disability

☐ Other:

☐ No impact identified

IMPACT ON HEALTH and SOCIAL CARE SERVICES

☐ Increased use of existing services

☐ Decreased use of existing services

☐ Re-organisation of existing services

☐ Need for new services

☐ Other:

☒ None identified

[c] Information provided by company

IMPACT ON COSTS and OTHER RESOURCE USE

☐ Increased drug treatment costs

☐ Reduced drug treatment costs

☒ Other increase in costs: Test to identify patients with IDH2 mutation

☐ Other reduction in costs:

☐ Other:

☐ None identified

OTHER ISSUES

☐ Clinical uncertainty or other research question identified:

☒ None identified

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