

**NIHR Innovation Observatory
Evidence Briefing: May 2018**

Gilteritinib for relapsed or refractory acute myeloid leukaemia (AML) with an FLT3 mutation – second line

NIHRIO (HSRIC) ID: 11486

NICE ID: 8749

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 FMS-like tyrosine kinase (FLT3) is the most often present mutation in patients with AML. There are currently no approved targeted therapies specifically for RR-AML with an FLT3 mutation. AML typically develops rapidly and is fatal unless treated.

Gilteritinib is a drug being developed for patients with RR-AML with FLT3 mutation. It is an inhibitor of mutant-FLT3 enzymes and acts by blocking the production of chemicals that cause the abnormal (cancerous) white blood cells to grow. Gilteritinib is given through the oral route once a day. As there are currently limited treatment options for patients with RR-AML that have a FLT3 mutation, gilteritinib, if licensed, has the potential to offer a new treatment option for this group of patients.

This briefing reflects the evidence available at the time of writing. A version of the briefing was sent to the company for a factual accuracy check. The company was available to provide comment. 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.

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 (FLT3 mutation, relapsed or refractory) – Second line

TECHNOLOGY

DESCRIPTION

Gilteritinib (ASP2215) is a small-molecule FLT3 inhibitor with a structure based on a pyrazine carboxamide scaffold.¹ Mutations in the Receptor Tyrosine Kinase (RTK) FMS-like tyrosine kinase-3 (FLT3) lead to constitutive phosphorylation of FLT3 and activation of its downstream signalling cascades, resulting ultimately in aberrant proliferation and survival of myeloid progenitor and precursor cells and a premature block in myeloid differentiation. Inhibition of FLT3 therefore leads to blockade of the aberrant proliferation of the myeloid cells.²

In the phase III trial, NCT02421939, gilteritinib was administered once daily over continuous 28-day cycles to patients with relapsed or refractory acute myeloid leukaemia (RR-AML) with FLT3 mutation.³

Gilteritinib does not currently have Marketing Authorisation in the EU for any indication.⁴

Besides RR-AML, gilteritinib is in phase III trials for post-chemotherapy maintenance AML and post-hematopoietic stem cell transplantation (HSCT) AML. It is also in a phase II/III for newly diagnosed AML with FLT3 mutation patients in combination with low intensity induction of chemotherapy.⁵

INNOVATION and/or ADVANTAGES

FLT3 is one of the most frequently mutated genes in acute myeloid leukaemia.⁶ By blocking FLT3, gilteritinib is expected to stop cell growth and lead to cell death, and thus slow down the development of the disease.⁷ If licensed, gilteritinib will offer an additional second line treatment option for patients with RR-AML with an FLT3 mutation.

DEVELOPER

Astellas Pharma, Inc.

REGULATORY INFORMATION/ MARKETING PLANS

Gilteritinib has the following drug designations by the FDA:

- Orphan drug designation for AML since July 2017.⁸
- Fast Track Designation for RR-AML. Since October 2017⁹

It was given orphan drug designation by the EMA for AML in January 2018.⁷

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.¹⁰

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.¹⁰

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 or refractory AML (RR-AML) are associated with a poor prognosis.¹¹ Without treatment, AML progresses rapidly (acute disease). AML is the most common acute form of leukaemia in adults.¹⁰

FLT3 is one of the most frequently mutated genes in acute myeloid leukaemia, with mutations occurring in up to 30% of patients.⁶ FLT3 receptors are normally expressed on the surface of hematopoietic progenitor cells¹ and FLT3 gene located on chromosome 13q12.¹² A FLT3-internal tandem duplication (ITD) mutation, found in approximately a quarter of patients with de novo AML, imparts a particularly poor prognosis. Rates of relapse are particularly high for these patients.¹³

Symptoms of AML include weakness, fatigue, shortness of breath (dyspnoea), recurrent infections (which may 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.¹⁰

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).¹⁴ For all types of leukaemia (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 2035.¹⁵ AML caused 2,601 deaths in the UK in 2016.¹⁶

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.¹⁷ 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.¹⁸

Approximately 30% of adult patients with AML have the FLT3 mutation.⁶

The population with RR-AML with the FLT3 mutation in the UK, likely to be eligible to receive gilteritinib, 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

- Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. 2017
- Clinical Guidelines for Leukaemia and other Myeloid Disorders – AML. 2016.¹⁹
- London Cancer. Acute Myeloid Leukaemia Guidelines. 2015.²⁰
- Guidelines on the management of acute myeloid leukaemia in adults. British Society for Haematology. 2006.²¹

CURRENT TREATMENT OPTIONS

Conventional treatment for AML has two phases - induction and consolidation.²²

- 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).²²
- 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.²²

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 5 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.²²

Currently, there are no approved selective mutated FLT3 inhibitor drugs for patients with RR-AML. According to the guidelines from the British Society for Haematology,²¹ 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.²³ Elderly patients with AML who are refractory to or relapse following frontline treatment constitute a poor-risk group with a poor long-term outcome.²⁴

EFFICACY and SAFETY	
Trial	NCT02421939 , 2215-CL-0301; 18 years and older; gilteritinib vs salvage chemotherapy; phase III
Sponsor	Astellas Pharma Global Development, Inc.
Status	Ongoing
Source of Information	Trial registry ³
Location	EU (incl UK), USA, Canada, Japan, Republic of Korea, Taiwan and Israel
Design	Randomised, open label, parallel assignment
Participants	n=371; aged 18 years and older; acute myeloid leukaemia; FLT3 mutation; refractory to or relapsed
Schedule	Gilteritinib was administered as an oral tablet over continuous 28-day cycles.
Follow-up	Active treatment will continue until patients meet any of the protocol discontinuation criteria (mostly intolerance or disease progression) and follow-up will be done every 3 months up to 3 years
Primary Outcomes	<ul style="list-style-type: none"> • Overall Survival (OS) [Time Frame: up to 30 months] • Complete Remission and Complete Remission with partial haematological recovery (CR/CRh) rate [Time Frame: up to 23 months]
Secondary Outcomes	<ul style="list-style-type: none"> • Event-free survival [Time Frame: up to 49 months] • Complete remission rate [Time Frame: up to 36 months] • Leukaemia-free survival [Time Frame: up to 49 months] • Duration of remission [Time Frame: up to 36 months] • Composite complete remission rate [Time Frame: up to 36 months] • Transplantation rate [Time Frame: up to 49 months] • Brief Fatigue Inventory [Time Frame: up to 36 months]. • Complete remission with partial haematological recovery (CRh) rate [Time Frame: up to 36 months] • Transfusion conversion rate [Time Frame: up to 36 months] • Transfusion maintenance rate [Time Frame: up to 36 months]
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Estimated primary completion date reported as October 2018

ESTIMATED COST and IMPACT

COST

The cost of gilteritinib is not yet known.

IMPACT – SPECULATIVE

IMPACT ON PATIENTS AND CARERS

- | | |
|--|--|
| <input checked="" type="checkbox"/> Reduced mortality/increased length of survival | <input checked="" type="checkbox"/> Reduced symptoms or disability |
| <input type="checkbox"/> Other: | <input type="checkbox"/> No impact identified |

IMPACT ON HEALTH and SOCIAL CARE SERVICES

- | | |
|---|---|
| <input type="checkbox"/> Increased use of existing services | <input type="checkbox"/> Decreased use of existing services |
| <input type="checkbox"/> Re-organisation of existing services | <input type="checkbox"/> Need for new services |
| <input checked="" type="checkbox"/> Other: | <input type="checkbox"/> None identified |

IMPACT ON COSTS and OTHER RESOURCE USE

- | | |
|---|---|
| <input type="checkbox"/> Increased drug treatment costs | <input type="checkbox"/> Reduced drug treatment costs |
| <input type="checkbox"/> Other increase in costs: | <input type="checkbox"/> Other reduction in costs: |
| <input type="checkbox"/> Other: | <input checked="" type="checkbox"/> None identified |

OTHER ISSUES

- | | |
|--|---|
| <input type="checkbox"/> Clinical uncertainty or other research question identified: | <input checked="" type="checkbox"/> None identified |
|--|---|

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