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Health Technology Briefing
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Quizartinib with chemotherapy for FLT3-ITD positive acute myeloid leukaemia

Company/Developer	Daiichi Sankyo Ltd.

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID: 23829	NICE ID: 10156	UKPS ID: 662145

Licensing and Market Availability Plans

Currently in phase III development.

Summary

Quizartinib is in development for the treatment of newly diagnosed, fms-like tyrosine kinase 3 internal tandem duplication (FLT3-ITD) positive acute myeloid leukaemia (AML), an aggressive, type of cancer that starts in the blood-forming cells of the bone marrow, and often quickly moves into the blood as well. AML typically develops rapidly and is fatal unless treated. Mutations in the gene FLT3 are the most often present mutations in patients with AML and the FLT3-ITD subtype has poor prognosis and risk.

Quizartinib is a medicinal product administered as an oral tablet and works by blocking a called receptor tyrosine kinase of the FLT3 type. By blocking this receptor, the medicine is expected to control the division of the cancerous cells and slow down the development of the disease. If licensed, quizartinib may be able to offer a treatment option for patients with newly diagnosed FLT3-ITD positive AML.

Proposed Indication

Treatment of newly diagnosed, fms-like tyrosine kinase-3-internal tandem duplication positive acute myeloid leukaemia (AML)[1]

Technology

Description

Quizartinib (AC220) is an investigational, oral small molecule that potently and selectively inhibits FLT-3-ITD, which is a growth driver of abnormal cells that contribute to the development of AML. Quizartinib binds to FLT3 tyrosine kinase receptor isoform, leading to the inhibition of cancer cell proliferation and causes cancer cell death.[2]

In the induction stage of phase III clinical trial (NCT02668653), participants receive up to 2 cycles with cytarabine and daunorubicin/idarubicin, followed by the quizartinib. In the consolidation stage of this trial, participants will receive up to 4 cycles of cytarabine followed by quizartinib and/or haematopoeitic stem cell transplant. Following this in the continuation stage, participants will receive up to 36 cycles with quizartinib.[1]

Key Innovation

Quizartinib is the first tyrosine kinase inhibitor designed as a selective FLT3 inhibitor with better pharmacokinetic characteristics, high specificity, more efficacy, better tolerance and other characteristics. It thus presents advantages as a very promising agent in the treatment of AML, especially in patients with FLT3-ITD mutations.[2]

Regulatory & Development Status

Quizartinib does not currently have Marketing Authorisation in the EU or UK for any indication.

Quizartinib has received an orphan drug designation in the EU in March 2009 for AML.[3]

Quizartinib is in phase III/II development for the following indications:[4]

- Myelodysplastic syndrome
- Relapsed/refractory AML

Patient Group

Disease Area and Clinical Need

AML is a cancer of the blood and bone marrow. It is the most common type of acute leukaemia in adults. It is also known as acute myelogenous leukaemia or acute nonlymphocytic leukaemia.[5] Mutations of the FLT3-ITD represents the most common type of FLT-3 mutation, approximately 25% of all AML cases.[6] Patients with FLT3-ITD mutations tend to have a particularly unfavourable prognosis with an increased risk of relapse and shorter overall survival compared with patients without the mutation.[6]
In addition to being a rapidly progressing disease, AML appears to be quite symptomatic, with the key signs/symptoms reported as dizziness, fatigue, fever and weakness in the literature.[7]

In 2017, 2534 cases of AML were newly diagnosed in the UK.[8] Using the figures above, we can estimate that around 634 FLT3-ITD positive cases will be newly diagnosed in the UK each year.

Recommended Treatment Options

NICE Pathway recommends the following treatment options for untreated AML patients:[9]

- Liposomal cytarabine-daunorubicin for untreated acute myeloid leukaemia
- Gemtuzumab ozogamicin for untreated acute myeloid leukaemia
- Midostaurin for adults with newly diagnosed acute FLT-3 mutation positive myeloid leukaemia with standard daunorubicin and cytarabine as induction therapy, with high-dose cytarabine as consolidation therapy and alone after complete response as maintenance therapy.

Clinical Trial Information

Trial	**QuANTUM-First,** NCT02668653, 2015-004856-24; A Phase III, Double-Blind, Placebo-controlled Study of Quizartinib Administered in Combination With Induction and Consolidation of Chemotherapy, and Administered as Continuation Therapy in Subjects 18 to 75 Years Old With Newly-Diagnosed FLT3-ITD (+) Acute Myeloid Leukemia (QuANTUM First) **Phase III** – Active not recruiting **Locations –** EU (including the UK), Canada, Unites States and other countries **Primary completion date:** April 2022
Trial Design	Randomised, double blind, placebo controlled, interventional study
Population	N=539; Adult patients with newly diagnosed, morphology documented primary AML or AML secondary to myelodysplastic syndrome or a myeloproliferative neoplasm
Intervention(s)	Quizartinib plus cytarabine and daunorubicin/idarubicin. In the induction phase participants will receive up to 2 cycles with cytarabine and daunorubicin/idarubicin, followed by the experimental product quizartinib. In the consolidation phase, they will receive up to 4 cycles of cytarabine followed by quizartinib and/or haematopoeitic stem cell transplant. In the continuation phase, participants will receive up to 36 cycles with quizartinib.
Comparator(s)	Chemotherapy plus placebo. In the induction phase, participants will receive up to 2 cycles with cytarabine and daunorubicin/idarubicin, followed by placebo. In the consolidation phase, participants will receive up to 4 cycles of cytarabine followed by placebo and/or hematopoietic stem cell transplant and in the continuation phase they will receive up to 36 cycles with placebo.

Outcome(s)	Primary outcome: Overall survival [Time frame: Approximately 3 years after study enrolment]. See trial record for full list of other outcomes.
Results (efficacy)	-
Results (safety)	-

Estimated Cost

The cost of quizartinib is not yet known.

Relevant Guidance

NICE Guidance

- NICE technology appraisal. Midostaurin for untreated acute myeloid leukaemia (TA523). June 2018.
- NICE clinical guideline. Haematological cancers: improving outcomes (NG47). May 2016.

NHS England (Policy/Commissioning) Guidance

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

Other Guidance

- European Society of Medical Oncology Guidelines Committee. Acute myeloid leukaemia in adult patients: ESMO clinical practice guidelines for diagnosis, treatment and follow up. 2020.[10]
- Thomas-Dewing R; Tholouli E; Dennis M. Greater Manchester Cancer Haematology Oncology Pathway: Guidelines for the management of acute myeloid leukaemia. 2019.[11]
- Tallman MS; Wang ES; Altman JK; Appelbaum FR; Bhatt VR; Bixby D et al. Acute myeloid leukemia. NCCN Clinical Practice Guidelines in Oncology. 2019.[12]

Additional Information

References

NB: 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.

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