NIHR | Innovation Observatory

Newcastle University

Health Technology Briefing
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Ivosidenib with azacitidine for previously untreated acute myeloid leukaemia with an IDH1 mutation

Company/Developer	Servier Laboratories Ltd

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID: 12720	NICE ID: 11804	UKPS ID: 665025

Licensing and Market Availability Plans

Currently in phase III clinical trials

Summary

Ivosidenib is in development with azacitidine for the treatment of patients with newly diagnosed acute myeloid leukaemia (AML) who have an isocitrate dehydrogenase 1 (IDH1) mutation and are ineligible for intensive induction chemotherapy. AML is a rare form of blood cancer that affects the white blood cells resulting in frequent infections for patients. AML also affects red blood cells resulting in other symptoms such as bleeding and breathlessness. AML is an acute cancer which means it progresses quickly and aggressively, needing immediate treatment. IDH1 mutations make the cells act in an abnormal way and multiply in an uncontrolled accelerated rate. There are currently no recommended targeted therapies for IDH1 mutations and prognosis is poor in this population of patients.

Ivosidenib is anIDH1 inhibitor drug intended to reduce formation of cancer cells and is delivered orally, in combination with azacitidine which is delivered via subcutaneous or intravenous injection. If licensed, ivosidenib will offer the first targeted therapy available to untreated AML patients with an IDH1 mutation who are ineligible for intensive induction chemotherapy.

Proposed Indication

Treatment of patients with previously untreated acute myeloid leukaemia with an IDH1 mutation.[1]

Technology

Description

Ivosidenib (Tibsovo) is a small-molecule inhibitor of IDH1 enzyme that targets gene mutations at position R132. This inhibition lowers 2-hydroxyglutarate levels, inducing myeloid differentiation that reduces blast counts and increases the percentage of mature myeloid cells in the blood.[2,3]

Ivosidenib is in development for previously untreated patients with AML who have an IDH1 mutation and are ineligible for intensive induction chemotherapy. In the phase III trial (NCT03173248), ivosidenib is administered orally, in 28 day cycles (500mg/day), in combination with azacitidine which is administered subcutaneously (SC) or intravenously (IV) once daily for the first week of each cycle.[1]

Key Innovation

Mutant IDH1 catalyses the production of D-2-hydroxyglutarate, leading to disruption in cellular metabolism and epigenetic regulation and contributing to oncogenesis. One strategy to improve outcomes is to use new agents that target molecular lesions involved in leukemogenesis. Ivosidenib — a first-in-class, oral, potent, targeted small-molecule inhibitor of mutant IDH1 has shown encouraging clinical activity with ivosidenib and azacitidine combination therapy in a phase 1b trial involving patients with newly diagnosed IDH1-mutated acute myeloid leukaemia.[4] Survival rates for AML patients ineligible for intensive chemotherapy are low and IDH1 mutations are associated with worse prognosis overall.[4] If licensed, ivosidenib will offer the first mutation targeted treatment for previously untreated patients with IDH1 mutated AML.[5]

Regulatory & Development Status

Ivosidenib does not currently have marketing authorisation in the EU/UK for any indication.

Ivosidenib has the following regulatory designations/ awards:

- An orphan drug designation in the EU in 2016 for the treatment of AML.[3]
- Breakthrough Therapy designation (in combination with azacitidine) by the US FDA in 2019 for the first-line treatment of AML patients with IDH1 mutations.[6]

Ivosidenib is currently in phase II and III clinical development for the treatment of:[7]

- Cholangiocarcinoma
- Chondrosarcoma
- Glioma
- Solid tumours

Patient Group

Disease Area and Clinical Need

Leukaemia is a cancer of the white blood cells with AML specifically affecting the patients myeloid cells which are important in fighting infections and controlling tissue damage.[8] Mutations in genes involved in haematopoiesis results in a clonal expansion of undifferentiated myeloid precursors (blasts) in the peripheral blood and bone marrow resulting in ineffective erythropoiesis and bone marrow failure.[9] Symptoms of AML usually develop rapidly, becoming worse over time and can include frequent infections, fatigue, weakness, breathlessness, and unusual/ frequent bruising or bleeding.[8] Risk factors of developing AML include age with most cases seen in those aged 85-89, smoking, obesity, exposure to radiation or benzene, genetic conditions such as Fanconi anaemia or Down's syndrome, previous treatment with chemotherapy drugs, and autoimmune conditions such as rheumatoid arthritis.[10] IDH1 mutations can be detected in 6-10% of AML patients and the presence of the mutation has been associated with worst overall survival rates.[11,12] Over half of patients with AML are ineligible for intensive chemotherapy and stem cell transplants due to factors such as age or comorbidities.[13]

In England (2017), there were 4,102 patients diagnosed with AML and 2,497 deaths registered where AML was the underlying cause.[14] AML accounts for less than 1% of all new cancer cases in the UK each year, but 2% of cancer deaths (2016-18).[15] The one-year survival rate for patients diagnosed with leukaemia in England between 2013 and 2017 was 72.4%, dropping to 53.5% over five years.[16,17] The age standardised incidence rate of AML in England is 6.2 and 4.1 per 100,000 amongst males and females respectively.[18] In England (2020-21), there were 49,708 finished consultant episodes (FCEs) and 47,027 admissions for AML (ICD-10 code C92.0), which resulted in 37,597 day cases and 100,038 FCE bed days.[19]

Recommended Treatment Options

The main treatment for AML is chemotherapy, with other treatments including targeted cancer drugs, growth factors, antibiotics, radiotherapy, or leukapheresis. Supportive treatments are often given with main treatment options to manage symptoms and include painkillers, anti-sickness medications, and blood or platelet transfusions.[20]

NICE recommends the following treatment options for adults with untreated AML when intensive chemotherapy is unsuitable

- Venetoclax with azacitidine
- Venetoclax with low dose cytarabine
- Enetoclax with low dose only if they have over 30% bone marrow blasts

There are no NICE recommended treatments specific for patients with untreated AML and IDH1 mutations.

Clinical Trial Information

Trial	**AGILE; NCT03173248, 2016-004907-30;** A Phase 3, Multicenter, Double-Blind, Randomized, Placebo-Controlled Study of AG-120 in Combination With Azacitidine in Subjects ≥ 18 Years of Age With Previously Untreated Acute Myeloid Leukaemia With an IDH1 Mutation **Phase III –** Active, not recruiting **Location(s):** 8 EU countries, UK, USA, and other countries **Primary completion date:** June 2024
Trial Design	Randomised, parallel assignment, triple-masked, placebo-controlled

Population	N= 146[a] patients with previously untreated AML with an IDH1 mutation; ineligible for intensive induction chemotherapy; aged 18 years and older
Intervention(s)	500mg ivosidenib (oral, once daily in 28 day cycles), azacitidine (75mg/m^2/day, subcutaneously or intravenously for the first week of each cycle)
Comparator(s)	Placebo (oral, once daily in 28 day cycles), azacitidine (75mg/m^2/day, subcutaneously or intravenously for the first week of each cycle)
Outcome(s)	Primary outcome measure: Event-free-survival (EFS) [Time frame: up to approximately 52 months] See trial record for full list of other outcomes.
Results (efficacy)	At a median follow-up of 12.4 months, event-free survival was significantly longer in the ivosidenib-and-azacitidine group than in the placebo-and-azacitidine group (hazard ratio for treatment failure, relapse from remission, or death, 0.33; 95% confidence interval [CI], 0.16 to 0.69; P=0.002). The estimated probability that a patient would remain event-free at 12 months was 37% in the ivosidenib-and-azacitidine group and 12% in the placebo-and-azacitidine group. The median overall survival was 24.0 months with ivosidenib and azacitidine and 7.9 months with placebo and azacitidine (hazard ratio for death, 0.44; 95% CI, 0.27 to 0.73; P=0.001).[4]
Results (safety)	Common adverse events of grade 3 or higher included febrile neutropenia (28% with ivosidenib and azacitidine and 34% with placebo and azacitidine) and neutropenia (27% and 16%, respectively); the incidence of bleeding events of any grade was 41% and 29%, respectively. The incidence of infection of any grade was 28% with ivosidenib and azacitidine and 49% with placebo and azacitidine. Differentiation syndrome of any grade occurred in 14% of the patients receiving ivosidenib and azacitidine and 8% of those receiving placebo and azacitidine.[4]

Estimated Cost

The cost of ivosidenib is not yet known.

Relevant Guidance

NICE Guidance

- NICE technology appraisal. Venetoclax with low dose cytarabine for untreated acute myeloid leukaemia when intensive chemotherapy is unsuitable (TA787). April 2022.
- NICE technology appraisal. Venetoclax with azacitidine for untreated acute myeloid leukaemia when intensive chemotherapy is unsuitable (TA765). February 2022.
- NICE clinical guideline. Haematological cancers: improving outcomes (NG47). May 2016.
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NHS England (Policy/Commissioning) Guidance

[a] Information provided by Servier Laboartories Inc.

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

Other Guidance

- European Society of Medical Oncology. Clinical practice guidelines- Acute myeloid leukaemia in adult patients. 2020.[21]
- West London Cancer Alliance (NHS). Pan-London haemato-oncology clinical guidelines. 2020.[22]
- West Midlands Cancer Alliance (NHS). West midlands guidelines for the treatment of adult acute myeloid leukaemia. 2020.[23]

Additional Information

References

1 ClinicalTrials.gov. *Study of AG-120 (Ivosidenib) vs. Placebo in Combination With Azacitidine in Patients With Previously Untreated Acute Myeloid Leukemia With an IDH1 Mutation (AGILE). Trial ID: NCT03173248*. 2017. Status: Active, not recruiting. Available from: https://clinicaltrials.gov/ct2/show/NCT03173248 [Accessed August 9th, 2022].

2 Merchant SL, Culos K, Wyatt H. Ivosidenib: IDH1 Inhibitor for the Treatment of Acute Myeloid Leukemia. *J Adv Pract Oncol*. 2019 Jul;10(5):494-500. Available from: https://doi.org/10.6004/jadpro.2019.10.5.7.

3 European Medicines Agency (EMA). *Public summary of opinion on orphan designation: ivosidenib for the treatment of acute myeloid leukaemia.* 2017. Available from: https://www.ema.europa.eu/en/documents/orphan-designation/eu/3/16/1802-public-summary-opinion-orphan-designation-ivosidenib-treatment-acute-myeloid-leukaemia_en.pdf [Accessed August 8th, 2022].

4 Montesinos P, Recher C, Vives S, Zarzycka E, Wang J, Bertani G, et al. Ivosidenib and Azacitidine in IDH1-Mutated Acute Myeloid Leukemia. *N Engl J Med*. 2022 Apr 21;386(16):1519-31. Available from: https://doi.org/10.1056/NEJMoa2117344.

5 National Institute for Health and Care Excellence (NICE). *36 results for acute myeloid leukaemia.* 2022. Available from: https://www.nice.org.uk/search?pa=1&ps=15&q=acute+myeloid+leukaemia&s=Date [Accessed August 9th, 2022].

6 Agios. *Agios Receives FDA Breakthrough Therapy Designation for TIBSOVO® (ivosidenib) in Combination with Azacitidine for the Treatment of Newly Diagnosed Acute Myeloid Leukemia (AML) with an IDH1 Mutation in Adult Patients Ineligible for Intensive Chemotherapy.* 2019. Available from: https://investor.agios.com/news-releases/news-release-details/agios-receives-fda-breakthrough-therapy-designation-tibsovor [Accessed August 8th, 2022].

7 ClinicalTrials.gov. *7 Studies found for: ivosidenib | Interventional Studies | Phase 2, 3 | Industry.* 2022. Available from: https://www.clinicaltrials.gov/ct2/results?term=ivosidenib&age_v=&gndr=&type=Intr&rslt=&phase=1&phase=2&fund=2&Search=Apply [Accessed August 8th, 2022].

8 National Health Service (NHS). *Overview- Acute myeloid leukaemia.* 2019. Available from: https://www.nhs.uk/conditions/acute-myeloid-leukaemia/ [Accessed March 7th, 2022].

9 Vakiti A, Mewawalla P. *Acute Myeloid Leukemia.* 2021. Available from: https://www.ncbi.nlm.nih.gov/books/NBK507875/ [Accessed March 7th, 2022].
10 Cancer Research UK. *Acute myeloid leukaemia- risks and causes.* 2020. Available from: https://www.cancerresearchuk.org/about-cancer/acute-myeloid-leukaemia-aml/risks-causes [Accessed March 7th, 2022].
11 Pirozzi CJ, Yan H. The implications of IDH mutations for cancer development and therapy. *Nature Reviews Clinical Oncology*. 2021;18(10):645-61. Available from: https://doi.org/10.1038/s41571-021-00521-0.
12 Bullinger L, Döhner K, Döhner H. Genomics of Acute Myeloid Leukemia Diagnosis and Pathways. *J Clin Oncol*. 2017 Mar 20;35(9):934-46. Available from: https://doi.org/10.1200/jco.2016.71.2208.
13 Griffiths EA, Carraway HE, Chandhok NS, Prebet T. Advances in non-intensive chemotherapy treatment options for adults diagnosed with acute myeloid leukemia. *Leukemia Research*. 2020;91:106339. Available from: https://doi.org/https://doi.org/10.1016/j.leukres.2020.106339
14 Office for National Statistics. *Cancer registration statistics, England.* 2019. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/datasets/cancerregistrationstatisticscancerregistrationstatisticsengland [Accessed August 22nd, 2022].
15 Cancer Research UK. *Acute myeloid leukaemia (AML) statistics.* Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/leukaemia-aml#heading-Zero [Accessed March 7th, 2022].
16 Office for National Statistics. *Cancer survival in England- adults diagnosed 2013-17 dataset.* 2019. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/datasets/cancersurvivalratescancersurvivalinenglandadultsdiagnosed [Accessed August 22nd, 2022].
17 Cancer Research UK. *Acute myeloid leukaemia (AML) survival statistics.* 2017. Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/leukaemia-aml/survival#ref-0 [Accessed March 7th, 2022].
18 Cancer Research UK. *Acute myeloid leukaemia (AML) incidence statistics.* 2021. Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/leukaemia-aml/incidence#heading-Zero [Accessed March 7th, 2022].
19 National Health Service (NHS) Digital Office for National Statistics. *Hospital Admitted Patient Care Activity, 2020-21: Diagnosis.* 2021. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2020-21#chapter-index [Accessed August 22nd, 2022].
20 Cancer Research UK. *AML: Treatment Options.* 2020. Available from: https://www.cancerresearchuk.org/about-cancer/acute-myeloid-leukaemia-aml/treating-aml/decisions-about-your-treatment [Accessed March 7th, 2022].
21 Heuser M, Ofran Y, Boissel N, Mauri SB, Craddock C, Janssen J, et al. Acute myeloid leukaemia in adult patients: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Annals of Oncology*. 2020;31(6):697-712. Available from: https://doi.org/10.1016/j.annonc.2020.02.018
22 West London Cancer Alliance, South East London Cancer Alliance, North Central and East London Cancer Alliance. *Pan-London haemato-oncology clinical guidelines.* 2020. Available from: https://rmpartners.nhs.uk/wp-content/uploads/2020/01/Pan-London-AML-Guidelines-Jan-2020.pdf [Accessed March 7th, 2022].
23 West Midlands Cancer Alliance. *West Midlands Guidelines for the Treatment of Adult Acute Myeloid Leukaemia.* 2020. Available from: https://wmcanceralliance.nhs.uk/images/Documents/Haematology/Final_Guidance_for_Ac

ute_Myeloid_Leukaemia_Treatment_in_Adults_in_the_West_Midlands_v18_clean.pdf
[Accessed March 7th, 2022].

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