Health Technology Briefing
April 2022

ASTX727 for acute myeloid leukaemia

Company/Developer	Otsuka Pharmaceutical Co. Ltd.

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID: 28579	NICE ID: 10605	UKPS ID: 659522

Licensing and Market Availability Plans

Currently in phase III clinical trials.

Summary

ASTX727 is in clinical development for patients with de novo or secondary acute myeloid leukaemia (AML), who are not candidates for standard induction chemotherapy. De novo AML is where there has been no past medical history of the condition or exposure to the drugs which commonly treat it, secondary AML is where patients have had previous conditions that have then developed into AML. 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. Over half of AML patients are not eligible for intensive chemotherapy due to age or other factors that may make the treatments too dangerous, leaving them with limited treatment options.

ASTX727 is a fixed-dose combination of the drugs decitabine and cedazuridine. Decitabine works by blocking the activity of certain proteins that promote cancer cells development and spread. Cedazuridine is added to stop the body from breaking down decitabine before it can be effective when the medicine is taken orally, so that it does not have to be given via intravenous (IV) infusion. Oral administration eliminates the risk of cannula-related infections and may reduce hospital visits. ASTX727 can be given in lower doses than IV decitabine, reducing toxicity related side effects while maintaining the same effectiveness. If licensed, ASTX727 will offer a new treatment option for patients with AML who are not candidates for standard induction chemotherapy.

Proposed Indication

The treatment of adult patients with de novo or secondary acute myeloid leukaemia.[1]

Technology

Description

ASTX727 (Inqovi) is a fixed-dose combination of decitabine (35mg) and cedazuridine (100mg).[2] Decitabine is a cytidine deoxynucleoside analogue which is converted into decitabine triphosphate in the body, and then incorporated into the recipients DNA where it blocks the activity of DNA methyltransferase (DNMTs) enzymes which promote the development and progression of cancer cells.[3] Cedazuridine works by inhibiting cytidine deaminase, an enzyme primarily found in the gastrointestinal tract and liver that breaks down cytidine and cytidine analogues such as decitabine. Cedazuridine increases the oral bioavailability of decitabine, enabling efficient oral administration of this fixed-dose combination.[4,5]

ASTX727 is in clinical development for patients with de novo or secondary AML who are ineligible standard induction chemotherapy.[1] In the phase III clinical trial (NCT03306264), ASTX727 will be given once daily via oral administration, for the first five days of a 28 day cycle.[1]

Key Innovation

ASTX727 has been designed to allow for oral administration of decitabine over five days of a cycle instead of requiring intravenous (IV) infusion, and is the only oral hypomethylating agent with equivalent exposure to its IV form, achieving comparable systemic exposure.[6] Oral administration eliminates the risk of cannula-related infections in patients and can often be given in an outpatient or home setting as the patient can administer the medication themselves.[7] Cedazuridine specifically prevents the breakdown of decitabine and increases its bioavailability and efficacy, allowing lower doses of decitabine which results in decreased decitabine associated gastrointestinal toxicity.[5] If licensed, ASTX727 will over a new treatment option for patients with de novo or secondary AML who are not candidates for standard induction chemotherapy.[1]

Regulatory & Development Status

ASTX727 does not currently have Marketing Authorisation in the EU/ UK for any indication.

ASTX727 was granted orphan drug designation by EMA in December 2021 for the treatment of AML.[8]

ASTX727 is currently in phase II and III clinical development for:[9]

- Malignant peripheral nerve sheath tumours (MPNST)
- Chronic myelomonocytic leukaemia
- Chronic myeloid leukaemia
- Myelodysplastic syndromes
- Head and neck cancer

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.[10] 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.[11] Symptoms of AML usually develop rapidly, becoming worse over time and can include frequent infections, fatigue, weakness, breathlessness, and unusual/ frequent bruising or bleeding.[10] 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.[12]

In England (2017), there were 4,102 patients diagnosed with AML and 2,497 deaths registered where AML was the underlying cause.[13] AML accounts for less than 1% of all new cancer cases in the UK each year, but 2% of cancer deaths (2016-18).[14] 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.[15,16] The age standardised incidence rate of AML in England is 6.2 and 4.1 per 100,000 amongst males and females respectively.[17] 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.[18]

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.[19] Over half of patients with AML are ineligible for intensive chemotherapy and stem cell transplants due to factors such as age or comorbidities, and for these patients there is no firmly established standard-of-care.[20]
Non-intensive treatment options currently recommended by NICE for untreated AML include venetoclax with azacytidine or liposomal cytarabine–daunorubicin.[21]

Clinical Trial Information

Trial	**ASCERTAIN; NCT03306264, 2018-003395-12**; A Phase 3, Randomized, Open-Label, Crossover Study of ASTX727 (Cedazuridine and Decitabine Fixed-Dose Combination) Versus IV Decitabine in Subjects With Myelodysplastic Syndromes (MDS), Chronic Myelomonocytic Leukemia (CMML), and Acute Myeloid Leukemia (AML) **Phase III-** Recruiting **Location(s):** UK, USA, Canada, and 7 EU countries. **Primary completion date:** July 2021	**NCT04093570, 2018-003942-18; An Open-Label, Multicenter, Extension Study for Participants Who Participated in Prior Clinical Studies of ASTX727 (Standard Dose), With a Food Effect Substudy at Select Study Centers** **Phase II-** Enrolling by invitation **Location(s):** USA and Canada **Primary completion date:** December 2024
Trial Design	Randomised, crossover assignment, open-label	Non-randomised, sequential assignment, open-label
Population	N=200 (planned); Participants (in North America) with MDS	N= 332 (planned); Participants who have previously participated in an Astex-

	previously treated or untreated with de novo or secondary MDS, including all French-American-British subtypes (refractory anaemia, refractory anaemia with ringed sideroblasts, refractory anaemia with excess blasts, refractory anaemia with excess blasts in transformation, and chronic myelomonocytic leukaemia [CMML]) or participants (in Europe) with de novo or secondary AML, who are not candidates for standard induction chemotherapy; aged 18 years and over.	sponsored ASTX727 clinical trial and was still on active treatment with ASTX727 at the time of study completion, diagnosed with MDS including all subtypes or AML of any subtype except M3; aged 18 years and over.
Intervention(s)	ASTX727 fixed dose combination of 100mg cedazuridine and 35mg decitabine, oral dose, once daily for 5 days every cycle (28 days).	The recommended starting dose is the fixed-dose combination (FDC) tablet, containing 100 mg cedazuridine and 35 mg decitabine, once daily, Days 1 through 5 in 28-day cycles. Participants should receive ASTX727 at the same dose they received in the last cycle of their parent study; if an adjustment from that dose is required, a different total cycle dose may be employed, as guided by the dose adjustment guidelines in the parent study protocol.
Comparator(s)	Decitabine 20mg/m^2, intravenous (IV) infusion	No active comparator
Outcome(s)	Total 5-day Area Under the Curve (AUC) exposures of decitabine [Time Frame: 18 months] See trial record for full list of all outcomes	Number of participants with treatment-emergent adverse events (TEAEs) [Time Frame: from date of transition into this extension study until 30 days following the last dose, up to approximately 2 years] See trial record for full list of all other outcomes
Results (efficacy)	Study achieved median overall survival of 31.7 months and an overall response rate of 62%, with 22% of patients achieving a complete response.[6]	-
Results (safety)	Safety findings from the study were similar to those anticipated with IV decitabine, with incidence of cytopenias slightly higher with	-

	INQOVI during Cycle 1 compared to IV decitabine. The most common adverse events (AEs) of thrombocytopenia, neutropenia, and anemia were consistent with expected AEs with parenteral hypomethylating agent treatment.[6]	

Estimated Cost

The cost of ASTX-727 is not yet known.

Relevant Guidance

NICE Guidance

- NICE technology appraisal in development. Talacotuzumab for untreated acute myeloid leukaemia (ID1262) (GID-TA10249). Expected publication date TBC.
- NICE technology appraisal in development. Pevonedistat with azacitidine for untreated myelodysplastic syndromes, chronic myelomonocytic leukaemia and acute myeloid leukaemia (ID3877). Expected publication date TBC.
- NICE technology appraisal in development. Venetoclax with low dose cytarabine for untreated acute myeloid leukaemia when intensive chemotherapy is unsuitable (ID4071) (GID-TA10976). Expected publication date April 2022.
- NICE technology appraisal. Venetoclax with azacitidine for untreated acute myeloid leukaemia when intensive chemotherapy is unsuitable (TA765). February 2022.
- NICE technology appraisal. Liposomal cytarabine–daunorubicin for untreated acute myeloid leukaemia (TA552). December 2018.
- NICE technology appraisal. Gemtuzumab ozogamicin for untreated acute myeloid leukaemia (TA545). November 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. Clinical practice guidelines- Acute myeloid leukaemia in adult patients. 2020.[22]
- West London Cancer Alliance (NHS). Pan-London haemato-oncology clinical guidelines. 2020.[23]
- West Midlands Cancer Alliance (NHS). West midlands guidelines for the treatment of adult acute myeloid leukaemia. 2020.[24]

Additional Information

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