NIHR | Innovation Observatory

Newcastle University

Health Technology Briefing
March 2025

Decitabine-cedazuridine with venetoclax for treating previously untreated acute myeloid leukaemia ineligible for induction chemotherapy

Company/Developer	Otsuka Pharmaceutical Co Ltd

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 39656	NICE ID: Not Available	UKPS ID: 675027

Licensing and Market Availability Plans

Currently in Phase III clinical trials

Summary

Decitabine-cedazuridine with venetoclax is in clinical development for patients with acute myeloid leukaemia (AML) that 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. Over half of AML patients are not eligible for intensive chemotherapy due to age, comorbidities, or other factors that make the treatments too dangerous, leaving them with limited treatment options.

Decitabine-cedazuridine and venetoclax are both approved for the treatment of AML. Decitabine and venetoclax both work by blocking the activity of certain proteins that promote cancer cell 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. In the phase I/II clinical trial, patients receive both decitabine-cedazuridine and venetoclax as oral tablets daily. If licensed, decitabine-cedazuridine and venetoclax will offer an additional therapeutic option for patients with AML that are ineligible for intensive induction chemotherapy.

Proposed Indication

This briefing reflects the evidence available at the time of writing and a limited literature search. 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. A version of the briefing was sent to the company for a factual accuracy check. The company was available to comment.
Copyright © National Institute for Health and Care Research Innovation Observatory, The University of Newcastle upon Tyne.

For the treatment of patients with acute myeloid leukaemia (AML)

Technology

Description

Decitabine-cedazuridine (Inaqovi, ASTX727) is a fixed-dose combination of decitabine (35mg) and cedazuridine (100mg). Decitabine is a nucleoside metabolic inhibitor that is believed to exert its antineoplastic effects after phosphorylation and direct incorporation into DNA and inhibition of DNA methyltransferase (DNMT), causing hypomethylation of DNA and cellular differentiation and/or apoptosis. Decitabine-induced hypomethylation in neoplastic cells may restore normal function to genes that are critical for the control of cellular differentiation and proliferation. In rapidly dividing cells, the cytotoxicity of decitabine may also be attributed to the formation of covalent adducts between DNA methyltransferase and decitabine incorporated into DNA. Cytidine deaminase (CDA) is an enzyme that is responsible for the degradation of cytidine nucleosides, including the cytidine analog decitabine. High levels of CDA in the gastrointestinal tract and liver rapidly degrade these nucleosides and prohibit or limit their oral bioavailability. Cedazuridine inhibits CDA. Oral administration of cedazuridine with decitabine increases the systemic exposure of decitabine via inhibition of first pass metabolism of decitabine in the gut and liver by CDA.[1]

Venetoclax (Venclyxto) is a potent, selective inhibitor of BCL-2, an anti-apoptotic protein. Overexpression of BCL-2 has been demonstrated in AML cells where it mediates tumour cell survival and has been associated with resistance to chemotherapeutics. Venetoclax binds directly to the BH3-binding groove of BCL-2, displacing BH3 motif containing pro-apoptotic proteins like BCL-2-like protein 11 to initiate mitochondrial outer membrane permeabilization, caspase activation, and programmed cell death. In non-clinical studies, venetoclax has demonstrated cytotoxic activity in tumour cells that overexpress BCL-2.[2]

Decitabine-cedazuridine in addition to venetoclax is currently in clinical development for the treatment of AML patients that are ineligible for intensive induction chemotherapy. In the phase I/II trial (NCT04657081) participants received daily oral decitabine-cedazuridine on a prescribed dosing regimen and venetoclax on day 1 (100mg), day 2 (200mg), and days 3-28 (400mg) on a 28-day cycle, followed by daily oral decitabine-cedazuridine on a prescribed dosing regimen and venetoclax (400mg) on a 28-day cycle.[3]

Key Innovation

Over half of patients with AML are ineligible for intensive chemotherapy due to factors such as age or comorbidities, and for these patients there is no firmly established standard-of-care.[4] The combination of the DNMT inhibitor, decitabine, with the BCL2 inhibitor, venetoclax, is a newly established standard-of-care regimen for patients with newly diagnosed AML ineligible to receive intensive induction chemotherapy.[5] Current approved parenteral DNMT inhibitor therapies for AML include daily subcutaneous or intravenous administration for 5-7 consecutive days.[6] Replacing the parenteral DNMT inhibitor with an oral DNMT inhibitor with equivalent exposure may provide the benefit of reducing patient and caregiver burden of chronic parenteral therapy and may help responding patients stay on treatment longer. Decitabine-cedazuridine is an oral DNMT inhibitor that provides equivalent exposure to its parenteral DNMT inhibitor at standard dosing and is under evaluation in combination with venetoclax as an all-oral regimen.[5]

If licensed, decitabine-cedazuridine in combination with venetoclax will offer an additional treatment option for AML patients that are ineligible for intensive induction chemotherapy.

Copyright © National Institute for Health and Care Research Innovation Observatory, The University of Newcastle upon Tyne.

Regulatory & Development Status

Venetoclax has Marketing Authorisation as combination therapy in UK/EU for the following indications:[2,7]

- Venetoclax with obinutuzumab for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL)
- Venetoclax with rituximab for the treatment of adult patients with CLL who have received at least one prior therapy
- Venetoclax with a hypomethylating agent or low-dose cytarabine is indicated for the treatment of adult patients with newly diagnosed AML who are ineligible for intensive chemotherapy

Decitabine-cedazuridine currently has Marketing Authorisation as a monotherapy in the EU/UK for newly diagnosed AML patients who are ineligible for standard induction chemotherapy.[8]

Decitabine-cedazuridine with venetoclax is currently in phase II/III clinical development for:[9]

- Chronic myelomonocytic leukaemia
- Acute biphenotypic leukaemia
- Chronic myelomonocytic leukaemia
- Relapsed or refractory AML

Patient Group

Disease Area and Clinical Need

Leukaemia is a cancer of the white blood cells. Acute leukaemia means it progresses quickly and aggressively, and usually requires immediate treatment. Acute leukaemia is classified according to the type of white blood cells affected. The two main types of white blood cells: monocytes and granulocytes, which come from myeloid stem cells, and lymphocytes, which come from lymphoid stem cells. AML is a cancer of the monocyte or granulocyte cells. The symptoms of AML usually develop over a few weeks and become worse over time. Symptoms can include looking pale, tiredness and weakness, breathlessness, frequent infections, unusual bleeding and weight loss.[10] The exact cause of AML is unknown, but risk factors include being older, smoking, certain genetic disorders, previous cancer treatment and radiation exposure.[11]

There are around 2,900 new AML cases and around 2,700 deaths registered from AML in the UK every year (2017-2019). AML accounts for less than 1% of all new cancer cases in the UK, but 2% of all cancer deaths (2017-2019). More than 40% of new cases are in people aged 75 years and over.[12] For patients diagnosed with leukaemia in England between 2013 and 2017, followed up to 2018, the 1-year and 5-year survival rates were 72.4% and 53.5% respectively.[13] In England (2023-2024), there were 63,893 finished consultant episodes (FCEs) and 59,929 admissions for AML (ICD-10 code C92.0), which resulted in 53,060 day cases and 126,765 FCE bed days.[14]

Recommended Treatment Options

The National Institute of Health and Care Excellence (NICE) recommends the following treatments for untreated AML when intensive chemotherapy is unsuitable:

- Venetoclax with azacitidine[15]
- Venetoclax with low dose cytarabine for patients with over 30% bone marrow blasts[16]

Clinical Trial Information

Copyright © National Institute for Health and Care Research Innovation Observatory, The University of Newcastle upon Tyne.

Trial	NCT04657081; A Single-Arm, Open-Label Pharmacokinetic, Safety, and Efficacy Study of ASTX727 in Combination With Venetoclax in Adult Patients With Acute Myeloid Leukemia **Phase I/II –** Active, not recruiting **Location(s):** One EU country, United States, Canada **Primary completion date:** December 2024
Trial Design	Open label, single group assignment, non-randomized
Population	N=188 (planned); participants diagnosed with AML that are considered ineligible for intensive induction chemotherapy; aged 18 years and older
Intervention(s)	Decitabine-cedazuridine + venetoclax oral tablets daily.
Comparator(s)	No comparator
Outcome(s)	Primary outcome measures: • Pharmacokinetic parameter: AUC0-24 [Time frame: on days 5 and 15 in cycle 2 (28 days per cycle)] • Pharmacokinetic parameter: Cmax [Time frame: on days 5 and 15 in cycle 2 (28 days per cycle)] • Number of participants with complete response in Phase 2, Parts A and B [Time frame: up to 36 months] See trial record for full list of other outcomes.
Results (efficacy)	-
Results (safety)	-

Estimated Cost

Decitabine-cedazuridine is already marketed in the UK as a monotherapy for AML; a unit of 5 tablets costs £3,595.00.[17]

Venetoclax is already marketed in the UK as a monotherapy for AML and CLL, and in combination for the treatment of adult patients with CLL; a unit of 112 tablets of venetoclax 100mg costs £4,789.47, a unit of 7 tablets of venetoclax 50mg costs £149.67, and a unit of 14 tablets of venetoclax 10mg costs £59.87.[18]

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. 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.

NHS England (Policy/Commissioning) Guidance

Copyright © National Institute for Health and Care Research Innovation Observatory, The University of Newcastle upon Tyne.

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.[19]
- West London Cancer Alliance (NHS). Pan-London haemato-oncology clinical guidelines. 2020.[20]
- West Midlands Cancer Alliance (NHS). West Midlands guidelines for the treatment of adult acute myeloid leukaemia. 2020.[21]

References

1 Electronic Medicines Compendium (EMC). *Inaqovi 35 mg/100 mg film coated tablets*. 2023. Available from: https://www.medicines.org.uk/emc/product/15177/smpc [Accessed 31 January 2025].

2 Electronic Medicines Compendium (EMC). *Venclyxto 50 mg film-coated tablets*. 2024. Available from: https://www.medicines.org.uk/emc/product/10475/smpc [Accessed 17 December 2024].

3 Clinicaltrials.gov. *Pharmacokinetics, Safety, and Efficacy of ASTX727 in Combination With Venetoclax in Acute Myeloid Leukemia (AML). Trial ID: NCT04657081*. 2021. Status: Active, not recruiting. Available from: https://clinicaltrials.gov/study/NCT04657081 [Accessed 17 December 2024].

4 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. https://doi.org/10.1016/j.leukres.2020.106339.

5 Astex Pharmaceuticals. *ASH 2021: A Phase 1 Study Evaluating ASTX727 (decitabine and cedazuridine) and Venetoclax in Combination Therapy in Newly Diagnosed AML Patients Unfit for Intensive Induction Chemotherapy*. 2021. Available from: https://astx.com/ash-2021-a-phase-1-study-evaluating-astx727-decitabine-and-cedazuridine-and-venetoclax-in-combination-therapy-in-newly-diagnosed-aml-patients-unfit-for-intensive-induction-chemotherapy/ [Accessed 17 December 2024].

6 Ramsey HE, Oganesian A, Gorska AE, Fuller L, Arrate M, Boyd K, et al. Oral azacitidine and cedazuridine approximate parenteral azacitidine efficacy in murine model. *Targeted Oncology*. 2020;15:231-40. https://doi.org/10.1007/s11523-020-00709-x.

7 European Medicines Agency (EMA). *Venclyxto*. 2024. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/venclyxto [Accessed 17 December 2024].

8 European Medicines Agency (EMA). *Inaqovi (decitabine/cedazuridine)*. 2023. Available from: https://www.ema.europa.eu/en/documents/overview/inaqovi-epar-medicine-overview_en.pdf [Accessed 17 December 2024].

9 Clinicaltrials.gov. *Venetoclax + inqovi | Phase: 2, 3, 4*. Available from: https://clinicaltrials.gov/search?intr=Venetoclax%20%2B%20inqovi&aggFilters=phase:2%203%204 [Accessed 6 January 2025].

10 National Health Service (NHS). *Overview - Acute Myeloid Leukaemia*. 2022. Available from: https://www.nhs.uk/conditions/acute-myeloid-leukaemia/ [Accessed 17 December 2024].

11 National Health Service (NHS). *Causes - Acute Myeloid Leukaemia*. 2022. Available from: https://www.nhs.uk/conditions/acute-myeloid-leukaemia/causes/ [Accessed 17 December 2024].

Copyright © National Institute for Health and Care Research Innovation Observatory, The University of Newcastle upon Tyne.

12 Cancer Research UK. *Acute myeloid leukaemia (AML) statistics*. 2024. Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/leukaemia-aml [Accessed 17 December 2024].
13 Office for National Statistics. *Cancer survival in England - adults diagnosed (2013-2017 dataset)*. 2019. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/datasets/cancersurvivalratescancersurvivalinenglandadultsdiagnosed [Accessed 17 February 2025].
14 National Health Service (NHS) Digital. *Hospital Admitted Patient Care Activity, 2023-2024*. 2024. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2023-24 [Accessed 17 February 2025].
15 National Institute for Health and Care Excellence (NICE). *Venetoclax with azacitidine for untreated acute myeloid leukaemia when intensive chemotherapy is unsuitable - Recommendations*. 2022. Available from: https://www.nice.org.uk/guidance/ta765/chapter/1-Recommendations [Accessed 17 December 2024].
16 National Institute for Health and Care Excellence (NICE). *Venetoclax with low dose cytarabine for untreated acute myeloid leukaemia when intensive chemotherapy is unsuitable - Recommendations*. 2022. Available from: https://www.nice.org.uk/guidance/ta787/chapter/1-Recommendations [Accessed 17 December 2024].
17 National Institute for Health and Care Excellence (NICE). *Decitabine with cedazuridine [Specialist drug] - Medicinal forms*. 2024. Available from: https://bnf.nice.org.uk/drugs/decitabine-with-cedazuridine-specialist-drug/medicinal-forms/ [Accessed 17 December 2024].
18 National Institute for Health and Care Excellence (NICE). *Venetoclax [Specialist drug] - Medicinal forms*. 2024. Available from: https://bnf.nice.org.uk/drugs/venetoclax-specialist-drug/medicinal-forms/ [Accessed 17 December 2024].
19 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. https://doi.org/10.1016/j.annonc.2020.02.018.
20 West London Cancer Alliance SELCA, 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 17 December 2024].
21 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_Acute_Myeloid_Leukaemia_Treatment_in_Adults_in_the_West_Midlands_v18_clean.pdf [Accessed 17 December 2024].

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

Copyright © National Institute for Health and Care Research Innovation Observatory, The University of Newcastle upon Tyne.