Health Technology Briefing
May 2024

Venetoclax with azacitidine for treating acute myeloid leukaemia following allogeneic stem cell transplantation

Company/Developer	AbbVie

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 28698	NICE ID: Not available	UKPS ID: Not available

Licensing and Market Availability Plans

Currently in phase III clinical development

Summary

Venetoclax in combination with azacitidine is currently in clinical development for the treatment of acute myeloid leukaemia (AML) following allogeneic stem cell transplantation in children and adults. 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.

Venetoclax blocks a protein called B-cell lymphoma 2 (BCL-2), which promotes cancer cell growth and survival. This protein is present in high amounts in leukaemia cancer cells, where it helps the cells survive for longer in the body and makes them resistant to cancer medicines. By blocking this protein, it can kill and slow down the growth of cancer cells. Venetoclax is taken orally as a tablet, once daily. Venetoclax may delay this progression and thereby increase survival. If licensed, venetoclax in combination with azacitidine will offer an additional treatment option for patients with AML who have undergone allogeneic stem cell transplantation who have no other treatment options available following their previous line of therapy.

Proposed Indication

Treatment of patients with acute myeloid leukaemia (AML) who will receive (or have received in the last 60 days) allogenic stem cell transplantation.[1]

Technology

Description

Venetoclax (Venclyxto) is a potent, selective inhibitor of BCL-2, an anti-apoptotic protein. Overexpression of BCL-2 has been demonstrated in chronic lymphocytic leukaemia (CLL) and 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 BIM, to initiate mitochondrial outer membrane permeabilization (MOMP), caspase activation, and programmed cell death. In non-clinical studies, venetoclax has demonstrated cytotoxic activity in tumour cells that overexpress BCL-2.[2]

Venetoclax in addition to azacitidine is currently in clinical development for the treatment of patients 12 years and older with acute myeloid leukaemia (AML) who will receive (or have received in the last 60 days) allogenic stem cell transplantation. In the phase III clinical trial (NCT04161885) participants received oral venetoclax once daily for 28 days, in combination with subcutaneous (SC) or intravenous (IV) azacytidine once daily on days 1-5 of each 28-day cycle for up to 6 cycles and best supportive care for 24 cycles (each cycle = 28 days).[1]

Key Innovation

AML relapse after allogeneic hematopoietic cell transplantation (alloHCT) remains a major therapeutic challenge. AlloHCT is a potentially curative treatment option for patients with AML; however, relapse accounts for approximately 40% of alloHCT treatment failures. Among relapsed patients, the 2-year postrelapse survival rate is reported at less than 20%. Availability of effective therapies for these patients is an urgent area of unmet need.[3,4] Therefore, if licensed, venetoclax with azacitidine will offer an additional treatment option for patients with AML who have undergone allogenic stem cell transplantation.

Regulatory & Development Status

Venetoclax has Marketing Authorisation as combination therapy in UK/EU for the following indications: [5,6]

- Venetoclax with obinutuzumab for the treatment of adult patients with previously untreated CLL
- Venetoclax with rituximab for the treatment of adult patients with CLL who have received at least one prior therapy
- Venclyxto 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

Venetoclax has Marketing Authorisation as monotherapy in UK/EU for the following indication: [2]

- CLL patients with particular genetic changes (17p deletion or TP53 mutation) who cannot be treated with medicines known as B-cell receptor pathway inhibitors (ibrutinib and idelalisib) or if these medicines have stopped working, or
- CLL patients who do not have these genetic changes, after treatments with chemotherapy combined with immunotherapy as well as a B-cell receptor pathway inhibitor have both not worked

Azacitidine has Marketing Authorisation in UK/EU for the following indications for the treatment of adult patients who are not eligible for haematopoietic stem cell transplantation (HSCT) with:[7]

- Intermediate-2 and high-risk myelodysplastic syndromes (MDS) according to the International Prognostic Scoring System (IPSS)
- Chronic myelomonocytic leukaemia (CMML) with 10-29% marrow blasts without myeloproliferative disorder
- AML with 20-30% blasts and multi-lineage dysplasia, according to World Health Organisation (WHO) classification
- AML with > 30% marrow blasts according to the WHO classification

Venetoclax in combination with azacitidine is currently in phase II and III trials for the treatment of:[8]

- AML
- T-cell acute lymphoblastic leukaemia
- Myelodysplastic syndrome
- Chronic myelomonocytic leukemia
- Myeloproliferative neoplasms

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 are: monocytes and granulocytes, which come from myeloid stem cells, and lymphocytes, which come from lymphoid stem cells.[9] 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.[9] The exact cause of most cases of AML is unknown, but risk factors include being older, smoking and ionising radiation.[10]

In England (2017), there were 4,102 patients diagnosed with AML and 2,497 deaths registered where AML was the underlying cause.[11] AML accounts for less than 1% of all new cancer cases in the UK each year (2016-18), but 2% of cancer deaths (2017-19).[12] 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.[12,13] The age standardised incidence rate of AML in England is 6.2 and 4.1 per 100,000 amongst males and females respectively.[14] In England (2022-23), there were 57,592 finished consultant episodes (FCE) and 54,272 admissions for AML (ICD-10 code C92.0), which resulted in 47,729 day cases and 116,955 FCE bed days.[15]

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.[16]
There is no treatment option recommended by the National Institute for Health and Care Excellence (NICE) for AML patients who will (or have received in the last 60 days) allogenic stem cell transplantation.

Clinical Trial Information

Trial	**VIALE-T;** NCT04161885, 2019-002621-30; A Randomized, Open Label Phase 3 Study Evaluating Safety and Efficacy of Venetoclax in Combination With Azacitidine After Allogeneic Stem Cell Transplantation in Subjects With Acute Myeloid Leukemia (AML) **Phase III** – Active, not recruiting **Location(s):** 7 EU countries, UK, USA, Canada, and other countries **Primary completion date:** November 2026
Trial Design	Randomised, parallel assignment, open label
Population	N=465 (actual); subjects with AML by World Health Organization criteria (2017) and either be planning for allogeneic stem cell transplantation or have received allogeneic stem cell transplantation within the past 60 days
Intervention(s)	• Venetoclax (oral) • Azacitidine (SC or IV injection)
Comparator(s)	Best supportive care
Outcome(s)	Primary outcome measures: • Number of participants with dose-limiting toxicities (DLTs) following administration of venetoclax and azacitidine (Part 1) [Time frame: up to the first treatment cycle (28 days)] • Overall Survival (OS) (Part 2) [Time frame: up to 45 months after the first participant is randomised] See trial record for full list of other outcomes
Results (efficacy)	-
Results (safety)	-

Estimated Cost

Venetoclax is already marketed in the UK as a monotherapy for AML and CLL, and in combinations 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.[17]

Azacitidine is already marketed in the UK for myelodysplastic syndromes and leukaemia. A 100mg vial costs £321 (NHS indicative price). [18]

Relevant Guidance

NICE Guidance
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.[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]

Additional Information

AbbVie did not enter information about this technology onto the UK PharmaScan database; the primary source of information for UK horizon scanning organisations on new medicines in development. As a result, the NIHR Innovation Observatory has had to obtain data from other sources. UK PharmaScan is an essential tool to support effective NHS forward planning; allowing more effective decision making and faster uptake of innovative new medicines for patients who could benefit. We urge pharmaceutical companies to use UK PharmaScan so that we can be assured of up-to-date, accurate and comprehensive information on new medicines.

References

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