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Venetoclax in combination with a hypomethylating agent or low dose cytarabine for newly diagnosed acute myeloid leukaemia

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Developer/Company	AbbVie Ltd	**UKPS ID**	645218

SUMMARY

Venetoclax is being developed for newly diagnosed patients with acute myeloid leukaemia (AML) who are ineligible for intensive chemotherapy. AML is an aggressive type of blood cancer that starts from certain types of young white blood cells called granulocytes or monocytes in the bone marrow. AML usually develops over a few weeks and becomes increasingly more severe. If left untreated it would cause death within a few weeks or months. High intensity chemotherapy followed by haematopoietic stem cell transplant (HSCT) is the standard treatment for AML in fit patients and is often very demanding with potentially severe side effects. Patients who cannot tolerate or who do not wish to receive high intensity chemotherapy are given low dose cytarabine or a hypomethylating agent (azacitidine or decitabine). Decitabine is not recommended for use by NICE however.

Venetoclax blocks the action of a specific protein which is present in high amounts in AML cells. This results in the death of the cancer cells and thereby slows the progression of the disease. Venetoclax is already licensed to treat other types of leukaemia and is thought that it might be of significant benefit for patients with AML when used in combination with other medicines in patients who cannot receive standard high dose treatment. Venetoclax in combination with a hypomethylating agent (azacitidine or decitabine) or low dose cytarabine may offer a first-line treatment option for newly diagnosed patients with AML.

PROPOSED INDICATION

Venetoclax in combination with a hypomethylating agent or in combination with low dose cytarabine is indicated for newly diagnosed patients with acute myeloid leukaemia (AML) who are ineligible for intensive chemotherapy.[a]

TECHNOLOGY

DESCRIPTION

Venetoclax (Venclyxto) is a potent, selective inhibitor of B-cell lymphoma-2 (BCL-2).[1] It is a medicine used for treating a blood cancer known as chronic lymphocytic leukaemia (CLL) when other treatments have failed or are unsuitable. Venetoclax attaches to a protein called BCL-2. This protein is present in high amounts in CLL cancer cells, where it helps the cells survive for longer in the body and makes them resistant to cancer medicines. By attaching to BCL-2 and blocking its actions, venetoclax causes the death of cancer cells and thereby slows the progression of the disease.[2]

Venetoclax in combination with a hypomethylating agent (azacitidine) or low dose cytarabine is in clinical development for patients with newly diagnosed AML who are ineligible for intensive chemotherapy. In the phase III clinical trial (NCT03069352), venetoclax is administered orally at a dose of 600mg daily for 28 days in combination with low dose cytarabine subcutaneously at a dose of 20mg/m^2 on first ten days of a 28-day cycle compared to placebo in combination with low dose cytarabine.[3] In the phase III clinical trial (NCT02993523), venetoclax is administered orally at a dose of 400mg daily for 28 days in combination with azacitidine subcutaneously at a dose of 75mg/m^2 on days 1 – 7 of a 28-day cycle compared to placebo in combination with azacitidine.[4]

INNOVATION AND/OR ADVANTAGES

Treatment for AML is complex and depends on a number of factors including the extent of the disease, whether it has been treated before, and the patient's age, symptoms, fitness and general state of health. At the time of designation, the main treatments for AML were chemotherapy (medicines to treat cancer) and haematopoietic (blood) stem-cell transplantation. According to the EMA, the sponsor has provided sufficient information to show that venetoclax might be of significant benefit for patients with AML because early studies show that, when used in combination with other medicines, it can produce a response in the disease in patients who cannot receive standard high dose treatment.[5]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Venetoclax is licensed in the UK for the treatment of CLL in the presence of 17p deletion or TP53 mutation in adult patients who either are unsuitable for or have failed a B-cell receptor pathway inhibitor. Also, for the treatment of CLL in the absence of 17p deletion or TP53 mutation in adult patients who have failed both chemoimmunotherapy and a B cell receptor pathway inhibitor.[6]

Very common side effects include; upper respiratory tract infection, neutropenia, anaemia, hyperphosphataemia, diarrhoea, vomiting, nausea, constipation and fatigue. Common side effects include; pneumonia, urinary tract infection, febrile neutropenia, lymphopenia, tumour lysis syndrome, hyperkalaemia, hyperuricaemia, hypocalcaemia and blood creatinine increased.[7]

[a] Information provided by AbbVie on UK PharmaScan

Venetoclax received Orphan Drug Designation for the treatment of AML by the EMA in February 2016.[5]

In the EU and globally, venetoclax is in phase III clinical development for the following indications:[8]

- Multiple Myeloma (MM)
- CLL - first line
- AML
- Myelodysplatic Syndrome (MDS)
- Follicular Lymphoma (FL)
- Diffuse Large B-cell Lymphoma (DLBCL)

Cytarabine is licensed in the UK for the treatment of:[9]

- AML
- Acute lymphoblastic leukaemia
- Acute non-lympoblastic leukaemia
- Acute lymphocytic leukaemia
- Erythroleukaemia
- Blast crises of chronic myeloid leukaemia
- Diffuse histiocytic lymphomas (non-Hodgkin's lymphoma of high malignancy)
- Meningeal leukaemia
  Meningeal neoplasms

PATIENT GROUP

DISEASE BACKGROUND

Leukaemia is cancer of the white blood cells. Acute leukaemia means it progresses rapidly and aggressively, and usually requires immediate treatment. Acute leukaemia is classified according to the type of white blood cells affected.[10] There are five types of white blood cell (leucocyte). These are divided into two main classes:[11]

- Granulocytes (includes Neutrophils, Eosinophils and Basophils)
- Agranulocytes (includes Lymphocytes and Monocytes)

Acute myeloid leukaemia (AML) is a type of blood cancer that starts from young granulocytes or monocytes in the bone marrow. The bone marrow is the soft inner part of the bones, where new blood cells are made.[12] The symptoms of AML usually develop over a few weeks and become increasingly more severe. Symptoms can include: pale skin, tiredness, breathlessness, frequent infections, unusual and frequent bleeding, such as bleeding gums or nosebleeds. In more advanced cases, AML can make the patient extremely vulnerable to life-threatening infections or serious internal bleeding.[10]

AML patients may experience a number of complications. These can be caused by the condition itself, although they can also occur as a side effect of treatment. Some of the main complications associated with AML are:[13]

- Weakened immune system: this is a common complication of AML. Even if patient's blood is restored to normal working order with treatment, many of the medications that are used to treat AML can temporarily weaken the immune system.
- Bleeding: patient will bleed and bruise more easily due to the low levels of in their blood. Bleeding may also be excessive. Serious bleeding can occur inside the skull, lung or inside the stomach.

- Infertility: many of the treatments that are used to treat AML can cause infertility. This is often temporary, but in some cases can be permanent.

The causes of AML are unknown. There are a number of factors that may increase a person's risk of developing AML. The following are known risk factors of AML:[14]

- Exposure to radiation
- Smoking
- Exposure to benzene
- Cancer treatments: rarely, some anti-cancer treatments such as chemotherapy or radiotherapy can cause leukaemia.
- Blood disorders: such as myelodysplasia or myeloproliferative disorders
- Genetic disorders: such as Down's syndrome and Fanconi anaemia

CLINICAL NEED AND BURDEN OF DISEASE

European age standardised incidence rates of AML in England and Wales in 2015 were 5.3 and 5.4 per 100,000 respectively.[15] AML accounted for less than 1% of all new cancer cases in the UK, and 32% of all leukaemia types combined in 2014. AML incidence is strongly related to age, with the highest incidence rates being in older males and females. In the UK in 2012-2014, on average each year almost 6 in 10 (55%) cases were diagnosed in people aged 70 years and over. Age-specific incidence rates rise gradually from around age 40-44 years and more steeply from around age 60-64 years, with the highest rates in the 85-89 years age group in males, and the 90+ year age group in females.[15]

European age standardised mortality rates of AML in England and Wales in 2016 were 4.3 and 4.6 per 100,000 population respectively. These rates do not differ significantly between the constituent countries of the UK for either sex.[16]

Five-year relative survival for AML in England (14%) and Wales (12%) are similar to the average for Europe (15%). Five-year relative survival for AML in women in England (16%) is below the average for Europe (18%). No five-year survival data is available for Wales.[17]

In 2016/17 there were 47,686 finished consultant episodes (FCEs), 44,807 hospital admissions with primary diagnosis of AML (ICD-10 code C92.0), resulting in 118,292 FCE bed days .[18]

PATIENT TREATMENT PATHWAY

PATIENT PATHWAY

High-dose chemotherapy is the main treatment for AML in patients fit enough to tolerate intensive treatment, although bone marrow or stem cell transplant may also be offered:[19]

NICE guidelines for AML recommend azacitidine as a treatment option for adults who are not eligible for haematopoietic stem cell transplantation and have acute myeloid leukaemia with 20–30% blasts

and multilineage dysplasia, according to the World Health Organization classification and if the manufacturer provides azacitidine with the discount agreed as part of the patient access scheme.[20]

Azacitidine is not recommended, within its marketing authorisation, for treating acute myeloid leukaemia with more than 30% bone marrow blasts in people of 65 years or older who are not eligible for haematopoietic stem cell transplant.[21]

Decitabine is not recommended, within its marketing authorisation, for treating acute myeloid leukaemia in people who are not candidates for standard induction chemotherapy.[22]

CURRENT TREATMENT OPTIONS

Chemotherapy for AML is in two phases:[19]

- Getting rid of the AML (induction): usually the patient is given two or more different chemotherapy drugs in cycles of treatment. The 2 main drugs are cytarabine and daunorubicin.
- Treatment to stop AML coming back (consolidation): When there are no signs of the leukaemia, it is in remission. The patient gets treatment to stop it coming back. Combinations of chemotherapy can be used in this phase. These include: amsacrine, high dose cytarabine, etoposide, daunorubicin, fludarabine, idarubicin. Some people have high dose chemotherapy and then a bone marrow or stem cell transplant.

PLACE OF TECHNOLOGY

If licenced, venetoclax in combination with a hypomethylating agent or in combination with low dose cytarabine may offer an additional first line treatment option for patients with newly diagnosed AML who are ineligible for intensive chemotherapy.

CLINICAL TRIAL INFORMATION

Trial	NCT03069352, MI6-043, 2016-003900-30 (EudraCT Number); venetoclax in combination with low dose cytarabine compared to low dose cytarabine alone; phase III
Sponsor	AbbVie Ltd
Status	Ongoing
Source of Information	Trial registry[3]
Location	UK, Eastern Europe, Western Europe, North America, South America, Asia, Australia
Design	Randomised, parallel assignment
Participants	n=210 (planned); ≥ 75 years of age OR ≥ 18 to 74 years of age ; newly diagnosed AML; ineligible for intensive induction chemotherapy
Schedule	Randomised to venetoclax orally at a dose of 600 mg every day for 28 days along with low dose cytarabine subcutaneously at a dose of 20 mg/m^2 on first ten days (28 day cycle) or to a placebo orally every day

	for 28 days along with low dose cytarabine subcutaneously at a dose of 20 mg/m^2 on first ten days (28 day cycle)
Follow-up	Active treatment until clinical benefit, death or patient withdrawal, follow-up 2 years
Primary Outcomes	Overall survival
Secondary Outcomes	• Event-free survival (EFS) • Composite Complete Remission Rate by Initiation of Cycle 2 • Complete Remission Rate • Composite Complete Remission Rate • Patient Reported Outcomes - items from the PROMIS and Fatigue SF 7a - items from EORTC QLQ-C30 - items from EQ-5D-5L • Complete Remission and Complete Remission With Partial Hematologic Recovery (CR + CRh) [Time Frame: Up to 2 years after the last participant is enrolled]
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Study completion date reported as November 2019.

Trial	NCT02993523, M15-656, 2016-001466-28 (EudraCT Number); venetoclax in combination with azacitidine compared to azacitidine alone; phase III
Sponsor	AbbVie Ltd
Status	Ongoing
Source of Information	Trial registry[4]
Location	Eastern Europe, Western Europe, North America, South America, Asia, Africa, Australia
Design	Randomised, parallel assignment
Participants	n=412; ≥ 75 years of age OR ≥ 18 to 74 years of age ; newly diagnosed AML; ineligible for intensive induction chemotherapy
Schedule	Randomised to venetoclax orally at a dose of 400 mg every day for 28 days along with azacitidine subcutaneously at a dose of 75 mg/m^2 on first seven days (28 day cycle) or to a placebo orally every day for 28 days along with azacitidine subcutaneously at a dose of 75 mg/m^2 on first seven days (28 day cycle)
Follow-up	Active treatment until clinical benefit, death or patient withdrawal, follow-up 2 years
Primary Outcomes	Overall survival Complete remission (CR) and complete remission with incomplete marrow recovery (CRi)
Secondary Outcomes	• Event-free survival (EFS) • Global health status/quality of life (GHS/QoL) • Proportion of participants achieving composite complete remission (CR or CRi) • Complete remission or complete remission with partial hematologic recovery rate (CR+CRh)

	• Post baseline transfusion independence rate • Complete remission (CR) rate • Fatigue/quality of life (QoL) • Patient Reported Outcomes - Patient Reported Outcomes Measurement Information System (PROMIS) - Cancer Fatigue Short Form (SF) 7a global fatigue score items from the PROMIS and Fatigue SF 7a [Time Frame: Up to 2 years after the last participant is enrolled]
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Study completion date reported as January 2021.

ESTIMATED COST

Venetoclax is already marketed in the UK for the treatment of relapsed/refractory CLL; a pack of 14 x 10mg tablets costs £59.87, a pack of 7 × 50mg tablets costs £149.67, a pack of 7 × 100mg tablets costs £299.34, a pack of 14 x 100mg tablets costs £589.68, and a pack of 112 x £100mg tablets costs £4,789.47.[1]

Cytarabine is already marketed in the UK for the treatment of AML; a 5mg vial (20mg/mL) costs on average £30.[23]

Azacitidine is already marketed in the UK for the treatment of high-risk myelodysplastic syndromes, chronic myelomonocytic leukaemia, and acute myeloid leukaemia; a 100mg vial costs £321.[24]

ADDITIONAL INFORMATION

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal. Venetoclax for treating chronic lymphocytic leukaemia (TA487). Nov 2017.
- NICE technology appraisal guidance in development (ID1097). Venetoclax in combination with rituximab for treating relapsed or refractory chronic lymphocytic leukaemia. Expected publication date: March 2019.
- NICE technology appraisal guidance in development (ID1402). Venetoclax with obinutuzumab for untreated chronic lymphocytic leukaemia. Expected publication date: TBC.
- NICE technology appraisal guidance in development (ID1270). Venetoclax with ibrutinib and obinutuzumab for untreated chronic lymphocytic leukaemia. Expected publication date: TBC.
- NICE technology appraisal guidance in development. Gemtuzumab ozogamicin for untreated acute myeloid leukaemia (ID982). Expected publication date: TBC.

- NICE technology appraisal guidance in development. Talacotuzumab for untreated acute myeloid leukaemia (ID1262). Expected publication date: TBC.
- NICE technology appraisal guidance in development. Guadecitabine for untreated acute myeloid leukaemia (ID1411). Expected publication date: TBC.
- NICE technology appraisal guidance in development. Decitabine for acute myeloid leukaemia (ID1114). Expected publication date: TBC.
- NICE technology appraisal guidance in development. Liposomal cytarabine and daunorubicin for untreated myeloid leukaemia (ID1225). Expected publication date: January 2019.
- NICE technology appraisal. Midostaurin for untreated acute myeloid leukaemia (TA523). June 2018.
- NICE technology appraisal. Azacitidine for treating acute myeloid leukaemia with more than 30% bone marrow blasts (TA399). July 2016.
- NICE technology appraisal. Azacitidine for the treatment of myelodysplastic syndromes, chronic myelomonocytic leukaemia and acute myeloid leukaemia (TA218). March 2011.
- NICE clinical guideline. Haematological cancers – improving outcomes (NG47). May 2016.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

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- NHS England. 2013/14 NHS Standard Contract for Haematopoietic Stem Cell Transplantation (Adult). B04/S/a.
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OTHER GUIDANCE

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4 ClinicalTrials.gov. *A Study of Venetoclax in Combination With Azacitidine Versus Azacitidine in Treatment Naïve Subjects With Acute Myeloid Leukemia Who Are Ineligible for Standard Induction Therapy*. 2018. Available from: https://clinicaltrials.gov/ct2/show/NCT02993523 [Accessed 4 October 2018]

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