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HEALTH TECHNOLOGY BRIEFING FEBRUARY 2019

Acalabrutinib for chronic lymphocytic leukaemia – first line

NIHRIO ID	14904	**NICE ID**	9644
Developer/Company	AstraZeneca UK Ltd	**UKPS ID**	645761

Licensing and market availability plans	Currently in phase III trials.

SUMMARY

Acalabrutinib is a novel oral anti-cancer drug in clinical development for people with chronic lymphocytic leukaemia (CLL) who have not received any previous treatment. CLL is a type of cancer in which too many white blood cells are produced. As these cells develop abnormally, they are unable to function and fight infection and reduce the production of healthy blood cells. The disease is chronic and develops slowly. Treatment for CLL is complex and depends on a number of factors, including extent of disease, previous treatment, patient's age, symptoms and general state of health. Patients whose CLL is not causing any symptoms or is getting worse only very slowly may not need treatment. Treatment for CLL is started only if symptoms become troublesome.

Acalabrutinib works by blocking a specific enzyme referred to as Bruton's Tyrosine Kinase, to slow the build-up of cancerous cells in CLL, thereby delaying or stopping the progression of the disease. The Bruton's Tyrosine Kinase enzyme has been identified as an important therapeutic target for the treatment of CLL. Acalabrutinib is thought to be a more selective and irreversible blocker of this enzyme and is specifically designed to improve on the safety and efficacy of first generation inhibitors. If licensed, acalabrutinib will offer an additional first-line treatment option for adult patients who have CLL. It may expand the first-line treatment options for elderly patients or those less than 65years who are deemed as unfit.

PROPOSED INDICATION

Adult patients with previously untreated chronic lymphocytic leukaemia (CLL) – first-line.[1]

TECHNOLOGY

DESCRIPTION

Acalabrutinib (Calquence, ACP-196) is an orally available inhibitor of Bruton's tyrosine kinase (BTK) with potential antineoplastic activity. BTK, a member of the src-related BTK/Tec family of cytoplasmic tyrosine kinases, is overexpressed in B-cell malignancies and plays an important role in B-cell development, activation, signalling, proliferation and survival. Acalabrutinib inhibits the activity of BTK and prevents the activation of the B-cell antigen (BCR) signalling pathway. This prevents both B-cell activation and BTK-mediated activation of downstream survival pathways.[2] Acalabrutinib is a more selective irreversible BTK inhibitor that is specifically designed to improve on the safety and efficacy of first generation BTK inhibitors.[3]

Acalabrutinib is in clinical development for the first-line treatment of CLL in adult patients. In the phase III clinical trial (NCT02475681), patients randomised to the monotherapy arm of the study were administered acalabrutinib orally on day 1 of cycle 1 until disease progression or unacceptable toxicity.[1]

INNOVATION AND/OR ADVANTAGES

The unique structure of BTK, characterised by a cysteine (C481) within the adenosine triphosphate (ATP) binding pocket, makes it an attractive therapeutic target. Irreversible inhibition of BTK represents an important therapeutic advance for the treatment of CLL. Acalabrutinib is a more selective, irreversible BTK inhibitor, specifically designed to improve on the safety and efficacy of first generation inhibitors.[4]

Early results suggest that acalabrutinib has encouraging efficacy in patients with CLL that have already been treated.[5] Additionally, a favourable safety profile has also been demonstrated compared to ibrutinib, a first generation BTK inhibitors.[4]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

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

Acalabrutinib is in phase III clinical development for mantle cell lymphoma and in phase II clinical trials for different types of cancers such as small lymphocytic lymphoma, diffuse large B-cell lymphoma, multiple myeloma, non-small cell lung cancer, etc.[6]

Acalabrutinib has been awarded an EU orphan drug designation for the treatment of CLL in April 2016.[7]

PATIENT GROUP

DISEASE BACKGROUND

CLL is a type of B-lymphocyte cancer. B-lymphocytes are a type of white blood cell. In CLL, abnormal white blood cells develop from the lymphoid blood stem cells. These white blood cells are unable to function as normal lymphocytes and can accumulate in the blood and bone marrow, preventing the production of healthy blood cells. As a chronic leukaemia, CLL develops slowly over time.[8]

CLL is one of the most common types of leukaemia in adults. It is most common in those over 60 years old and rarely occurs in those under 40 years old.[9] Because CLL develops slowly, people often have no symptoms in early stages. General symptoms of CLL include: fatigue, frequent infections, swollen lymph nodes (commonly in the neck, armpits and groin), anaemia, easy bruising/bleeding, enlarged spleen (causing tender lump in upper left abdomen), night sweats and weight loss.[10]

Various risk factors CLL have been identified, including: a family history of CLL, exposure to electromagnetic radiation, the presence of a compromised immune system (HIV/AIDS patients or individuals on immunosuppressive medication) and exposure to certain hair dyes. CLL is also more common in men and people of Australian, American and European origin.[11]

CLINICAL NEED AND BURDEN OF DISEASE

In 2015, there were 3,709 new cases of CLL in the UK; just over 60% of which were in men. The crude incidence rate of CLL (ICD-10: C91.1) in England in 2015 was 5.9 per 100,000 population and in the UK, the crude incidence rate was 5.7 per 100,000 population.[12]

In 2016, CLL accounted for less than 1% of cancer deaths in the UK. There were 624 (62%) CLL deaths in males and 384 (38%) CLL deaths in females. This equates to a crude mortality rate of 1.9 per 100,000 in males and 1.2 per 100,000 in females.[13]

Between 2008 and 2010, the five-year survival rates for CLL in England was 70% for men and 75% for women.[14]

In 2017-18, there were 24,071 admissions for CLL of B-cell type (ICD10:C91.1) in England, resulting in 12,441 bed days and 24,935 finished consultant episodes.[15]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

Treatment for CLL 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 and general state of health. Patients whose CLL is not causing any symptoms or is getting worse only very slowly may not need treatment. Treatment for CLL is started only if symptoms become troublesome.[7]

CURRENT TREATMENT OPTIONS

The following first-line treatment recommendations have been made by NICE for patients with CLL:[16]

- Venetoclax is recommended for use as an option for treating CLL, that is in adults with a 17p deletion or TP53 mutation and when a B-cell receptor pathway inhibitor is unsuitable

- Ibrutinib alone is recommended as an option for treating CLL in adults who have a 17p deletion or TP53 mutation and in whom chemo-immunotherapy is unsuitable
- Idelalisib as a first-line therapy in the presence of 17p deletion or TP53 mutation in patients who are not eligible for any other therapies
- Idelalisib, in combination with rituximab, is recommended for untreated CLL in adults with a 17p deletion or TP53 mutation
- Obinutuzumab, in combination with chlorambucil, is recommended as an option for adults with untreated CLL who have comorbidities that make full-dose fludarabine-based therapy unsuitable for them, only if bendamustine-based therapy is not suitable
- Obinutuzumab, in combination with chlorambucil, is recommended as an option for adults with untreated CLL who have comorbidities that make full-dose fludarabine-based therapy unsuitable for them, only if bendamustine-based therapy is not suitable
- Bendamustine is recommended as an option for the first-line treatment of CLL (Binet stage B or C) in patients for whom fludarabine combination chemotherapy is not appropriate
- Rituximab in combination with fludarabine and cyclophosphamide is recommended as an option for the first-line treatment of CLL in people for whom fludarabine in combination with cyclophosphamide is considered appropriate

PLACE OF TECHNOLOGY

If licensed, acalabrutinib will offer an additional first-line treatment option for adult patients who have CLL. It may expand the first-line treatment option for elderly patients or those less than 65years who are classified as unfit.

CLINICAL TRIAL INFORMATION

Trial	**NCT02475681, ACE-CL-007; adults aged 18 years and older; obinutuzumab in addition to chlorambucil vrs. acalabrutinib monotherapy or in addition to obituzumab; phase III**
Sponsor	Acerta Pharma BV
Status	Ongoing
Source of Information	Trial registry[1]
Location	10 EU countries including UK
Design	Randomised; active-controlled; parallel assignment
Participants	n=535; aged 18 years and older; chronic lymphocytic leukaemia
Schedule	Randomised to either: • Experimental arm 1: Patients will be randomised to acalabrutinib administered orally starting on day 1 of cycle 1. Obinutuzumab IV infusions will be administered over a total of 6 treatment cycles. Daily administration of acalabrutinib will continue until disease progression or unacceptable toxicity. • Experimental arm 2: Acalabrutinib will be orally administered on day 1 of cycle 1 until disease progression or unacceptable toxicity. • Active comparator arm: Obinutuzumab IV infusions will be administered over a total of 6 treatment cycles. Chlorambucil will be orally administered on Days 1 and 15 of Cycles 1 through 6.
Follow-up	Not reported
Primary Outcomes	Progression-free survival in arm A compared to arm B [Time frame: 49 months]

Secondary Outcomes	At 49 months: • IRC-assessed objective response rate (ORR) in arm A versus arm B and arm A versus arm C • Time to next treatment (TTNT) in arm A versus arm B and arm A versus arm C • Incidence of adverse events, serious adverse events and changes in laboratory measurements in arm A versus arm B and arm A versus arm C • Overall survival in arm A versus arm B and arm A versus arm C
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Primary completion date reported as December 2019

ESTIMATED COST

The cost of acalabrutinib is not yet known.

ADDITIONAL INFORMATION

Acalabrutinib is a molecule being developed by Acerta Pharma. AstraZeneca acquired a majority equity stake in Acerta in February 2016 and Acerta is now a member of the AstraZeneca group.[17]

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal in development. Venetoclax with obinutuzumab for untreated chronic lymphocytic leukaemia (GID-TA10328). Expected publication date: TBC.
- NICE technology appraisal in development. Venetoclax for treating chronic lymphocytic leukaemia (TA487). November 2017.
- NICE technology appraisal guidance. Idelalisib for treating chronic lymphocytic leukaemia (TA359). October 2015.
- NICE technology appraisal guidance. Obinutuzumab in combination with chlorambucil for untreated chronic lymphocytic leukaemia (TA343). June 2015.
- NICE technology appraisal guidance. Ofatumumab in combination with chlorambucil or bendamustine for untreated chronic lymphocytic leukaemia (TA344). June 2015.
- NICE technology appraisal guidance. Bendamustine for the first-line treatment of chronic lymphocytic leukaemia (TA216). February 2011.
- NICE technology appraisal guidance. Rituximab for the first-line treatment of chronic lymphocytic leukaemia (TA174). July 2009.
- NICE technology appraisal guidance. Fludarabine monotherapy for the first-line treatment of chronic lymphocytic leukaemia (TA119). February 2007.
- NICE technology appraisal guidance. Guidance on the use of fludarabine for B-cell chronic lymphocytic leukaemia (TA29). September 2001.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for Cancer: Chemotherapy (Adult). B15/S/a.
- NHS England. 2013/14 NHS Standard Contract for Cancer: Radiotherapy (All Ages). B01/S/a.

OTHER GUIDANCE

- European Society for Medical Oncology. Chronic lymphocytic leukaemia: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. 2015.[18]
- London Cancer Alliance. LCA Haemato-Oncology Clinical Guidelines. 2015.[19]
- British Journal of Haematology. Guidelines on the diagnosis, investigation and management of chronic lymphocytic leukaemia. 2012.[20]

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