NIHR | Innovation Observatory

Newcastle University

Health Technology Briefing
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Acalabrutinib with venetoclax for previously untreated chronic lymphocytic leukaemia or small lymphocytic lymphoma

Company/Developer	AstraZeneca UK Ltd

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 33831	NICE ID: 11823	UKPS ID: Not Available

Licensing and Market Availability Plans

Currently in phase III clinical development.

Summary

Acalabrutinib in combination with venetoclax is in clinical development for the first-line treatment of chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL). CLL and SLL are a type of cancer that affects the white blood cells. In CLL the spongy material found inside some bones (bone marrow) produces too many white blood cells called lymphocytes, which are not fully developed and do not work properly. This can cause a range of problems, such as an increased risk of infections, tiredness, swollen glands, and unusual bleeding or bruising. Despite there being several therapeutic options, CLL still has poor outcomes and often returns after treatment.

Acalabrutinib, administered orally, blocks an enzyme called Bruton's tyrosine kinase (BTK), which helps B cells (B-lymphocytes) to survive and grow. By blocking BTK, acalabrutinib can slow down the build-up of cancerous white blood cells in CLL, thereby delaying progression of the cancer. Venetoclax, also administered orally, attaches to a protein called BCL-2, which is present in high amounts in leukaemia cancer cells. By attaching to and blocking BCL-2, venetoclax causes the death of cancer cells and slows down progression of the disease. If licensed, the combination of acalabrutinib and venetoclax will provide an additional first-line treatment option for patients with CLL or SLL.

Proposed Indication

Previously untreated chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL).[1]

Technology

Description

Acalabrutinib (Calquence) is a selective inhibitor of Bruton tyrosine kinase (BTK). BTK is a signalling molecule of the B-cell antigen receptor (BCR) and cytokine receptor pathways. In B-cells, BTK signalling results in B-cell survival and proliferation, and is required for cellular adhesion, trafficking, and chemotaxis. Acalabrutinib and its active metabolite, ACP-5862, form a covalent bond with a cysteine residue in the BTK active site, leading to irreversible inactivation of BTK with minimal off-target interactions.[2]

Venetoclax is a potent, selective inhibitor of B-cell lymphoma (BCL)-2, an anti-apoptotic protein. Overexpression of BCL-2 has been demonstrated in 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 permeabilisation (MOMP), caspase activation, and programmed cell death.[3]

Acalabrutinib in combination with venetoclax is currently in clinical development for the first-line treatment of CLL and SLL. In the phase III clinical trial (MAJIC, NCT05057494) patients will be given acalabrutinib as an oral capsule and venetoclax as an oral tablet.[1]

Key Innovation

Current first-line treatment for CLL includes targeted drugs and chemotherapy.[4] It has been found that BTK and BCL-2 inhibitors are synergistic in the preclinical setting in CLL. The combination of the first-generation BTK inhibitor ibrutinib plus venetoclax can lead to deep responses (i.e., a high proportion of patients who achieve complete remission or undetectable minimal residual disease (MRD), or both, in the peripheral blood and bone marrow), with high rates of undetectable MRD in previously untreated patients with CLL. Data from the ELEVATE-RR study comparing ibrutinib head-to-head with the more specific, second-generation BTK inhibitor acalabrutinib in CLL showed that acalabrutinib has similar efficacy but an improved toxicity profile compared with ibrutinib. Moreover, unlike ibrutinib, which increases venetoclax exposure when given in combination, acalabrutinib does not alter venetoclax exposure, suggesting that their combination might achieve deep responses with less toxicity than ibrutinib-based combination regimens.[5,6]

If licensed, acalabrutinib in combination with ventoclax will provide an additional first-line treatment option for patients with CLL or SLL.

Regulatory & Development Status

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

Acalabrutinib as monotherapy or in combination with obinutuzumab has Marketing Authorisation in the EU/UK for the first-line treatment of adult patients with CLL. As a monotherapy, acalabrutinib is also indicated for the treatment of adult patients with CLL who have received at least one prior therapy.[2]

Acalabrutinib in combination with venetoclax is also in phase II/III development for:[7]

- refractory or recurrent CLL
- relapsed or refractory mantle cell lymphoma

Patient Group

Disease Area and Clinical Need

CLL and SLL are slow-growing cancers in which immature lymphocytes are found in the blood and bone marrow and/or in the lymph nodes. CLL and SLL are the same disease, but in CLL cancer cells are found mostly in the blood and bone marrow. In SLL cancer cells are found mostly in the lymph nodes.[8] CLL is the most common type of leukaemia, which affects blood cells in the bone marrow and progresses slowly over time. In CLL, the bone marrow makes too many abnormal white blood cells called lymphocytes. The abnormal lymphocytes that are produced are not fully developed and do not work properly. Over time, these abnormal lymphocytes build up in the lymphatic system and may cause large, swollen lymph nodes. The abnormal lymphocytes can also build up in the bone marrow. This leaves less space for normal white blood cells, red blood cells and platelets to develop. Symptoms include regular infections, anaemia, tiredness, bleeding and bruising easily, high temperature, night sweats, swollen glands and unintentional weight loss.[9,10] It is not known what causes CLL but risk factors include increased age, being male, having a close relative with CLL, and European descent.[9]

CLL accounted for 1% of all new cancer cases in the UK in 2016-18 and there were on average 3,803 new cases of CLL each year. The age standardised incidence rate of CLL in England is 8.8 and 4.4 per 100,000 amongst males and females respectively (2016-18).[11] In England (2021-22), there were 22,261 finished consultant episodes (FCEs) and 21,268 admissions for CLL of B-cell type (ICD-10 code C91.1), which resulted in 18,957 day cases and 13,071 FCE bed days.[12] In England (2017), there were 4,226 patients diagnosed with lymphoid leukaemia (ICD-10 code C91) and 1,085 deaths where lymphoid leukaemia was the underlying cause.[13]

Recommended Treatment Options

CLL and SLL are treated in the same way.[14] The most common first-line treatments for CLL are targeted drugs (such as acalabrutinib, ibrutinib, venetoclax, idelalisib, rituximab and obinutuzumab) or chemotherapy.[4] The National Institute for Health and Care Excellence (NICE) currently recommends the following therapies for the first-line treatment of CLL:[15]

- acalabrutinib
- venetoclax in combination with obinutuzumab
- idelalisib in combination with rituximab
- obinutuzumab in combination with chlorambucil
- bendamustine
- rituximab in combination with fludarabine and cyclophosphamide

Clinical Trial Information

Trial	**MAJIC**, NCT05057494, 2021-003936-10; A Phase III Prospective, Multicenter, Randomized, Open-Label Trial of Acalabrutinib Plus Venetoclax Versus Venetoclax Plus Obinutuzumab in Previously Untreated Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma **Phase III** – Recruiting **Locations:** 3 EU countries, USA and other countries

	Primary completion date: April 2029
Trial Design	Randomised, parallel assignment, open-label
Population	N=600 (estimated); documented treatment-naive CLL/SLL requiring treatment according to iwCLL guidelines 2018; aged 18 years to 130 years
Intervention(s)	Acalabrutinib (oral) and venetoclax (oral)
Comparator(s)	Venetoclax (oral) and obinutuzumab (IV)
Outcome(s)	**Primary outcome:** • Progression-free survival (PFS) [Time frame: until progressive disease (PD) [assessed up to 6.6 years].] See trial record for full list of other outcomes
Results (efficacy)	-
Results (safety)	-

Estimated Cost

Acalabrutinib is already marketed in the UK; a pack of 60 x 100mg capsules costs £5,059.[16]

Venetoclax is already marketed in the UK; a pack of 14 x 10mg tablets costs £59.87, a pack of 7 x 50mg tablets costs £149.67, a pack of 7 x 100mg tablets costs £299.34, a pack of 14 x 100mg tablets costs £598.68 and a pack of 112 x 100mg tablets costs £4,789.47.[17]

Relevant Guidance

NICE Guidance

- NICE technology appraisal in development. Zanubrutinib for untreated chronic lymphocytic leukaemia (GID-TA10966). Expected date of issue to be confirmed.
- NICE technology appraisal in development. Ibrutinib with venetoclax for untreated chronic lymphocytic leukaemia (GID-TA10746). Expected May 2023.
- NICE technology appraisal. Venetoclax for treating chronic lymphocytic leukaemia (TA796). June 2022.
- NICE technology appraisal. Acalabrutinib for treating chronic lymphocytic leukaemia (TA689). April 2021.
- NICE technology appraisal. Venetoclax with obinutuzumab for untreated chronic lymphocytic leukaemia (TA663). December 2020.
- NICE technology appraisal. Ibrutinib for previously treated chronic lymphocytic leukaemia and untreated chronic lymphocytic leukaemia with 17p deletion or TP53 mutation (TA429). January 2017.
- NICE technology appraisal. Idelalisib for treating chronic lymphocytic leukaemia (TA359). October 2015.
- NICE technology appraisal. Obinutuzumab in combination with chlorambucil for untreated chronic lymphocytic leukaemia (TA343). June 2015.
- NICE technology appraisal. Bendamustine for the first-line treatment of chronic lymphocytic leukaemia (TA216). February 2011.

- NICE technology appraisal. Rituximab for the first-line treatment of chronic lymphocytic leukaemia (TA174). July 2009.
- NICE technology appraisal. Fludarabine monotherapy for the first-line treatment of chronic lymphocytic leukaemia (TA119). February 2007.

NHS England (Policy/Commissioning) Guidance

- NHS Northern Cancer Alliance. Haematology Cancer Clinical Guidelines. November 2019.
- 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

- British Society for Haematology. Guideline for the treatment of chronic lymphocytic leukaemia. March 2022.[18]
- European Society for Medical Oncology (ESMO). Chronic Lymphocytic Leukaemia: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. October 2020.[19]
- International Workshop on Chronic Lymphocytic Leukaemia. iwCLL guidelines for diagnosis, indications for treatment, response assessment, and supportive management of CLL. June 2018.[20]
- British Committee for Standards in Haematology. Guidelines on the diagnosis, investigation and management of chronic lymphocytic leukaemia. October 2012.[21]

Additional Information

AstraZeneca 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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