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Health Technology Briefing
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Acalabrutinib with bendamustine and rituximab for treating previously untreated mantle cell lymphoma

Company/Developer	AstraZeneca UK Ltd

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 24111	NICE ID: 10553	UKPS ID: 660033

Licensing and Market Availability Plans

Currently in phase II and III clinical trials.

Summary

Acalabrutinib in combination with bendamustine and rituximab is in clinical development for the first line treatment of mantle cell lymphoma (MCL). MCL is a rare and aggressive form of non-Hodgkin lymphoma. It affects the B-cells (a type of white blood cells) and develops in the lymph nodes. The abnormal B-cells start to collect in the lymph nodes or body organs, where they can form tumours and begin to cause problems within the lymphatic system or the organ where they are growing. Current first-line treatment of MCL involves treatment options that can be high intensity and unsuitable for the elderly, thus There is a medical need for novel strategies to improve disease control in patients with MCL.

Acalabrutinib works by blocking an enzyme called Bruton's tyrosine kinase (BTK), which is found in B-cells that promotes their growth and survival. By blocking BTK, acalabrutinib slows down the build-up of cancerous B-cells in MCL, thereby delaying or stopping the progression of the disease. Acalabrutinib will be administered orally in combination with intravenous bendamustine and rituximab, which is a novel combination. Acalabrutinib with bendamustine and rituximab in treatment-naive patients with MCL may improve disease control, and if licensed it will provide an alternative first-line treatment option.

Proposed Indication

Treatment of previously untreated mantle cell lymphoma (MCL).[1]

Technology

Description

Acalabrutinib (Calquence, ACP-196) 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.[1,2]

Acalabrutinib in combination with bendamustine and rituximab is currently in development for the first line treatment of MCL. In the phase III clinical trial (NCT02972840), acalabrutinib will be administered twice per day (BID) orally (PO), in combination with intravenous (IV) administration of bendamustine on days 1 and 2 and IV rituximab on day 1, with cycles repeated every 28 days.[1]

Key Innovation

MCL is an aggressive B-cell non-Hodgkin's lymphoma (NHL) that remains incurable with current therapies, including standard first line bendamustine and rituximab. There is a medical need for novel strategies to improve disease control in elderly patients with MCL. Acalabrutinib is a highly selective, potent, covalent BTK inhibitor with minimal off-target activities. For patients with relapsed/refractory MCL, acalabrutinib demonstrated an overall response rate of 81%, with 40% of patients achieving a complete response. Taken together, combining acalabrutinib with bendamustine and rituximab in treatment-naive patients with MCL may improve disease control.[3]

If licensed, acalabrutinib in combination with bendamustine and rituximab will provide an additional treatment option for patients with MCL.

Regulatory & Development Status

Acalabrutinib in combination with bendamustine and rituximab does not currently have marketing authorization in the EU/UK for any indication.

Acalabrutinib is licensed for the following indications:[2]

- As monotherapy or in combination with obinutuzumab for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL).
- As monotherapy for the treatment of adult patients with CLL who have received at least one prior therapy.

Acalabrutinib as combination therapy is currently in phase II and III development for several indications which are as follows:[4]

- CLL
- Small lymphocytic lymphoma
- Diffuse large B cell lymphoma
- Marginal zone lymphoma
- Waldenström Macroglobulinemia

Acalabrutinib has received an orphan drug designation in the EU in March 2016 for MCL.[5]

Patient Group

Disease Area and Clinical Need

MCL is a rare type of B-cell NHL. NHL is a cancer of the lymphatic system. It affects the B-cells and develops in the part of the lymph node called the mantle zone. The abnormal B-cells start to collect in the lymph nodes or body organs. They can then form tumours and begin to cause problems within the lymphatic system or the organ where they are growing.[6] Although the exact underlying cause is unknown, researchers have identified several genetic changes in the B-cells, which contribute to the multiplication of the cancer cells. For MCL, a mutation referred to as t(11;14), leads to the overproduction of a protein called cyclin D1 in the lymphoma cells. Cyclin D1 protein is involved in regulating cell cycle progression and cell proliferation, therefore overexpression of cyclin D1 likely contributes to malignant transformation of cells and excessive growth of malignant B-lymphocytes. However, increased expression of cyclin D1 is not sufficient to cause MCL on its own. Investigators also indicate that abnormalities in the expression of other genes (e.g., the p53 gene, which normally functions as a tumour suppressor gene) may play some role in leading to MCL.[7] MCL presents with similar symptoms as most other NHLs, which includes painless swelling in the neck, armpits or groin, heavy sweating, weight-loss and unexplained itching.[6]

Around 600 people are diagnosed with MCL each year in the UK.[8] The hospital episode statistics (HES) for diagnosis in England in 2020-2021, recorded a total of 6,364 finished consultant episodes (FCEs) for MCL (ICD-10: C83.1), resulting in a total of 5,894 admissions. Of them, 4,115 primary diagnosed cases were aged 65 years or older.[9] For patients aged 60-79 years, almost 45% will survive their lymphoma for 5 years or more after diagnosis, and for those 80 years or older, around 10% will survive their lymphoma for 5 years or more after they are diagnosed.[10]

Recommended Treatment Options

NICE recommends the following treatment option for first line treatment of MCL:[11]

- Chemotherapy in combination with rituximab as first-line treatment for people with advanced-stage MCL who are symptomatic. This takes the person's fitness into account when deciding on the intensity of chemotherapy.
- Cytarabine-containing immunochemotherapy for people with advanced-stage MCL who are fit enough to tolerate an intensive approach.
- Radiotherapy for people with localised stage I or II MCL.
- Bortezomib is recommended, as an option for previously untreated MCL in adults for whom haematopoietic stem cell transplantation is unsuitable.

Clinical Trial Information

Trial	NCT02972840; A Phase 3, Randomized, Double-blind, Placebo-controlled, Multicenter Study of Bendamustine and Rituximab (BR) Alone Versus in Combination With Acalabrutinib (ACP-196) in Subjects With Previously Untreated Mantle Cell Lymphoma. **Phase III –** Recruiting **Location(s) –** 12 EU countries, USA, Canada, and other countries

	Primary completion date – April 2023
Trial Design	Randomised, parallel assignment, triple-blinded
Population	N = 626 (planned); participants aged 65 years and older with previously untreated MCL, with documentation of a chromosome translocation t(11;14)(q13;q32) and/or overexpression of cyclin D1 in association with other relevant markers.
Intervention(s)	Acalabrutinib will be administered BID orally, in combination with IV bendamustine on days 1 and 2 and IV rituximab on day 1, with cycles repeated every 28 days.
Comparator(s)	Placebo in combination with bendamustine and rituximab
Outcome(s)	• Progression-free survival per the Lugano Classification for NHL in Arm 1 compared to Arm 2 [Time frame: Up to 6 years] See trial record for full list of other outcomes
Results (efficacy)	-
Results (safety)	-

Estimated Cost

The NHS indicative price (hospital only) of acalabrutinib is £5,059 for a pack of 60 x 100mg capsules.[12]

Relevant Guidance

NICE Guidance

- NICE technology appraisal in development. Ibrutinib for untreated mantle cell lymphoma (GID-TA10185). Expected date of issue to be confirmed.
- NICE technology appraisal guidance. Bortezomib for previously untreated mantle cell lymphoma (TA370). December 2015.
- NICE guideline. Non-Hodgkin's lymphoma: diagnosis and management (NG52). July 2016.
- NICE guideline. Haematological cancers: improving outcomes (NG47). May 2016.
- NICE quality standard. Haematological cancers (QS150). June 2017.

NHS England (Policy/Commissioning) Guidance

No relevant guidance identified.

Other Guidance

- British Society for Haematology. Guideline for the management of mantle cell lymphoma. May 2018.[13]
- European Society for Medical Oncology (ESMO). Newly diagnosed and relapsed mantle cell lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. May 2017.[14]

Additional Information

References

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