NIHR | Innovation Observatory

Newcastle University

Health Technology Briefing
January 2022

Zanubrutinib for treating marginal zone lymphoma

Company/Developer	BeiGene Ltd

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 27788	NICE ID: 10746	UKPS ID: Not Available

Licensing and Market Availability Plans

Currently in phase III clinical trials.

Summary

Zanubrutinib is currently in clinical development for treating relapsed or refractory marginal zone lymphoma (MZL). MZL is a rare group of non-Hodgkin's lymphomas that affect a type of immune cell called B-cells. These MZLs are slow growing and do not always cause symptoms. Broad symptoms that do sometimes appear in MZL patients include unexplained weight loss, night sweats and fever. There are a limited number of treatment options available to MZL patients who are relapsed or refractory to initial treatment, and current treatments often result in adverse side-effects. Therefore, there is a need to develop additional treatment options for these patients.

Zanubrutinib is given to patients by oral administration and works by blocking the action of a protein known as Bruton's tyrosine kinase (BTK). BTK is an important protein involved in the growth of cancerous B-cells found in MZL. By blocking the action of BTK, zanubrutinib is expected to slow tumour growth in MZL. Zanubrutinib is thought to be more effective than current treatments for MZL because it is more selective to BTK. This means there will be fewer adverse side-effects associated with the treatment. If licensed, zanubrutinib will offer an additional treatment option to patients with relapsed or refractory MZL who currently have limited treatment options available.

Proposed Indication

This briefing reflects the evidence available at the time of writing and a limited literature search. It is not intended to be a definitive statement on the safety, efficacy or effectiveness of the health technology covered and should not be used for commercial purposes or commissioning without additional information. A version of the briefing was sent to the company for a factual accuracy check. The company was available to comment.
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Monotherapy treatment of adult patients with marginal zone lymphoma (MZL) who have received at least one prior anti-CD20-based therapy.[1]

Technology

Description

Zanubrutinib (Brukinsa, BGB-3111) a small molecule inhibitor of Bruton's tyrosine kinase (BTK). BTK is an enzyme that plays a role in oncogenic signalling pathways, where it promotes the survival and proliferation of malignant B-cells. Zanubrutinib inhibits BTK by forming a covalent bond with cysteine 481 residue in the adenosine triphosphate (ATP)-binding pocket of BTK. By blocking the action of BTK, zanubrutinib inhibits the proliferation, trafficking, chemotaxis, and adhesion of malignant B-cells, ultimately leading to reduced tumour size. Zanubrutinib was also shown to downregulate programmed death-ligand 1 (PD-1) and cytotoxic T lymphocyte-associated antigen-4 (CTLA-4) on CD4+ T-cells.[1,2]

Zanubrutinib is currently in clinical development for adult patients with MZL who are relapsed or refractory to at least one prior line of systemic therapy, including an anti-CD20 agent. In the phase II (MAGNOLIA trial; NCT03846427) participants received 160mg zanubrutinib by oral administration twice per day.[1]

Key Innovation

Currently available targeted therapies for patients with MZL are designed to inhibit intracellular signalling pathways, including the B-cell receptor (BCR), that are associated with the disease. However, these existing targeted therapies also inhibit off-target tyrosine kinases causing adverse events that can result in treatment discontinuation. Therefore, there is an unmet need to develop more effective, and better tolerated treatment options to improve long-term outcomes for patients with MZL.[3] BTK was developed to optimise bioavailability, half-life, and selectivity in order to deliver complete and sustained inhibition of BTK which is continuously synthesised.[4] Due to the enhanced selectivity of zanubrutinib to BTK, it displays higher potency and fewer off-target effects compared to first generation BTK inhibitors.[2]

In the phase II MAGNOLIA trial (NCT03846427), zanubrutinib demonstrated a high overall response rate (ORR) and complete response (CR) with durable disease control, and a favourable safety profile in patients with relapsed or refractory MLZ.[1,3]

Regulatory & Development Status

Zanubrutinib currently has Marketing Authorisation in the EU/UK for the treatment of adult patients with Waldenstrom's macroglobulinaemia who have received at least one prior therapy, or as first-line treatment for patients unsuitable for chemo-immunotherapy.[5,6]

Zanubrutinib has been awarded the following regulatory designations:

- Accelerated approval by the US FDA in September 2021 for the treatment of MZL.[7]

Zanubrutinib is also in clinical development for the treatment of other B-cell malignancies .[8]

Patient Group

Disease Area and Clinical Need

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Marginal zone lymphoma (MZL) is a type of low-grade (slow-growing) non-Hodgkin lymphoma (NHL) that develops from B-cells that are normally found at the edge of areas of lymphoid tissue (collection of lymphocytes which is known as the marginal zone.[9] Approximately 8% of all NHL cases are MZL.[10] There are three types of MZL: mucosa-associated lymphoid tissue (MALT), which most commonly develops in the stomach; splenic, which develops in the spleen; and nodal which develops in the lymph nodes.[9,11,12] Risk factors associated with MZL include infection such as hepatitis C (nodal and splenic MZL) or *H. pylori* infection (gastric MZL), and autoimmune conditions that trigger inflammation. Symptoms vary according on the type of MZL however, symptoms associated with all forms of the disease include: fever without an infection; night sweats; unexplained weight loss; skin rash; chest or abdominal pain; and fatigue.[13]

Refractory MZL refers to when the lymphoma does not respond to treatment or when the response to treatment is limited. Relapsed MZL is when the lymphoma reappears after a period of remission following successful treatment.[14] MZL is a slow growing lymphoma and with treatment can be kept under control. However, if there is a relapse there is a risk of transformation of the cancer into a faster growing type of lymphoma. This occurs in around 10% of people with MALT lymphoma, and around 10-20% of people with nodal or splenic MZL.[9,11,12]

In England 2020-21, there were 2,100 finished consultant episodes (FCEs) and 2,007 admissions for extranodal marginal zone B-cell lymphoma of MALT (ICD-10 code C88.4) that resulted in 1,739 day cases and 1,326 FCE bed days. There were 5,113 FCE and 4,896 admissions for patients with primary diagnosis of small cell B-cell lymphoma (ICD-10 code C83.0), which includes nodal and splenic MZL. This resulted in 4,363 and 2,878 FCE bed days.[15] The age-standardised incidence rates of MZL per 100,000 of the UK population was 26.2 between 2004 and 2012. Across the same time period, the 5-year relative survival rate was 77.2%.[16]

Recommended Treatment Options

Currently there are no treatment options recommended by NICE for the treatment of relapsed or refractory MZL.

The European Society for Medical Oncology (ESMO) management guidelines recommend that all patients with gastric MZL be treated with an anti *H. pylori* antibiotic regimen to eradicate the infection. For patients with non-gastric MZL or patients who do not achieve lymphoma regression following antibiotic therapy, irradiation and systemic oncological therapies are recommended.[17] The most likely treatment option offered to patients with advanced stage MZL is an antibody therapy such as rituximab either as a monotherapy or in combination with chemotherapy (chemo-immunotherapy).[9,11,12]

Clinical Trial Information

Trial	NCT04170283; An Open-label, Multi-centre, Long-term Extension Study of Zanubrutinib (BGB-3111) Regimens in Patients With B-cell Malignancies **Phase III:** Enrolling by invitation **Locations:** 1 EU country, UK, United States and other countries **Primary completion date:** December 2024
Trial Design	Single group assignment, open-label, non-randomised
Population	N=500; adults aged 18 years and older; currently participating or participated recently in a BeiGene parent study; intend to continue or start zanubrutinib treatment; does not meet any protocol specified criteria for zanubrutinib hold or

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	permanent discontinuation, and, in the opinion of the investigator, will continue to benefit from zanubrutinib treatment
Intervention(s)	Zanubrutinib (oral administration)
Comparator(s)	No comparator
Outcome(s)	Primary outcome measure: • Incidence of adverse events (AEs) [Time frame: Up to 5 years] See trial record for full list of outcome measures
Results (efficacy)	
Results (safety)	

Trial	**MAGNOLIA**, NCT03846427, 2018-001284-24; A Phase 2, Open-label Study of Zanubrutinib (BGB-3111) in Patients With Relapsed or Refractory Marginal Zone Lymphoma **Phase II:** Active, not recruiting **Locations:** 3 EU countries, UK, United States and other countries **Primary completion date:** December 2021
Trial Design	Single group assignment, open-label
Population	N=68; adults aged 18 years and older; histologically confirmed diagnosis of MZL including splenic, nodal and extranodal subtypes; previously received one or more lines of therapy including at least one CD20-rirected regimen (either as monotherapy or as chemoimmunotherapy), with documented failure to achieve at least partial response (PR) or documented progressive disease (PD) after, the most recent systemic treatment
Intervention(s)	Zanubrutinib (oral administration)
Comparator(s)	No comparator
Outcome(s)	Primary outcome measure: • Overall response rate (ORR) determined by independent central review (ICR) [Time frame: Up to 3 years] See trial record for full list of outcome measures
Results (efficacy)	After a median follow-up of 15.7 months (range, 1.6 to 21.9 months), the IRC-assessed ORR was 68.2% and complete response (CR) was 25.8%. The ORR by investigator assessment was 74.2%, and the CR rate was 25.8%. The median duration of response (DOR) and median progression-free survival (PFS) by independent review was not reached. The IRC-assessed DOR rate at 12 months was 93.0%, and IRC-assessed PFS rate was 82.5% at both 12 and 15 months.[3]
Results (safety)	Treatment was well tolerated with the majority of adverse events (AEs) being grade 1 or 2. The most common AEs were diarrhoea (22.1%), contusion (20.6%), and constipation (14.7%). Atrial fibrillation/flutter was reported in 2 patients; 1

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	patient had grade 3 hypertension. No patient experienced major haemorrhage. In total, 4 patients discontinued treatment due to AEs, none of which were considered treatment-related by the investigators.[3]

Estimated Cost

The cost of zanubrutinib is not yet known.

Relevant Guidance

NICE Guidance

- NICE technology appraisal in development. Pralsetenib for treating relapsed or refractory marginal zone lymphoma (GID-TA10863). Expected date of issue to be confirmed.
- NICE clinical guideline. Non-Hodgkin's lymphoma: diagnosis and management (NG52). July 2016.

NHS England (Policy/Commissioning) Guidance

- Haematology Expert Advisory Group (EAG) on behalf of NHS Northern Cancer Alliance. Haematology Cancer Clinical Guidelines (V17). April 2018.

Other Guidance

- European Society for Medical Oncology. Marginal Zone Lymphomas: ESMO Clinical Practical Guidelines for diagnosis, treatment and follow-up. 2020.[17]
- National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines on Oncology: Non-Hodgkin's Lymphomas: Marginal Zone Lymphomas. 2015.[18]

Additional Information

BeiGene 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.

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