NIHR | Innovation Observatory

Newcastle University

Health Technology Briefing
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Zanubrutinib plus obinutuzumab for treating relapsed or refractory follicular lymphoma

Company/Developer	BeiGene UK Ltd

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 20511	NICE TSID: Not available	UKPS ID: Not available

Licensing and Market Availability Plans

Currently in phase II clinical trials.

Summary

Zanubrutinib, combined with an already licensed medicine, obinutuzumab, is in clinical development for the treatment of patients with relapsed or refractory B-cell follicular lymphoma. Follicular lymphoma is a slow-growing blood cancer that affects white blood cells. In follicular lymphoma, the affected white blood cells multiply abnormally and aggregate in certain parts of the body, such as the lymph nodes. Recurrence of lymphoma following remission, known as a relapse, and lymphoma unresponsive to therapy, known as refractory lymphoma, can make the condition more difficult to treat as treatment options are limited. The most common symptom of follicular lymphoma includes enlargement of lymph nodes in the neck, underarms, abdomen or groin. Typically follicular lymphoma is not considered curable, although patients can live for many years. Therefore, there is an unmet need for a more effective treatment option.

Orally delivered zanubrutinab is a next-generation medicine which works by inhibiting the action of an enzyme called bruton's tyrosine kinase (BTK). BTK is involved in all B-cell growth, including those multiplying abnormally. By inhibiting the activity of BTK, zanubrutinab, is expected to slow the progression of follicular lymphoma. If licensed, zanubrutinib, in combination with obinutuzumab, will offer an additional treatment option for adults with relapsed or refractory B-cell follicular lymphoma (FL).

Proposed Indication

Adults with relapsed/refractory B-cell follicular lymphoma and who have received two or more systemic treatments for follicular lymphoma.[1]

Technology

Description

Zanubrutinib (BRUKINSA) is a small molecule inhibitor of Bruton's tyrosine kinase (BTK) that is currently being evaluated in clinical trial programmes as a monotherapy and in combination with other therapies, such as obinutuzumab (Gazyvaro), to treat various B-cell malignancies including follicular lymphoma.[2] Zanubrutinib forms a covalent bond with a cysteine residue in the BTK active site, inhibiting BTK activity and preventing B-cell proliferation. BTK is a signalling molecule of the B-cell antigen receptor (BCR) and cytokine receptor pathways. In B cells, BTK signalling activates pathways necessary for B-cell proliferation, trafficking, chemotaxis, and adhesion.[3]

In the pivotal phase II clinical trial, ROSEWOOD (NCT03332017)[1] patients received oral zanubrutinib 160 mg twice daily + obinutuzumab or obinutuzumab alone in the control arm (both arms in 28-day cycles, at 1000 mg intravenously on days 1, 8, and 15 of cycle 1; day 1 of cycles 2-6; and then once every 8 weeks) until progressive disease, toxicity or a maximum of 30 months of obinutuzumab.[4]

Key Innovation

Current treatments for follicular lymphoma are based on anti-CD20 antibodies and classical chemotherapy regimens. Newer, next-generation medicines such as zanubrutinab irreversibly target molecules such as BTK inhibitors preventing cell growth.[5] Because new BTK is continuously synthesized, zanubrutinib was specifically designed to deliver complete and sustained inhibition of the BTK protein by optimising bioavailability, half-life, and selectivity.[2] Results from the pivotal trial, ROSEWOOD, suggest that zanubrutinib in combination with obinutuzumab is safe and effective in treating patients with relapsed or refractory follicular lymphoma, resulting in improved overall response rates (ORRs).[2]

Regulatory & Development Status

Zanubrutinib currently has marketing authorisation in the UK as a monotherapy for adults with previously treated Waldenström's macroglobulinaemia and marginal zone lymphoma, and adults with chronic lymphocytic leukaemia.[3]

Zanubrutinib is currently in phase II and III clinical development for the treatment of the following:[6]

- primary membranous nephropathy
- B-cell malignancies
- chronic lymphocytic leukaemia
- small lymphocytic lymphoma
- mantle cell lymphoma
- marginal zone lymphoma
- waldenstrom macroglobulinaemia
- lupus nephritis
- non-hodgkin lymphoma
- primary and secondary central nervous system lymphoma
- leukaemia
- follicular lymphoma

Patient Group

Disease Area and Clinical Need

Follicular lymphoma is a type of non-Hodgkin lymphoma and a cancer of the lymphatic system. Follicular lymphoma develops when the body makes abnormal B lymphocytes. These lymphocytes are a type of white blood cell that usually helps us fight infections. When you have lymphoma, abnormal lymphocytes build up in the lymph nodes or other organs in the body. Follicular lymphoma is slow growing, and you might not need treatment immediately.[7] Early symptoms of follicular lymphoma may be subtle and progress gradually over time; however, commonly reported symptoms are lump formation in the lymph nodes in the neck or collar bone, unexplained weight loss, fever, night sweats, frequent infections and fatigue.[8] It is common for follicular lymphoma patients to relapse, and several courses of treatment may be needed. Occasionally, follicular lymphoma patients may be refractory (doesn't respond well) to initial treatments and will require second and third-line treatments.[8] There is no known cause for follicular lymphoma, and it is not thought to have a hereditary familial link.[8]

Non-Hodgkin lymphoma is the 6th most common cancer in the UK, accounting for 4% of all new cancer cases (2016-2018).[9] The age standardised incidence rate of non-Hodgkin lymphoma in England is 19.6 and 27.8 per 100,000 amongst females and males, respectively.[9] In England (2021-22), there were 21,163 finished consultant episodes (FCEs) and 20,446 admissions for follicular lymphoma (ICD-10 code C82), which resulted in 18,999 day cases and 11,598 FCE bed days.[10] In England (2017), there were 2,168 patients diagnosed with follicular lymphoma and 202 deaths registered where follicular lymphoma was the underlying cause.[11] For patients diagnosed between 2013 and 2017, followed up to 2018, the 1-year and 5-year survival rates were 79.4% and 65.6%, respectively.[12]

Recommended Treatment Options

The National Institute for Health and Care Excellence (NICE) recommends the following treatment options for adults with previously treated follicular lymphoma include:

- rituximab with chemotherapy[13]
- lenalidomide with rituximab[14]
- obinutuzumab with bendamustine[15]

Clinical Trial Information

Trial	**ROSEWOOD**, NCT03332017, EudraCT 2017-001552-54; An International, Phase 2, Open-Label, Randomized Study of BGB-3111 Combined With Obinutuzumab Compared With Obinutuzumab Monotherapy in Relapsed/ Refractory Follicular Lymphoma **Phase II**: Active, not recruiting **Location(s):** Six EU countries, UK, USA, Canada and other countries **Primary Completion date:** June 2022
Trial Design	Randomised, parallel assigned, open label
Population	N=217; People with relapsed/refractory follicular lymphoma; aged 18 years and over
Intervention(s)	Zanubrutinib oral capsules (160 mg twice per day) plus obinutuzumab intravenously (1,000 mg on days 1, 8 and 15 of cycle 1 (28 days), then 1,000mg on day 1 of cycles 2 to 6, then 1,000mg every 8 weeks).

Comparator(s)	Obinutuzumab (1,000 mg intravenously on days 1, 8, and 15 of cycle 1 (28 days), then 1,000 mg on day 1 of cycles 2 to 6, then 1,000 mg every 8 weeks).
Outcome(s)	Primary Outcome(s): Overall response rate (ORR) as assessed by independent central review [time frame: up to 3 years] See trial record for a full list of other outcomes
Results (efficacy)	The ROSEWOOD trial met its primary endpoint, with a 69% overall response rate in the zanubrutinib plus obinutuzumab arm versus 45.8% in the obinutuzumab arm (p = 0.0012) and median follow-up of 20.2 months.[16] Zanubrutinib plus obinutuzumab complete response rate was 39.3% compared to 19.4% for obinutuzumab alone; 18-month duration of response rate was 69.3% in the zanubrutinib plus obinutuzumab arm versus 41.9% in the obinutuzumab arm.[16] Median progression-free survival was 28 months in the zanubrutinib plus obinutuzumab arm compared to 10.4 months in the obinutuzumab arm (hazard ratio: 0.50 [95% CI, 0.33, 0.75]; p=0.0007).[16]
Results (safety)	Zanubrutinib plus obinutuzumab was generally well-tolerated.[16] Non-haematological treatment-emergent adverse events of any grade that occurred more frequently in the zanubrutinib plus obinutuzumab arm vs obinutuzumab (>5% difference) were petechiae (6.3% vs 0%) and herpes zoster infection (6.3% vs 0%); in contrast, pyrexia (13.3% vs 19.7%) and infusion-related reaction (2.8% vs 9.9%) occurred more frequently in patients on obinutuzumab. When adjusted for duration of treatment exposure, incidences of infection and cytopenia were similar, and incidence of all grades of haemorrhage was 2.4 in the zanubrutinib plus Obinutuzumab arm vs 1.3 in Obinutuzumab persons per 100 person-months. Two patients in each treatment group reported major haemorrhage. Incidences of atrial fibrillation and hypertension were low and similar in both treatment arms.[16]

Estimated Cost

Zanubrutinib is already licensed in the UK. The NHS indicative cost of a pack of 120 x 80mg capsules of zanubrutinib is £4,928.65.[17]

Relevant Guidance

NICE Guidance

- NICE technology appraisal in development. Ibrutinib for treating relapsed or refractory follicular lymphoma (GID-TA10223). Expected date of issue to be confirmed.
- NICE technology appraisal awaiting development. Ibrutinib for treating relapsed or refractory follicular lymphoma and marginal zone lymphoma (GID-TA10525). Expected date of issue to be confirmed.
- NICE technology appraisal. Lenalidomide with rituximab for previously treated follicular lymphoma (TA627). April 2020.
- NICE technology appraisal. Rituximab for the treatment of relapsed or refractory stage III or IV follicular non-Hodgkin's lymphoma (TA137). February 2008.

- NICE clinical guideline. Non-Hodgkin's lymphoma: diagnosis and management (NG52). July 2016.

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.
- NHS England. 2013/14 NHS Standard Contract for Cancer: Teenagers & Young Adults. B17/S/a.

Other Guidance

- British Society for Haematology. The investigation and management of follicular lymphoma. 2020.[18]
- European Society of Medical Oncology. Newly diagnosed and relapsed follicular lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. 2020.[19]
- European Society of Medical Oncology. ESMO Consensus conferences: guidelines on malignant lymphoma. Part 2: marginal zone lymphoma, mantle cell lymphoma, peripheral T-cell lymphoma. 2013.[20]

Additional Information

BeiGene UK Ltd 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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