Health Technology Briefing
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Zanubrutinib for previously treated mantle cell lymphoma

Company/Developer	BeiGene Ltd

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 37640	NICE ID: Not available	UKPS ID: 672481

Licensing and Market Availability Plans

Currently in phase II clinical trials

Summary

Zanubrutinib is in clinical development for the treatment of mantle cell lymphoma (MCL) in adults who have received at least one prior treatment. MCL is a rare type of B-cell non-Hodgkin lymphoma (NHL), a cancer of the lymphatic system. The lymphatic system branches through all parts of the body carrying a liquid called lymph. The lymph contains a high number of white blood cells (lymphocytes) which fight infection. There are two main types of lymphocytes: B-cells and T- cells. MCL affects the B-cells. It develops in the part of the lymph node called the mantle zone. These abnormal B lymphocytes start to collect in the lymph nodes or body organs where they can then form tumours and begin to cause problems within the lymphatic system or other organs. A relapsed MCL is one that comes back after treatment and refractory MCL is one that fails to respond to medical treatment. Some symptoms of MCL include heavy sweating at night, fluctuating body temperatures, weight loss and unexplained itching. Relapsed/refractory MCL responds poorly to chemotherapy thereby posing a major therapeutic challenge.

Zanubrutinib is administered orally. It works by blocking the activity of a protein called bruton's tyrosine kinase (BTK) leading to a reduction in the growth of abnormal B-cells in MCL. By blocking BTK activity, zanubrutinib is expected to slow the progression of the disease. If licensed, zanubrutinib will offer an additional treatment option for patients with MCL who have previously received at least one prior therapy.

Proposed Indication

Treatment of relapsed or refractory mantle cell lymphoma (MCL) in adults who have received one or more treatments.[1]

Technology

Description

Zanubrutinib (Brukinsa, BGB-3111) is an inhibitor of bruton's tyrosine kinase (BTK). It forms a covalent bond with a cysteine residue in the BTK active site, leading to inhibition of BTK activity. BTK is a signalling molecule of the B-cell antigen receptor (BCR) and cytokine receptor pathways. In B-cells, BTK signalling results in activation of pathways necessary for B-cell proliferation, trafficking, chemotaxis, and adhesion.[1,2] By blocking the action of BTK, zanubrutinib is expected to slow the progression of the disease.[3]

Zanubrutinib is in clinical development for the treatment of MCL in patients who have previously received at least one prior therapy. In the phase I/II clinical trial (NCT02343120), participants received zanubrutinib as oral capsules up to 320mg once daily, and 160mg twice daily in the phase II trial (NCT03206970).[1,4]

Key Innovation

Despite advances in treatment, including the use of more intensive frontline therapies, relapses in MCL are inevitable. Relapsed/refractory (R/R) MCL responds poorly to chemotherapy, and the expected survival is approximately one to three years. While the optimal treatment approach to R/R MCL remains to be defined, BTK inhibitors have been validated as being among the most effective agents in this setting.[5] Compared to the first-generation BTK inhibitor ibrutinib, zanubrutinib displays higher potency and selectivity for BTK with fewer off-target effects. Due to this enhanced selectivity towards BTK, zanubrutinib belongs to the second-generation BTK inhibitor drug group.[6] Of the three BTK inhibitors currently approved, two have been shown to be associated with off-target toxicities that can limit their continuous/extended use. Zanubrutinib is a highly selective, potent, irreversible BTK inhibitor with favourable oral bioavailability. It was designed to achieve maximal exposure while minimizing inhibition of off-target kinases.[5] In the phase II (NCT03206970) study, after extended follow-up of 35 months, zanubrutinib demonstrated long-term benefit and tolerability for patients with relapsed/refractory MCL.[7]

If licensed, zanubrutinib will offer an additional treatment option for patients with relapsed/refractory MCL who have been previously treated and currently have few well tolerated options.

Regulatory & Development Status

In the UK, zanubrutinib as monotherapy has Marketing Authorisation for the following:[2]

- treatment of adult patients with waldenström's macroglobulinaemia (WM) who have received at least one prior therapy, or in first line treatment for patients unsuitable for chemo-immunotherapy.
- treatment of adult patients with marginal zone lymphoma (MZL) who have received at least one prior anti-CD20-based therapy.
- treatment of adult patients with chronic lymphocytic leukaemia (CLL).

Zanubrutinib is in phase II/III clinical development for the treatment of:[8]

- primary membranous nephropathy

- B-cell malignancies
- small lymphocytic lymphoma
- lupus nephritis
- relapsed/refractory diffuse large B-cell lymphoma
- relapsed/refractory follicular lymphoma
- diffuse large B-cell lymphoma

Zanubrutinib has the following designations:

- a breakthrough therapy by the US FDA for MCL granted in January 2019.[9]
- an orphan drug in the USA granted in 2016 for MCL.[10]

Patient Group

Disease Area and Clinical Need

MCL is a rare type of B-cell non-Hodgkin lymphoma (NHL). NHL is a cancer of the lymphatic system. MCL affects the B-cells and develops in the part of the lymph node called the mantle zone.[11] B-cells are white blood cells that normally help fight infection. They are sometimes called B-lymphocytes. The abnormal B-cells (lymphoma cells) usually build up in lymph nodes, but they can affect other parts of the body.[12] A relapsed MCL is one that reappears or grows again after a period of remission, and refractory MCL is one that fails to respond to medical treatment.[13] Virtually all patients will eventually experience refractory or relapsed disease, with a virulent course of resistance and serial relapses, making treatment challenging.[14] The most common symptom of MCL (like NHL) is one or more painless swellings in the neck, armpit, or groin. Other symptoms include heavy sweating at night, high temperatures with no obvious cause, losing a lot of weight, unexplained itching, diarrhoea, tummy pain and sickness.[11] In almost all cases, the cause of MCL is unknown. Most cases of MCL have a particular genetic change (mutation) in the abnormal cells. The mutation means the B-cells make too much of a protein called cyclin D1. Too much cyclin D1 makes the B-cells grow out of control, and lymphoma develops. It is much more common in men than in women. It is usually diagnosed in people who are middle-aged or older. It is very rare in young people.[15]

Around 600 people are diagnosed with MCL each year in the UK.[15] MCL accounts for approximately 5% of all B-cell non-Hodgkin's lymphomas.[16] Results from a systematic review of the epidemiology and economic burden of MCL published in 2019 reported prevalence of MCL to be 3.0 per 100,000 persons in the UK (year 2011). Median overall survival ranged from 28.8 to 52.0 months in Europe (2004-2017). Three-year overall survival was reported as 43.9% in the UK (2004-2017).[17] In England (2022-23), there were 7,922 finished consultant episodes (FCEs) and 7,389 admissions for MCL (ICD-10 code C83.1), which resulted in 6,176 day cases and 11,243 FCE bed days.[18]

Recommended Treatment Options

National Institute for Health and Care Excellence (NICE) recommends ibrutinib and brexucabtagene autoleucel for treating relapsed or refractory MCL.[19,20]

Clinical Trial Information

Trial	NCT03206970; A Single-Arm, Open-Label, Multicenter Phase 2 Study to Evaluate Efficacy and Safety of BGB-3111, a Bruton's Tyrosine Kinase (BTK) Inhibitor, in Subjects with Relapsed or Refractory Mantle Cell Lymphoma (MCL) **Phase II:** Completed

	Location: China **Primary completion date (actual):** February 2019
Trial Design	Single group assignment, open label
Population	N=86 (actual); Subjects with relapsed or refractory MCL who had received prior regimens for MCL or failed to achieve any response, (stable disease or progressive disease during treatment) or documented progressive disease after response to the most recent treatment regimen aged 18 to 75 years
Intervention(s)	Zanubrutinib (160 milligrams) administered orally twice daily
Comparator(s)	-
Outcome(s)	Primary outcome: Overall Response Rate (ORR) as assessed by independent review committee [Time Frame: Up to 1 year and 11 months] See trial record for full list of all outcomes
Results (efficacy)	After a median follow-up of 35.3 months, the ORR was 83.7%, with 77.9% achieving complete response (CR); the median duration of response was not reached. Median progression-free survival (PFS) was 33.0 months (95% confidence interval [CI], 19.4-NE). The 36-month PFS and overall survival (OS) rates were 47.6% (95% CI, 36.2-58.1) and 74.8% (95% CI, 63.7-83.0), respectively.[5]
Results (safety)	The safety profile was largely unchanged with extended follow-up. Most common (≥20%) all-grade adverse events (AEs) were neutrophil count decreased (46.5%), upper respiratory tract infection (38.4%), rash (36.0%), white blood cell count decreased (33.7%), and platelet count decreased (32.6%); most were grade 1/2 events. Most common (≥10%) grade ≥3 AEs were neutrophil count decreased (18.6%) and pneumonia (12.8%). Rates of infection, neutropenia, and bleeding were highest in the first 6 months of therapy and decreased thereafter. No cases of atrial fibrillation/flutter, grade ≥3 cardiac AEs, second primary malignancies, or tumour lysis syndrome were reported.[5]

Trial	NCT02343120; A Phase I/II, Open-Label, Multiple-Dose, Dose Escalation and Expansion Study to Investigate the Safety and Pharmacokinetics of the BTK Inhibitor BGB-3111 in Subjects With B-Cell Lymphoid Malignancies **Phase I/II:** Completed **Locations:** Italy, UK, USA, Australia, Korea, and New Zealand **Primary completion date (actual):** March 2021
Trial Design	Single group assignment, open label
Population	N=385 (actual); Subjects with relapsed or refractory B-cell lymphoid malignancies who have received at least one line of therapy aged 18 years and older
Intervention(s)	Zanubrutinib oral capsules up to 320mg total daily dose
Comparator(s)	-

Outcome(s)	Primary outcomes: • Part 1 and Part 2: Number of participants with adverse events [Time Frame: Up to approximately 6 years and 7 months] • Part 1: Recommended Phase 2 Dose (RP2D) for zanubrutinib [Time Frame: Month 9] See trial record for full list of all outcomes
Results (efficacy)	Overall response rate was 84%, with 25% achieving a complete response. Median duration of response was 18.5 months. Median progression-free survival (PFS) was 21.1 months.[21]
Results (safety)	Eighteen patients discontinued treatment, 10 because of progressive disease and 8 because of adverse events (AEs); 1 AE (peripheral edema) was considered to be related to zanubrutinib treatment. The most common AEs were diarrhea (43.8%), contusion (37.5%), constipation (31.3%), and upper respiratory tract infection (31.3%). Infection was the most reported AE of interest (18.8% of patients experienced grade ≥3 infection). At least 1 AE of grade ≥3 was reported in 59.4% of patients; grade ≥3 AEs that were reported in >2 patients were anaemia (12.5%), pneumonia (9.4%), and myalgia (9.4%).[21]

Estimated Cost

The NHS indicative price for 120 capsules of zanubrutinib 80mg is £4,928.65.[22]

Relevant Guidance

NICE Guidance

- NICE technology appraisal in development. Venetoclax with ibrutinib for treating relapsed mantle cell lymphoma (GID-TA10774). Expected date of issue to be confirmed.
- NICE technology appraisal in development. Pirtobrutinib for treating relapsed or refractory mantle cell lymphoma (GID-TA10858). Expected date of issue to be confirmed.
- NICE technology appraisal. Brexucabtagene autoleucel for treating relapsed or refractory mantle cell lymphoma (TA677). February 2021.
- NICE technology appraisal. Ibrutinib for treating relapsed or refractory mantle cell lymphoma (TA502). January 2018.

NHS England (Policy/Commissioning) Guidance

- NHS England. Clinical Commissioning Policy: Bendamustine with rituximab for relapsed and refractory mantle cell lymphoma (all ages). 170054P. June 2018.
- NHS England. Clinical Commissioning Policy: Bortezomib for relapsed/refractory mantle cell lymphoma (all ages). 170035P.March 2018.
- NHS England. 2013/14 NHS Standard Contract for Cancer: Chemotherapy (Adult). B15/S/a.

Other Guidance

- British Society for Haematology. Guideline for the management of mantle cell lymphoma. May 2018.[23]

- 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.[24]

Additional Information

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