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Health Technology Briefing
July 2025

Zanubrutinib with rituximab for previously untreated mantle cell lymphoma who are ineligible for stem cell transplantation

Company/Developer	BeOne Medicines UK

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 27402	NICE ID: Not Available	UKPS ID: 675014

Licensing and Market Availability Plans

Currently in phase lll clinical development.

Summary

Zanubrutinib plus rituximab is in clinical development for the treatment of mantle cell lymphoma (MCL) in adults with previously untreated MCL. 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. Mantle cell lymphoma is generally considered an aggressive NHL. The exact cause of MCL is unknown. Zanubrutinib offers a safer and more targeted treatment option than older medicines.

Zanubrutinib is administered orally, while rituximab is administered intravenously. Zanubrutinib works by blocking a protein called bruton's tyrosine kinase (BTK) that helps cancerous B-cells grow, which may help slow the disease. Rituximab targets a marker on B-cells, leading to their destruction. If licensed for this indication, zanubrutinib will offer an additional treatment option for patients with previously untreated MCL.

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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Proposed Indication

Previously untreated MCL in adult patients who are ineligible for stem cell transplantation.[1]

Technology

Description

Zanubrutinib (Brukinsa) is a potent next-generation Bruton tyrosine kinase (BTK) inhibitor that is currently being evaluated in clinical trial programmes as a monotherapy and in combination with other therapies, such as rituximab (Rituxan), to treat various B-cell malignancies including mantle cell lymphoma.[1,2] Zanubrutinib 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.[3] By blocking the action of BTK, zanubrutinib is expected to slow the progression of the disease.[4] Rituximab, an anti-CD20 monoclonal antibody, is widely used in the treatment of different types of B-cell malignancies both as a single agent and in combination regimens.[2] It binds specifically to the transmembrane antigen, CD20, a non-glycosylated phosphoprotein, located on pre-B and mature B lymphocytes resulting in the death of B-lymphocytes.[5]

Zanubrutinib with rituximab is in clinical development for previously untreated MCL in patients who are ineligible for stem cell transplantation. In the Phase III clinical trial (NCT04002297), participants were randomised to receive zanubrutinib orally at a dose of 160 mg twice daily (two 80 mg capsules), and rituximab intravenously at a dose of 375 mg/m² on day 1 of cycles 1 through 6.[1]

Key Innovation

Zanubrutinib is a second-generation BTK inhibitor that demonstrates greater potency and selectivity for BTK, with reduced off-target effects relative to first-generation BTK inhibitors and prior treatments.[6] The chemical design of zanubrutinib was guided by a structure-activity strategy to enhance specificity for BTK, minimize off-target binding and associated toxicities, and improve pharmacokinetic properties. Zanubrutinib showed greater selectivity versus other kinases during profile assessment of 370 kinases.[7] Also, zanubrutinib demonstrated good combination activity with rituximab in preclinical xenograft models.[8] Moreover, since rituximab is a monoclonal antibody (biologic), no pharmacokinetic (PK) drug–drug interaction between zanubrutinib and rituximab is expected.[1]

If licensed, the combination of zanubrutinib with rituximab has the potential to improve outcomes in patients with previously untreated MCL who are ineligible for stem cell transplantation and currently have limited treatment options.[2]

Regulatory & Development Status

Zanubrutinib currently has Marketing Authorisation (MA) in the EU/UK as monotherapy treatment for:[3]

- Waldenström's macroglobulinaemia in adult patients who have received at least one prior therapy, or as first-line treatment for patients unsuitable for chemo-immunotherapy
- Marginal zone lymphoma in adult patients who have received at least one prior anti-CD20-based therapy
- Chronic lymphocytic leukaemia
- MCL who have received at least one prior therapy

In addition, zanubrutinib also has MA in the EU/UK:[3]

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- In combination with obinutuzumab for the treatment of adult patients with refractory or relapsed follicular lymphoma who have received at least two prior systemic therapies

Rituximab currently has MA in the EU/UK as monotherapy treatment for:[9]

- Follicular lymphoma patients responding to induction therapy
- Stage III-IV follicular lymphoma in adult patients who are chemo resistant or are in their second or subsequent relapse after chemotherapy

Rituximab currently has MA in the EU/UK:[9]

- In combination with CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone) chemotherapy for the treatment of adult patients with CD20 positive diffuse large B-cell non-Hodgkin's lymphoma
- In combination with chemotherapy for the treatment of previously untreated adult patients with stage III-IV follicular lymphoma
- In combination with chemotherapy for the treatment of paediatric patients (aged 6 months to less than 18 years old) with previously untreated advanced stage CD20 positive diffuse large B-cell lymphoma, Burkitt lymphoma /Burkitt leukaemia (mature B-cell acute leukaemia) or Burkitt-like lymphoma

Zanubrutinib (capsules) is in phase III/II clinical development for:[10]

- B-cell lymphomas
- Chronic lymphocytic leukaemia/small lymphocytic lymphoma
- Marginal zone lymphoma
- Primary membranous neuropathy
- Monoclonal gammopathy
- Central nervous system lymphomas

Rituximab is in phase III/II clinical development for:[11]

- Relapsed/Refractory Follicular Lymphoma
- Chronic lymphocytic leukaemia/small lymphocytic lymphoma
- Marginal zone lymphoma

Zanubrutinib has received orphan drug designation from the FDA for the treatment of MCL in June 2016, and for follicular lymphoma (in combination with obinutuzumab) in November 2022.[12,13]

Patient Group

Disease Area and Clinical Need

MCL is a rare and aggressive subtype of non-Hodgkin lymphoma (NHL) that originates in B lymphocytes located in the mantle zone of lymph nodes. MCL starts in white blood cells in lymph nodes and spreads quickly throughout the lymphatic system and to other parts of the body.[14] It accounts for approximately 5–6% of all NHL cases and typically affects older adults, with a higher prevalence in males.[15] MCL can present in two clinical forms: rarely as a slow-growing (indolent) type and more commonly as a rapidly progressing (aggressive) type.[14] The disease is characterized by a chromosomal translocation between chromosomes 11 and 14, leading to overexpression of the cyclin D1 protein, which drives abnormal B-cell proliferation. Common signs and symptoms include swollen lymph nodes, fever, night sweats, unintentional weight loss, fatigue, and gastrointestinal discomfort due to organ involvement such as

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hepatosplenomegaly. The exact cause of MCL is unknown, but risk factors include advanced age, male sex, and a weakened immune system.[15]

NHL is the 7th most common cancer in the UK, accounting for 4% of all new cancer cases (2017-2019).[16] The age-standardised incidence rate of NHL in England is 26.3 and 18.0 per 100,000 amongst males and females respectively.[17] In England (2017), there were 12,065 patients diagnosed with non-Hodgkin lymphoma and 4,096 deaths registered where non-Hodgkin lymphoma was the underlying cause.[18] For patients diagnosed between 2013 and 2017, followed up to 2018, the 1-year and 5-year survival rates were 79.4% and 63.7% respectively.[19] Each year around 600 people are diagnosed with MCL in the UK. Out of all people with NHL in the UK, around 5 in every 100 people (around 5%) have MCL.[20] In England in 2023-24, there were 8,615 finished consultant episodes (FCE) and 8,071 hospital admissions for MCL (ICD-10 code C83.1), resulting in 11,555 FCE bed days and 6,880 day cases.[21] Survival rates for mantle cell lymphoma vary significantly by age. Overall, more than 45 out of 100 people (over 45%) survive for five years or more after diagnosis, regardless of age. However, younger individuals generally have better outcomes. Among those younger than 60, nearly 65 out of 100 (about 65%) survive for five years or more. For individuals aged between 60 and 79, the five-year survival rate is nearly 55 out of 100 (approximately 55%). In contrast, for those aged 80 and over, around 20 out of 100 (roughly 20%) are expected to survive five years or more after diagnosis.[22]

Recommended Treatment Options

The National Institute for Health and Care Excellence (NICE) technology appraisal published in 2015 recommends bortezomib for previously untreated MCL in patients who are unsuitable for stem cell transplantation.[23] However, in clinical practice rituximab-based chemotherapy is considered the standard of care.[24]

Clinical Trial Information

Trial	**MANGROVE; NCT04002297, 2019-000413-36**; A phase 3 randomized, open-label, multicentre study comparing zanubrutinib (bgb-3111) plus rituximab versus bendamustine plus rituximab in patients with previously untreated mantle cell lymphoma who are ineligible for stem cell transplantation **Phase III** – Active, not recruiting. **Location(s):** 13 EU countries, UK, USA, Canada and other countries **Primary completion date:** March 2027
Trial Design	Randomised, parallel assignment, open label
Population	N=510; aged 60 years and older (adult, older adult); patients with histologically confirmed diagnosis of MCL and comorbidities that preclude eligibility for autologous stem cell transplantation
Intervention(s)	• Zanubrutinib: 80 mg capsules (two capsules, oral) twice daily plus • Rituximab: 375 mg/m² administered intravenously on day 1 of cycles 1-6
Comparator(s)	• Bendamustine: 90 mg/m²/day administered intravenously on days 1 and 2 of cycles 1-6 plus • Rituximab: 375 mg/m² administered intravenously on day 1 of cycles 1-6
Outcome(s)	Primary outcome measure:

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	• Progression-free survival (PFS) determined by independent central review [Time Frame: Up to approximately 7 years] ○ PFS is defined as the time from randomization to the date of first documentation of disease progression or death, whichever occurs first. See trial record for full list of other outcomes.
Results (efficacy)	-
Results (safety)	-
Clinical Trial Information	
Trial	NCT05504603; Zanubrutinib-rituximab in patients with or without autologous stem cell transplant. with newly diagnosed untreated mantle cell lymphoma **Phase II** – Active, recruiting. **Location(s):** China **Primary completion date;** July 2023 (July 2025 Study completion)
Trial Design	Single-centre, single group assignment, open label
Population	N=20; aged 18 years and older; patients histopathologically or cytologically confirmed Mantle Cell Lymphoma
Intervention(s)	• Oral zanubrutinib (160 mg twice daily), • Rituximab (375 mg/m^2 weekly for cycle 1 and then on day 1 of cycles 2-5, 4 weeks per cycle) as induction therapy. • Those experiencing complete remission or partial remission were followed by zanubrutinib maintenance for elderly (age>70y) or unfit patients until intolerable toxicities or relapsed, • ASCT (Autologous Stem Cell Transplantation) was given to younger (age≤70y) and fit patients.
Comparator(s)	None

Outcome(s)	Primary outcome measures:
	• Overall response rate in all patients [time frame: at the end of cycle 3 and cycle 5 (each cycle is 28 days)]
	  ○ The rate of patients who achieved complete response and partial response after ZR combined immunotherapy
	• Complete response rate in all patients [time frame: at the end of cycle 3 and cycle 5 (each cycle is 28 days)]
	  ○ The rate of patients who achieved complete response after ZR combined immunotherapy.
	• Overall response rate in patients received ASCT [Time Frame: 1 month after ASCT]
	  ○ The rate of patients who achieved complete response and partial response after ASCT.
	• Complete response rate in patients received ASCT [Time Frame: 1 month after ASCT]

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	○ The rate of patients who achieved complete response after ASCT. See trial record for full list of other outcomes.
Results (efficacy)	-
Results (safety)	-

Estimated Cost

Zanubrutinib is already marketed in the UK in capsule form; the list price for a pack of 120 x 80 mg capsules is £4,928.65.[25]

Relevant Guidance

NICE Guidance

- NICE clinical guidance awaiting development. Acalabrutinib with bendamustine and rituximab for untreated mantle cell lymphoma (GID-TA11091). Expected date of issue to be confirmed.
- NICE clinical guidance. 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.

Other Guidance

- British Society of Haematology. Diagnosis and management of mantle cell lymphoma: A British Society for Haematology guideline. 2023.[26]
- European Society for Medical Oncology. Newly diagnosed and relapsed mantle cell lymphoma: ESMO Clinical Practice Guidelines. 2017.[27]

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