

**NIHR Innovation Observatory
Evidence Briefing: January 2018****Zanubrutinib for Waldenstrom's
macroglobulinemia**

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LAY SUMMARY

Waldenstrom's Macroglobulinaemia (WM) is a rare type of slow developing cancer which affects a type of cell of the immune system called B-cells. It is caused when abnormal B-cells build up in the bone marrow and other parts of the immune system which can block other normal blood cells from being produced. The abnormal B-cells also release large amounts of a protein called IgM which can build up in the blood making it thicker. People can live with WM for many years and will only usually receive treatment when the disease of symptoms begin to worsen. Treatments which are currently available include chemotherapy, stem cell transplants and plasma replacement.

Zanubrutinib is an oral drug taken twice a day which is currently in clinical trials for the treatment of patients with WM. Zanubrutinib works by blocking a protein called Bruton's Tyrosine Kinase (BTK) in the abnormal B-cells which prevents the growth of these cells. As this drug specifically targets the abnormal B-cells, unlike chemotherapy drugs, this type of drug may provide fewer side effects than existing treatment for WM.

This briefing reflects the evidence available at the time of writing. A version of the briefing was sent to the company for a factual accuracy check. The company was unavailable to provide comment. 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.

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TARGET GROUP

Waldenstrom's macroglobulinemia

TECHNOLOGY

DESCRIPTION

Zanubrutinib (BGB3111) is a potent and highly selective small molecule Bruton's Tyrosine Kinase (BTK) inhibitor. Zanubrutinib works by binding to and inhibiting BTK which prevents the activation of the B cell antigen receptor (BCR) signalling pathway. This inhibits B-cell activation and the growth of malignant B-cells which overexpress BTK (which plays an important role in the development, activation, signalling, proliferation and survival of B-lymphocytes).^{1,2}

Zanubrutinib is intended for the treatment of B-cell cancers such as Waldenstrom's macroglobulinaemia. In the phase III trial (NCT03053440), 160mg oral zanubrutinib will be taken twice a day till progressive disease, unacceptable toxicity, death, withdrawal of consent or study termination.¹²

Zanubrutinib does not currently have Marketing Authorisation in the EU for any indication.

Zanubrutinib is currently in phase III trials for chronic lymphocytic leukaemia – first line and Waldenstrom's Macroglobulinaemia.

Zanubrutinib is currently in phase II trials for:

- Follicular lymphoma – third line
- Relapsed chronic lymphocytic leukaemia
- Refractory chronic lymphocytic leukaemia
- Diffuse Large B-cell lymphoma
- Mantle cell lymphoma

INNOVATION and/or ADVANTAGES

As zanubrutinib is a potentially a highly specific BTK inhibitor, this may confer advantages over less specific BTK inhibitors, such as ibrutinib, regarding safety and tolerability. It has also been claimed that in preclinical studies, zanubrutinib showed more sustained inhibition in disease causing tissue and better bioavailability than ibrutinib. Preclinical data also showed zanubrutinib may have a synergistic effect with rituximab and so this drug may have the potential to be used in combination with chemotherapy to improve outcomes.¹

DEVELOPER

BeiGene Co Ltd.

AVAILABILITY, LAUNCH or MARKETING

Zanubrutinib was a designated orphan drug in the USA for Waldenstrom's Macroglobulinaemia in June 2016.³

PATIENT GROUP

BACKGROUND

Waldenstrom's Macroglobulinaemia (WM) is a rare form of slow growing non-Hodgkin's lymphoma which affects a type of B-cell called plasma cells (or effector B-cells). In WM, abnormal plasma cells build up in the bone marrow and lymphatic system which can impair the bone marrow from producing normal amounts of red and white blood cells, resulting in anaemia, neutropenia and thrombocytopenia. Abnormal plasma cells in WM can also make large amounts of the IgM protein which can make the blood thicker than usual. WM may not initially cause specific symptoms, but some general symptoms may include; tiredness, bruising and bleeding, infections, night sweats, weight loss, headaches and blurred vision.^{4,5}

WM is a rare lymphoma, mostly affecting people over 65 years. The cause of WM is unknown however it has been observed to occur in clusters within families, with 1 in 5 people with WM having a family member with WM or a similar type of non-Hodgkin's lymphoma (e.g. chronic lymphocytic leukaemia). Certain mutations have also been observed in people with WM such as that in the MYD88 gene (coding for the myeloid differentiation primary response 88 protein), which occurs in the majority of people with WM. Mutations in the CXCR4 gene (coding for chemokine receptor type 4 protein) are also found in approximately a third of people with WM.⁶

As WM is a slow growing lymphoma some patients may not require treatment for months or years after diagnosis. Regular check-ups and blood tests will be conducted and treatment started if there are troubling symptoms, increased IgM levels in the blood or if there are changes to blood cell counts. The current treatment options for WM are outlined below and most are provided as part of outpatient visits.⁴ Most people live with WM for many years and patients have to cope with many of the issues common in those with chronic disease such as coping with tiredness, effects of diagnosis on feelings and relationships, finances and travel.⁶

CLINICAL NEED and BURDEN OF DISEASE

WM affects <2% patient with non-Hodgkin's lymphoma⁵ and more than 400 people a year a diagnosed with WM in the UK.⁷

The age standardised annual incidence of WM in the UK is 0.55 per 100,000.⁹ The prevalence of WM in Europe is estimated at 1 in 102,220 people and overall prevalence is estimated at 1-9 per 100,000 people.⁸

The median age of presentation is 71 years and median survival time in 60 months.⁹

In 2016-2017 in the UK there were 5,629 admissions and 5,816 finished consultant episodes for Waldenström macroglobulinaemia (ICD 10: C88.0).¹⁰

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE Technology appraisal guidance in development. Ibrutinib with rituximab for treating Waldenstrom's macroglobulinemia [1127]. Expected publication date TBC.

- NICE Technology appraisal in development. Waldenstrom's macroglobulinemia – ibrutinib [ID884]. Expected publication date 22 November 2017.
- NICE Technology appraisal guidance. Ibrutinib for treating Waldenstrom's macroglobulinemia (TA491). November 2017.

NHS ENGLAND and POLICY GUIDANCE

- NHS England. Clinical Commissioning Policy: Haematopoietic Stem Cell Transplantation (HSCT) for lymphoplasmacytic lymphoma (adults). NHS England: 16067/P. 12 December 2016.

OTHER GUIDANCE

- National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology for Waldenström's Macroglobulinemia/Lymphoplasmacytic Lymphoma. 2017
- London Cancer LPL. Lymphoplasmacytic Lymphoma/Waldenström's Macroglobulinaemia Guidelines. 2015
- British Journal of Haematology. Guidelines on the diagnosis and management of Waldenström's macroglobulinaemia. 2014.
- European Society for Medical Oncology (ESMO). Waldenstrom's Macroglobulinaemia: ESMO Clinical Practice Guidelines. 2013

CURRENT TREATMENT OPTIONS

There is currently no cure for WM and treatments aim to control the disease and symptoms. Many people will be asymptomatic and will not require treatment for years (a few people will never require treatment). During this time a 'watch and wait' strategy is employed with patients having regular (3-6 months) check-ups and blood tests (to measure IgM levels and blood cell counts).⁶

Treatment will start if troublesome symptoms start, blood IgM levels increase or blood cell counts change (development of anaemia, neutropenia or thrombocytopenia). There are several different types of treatment available for WM, including:⁶

- Chemotherapy – first line^{4, 6}
 - Rituximab in combination with:
 - Dexamethasone and cyclophosphamide (DRC)
 - Bendamustine (BR)
 - Fludarabine (FR)
 - Fludarabine and cyclophosphamide (FCR)
 - Cladribine (Clad-R)
 - Chemotherapy regimens without rituximab:
 - Cyclophosphamide, vincristine, doxorubicin and prednisolone (CHOP)
- Stem cell transplant
 - Autologous – where stem cells are taken from the patient and returned by drip infusion after treatment with high dose chemotherapy (high dose chemotherapy with stem cell support)

- Allogenic – stem cells are donated by a another person (donor) and administered to the patient
- Plasma exchange (plasmapheresis) – where the patient is connected to a machine (cell separator) via a cannula where blood is circulated though and separated into plasma and blood cells. The patient’s plasma (containing IgM) is removed and a plasma substitute returned along with the blood cells.⁴
- Other drugs (not licenced or not approved for use in WM by NICE in the UK)¹¹
 - Bortezomib – proteasome inhibitor
 - Bendamustine – DNA synthesis inhibitor
 - Thalidomide – TNF Inhibitor
 - Ofatumumab – monoclonal antibody
 - Idelalisib – phosphoinositide 3-kinase inhibitor
 - Ibrutinib – brunton’s tyrosine kinase inhibitor (NICE technology appraisal currently in development for use in WM)

Chemotherapy regimens are given over several months with one drug administered over several weeks followed by a break and another drug over the following weeks. The chemotherapy regime chosen will depend on individual factors such as general health, symptoms and potential future treatments required (e.g. stem cell transplant).⁶

EFFICACY and SAFETY

Trial	BGB-3111-302, NCT03053440 , EudraCT-2016-002980-33, 2016-002980-33, NCI-2017-00526, CDR788090; zanubrutinib vs ibrutinib; phase III
Sponsor	BeiGene
Status	Ongoing - recruiting
Source of Information	Trial registry ¹²
Location	USA, Australia, 11 EU countries including the UK
Design	Randomised, active-controlled
Participants	n=167 (planned); aged 18 years and older; clinical and definitive histologic diagnosis of Waldenström's Macroglobulinemia (WM); no prior therapy for WM/ considered inappropriate candidates for standard chemoimmunotherapy
Schedule	Participants are randomised to one of three treatment arms: <ol style="list-style-type: none"> 1. Arm A (active treatment arm – cohort 1) – n=75 (planned), 160mg oral zanubrutinib taken twice a day till progressive disease, unacceptable toxicity, death, withdrawal of consent or study termination. 2. Arm B (active comparator) – n=75 (planned), 420mg oral ibrutinib per day till progressive disease, unacceptable toxicity, death, withdrawal of consent or study termination. 3. Arm C (active treatment arm – cohort 2) – n=15-20 (planned), 160mg oral zanubrutinib taken twice a day till progressive disease, unacceptable toxicity, death, withdrawal of consent or study termination.

Follow-up	Active treatment till progressive disease, unacceptable toxicity, death, withdrawal of consent or study termination.
Primary Outcomes	Proportion of subjects achieving either a complete response (CR) or very good partial response (VGPR) in Cohort 1 using an adaptation of the response criteria updated at the Sixth IWWM as assessed by an independent review committee. - Up to 3 years
Secondary Outcomes	<ul style="list-style-type: none"> • Efficacy measured by major response rate (MRR) in Cohort 1 - Up to 5 years • MRR defined as the proportion of subjects achieving a best response of response of CR, VGPR, or partial response (PR) • Efficacy measured by duration of response (DOR) in Cohort 1 - Up to 5 years • DOR defined as the time from first determination of response (CR, VGPR or PR) until first documentation of progression or death, whichever comes first • Efficacy measured by progression-free survival (PFS) in Cohort 1 - Up to 5 years • PFS defined as time from randomization to the first documentation of progression or death, whichever occurs first • Resolution of treatment-precipitating symptoms in Cohort 1, measured by the absence of the symptoms that triggered initiation of study treatment (per the IWWM treatment guidelines) at any point during study treatment - Up to 5 years • Anti-lymphoma effect in Cohort 1, as measured by any reduction in bone marrow involvement by lymphoplasmacytoid lymphocytes and/or size of lymphadenopathy and/or hepatosplenomegaly - Up to 5 years • Safety measured by the incidence, timing, and severity of treatment-emergent AEs in Cohort 1 - Up to 5 years • The incidence of AEs of Special Interest in Cohort 1 -Up to 5 years
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Estimated Primary completion date reported as June 2021.

Trial	BGB-3111-210, NCT03332173 ; zanubrutinib; phase II
Sponsor	BeiGene
Status	Ongoing - recruiting
Source of Information	Trial registry ¹³
Location	China
Design	Non-randomised, uncontrolled
Participants	n= 40 (planned); aged 18 years and older; clinical and definitive histologic diagnosis of WM; disease progression on least one prior treatment; for WM

Schedule	Single group assignment to receive 160mg oral zanubrutinib twice daily (as 2x 80mg white opaque capsules) until disease progression, unacceptable toxicity or death, withdrawal of consent, lost to follow-up, or study termination
Follow-up	Until disease progression, unacceptable toxicity or death, withdrawal of consent, lost to follow-up, or study termination - up to 3 years
Primary Outcomes	Major response rate (MRR) - up to 3 years
Secondary Outcomes	<ul style="list-style-type: none"> • Progression free survival (PFS) - up to 3 years • Overall response rate (ORR) - up to 3 years • ORR is the proportion of subjects with a minor, partial, very good partial, and complete response • Duration of major response (DOMR) - up to 3 years • Resolution of treatment precipitating symptoms - up to 3 years • Anti-lymphoma effect - up to 3 years defined as any reduction during the course of study treatment in bone marrow involvement by lymphoplasmacytoid lymphocytes and/or size of lymphadenopathy and/or hepatosplenomegaly by CT scan. Lymphadenopathy is defined as any node with longest diameter (LDi) > 1.5 cm and splenomegaly is defined as vertical spleen length > 13 cm.
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Estimated primary completion date April 2019.

ESTIMATED COST and IMPACT

COST

The cost of zanubrutinib is not yet known.

IMPACT – SPECULATIVE

IMPACT ON PATIENTS AND CARERS

- Reduced mortality/increased length of survival
 Reduced symptoms or disability
- Other
 No impact identified: no clinical trial data on effectiveness yet available

IMPACT ON HEALTH and SOCIAL CARE SERVICES

¹⁰ NHS Digital, Hospital Episode Statistics for England. Admitted Patient Care statistics, 2016-17. Available from: <https://digital.nhs.uk/catalogue/PUB30098> [Accessed 05 January 2018].

¹¹ Waldenström's Macroglobulinaemia UK. *Treatment*. Available from: <http://www.wmuk.org.uk/about-wm/treatment> [Accessed 05 January 2018].

¹² ClinicalTrials.gov. *A Study Comparing BGB-3111 and Ibrutinib in Subjects With Waldenström's Macroglobulinemia (WM)*. Available from: <https://clinicaltrials.gov/ct2/show/NCT03053440> [Accessed 15 December 2017]. Last Updated 1 November 2017.

¹³ ClinicalTrials.gov. *Study of BTK Inhibitor BGB-3111 in Chinese Subjects With Relapsed/Refractory Waldenström's Macroglobulinemia (WM)*. Available from: <https://clinicaltrials.gov/ct2/show/NCT03332173?term=NCT03332173&recrs=ab&rank=1> [Accessed December 2017]. Last Updated 22 November 2017.