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HEALTH TECHNOLOGY BRIEFING
JANUARY 2021

Mosunetuzumab for relapsed or refractory B-cell follicular lymphoma – third-line and greater

NIHRIO ID	30253	**NICE ID**	10527
Developer/Company	Roche Products Ltd	**UKPS ID**	658337

Licensing and market availability plans	Currently in phase I/Ib clinical trials

SUMMARY

Mosunetuzumab is in clinical development for the treatment of patients with relapsed or refractory B-cell follicular lymphoma (FL). FL is a type of slow growing blood cancer that affects white blood cells. In FL, the affected white blood cells start to multiply in an abnormal way and begin to aggregate in certain parts of the body such as the lymph nodes. A reccurrence of lymphoma after going into complete remission is known as a relapse. Lymphoma that is unresponsive to therapy it is called refractory lymphoma. The condition can become more difficult to treat if it is relapsed or refractory, as treatment options are limited.

Mosunetuzumab is a medicinal product administered intravenously. It works by binding to proteins called CD3 and CD20 expressed on the surface of B-cells and T-cells. This then reduces the growth and expression of cancer causing CD20 on B-cells. If licensed, mosunetuzumab will offer an additional treatment option for adults with relapsed or refractory B-cell follicular lymphoma (FL).

PROPOSED INDICATION

For the treatment of patients with relapsed or refractory B-cell follicular lymphoma (FL).[1-3]

TECHNOLOGY

DESCRIPTION

Mosunetuzumab (BTCT4465A; RG7828) is a bispecific investigational fully humanised immunoglobulin G1 (IgG1) that can bind simultaneously to CD3 that is part of the T-cell receptor complex protein expressed on the surface of T-cells, and CD20 expressed on the surface of B-cells expressed in majority of B-cell malignancies.[4,5] Mosunetuzumab is structurally similar to a natural human antibody as it has two 'Fab' regions however, it differs from naturally occurring antibodies in that one 'Fab' region targets CD3 and the other targets CD20.[6] This results in the induction of downstream signalling events that lead to the death of CD20 expressing B-cells through the crosslinking of the T-cell receptor complex. The structural features of mosunetuzumab equips it to promote the recruitment and retention of T-cells resulting in an anti-tumour effect.[7]

Mosunetuzumab is in clinical development for the treatment of adults with relapsed or refractory B-cell FL as a third-line treatment. In the phase I/Ib registrational clinical trial (NCT02500407), patients receive both escalating and expansion doses of mosunetuzumab.

INNOVATION AND/OR ADVANTAGES

There are currently no bispecific antibodies licensed for the treatment of B-cell FL, and there are limited options for third-line or greater treatment. There remains an unmet need in follicular lymphomas.[8]

Mosunetuzumab is a cancer immunotherapy that is CD20xCD3 bispecific and has demonstrated encouraging efficacy in the treatment of relapsed or refractory FL, and if approved, would be the first bispecific antibody therapy used for B-cell FL.[6] In adults with relapsed or refractory FL, mosunetuzumab has shown high response rates and durable complete remissions in phase I/Ib clinical trials.[6]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Multiple clinical trials are ongoing, and are investigating the use of mosunetuzumab both as monotherapy and in combination with other therapies.

Mosunetuzumab does not currently have Marketing Authorisation in the EU/UK for any indication.

PATIENT GROUP

DISEASE BACKGROUND

Lymphoma is a cancer of the lymphatic system. The lymphatic system is a system of lymphatic vessels and lymph nodes that run throughout the body. Tissue fluid called lymph circulates around the body in these vessels and flows through the lymph nodes. The lymphatic system is an important part of our immune system which plays a role in fighting bacteria and other infections and it tries to destroy old or abnormal cells, such as cancer cells.[9]

There are 2 main types of lymphoma. They are called Hodgkin lymphoma (HL) and Non Hodgkin lymphoma (NHL).[9] NHL is grouped into 2 grades; low grade and high grade. Low grade NHL tends to grow very slowly and is called indolent lymphoma. Types of low grade NHL include follicular and marginal zone lymphoma. Follicular lymphoma (FL) is the most common type of low grade lymphoma. It mainly affects adults over the age of 60 years.[10] In most cases, there is no known cause for FL. Some acquired genetic changes are common in FL, but it is not known what causes them. Around 1 in 5 people with FL never need treatment or the lymphoma does not cause problems for many years.[11]

Lymphoma which reoccurs after successful treatment is called relapsed lymphoma. Lymphoma that does not respond well to treatment is known as refractory lymphoma. Refractory lymphoma is often treated in the same way as relapsed lymphoma.[12]

Symptoms of FL include enlarged lymph nodes, night sweats, fever that comes and goes, weight loss, unexplained itching, breathlessness and persistent itch of the skin all over the body.[13] The exact cause of FL remains unknown. However, the risk of developing the condition is increased if an individual who has had or currently has a medical condition that weakens the immune system, taking immunosuppressant medication, exposed to a common virus called the Epstein-Barr virus. The risk of developing FL also increases if a first-degree relative (such as a parent or sibling) has had the condition.[13]

CLINICAL NEED AND BURDEN OF DISEASE

In the UK, more than 13,000 people are diagnosed with NHL each year.[13] According to the 2019-2020 Hospital Episodes Statistics data, there were 23,027 finished consultant episodes, 22,321 hospital admissions which led to 19,654 day cases, and 12,240 bed days due to follicular lymphoma (ICD-10 code: C82).[14]

According to the Haematological Malignancy Research Network, in 2016, the number of people with follicular lymphoma per year in the UK was estimated to be 2,220.[15] The latest available Cancer Registration Statistics, England, 2017-18 shows 12,065 newly diagnosed cases of NHL (ICD-10 code C82 – C85) for all ages. Out of these 2,168 have follicular lymphoma which is about 18% of the total number of new cases.[10,16] Overall, European age-standardised incidence rates are projected to decrease from 32.45 per 100,000 in 2014 to 31.56 per 100,000 in 2035 in males, and from 22.67 per 100,000 in 2014 to 21.92 per 100,000 in 2035 in females for NHL (ICD-10 code: C82-C86).[17]

Over the period of 2013 and 2017, followed up to 2018, the age-standardised one-year and five-year survival rates for NHL (all subtypes combined) in England show that 78.4% of men are expected to survive for at least 1 year, with almost 63.7% surviving 5 years or more. In women, the survival rates are slightly higher with 80.6% expected to live for 1 year and almost 68.1% for at least 5 years.[18]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

The treatment administered for NHL will depend on the type of NHL. It is important that the patient receive the right diagnosis of NHL which is dependent on the affected lymphocyte (B-cells or T-cells). The decisions made about the type of therapy to use may vary depending on various factors such as the stage of the cancer, age, general health, and the possible side effects of therapy.[9] The main types of treatment available for NHL are chemotherapy, radiotherapy, and targeted cancer drugs. Other treatments include surgery and stem cell transplantation.[9]

For the treatment of relapsed and refractory follicular lymphoma, the European Society of Medical Oncology (ESMO) recommend a new biopsy be taken for the patient in order to exclude any indication of transformation to an aggressive lyphoma.[19,20] At first presentation of relapse or progression, an accepted approach is observation in asymptomatic patients with confirmed follicular histology and low tumour burden. Selection of salvage treatment depends on efficacy of prior regimens.[19] In addition to these therapies palliative care can also be given in order to help the patients with their emotional, physical, spiritual and social needs.[21]

CURRENT TREATMENT OPTIONS

The NICE recommendation for treating relapsed or refractory FL that has progressed up tp 6 months post treatment or did not respond to rituximab or a rituximab containing regimen or recommends that obinutuzumab with bendamustine be administered followed by obinutuzumab maintenance.[8] According to ESMO guidelines, in early relapses of asymptomatic cases in follicular lymphoma, a non-cross-resistant scheme is the preferred treatment (e.g. bendamustine after CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone), or vice versa). In symptomatic cases with low tumour burden, rituximab monotherapy may be applied. In later relapses, monotherapy is a well established option with palliative intent, survival can be achieved long-term.[19,20]

PLACE OF TECHNOLOGY

If licensed, mosunetuzumab will offer an additional third line or greater therapy option for patients with relapsed or refractory FL.

CLINICAL TRIAL INFORMATION

Trial	NCT02500407; **An Open-Label, Multicenter, Phase I/IB Trial Evaluating the Safety and Pharmacokinetics of Escalating Doses of BTCT4465A as a Single Agent and Combined With Atezolizumab in Patients With Relapsed or Refractory B-Cell Non-Hodgkin's Lymphoma and Chronic Lymphocytic Leukemia** **Phase I: Recruiting** **Location(s):** EU (incl UK), USA, Canada, Australia, and Republic of Korea **Primary completion date:** October 2021
Trial design	Non-Randomised, open-label, sequential assignment
Population	N=746 (planned); 18 years and older with an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1; participants must have B-cell haematologic malignancies expected to express the cluster of differentiation 20 (CD20) antigen who have relapsed after or failed to respond to at least one prior treatment regimen and for whom there is no available therapy expected to improve survival; Adequate hepatic, haematologic, and renal function.
Intervention(s)	- Participants with B-cell NHL and CLL will receive Mosunetuzumab via IV infusion. - Participants with B-cell NHL and CLL will receive BTCT4465A (Mosunetuzumab) via SC injection.
Comparator(s)	-
Outcome(s)	- Maximum Tolerated Dose (MTD) of Mosunetuzumab [Time Frame: Mosunetuzumab single agent: Cycle 1; Mosunetuzumab in combination with atezolizumab: during the first cycle that Mosunetuzumab and atezolizumab are administered concurrently (cycle length = 21 days)] - Percentage of Participants With Adverse Events [Time Frame: From Cycle 1 Day 1 until 90 days after the last infusion (cycle length = 21 days; up to approximately 14 months)]

	- Mosunetuzumab Serum Concentration [Time Frame: Baseline up to 30 days after the last infusion of Mosunetuzumab (up to approximately 12 months)] - Atezolizumab Serum Concentration [Time Frame: Baseline up to 30 days after the last infusion of Mosunetuzumab (up to approximately 12 months)] - Percentage of Participants with Complete Response as Assessed Using Standard Criteria for NHL [Time Frame: Baseline up to approximately 4 years (assessed at screening and then every 3 months until disease progression, start of new anti-cancer therapy, or withdrawal)] See trial record for full list of other outcomes.
Results (efficacy)	-
Results (safety)	-

ESTIMATED COST

The cost of Mosunetuzumab is not yet known.

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal in development. Axicabtagene ciloleucel for treating relapsed or refractory diffuse large B-cell lymphoma after 1 systemic therapy (TA10580). Expected date of publication: TBC
- NICE technology appraisal guidance in development. Lenalidomide for previously treated follicular lymphoma and marginal zone lymphoma (GID-TA10323). Expected date of publication: TBC.
- NICE technology appraisal guidance in development. Ibrutinib for treating relapsed or refractory follicular lymphoma (GID-TA10223). Expected date of publication: TBC.
- NICE technology appraisal guidance in development. Duvelisib for treating relapsed follicular lymphoma after 2 systemic therapies (GID-TA10209). Expected date of publication: TBC.
- NICE technology appraisal guidance. Idelalisib for treating refractory follicular lymphoma (TA604). October 2019.
- NICE guideline. Non-Hodgkin's lymphoma: diagnosis and management (NG52). 2016.
- NICE guideline. Suspected cancer: recognition and referral (NG12). June 2015.
- NICE Quality Standards. Haematological cancers (QS150). 2017.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- No relevance guidance found.

OTHER GUIDANCE

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- London Cancer. Guidelines for the management of non-Hodgkin's and Hodgkin's lymphoma in adults. 2015.[22]
- NICE evidence summary. Non-Hodgkin's lymphoma: rituximab subcutaneous injection (ESNM46). September 2014.

ADDITIONAL INFORMATION

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NB: This briefing presents independent research funded by the National Institute for Health Research (NIHR). The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health.