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Newcastle University

Health Technology Briefing
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Glofitamab with gemcitabine, oxaliplatin and rituximab for treating relapsed or refractory diffuse large B-cell lymphoma

Company/Developer	Roche Products Ltd

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID: 29958	NICE TSID: 11800	UKPS ID: 665187

Licensing and Market Availability Plans

Currently in phase II/III trials

Summary

Glofitamab in combination with gemcitabine, oxaliplatin and rituximab is currently in clinical development for relapsed/refractory diffuse large B-cell lymphoma (DLBCL). DLBCL is a type of non-Hodgkin lymphoma. Most people with DLBCL first notice painless lumps, often in their neck, armpit, groin, or abdomen, or in testicles for men. These are enlarged lymph nodes. They usually grow quite quickly, over just a few weeks. Relapsed cancer refers to cancer that initially responded to treatment but then returned. Refractory cancer refers to cancer that did not respond to treatment. The prognosis for patients with relapsed or refractory DLBCL remains poor, so there is a need to develop additional treatment options.

Glofitamab in combination with gemcitabine, oxaliplatin and rituximab is in development as an intravenous infusion to target and eliminate certain white blood cells allowing treatment of B-cell cancers. In both pre-clinical and human studies, glofitamab has been shown to be effective. If licensed, glofitamab will offer an additional treatment option for patients with relapsed/refractory DLBCL.

Proposed Indication

Treatment for patients with relapsed/refractory diffuse large B-cell lymphoma (DLBCL).[1]

Technology

Description

Glofitamab (RO7082859) is a T-cell–engaging bispecific antibody possessing a novel 2:1 structure with bivalency for CD20 on B cells and monovalency for CD3 on T cells.[2] By engaging both targets simultaneously, the antibody activates the T cells to attack and eliminate the B-cells, allowing treatment of B-cell cancers such as non-Hodgkin's lymphoma.[3]

Glofitamab in combination with gemcitabine, oxaliplatin and rituximab is currently in clinical development for relapsed/refractory DLBCL. In the phase III trial (NCT04408638), glofitamab is being administered via intravenous (IV) injection. Cycles are 21 days. Glofitamab is given in combination with gemcitabine and oxaliplatin for up to 8 cycles, followed by up to 4 cycles of glofitamab monotherapy.[1]

Key Innovation

The 2:1 configuration of glofitamab enables bivalent binding to CD20 on B cells and monovalent binding to CD3 on T cells. Its CD3-binding region is fused to one of the CD20-binding regions in a head-to-tail manner via a flexible linker for improved target-effector cell binding. This endows glofitamab with superior *in vitro* potency versus other CD20-CD3 bispecific antibodies with a 1:1 configuration and leads to profound antitumour efficacy in preclinical DLBCL models. CD20 bivalency preserves this potency in the presence of competing anti-CD20 antibodies, providing the opportunity for pre- or co-treatment with these agents.[2]

In pre-clinical studies, glofitamab demonstrated an average 40-fold increase in *ex vivo* tumour lysis compared to alternative 1:1 configurations. This allows for activity even in the presence of prior or concurrent CD20-directed antibody therapy. This is important, as current marketed CD20 antibodies such as rituximab have a long half-life and many patients with relapsed disease will have CD20 antibody present at the time of salvage treatment. Furthermore, this property allows the use of CD20-depleting agents to mitigate cytokine release syndrome without compromising efficacy. The human studies also show promising results. It has been shown that glofitamab results in clinical efficacy at all dose levels, and consistently above a threshold dose of 600 mcg.[4] If licensed, glofitamab will offer an additional treatment option for patients with relapsed/refractory DLBCL.

Regulatory & Development Status

Glofitamab does not currently have Marketing Authorisation in the EU/UK for any indication. It has been submitted to the EMA for the indication, glofitamab as monotherapy for the treatment of adult patients with relapsed or refractory DLBCL, after two or more lines of systemic therapy.[5]

Glofitamab is in phase II/III trials for various types of lymphoma.[6]

Patient Group

Disease Area and Clinical Need

DLBCL is a type of non-Hodgkin lymphoma (NHL), and it is the most common type of high-grade NHL.[7,8] NHL is a cancer of the lymphatic system. It develops when the body makes abnormal B lymphocytes. These lymphocytes are a type of white blood cell that normally help to fight infections. With lymphoma, the abnormal lymphocytes build up in lymph nodes or other body organs.[7] The causes of DLBCL are mostly unknown, but a weak immune system, autoimmune diseases and having a parent or sibling with DLBCL

may increase the risk of developing it.[9] Most people with DLBCL first notice painless lumps, often in their neck, armpit, groin or abdomen, or in testicles for men. These are swollen (enlarged) lymph nodes. They usually grow quite quickly, over just a few weeks. Sometimes, DLBCL can develop in lymph nodes deep inside the body where they cannot be felt from the outside. The swollen nodes can form large lumps – known as 'bulky disease'. DLBCL can also develop outside lymph nodes, called 'extranodal' disease.[10] DLBCL can affect people of all ages, but it is more common around the age of 70. It is slightly more common in men than in women.[9] The term "relapsed" refers to disease that reappears or grows again after a period of remission. The term "refractory" is used to describe when the lymphoma does not respond to treatment (meaning that the cancer cells continue to grow) or when the response to treatment does not last very long.[11]

Each year about 5,500 people are diagnosed with DLBCL in the UK.[10] This makes up about 40 out of 100 cases (40%) of NHL in adults.[7] The age standardised registrations of newly diagnosed cases of diffuse NHL (ICD-10 code C83) in England, in 2017, were 15.2 and 9.8 per 100,000 in males and females respectively. There were 4,816 newly diagnosed cases of DLBCL (ICD-10 code C83.3).[12] Up to 50% of patients become refractory to or relapse after treatment.[13] The age standardised rates per 100,000 population of registered deaths from diffuse NHL (ICD-code C83) is 2.8 for males and 1.6 for females.[12] In England, between 2013 and 2017 for a total of 56,350 NHL patients followed up to 2018, the age standardised one-year and five-year survival rate was 79.4% and 65.6% respectively.[14] According to the 2020-21 Hospital Episodes Statistics data, there were 35,113 finished consultant episodes (FCE) for DLBCL (ICD-10 code C83.3) which resulted in 31,231 admissions, 23,709 day cases and 76,363 FCE bed days.[15]

Recommended Treatment Options

The National Institute for Health and Care Excellence (NICE) recommends chemotherapy with rituximab as the first line treatment for DLBCL. If the lymphoma comes back, it is common practice to be offered high dose of chemotherapy and rituximab followed by stem cell transplant.[16]

Clinical Trial Information

Trial	NCT04408638; EudraCT 2020-001021-31; A Phase III, Open-Label, Multicenter, Randomized Study Evaluating the Efficacy and Safety of Glofitamab in Combination With Gemcitabine Plus Oxaliplatin Versus Rituximab in Combination With Gemcitabine and Oxaliplatin in Patients With Relapsed/Refractory Diffuse Large B-Cell Lymphoma **Phase III** – Recruiting **Location(s):** Six EU countries, UK, USA, and other countries **Primary completion date:** November 2022
Trial Design	Randomised, parallel assignment, open-label
Population	N= 270 (estimated); adults (18 years and older) who have been diagnosed with histologically confirmed DLBCL which is relapsed/refractory
Intervention(s)	• IV obinutuzumab single dose 7 days prior to the first dose of glofitamab • IV glofitamab for up to 12 cycles • IV tocilizumab participants will receive as needed for treatment of cytokine-release syndrome • IV gemcitabine for up to 8 cycles • IV oxaliplatin after gemcitabine administration for up to 8 cycles

Comparator(s)	• IV rituximab on day 1 of each cycle for up to 8 cycles • IV gemcitabine prior to oxaliplatin administration for up to 8 cycles • IV oxaliplatin after gemcitabine administration for up to 8 cycles
Outcome(s)	Primary outcome measure: overall survival [time frame: up to 3.5 years] See trial record for full list of other outcomes.
Results (efficacy)	-
Results (safety)	-

Estimated Cost

The cost of glofitamab is not yet known.

Relevant Guidance

NICE Guidance

- NICE technology appraisal in development. Glofitamab for treating relapsed or refractory diffuse large B-cell lymphoma after 2 or more systemic therapies (ID3970). Expected date of issue to be confirmed.
- NICE technology appraisal in development. Loncastuximab tesirine for treating relapsed or refractory diffuse large B-cell lymphoma after 2 or more systemic therapies (ID3943). Expected date of issue to be confirmed.
- NICE technology appraisal in development. Zamtocabtagene autoleucel for treating relapsed or refractory diffuse large B-cell lymphoma after 2 or more therapies (ID10765). Expected date of issue to be confirmed.
- NICE technology appraisal in development. Nivolumab for treating relapsed or refractory diffuse large B-cell lymphoma (ID986). Expected date of issue to be confirmed.
- NICE technology appraisal in development. Tafasitamab with lenalidomide for treating relapsed or refractory diffuse large B-cell lymphoma (ID3795). Expected October 2022.
- NICE technology appraisal. Polatuzumab vedotin with rituximab and bendamustine for treating relapsed or refractory diffuse large B-cell lymphoma (TA649). September 2020.
- NICE technology appraisal. Tisaenlecleucel for treating relapsed or refractory diffuse large B-cell lymphoma and after 2 or more systemic therapies (TA567). March 2019.
- NICE technology appraisal. Axicabtagene ciloleucel for treating diffuse large B-cell lymphoma and primary mediastinal large B-cell lymphoma after 2 or more systemic therapies (TA559). January 2019.
- 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 Haematopoietic Stem Cell Transplantation (Adult). B04/S/a.
- NHS England. Interim Clinical Commissioning Policy Statement: Use of Plerixafor for Stem Cell Mobilisation. B04/PS/a. September 2013.
- NHS Commissioning Board. Clinical Commissioning Policy: Haematopoietic Stem Cell Transplantation (HSCT) (All Ages): Revised. NHSCB/B04/P/a. April 2013.

Other Guidance

- British Society for Haematology. Guidelines for the management of diffuse large B-cell lymphoma. 2016.[17]
- European Society for Medical Oncology. Diffuse large B-cell lymphoma (DLBCL): ESMO clinical practice guidelines for diagnosis, treatment and follow-up. 2015.[18]
- National Comprehensive Cancer Network. Clinical practice guidelines in oncology. Non-Hodgkin's Lymphomas. 2010.[19]

Additional Information

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