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HEALTH TECHNOLOGY BRIEFING
JUNE 2021

Glofitamab for relapsed or refractory diffuse large B-cell lymphoma

NIHRIO ID	31086	**NICE ID**	10627
Developer/Company	Roche Products Ltd	**UKPS ID**	660417

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

SUMMARY

Glofitamab is in clinical development for the treatment of relapsed or refractory diffuse large B-cell lymphoma (DLBCL), high grade B cell lymphoma (HGBCL) and primary mediastinal large B-cell lymphoma (PMBCL). HGBCL and PMBCL are subtypes of DLBCL which is a type of blood cancer that develops when white blood cells, called lymphocytes, grow out of control. 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 is developed as an intravenous infusion to target and eliminate certain white blood cells allowing treatment of B-cell cancers. If licensed, glofitamab would offer an alternative treatment option for adult patients with relapsed or refractory DLBCL, HGBCL and PMBCL.

PROPOSED INDICATION

Treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), high grade B cell lymphoma (HGBCL) or primary mediastinal large B-cell lymphoma (PMBCL) – after two or more lines of systemic treatment.[a]

TECHNOLOGY

DESCRIPTION

Glofitamab (Anti-CD20 CD3 TCB, RG6026, 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.[1] 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.[2]

Glofitamab is in clinical development for the treatment of relapsed/refractory B-cell non-Hodgkin's lymphoma. In the phase I/II clinical trial (NCT03075696), glofitamab will be administered by intravenous (IV) infusion at a dose and as per the schedule specified in the respective treatment arms. Glofitamab dosing will be initiated at 5 mcg (flat dose) followed by doses of 15 mcg, 45 mcg, 135 mcg, 405 mcg and 810 mcg.[3]

INNOVATION AND/OR ADVANTAGES

Even with the emergence of CAR T-cell therapies (a type of immunotherapy) in the B-cell lymphoma treatment paradigm, there is an unmet need for alternative therapies that offer the opportunity for off-the-shelf availability, high response rates, durable remissions, and a manageable safety profile. Data from the clinical trial (NCT03075696) shows glofitamab demonstrated frequent, durable complete responses, a manageable tolerability profile and allows off-the-shelf treatment for patients with refractory B-cell lymphoma in need of timely therapy.[1,4]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

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

Glofitamab is in phase II and phase III clinical development for relapsed/refractory lymphomas including relapsed/refractory diffuse large B-cell lymphoma.[5,6]

[a] Information provided by Roche Products Ltd on UKPharmaScan

PATIENT GROUP

DISEASE BACKGROUND

Diffuse large B-cell lymphoma (DLBCL) is a cancer of B cells and the most common type of fast-growing non-Hodgkin's lymphoma (NHL).[7] B cells (or B lymphocytes) play a major role in the immune system, which guards the body against infection.[8] In DLBCL, the body makes abnormal B lymphocytes which build up in lymph nodes or other body organs. These abnormal cells are spread out (diffuse) rather than group together when they are examined under a microscope.[9,10] The affected lymphocytes start to divide before they are fully mature and lose their infection-fighting properties which makes the body more vulnerable to infection.[11,12] Relapsed/refractory DLBCL refers to the disease reappearing after a period of remission or when the lymphoma becomes non-responsive to treatment.[13]

HGBCL is an aggressive subset of DLBCL associated with genomic alterations in *MYC*, *BCL2*, and/or *BCL6* oncogenes.[14,15] This aggressive lymphoma has been shown to be associated with a very poor outcome.[14] PMBCL is also a distinct subtype of DLBCL in which abnormal B-cells develop in the thymus gland, and then build up in lymph nodes in the space behind the breast bone and between the lungs (mediastinum).[16,17]

The causes of DLBCL, HGBCL and PMBCL are unknown.[16,18] However, factors that may increase the risk of developing DLBCL include: a weak immune system; autoimmune diseases such as rheumatoid arthritis; heredity; ethnicity (more likely in Caucasians); and gender (slightly higher in men).[18,19] PMBCL usually occurs in young adults with a median age of approximately 35 years and a female predominance (twice as many women as men).[17] There are also cases of PMBCL among children and adolescents.[20]

There is an overlap in the signs and symptoms of DLBCL, HGBCL and PMBCL. Generally, symptoms of DLBCL include: painless swelling in neck, armpit or groin; 'B symptoms' such as drenching night sweats, high temperatures (fevers) with no obvious cause, unexplained weight loss; loss of appetite and tiredness.[16,18]

CLINICAL NEED AND BURDEN OF DISEASE

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.[9] The crude incidence of DLBCL in Europe per year is 3.8 cases per 100,000 people, and incidence increases with age and varies considerably across Europe.[21] The age standardised registrations of newly diagnosed cases of diffuse NHL In England, in 2017, were 15.2 per 100,000 in males and 9.8 per 100,000 in females. There were 4,816 newly diagnosed cases of DLBCL (ICD-10 code C83.3).[22] Roughly one-third of patients with DLBCL relapse after receiving first-line treatment. Out of those patients diagnosed with DLBCL, about 10% have refractory disease. For patients who relapse or don't respond to initial therapy, there are limited treatment options that provide durable responses and median life expectancy is approximately six months.[21]

For deaths registered in England in 2017, there were 1,105 deaths where diffuse NHL (ICD10 code C83) was recorded as the underlying cause. The age standardised rates per 100,000 population of registered deaths from diffuse NHL (ICD-code C83) was 2.8 for males and 1.6 for females.[22] 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.[23]

According to the 2019-20 Hospital Episodes Statistics data, there were 39,515 finished consultant episodes (FCE) for DLBCL (ICD-10 code C83.3) which resulted in 35,369 admissions, 27,422 day cases and 86,774 FCE bed days.[24]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

Generally when patients first present with DLBCL the aim of treatment is to cure. It often responds well to treatment and many people go into complete remission. Treatment will depend on the stage of lymphoma the patient has, as well as age, general health and fitness and the patient's feelings towards treatment.[10] Since DLBCL can advance quickly, it usually requires immediate treatment which can lead to disease remission in a large number of patients with this form of lymphoma.[25]

Approximately 50-60% of DLBCL patients achieve and maintain complete remission after first-line therapy. The prognosis of relapsed and refractory DLBCL is poor.[26] Most people with relapsed or refractory lymphoma are offered further chemo-immunotherapy, known as salvage treatment. The aim of salvage treatment is to reduce the lymphoma as much as possible rather than provide curative or overall survival benefit. In those patients who are fit enough after salvage treatment a stem cell transplant may increase the chance of having longlasting remission.[10,27,28]

CURRENT TREATMENT OPTIONS

The most commonly used salvage treatment regimens for relapsed or refractory DLBCL include:[10,29]

- R-GDP – rituximab with gemcitabine, dexamethasone and cisplatin
- R-DHAP – rituximab with dexamethasone, high-dose cytarabine and cisplatin
- R-ICE – rituximab with ifosfamide, carboplatin and etoposide

For adults whose DLBCL is relapsed or refractory after 2 or more systemic therapies, NICE recommends:[30]

- Tisagenlecleucel
- Axicabtagene ciloleucel
- Polatuzumab vedotin with rituximab and bendamustine for adults who cannot have a haematopoietic stem cell transplant.

PLACE OF TECHNOLOGY

If licensed, glofitamab would offer an alternative treatment option for adult patients with relapsed or refractory DLBCL, HGBCL and PMBCL, who have received two or more lines of systemic treatment.

CLINICAL TRIAL INFORMATION

Trial	**NCT03075696;** A Multicenter, Open-Label, Phase I/II Study to Evaluate the Safety, Efficacy, Tolerability and Pharmacokinetics of Escalating Doses of Glofitamab (RO7082859) as a Single Agent and in Combination With Obinutuzumab Administered After a Fixed, Single Dose Pre-Treatment of Obinutuzumab (Gazyvaro™) in Patients With Relapsed/Refractory B-Cell Non-Hodgkin's Lymphoma **Phase I/II –** Ongoing **Location(s):** 8 EU countries (not inc UK), USA, Canada, Australia, New Zealand and Taiwan. **Primary completion date:** June 2023
Trial design	Non-randomised, parallel assignment, open-label
Population	N=860; patients with relapsed/refractory B-Cell non-Hodgkin's lymphoma; all sexes; aged 18 years and older
Intervention(s)	IV glofitamab administered at a dose and as per the schedule specified in the respective arms. See trial record for further details
Comparator(s)	No comparator
Outcome(s)	Primary outcome measures : Part I and II: Percentage of participants with dose limiting toxicities (DLTs) [Time frame: from baseline up to 4 weeks] See trial record for full list of other outcomes
Results (efficacy)	Among the 171 patients treated in part II of the study, glofitamab elicited an overall response rate (ORR) of 53.8%, with 36.8% of patients achieving a complete response (CR). For patients who specifically received the recommended phase 2 dose of 2.5 mg given in cycle 1 day 1, 10 mg given on cycle 1 day 8, and 30 mg given on cycle 2 day 1, the ORR was 65.7%, with 57.1% of patients achieving a CR. Additionally, of the 63 patients who achieved a CR, 84.1% (n = 53) had an ongoing CR after 27.4 months of observation.[1,4]
Results (safety)	Adverse effects (AEs) were observed in 98.2% of patients (n = 168), with 83.6% (n =143) experiencing at least 1 treatment emergent adverse effect associated with glofitamab. The most common AE observed with the agent was cytokine release syndrome, which occurred in 50.3% of patients (n = 86). Grade 3 or higher AEs were observed in 56.7% of patients (n = 97), the most common of which included neutropenia (25.1%), thrombocytopenia (8.2%), and anaemia (7.6%). Serious AEs were reported in 58.5% of patients, with 45.0% of effects determined to be related to glofitamab.[1,4]

ESTIMATED COST

The cost of glofitamab is not yet known.

RELEVANT GUIDANCE

NICE GUIDANCE

- 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. Nivolumab for treating relapsed or refractory diffuse large B-cell lymphoma (ID986). Expected publication date to be confirmed.
- NICE technology appraisal in development. Tafasitamab with lenalidomide for treating relapsed or refractory diffuse large B-cell lymphoma (ID3795). Expected August 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.
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- NHS Commissioning Board. Clinical Commissioning Policy: Haematopoietic Stem Cell Transplantation (HSCT) (All Ages): Revised. NHSCB/B04/P/a. April 2013.

OTHER GUIDANCE

- European Society for Medical Oncology. Diffuse large B-cell lymphoma (DLBCL): ESMO clinical practice guidelines for diagnosis, treatment and follow-up. 2015.[29]
- National Comprehensive Cancer Network. Clinical practice guidelines in oncology. Non-Hodgkin's Lymphomas. 2010.[31]

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.