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ADISINSIGHT REPORT

Glofitamab: First Approval

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Abstract
Glofitamab (Columvi®) is a CD20 × CD3 T-cell-engaging bispecific monoclonal antibody being developed by Roche for the treatment of B-cell non-Hodgkin lymphomas, including diffuse large B-cell lymphoma (DLBCL). Glofitamab received its first approval (with conditions) on 25 March 2023, in Canada, for the treatment of adult patients with relapsed or refractory DLBCL not otherwise specified, DLBCL arising from follicular lymphoma, or primary mediastinal B-cell lymphoma, who have received two or more lines of systemic therapy and are ineligible to receive or cannot receive CAR T-cell therapy or have previously received CAR T-cell therapy. Glofitamab is also under regulatory review for relapsed or refractory DLBCL in the EU and USA and in April 2023 received a positive opinion recommending the granting of a conditional marketing authorization in the EU. Clinical development of glofitamab, as a monotherapy and in combination with other agents for the treatment of non-Hodgkin lymphomas, is continuing worldwide. This article summarizes the milestones in the development of glofitamab leading to this first approval for relapsed or refractory DLBCL.

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Glofitamab (Columvi®): Key Points

A CD20 × CD3 bispecific monoclonal antibody is being developed by Roche for the treatment of B-cell non-Hodgkin lymphomas

Received its first approval on 25 March 2023 in Canada

Approved for use in relapsed or refractory DLBCL in adults

This profile has been extracted and modified from the *AdisInsight* database. *AdisInsight* tracks drug development worldwide through the entire development process, from discovery, through pre-clinical and clinical studies to market launch and beyond.

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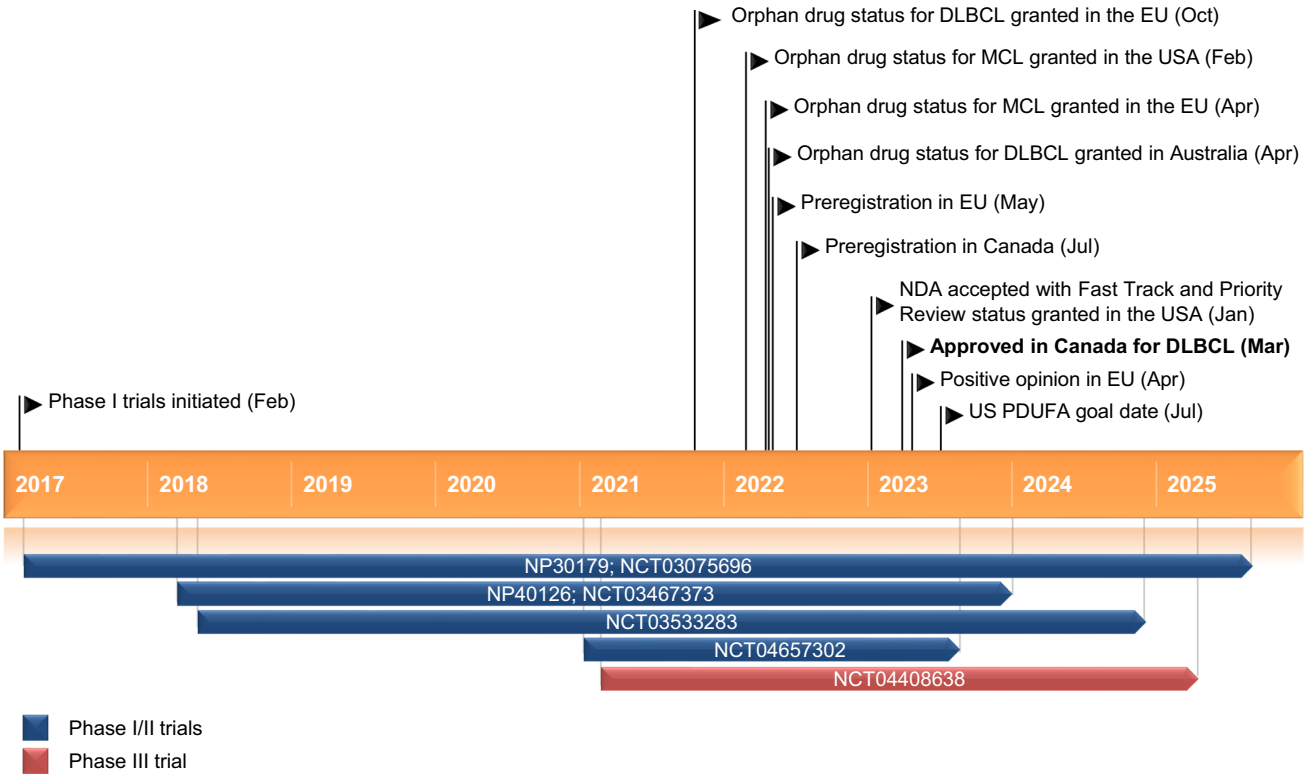
1 Introduction

Glofitamab (Columvi®) is a T-cell-engaging bispecific monoclonal antibody being developed by Roche for the treatment of B-cell non-Hodgkin lymphomas, including diffuse large B-cell lymphoma (DLBCL) [1, 2]. As a CD20 × CD3 bispecific antibody, glofitamab simultaneously binds CD20 expressed on the surface of B-cells and CD3 in the T-cell receptor complex expressed on the surface of T-cells [2]. Through this process of simultaneous binding, glofitamab is designed to redirect a patient's existing T-cells to target and kill malignant B-cells in B-cell non-Hodgkin lymphomas.

Glofitamab received its first approval on 25 March 2023, in Canada, for the treatment of adult patients with relapsed or refractory DLBCL not otherwise specified, DLBCL arising from follicular lymphoma (trFL), or primary mediastinal B-cell lymphoma (PMBCL), who have received two or more lines of systemic therapy and are ineligible to receive or cannot receive chimeric antigen receptor (CAR) T-cell therapy or have previously received CAR T-cell therapy [1, 2]. The marketing authorization for glofitamab has been issued by Health Canada with conditions, pending the results of trials to verify the clinical benefit of the drug [1, 2].

Glofitamab is available as a 1 mg/mL solution which is to be diluted prior to administration by intravenous infusion [2]. Glofitamab is administered in 21-day cycles. Seven days prior to the initiation of glofitamab, all patients must receive



Key milestones in the development of glofitamab. *DLBCL* diffuse large B-cell lymphoma, *MCL* mantle cell lymphoma, *NDA* New Drug Application, *PDUFA* Prescription Drug User Fee Act

pretreatment with a single intravenous dose of obinutuzumab 1000 mg, which is used to deplete circulating and lymphoid tissue B-cells and to reduce the risk of cytokine release syndrome. Glofitamab therapy is to be initiated using a step-up dosing schedule commencing with glofitamab 2.5 mg 7 days after obinutuzumab pretreatment (i.e. on day 8) followed by glofitamab 10 mg on day 15. The recommended glofitamab dose after step-up is 30 mg, administered on day 1 of cycle 2 and of each subsequent cycle, with treatment to continue for a maximum of 12 cycles or until disease progression or unmanageable toxicity.

Glofitamab carries a boxed warning for cytokine release syndrome, which may be serious or life-threatening [2]. In addition to pretreatment with obinutuzumab and the use of a step-up dosing schedule, to reduce the risk of cytokine release syndrome, patients receiving glofitamab should be well hydrated prior to infusion. Additionally, premedication with an oral analgesic/anti-pyretic and an anti-histamine should be administered prior to each glofitamab infusion, with an intravenous glucocorticoid also used in all patients prior to the first four glofitamab infusions and at all subsequent infusions for any patient who experienced cytokine release syndrome with the previous glofitamab dose. Patients should be monitored for ≥ 10 h following the first infusion of glofitamab and as clinically indicated for subsequent infusions. Severe or life-threatening cytokine release syndrome should be treated with tocilizumab, with or without corticosteroids. At least one dose of tocilizumab must be available at cycles 1 and 2 prior to initiating glofitamab infusion, with an additional dose of tocilizumab accessible within 8 h. If cytokine release syndrome occurs, glofitamab should be withheld until resolution. Alternatively, permanent discontinuation of glofitamab may be required based on cytokine release syndrome severity. Glofitamab must not be administered to patients with an active infection [2].

On 26 April 2023, the European Medicines Agency (EMA) Committee for Medicinal Products for Human Use adopted a positive opinion, recommending the granting of a conditional marketing authorization for glofitamab for the treatment of DLBCL [3]. Glofitamab is also under regulatory review for DLBCL in the USA, with the drug receiving a Fast Track designation from the US FDA in January 2023 [4]. Clinical development of glofitamab, as a monotherapy and in combination with other agents for the treatment of non-Hodgkin lymphomas, is continuing worldwide.

1.1 Company Agreements

Glofitamab was originated and developed by Roche. As of July 2022, Chugai Pharmaceutical in-licensed various drugs from Roche, including glofitamab, for their development and distribution in Japan [5].

Features and properties of glofitamab

Alternative names	aCD20/CD3 TCB 2; aCD20/CD3 TCBs; anti-CD20 CD3 TCB; anti-CD20/CD3 bispecific monoclonal antibody; CD20-TCB; Columvi®; RG 6026; RG6026-2; RO 7082859
Class	Antineoplastics; bispecific antibodies; immunotherapies; monoclonal antibodies
Mechanism of action	Antibody-dependent cell cytotoxicity; T lymphocyte stimulation
Route of administration	Intravenous infusion
Pharmacodynamics	Simultaneously binds to CD20 on B-cells and to CD3 on T-cells leading to the formation of an immunological synapse between CD20+ B-cells and CD3+ T-cells; promotes T-cell mediated lysis of CD20-expressing B-cells
Pharmacokinetics	After a single 10-mg dose: C_{max} = 2.34 µg/mL; T_{max} = 8.05 h, $t_{½}$ = 106 h; AUC_{inf} = 244 h·µg/mL; CL = 40.4 mL/h; Vz = 6180 mL
Most common adverse events	Cytokine release syndrome, neutropenia, anaemia, thrombocytopenia
ATC codes	
WHO ATC code	L01 (antineoplastic agents)
EphMRA ATC code	L1 (antineoplastics)

2 Scientific Summary

Glofitamab is a CD20 × CD3 T-cell-engaging bispecific antibody engineered with a novel 2 · 1 configuration of anti-CD20 · anti-CD3 [2].

2.1 Pharmacodynamics

Glofitamab acts in the treatment of B-cell non-Hodgkin lymphomas by promoting T-cell–mediated lysis of CD20-expressing B-cells [2]. Glofitamab simultaneously binds bivalently to CD20 on B-cells and monovalently to CD3 on T-cells leading to the formation of an immunological synapse between CD20-expressing B-cells and CD3-expressing T-cells. Formation of the immunological synapse leads to T-cell activation and proliferation [2]. In addition to inducing the expansion of pre-existing intra-tumour resident T-cell populations, a preclinical study has shown that glofitamab also promotes the recruitment of peripheral blood T-cells [6]. Glofitamab treatment has also been shown to result in a dose-dependent and transient induction of proinflammatory cytokines (including interferon-γ, IL-6, IL-2, IL-8, IL-10, IL-15 and IL-17) [7].

2.2 Pharmacokinetics

Glofitamab pharmacokinetics are linear and dose proportional over the dose range of 0.005 mg to 30 mg [2]. Maximum serum concentrations are reached at the end of the intravenous infusion, after which glofitamab concentrations decline in a bi-exponential fashion. The central volume of distribution is 3.33 L and the peripheral volume of distribution is 2.18 L, based on estimations from population pharmacokinetic modelling [2]. Glofitamab has an estimated half-life of 4–8 days. Although the specific pathways have not been characterized, as an antibody, glofitamab is expected to be principally cleared by catabolism.

2.3 Therapeutic Trials

2.3.1 In Relapsed/Refractory B-Cell Lymphoma

2.3.1.1 Pivotal NP30179 Trial A fixed-duration course of glofitamab monotherapy (following obinutuzumab pretreatment) was associated with a high response rate in patients with relapsed or refractory DLBCL in the open-label, multi-centre, multi-cohort phase I/II trial NP30179 (NCT03075696) [8]. At a median follow-up of 12.6 months, 39% (95% CI 32–48) of patients in the intent-to-treat population ($n = 155$) in the phase II part of the trial had had a complete response (as the best overall response) as assessed by an independent review committee (IRC; primary endpoint). For these patients, the median time to a complete response was 42 days [8].

In a prespecified subgroup analysis, the treatment effect was generally consistent among patients who had received previous CAR-T cell therapy ($n = 52$) and those who had not ($n = 103$), with 35% and 42% of patients in the respective groups achieving a complete response [8]. In other prespecified subgroup analyses, patients with relapsed disease ($n = 23$) had a complete response rate of 70% whereas patients with disease that was refractory ($n = 132$) to the last previous treatment had a complete response rate of 34% [8].

The objective response rate (complete or partial response) in the intent-to-treat population was 52% [8]. The median duration of objective response was 18.4 months (95% CI 13.7 to not reached). Complete responses were generally durable, with the median duration of complete response not reached (95% CI 16.8 to not reached) at data cut-off. Median IRC-assessed progression-free survival (PFS) was 4.9 months and median overall survival was 11.5 months [8].

In the pivotal cohort ($n = 108$), 35% (95% CI 26–45) of patients had a complete response as assessed by the IRC at a median follow-up of 9.0 months, significantly ($p < 0.001$) higher than the rate (20%) observed in a historical control cohort [8].

Key clinical trials of glofitamab

Identifier(s)	Indication	Phase	Drug(s)	Location(s)	Sponsor(s)	Status
NCT03075696; NP30179	r/r DLBCL	I/II	Glofitamab, obinutuzumab, tocilizumab	Multinational	Hoffmann-La Roche	Active
NCT04657302	r/r DLBCL	I	Glofitamab, obinutuzumab, tocilizumab	China	Hoffmann-La Roche	Active
NCT04408638	r/r DLBCL	III	Glofitamab, obinutuzumab, tocilizumab, rituximab, gemcitabine, oxaliplatin	Multinational	Hoffmann-La Roche	Recruiting
NCT05335018	r/r DLBCL	II	Glofitamab, poseltinib, lenalidomide	Republic of Korea	Seoul National University Hospital	Recruiting
NCT05364424	r/r DLBCL	I	Glofitamab, obinutuzumab, tocilizumab, rituximab, ifosfamide, carboplatin, etoposide	USA	Hoffmann-La Roche	Recruiting
NCT04313608	r/r DLBCL or HGBCL	I	Glofitamab, mosunetuzumab, obinutuzumab, tocilizumab, gemcitabine, oxaliplatin	Australia	Hoffmann-La Roche	Completed
NCT04889716	r/r DLBCL or trFL	II	Glofitamab, mosunetuzumab, obinutuzumab	USA	Abramson Cancer Center at Penn Medicine; Genentech	Recruiting
NCT04703686	r/r lymphomas	II	Glofitamab, obinutuzumab	France	Lymphoma Academic Research Organisation	Recruiting
NCT03533283	r/r NHL	Ib/II	Glofitamab, atezolizumab, crefmirlimab, obinutuzumab, polatuzumab vedotin, tocilizumab	Belgium, Denmark, Israel, Italy, Spain, UK, USA	Hoffmann-La Roche	Active
NCT05533775; iMATRIX GLO	r/r NHL	I/II	Glofitamab, obinutuzumab, tocilizumab, rituximab, ifosfamide, carboplatin, etoposide	Denmark, Germany, Italy, Republic of Korea, Spain, USA	Hoffmann-La Roche	Recruiting
NCT05169515	r/r NHL	I	Glofitamab, mosunetuzumab, obinutuzumab, tocilizumab, CC-220, CC-99282	Israel, Italy, Spain, UK, USA	Hoffmann-La Roche	Recruiting
NCT04077723	r/r NHL	I	Glofitamab, obinutuzumab, tocilizumab, RO7227166	Australia, Belgium, Denmark, France, Italy, Spain, UK, USA	Hoffmann-La Roche	Recruiting
NCT05219513	r/r NHL	I	Glofitamab, obinutuzumab, tocilizumab, RO7443904	Australia, Denmark, France, Italy, UK, USA	Hoffmann-La Roche	Recruiting
NCT04970901	r/r NHL	Ib	Glofitamab, loncastuximab tesirine, mosunetuzumab, obinutuzumab, polatuzumab vedotin	Belgium, Czechia, Italy, Spain, UK, USA	ADC Therapeutics	Recruiting
NCT03467373; NP40126	Untreated DLBCL	Ib	Glofitamab, obinutuzumab, polatuzumab vedotin, tocilizumab, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone	Australia, Canada, Denmark, France, Germany, Italy, Spain, UK, USA	Hoffmann-La Roche	Active
NCT04980222	Untreated DLBCL	II	Glofitamab, tocilizumab, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone	Denmark, France, Netherlands, Poland, Spain, USA	Hoffmann-La Roche	Recruiting
NCT04914741; COALITION	Untreated DLBCL or HGBCL	I/II	Glofitamab, polatuzumab vedotin, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone	Australia	Peter MacCallum Cancer Centre; Hoffmann-La Roche	Recruiting

DLBCL diffuse large B-cell lymphoma, *HGBCL* high-grade B-cell lymphoma, *NHL* non-Hodgkin lymphoma, *r/r* relapsed or refractory, *trFL* transformed follicular lymphoma

In the phase II part of the NP30179 trial, patients were ≥ 18 years old and had histologically confirmed DLBCL not otherwise specified (71% of patients), trFL (18%), high-grade B-cell lymphoma (7%), or PMBCL (4%), an Eastern Cooperative Oncology Group performance-status score of 0 or 1, and disease that had relapsed after, or was refractory to, two or more previous lines of therapy [8]. Patients had received a median of three prior therapies (range, 2–7), with 60% of patients having received at least three prior therapies [8]. Glofitamab was administered for 12 cycles (or until disease progression or unacceptable toxicity), according to the dosing schedule detailed in Sect. 1, including the pretreatment with intravenous obinutuzumab and the use of premedications to reduce infusion-related reactions (including cytokine-release syndrome). This recommended phase II dosing schedule was established in the phase I part of the trial [9]. Patients in NP30179 were hospitalized for administration of the first dose of glofitamab [8].

2.3.1.2 Other Trials Similar results to those observed in NP30179 were reported in a phase I trial (NCT04657302) of fixed-duration glofitamab monotherapy in 30 Chinese patients with relapsed or refractory DLBCL treated with two or more previous lines of therapy [10]. At a median follow-up of 10 months, 52% of evaluable patients ($n = 27$) in NCT04657302 had had a complete response as assessed by IRC (primary endpoint). For these patients, the median time to a complete response was 43 days. The objective response rate (based on IRC assessment) was 63%. At data cut-off, 79% (11/14) of complete responses and 76% (13/17) of objective responses were ongoing. Median IRC-assessed PFS was 8 months (95% CI 3 to not reached) and median overall survival was 11 months (95% CI 9 to not reached) [10].

Glofitamab in combination with polatuzumab vedotin has demonstrated promising efficacy in patients with relapsed or refractory B-cell non-Hodgkin lymphoma based on preliminary results from a phase Ib/II dose-escalation and expansion study (NCT03533283) [11]. At data cut-off, 59 patients had been enrolled, with 49 patients evaluable for interim efficacy. At a median follow-up of 3.7 months, 51% of evaluable patients had a complete response (as the best overall response) while the objective response rate was 80%. Patients in NCT03533283 had received a median of two prior lines of therapy, with 70% of patients being refractory to their last therapy. In the trial, glofitamab was administered as for NP30179 (including with use of pretreatment with obinutuzumab on cycle 1 day 1) and continued for 12 cycles. Polatuzumab vedotin 1.8 mg/kg was administered on cycle 1 day 2 and then on day 1 of each cycle up to cycle 6 [11].

2.3.2 In Newly-Diagnosed Diffuse Large B-Cell Lymphoma

Glofitamab administered in combination with rituximab plus cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP) as first-line therapy induced high response rates in patients with newly diagnosed DLBCL in the phase Ib, multi-centre, dose-finding study NP40126 (NCT03467373) [12]. At data cut-off, 56 patients had been enrolled, with 46 patients having reached their scheduled end-of-treatment assessment and evaluated for efficacy. At a median follow-up of 5.6 months, 76.1% of patients in the end-of-treatment population had a complete response (as the best overall response) while the objective response rate was 93.5%. In NP40126, patients received 6–8 cycles of R-CHOP with intravenous glofitamab included from cycle 2 (with step-up dosing starting on cycle 2 day 8) [12].

2.4 Adverse Events

Glofitamab has manageable tolerability in patients with haematological malignancies, based on currently available data [8–12]. In the phase II part of the NP30179 trial (Sect. 2.3.1.1), with glofitamab used as monotherapy in patients ($n = 154$) with relapsed or refractory DLBCL, 62% of patients experienced adverse events of grade ≥ 3, with these mostly being haematological events (e.g. neutropenia, anaemia, thrombocytopenia) [8]. In total, 9% of patients discontinued treatment due to adverse events, with 3% of patients discontinuing treatment due to adverse events that were considered to be related to glofitamab. Serious adverse events occurred in 47% of patients, most commonly cytokine release syndrome [in 21% of patients, per American Society for Transplantation and Cellular Therapy (ASTCT) criteria] and sepsis (4%). Eight patients (5%) died during the phase II part of the trial (not including deaths due to progressive disease); no deaths were considered related to glofitamab treatment [8].

The most commonly reported adverse event was cytokine release syndrome, which occurred in 63% of patients by ASTCT criteria [8]. Cytokine release syndrome was generally mild to moderate in severity, with the most common manifestations including pyrexia (99%), tachycardia (27%) and hypotension (24%). Grade 3 and grade 4 cytokine release syndrome was reported in 2.6% and 1.3% of patients, respectively; there were no deaths due to cytokine release syndrome. Events of cytokine release syndrome were most commonly observed in association with the first three doses of glofitamab, occurring in 53.9% of patients after the first dose (2.5 mg on cycle 1 day 8), in 32.5% of patients after

the second dose (10 mg on cycle 1 day 15), and in 28.4% of patients after the third dose (30 mg on cycle 2 day 1). Few patients (2.0%) experienced cytokine release syndrome beyond cycle 3. All cases of cytokine release syndrome resolved except for one event which was ongoing at the time the patient died from progressive disease. One patient discontinued treatment due to cytokine release syndrome. Mitigation strategies used in NP30179 to reduce the incidence and severity of cytokine release syndrome included pretreatment with obinutuzumab and step-up dosing of glofitamab [8]. Management of cytokine release syndrome most commonly involved corticosteroids and/or tocilizumab. In a cohort of patients in the phase II part of NP30179 for whom pretreatment with dexamethasone was mandated ($n = 40$), cytokine release syndrome occurred in 48% of patients compared with 68% of patients pretreated with investigator's choice of corticosteroid [8]. In the mandatory dexamethasone cohort, no grade ≥ 2 events of cytokine release syndrome were observed following the second or later doses of glofitamab.

Infections of any grade occurred in 38% of patients, with infections of grade ≥ 3 severity occurring in 15% of patients [8]. The most commonly observed infections were Covid-19/Covid-19-related pneumonia (incidence, 9%; grade ≥ 3, 6%) and sepsis (4%, all grade ≥ 3). There were seven infection-related deaths, due to Covid-19/Covid-19-related pneumonia (five) and sepsis (two) [8].

Other adverse events of special interest occurring during treatment with glofitamab include neurological events, tumour flare and tumour lysis syndrome [2]. Neurological adverse events of grade ≥ 2 occurred in 15% of patients in the phase II part of NP30179; grade ≥ 3 neurological adverse events occurred in five patients (3.2%), including one patient with grade 5 delirium [8]. Tumour flare was reported in 11.0% of patients (grade ≥ 3 in 2.6%) [8], with 16 of 17 tumour flare events occurring during cycle 1 of glofitamab treatment [2]. Tumour lysis syndrome occurred in two patients, with both cases of grade ≥ 3 severity [8].

In addition to the manageable tolerability of glofitamab monotherapy demonstrated in NP30179, based on early data from phase I and II trials [11–13], glofitamab also appears to have manageable tolerability during use in combination with chemotherapy and other agents used or being investigated for the treatment of haematological malignancies.

2.5 Ongoing Clinical Trials

In addition to the trials discussed in Sect. 2.3, which are all ongoing, glofitamab (as monotherapy, or in combination with chemotherapy or other agents) is being investigated in several other trials in relapsed and refractory or previously untreated haematological malignancies. These trials include (but are not limited to):

- NCT04408638, a randomized, open-label, phase III trial evaluating the efficacy and safety of glofitamab plus gemcitabine and oxaliplatin versus rituximab plus gemcitabine and oxaliplatin in patients with relapsed or refractory DLBCL [14].
- NCT04980222, a single-arm phase II trial evaluating the safety, efficacy, and pharmacokinetics of glofitamab in combination with R-CHOP as the first line of treatment in patients with circulating tumour DNA high-risk DLBCL.
- COALITION (NCT04914741), a randomized, open-label, phase Ib/II trial evaluating the safety and tolerability of glofitamab in combination with chemotherapy consisting of R-CHOP or polatuzumab vedotin and rituximab plus cyclophosphamide, doxorubicin and prednisone (R-CHP) as the first line of treatment for younger patients (aged 18–65 years) with higher-risk DLBCL or high-grade B-cell lymphoma [15].
- iMATRIX GLO (NCT05533775), a single-arm, two-part, phase I/II trial evaluating the safety and efficacy of glofitamab, as monotherapy and in combination with a rituximab, ifosfamide, carboplatin and etoposide (R-ICE) chemoimmunotherapy regimen, in paediatric and young adult patients (aged 6 months to ≤ 30 years) with relapsed or refractory mature B-cell non-Hodgkin lymphoma.
- NCT05169515, a non-randomized, parallel-assignment, open-label, phase I/II trial evaluating the safety, efficacy and pharmacokinetics of glofitamab or mosunetuzumab in combination with ubiquitin protein ligase complex modulators CC-220 (iberdomide) and CC-99282 in patients with B-cell non-Hodgkin lymphoma.
- NCT04077723, a randomized, open-label, phase I dose-escalation trial evaluating the safety, pharmacokinetics and preliminary efficacy of RO7227166 (a bispecific monoclonal antibody targeting CD19 and 4-1BB) in combination with glofitamab in patients with relapsed or refractory B-cell non-Hodgkin lymphoma [13].
- NCT05219513, a non-randomized, open-label, phase I dose-escalation trial evaluating the safety, tolerability, pharmacokinetics and preliminary efficacy of RO7443904 (a bispecific antibody-like fusion protein targeting CD19 and CD28) in combination with glofitamab in patients with relapsed or refractory B-cell non-Hodgkin lymphoma [16].

3 Current Status

Glofitamab received its first approval on 25 March 2023, in Canada, for relapsed or refractory DLBCL [1]. Glofitamab subsequently received a positive opinion from the EMA in April 2023 recommending the granting of a conditional marketing authorization in the EU for relapsed or refractory DLBCL [3].

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Declarations

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Ethics approval, Consent to participate, Consent to publish, Availability of data and material, Code availability Not applicable.

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