Glofitamab (Columvi®) as monotherapy for the treatment of relapsed or refractory (R/R) diffuse large B-cell lymphoma (DLBCL)

General information [1]

Drug description	Indication
The active substance of Columvi® is glofitamab (RO7082859), a monoclonal bispecific antibody. By simultaneously binding to CD20 on the B cell and CD3 on the T cell, glofitamab mediates the formation of an immunological synapse with subsequent T-cell activation and proliferation, secretion of cytokines and release of cytolytic proteins resulting in the lysis of CD20-expressing B cells.	Glofitamab (Columvi®) as monotherapy is indicated for the treatment of adult patients with R/R DLBCL, after two or more lines of systemic therapy.

Incidence

The incidence of DLBCL is 3 to 7 cases per 100,000 persons; the disease is more common in men. The median age of disease onset is approximately 70 years [2].
About 30% of patients with DLBCL ultimately relapse, suggesting the incidence of relapsed or refractory DLBCL is about 1 case per 100 000 persons [3].

Current treatment

❖ According to the Onkopedia guideline for DLBCL, the following is recommended [2]:

- For patients with refractory disease or early relapse (within 12 months from completion of first-line therapy) who are eligible for high-dose therapy, treatment with axicabtagene ciloleucel or lisocabtagene maraleucel can be considered – following approval and cost assumption - as new standard of care. This is based on the results of the ZUMA-7 trial, showing a significant improvement of event-free survival (EFS) in patients who received axicabtagene ciloleucel. Patients of the TRANSFORM trial receiving lisocabtagene maraleucel also achieved significant improvement of EFS.
- However, there was no significant difference between CAR T-cell therapy as compared with standard salvage therapy among patients of the BELINDA trial.

Regulatory status

EMA [1, 4]	FDA
Approval status for this indication: On 26 April 2023, the CHMP adopted a positive opinion, recommending the granting of a conditional marketing authorisation for Columvi®. UPDATE: Date of issue of marketing authorisation valid throughout the European Union: 07/07/2023. <u>The full indication is:</u> • Columvi® as monotherapy is indicated for the treatment of adult patients with R/R DLBCL, after two or more lines of systemic therapy. **Other indications**: none ✓ **Orphan status** ✓ **Medicine under additional monitoring** ✓ **Medicine received a conditional marketing authorisation**[1]	**Approval status for this indication**: In April 2023, the FDA granted priority review to glofitamab for the treatment of R/R large B-cell lymphoma (LBCL) in adults. The FDA's approval decision is expected by 1 July 2023. [4]. UPDATE: On 15 June 2023, the FDA granted accelerated approval to glofitamab-gxbm (Columvi,®) for R/R DLBCL, not otherwise specified or large B-cell lymphoma (LBCL) arising from follicular lymphoma, after two or more lines of systemic therapy . ✓ This application was granted priority review and fast track designation [5]. **Other indications**: none

Manufacturer

F Hoffman-La Roche Ltd is the manufacturer of Columvi®

Costs [6]

Posology [7, 8]

❖ Columvi® must only be administered under the supervision of a healthcare professional experienced in the diagnosis and treatment of cancer patients and who has access to appropriate medical support to manage severe reactions associated with **cytokine release syndrome (CRS).**

[1] The approval of a medicine that address unmet medical needs of patients on the basis of less comprehensive data than normally required. The available data must indicate that the medicine's benefits outweigh its risks and the applicant should be in a position to provide the comprehensive clinical data in the future.

- ❖ At least 1 dose of tocilizumab for use in the event of CRS must be available prior to Columvi® infusion at Cycles 1 and 2. Access to an additional dose of tocilizumab within 8 hours of use of the previous tocilizumab dose must be ensured.
- ❖ **Pre-treatment with obinutuzumab[2]**
  - All patients in study NP30179 received a single 1 000 mg dose of obinutuzumab as pre-treatment on Cycle 1 Day 1 (7 days prior to initiation of Columvi® treatment) to lower the circulating and lymphoid B cells.
  - Obinutuzumab was administered as an intravenous infusion at 50 mg/h. The rate of infusion was escalated in 50 mg/h increments every 30 minutes to a maximum of 400 mg/h.
- ❖ **Cytokine release syndrome prophylaxis**
  - Columvi® should be administered to well-hydrated patients.

Special warnings and precautions for use [7]

- ❖ **Traceability**
  - In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.
- ❖ **CD20-negative disease**
  - There are limited data available on patients with CD20-negative DLBCL treated with Columvi® and it is possible that patients with CD20-negative DLBCL may have less benefit compared to patients with CD20-positive DLBCL. The potential risks and benefits associated with treatment of patients with CD20-negative DLBCL with Columvi® should be considered.
- ❖ **CRS**
  - CRS, including life-threatening reactions, has been reported in patients receiving Columvi®. The most common manifestations of CRS were pyrexia, tachycardia, hypotension, chills and hypoxia. Infusion-related reactions may be clinically indistinguishable from manifestations of CRS.
  - Most CRS events occurred following the first dose of Columvi®. Elevated liver function tests (AST and ALT > 3 × ULN and/or total bilirubin > 2 × ULN) concurrent with CRS have been reported after Columvi® use.
  - Patients in study NP30179 were pre-treated with obinutuzumab, 7 days prior to initiation of Columvi® therapy, and patients should be premedicated with an anti-pyretic, antihistamine and a glucocorticoid.
  - At least 1 dose of tocilizumab for use in the event of CRS must be available prior to Columvi® infusion at Cycles 1 and 2. Access to an additional dose of tocilizumab within 8 hours of use of the previous tocilizumab dose must be ensured.
  - Patients must be monitored during all Columvi® infusions and for at least 10 hours after completion of the first infusion. Patients must be counselled to seek immediate medical attention should signs or symptoms of CRS occur at any time (see Patient card below).
  - Patients should be evaluated for other causes of fever, hypoxia and hypotension, such as infections or sepsis. CRS should be managed based on the patient's clinical presentation and according to the CRS management guidance provided in the label information.
- ❖ **Patient card**
  - The prescriber must inform the patient of the risk of CRS and signs and symptoms of CRS. Patients must be instructed to seek immediate medical attention if they experience signs and symptoms of CRS. Patients should be provided with the patient card and instructed to carry the card at all times. This card describes symptoms of CRS which, if experienced, should prompt the patient to seek immediate medical attention.
- ❖ **Interaction with CYP450 substrates**
  - The initial release of cytokines associated with the start of Columvi® treatment could suppress CYP450 enzymes and lead to fluctuations in concentrations of concomitantly administered drugs. On initiation of Columvi® therapy, patients being treated with CYP450 substrates with a narrow therapeutic index should be monitored as fluctuations in the concentration of concomitant drugs may lead to toxicity, loss of effect or adverse events.
- ❖ **Serious infections**
  - Serious infections (such as sepsis and pneumonia) have occurred in patients treated with Columvi®. Columvi® must not be administered to patients with an active infection. Caution should be exercised when considering the use of Columvi® in patients with a history of chronic or recurrent infection, those with underlying conditions that may predispose them to infections, or those who have had significant prior immunosuppressive treatment. Patients should be monitored before and during Columvi® treatment for the emergence of possible bacterial, fungal, and new or reactivated viral infections and treated appropriately.

[2] Of note, Roche Registration GmbH withdrew its application for the use of obinutuzumab (Gazyvaro®) as a pre-treatment to reduce the risk of CRS associated with glofitamab (Columvi®) on 4 July 2023. The company stated that its decision was based on the Agency's view that the data did not allow to conclude on a positive benefit-risk balance for the use of Gazyvaro® as a pre-treatment to reduce the risk of CRS associated with Columvi®.

- Columvi® should be temporarily withheld in the presence of an active infection until the infection has resolved. Patients should be instructed to seek medical advice if signs or symptoms suggestive of an infection occur.
- Febrile neutropenia has been reported during treatment with Columvi®. Patients with febrile neutropenia should be evaluated for infection and treated promptly.

❖ **Tumour flare**

- Tumour flare has been reported in patients receiving Columvi®. Manifestations included localised pain and swelling.
- Consistent with the mechanism of action of Columvi®, tumour flare is likely due to the influx of T cells into tumour sites following Columvi® administration and may mimic progression of disease. Tumour flare does not imply treatment failure or represent tumour progression.
- Specific risk factors for tumour flare have not been identified, however, there is a heightened risk of compromise and morbidity due to mass effect secondary to tumour flare in patients with bulky tumours located in close proximity to airways and/or a vital organ. Monitoring and evaluation for tumour flare at critical anatomical sites is recommended in patients treated with Columvi® and managed as clinically indicated. Corticosteroids and analgesics should be considered to treat tumour flare.

❖ **Tumour lysis syndrome (TLS)**

- TLS has been reported in patients receiving Columvi®.
- Patients with high tumour burden, rapidly proliferative tumours, renal dysfunction or dehydration are at greater risk of tumour lysis syndrome. Patients at risk should be monitored closely by appropriate laboratory and clinical tests for electrolyte status, hydration and renal function.
- Appropriate prophylactic measures with anti-hyperuricaemics (e.g., allopurinol or rasburicase) and adequate hydration should be considered prior to obinutuzumab pre-treatment and prior to Columvi® infusion.
- Management of TLS may include aggressive hydration, correction of electrolyte abnormalities, anti-hyperuricaemic therapy and supportive care.

❖ **Immunisation**

The safety of immunisation with live vaccines during or following Columvi therapy has not been studied. Immunisation with live vaccines is not recommended during Columvi® therapy.

Study characteristics [9-11]

Trial name	*n*	Intervention (I)	Comparator (C)	PE	Median follow-up	Characteristics	Biomarker	Funding	Publication(s)
NP30179 NCT03075696	155[3]	glofitamab[4] IV as step-up doses on day 8 (2.5 mg) and day 15 (10 mg) of cycle[5] 1, followed by a dose of 30 mg on day 1 of cycles 2-12	-	CR by IRC	12.6 months	**ongoing**[6], multicentre, open-label, phase 1–2 trial	-	F. Hoffmann–La Roche	NP30179 trial [10]

Inclusion criteria[7]	Exclusion criteria	Patient characteristics at baseline
❖ Age ≥18 years with histologically confirmed DLBCL (not otherwise specified), transformed FL, high-grade B-cell lymphoma, or primary mediastinal large B-cell lymphoma. ❖ Patients must have relapsed after or failed to respond to at least 2 prior systemic treatment regimens	❖ Patients with CLL, Burkitt lymphoma, and lymphoplasmacytic lymphoma ❖ Patients with history of macrophage activation syndrome or hemophagocytic lymphohistiocytosis ❖ Known active bacterial, viral, fungal, mycobacterial, parasitic, or other infection ❖ Pregnant or breast-feeding or intending to become pregnant during the study ❖ Prior treatment with systemic immunotherapeutic agents, including, but not limited to, radio-immunoconjugates, antibody-drug conjugates, immune/cytokines, and monoclonal antibodies	❖ Median age: 66 years (range, 21–90) ❖ Male sex: 65% ❖ ECOG PS score 0: 45% ❖ ECOG PS score 1: 55% ❖ Ann Arbor stage at time of study entry: I (6%); II (16%); III (20%); IV (55%); missing data (2%) ❖ Non-Hodgkin's lymphoma subtype: • DLBCL, not otherwise specified: 71%

[3] In the initial protocol (July 2016) it was planned to enrol 15-80 patients in the dose escalation phase and 60 patients in the dose expansion phase (40 patients with R/R DLBCL and 20 patients with R/R FL). In protocol version 6 (August 2018) the target sample size in the dose expansion monotherapy cohorts was increased to 100 patients with R/R DLBCL and 80 patients with R/R FL. In protocol version 8 (August 2019), step-up dosing was introduced, with the aim of reducing the incidence and severity of cytokine release syndrome, including the addition of a dose expansion cohort in patients with R/R DLBCL (n=100). Between 2018 and 2020, further dose escalation cohorts were added to the dose escalation phase to explore combination therapy, extend step-up dosing, and double obinutuzumab pretreatment, with the maximum sample size increasing to 220 patients. In protocol version 10 (December 2020), an expansion cohort (40 additional patients) was added to investigate 2.5/10/30 mg step-up dosing after premedication with dexamethasone.

[4] Pre-treatment with obinutuzumab (1000 mg) was administered IV 7 days before the first dose of glofitamab.

[5] Cycles lasted 21 days.

[6] NCT03075696 is currently ongoing; estimated study completion date is 08/2025.

[7] For detailed in- and exclusion criteria, please see study protocol.

❖ Measurable disease, defined as at least one bi-dimensionally measurable nodal lesion, or at least one bi-dimensionally measurable extranodal lesion ❖ ECOG PS of 0 or 1 ❖ Life expectancy of >12 weeks ❖ AEs from prior anti-cancer therapy must have resolved to grade ≤1 ❖ Adequate liver-, haematologic- and renal function ❖ Negative serum pregnancy test within 7 days prior to study treatment in women of childbearing potential ❖ Negative serologic or polymerase chain reaction test results for acute or chronic HBV infection, HCV, and HIV ❖ Effective contraceptive methods in women of childbearing potential and men; men must also agree to refrain from donating sperm	❖ History of treatment-emergent immune-relate AEs associated with prior immunotherapeutic agents ❖ Documented refractoriness to an obinutuzumab monotherapy-containing regimen ❖ Treatment with standard radiotherapy, any chemotherapeutic agent, or treatment with any other investigational anti-cancer agent infusion ❖ Prior solid organ transplantation or allogenic SCT ❖ Autologous SCT within 100 days prior to obinutuzumab pretreatment infusion ❖ History of autoimmune disease ❖ History of severe allergic or anaphylactic reactions to monoclonal antibody therapy ❖ History of confirmed progressive multifocal leukoencephalopathy ❖ Current or history of CNS lymphoma or CNS disease ❖ Another invasive malignancy in the last 2 years ❖ Significant cardiovascular disease ❖ Received systemic immunosuppressive medications	• Transformed FL: 18% • High-grade B-cell lymphoma: 7% • Primary mediastinal B-cell lymphoma: 4% ❖ Bulky disease at study entry • >6 cm: 42% • >10 cm: 12% ❖ Previous lines of therapy • median no. of lines: 3 (range, 2–7) • Only 2 previous lines: 40% • ≥3 previous lines: 60% ❖ R/R status: • Refractory to any previous therapy: 90% • Refractory to last previous therapy: 86% • Primary refractory: 58% • Refractory to any previous anti-CD20 therapy: 83% • Refractory to previous CAR T-cell therapy: 30%

Efficacy (I vs. C)	**Safety** (I vs. C)
<u>Median follow-up 12.6 months (n=155)</u> CR by IRC[8]: 39% (95% CI, 32-48) OR: 52% (95% CI, 43-60) Median time to a complete CR: 42 days (95% CI, 42-44) Median duration of OR: 18.4 months (95% CI, 13.7-NR) Ongoing OR in patients with an OR at 12 months: 64% (95% CI, 51-76) Median duration of CR: not reached (95% CI, 16.8-NR) Ongoing CR in patients with a response at 12 months: 78% (95% CI, 64-91) 6-month PFS in the ITT-population: 46% (95% CI, 37-54) 12-month PFS in the ITT-population: 37% (95% CI, 28-46) Median PFS by IRC: 4.9 months (95% CI, 3.4-8.1) Estimated 12-month OS: 50% (95% CI, 41-58)[9] **<u>Primary analysis in the pivotal cohort (14 September 2021, n=108, median follow-up of 9.0 months)</u>** CR: 35% (95% CI, 26-45) Median OS: 8.9 months (95% CI, 7.1-15.3)	**AEs grade ≥3**: 62% **Any serious AE**: n=73/154 (47%) **AEs grade 5**: n=8[10]/154 (5%) **Discontinuation due to AEs**: n=14/154 (9%) **Glofitamab-related AEs leading to treatment discontinuation**: n=5[11]/154 (3%) **Cytokine release syndrome, grade ≥2 per ASTCT**: n=24/154 (16%) **Neurologic event grade ≥2:** n=23/154 (15%) **CTCAE-defined neurologic AEs consistent with ICANS[12]:** n=12/154 (8%; with events of grade ≥3 in 3%) **Infections of any grade**: n=59/154 (38%) **Infections of grade ≥3**: n=23/154 (15%)

[8] Concordance between results according to independent-review assessment and investigator assessment was 93% for complete response and 86% for objective response.
[9] These data included 5 deaths related to Covid-19.
[10] Covid-19–related pneumonia or Covid-19 (n=5), sepsis (n=2), delirium (n=1)
[11] Gastrointestinal haemorrhage (n=1), myelitis (n=1), cytokine release syndrome (n=1), neutropenia (n=2)
[12] These events were considered by the investigator to be related to glofitamab therapy in n=3 (2%).

12-month OS rate: 45.6% (95% CI, 35.9-55.4)

Supporting cohort (n=101)

CR: 35%

Median duration of CR: 34.2 months (95% CI, 17.9-not reached)

Late events in the supporting cohort: progressive disease at 17.9 months, progressive disease at 22.1 months, death from unknown cause at 24.7 months, and death from acute myeloid leukaemia at 34.2 months.

UPDATE: Median follow-up 15 months (range: 0 to 21 months); median follow-up for DOR was 12.8 months (range: 0 to 20 months):

Patients with CR: 35.2% (95% CI, 26.24-44.96)

Patients with CR or PR: 50.0 (95% CI, 40.22-59.78)

Median duration of CR: NE (95% CI, 18.4-NE)

12-month duration of CR: 74.6% (95% CI, 59.19-89.93)

Median duration:14.4 months (95% CI, 8.6-NE)

Median time to first CR

Median time to first CR: 42 months (95% CI, 41-47)

Patient-reported outcomes

Currently, there are no patient-reported outcomes available.

ESMO-MCBS version 1.1

Disclaimer: Though not finally validated, but feasibility tested in [12], the original ESMO-MCBS v1.1. was found to be widely applicable also for haematological malignancies. Hence, from October 2022, ESMO assessments were also carried out for haematological indications in new fact sheets and updates.

Scale	Int.	Form	MG ST	MG	HR (95% CI)	Score calculation	PM	Toxicity	QoL	AJ	FM

The ESMO-MCBS cannot be applied, as the primary outcome is not ORR or PFS.

Risk of bias - study level (case series) [13]

1.	2.	3.	4.	5.	6.	7.	8.	9.
Was the hypothesis/ aim/ objective of the study clearly stated?	Were the cases collected in more than one centre?	Were patients recruited consecutively?	Were the eligibility criteria (inclusion and exclusion criteria) for entry into the study clearly stated?	Did participants enter the study at similar point in the disease?	Was the intervention clearly described?	Were additional interventions (co-interventions) clearly described?	Were relevant outcome measures established a priori?	Were outcome assessors blinded to the intervention that patients received?
yes	yes	yes	yes	partial[13]	yes	yes	yes	no
10.	11.	12.	13.	14.	15.	16.	17.	18.
Were the relevant outcomes measured using appropriate objective/ subjective methods?	Were the relevant outcomes measured before and after intervention?	Were the statistical tests used to assess the relevant outcomes appropriate?	Was the length of follow-up reported?	Was the loss to follow-up reported?	Did the study provide estimates of random variability in the data analysis of relevant outcomes?	Were adverse events reported?	Were the conclusions of the study supported by results?	Were both competing interest and source of support for the study reported?
yes	yes	yes	yes	unclear	partial	yes	unclear[14]	yes

Overall risk of bias: moderate

Ongoing trials [14]

NCT number/trial name	Description	Estimated study completion date
NCT03075696	Please see above.	08/2025

[13] Patient characteristics at baseline were heterogenous.

[14] No final analysis data available.

NCT04408638	A phase III, open-label, multicentre, randomised study evaluating the efficacy and safety of glofitamab in combination with gemcitabine plus oxaliplatin vs. rituximab in combination with gemcitabine and oxaliplatin in patients with R/R DLBCL.	04/2025

Available assessments

- In August 2023, NICE published "Glofitamab for treating relapsed or refractory diffuse large B-cell lymphoma after 2 or more systemic treatments [15].
- In June 2021, the National Institute for Health Research published a Health Technology Briefing "Glofitamab for relapsed or refractory diffuse large B-cell lymphoma" [16].No further assessments were identified.

Other aspects and conclusions

- In April 2023, the CHMP adopted a positive opinion, recommending granting conditional marketing authorisation for glofitamab (Columvi®) as monotherapy for treating adult patients with R/R DLBCL after two or more lines of systemic therapy. This indication is currently not approved by the FDA; however, priority review was granted, and the FDA's approval decision is expected by July 2023.
- NCT03075696 is an open-label, phase I/II study to evaluate the safety and efficacy of glofitamab in patients with R/R B-cell non-Hodgkin's lymphoma. Patients ≥18 years with histologically confirmed DLBCL (not otherwise specified), transformed FL, high-grade B-cell lymphoma, or primary mediastinal large B-cell lymphoma and an ECOG PS score of 0 or 1 were included. All the patients had disease that had relapsed after or was refractory to at least 2 previous lines of therapy. There is a wide range of exclusion criteria, including, e.g., patients with CLL, Burkitt lymphoma, and lymphoplasmacytic lymphoma.
- NCT03075696 is currently ongoing; there is no final analysis data available.
- Patient-reported outcomes are not (yet) available.
- The RoB of NCT03075696 was considered moderate; it increased due to the open-label- and single-arm design, the heterogeneous patient characteristics at baseline, the ongoing status and the sponsor's involvement.
- According to ISHI, given the limitations of existing treatment options, the prognosis for patients with R/R DLBCL is very poor, particularly for patients who are ineligible for or have already received CAR-T therapy. Thus, an unmet clinical need exists for novel, safe, and effective treatment options that can prevent disease progression and improve outcomes for this patient population [3].
- Nevertheless, since 62% of the study patients experienced grade ≥3 toxic effects (with cytokine release syndrome as the most frequent AE occurring in 63% of patients), special attention should be focused on the safety of glofitamab.
- Besides, several protocol amendments, the small sample size of the different non-Hodgkin's lymphoma sub-groups, and the median follow-up time of 12.5 months need to be considered when interpreting the presented efficacy and safety results of NCT03075696.
- Final analysis data of NCT03075696 and long-term- and patient-reported outcome data from RCTs is required to elucidate the role of glofitamab for R/R DLBCL patients entirely.
- One phase 3 trial (NCT04408638) evaluating the efficacy and safety of glofitamab in combination with gemcitabine plus oxaliplatin compared with rituximab in combination with gemcitabine plus oxaliplatin in patients with R/R DLBCL, were identified among ongoing trials.

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Abbreviations: AE=adverse event, AJ=adjustment, ASTCT=American Society for Transplantation and Cellular Therapy, C=comparator, CAR= chimeric antigen receptor, CHMP=Committee for Medicinal Products for Human Use, CI=confidence interval, CLL=chronic lymphocytic leukaemia, CNS=central nervous system, CR=complete response, CTCAE=Common Terminology Criteria for Adverse Events, DLBCL= diffuse large B-cell lymphoma, DoR=duration of response, ECOG PS=Eastern Cooperative Oncology Group performance status, EFS= event-free survival, EMA=European Medicines Agency, ESMO-MCBS= European Society of Medical Oncology – Magnitude of Clinical Benefit Scale, FDA=Food and Drug Administration, FL=follicular lymphoma, FM=final magnitude of clinical benefit grade, HBV=hepatitis B virus, HCV=hepatitis C virus, HIV=human immunodeficiency virus, HR=hazard ratio, I=intervention, ICANS= immune effector cell–associated neurotoxicity syndrome, Int.=intention, IRC=independent review committee, ISHI=International Horizon Scanning Initiative, ITT=intention-to-treat, IV=intravenous, LBCL=large B-cell lymphoma, MG=median gain, n=number of patients, NA=not available, NICE=National Institute for Health Care Excellence, NR=not reached, ORR=overall response rate, OS=overall survival, OR(R) = objective response (rate), PE=primary endpoint, PFS=progression-free survival, PM=preliminary grade, QoL=quality of life, R/R=relapsed/refractory, SAE=serious adverse event, SCT=stem cell transplantation, ST=standard treatment

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