Australian Government
Department of Health and Aged Care
Therapeutic Goods Administration

Australian Public Assessment Report for Gazyva

Active ingredient: Obinutuzumab
Sponsor: Roche Products Pty Ltd

December 2024

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and Aged Care and is responsible for regulating therapeutic goods, including medicines, medical devices, and biologicals.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety, and efficacy.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to the Australian public outweigh any risks associated with the use of therapeutic goods.
- The TGA relies on the public, healthcare professionals and industry to report problems with therapeutic goods. The TGA investigates reports received to determine any necessary regulatory action.
- To report a problem with a therapeutic good, please see the information on the TGA website.

About AusPARs

- The Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission. Further information can be found in Australian Public Assessment Report (AusPAR) guidance.
- AusPARs are prepared and published by the TGA.
- AusPARs are static documents that provide information that relates to a submission at a particular point in time. The publication of an AusPAR is an important part of the transparency of the TGA's decision-making process.
- A new AusPAR may be provided to reflect changes to indications or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

List of abbreviations

Abbreviation	Meaning
ACM	Advisory Committee on Medicines
ADR	Adverse drug reaction(s)
ARTG	Australian Register of Therapeutic Goods
ASA	Australia-specific annex
ASTCT	American Society for Transplantation and Cellular Therapy
C1D1 and analogous terms	Cycle 1, Day 1 and analogous meanings
CMI	Consumer Medicines Information
CRS	Cytokine release syndrome
DLBCL	Diffuse large B cell lymphoma
DLP	Data lock point
FL	Follicular lymphoma
HGBCL	High-grade B cell lymphoma
IRR	Infusion related reaction(s)
NHL	Non-Hodgkin lymphoma
PI	Product Information
PK	Pharmacokinetic(s)
PMBCL	Primary mediastinal B cell lymphoma
PSUR	Periodic safety update report
RMP	Risk management plan
RO	Receptor occupancy
R/R	Relapsed/refractory
TGA	Therapeutic Goods Administration

Product submission

Submission details

Type of submission:	Extension of indication
Product name:	Gazyva
Active ingredient:	Obinutuzumab (rch)
Decision:	Approved
Date of decision:	3 May 2023
Date of entry into ARTG:	4 May 2023
ARTG number:	210562
, *Black Triangle Scheme*	No
Sponsor's name and address:	Roche Products Pty Ltd Level 8, 30-34 Hickson Road Sydney NSW 2000
Dose form:	Concentrate solution for infusion
Strength:	1000 mg/40 mL
Container:	Vial
Pack size:	One vial
Approved therapeutic use for the current submission:	*Gazyva is indicated as a pre-treatment to reduce the risk of cytokine release syndrome (CRS) induced by glofitamab.*
Route of administration:	Intravenous infusion
Dosage:	Pre-treatment to reduce the risk of CRS induced by glofitamab: The recommended dose for pre-treatment is a single 1000 mg dose of Gazyva administered intravenously, 7 days prior to initiation of glofitamab. Administer Gazyva at 50 mg/hour. The rate of infusion can be escalated in 50 mg/hour increments every 30 minutes to a maximum of 400 mg/hour. For further information, refer to the Product Information (PI).
Pregnancy category:	C Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human fetus or neonate without causing malformations. These effects may be reversible. Accompanying texts should be consulted for further details. The use of any medicine during pregnancy requires careful consideration of both risks and benefits by the treating health professional. The pregnancy database

must not be used as the sole basis of decision making in the use of medicines during pregnancy. The TGA does not provide advice on the use of medicines in pregnancy for specific cases. More information is available from obstetric drug information services in your state or territory.

Product background

This AusPAR describes the submission by Roche Product Pty Ltd (the sponsor) to register Gazyva (obinutuzumab (rch)) 1000 mg/40 mL concentrate solution for infusion in vials for the following proposed extension of indications:[1]

> *Gazyva is indicated as a pre-treatment to reduce the risk of cytokine release syndrome (CRS) induced by glofitamab.*

The product

Obinutuzumab is a recombinant monoclonal humanised and glycoengineered Type II anti-CD20 antibody of the immunoglobulin (Ig) G1 isotype. It specifically targets the extracellular loop of the CD20 transmembrane antigen on the surface of non-malignant and malignant pre B and mature B lymphocytes. It induces death of normal and malignant B lymphocytes directly and through antibody-dependent cellular cytotoxicity, antibody-dependent cellular phagocytosis and complement-dependent cytotoxicity.

The proposed pre-treatment dose is the same as the approved initial dose in patients with relapsed/refractory follicular lymphoma (FL) and as the standard, subsequent dose in patients with either chronic lymphocytic leukaemia or FL.

The condition

Symptoms of CRS can be mild flu-like symptoms (most usual) or severe or life-threatening complications of systemic inflammation such as hypotension, hypoxia, coagulopathy and multi-organ failure. Cytokine Release Syndrome is usually manageable but can be associated with activation of endogenous or infused T cells and/or other immune effector cells such as macrophages, dendritic cells, monocytes and endothelial cells, leading to cytokine release and subsequent clinical features. The cytokines released include interleukin-2, soluble interleukin-2 receptor a, interferon g, interleukin-6, and soluble interleukin-6 receptor, as well as granulocyte macrophage-colony stimulating factor.

Current treatment options

The current application seeks to extend the indication for obinutuzumab to include pre-treatment to reduce the risk of glofitamab-induced cytokine-release syndrome (CRS). As glofitamab is a new biological product there are no approved treatment options for pre-treatment to reduce the risk of glofitamab-induced CRS.

Current treatments in the context of T cell engaging bispecific antibody-induced CRS include interrupting or discontinuing the drug infusion; symptomatic management of constitutional symptoms including hypotension with IV fluids and vasopressors; management of hypoxia with

[1] This is the original indication proposed by the sponsor when the TGA commenced the evaluation of this submission. It may differ to the final indication approved by the TGA and registered in the Australian Register of Therapeutic Goods.

supplemental oxygen or mechanical ventilation; and corticosteroids and anti-interleukin-6 treatment (for example, tocilizumab).[2]

In patients with refractory CRS, anti-cytokine targeted therapies include siltuximab for interleukin-6,[3] adalimumab or etanercept for tumour necrosis factor-α,[4] and anakinra for interleukin-1 β.[5] None of these treatments have specific indications for CRS.

Regulatory status

Australian regulatory status

Obinutuzumab received initial registration in the Australian Register of Therapeutic Goods (ARTG) on 15 May 2014, for the indication:

> *Gazyva in combination with chlorambucil is indicated for the treatment of patients with previously untreated chronic lymphocytic leukaemia (CLL).*[6]

On 30 August 2016 an extension of indication was added in the ARTG:

> *Gazyva in combination with bendamustine, followed by Gazyva maintenance, is indicated for the treatment of patients with follicular lymphoma who did not respond to, or who progressed during or up to 6 months after treatment with rituximab or a rituximab-containing regimen.*[7]

On 5 December 2017 an extension of indication was added in the ARTG:

> *Gazyva in combination with chemotherapy followed by Gazyva maintenance is indicated for the treatment of patients with previously untreated advanced follicular lymphoma.*[8]

International regulatory status

At the time the TGA considered this submission, a similar submission was under consideration in the European Union (submitted on 29 November 2022) and Switzerland (submitted on 20 December 2022).

Concurrent submission

The submission for provisional approval of the new biological entity glofitamab (Columvi) (submission PM-2022-01989-1-6) for *the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) after two or more lines of systemic therapy* was submitted concurrently with this submission for Gazyva and relied on the same clinical dataset.

[2] Tocilizumab was first registered in Australia in 2009.

[3] Siltuximab was first registered in Australia in 2015.

[4] Adalimumab was first registered in Australia in 2012. Etanercept was first registered in Australia in 2003.

[5] Anakinra was first registered in Australia in 2003.

[6] AusPAR for Gazyva as a new biological entity, published August 2014; see Australian Public Assessment Report for obinutuzumab (tga.gov.au).

[7] No AusPAR was produced for this submission.

[8] AusPAR for Gazyva for follicular lymphoma indication, published May 2018; see Australian Public Assessment Report Obinutuzumab (tga.gov.au)

Registration timeline

The following table captures the key steps and dates for this submission.

This submission was evaluated under the standard prescription medicines registration process.

Table 1: Timeline for Submission PM-2022-03031-1-6

Description	Date
Submission dossier accepted and first round evaluation commenced	31 August 2022
First round evaluation completed	16 December 2022
Sponsor provides responses on questions raised in first round evaluation	11 January 2023
Second round evaluation completed	3 February 2023
Sponsor's notification to the TGA of errors/omissions in evaluation reports	14 February 2023
Delegate's Overall benefit-risk assessment and request for Advisory Committee advice[9]	22 February 2023
Sponsor's pre-Advisory Committee response	13 March 2023
Advisory Committee meeting	30 and 31 March 2023
Registration decision (Outcome)	3 May 2023
Administrative activities and registration in the ARTG completed	4 May 2023
Number of working days from submission dossier acceptance to registration decision*	147

*Statutory timeframe for standard submissions is 255 working days

Submission overview and risk/benefit assessment

A summary of the TGA's assessment for this submission is provided below.

Quality

Quality evaluation is not required for this submission as there are no proposed changes to the quality of the currently approved product in Australia. The quality of the currently approved product is suitable for the proposed changes in this submission. A full quality evaluation was conducted at the time Gazyva received initial registration.

[9] In this report the 'Delegate' is the Delegate of the Secretary of the Department of Health and Aged Care who decided the submission under section 25 of the Act.

Nonclinical

Nonclinical data support the utility of obinutuzumab for the proposed indication. There are no nonclinical objections to the proposed extension of indication for Gazyva.

Obinutuzumab is an anti-CD20 monoclonal antibody that induces death of normal and malignant B lymphocytes directly and through antibody-dependent cellular cytotoxicity, antibody-dependent cellular phagocytosis and complement-dependent cytotoxicity. Glofitamab is an anti-CD20 and anti-CD3 bispecific monoclonal antibody that induces death of normal and malignant B lymphocytes by T cell-mediated cytotoxicity.

Nonclinical studies submitted for the registration of obinutuzumab, and glofitamab, as new biological entities included examination of the B-cell depleting effect of obinutuzumab and the effect of obinutuzumab pre-treatment on the pharmacology and toxicity of glofitamab.

Findings relating to cytokine release were transient and most prominent after the first dose of glofitamab. They were shown to be attenuated by the use of glofitamab step-up dosing and by obinutuzumab pre-treatment in separate studies. This is consistent with the extent of cytokine release being mainly driven by the number of B-cells.

In cynomolgus monkeys, pre-treatment with obinutuzumab (50 mg/kg IV) 4 days prior to administration of glofitamab was shown to be associated with smaller increases in serum levels of inflammatory cytokines, along with a lessening of clinical signs. Obinutuzumab pre-treatment allowed an at least 10-fold higher dose of glofitamab (1 mg/kg compared to 0.1 mg/kg and lower IV) to be tolerated in monkeys.

B-cell depletion in peripheral blood and lymph nodes induced by obinutuzumab in cynomolgus monkeys was shown to be rapid, extensive and durable (more so than with rituximab).

In tumour-bearing humanised mice, obinutuzumab pre-treatment strongly reduced glofitamab-mediated cytokine release and prevented the transient T cell decrease in peripheral blood (reflecting margination) without interfering with glofitamab-mediated B-cell depletion or anti-tumour activity. Obinutuzumab pre-treatment markedly reduced the increase in perivascular CD3+ T cells in the lungs of glofitamab-treated mice.

Reduction of glofitamab-mediated T cell activation and cytokine release with prior treatment with obinutuzumab was also demonstrated in vitro in healthy human whole blood (occurring as a consequence of the lower B-cell numbers at the time of glofitamab treatment).

Clinical

Summary of clinical studies

The clinical dossier consisted of:

- one Phase I/II study, Study NP30179, an ongoing, multicentre, open-label study evaluating the safety, efficacy, and tolerability, and pharmacokinetics of escalating doses of glofitamab as a single agent and in combination with obinutuzumab administered as a fixed, single dose pre-treatment, in patients with relapsed/refractory B-cell Non-Hodgkin Lymphoma (NHL).

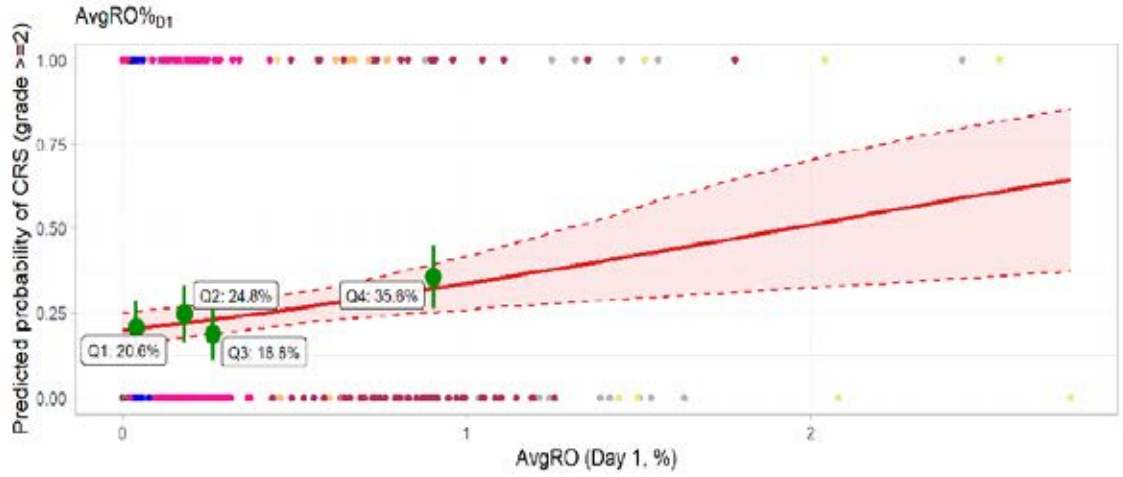
Pharmacology

Pharmacokinetic (PK) analysis of serum obinutuzumab levels in the Phase I/II study NP30179 were compatible with earlier obinutuzumab concentration data. Serum concentration data were available for 406 patients with a total of 971 observations.

Glofitamab and obinutuzumab bind to CD20 on the same epitope, and circulating obinutuzumab will compete with glofitamab. In order to account for the impact of circulating obinutuzumab and glofitamab concentrations, the PK exposure parameter utilised in the Exposure-Response analysis was glofitamab receptor occupancy (RO).

An exposure-response analysis for CRS was performed and focused on the relationship between model-derived glofitamab average CD20 RO% over the first 24 hours following the first glofitamab administration and the occurrence of CRS assessed as Grade 2 or higher.[10] The exposure-CRS analysis on the total PK-evaluable population (covering a wide range of exposures and dosing regimens), indicates that the risk of experiencing CRS of Grade 2 or higher significantly increases (p-value=0.00380, Figure 1) with increasing glofitamab average RO% over the first 24 hours (AvRO%D1). This observation was confirmed when looking at the AvRO%D1 quartiles with 20.6%, 24.8%, 18.8%, and 35.6% in quartiles 1 to 4, respectively.

Figure 1: Study NP30179 Exposure-response analysis relating the glofitamab average CD20 receptor occupancy over the first 24 hours to the risk of Grade 2 and higher CRS (pharmacokinetics-evaluable population)



p-value = 0.00380

The average RO after the first glofitamab administration (2.5 mg) is approximately 0.1%. The glofitamab step-up dosing regimen was selected with the intent to achieve a RO value in this range, to mitigate CRS and maximise the potential for benefit by facilitating rapid increases to the target dose. The high CD20 binding potency of glofitamab, in the absence of a competing anti-CD20 antibody, would result in a substantially higher RO, particularly after first administration and consequently, an extremely high T cell recruitment to the target site would be expected. In the absence of Gazyva pre-treatment this would likely result in unacceptably high rate and severity of CRS at the doses currently administered.

The sponsor has concluded that without obinutuzumab, a prolonged step-up dosing regimen with insufficient therapeutic doses of glofitamab (less than 0.6 mg) would likely be required to achieve tolerable glofitamab dosing. The relationship between glofitamab dose, RO, and CRS of Grade 2 and higher is non-linear, and without obinutuzumab the glofitamab step-up dose would start in the low microgram range. The exposure-response CRS analysis supports that conclusion.

[10] The Common Terminology Criteria for Adverse Events (CTCAE) is a standardised classification of side effects used in assessing drugs, for cancer therapy in particular. Specific conditions and symptoms may have values or descriptive comment for each level but are generally classified as follows: Grade 1 = Mild; Grade 2 = Moderate; Grade 3 = Severe; Grade 4 = Life threatening; Grade 5 = Death related to adverse event.

Data on B-cell counts from Study NP30179 support the depletion of peripheral B-cells by obinutuzumab treatment in patients with relapsed/refractory (R/R) NHL. In the overall safety population (N = 469), 73.2% of patients (336 of 459) had B-cell counts under 70 cells/µL at study entry, likely reflective of prior anti-CD20 therapy. Following obinutuzumab and prior to glofitamab administration, almost all patients had B-cell counts under 70 cells/µL (94.3% [378 of 401] at Cycle 1, Day 7 [C1D7]; 93.7% [74 of 79] at C1D8), reflecting the depletion of peripheral B-cells with obinutuzumab.

Efficacy

Study NP30179 is an ongoing, Phase I/II multicentre, open-label study to evaluate safety, efficacy, tolerability and PK of escalating doses of glofitamab as a single agent and as combination with obinutuzumab given after obinutuzumab pre-treatment, in patients with R/R B-cell NHL.

This ongoing study involves patients 18 years of age and older with histologically-confirmed NHL expected to express CD20 with relapse after or failure to respond to at least 1 prior treatment regimen. [Interim reports of this study that consider efficacy of the dose regimen in R/R diffuse large B-cell lymphoma (DLBCL) are reviewed in the concurrent glofitamab submission.]

Administration of a single 1000 mg dose of obinutuzumab 7 days prior to the first dose of glofitamab is a strategy to help mitigate the risk of glofitamab-induced CRS, depleting (de-bulking) peripheral blood and secondary lymphoid organ B-cells and limiting the initial glofitamab CD20 receptor binding, thereby attenuating cytokine release that occurs subsequent to the first infusion of glofitamab. The obinutuzumab dose was chosen based on the recommended dosage of obinutuzumab used in the treatment of chronic lymphocytic leukaemia and follicular lymphoma. The dose and rate of administration is the same as for Cycle 1, Day 1 (C1D1) of obinutuzumab for treatment of follicular lymphoma.

The study is divided into three parts: dose-escalation (Parts I [single patient cohorts] and II [multiple patient cohorts]) and dose-expansion (Part III). The study planned to enrol at least 15 patients and up to approximately 300 patients during the dose-escalation phase (Parts I and II; the exact sample size could not be pre-determined and depended on the number of cohorts needed to reach the maximum tolerated dose/optimal biological dose, and approximately 560 patients during the dose-expansion phase (Part III).

The primary objectives of this study all considered glofitamab as a single agent and in combination with obinutuzumab. Efficacy data were available only for R/R DLBCL and will be discussed in the AusPAR for glofitamab.[11]

Safety

As already known for Gazyva,[12] the most frequently observed adverse drug reactions (ADRs) in patients receiving Gazyva were infusion related reactions (IRRs) which occurred predominantly during infusion of the first 1000 mg. The most frequently reported (5% or more) symptoms associated with an IRR were nausea, vomiting, diarrhoea, headache, dizziness, fatigue, chills, pyrexia, hypotension, flushing, hypertension, tachycardia, dyspnoea, and chest discomfort. Respiratory symptoms such as bronchospasm, larynx and throat irritation, wheezing and laryngeal oedema, and cardiac symptoms such as atrial fibrillation, have also been reported.

[11] AusPAR for glofitamab will be available from Australian Public Assessment Reports (AusPAR) | Therapeutic Goods Administration (TGA)

[12] Product Information for Gazyva available from the TGA website.

The overall safety population (N = 469) from Study NP30179 was defined as all patients with R/R NHL who received glofitamab doses of 0.6 mg or more with obinutuzumab. Patients were predominantly white (78.5%), male (61.8%) with a median age of 65.0 years (range: 21 to 90 years). An Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 1 was reported in 51.8% of patients.[13] The overall safety population included patients with R/R NHL with the following histologies: DLBCL arising from FL (55.5%); FL Grades 1-3A (24.9%); mantle cell lymphoma (10.0%); high-grade B-cell lymphoma (HGBCL; 4.1%); primary mediastinal B-cell lymphoma (PMBCL; 2.6%); Richter's transformation (2.3%); and other histologies (0.6%).

The primary safety population (N =154) from Study NP30179 was defined as patients with R/R DLBCL (DLBCL not otherwise specified, transformed FL, HGBCL, PMBCL)who have received at least one dose of study medication (obinutuzumab pre-treatment, glofitamab) treated with 2.5/10/30 mg step-up doses of glofitamab in the proposed indication. Patients were predominantly white (76.6%), male (64.9%) and with a median age of 66.0 years (range: 21 to 90 years). At baseline, 44.8% of patients had an ECOG PS of 0 and 54.5% had an ECOG PS of 1. The majority of patients (71.4%) had DLBCL not otherwise specified at study entry; 18.2% had transformed FL; 6.5% had HGBCL; and 3.9% had PMBCL.

The assessment of the use of obinutuzumab as pretreatment for patients receiving glofitamab is focused on CRS. CRS of any grade (per American Society for Transplantation and Cellular Therapy [ASTCT] consensus grading)[14] in Study NP30179 was experienced by a similar proportion of patients in both the overall safety population (64.0% [300 of 469 patients]) and primary safety population (64.3% [99 of 154 patients]). However, the incidences of Grade 3 and Grade 4 CRS [5.1% versus 3.9%, respectively) and serious CRS (31.1% versus 20.8%, respectively) were higher in the overall safety population, primarily due to the influence of the fixed dosing cohort (10 mg and higher; N = 100). This cohort included patients treated with glofitamab fixed doses of 10 mg, 16 mg, and 25 mg as well as those treated with step-up doses of 10/16 mg or 2.5/10/16 mg and showed higher rates of Grade 3 and Grade 4 CRS and serious CRS compared with other cohorts. As a consequence, the glofitamab primary safety population, which reflects the safety profile of glofitamab at the proposed registrational dose, is considered to be the most appropriate population to evaluate obinutuzumab as a pre-treatment to reduce the risk of glofitamab-induced CRS.

Although over half the patients in the primary safety population, exposed to glofitamab following glofitamab pre-treatment at C1D8 experienced CRS (**Figure 1**), the vast majority of patients experienced low-grade events (Grade 1 or 2), which resolved promptly (median duration 31.8 hours across all grades) and the severity of CRS was reduced by each subsequent glofitamab dose with only 3 patients experiencing CRS (all Grade 1 events) from Cycle 3 onwards. Only one patient discontinued glofitamab due to CRS (Grade 4 following the glofitamab 2.5 mg dose – the patient died due to progressive disease while CRS Grade 4 was ongoing.

[13] Eastern Cooperative Oncology Group Performance Status: The ECOG has developed criteria used by doctors and researchers to assess how a patient's disease is progressing, to assess how the disease affects the patient's daily living, and to determine appropriate treatment and prognosis. The ECOG Performance Status Scale is as follows: Grade 0 = Fully active, able to carry on all pre-disease performance without restriction; Grade 1 = Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, for example, light house work, office work; Grade 2 = Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours; Grade 3 = Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours; Grade 4 = Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair; Grade 5 = Dead.

[14] Lee DW, Santomasso BD, Locke FL, Ghobadi A, Turtle CJ, Brudno JN, et al. ASTCT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells. *Biol Blood Marrow Transplant.* 2019 Apr;25(4):625-638. doi: 10.1016/j.bbmt.2018.12.758.

Figure 2: Study NP30179 Cytokine Release Syndrome adverse events after each dose of glofitamab in Cycle 1 and Cycle 2 (primary safety population – third-line or higher DLBCL; clinical cut-off date 15 June 2022)

	Cycle 1		Cycle 2	
	After Glofitamab 2.5 mg dose (C1D8) n=145	After Glofitamab 10 mg dose (C1D15) n=135	After Glofitamab 30 mg dose (C2D1) n=127	Overall across all cycles, most extreme grade
Any Grade	79 (54.5%)	45 (33.3%)	34 (26.8%)	99 (64.3%)
1	61 (42.1%)	38 (28.1%)	33 (26.0%)	74 (48.1%)
2	13 (9.0%)	6 (4.4%)	1 (0.8%)	19 (12.3%)
3	3 (2.1%)	1 (0.7%)	0	4 (2.6%)
4	2 (1.4%)	0	0	2 (1.3%)

CCOD = clinical cutoff date; C1D8 = Cycle 1, Day 8; C1D15 = Cycle 1, Day 15; C2D1 = Cycle 2, Day 1.

Primary safety population comprises patients with R/R DLBCL having received ≥2 prior systemic therapies from Cohort D3 (2.5/10/30 mg), Cohort D2 subcohort 2 (2.5/10/30 mg), and Cohort D5 (2.5/10/30 mg with mandatory dexamethasone premedication).

By ASTCT grade; no Grade 5 CRS reported.

As of 15 June 2022, 503 patients with R/R NHL had been exposed to obinutuzumab in glofitamab monotherapy cohorts in Study NP30179, 469 of whom were enrolled in glofitamab monotherapy 0.6 mg and above dosing cohorts.

In the overall safety population, during the pre-treatment with a dose of 1000 mg obinutuzumab phase (C1D1 to C1D8) prior to receiving the first glofitamab dose:

- There were 233 of 469 patients (49.7%) who reported an adverse event (AE) of any grade, irrespective of causality.
- The most common AEs (incidence by Preferred Term [PT] of at least 5%)[15] during the glofitamab pre-treatment period were thrombocytopenia (47 patients; 10.0%), infusion-related reaction (44 patients; 9.4%) and anaemia (25 patients; 5.3%).
- Adverse events of Grade 3 and higher during the glofitamab pre-treatment period were reported by 65 patients (13.9%) and included two Grade 5 AEs: COVID-19 pneumonia and myocardial infarction, both considered not related to obinutuzumab per the investigator.
- There were 160 of 469 patients (34.1%) who had reported AEs that were considered by the investigator as related to obinutuzumab.
- The most common AEs considered as related by the investigator (at least 2% incidence by PT) were infusion-related reactions (45 patients; 9.6%), thrombocytopenia (28 patients; 6.0%), neutropenia (25 patients; 5.3%) and anaemia (13 patients; 2.8%).
- Two patients discontinued all other study treatment due to AEs occurring following glofitamab pre-treatment (Grade 5 myocardial infarction and Grade 4 ventricular tachycardia in one patient, both events with onset during the glofitamab pre-treatment period but considered not related to obinutuzumab per the investigator and Grade 4

[15] The Medical Dictionary for Regulatory Activities (MedDRA) is an internationally used set of terms relating to medical conditions, medicines and medical devices. It was created to assist regulators to share information. It is also used by industry, academics, health professionals and other organisations that communicate medical information, Preferred Terms (PT) are single concepts for symptoms, signs, disease diagnosis, therapeutic indications, investigations, procedures, and characteristics. There are over 20,000 Preferred Terms.

thrombocytopenia in one patient, with onset during the glofitamab pre-treatment period and considered related to obinutuzumab per the investigator). The patient with Grade 5 myocardial infarction and Grade 4 ventricular tachycardia had pre-existing medical conditions including hypercholesterolemia, multilobar pulmonary embolism, paroxysmal atrial fibrillation, and hypertension. The patient with Grade 4 thrombocytopenia had pre-existing medical conditions including ongoing. hypertension, type 2 diabetes, benign prostatic hyperplasia and anaemia at baseline. The patient received platelet transfusions and the event resolved.

- One patient had a Grade 3, serious event of tumour lysis syndrome with onset during the glofitamab pre-treatment period, which was considered related to obinutuzumab and resolved after 2 days.
- The majority of IRRs following glofitamab pre-treatment were Grade 1 or 2. The frequency of IRRS of Grade 3 and higher in the glofitamab pre-treatment period was 1.1% and included 4 patients with Grade 3 and 1 patient with a Grade 4 IRR. Infusion-related reactions following glofitamab pre-treatment were reported as serious AEs in 10 patients (2.4%).
- No patient in the safety analysis received combination therapy. All glofitamab was given as monotherapy.

Risk management plan

The sponsor is required to comply with product vigilance and risk minimisation requirements.

The TGA decided an updated RMP was not required for this submission. The disease and age group for the extension of indication does not result in a significant change to the target population. The overall dose that patients will receive is less than administered for currently approved indications. Therapy would be administered under the supervision of a healthcare professional experienced in the treatment of cancer patients. No new safety issues have been identified due to the newly proposed indication.

The TGA may request an updated RMP at any stage of a product's life-cycle, during both the pre-approval and post-approval phases. Further information regarding the TGA's risk management approach can be found in risk management plans for medicines and biologicals and the TGA's risk management approach.

Risk-benefit analysis

Delegate's considerations

Nonclinical and pharmacology data have shown that glofitamab alone results in a very large T-cell activation and release of cytokines. That effect is reduced by a single 1000 mg dose of obinutuzumab given 7 days prior to glofitamab exposure, which is given in a step-up dose regimen in the first treatment cycle then as a single dose in subsequent cycles, with no obinutuzumab given in subsequent cycles.

Glofitamab and obinutuzumab both bind to CD20 on the same epitope, and the high concentrations of circulating obinutuzumab will compete with glofitamab for receptor occupancy. As shown in **Figure 1**, the average receptor occupancy (RO) after the first glofitamab administration (2.5 mg) is approximately 0.1%. The low receptor occupancy at the time of the initial dose of glofitamab strongly suggests that obinutuzumab will have minimal effect on the efficacy of glofitamab. By depleting T-cells it will also allow for higher doses of glofitamab. The selected dose regimens for both obinutuzumab and the step-up regimen for glofitamab have

been assessed in interim analyses of a single study in which dose regimens were amended according to initial results within the study. The current regimen has an acceptable balance between risk and benefit in the treatment of R/R DLBCL.

The frequency and severity of CRS has been assessed using the proposed obinutuzumab pre-treatment regimen and the proposed step-up dose regimen for glofitamab only for R/R DLBCL. The larger safety population included patients with other R/R NHL and other dose regimens and a higher frequency of CRS Grade 2 and higher was reported.

The Delegate considered that it is reasonable to extrapolate the effect of obinutuzumab on CRS when the proposed glofitamab dose regimen is given for other indications; however, the Delegate requested the advice of the relevant advisory committee regarding this approach.

Proposed action

The Delegate proposed to approve the extension to the registration of Gazyva (obinutuzumab) to include *Gazyva is indicated as a pre-treatment to reduce the risk of cytokine release syndrome (CRS) induced by glofitamab.*

Approval is subject to finalisation of the provisional approval of Columvi (glofitamab).

Advisory Committee considerations

The Advisory Committee on Medicines (ACM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following.

Specific advice to the Delegate

1. ***Does the Committee consider that the proposed pre-treatment regimen for obinutuzumab should apply to all current and future indications for glofitamab?***

The ACM considered the proposed pre-treatment regimen for obinutuzumab and agreed this regimen should apply to all current and future indications for glofitamab as all clinical trials to date have included pre-treatment with obinutuzumab prior to glofitamab. Unless used in patients with very low levels of disease it is associated with high levels of tumour lysis. The ACM noted that if used in patients with low levels of disease obinutuzumab would not cause harm.

2. ***Does the Committee consider that the proposed pre-treatment indication be restricted to either R/R DLBCL or to R/R NHL?***

The ACM advised that the proposed pre-treatment indication includes all current and future indications of glofitamab and should not be restricted to either R/R DLBCL or to R/R NHL.

3. ***Does the Committee consider that if glofitamab is given in combination with other medications the effect of pre-treatment with obinutuzumab on the frequency and severity of CRS is likely to be altered?***

The ACM was of the view that obinutuzumab is an effective pre-treatment at eliminating significant tumour burden and as it is given 7 days prior to treatment with glofitamab, any addition of other treatments to glofitamab will not alter the benefit of obinutuzumab. There would be no effect on the efficacy of obinutuzumab or on the severity of CRS.

ACM conclusion

The ACM considered this product to have an overall positive benefit-risk profile for the indication:

Gazyva is indicated as a pre-treatment to reduce the risk of cytokine release syndrome (CRS) induced by glofitamab.

Outcome

Based on a review of quality, safety, and efficacy, the TGA decided to register Gazyva (obinutuzumab (rch)) 1000 mg/40 mL concentrate solution for infusion in vials, indicated for the following extension of indications:

Gazyva is indicated as a pre-treatment to reduce the risk of cytokine release syndrome (CRS) induced by glofitamab.

As such, the full indications at this time were:

Chronic Lymphocytic Leukaemia

Gazyva in combination with chlorambucil is indicated for the treatment of patients with previously untreated chronic lymphocytic leukaemia (CLL).

Follicular Lymphoma

Gazyva in combination with chemotherapy followed by Gazyva maintenance is indicated for the treatment of patients with previously untreated advanced follicular lymphoma.

Gazyva in combination with bendamustine, followed by Gazyva maintenance, is indicated for the treatment of patients with follicular lymphoma (FL) who did not respond to, or who progressed during or up to 6 months after treatment with rituximab or a rituximab-containing regimen.

Pre-treatment to reduce the risk of Cytokine Release Syndrome (CRS) induced by glofitamab

Gazyva is indicated as a pre-treatment to reduce the risk of cytokine release syndrome (CRS) induced by glofitamab.

Specific conditions of registration applying to these goods

No new conditions.

Attachment 1. Product Information

The Product Information (PI) approved with the submission for Gazyva, which is described in this AusPAR can be found at Attachment 1. It may have been superseded. For the most recent PI and Consumer Medicines Information (CMI), please refer to the TGA PI/CMI search facility.

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