27 February 2025
EMA/178017/2025
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Columvi

International non-proprietary name: Glofitamab

Procedure No. EMEA/H/C/005751/II/0005

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

Abbreviation	Full Term
1L	first line
2L	second line
3L	third line
ADA	anti-drug antibodies
ADR	Adverse Drug Reactions
AE	adverse event
AEGT	adverse event group term
AESI	AEs of special interest
ASCT	autologous hematopoietic stem cell transplant
ASTCT	American Society for Transplantation and Cellular Therapy
B/R	benefit risk
BLA	Biologics License Application
BLQ	Below the Limit of Quantification
B-NHL	B-cell non-Hodgkin lymphoma
BR	bendamustine and rituximab
BTD	Breakthrough designation
CAPA	Corrective and Preventive Action
CAR-T	chimeric antigen receptor T-cells
CARTOX10	CAR T cell-therapy-associated toxicity 10 point
CCOD	clinical cutoff date
CHOP	cyclophosphamide, doxorubicin, vincristine, and prednisone
CLT	time-varying clearance
CO	Clinical Overview
COMP	Committee for Orphan Medicinal Products
COVID-19	coronavirus disease 2019
CR	complete response
CRP	C-reactive protein
CRR	complete response rate
CRS	Cytokine Release Syndrome

CSR	Clinical Study Report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DDI	drug-drug interaction
DHAP	dexamethasone+cytarabine+cisplatin
DIL	Dear Investigator Letter
DKMA	Danish Medicines Agency
DLBCL	diffuse large B-cell lymphoma
DLBCL NOS	diffuse large B-cell lymphoma not otherwise specified
DOCR	duration of complete response
DOR	duration or response
ECG	electrocardiogram
eCRF	electronic Case Report Form
EFS	event-free survival
EMA	European Medicines Agency
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30
ER	exposure-response
ESMO	European Society for Medical Oncology
EU	European Union
FACT-Lym LymS	Functional Assessment of Cancer Therapy-Lymphoma Lymphoma Subscale
FDA	Food and Drug Administration
FL	follicular lymphoma
FPI	first patient enrolled
GCP	Good Clinical Practice
GemOx	gemcitabine and oxaliplatin
Glofit-GemOx	glofitamab in combination with gemcitabine and oxaliplatin
Gpt	Gazyva/Gazyvaro (obinutuzumab) pre-treatment
HCP	healthcare professional
HGBCL	High-grade B-cell lymphoma
HR	hazard ratio

HSC	hematopoietic stem cell
IBD	International Birth Date
ICANS	immune effector cell-associated neurotoxicity syndrome
ICE	ifosfamide+carboplatin + etoposide
ICF	Informed Consent Form
iDMC	independent Data Monitoring Committee
IgG	immunoglobulin G
IMC	Internal monitoring committee
IND	Investigational New Drug
INV	investigator
IPI	International Prognostic Index
IRC	Independent Review Committee
ISS	Integrated Summary of Immunogenicity
ITT	intent-to-treat
IV	intravenous
IxRS	Interactive Web/Voice Response System
K-M	Kaplan-Meier
LBCL	large B-cell lymphoma
LDH	lactate dehydrogenase
LFT	liver function test
LPI	last patient enrolled
LPLV	last patient last visit
MAA	Marketing Authorisation Application
mAb	monoclonal antibody
MAH	Marketing Authorisation Holder
MCL	mantle cell lymphoma
MoA	mechanism of action
NAE	neurologic adverse event
NALT	new anti-lymphoma therapy
NCCN	National Comprehensive Cancer Network
NCI CTCAE	National Cancer Institute Common Toxicity Criteria for Adverse Events
NE	not estimable

NHL	non-Hodgkin’s lymphoma
NOS	not otherwise specified
NSG	NOD.Cg-Prkdc^{scid}Il2rg^{tm1Wjl}/SzJ
ODD	orphan drug designation
ORR	objective response rate
OS	overall survival
PD	progressive disease
PDCO	Paediatric Committee
PEI	Paul-Ehrlich Institut
PET	positive-electron tomography
PFS	progression-free survival
PIP	Paediatric Investigation Plan
PK	pharmacokinetic
PMR	postmarketing requirement
Pola + R-CHP	polatuzumab vedotin + rituximab, cyclophosphamide, doxorubicin, and prednisone
popPK	population PK
PRAC	Pharmacovigilance Risk Assessment Committee
PRO	patient-reported outcome
Q	intercompartmental clearance
Q3W	every 3 weeks
R/R	relapsed or refractory
R-CHOP	cyclophosphamide, doxorubicin, vincristine, and prednisone in combination with rituximab
R-GemOx	rituximab in combination with gemcitabine plus oxaliplatin
SAE	serious adverse events
SAP	Statistical Analysis Plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
sBLA	supplemental Biologics License Application
SBP	Summary of Biopharmaceutic Studies and Associated Analytical Methods
SCE	Summary of Clinical Efficacy
SCP	Summary of Clinical Pharmacology

SCS	Summary of Clinical Safety
SCT	stem cell transplant
SmPC	Summary of Product Characteristics
SOC	System Organ Class
SPD	sum of products of diameters
SUD	step-up dosing
TCB	T-cell bispecific
TCR	T-cell receptor
TCZ	tocilizumab
TEAE	treatment-emergent adverse event
TLS	tumour lysis syndrome
TTD	time to deterioration
TTE	time-to-event
TTNT	time-to-next-treatment
US	United States
USM	Urgent Safety Measure
USPI	US Prescribing Information
V1	central volume of distribution
V2	peripheral volume of distribution

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Roche Registration GmbH submitted to the European Medicines Agency on 29 July 2024 an application for a variation.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II, IIIA and IIIB

Extension of indication to include in combination with gemcitabine and oxaliplatin the treatment of adult patients with relapse or refractory diffuse large B-cell lymphoma not otherwise specified (DLBCL NOS) who are not candidates for autologous stem cell transplant (ASCT) for COLUMVI, based on results of primary and updated analyses from study GO41944 (STARGLO) listed as a Specific Obligation in the Annex II of the Product Information, as well supportive data from the Phase Ib study GO41943. Study GO41944 (STARGLO) is a Phase III, open-label, multicenter, randomised study of glofitamab in combination with GemOx (Glofit-GemOx) vs. rituximab in combination with GemOx (R-GemOx) in patients with R/R DLBCL. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC are updated. The Annex II and Package Leaflet are updated in accordance. Version 2.0 of the RMP was also submitted. In addition, the MAH took the opportunity to introduce minor editorial changes to the PI and update the list of local representatives in the Package Leaflet. As part of the application, the MAH was requesting a 1-year extension of the market protection.

The variation requested amendments to the Summary of Product Characteristics, Annex II, Labelling and Package Leaflet and to the Risk Management Plan (RMP).

Information relating to orphan designation

Columvi, was designated as an orphan medicinal product EU/3/21/2497 on 15 October 2021 in the following indication: Treatment of diffuse large B-cell lymphoma.

Following the CHMP positive opinion on this marketing authorisation and at the time of the review of the orphan designation by the Committee for Orphan Medicinal Products (COMP), this product was withdrawn from the Community Register of designated orphan medicinal products on 19 March 2025 on request of the sponsor. The relevant orphan designation withdrawal assessment report can be found under the 'Assessment history' tab on the Agency's website: www.ema.europa.eu/en/medicines/human/EPAR/Columvi

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included EMA Decision P/0094/2020 on the granting of a product-specific waiver and the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0094/2020 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the application included a critical report addressing the possible similarity with authorised orphan medicinal products.

MAH request for additional market protection

The MAH initially requested consideration of its application in accordance with Article 14(11) of Regulation (EC) 726/2004 - one year of market protection for a new indication.

The MAH has since withdrawn the request for consideration of one additional year of market protection for a new indication.

Protocol assistance

The MAH received Protocol Assistance from the CHMP on 30 January 2020 (EMEA/H/SA/4023/3/2019/III). The Protocol Assistance pertained to non-clinical and clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Boje Kvorning Pires Ehmsen Co-Rapporteur: N/A

Timetable	Actual dates
Submission date	29 July 2024
Start of procedure:	17 August 2024
CHMP Rapporteur Assessment Report	16 October 2024
CHMP Co-Rapporteur Assessment Report	17 October 2024
PRAC Rapporteur Assessment Report	18 October 2024
PRAC members comments	23 October 2024
PRAC Outcome	31 October 2024
CHMP members comments	4 November 2024
Updated CHMP Rapporteur~~(s) (Joint)~~ Assessment Report	7 November 2024
Request for supplementary information (RSI)	14 November 2024
CHMP Rapporteur Assessment Report	8 January 2025
PRAC Rapporteur Assessment Report	9 January 2025
PRAC members comments	8 January 2025

Timetable	Actual dates
PRAC Outcome	16 January 2025

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

This is an extension of indication to include treatment of relapsed or refractory diffuse large B-cell lymphoma not otherwise specified (DLBCL NOS, according to WHO 2016) who are ineligible for autologous stem cell transplant (ASCT).

The purpose of this application is to extend the licensed indication for COLUMVI to include the proposed indication as follows:

COLUMVI in combination with gemcitabine and oxaliplatin is indicated for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma not otherwise specified (DLBCL NOS) who are ineligible for autologous stem cell transplant (ASCT).

This submission also intends to provide information to fulfil SOB-CLIN-002 in the EU (i.e., the provision of data for Study GO41944 [also known as STARGLO]) agreed at time of initial approval to provide further evidence of efficacy and safety of glofitamab in DLBCL.

Claimed therapeutic indication

COLUMVI in combination with gemcitabine and oxaliplatin is indicated for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma not otherwise specified (DLBCL NOS) who are ineligible for autologous stem cell transplant (ASCT).

Epidemiology

Large B-cell lymphomas (LBCL), comprised predominantly of DLBCL, represent almost 30% of all cases of NHL (Sehn and Salles 2021). DLBCL is a life-threatening disease with an aggressive natural history and is fatal if not treated. The incidence of DLBCL increases with age, with a median age of 66 years at diagnosis (SEER). Despite the availability of treatment regimens in 1L DLBCL, up to 40% of patients will ultimately relapse following R-CHOP, polatuzumab + R-CHP, or similar regimens, and patients with primary refractory disease or who relapse after transplant fare particularly poorly (Roschewski et al. 2022). The incidence in the European Union is estimated to be around 1/100 000/year (Tilly et al Ann Oncol 2015). Up to 50% of patients with R/R DLBCL will be ineligible for intensive therapies such as ASCT (Sehn and Salles 2021). Current treatments in R/R DLBCL outside of ASCT or CAR-T generally aim to achieve durable disease control/remission but are not considered to be curative (Sehn and Salles 2021). Almost all patients eventually relapse and become resistant to available treatment, where the remission duration generally decreases with each subsequent treatment regimen.

Biologic features

DLBCL NOS generally expresses CD20 (the target on the malignant cells of glofitamab). This is also true in the R/R setting, however, since (almost) all patients with R/R DLBCL NOS will have been

previously exposed to CD20-targeting therapy, some may have lost expression of this target as a mechanism of resistance.

Management

The historical standard of care for first-line (1L) treatment for DLBCL is based on a therapeutic backbone of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) in combination with an anti-CD20 monoclonal antibody (mAb) rituximab (R-CHOP) (Coiffier et al. 2010). The Phase III POLARIX study met its primary endpoint demonstrating a statistically significant and clinically meaningful improvement in investigator (INV)-assessed PFS with POLIVY (polatuzumab vedotin) + rituximab, cyclophosphamide, doxorubicin, and prednisolone (pola + R-CHP) compared to R-CHOP in patients with previously untreated DLBCL (Tilly et al. 2022), resulting in the approvals of pola + R-CHP as a new standard of care. Despite the availability of treatment regimens in 1L DLBCL, up to 40% of patients will ultimately relapse following R-CHOP, pola + R-CHP, or similar regimens, and patients with primary refractory disease or who relapse after transplant fare particularly poorly (Roschewski et al. 2022).

Current options and the proposed position of Glofit-GemOx in the treatment landscape of DLBCL are presented in Table 1 below.

Table 1 Currently Available Treatment Options Based on Line of Therapy

<table>
<tr><th>Patient segment</th><th>1L</th><th>2L</th><th>3L and beyond</th></tr>
<tr><td>All patients</td><td>R-CHOP or R-CHOP-like regimens
pola + R-CHP</td><td colspan="2"></td></tr>
<tr><td rowspan="4">Transplant-eligible
~50%[f]</td><td rowspan="4"></td><td colspan="2">Intensive salvage chemotherapy (R-DHAP/ICE/GDP)</td></tr>
<tr><td>HDCT + ASCT[a]</td><td></td></tr>
<tr><td colspan="2">allogeneic transplant[e]</td></tr>
<tr><td colspan="2">CAR-T therapies: lisocabtagene maraleucel[b], axicabtagene ciloleucel[b]</td></tr>
<tr><td>Transplant-ineligible
~50%[f]</td><td></td><td colspan="2">platinum-based and/or gemcitabine-based regimens
(R-GemOx)
pola + BR[c]
tafasitamab + lenalidomide
rituximab + lenalidomide</td></tr>
<tr><td>All patients</td><td colspan="2"></td><td>glofitamab monotherapy
tisagenlecleucel
loncastuximab tesirine
pixantrone[d]
epcoritamab
odronextamab</td></tr>
</table>

	clinical trials with novel drugs (incl. new MoAs) and new combinations

ASCT=autologous stem cell transplant; BR=bendamustine+rituximab; CAR=chimeric antigen receptor; Glofit-GemOx=glofitamab + gemcitabine and oxaliplatin; HDCT=high dose chemotherapy; MoA=mechanism of action; polatuzumab vedotin=pola; R-CHOP=rituximab+cyclophosphamide, doxorubicin, vincristine, and prednisone; R-DHAP=rituximab+dexamethasone, cytarabin, cisplatin; R-GDP=rituximab+gemcitabine, cisplatin, dexamethasone; R-ICE=rituximab+ifosfamide, carboplatin, etoposide.

[a] NCCN (NCCN 2024) and ESMO (Tilly et al. 2015) guidelines suggest patients who relapse after 2L therapy are unlikely to respond to subsequent therapy and therefore generally are not eligible for ASCT.

[b] Use in 2L setting restricted to patients with primary refractory disease or relapsed within 12 months from completion of first-line chemoimmunotherapy.

[c] Pola-BR is approved in the EU for R/R DLBCL after ≥1 prior line of therapy and in the US after ≥2 prior lines, though with NCCN guidelines endorsing its use as early as the 2L setting (NCCN 2024).

[d] Benefit of pixantrone has not been established in 5L+ for patients refractory to last therapy. Pixantrone was approved in the EU (the marketing authorization for Pixuvri expired on 12 June 2024); not approved in the US.

[e] Consider allogeneic transplantation in patients relapsed after R-HDCT with ASCT or in patients with poor-risk factors at relapse (Tilly et al. 2015). Allogenic transplant potentially available as consolidation after achieving sufficient response to salvage therapy.

[f] The approximate percentages of patients who are transplant-eligible and transplant-ineligible, respectively, are described by Sehn and Salles 2021.

2.1.2. About the product

Glofitamab (COLUMVI, also known as RO7082859) is a full-length, fully humanized, immunoglobulin G1 (IgG1), T-cell-engaging bispecific antibody (TCB). As a TCB targeting CD20-expressing B cells, glofitamab binds to CD20 expressed on target B cells and CD3 epsilon chain (CD3ε) present on effector T cells. By simultaneously binding to human CD20-expressing tumour cells and to the CD3 ε of the T-cell receptor (TCR) complex on T cells, it induces tumour cell lysis, in addition to T-cell activation, proliferation and cytokine release. Glofitamab is being developed as an anti-cancer agent both as monotherapy and in multiple combination therapies for patients with B-cell non-Hodgkin lymphoma (NHL) with several studies ongoing (Appendix 1).

As of 7 July 2023, COLUMVI has been approved as a conditional marketing authorization for the treatment of relapsed/refractory (R/R) diffuse large B-cell lymphoma (DLBCL) after two or more lines of systemic therapy in the European Union (EU). Initial approval for this indication was based on results from the ongoing Phase I/II Study NP30179 in patients with R/R DLBCL.

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

The primary evidence supporting this filing comes from the pivotal Study GO41944 supported by Study GO41943.

Study GO41944 is a Phase III, open label, multiregional randomised study designed to evaluate the efficacy and safety of glofitamab in combination with GemOx (Glofit-GemOx) versus rituximab in combination with GemOx (R-GemOx) in patients with R/R DLBCL NOS who have failed one line of therapy and are ineligible for transplant, as well as those patients who have failed at least two lines of therapy. The primary efficacy endpoint of Study GO41944 is overall survival (OS), with key secondary efficacy endpoints of independent review committee (IRC)-assessed progression-free survival (PFS), IRC-assessed complete response (CR) and duration of complete response (DOCR).

The supportive Study GO41943 was a Phase Ib, open-label, multicenter study designed to evaluate the safety and preliminary efficacy of a CD20-CD3-bispecific antibody, either glofitamab or mosunetuzumab, in combination with GemOx in patients with R/R B-cell lymphoma, including patients with DLBCL NOS; high-grade B-cell lymphoma (HGBCL) with *MYC*, *BCL2*, and/or *BCL6* rearrangements; and HGBCL, NOS.

The MAH received Scientific Advice on the development of CD20-TCB, for the treatment of relapsed or refractory B-cell lymphoma, from the CHMP on 30 January 2020. The Scientific Advice pertained to the following non-clinical and clinical aspects:

- The adequacy of the nonclinical package to support MAA,
- The Phase Ib study GO41943 to confirm the dose and dosing schedule and to provide preliminary safety and tolerability information on the combination of RO7082859 with gemcitabine and oxaliplatin,
- The Phase III study GO41944 to support full approval, in particular: the choice of primary (OS) and secondary endpoints (including health-related quality of life questionnaires), the patient population, the use of R-GemOx as comparator, the stratification factors, the statistical analysis plan,
- The use of EORTC QLC-C30 and FACT-LymS to demonstrate maintenance of health-related quality of life (HRQoL) The acceptability of the anticipated safety database to support approval, as well as the proposed strategy for safety monitoring and risk mitigation.

2.1.4. General comments on compliance with GCP

Study GO41944 and supportive Study GO41943 were conducted in accordance with the principles of GCP, the principles of the Declaration of Helsinki, and applicable local, state, and federal laws, as well as other applicable national legal requirements. The appropriate Ethics Committees and Institutional Review Boards reviewed and approved this study. For GO41944, two Investigator Site audits as well as one Internal Process audit, one System audit, and one Service Provider audit. No critical audit findings were observed.

2.2. Non-clinical aspects

2.2.1. Introduction

To support the extension of indication to include combination therapy with gemcitabine and oxaliplatin, a nonclinical pharmacology study was conducted in tumour-bearing mice, describing intratumoral T-cell infiltration and anti-tumour activity of glofitamab in combination with gemcitabine and oxaliplatin (Glofit-GemOx). In line with [ICH S9] recommendations, limited toxicity endpoints were assessed in this study, in order to provide evidence of increased activity in the absence of a substantial increase in toxicity in combination pharmacology studies. These new data contribute to the overall evaluation of glofitamab's biological activity profile and are discussed here in the context of the general nonclinical pharmacology program.

All relevant nonclinical pharmacology, pharmacokinetics, and toxicology studies conducted in support of glofitamab's development were included in the initial MAA.

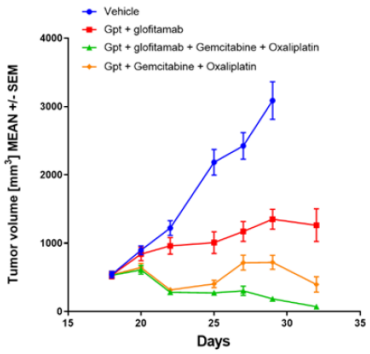
2.2.2. Pharmacology

Beyond increased anti-tumour efficacy, there is an additional immunotherapeutic rationale for the combination of the GemOx regimen with glofitamab because these agents maintain or enhance antigenicity and immunogenicity of tumours. Furthermore, gemcitabine specifically enhances tumour antigen cross-presentation without inducing CD8+ T-lymphocyte tolerance ([Liu et al. 2010]; [Nowak et al. 2003]). Gemcitabine and oxaliplatin also alter the tumour microenvironment to reduce the numbers of tumour suppressor cells, thus reducing a potential barrier to CD20 bispecific activity ([Vincent et al. 2010]; [Mundy-Bosse et al. 2011]). Moreover, gemcitabine upregulates CD20 on diffuse large B-cell lymphoma (DLBCL) cell lines and promotes increased binding and activity of rituximab [Hayashi et al. 2016]. This nonclinical rationale, combined with the individual efficacies and non-overlapping toxicities of glofitamab and GemOx, led to the development of Glofit-GemOx as a novel combination regimen in DLBCL.

An *in vivo* study was conducted in tumour-bearing hematopoietic stem cell-engrafted NOD.Cg-PrkdcscidIl2rgtm1Wjl/SzJ (HSC-NSG) mice to assess the anti-tumour activity of Glofit-GemOx [1101108]. Key results are summarized below.

In HSC-NSG mice bearing the OCI-Ly18 (human DLBCL) tumour model, the combination of glofitamab with GemOx improved the anti-tumour activity compared with that in the respective monotherapy groups (Figure 1). In addition, the combination treatment did not negatively impact, and even increased the intratumoral T-cell infiltration (CD3+ and CD8+ T-cell counts), proliferation (Ki-67+), and cytotoxicity/activation (GzB+) on Day 29 compared with glofitamab monotherapy, as evidenced by the analysis of intratumour T cells post treatment (Figure 2). It was also demonstrated that there were no statistically significant changes in T-cell frequencies, activation, and proliferation in the spleen of treated animals.

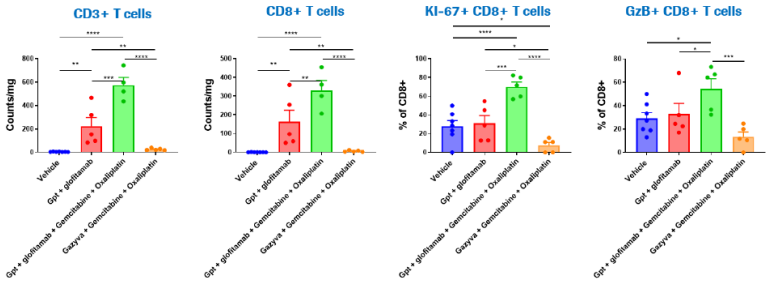
Figure 1 Anti-tumour activity of glofitamab in combination with GemOx vs monotherapy



DLBCL = diffuse large B-cell lymphoma; SUD = step-up dosing; HSC-NSG; Gpt = obinutuzumab (Gazyva, Gazyvaro) pretreatment.

Figure 2 Analysis of intratumour T cells post treatment with glofitamab in combination with GemOx vs monotherapy

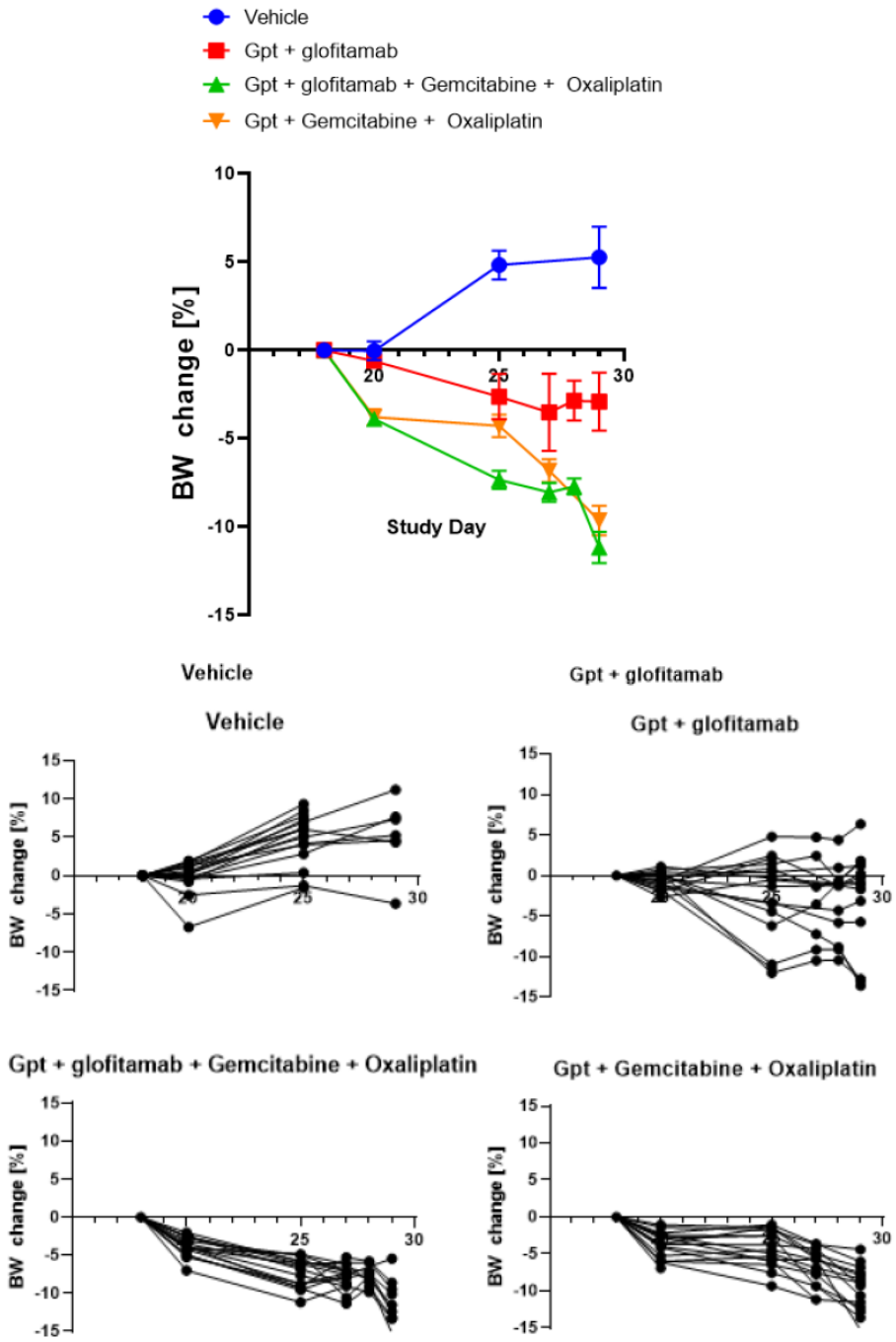
Figure 2 Analysis of Intratumor T Cells Post Treatment Combination of Glofitamab with Gemcitabine and Oxaliplatin versus Glofitamab Monotherapy



Gpt = obinutuzumab (Gazyva, Gazyvaro) pretreatment.
On Day 29 (1 day after the second glofitamab treatment), scout animals were collected from all groups to evaluate human intratumor T-cell infiltration (CD3$^+$ and CD8$^+$ T-cell counts per mg of tumor tissue), proliferation (Ki67$^+$ cells), and cytotoxicity potential (Granzyme B expression).
Statistics: one-way ANOVA for multiple comparisons and Tukey's correction; *$p<0.05$, **$p<0.01$, ***$p<0.001$, ****$p<0.0001$.

Analysis showed a slight body weight drop in a few mice (3 of 16) that were treated with obinutuzumab (Gazyva/Gazyvaro) pretreatment (Gpt) and glofitamab. The majority of mice that received GemOx, in monotherapy or in combination with glofitamab, revealed stronger body weight drop over the duration of the study. In those chemotherapy groups, mice also had scruffy fur, arched back, and thin appearance. This change in body weight over time seemed to be driven by GemOx, and, overall, no stronger body weight drop was detected in the combination group with glofitamab (Figure 3).

Figure 3 Body weight measurements upon treatment with glofitamab in combination with GemOx vs monotherapy and vehicle control groups



BW = body weight; Gpt = obinutuzumab (Gazyva, Gazyvaro) pretreatment.
Body weight was measured over time in all treatment groups and vehicle control. Data are presented as mean values ± SEM (top panel), as well as individual body weight curves over time (bottom panel).

The body weight losses led to termination of mice in the treated groups as summarised in the table below, and all mice had scruffy fur, arched back, and thin appearance.

Table 2 Mice termination because of body weight loss and/or other clinical symptoms before study termination

Treatment	Mice Terminated of Total Mice
Vehicle	1 of 16
Gpt + glofitamab	3 of 16
Gpt + glofitamab + gemcitabine + oxaliplatin	8 of 16
Gpt + gemcitabine + oxaliplatin	7 of 16

Gpt = obinutuzumab (Gazyva, Gazyvaro) pretreatment.
Termination criteria according to local veterinarian license: –15% of body weight loss.

2.2.3. Ecotoxicity/environmental risk assessment

The active substance is a monoclonal antibody which will be broken down by proteolysis into peptides or amino acids, and is therefore considered a naturally-occurring substance. The use of Columvi will not alter the concentration or distribution of the substance in the environment. In line with the EMA Guideline on the environmental risk assessment of medicinal products for human use revision 1 (EMEA/CHMP/SWP/4447/00 Rev. 1), supportive documentation was provided, showing that monoclonal antibodies in general can be expected to be readily biodegradable and of low ecotoxicity. Based on these considerations, it is agreed glofitamab is not expected to pose a risk to the environment and that new ERA studies were not required to support this application.

2.2.4. Discussion on non-clinical aspects

In support of the application to extend the indication for Columvi to include the combination therapy with gemcitabine and oxaliplatin, the MAH submitted a new DLBCL tumour model pharmacology study in HSC-NSG mice. The study included a vehicle group as well as treated groups with either Gazyvaro pretreatment (Gpt) with glofitamab alone, Gpt with glofitamab+gemcitabine+oxaliplatin or Gpt with gemcitabine+oxaliplatin. The MAH demonstrated that glofitamab in combination with gemcitabine+oxaliplatin is superior in reducing tumour cell growth and tumour size compared to glofitamab alone or gemcitabine+oxaliplatin. Compared with glofitamab monotherapy, the combination treatment of glofitamab with gemcitabine and oxaliplatin did not negatively impact, and even increased, the intratumoral T-cell infiltration (CD3+ and CD8+ T-cell counts), proliferation (Ki-67+), and cytotoxicity/activation (GzB+) on Day 29, supporting the increased efficacy of the combination therapy. There were no statistically significant changes in T-cell frequencies, activation, and proliferation in the spleen of treated animals. The superior effect of the combination therapy of glofitamab with gemcitabine and oxaliplatin is therefore agreed from a non-clinical perspective.

The MAH also included limited investigations of the impact on safety parameters in the PD study for the combination therapy by evaluation of body weight changes. In the HSC-NSG mouse model, significant reductions in body weight were observed over the duration of the study for mice treated with the combination therapy of glofitamab with gemcitabine and oxaliplatin, however these reductions reached similar levels to those observed for gemcitabine and oxaliplatin (10-13%). This indicates that gemcitabine and oxaliplatin therapy is the main driver for increased body weight loss, whereas treatment with glofitamab alone reached a stable low level of body weight reduction by the end of the study (3%). The body weight losses led to termination of mice in the treated groups and all mice had scruffy fur, arched back, and thin appearance. The MAH argues that the HSC-NSG mouse model is fragile due to its specific genetic modifications, and that findings should be interpreted with caution when considering clinical relevance. Nausea, vomiting and reduced appetite are however well-known undesirable effects of gemcitabine and oxaliplatin therapy potentially leading to weight loss, and these effects are already addressed in Section 4.8 in the SmPC. Therefore, these findings in the mouse model do not lead to increased concern, especially since the body weight changes are similar to what is seen for gemcitabine and oxaliplatin therapy.

2.2.5. Conclusion on the non-clinical aspects

The combination therapy of glofitamab with gemcitabine and oxaliplatin (including pre-treatment with Gazyvaro) was demonstrated to be superior compared to treatment with glofitamab alone or treatment with gemcitabine and oxaliplatin. Non-clinical findings do not result in an increased safety concern, and the extension of indication is therefore supported from a non-clinical point of view.

A justification for not submitting ERA studies, due to the nature of the active substance – is acceptable in accordance with EMEA/CHMP/SWP/4447 as glofitamab is not expected to pose a risk to the environment.

2.3. Clinical aspects

2.3.1. Introduction

The use of glofitamab in combination with gemcitabine plus oxaliplatin (Glofit-GemOx) and including obinutuzumab pre-treatment in patients with R/R DLBCL (who are ineligible for autologous stem cell transplant) is supported by results from pivotal Study GO41944 (STARGLO) and Phase Ib Study GO41943. The recommended dose regimens consist of a single 1000 mg IV dose of obinutuzumab given on C1 Day 1 followed by the step-up dose regimen of glofitamab with 2.5 mg on C1 Day 8, 10 mg on C1 Day 15 and 30 mg on Day 1 C2-C12 Q3W, administered intravenously in combination with GemOx.

GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Table 3 Overview of clinical studies submitted in support of this application

Study Number	Overall Design	Patient Population	Objectives and Endpoints	Number of Patients	Participating countries (including US number of patients and sites)
GO41944 (STARGLO)	Phase III, randomized study of glofitamab in combination with GemOx versus rituximab in combination with GemOx	R/R DLBCL	Primary endpoint OS Secondary endpoints/objectives PFS, CR, ORR, DOR, DOCR, HRQoL Safety and tolerability, QoL	Planned N=270 2:1 randomization Enrolled N=274 No longer enrolling	Australia, Belgium, China, Denmark, France, Germany Korea, Poland, Spain, Switzerland, Taiwan, UK, USA (25 patients; 10 sites)
GO41943	Phase Ib study of glofitamab or mosunetuzumab in combination with GemOx	R/R DLBCL and HGBCL	Primary objective Safety Secondary objectives/endpoints Tolerability, CR, ORR, PK, ADAs	Glofitamab + GemOx arm: Planned N=20 Enrolled N=17 No longer enrolling	Australia
NP30179	Phase I/II study of glofitamab as a single agent and in combination with obinutuzumab	R/R NHL	Primary objectives/endpoints Safety, tolerability, PK of glofitamab MTD or OBD, DLT, recommended dose and schedule, CR rate Secondary objectives/endpoints Safety, tolerability, and PK of obinutuzmab pretreatment, anti-tumor activity, ADAs, PD, PRO (Part III only)	Parts I and II: Planned N=330 Enrolled N=316 Part III overall: Planned N=560 Enrolled N=262 Part III SUDa R/R DLBCL monotherapy (Cohort D3): Planned approximately N=100 Enrolled N=109 No longer enrolling	Australia, Belgium, Canada, Czech, Denmark, Finland, France, Italy, New Zealand, Poland, Spain, Taiwan, USA (41 patients; 6 sites)

2.3.2. Pharmacokinetics

Analytical methods

Target-binding competent sandwich enzyme linked immunoassay (ELISA) were used to determine glofitamab and obinutuzumab concentrations in human serum samples. Anti-drug antibodies to glofitamab in human serum were determined using a bridging ELISA. The ADA assay was used following a three-tiered approach for screening, confirmation and titration analysis with separate cut-points. All bioanalyses of glofitamab, ADA-glofitamab and obinitizumab for Study GO41943 and Study GO41944 were conducted at PPD Laboratories using their validated methods.

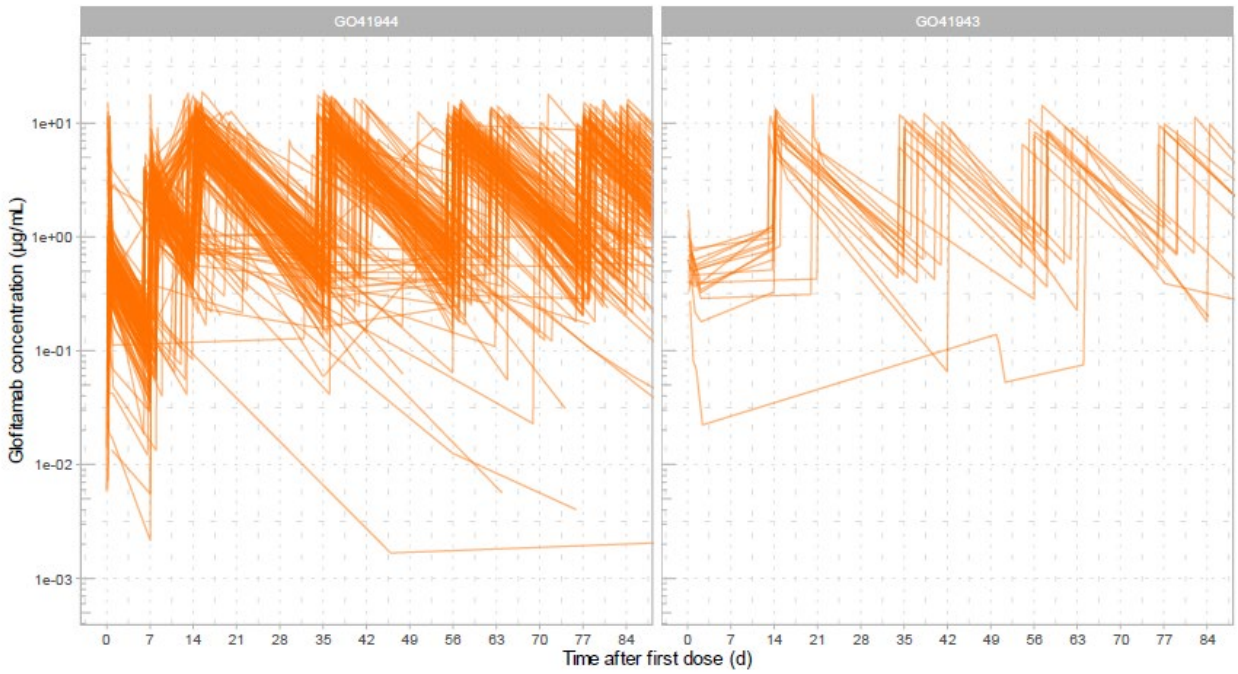
Evaluation and qualification of models

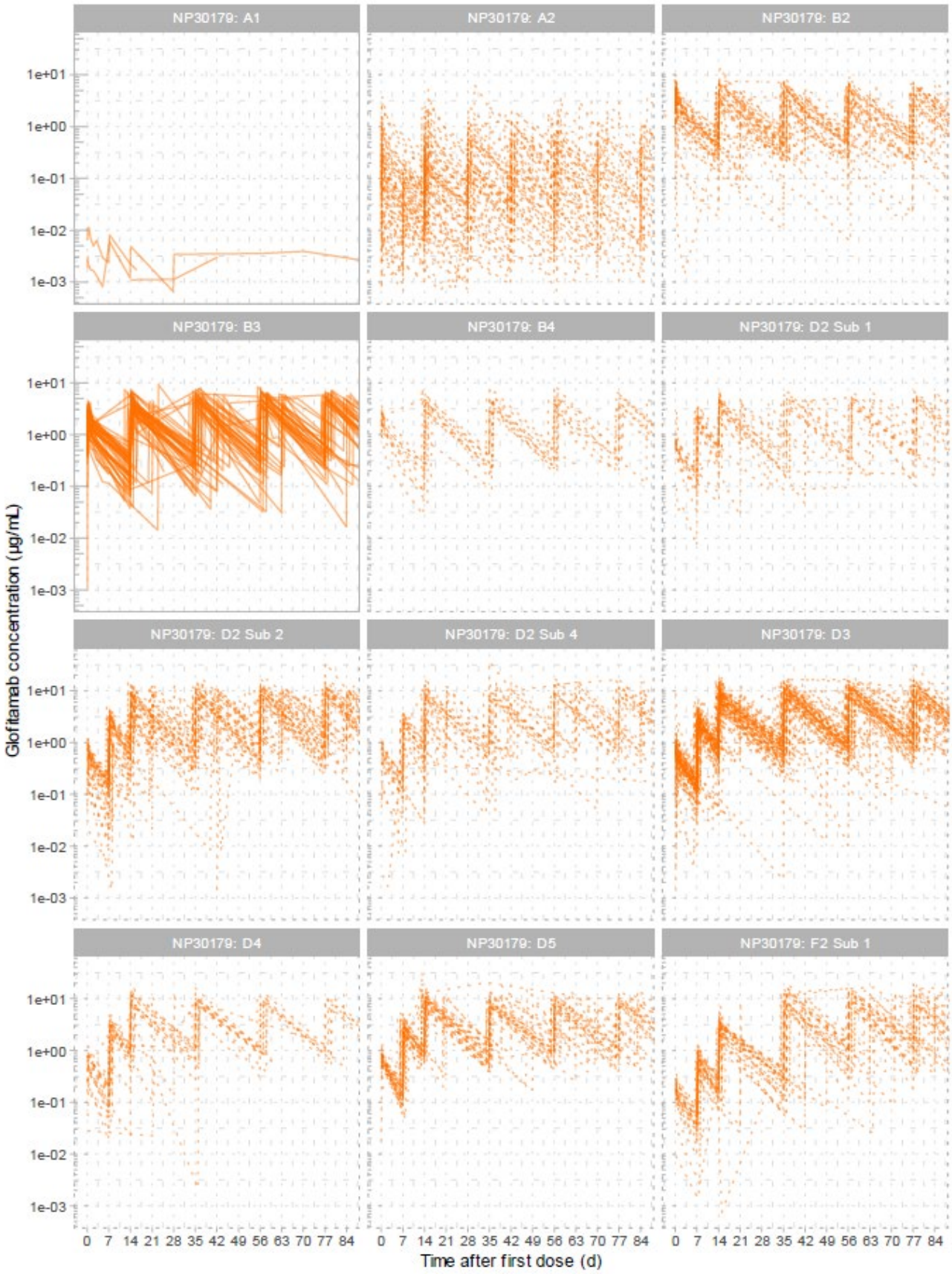
Population analyses and simulations were performed using the nonlinear mixed-effects modelling (NONMEM) software (version 7.5.0), supplemented with Perl-speaks-NONMEM; R software was used for general scripting, data management, goodness of fit analyses, model evaluation, simulations and aspects of reporting. The simulation tool rxode2 in R was used to simulate glofitamab and obinutuzumab concentration-time profiles.

Glofitamab Pop PK

For population PK analyses, 648 individuals with evaluable glofitamab PK data were available, comprising 14582 concentration-time observations across a wide range of doses (5 µg to 30 mg) and regimens, from Study NP30179, Study GO41944 and Study GO41943. Data below the limit of quantification (BLQ) results were excluded: 487 (12.7%) of Study GO41944; 17 (6.91%) of Study GO41943; and 568 (4.86%) of study NP30179. Samples deemed as outliers were excluded: 51 observations with absolute values of CWRES >5 and 23 observations from 10 individuals with unusually high concentrations during the first few days of treatment in Study GO41944. Seven treated subjects did not have measurable concentrations.

Figure 4 Glofitamab concentration-time profiles in patients in the pop PK population for the first 84 days after the first dose of glofitamab, conditioned by study / cohort.





No changes were made to the structure of the previous PK model for glofitamab, which was two-compartmental, with parallel time-dependent and linear clearances (CLT and CLL respectively) governed by decay coefficient kdes. Allometric weight was applied a priori to clearance and volume

parameters with estimated exponents, except on CLT and Q which were fixed. Other included covariates were: effect of baseline CRP, baseline tumour burden on CLL, MCL history on T, baseline obinutuzumab concentration and FL (Grade 1-3A) histology on kdes; and baseline CRP on V1. Correlations between CLL and V1, and between kdes and CLT, were accounted for by off-diagonal elements of ω. Parameters for the final Pop PK model (run 235) are listed in the table below.

Table 4 Model parameter estimates for the final reduced population PK model for glofitamab

Parameter	Estimate	% RSE	95% CI	Shrinkage
Time-invariant clearance (CL_L, L/d)	0.633	1.23	0.617 ; 0.648	-
Central volume of distribution (V1, L)	3.34	1.05	3.27 ; 3.41	-
Peripheral volume of distribution (V2, L)	2.35	2.58	2.23 ; 2.47	-
Intercompartmental clearance (Q, L/d)	0.562	3.73	0.521 ; 0.603	-
Decay constant (k_{des}, /d)	1.50	20.5	0.897 ; 2.11	-
Time-varying clearance (CL_T, L/d)	0.814	26.2	0.396 ; 1.23	-
Baseline weight on CL_L ($\theta_{CL_L,WT}$)	0.511	11.5	0.395 ; 0.626	-
Baseline SPD on CL_L ($\theta_{CL_L,SPD}$)	0.251	29.7	0.105 ; 0.397	-
Baseline CRP on CL_L ($\theta_{CL_L,CRP}$)	0.0359	24.5	0.0187 ; 0.0530	-
Baseline weight on V1 ($\theta_{V1,WT}$)	0.617	7.69	0.524 ; 0.710	-
Baseline CRP on V1 ($\theta_{V1,CRP}$)	0.0281	23.2	0.0153 ; 0.0409	-
Baseline weight on V2 ($\theta_{V2,WT}$)	0.547	19.4	0.339 ; 0.755	-
Baseline weight on Q ($\theta_{Q,WT}$)	0.750	Fixed	-	-
Baseline obinutuzumab concentration on k_{des} ($\theta_{k_{des},Gpt}$)	1.99	4.21	1.83 ; 2.15	-
FL (Grade 1-3A) histology on k_{des} ($\theta_{k_{des},FL13A}$)	-0.376	16.9	-0.500 ; -0.251	-
Baseline weight on CL_T ($\theta_{CL_T,WT}$)	0.750	Fixed	-	-
MCL histology type on CL_T ($\theta_{CL_T,MCL}$)	4.27	31.4	1.64 ; 6.89	-
IIV on CL_L ($\omega^2_{CL_L}$, variance)	0.0767	5.78	0.0681 ; 0.0854	6.15
CL_L-V1 covariance ($\omega_{CL_L,V1}$)	0.0382	8.25	0.0321 ; 0.0444	-
IIV on V1 (ω^2_{V1}, variance)	0.0512	6.02	0.0451 ; 0.0572	6.89
IIV on V2 (ω^2_{V2}, variance)	0.152	10.2	0.122 ; 0.182	32
IIV on Q (ω^2_{Q}, variance)	0.222	13.5	0.163 ; 0.280	44.8
IIV on k_{des} ($\omega^2_{k_{des}}$, variance)	2.20	13.6	1.61 ; 2.78	37.8
k_{des}-CL_T covariance (ω_{k_{des},CL_T})	3.91	14.6	2.79 ; 5.02	-
IIV on CL_T ($\omega^2_{CL_T}$, variance)	8.98	11.8	6.91 ; 11.0	25.6
Proportional residual error (variance)	0.0620	0.573	0.0613 ; 0.0627	5.54

Condition number: 2217.6. Covariance step based on importance sampling (10 iterations, 3000 samples) and MATRIX=S. Shrinkage is NONMEM SD-shrinkage. RSE=relative standard error, CI=asymptotic confidence interval based on NONMEM standard errors, CL=clearance, CL_L=time-invariant CL, CL_T=time-varying CL, V1=central volume of distribution, V2=peripheral volume of distribution, Q=intercompartmental clearance, IIV=interindividual variability, CRP=C-reactive protein, FL=follicular lymphoma, MCL=mantle cell lymphoma, SPD=sum of products of tumour diameters.

The model was evaluated by various GoF plots and pc-VPCs. Examples are shown in the following figures.

Figure 5 Conditional weighted residuals plotted against population predictions and time for the final reduced population PK model for glofitamab

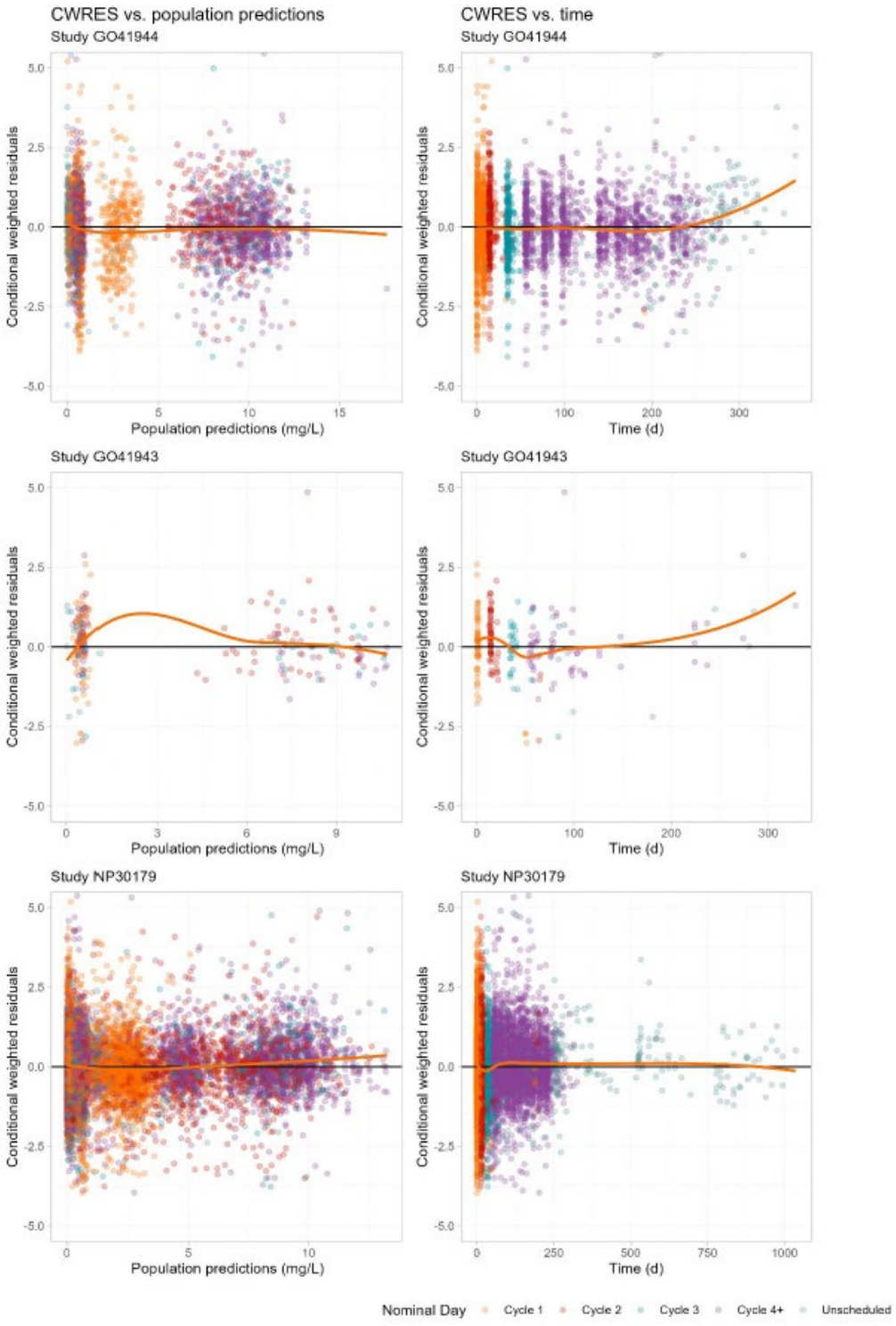
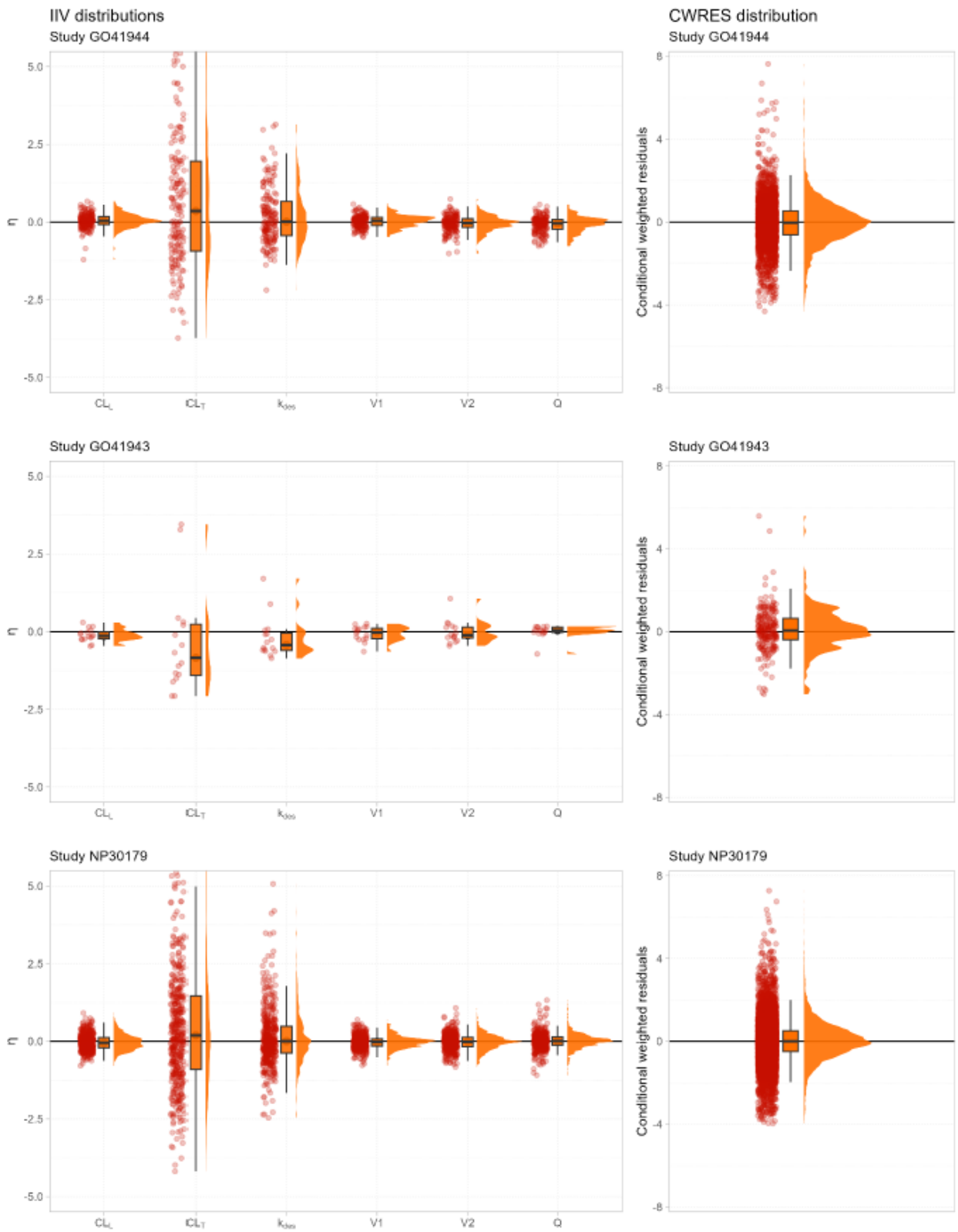
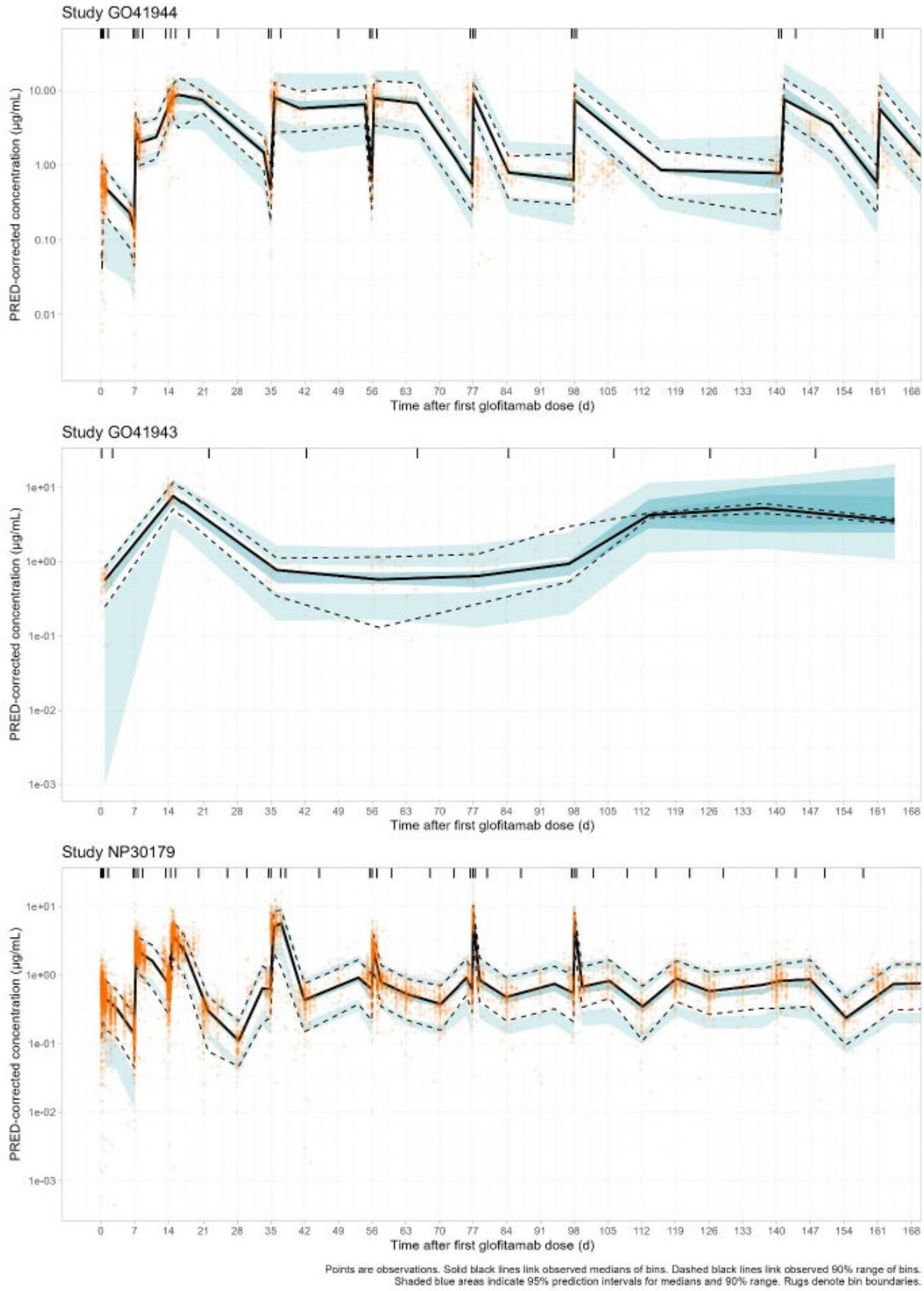


Figure 6 Random-effects distributions for the final reduced PK model for glofitamab



Points are ETAs/residuals. Boxplots represent medians and interquartile ranges (IQR, boxes), and largest and smallest values no further than 1.5 * IQR from the edges of the boxes. Orange shaded areas are density plots.

Figure 7 Prediction – corrected visual predictive checks for the final reduced population PK model for glofitamab



Points are observations. Solid black lines link observed medians of bins. Dashed black lines link observed 90% range of bins. Shaded blue areas indicate 95% prediction intervals for medians and 90% range. Rugs denote bin boundaries.

Effect of covariates on glofitamab exposure

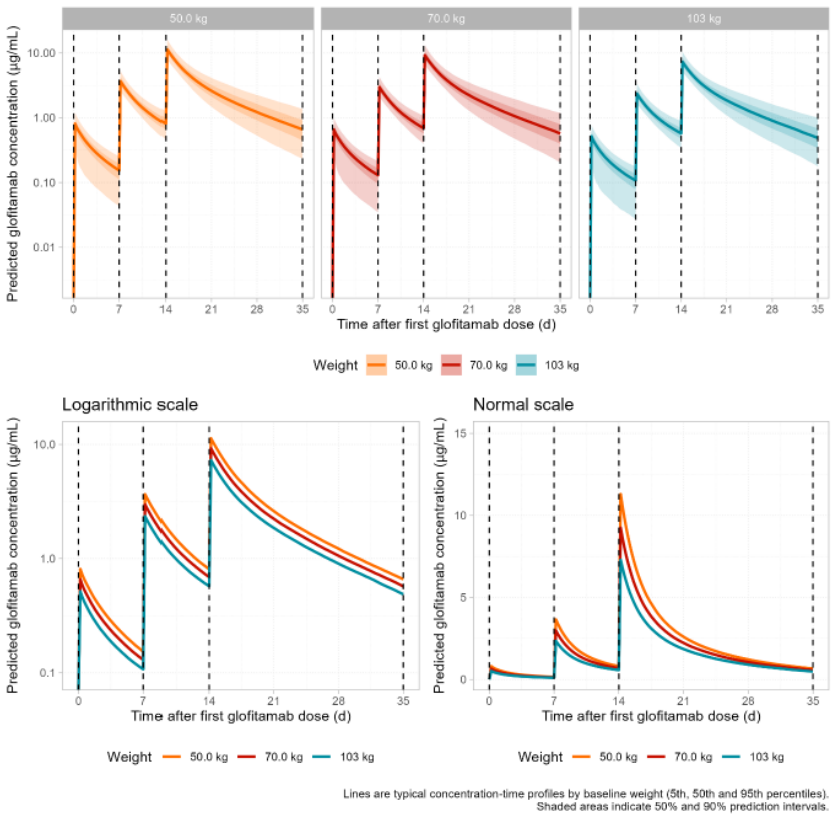
Effects of significant covariates on exposure are shown below. Baseline body weight evaluated across 46.6 kg to 110 kg had largest impact on glofitamab exposure.

Table 5 Effects of extremes of covariate values on exposure in the final pop PK model for glofitamab

Scenario	AUC_{D1} (µg.d/mL)	AUC_{C1+C2} (µg.d/mL)	Percentage change (AUC_{D1})	Percentage change (AUC_{C1+C2})
Typical	0.529	62.0		
Low baseline weight (46.6 kg)	0.694	77.7	31.2	25.2
High baseline weight (110 kg)	0.407	49.9	-23.1	-19.6
Low baseline CRP (0.782 mg/L)	0.563	67.4	6.51	8.72
High baseline CRP (158 mg/L)	0.493	56.7	-6.70	-8.63
Low baseline SPD (254 mm^2)	0.533	67.0	0.723	8.05
High baseline SPD (17320 mm^2)	0.527	59.2	-0.443	-4.46
Low baseline obinutuzumab (53.8 µg/mL)	0.509	54.0	-3.72	-12.8
High baseline obinutuzumab (404 µg/mL)	0.555	62.4	4.97	0.573
MCL	0.408	60.7	-22.8	-2.06
FL (Grade 1-3A)	0.522	61.8	-1.28	-0.326

Calculated from point estimates in the final glofitamab population PK model (run 235). Covariate extremes are 2.5th and 97.5th percentile values in the glofitamab population PK population. Percentage change from the typical value is shown. AUC_{D1}=area under the glofitamab concentration-time curve (day 1), AUC_{C1+C2}=area under the glofitamab concentration-time curve (cycle 1+2), CRP=C-reactive protein, SPD=sum of products of diameters (tumour burden), MCL=mantle cell lymphoma, FL=follicular lymphoma.

Table 6 Predicted Effect of baseline weight on exposure in the final pop PK model for glofitamab



Lines are typical concentration-time profiles by baseline weight (5th, 50th and 95th percentiles). Shaded areas indicate 50% and 90% prediction intervals.

Obinutuzumab Pop PK

In order to generate estimates of glofitamab receptor occupancy in the presence of obinutuzumab, a previously-developed population PK model for obinutuzumab was applied to generate predictions of obinutuzumab concentrations. A total of 1614 evaluable obinutuzumab observations from 675 individuals were available. However, to fit the data from Study NP30179, the original model was adapted by re-estimation of covariate effects and IIV and removing the IIV on the residual error.

Table 6. Obinutuzumab population PK model parameter estimates for the original and adapted models.

Parameter	Original*	Adapted**
Decay constant (/d)	0.0359	0.0359
Time-dependent CL (L/d)	0.231	0.231
Linear CL (L/d)	0.0828	0.0828
V1 (L)	2.76	2.76
V2 (L)	1.01	1.01
Q (L/d)	1.29	1.29
Weight on CL	0.615	0.961
Weight on V1	0.383	0.871
Sex on time-dependent CL	1.49	0.970
Sex on linear CL	1.22	0.735
Sex on V1	1.18	0.860
DLBCL and BCL on decay coefficient	2.08	1.66
DLBCL and BCL on clearance	0.834	0.771
Tumour size on decay coefficient	1.75	4.10
MCL on clearance	2.65	1.10
IIV on decay coefficient (variance)	1.62	0.649
IIV on time-dependent CL (variance)	0.907	0.665
IIV on linear CL (variance)	0.159	0.126
IIV on V1 (variance)	0.0340	0.0815
IIV on V2 (variance)	0.361	0.214
IIV on Q (variance)	0.890	0.932
IIV on residual error (variance)	0.274	0.00
Additive residual error (variance)	0.0318	0.0682
Proportional residual error (variance)	0.0271	0.000818

* Gibiansky et al (21). ** Update generated during previous analysis of Study NP30179 PK data (Report Number: 1118852).
OFV=NONMEM objective function value, CL=clearance, V1=central volume of distribution, V2=peripheral volume of distribution, Q=intercompartmental clearance, DLBCL=diffuse large B-cell lymphoma, BCL=B-cell lymphoma, MCL=mantle cell lymphoma, IIV=interindividual variability.

Glofitamab exposure metrics and receptor occupancy

Empirical Bayes estimates (EBEs) generated for all 418 (of 648) subjects with evaluable glofitamab exposures and receiving the 2.5/10/30 mg glofitamab dose regimen using the obinutuzumab and glofitamab PK models.

Average receptor occupancy values over the first 24 hours after glofitamab dosing (AvgRO%24) and over the first two cycles of glofitamab treatment (AvgRO%C1+C2) were calculated using individual predicted obinutuzumab concentrations and individual predicted glofitamab concentrations based on the final models for these two drugs.

Table 7 Metrics of exposure for patients receiving the 2.5/10/30 mg regimen

N	$AvgRO\%_{D1}$	$AvgRO\%_{C1+C2}$	AUC_{D1} (µg.d/mL)	AUC_{C1+C2} (µg.d/mL)	$Cmax_{D1}$ (µg/mL)	$Cmax_{C1+C2}$ (µg/mL)
418	0.218 (0.207) [0.0515 ; 0.487] {0.187}	1.24 (1.13) [0.0645 ; 4.24] {1.36}	0.494 (0.450) [0.141 ; 0.831] {0.169}	58.1 (46.6) [2.43 ; 94.4] {22.5}	0.666 (0.631) [0.245 ; 1.14] {0.208}	9.01 (7.72) [0.656 ; 15.1] {3.30}

Values are expressed as median (geometric mean) [95% range] {standard deviation}. $AvgRO_{D1}$=average glofitamab receptor occupancy (day 1), $AvgRO\%_{C1+C2}$=average glofitamab receptor occupancy (cycle 1+2), AUC_{D1}=area under the glofitamab concentration-time curve (day 1), AUC_{C1+C2}=area under the glofitamab concentration-time curve (cycle 1+2), $Cmax_{D1}$=maximal glofitamab concentration (day 1), $Cmax_{C1+C2}$=maximal glofitamab concentration (cycle 1+2).

Table 95. $AvgRO_{C1+C2}$ distributions by quartiles of baseline weight in the PK population of Study GO41944.

Quartiles of baseline weight	N	$AvgRO_{C1+C2}$ (%)		
		Mean (SD)	Geometric mean (CV)	Median (Range)
Q1: [41.8,58] kg	47	1.40 (0.828)	1.20 (0.612)	1.15 (0.268-4.20)
Q2: (58,66.3] kg	39	1.67 (1.64)	1.33 (0.638)	1.16 (0.665-9.30)
Q3: (66.3,78.9] kg	43	1.54 (1.27)	1.07 (1.53)	1.18 (0.0177-7.12)
Q4: (78.9,136] kg	43	1.82 (2.38)	1.19 (1.68)	1.40 (0.00440-15.5)

ADME Summary

Based on the parameters of the final Pop PK model and the PK data from GO41943, GO41944 and NP30179, the time independent clearance (CLL) was estimated to 0.633 L/day and the initial time varying clearance (CLT) as 0.814 L/day, with a relatively quick exponential decay over time (kdes) ~ 1.5 day-1. Half-life of elimination (t1/2) is not readily calculated or interpreted in the presence of nonlinear clearance. However, the effective half-life in the linear phase (after the contribution of time-varying clearance has collapsed to a negligible amount) was calculated from empirical Bayes estimates of CLL, V1, V2 and Q from the Pop PK population. Based on the final model and the current population (n=648), it was calculated to be 7.92 days (geometric mean; 95% CI 4.69-11.9 days). The half-life of CLT in most patients in the current population was estimated to have a geometric mean of 0.471 days (95% CI: 0.0424-7.56 days). The inter-compartmental clearance (Q) was estimated to 0.562 L/day. The central volume of distribution (V1) was 3.34 L and close to total serum volume. The peripheral volume of distribution (V2) was 2.35 L.

Baseline body weight had the largest impact on glofitamab exposure. No significant effects of race, GemOx combination, baseline age, sex, baseline creatinine clearance, baseline albumin, baseline lactate dehydrogenase (LDH), antidrug antibodies, baseline hepatic impairment or baseline renal impairment were identified for glofitamab PK (data not shown).

2.3.3. Pharmacodynamics

Mechanism of action

N/A

Primary and secondary pharmacology

Immunogenicity

The potential for glofitamab to induce an immunogenic response has been assessed in the clinical Study GO41944 and GO41943 by collecting samples from all patients, before, during, and after the treatment period with glofitamab.

In Study GO41943, all 16 patients (100%) tested negative for ADAs at baseline and tested negative on treatment. In study GO41944, of the 166 patients in the Glofit-GemOx population with a valid pre- and post- baseline assessment, 156/166 patients (94.5%) tested ADA negative at baseline and post glofitamab treatment, 2/166 patients (1.2%) were negative at baseline and positive post-treatment with glofitamab, 6/166 patients (3.6%) were positive at baseline and negative post-treatment with glofitamab, and 1/166 patients (0.6%) were positive at baseline and post treatment with glofitamab. One patient had no baseline ADA status recorded so is not included in these analyses. Table 8 shows a summary of ADA status in Study GO1944.

Table 8 Summary of Anti-Drug antibody status

/ Baseline ADA Status / Post Dose ADA Status	Glofit-GemOx (Glofit Exposed) (N=166)	Glofit-GemOx (Any Treatment Exposed) (N=167)
Negative / All negative	156 (94.5%)	157 (94.6%)
Negative / At least 1 positive	2 (1.2%)	2 (1.2%)
Positive / All negative	6 (3.6%)	6 (3.6%)
Positive / At least 1 positive	1 (0.6%)	1 (0.6%)

One patient had only an Unscheduled visit prior to treatment start, therefore the "Baseline ADA Status" is missing for this patient and so they are not included in any of the categories shown in the output.

Seven patients in the Glofit-GemOx population had positive ADAs at baseline and a valid pre- and post-baseline assessment. All 7 patients had an an immune-related adverse event (five patients Grade 1−2, two patients Grade 3).

Ten patients were confirmed ADA-glofitamab positive in Study GO1944 (N=166) of which 3 were positive post-treatment. No patients tested ADA-glofitamab positive in Study GO41943. Thus, immunogenicity of glofitamab is not considered to have clinically relevant impact on treatment.

2.3.4. PK/PD modelling

The clinical data for evaluation of potential exposure-safety relations came from studies GO41943 and GO41944 while only data from GO41944 contributed efficacy data. See Table 19. Exposure metrics (AvgRO%D1, AvgRO%C1+C2, AUCD1, AUCC1+C2, CmaxD1 and CmaxC1+C2) were merged into the exposure-response datasets.

Table 9 Available exposure – response data by endpoint

Endpoint	DVID	Population	Unique patients	Observations
BOR (CR/OR) by IRC (PET-Lugano 2014)	13	Study GO41944	161	161
DOCR by IRC	16	Study GO41944	169	169
DOR by IRC	15	Study GO41944	170	170
OS by IRC	60	Study GO41944	172	172
PFS (earliest contributing event by IRC; censored before NALT)	61	Study GO41944	172	172
CRS	21	Study GO41944, Study GO41943	188	274
CRS (Grade ≥2)	21	Study GO41944, Study GO41943	188	188
Neutropenia	29	Study GO41944, Study GO41943	188	3487*
Neutropenia (Grade ≥2)	29	Study GO41944, Study GO41943	188	188
Febrile neutropenia	23	Study GO41944, Study GO41943	188	188
Febrile neutropenia (Grade ≥3)	23	Study GO41944, Study GO41943	188	188
Pneumonia	24	Study GO41944, Study GO41943	188	188
Pneumonia (Grade ≥2)	24	Study GO41944, Study GO41943	188	188
Infection	25	Study GO41944, Study GO41943	188	188
Infection (Grade ≥2)	25	Study GO41944, Study GO41943	188	188
Anemia	91	Study GO41944, Study GO41943	188	3404*
Anemia (Grade ≥2)	91	Study GO41944, Study GO41943	188	188
Thrombocytopenia	92	Study GO41944, Study GO41943	188	3417*
Thrombocytopenia (Grade ≥2)	92	Study GO41944, Study GO41943	188	188
Leukopenia	93	Study GO41944, Study GO41943	188	3412*
Leukopenia (Grade ≥2)	93	Study GO41944, Study GO41943	188	188
Lymphopenia	94	Study GO41944, Study GO41943	159	2861*
Lymphopenia (Grade ≥2)	94	Study GO41944, Study GO41943	159	159

BOR: best overall response; IRC: independent review committee; PET: positron emission topography; DOCR: duration of complete response; DOR: duration of response; PFS: progression-free survival; OS: overall survival; CRS: cytokine release syndrome.
* Grade assessed using laboratory data.

E-R modelling

The exposure metrics (AvgRO%D1; AvgRO%C1+C2; AUCD1; AUCC1+C2; CmaxD1) derived during the population PK analysis were used to fit Cox proportional hazards regression analyses for OS and PFS (efficacy), logistic exposure-response models for CRR and ORR (efficacy), and incidence rates of CRS (Grade ≥2), neutropenia (Grade ≥2), febrile neutropenia (Grade ≥3), pneumonia (Grade ≥2), infection (Grade ≥2), anaemia (Grade ≥2), thrombocytopenia (Grade ≥2), leukopenia (Grade ≥2) and lymphopenia (Grade ≥2). Duration of complete response (DOCR) and DOR were analyzed graphically.

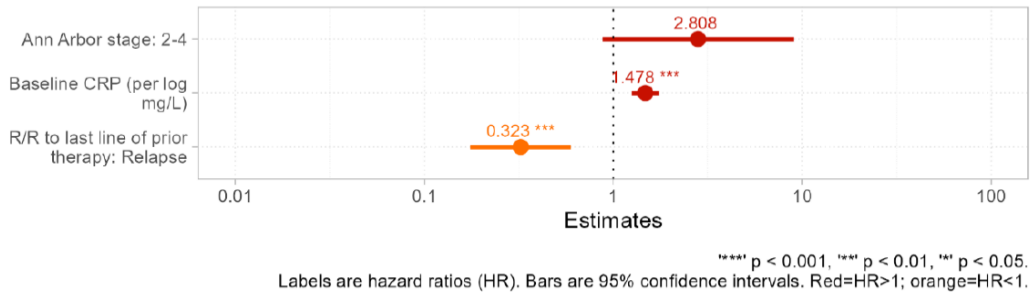
Baseline values of predictors were used for identifying and quantifying relationships with binary outcomes of interest. Continuous predictors were used where available; categorical predictors were dichotomized if possible. Continuous predictors which were significantly non-normally-distributed were log-transformed prior to analysis. Correlations between variables of interest were identified from a correlation plot. Exposure metrics were first tested in univariate models. Then predictors within the scope of the analysis were added and tested using -2LL and a step-wise elimination procedure ($p<0.05$). Non-parametric bootstrapping (n=1000) was used in order to assess parameter uncertainty and stability.

Exposure-efficacy

In order to account for potential bias arising from BOR, OS or PFS assessments associated with patients exiting the study before the conclusion of Cycle 2, only BOR, OS or PFS data collected 21 days post-dose of Cycle 2 and onwards were included. Thus, 148 patients remained in the BOR population, 156 patient remained in the OS population and 152 patients remained in the PFS population.

OS: A clear relationship was observed in Kaplan-Meier plot for OS, between increasing quartiles of AUCC1+C2 and increasing OS. AvgRO%C1+C2 and AUCC1+C2 were tested as univariable glofitamab exposure predictors of OS hazard. Neither metric showed a significant relationship with OS, but the trend for AvgRO%C1+C2 was marginally stronger (p=0.0799) and selected for further analysis. In the full model, increasing log-transformed baseline CRP significantly increased the hazard, but no other covariate relationships were significant at the p <0.05 level. OS was greater in patients who had relapsed after their last prior line of treatment but decreased with increasing log-transformed baseline CRP and was lower in patients with Ann Arbor stage 2-4. Thus interference, from the covariate "relapse after last prior therapy" should be interpreted with caution.

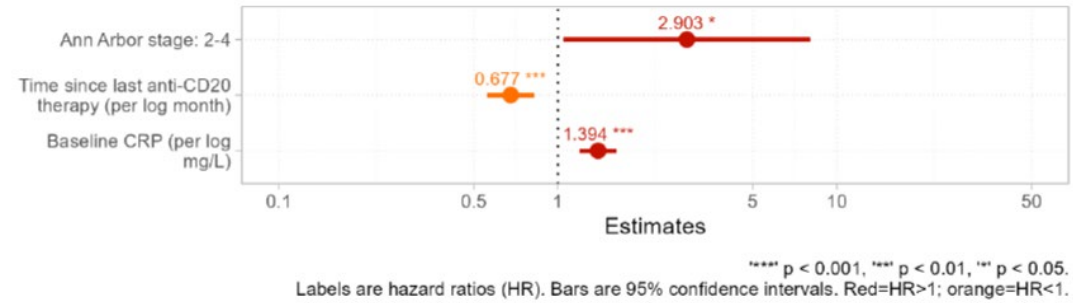
Figure 8 Forest plot of Hazard Ratios for covariates for the reduced model for OS in study GO41944



PFS: A clearly ordered relationship was observed between increasing quartiles of AUCC1+C2 and increasing PFS in the Kaplan-Meier plot for PFS. AvgRO%C1+C2 and AUCC1+C2 were tested as univariable glofitamab exposure predictors of PFS hazard. No clear exposure-response relationship for PFS was seen in either metric, but AUCC1+C2 was selected for further analysis (p=0.145). Increasing log-transformed baseline CRP and Ann Arbor stage 2-4 significantly increased the hazard for PFS, and the hazard ratio decreased with increasing time since last prior anti-CD20 therapy in the full model. In the reduced model, PFS increased with increased time since last prior anti-CD20 treatment, but decreased with increasing log-transformed baseline CRP, and was reduced in patients with Ann Arbor stage >1.

The assumption of proportional hazard did not hold for Ann Arbor stage (post 9 months) and time since last anti-CD20 therapy, thus interferences from these covariates should be interpreted with caution.

Figure 9 Forest plot of Hazard Ratios for covariates for the reduced model for PFS in study GO41944



CR: AvgRO%C1+C2 and AUCC1+C2 were tested as univariable glofitamab exposure predictors of CR in the BOR patient population. No exposure-response relationship for CR was seen in either metric, but AUCC1+C2 was selected for further analysis (p=0.430). Baseline SPD, baseline obinutuzumab concentration and baseline CRP showed strong correlations with the likelihood of CR in the full model. In the reduced final model, increased baseline CRP was associated with lower rates of CR and

increased time since last anti-CD20 treatment was associated with increased rates of CR. The reduced model for CR had an AUC [ROC] of 0.753 indicating a reasonable predictive power.

ORR: AvgRO%C1+C2 and AUCC1+C2 were tested as univariable glofitamab exposure predictors of OR in the BOR patient population. No exposure-response relationship for OR was seen either metric, but AvgRO%C1+C2 was selected for further analysis (p=0.692). Baseline weight, baseline obinutuzumab concentration, time since last prior anti-CD20 treatment, and dexamethasone pretreatment appeared significantly correlated with the likelihood of OR in the full model. In the reduced final model, increasing time since last prior anti-CD20 treatment were associated with increased likelihood of OR.

Table 45. Parameter estimates and odds ratios for the reduced model for OR in the BOR efficacy population of Study GO41944.

Parameter	Estimate			Odds ratio		
	Estimate	Lower 95%	Upper 95%	OR	Lower 95%	Upper 95%
Intercept	0.334	-0.393	1.08			
Time since last anti-CD20 therapy (per log month)	0.862	0.416	1.39	2.37	1.52	4.03

OR=odds ratio, AUC=area under the glofitamab concentration-time curve.

An AUC [ROC] of 0.745 indicated a reasonable predictive power of the reduced model for OR.

Exposure-safety

CRS: Of patients with at least 1 CRS event of Grade ≥2 (n=25, 13.3%), 2 (8.00%; 1.06% overall) had more than 1. Exploration of the time course of CRS incidence indicated that almost all patients experienced their first CRS (Grade ≥2) event during the first 7 days of glofitamab treatment. Thus, AvgRO%D1, AUCD1 and CmaxD1 were tested as univariable glofitamab exposure predictors of CRS (Grade ≥2). No unambiguous exposure-response relationships were seen. Risk of CRS (Grade ≥2) was not associated with exposure or receptor occupancy on Day 1 but increased with increasing baseline tumour burden and baseline CRP, and decreased with increasing baseline weight. Risk was also lower in patients of Asian race. AUC [ROC] was 0.821 indicating good predictive power of the final model.

Table 10 Parameter estimates and odds ratios for the final model for CRS (Grade ≥ 2) in the CRS safety population

Parameter	Estimate			Odds ratio		
	Estimate	Lower 95%	Upper 95%	OR	Lower 95%	Upper 95%
Intercept	-5.41	-9.63	-1.63			
Baseline weight (per 15 kg)	-0.496	-1.05	-0.0000716	0.609	0.348	1.00
Race: Asian	-1.10	-2.29	-0.0160	0.333	0.102	0.984
Baseline SPD (per log mm²)	0.559	0.150	1.03	1.75	1.16	2.81
Baseline CRP (per log mg/L)	0.569	0.228	0.949	1.77	1.26	2.58

OR=odds ratio, LDH=lactate dehydrogenase, CRP=C-reactive protein.

Neutropenia (Grade ≥2): Events of neutropenia Grade ≥2 took place gradually over time, suggesting that Cycle 1 + Cycle 2 metrics of exposure would be the most appropriate for this analysis. AvgRO%C1+C2 and AUCC1+C2 were tested as univariable glofitamab exposure predictors of neutropenia (Grade ≥2). No significant relationships were observed related to Cycle 1+2 exposure. Risk of neutropenia decreased with increasing tumour burden, but no other covariate relationships

were identified. However, the predictive power of the reduced model was poor (ROCauc 0.59) thus no investigated covariate could explain the incidence of neutropenia (Grade ≥2).

Table 11 Parameter estimates and odds ratios for the reduced model for neutropenia (Grade ≥ 2) in the neutropenia safety population

Parameter	Estimate			Odds ratio		
	Estimate	Lower 95%	Upper 95%	OR	Lower 95%	Upper 95%
Intercept	2.45	0.562	4.47			
Baseline SPD (per log mm²)	-0.281	-0.537	-0.0397	0.755	0.584	0.961

OR=odds ratio, SPD=sum of products of diameters (tumour burden).

Febrile neutropenia (Grade ≥3): Of patients with at least 1 febrile neutropenia event of Grade ≥3 (n=4, 2.21%), none had more than 1. No further statistical analysis was performed.

Pneumonia (Grade ≥2): Of patients with at least 1 pneumonia assessment of Grade ≥2 (n=21, 11.2%), none had more than 1 occurrence. AvgRO%C1+C2 and AUCC1+C2 were tested as univariable glofitamab exposure predictors of pneumonia (Grade ≥2). No unambiguous exposure-response relationships were seen. No significant predictors were identified at $p < 0.05$ in the full model.

Anaemia (Grade ≥2): Of patients with at least 1 anaemia assessment of Grade ≥2 (n=92, 49.2%), 76 (82.6%; 40.6% overall) had more than 1. Anaemia events of Grade ≥2 took place within the first two cycles. AvgRO%C1+C2 and AUCC1+C2 were tested as univariable glofitamab exposure predictors of anaemia (Grade ≥2). No significant relationship between increasing exposure and incidence of anaemia (Grade ≥2) was observed. The strongest trend was seen for AvgRO%C1+C2 (p=0.0531), and was selected for further analysis. However only significant relationships between risk of anaemia (Grade ≥2) and baseline weight, baseline SPD, baseline CRP, time since last prior anti-CD20 treatment and Ann Arbor stage were identified and remained in the reduced model. AUC [ROC] was 0.827 indicating good predictive power of the final model for anaemia (Grade ≥2).

Table 12 Parameter estimates and odds ratios for the reduced model for anaemia (Grade ≥ 2) in the anaemia safety population

Parameter	Estimate			Odds ratio		
	Estimate	Lower 95%	Upper 95%	OR	Lower 95%	Upper 95%
Intercept	-2.07	-4.69	0.517			
Baseline weight (per 15 kg)	-0.550	-0.916	-0.214	0.577	0.400	0.808
Baseline SPD (per log mm²)	0.396	0.0693	0.734	1.49	1.07	2.08
Baseline CRP (per log mg/L)	0.604	0.379	0.853	1.83	1.46	2.35
Time since last anti-CD20 therapy (per log month)	-0.299	-0.587	-0.0225	0.741	0.556	0.978
Ann Arbor: 3-4	0.981	0.222	1.77	2.67	1.25	5.88

OR=odds ratio, CRP=C-reactive protein, SPD=sum of products of diameters (tumour burden).

Thrombocytopenia (Grade ≥2): Of patients with at least 1 thrombocytopenia assessment of Grade ≥2 (n=74, 39.6%), 51 (68.9%; 27.3% overall) had more than 1. Thrombocytopenia events of Grade ≥2 took place within the first two cycles. AvgRO%C1+C2 and AUCC1+C2 were tested as univariable glofitamab exposure predictors of thrombocytopenia (Grade ≥2). No significant relationship between increasing exposure and incidence of thrombocytopenia (Grade ≥2) was observed in either exposure metric. AUCC1+C2 was selected for further analysis but did not remain in the final model. Risk of thrombocytopenia (Grade ≥2) decreased with increasing time since last prior anti-CD20 treatment,

and increased with increasing number of prior lines of treatment and with Ann Arbor stage >2. AUC [ROC] was 0.7 indicating reasonable predictive power of the final reduced model.

Leukopenia (Grade ≥2): Of patients with at least 1 leukopenia assessment of Grade ≥2 (n=83, 44.4%), 53 (63.9%; 28.3% overall) had more than 1. AvgRO%C1+C2 and AUCC1+C2 were tested as univariable glofitamab exposure predictors of leukopenia (Grade ≥2). No significant relationship between increasing exposure and incidence of thrombocytopenia (Grade ≥2) was observed in either exposure metric, but AUCC1+C2 was selected for further analysis. No covariates were retained at $p < 0.05$ in the full model.

Lymphopenia (Grade ≥2): Of patients with at least 1 lymphopenia assessment of Grade ≥2 (n=130, 82.8%), 99 (76.2%; 63.1% overall) had more than 1. AvgRO%C1+C2 and AUCC1+C2 were tested as univariable glofitamab exposure predictors of lymphopenia (Grade ≥2). No significant relationship between increasing exposure and incidence of thrombocytopenia (Grade ≥2) was observed in either exposure metric; AUCC1+C2 was selected for further analysis. No covariates were retained at $p < 0.05$ in the full model.

2.3.5. Discussion on clinical pharmacology

The clinical pharmacology of glofitamab as a single agent or with obinutuzumab pre-treatment and the approved glofitamab step-up dosing 2.5/10/30 mg have been investigated previously in Study NP30179 in patients with R/R DLBCL who have received ≥2 prior lines of therapy. Glofitamab in combination with gemcitabine plus oxaliplatin (Glofit-GemOx) and including obinutuzumab pre-treatment in patients with R/R DLBCL (who are ineligible for autologous stem cell transplant) is supported by results from pivotal Study GO41944 (STARGLO) and Phase Ib Study GO41943. The recommended dose regimens consist of a single 1000 mg IV dose of obinutuzumab given on C1 Day 1 followed by the step-up dose regimen of glofitamab with 2.5 mg on C1 Day 8, 10 mg on C1 Day 15 and 30 mg on Day 1 C2-C12 Q3W, administered intravenously in combination with GemOx.

Target-binding competent sandwich enzyme linked immunoassay were used to determine glofitamab and obinutuzumab concentrations in human serum samples. Anti-drug antibodies to glofitamab in human serum were determined using a bridging enzyme linked immunoassay. All methods were validated and previously assessed with the exception of the applied ADA-glofitamab assay. Ten patients were confirmed ADA-glofitamab positive in Study GO1944 (N=166) of which 3 were positive post-treatment. The final bioanalytical reports for Study GO41944 to inform further presence of ADA will be submitted post-authorisation.

Glofitamab data covering doses from 5 µg to 30 mg from 648 individuals with 14582 samples from Study NP30179, Study GO41944 and Study GO41943 were used to build a Pop PK model based on the previous model structure. The model was 2-compartmental with time-varying clearance including a decay constant and parallel linear clearance. Effect of body weight was included by allometric scaling. Other covariate effects included were effect of baseline CRP, baseline tumour burden on CLL, MCL history on T, baseline obinutuzumab concentration and FL (Grade 1-3A) histology on k_{des}; and baseline CRP on V1. The GoF plots and VPCs indicated the model could adequately describe the observed glofitamab data in the 3 studies. The PK characteristics for glofitamab were determined in previous procedures. The SmPC Section 5.2 has been updated with relevant parameters for distribution and elimination based on the new Pop PK model.

The average receptor occupancy over 24 hours following the first glofitamab dose or over C1 + C2 was calculated by means of predicted glofitamab and obinutuzumab concentrations over time. Obinutuzumab concentrations were estimated by an adapted Pop PK model for obinutuzumab, in which covariate effect coefficients and IIV parameters were re-estimated and the IIV term on residual error

removed based on data from Study NP30179. The predicted RO-values indicated sufficient receptor occupancy in Cycle 1 and 2 following the obinutuzumab dose and the step-up dosing of glofitamab including the first 30 mg dose. In vitro, half-maximal tumour lysis was achieved at less than 0.5% CD20 receptor occupancy by glofitamab.

Effect of body weight was evaluated on Day 1 or across Cycle 1+2 during the initial MAA and was not assessed to have clinically significant impact on glofitamab PK. The treatment with GemOx did not have direct impact on glofitamab exposure but may cause loss of body weight during treatment due to side effects such as nausea and vomiting and thus lead to increased exposure over time.

The clinical data for evaluation of potential exposure-safety relations came from studies GO41943 and GO41944 while only data from GO41944 contributed efficacy data. Both studies utilised only the 2.5/10/30 mg step-up dosing of glofitamab with obinutuzumab pre-treatment and concomitant GemOx.

Cox proportional hazards regression modelling was applied for survival endpoints OS and PFS. CR and OR were investigated in the BOR population by logistic regression analyses. DOCR and DOR in the context of PFS were evaluated by graphical analyses. No significant relations of exposure or receptor occupancy Day 1 or across Cycle 1+2 to any efficacy measures were identified. Exposure-safety relations were explored by graphical analysis and linear regression where possible. No significant relations of glofitamab exposure or receptor occupancy Day 1 or across Cycle 1+2 were identified for any safety measures.

2.3.6. Conclusions on clinical pharmacology

Overall, the clinical pharmacology of glofitamab in combination with GemOx is considered well described.

The MAH agreed with the CHMP recommendation to submit the final bioanalytical reports for Study GO41944 to inform further presence of ADA with the final CSR at the end of study.

2.4. Clinical efficacy

2.4.1. Dose response study

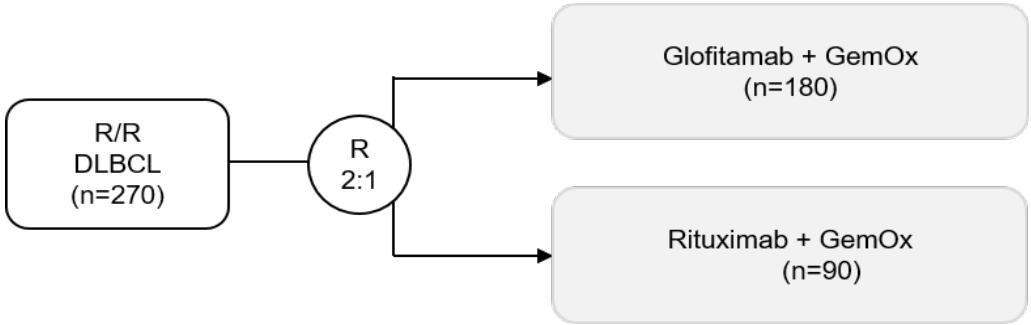
Not applicable

2.4.2. Main study

Study GO41944 ("Starglo")

This is a Phase III, open-label, multicenter, randomised study evaluating the efficacy and safety of Glofit-GemOx versus R-GemOx in patients with R/R DLBCL NOS who have failed one line of therapy and are not candidates for transplant, as well as those patients who have failed at least two lines of therapy. Patients were randomised in a 2:1 ratio to receive either Glofit-GemOx or R-GemOx.

Figure 10 Overview of GO41944 Study Design



DLBCL: diffuse large B-cell lymphoma; GemOx: gemcitabine plus oxaliplatin; R: randomised; R/R: relapsed or refractory.

Note: The planned enrollment was 270 patients, and the actual enrollment was 274 patients.

Randomization stratification factors included:

Number of previous lines of systemic therapy for DLBCL (1 vs. ≥ 2)

CAR T-cell plus bridging therapy was counted as one line of therapy.

Local therapies (e.g., radiotherapy) were not considered as a line of therapy.

Outcome of last systemic therapy (relapsed vs. refractory)

Relapsed disease in this study was defined as disease that had recurred following a response that lasted < 6 months after completion of the last line of therapy.

Refractory disease was defined as disease that did not respond to or that progressed < 6 months after completion of the last line of therapy.

Patients who discontinued last line of therapy before sufficient time for response assessment (for example, due to toxicity) were assessed for refractoriness based on the previous line of therapy.

Enrolment of patients with platinum-refractory disease was limited to approximately 20% of the total number of randomised patients. Platinum-refractory is defined as disease that did not respond to or that progressed < 6 months after treatment with platinum-containing regimens, with or without rituximab, including ICE (ifosfamide, carboplatin, etoposide), DHAP (dexamethasone, cytarabine, cisplatin), DHAC (dexamethasone, cytarabine, carboplatin), GDP (gemcitabine, dexamethasone, cisplatin or carboplatin), or other intensive platinum-containing regimens intended as pre-ASCT salvage therapy. Enrollment of patients who had received more than one prior line of therapy was limited to approximately 65% of the total number of randomised patients.

Methods

Study participants

Key Inclusion Criteria

- Age ≥ 18 years at time of signing the informed consent form.
- Histologically confirmed DLBCL, NOS.
- R/R disease, defined as follows:

- Relapsed: disease that had recurred following a response that lasted ≥ 6 months after completion of the last line of therapy.
- Refractory: disease that did not respond to, or that progressed < 6 months after, completion of the last line of therapy.

Patients who discontinued last line of therapy before sufficient time for response assessment (for example, due to toxicity) were assessed for refractoriness based on the previous line of therapy.

- At least one (≥ 1) line of prior systemic therapy
  - Patients may have undergone autologous hematopoietic stem cell transplant (HSCT) prior to recruitment.
  - CAR T-cell plus bridging therapy were counted as one line of therapy.
  - Local therapies (e.g., radiotherapy) were not considered as lines of therapy.
- Patients who had failed only one prior line of therapy and were not a candidate for high-dose chemotherapy followed by ASCT by meeting at least one of the following criteria:
  - Left ventricular ejection fraction ≤ 40%
  - Creatinine clearance (CrCl) or glomerular filtration rate ≤ 45 mL/min
  - Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) of ≥ 2
  - Age ≥ 70 years
  - Patient refused high-dose chemotherapy and/or transplant
  - Patient had insufficient response to pre-transplant chemotherapy to be able to proceed to transplant
  - Other comorbidities or criteria that precluded use of transplant based on local practice standards or in the investigator's opinion. The rationale for transplant ineligibility had to be recorded in the electronic Case Report Form (eCRF).
- At least one bi-dimensionally measurable (≥ 1.5 cm) nodal lesion, or one bi dimensionally measurable (≥ 1 cm) extranodal lesion, as measured on computed tomography (CT) scan.
- ECOG Performance Status of 0, 1, or 2.

Key Exclusion Criteria

- Patients who had failed only one prior line of therapy and were a candidate for stem cell transplantation.
- History of transformation of indolent disease to DLBCL.
- High-grade B-cell lymphoma with MYC and BCL2 and/or BCL6 rearrangements, and high-grade B-cell lymphoma NOS, as defined by 2016 WHO guidelines.
- Primary mediastinal B-cell lymphoma.
- Prior treatment with glofitamab or other bispecific antibodies targeting both CD20 and CD3.
- Prior treatment with R-GemOx or GemOx.
- Primary or secondary central nervous system (CNS) lymphoma at the time of recruitment or history of CNS lymphoma.

- Prior allogeneic stem cell transplant.
- Ongoing corticosteroid use > 30 mg/day of prednisone or equivalent; stable low dose or short high-dose courses of steroid administration were permissible (see the protocol for definitions and exceptions).

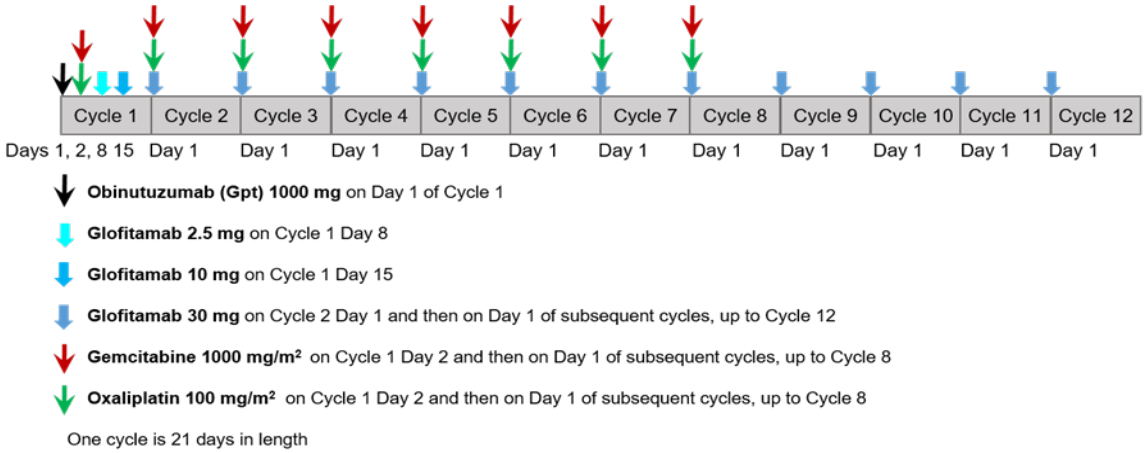
Treatments

Glofit-GemOx Arm

Patients in the Glofit-GemOx arm received a single dose of 1000 mg obinutuzumab pretreatment (Gpt) on Cycle 1 Day 1 (C1D1), 7 days before the first dose of glofitamab.

Using a step-up dosing schedule, the first dose of 2.5 mg glofitamab was administered on Cycle 1 Day 8 (C1D8), followed by 10 mg C1D15, and 30 mg on C2D1 (21-day cycles). Patients received up to 8 cycles of glofitamab in combination with gemcitabine (1000 mg/m^2) plus oxaliplatin (100 mg/m^2), which was given on C1D2 and subsequently on D1 of each cycle, followed by up to 4 cycles of glofitamab monotherapy (30 mg), to complete up to a total of 12 cycles of glofitamab (Figure 2).

Figure 11 Treatment Regimen in the Study Treatment Group: Glofitamab in Combination with Gemcitabine Plus Oxaliplatin (Glofit-GemOx Arm): Study GO41944



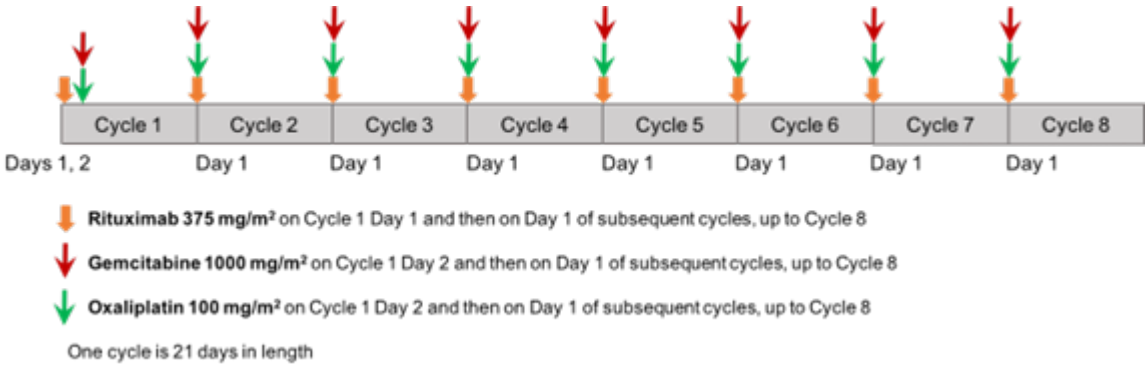
Note: For Cycles 1-8, gemcitabine should have been administered before oxaliplatin. For Cycles 2–8, glofitamab should have been given before gemcitabine and oxaliplatin. Gemcitabine and oxaliplatin could be given on Day 1 or Day 2.

R-GemOx Arm

The first dose of rituximab (375 mg/m^2) was administered on C1D1. Patients received up to 8 cycles of rituximab (21-day cycles) in combination with gemcitabine (1000 mg/m^2) and oxaliplatin (100 mg/m^2) which was given on C1D2 and subsequently on D1 of each cycle.

All study treatments were administered by IV infusion.

Figure 12 Treatment Regimen in the Control Group: Rituximab in Combination with Gemcitabine Plus Oxaliplatin (R-GemOx Arm): Study GO41944



Note: For Cycles 1-8, gemcitabine should have been administered before oxaliplatin. For Cycles 2–8, rituximab should have been given before gemcitabine and then oxaliplatin. Gemcitabine and oxaliplatin could be given on Day 1 or Day 2.

Objectives/Endpoints

Table 13 Objectives and endpoints in **Study GO41944**

Objectives	Corresponding Endpoints
Primary Efficacy Objective	
• To evaluate the efficacy of Glofit-GemOx compared with R-GemOx with respect to OS	• OS, defined as the time from randomization to date of death from any cause
Secondary Efficacy Objective	
• To evaluate the efficacy of Glofit-GemOx compared with R-GemOx with respect to the secondary efficacy endpoints	Key secondary endpoints included in the hierarchical order: [a] • PFS, defined as the time from randomization to the first occurrence of disease progression or death from any cause, whichever occurred first, by IRC • CR rate, defined as the proportion of patients whose best overall response was a CR on PET/CT during the study, by IRC • DOCR, defined as the time from the first occurrence of a documented CR to disease progression, or death from any cause, whichever occurs first, by IRC Additional secondary endpoints that were not adjusted for testing multiplicity: [a] • PFS, as defined previously, by investigator • CR rate, as defined previously, by investigator • ORR, defined as the proportion of patients whose best overall response was a PR or a CR on PET/CT during the study, by IRC and investigator • DOCR, as defined previously, by investigator • DOR, defined as the time from the first occurrence of a documented objective response (CR or PR) to disease progression, or death from any cause, whichever occurred first, by IRC and investigator • Time to deterioration in physical functioning and fatigue, as measured by the EORTC QLQ-C30, and in lymphoma symptoms, as measured by the FACT-Lym LymS

Exploratory Efficacy Objective	Corresponding Endpoints
• To evaluate the efficacy of Glofit-GemOx compared with R-GemOx with respect to the exploratory endpoints	• Descriptive summary statistics of PROs and the change from baseline by treatment arm at each assessment for the following: – All remaining scales of the EORTC QLQ-C30 – FACT-Lym LymS • Characterization of patients who became HSCT candidates after study therapy and were in the autologous or allogeneic HSCT, including: – Incidence of autologous and allogeneic HSCT after study therapy – Survival post HSCT, defined as the time from date of transplantation to date of death from any cause • Characterization of patients who received CAR T-cell therapy after study therapy and were in the CAR T-cell therapy, including: • Incidence of treatment with CAR T-cell therapy • Survival post-CAR-T-cell therapy, defined as the time from date of CAR T-cell infusion to date of death from any cause
Safety Objective	
• To evaluate the safety and tolerability of Glofit-GemOx compared with R-GemOx	• Incidence and severity of AEs, with severity determined according to the NCI CTCAE Version 5.0, including CRS, with severity determined according to the American Society for Transplantation and Cellular Therapy (ASTCT) CRS grading criteria (Lee et al. 2019 and the GO41944 Protocol v6, Appendix 4) • Change from baseline in targeted vital signs • Change from baseline in targeted clinical laboratory test results • Tolerability, as assessed by dose interruptions, dose reductions, and dose intensity, and study treatment discontinuation because of AEs

Primary endpoint - OS

The primary endpoint OS, is defined as the time from randomisation to death from any cause. For patients who have not died at the clinical cutoff date for analysis, OS will be censored on the last date when the patients are known to be alive. Patients who do not have information after baseline will be censored at the date of randomization.

The primary estimand is defined as follows:

• Population: patients in the ITT population

• Variables: OS, defined as the time from randomisation to date of death from any cause

• Treatments: patients will receive either Glofit-GemOx or R-GemOx

• Intercurrent event and handling strategies:

-Early discontinuation from study treatment: treatment policy strategy

-Start of non-protocol anti-cancer therapy prior to disease progression: treatment policy strategy

• Population level summary: HR for OS

The detailed censoring rules for OS are summarized.

Table 14 Censoring rules for OS analysis

Situation	Date of PFS event or censoring	Outcome
Death	Death date	Event
No death	Last known alive date[1] before data cutoff	Censored
No death and no post-baseline survival information available	Randomization date	Censored

[1]Last known alive date is defined as the last date the patient has documented clinical data to show him/her alive. Scenarios considered in this definition may include last survival follow-up date with patient status of "alive", date of last tumor assessment with a valid response, date of last treatment administration with a valid dose, date of last lab assessment with valid results, and date of last update of adverse event information.

Key secondary endpoint - PFS

Progression-free survival is defined as the time from randomisation to the first occurrence of disease progression, or death due to any cause, whichever occurs first. Disease progression will be determined by the IRC and also by the investigator. Patients who have neither progressed nor died at the time of analysis (CCOD) and patients who are lost to follow-up will be censored according to the censoring rules in Table 7. Patients who did not undergo a postbaseline tumour assessment will be censored at the time of randomization.

The estimand for the secondary end point is defined as follows:

• Population: patients in the ITT population.

• Variable: PFS, defined as the time from randomization to the first occurrence of disease progression, or death due to any cause, whichever occurs first. Disease progression will be determined by the IRC and also by the investigator according to 2014 Lugano Response Criteria.

• Treatment: patients will receive either Glofit-GemOx or R-GemOx

• Intercurrent event and handling strategies:

-Early discontinuation from study treatment: treatment policy strategy

-Start of non-protocol anti-cancer therapy prior to disease progression: hypothetical strategy

• Population level summary: HR for PFS

Table 15 Censoring rules Analysis of PFS (secondary endpoint)

Situation	Date of PFS event or censoring	Outcome
No baseline disease assessments	Date of randomization	Censored
New anti-lymphoma therapy started before documentation of disease progression or death	Date of last adequate disease assessment prior to start of new anti-lymphoma therapy	Censored
Alive and without disease progression documentation	Date of last adequate[1] disease assessment	Censored
Patients had two or more consecutive missed response assessments	Date of last adequate disease assessment before the missing assessments with documented non-progression	Censored
Death or disease progression between planned disease assessments	Date of death or first disease assessment showing disease progression, whichever occurs first	Event
Death after first on-treatment disease assessment	Date of death	Event

[1] To be considered adequate, a response assessment not including PET should have CR, PR, SD or PD as outcome; and/or a response assessment including PET-CT should have CMR, PMR, NMR, or PMD using Lugano criteria. Assessments that are "unevaluable" and "not done" are considered not adequate.

PFS = progression-free survival

Key secondary endpoint - CR Rate

The CR rate is defined as the proportion of patients whose best overall response is a CR on PET/CT during the study, according to the 2014 Lugano Response Criteria, as determined by the IRC and the investigator.

The estimand for the key secondary end point is defined as follows:

• Population: patients in the ITT population

• Variable: CR rate, defined as the proportion of patients whose best overall response is a CR on PET/CT during the study, according to the 2014 Lugano Response Criteria, as determined by the IRC and the investigator

The **ORR** is defined as the proportion of patients whose best overall response is a partial response (PR) or a CR du ring the study, according to the 2014 Lugano Response Criteria, as determined by the IRC and the investigator.

• ORR, defined as the proportion of patients whose best overall response is a PR or a CR during the study, according to the 2014 Lugano Response Criteria, as determined by the IRC and the investigator

• Treatment: patients will receive either Glofit-GemOx or R-GemOx

• Intercurrent event and handling strategies:

-Missing response assessment because of early study withdrawal: composite strategy

-Study discontinuation: composite strategy

• Population Level Summary: 95% Cis for CR rate and ORR for each treatment

Key Secondary endpoint – Duration of objective response

Duration of objective response is defined as the time interval from the date of the first occurrence of an objective response (PR or CR) until the first date that progressive disease or death is documented, whichever occurs first. Duration of CR is defined as the time interval from the date of the first

occurrence of CR until the first date that progressive disease or death is documented, whichever occurs first. The same PFS censoring rules as described in Table 7 will be applied to the duration of objective response and duration of CR except the first scenario in Table 7 because all responders will have at least one baseline assessment.

The estimand for the secondary endpoint is defined as follows:

• Population: patients in the ITT population

• Variable: duration of objective response, defined as the time interval from the date of the first occurrence of an objective response (PR or CR) until the first date that progressive disease or death is documented, whichever occurs first, as determined by the IRC and the investigator

• Duration of CR, defined as the time interval from the date of the first occurrence of CR until the first date that progressive disease or death is documented, whichever occurs first, as determined by the IRC and the investigator

• Treatment: patients will receive either Glofit-GemOx or R-GemOx

• Intercurrent event and handling strategies:

-Patients who discontinue or withdraw from the study while responding: composite strategy

-Patients who discontinue treatment when starting a new anti-lymphoma therapy: hypothetical strategy

• Population Level Summary: HR for du ration of objective response and du ration of CR

Sample size

The primary objective of this study is to evaluate the efficacy of Glofit-GemOx relative to R-GemOx in patients with R/R DLBCL as measured by OS. Assuming a median OS of 11 months in the R-GemOx arm based on the median OS reported in the largest multisite Phase II study of R-GemOx and other similar references, and a randomization ratio of 2:1, and considering an interim analysis for efficacy when 70% of events have been documented, 138 events are required to detect a between-group difference of 7.3 months in median OS (hazard ratio=0.6) assuming an exponential distribution of OS using a log-rank test

with 80% power and a two-sided α of 0.05. Based on the above statistical assumptions and anticipating a recruitment period of approximately 17 months and follow-up of 9 months after the last patient is randomised, a total of approximately 270 patients will be randomised in the global enrollment phase of this study, taking into account an estimated annual dropout rate of 2%.

Randomisation

Patients will be randomly assigned to one of two treatment arms: Glofit-GemOx or R-GemOx. Randomization will occur via interactive voice or web-based response system (IxRS) in a 2:1 ratio.

Patients will be stratified at the time of randomization for the following factors:

-Number of previous lines of systemic therapy for DLBCL (1 vs. ≥ 2)

- CAR T-cell plus bridging therapy will be counted as one line of therapy.
- Local therapies (e.g., radiotherapy) will not be considered as a line of therapy.

-Outcome of last systemic therapy (relapsed vs. refractory)

- Relapsed disease in this study is defined as disease that has recurred following a response that lasted ≥ 6 months after completion of the last line of therapy.
- Refractory disease is defined as disease that did not respond to or that progressed ≤ 6 months after completion of the last line of therapy.

Blinding (masking)

Because of the use of different dosing schedules between the treatment arms, this will be an open-label study. To minimize bias, the IRC will remain blinded to treatment assignment and the Sponsor will not have access to efficacy and safety summaries which compare treatment arms prior to the formal reporting of study results, with the exception that the randomization code may be made available to facilitate the analysis of PK samples.

An iDMC will be used to evaluate interim analysis results and to determine whether the trial results should be released early to allow for a potential marketing application based on superior efficacy or continue to final analysis. All summaries and analyses by treatment arm for the iDMC review will be prepared by an iDCC. Members of the iDMC will be external to the Sponsor and the Sponsor's study management team and will follow a charter that outlines their roles and responsibilities. In addition to the periodic safety data reviews by iDMC, the iDMC will evaluate efficacy and safety at one formal interim analysis of OS and recommend if the study efficacy data should be released early.

Analysis sets

The following populations are defined:

Population	Definition
ITT	All randomized patients, whether or not the patient received the assigned treatment.
Safety-evaluable	Patients who receive any amount of any study treatment.
PK-evaluable	All patients who receive at least 1 dose of study treatment in the Glofit-GemOx arm and have at least 1 post-dose concentration result (obinutuzumab or glofitamab).
Immunogenicity	All patients who have at least 1 pre-dose and 1 post-dose ADA assessment.

ADA = anti-drug antibody; Glofit-GemOx = glofitamab + gemcitabine + oxaliplatin; ITT = intent-to-treat, PK = pharmacokinetic.

The analysis populations are defined as follows:

Intent-to-treat (ITT) population: all randomised patients.

Safety-evaluable population: patients who receive any amount of any study treatment.

PRO-evaluable population: all randomised patients who have a baseline and at least one postbaseline assessment. PRO-evaluable population will be used for descriptive analyses of visit summary and change from baseline analyses. All randomised patients (ITT) will be used for completion analyses and time to deterioration analyses.

PK-evaluable population: all patients who receive at least one dose of study treatment in the Glofit-GemOx arm and have at least one post-dose concentration result.

Immunogenicity population: all patients who have at least one pre-dose and one post-dose ADA assessment.

For all efficacy analyses (including PROs), patients will be grouped according to the treatment assigned at randomisation (intent-to-treat [ITT] population). For all safety analyses, patients will be grouped according to the treatment received (patients with any dose of glofitamab or obinutuzumab will be analyzed in the Glofit-GemOx arm).

Statistical methods

OS

Treatment comparison will be made using a two-sided level 0.05 stratified log-rank test. The Kaplan-Meier method will be used to estimate the median OS, if reached, and OS distribution for each treatment arm. The Brookmeyer-Crowley methodology will be used to construct the 95% (confidence interval) Cl for the median OS for each treatment arm. Cox proportional-hazards models will be used to estimate the stratified HR and its 95% Cl.

Sensitivity analyses for OS

The ITT population is the primary population for all efficacy measures and will be the only population examined in all sensitivity analyses. The following sensitivity analyses for OS will be performed:

• lf 5% or more patients have stratification discrepancies between the eCRF and lxRS, eCRF recorded stratification factors will be performed for the primary endpoint with ITT and safety populations.

• lf 5 or more patients die due to coronavirus disease 2019 (COVID-19): an analysis of the safety profile for patients with COVID-19 will be performed with two approaches applied:

-Patients who died due to COVID-19 within three months of treatment discontinuation or completion censored to date of study treatment discontinuation, and key safety summaries for these patients will be

produced separately.

-OS analysis will be performed with all such patients censored to date of death.

• lf 5 or more patients discontinue study treatment due to COVID-19 AE: the main analytic approach for the OS will be performed with such patients censored to date of study treatment discontinuation.

• lf 5 or more patients discontinue prior to Cycle 4 due to drug supply issues caused by COVID-19: the main analytic approach for the OS will be performed with such patients censored to date of study treatment discontinuation.

The proportional hazards assumption on OS may be examined using both graphical and analytical methods if hazards are not proportional. The log [-log] of the survival function versus time for OS may be plotted for the comparison between Glofit-GemOx and R-GemOx. lf the curves are not parallel, indicating that hazards are not proportional, supportive analyses may be conducted to account for the possible non-proportional hazards effect using the restricted mean survival time (RMST) method.

The RMST will be computed for OS using the area under the curve from baseline to several timepoints (6, 12, and 18 months). The RMST will be computed for each treatment arm and the difference with its 95% Cl (by Greenwood method) and p-values (by Z test) will be provided for descriptive purpose.

Subgroup Analyses for Primary Endpoint(s)

Subgroup analyses will be done for the primary endpoint only. A forest plot will be produced based on the primary endpoint sub-grouped by demography data.

Summaries of OS for these subgroups will be provided in forest plots. Continuous variables will be categorized into clinically meaningful groups for the subgroup analysis. Table 4 specifies the subgroups

that will be explored; other subgroups may be included in the analysis. The subgroup analyses will not be adjusted for multiplicity, and all subgroup analyses will be exploratory only.

Table 16 Subgroups for subgroup analysis

Subgroup	Grouping
Age (in years)	< 65, ≥ 65
Sex	Male, Female
Ethnicity	Hispanic or Latino, Not Hispanic or Latino, Not Stated and Unknown
Race	White, Black/African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Unknown
Body mass index	Split into quartiles
ECOG status	0, 1, 2
Number of previous lines of systemic therapy for DLBCL (IxRS)	1, ≥2
Relapsed/refractory to last line of therapy (IxRS)	Relapsed, refractory
Initial diagnosis	Non-GCB, GCB, ABC, Unclassified
Ann Arbor stage at study entry	Stage I, Stage II, Stage III, Stage IV
Prior autologous stem-cell transplant	Yes, No
Double expresser (*MYC* and *BCL2* overexpression)	Yes, No
IPI score at study entry (CRF and derived)	0, 1, 2, 3, 4, 5
Prior CAR-T therapy	Yes, No
Relapsed or refractory to any prior platinum therapy	Relapsed, refractory
Relapsed or refractory to any prior anti-CD20 therapy	Relapsed, refractory
Primary refractory disease or relapse within one year of initial diagnosis	Yes, No
Primary refractory disease or relapse within one year of first line therapy	Yes, No
Refractory to first line of therapy	Yes, No
Refractory to any line of therapy	Yes, No
Early relapse from ASCT (PD ≤ 12 months from completion)	Yes, No
Double refractory to any prior anti-CD20 and anthracycline based regimen	Yes, No
Bulky disease (defined as size of the largest node lesion ≥ 10 cm)	Yes, No
Cell of origin (grouped data by IHC and gene expression)	Activated B-cell-like, Germinal Center B-cell-like, Unclassified
Enrollment by geographic region	North America, Europe, and the rest of the world

ABC = activated B cell type; ASCT = autologous stem cell transplantation; CAR = chimeric antigen receptor; CD = cluster of differentiation; DLBCL = diffuse large B-cell lymphoma; ECOG = Eastern Cooperative Oncology Group; GCB = germinal center B cell type; IHC = immunohistochemistry; NOS = not otherwise specified; PD = progressive disease; SD = stable disease.

Supportive Analyses for Primary Endpoint

As a supportive analysis, a competing risk analysis of cause-specific death (with event types "death due to progression of disease" and "death due to adverse event or other reasons") as an exploratory analysis will be performed including the following:

- A visualization of the corresponding cumulative incidence functions
- A cause-specific hazard and Fine-Gray regression models for the competing events

With randomised treatment assignment as the main covariate and potential adjustment for additional potential prognostic variables.

PFS

The methodologies detailed for the OS analysis will be used for the PFS analysis.

Sensitivity analyses for PFS

Sensitivity analyses will be performed to study the impact on the analysis of PFS for missing data/assessments due to COVID-19 pandemic, and any loss to follow-up or discontinuation of assessments of PFS not due to an event:

• If 5% or more patients in either arm who had two or more consecutive missed response assessments due to COVID-19 pandemic without PFS events prior to the last adequate response assessment and didn't receive new anti-lymphoma therapy (NALT), a less conservative estimate of PFS will be triggered. For such patients without subsequent adequate assessments, the PFS will be censored to the date of last adequate disease assessment plus three months whether or not a late PFS event occurs after the missed assessments. If the patients had follow-up and adequate response assessments of non-progression after the missed assessments, the PFS will be censored to the last adequate and new response assessments.

The censoring rule for the sensitivity analysis of PFS is based on the hypothetical assumption that patients who missed two or more consecutive response assessments due to COVID-19 pandemic would have been able to receive at least one response assessment to determine the PFS.

If 5% or more patients in either arm who had discontinued response assessments or lost to follow-up not due to PFS event nor any NALT taken, a less conservative sensitivity analysis of PFS will be applied to such patients by censoring to the date of last adequate disease assessment plus three months if no event occurred within three months of last assessment.

Additional sensitivity analyses will also be performed on PFS without censoring for NALT and censoring for NALT except for HSCT.

The proportional hazards assumption on PFS may be examined using both graphical and analytical methods if hazards are not proportional. The log [-log] of the survival function versus time for PFS may be plotted for the comparison between Glofit-GemOx and R-GemOx. If the curves are not parallel, indicating that hazards are not proportional, supportive analyses may be conducted to account for the possible non-proportional hazards effect using the RMST method.

The RMST will be computed for PFS using the area under the curve from baseline to several timepoints (6, 12, and 18 months). The RMST will be computed for each treatment arm and the difference with its 95% CI (by Greenwood method) and p values (by Z test) will be provided for descriptive purpose.

Impact of NALT Prior to or in the Absence of Progression on PFS

The impact of NALT prior to disease progression due to efficacy reason will be assessed by the discount method to investigate how the PFS results would have looked if the NALT was not available. More specifically, the time interval during which patients received NALT until the event or censoring time will be discounted at 10%, 30%, and 50% for both arms. Note that the secondary analysis of PFS corresponds to a discount analysis with a discount rate of 100% on PFS time *after* NALT.

Concordance Analysis of PFS

Agreement/disagreement between the investigator assessment and assessment by the IRC of PFS will be summarized. A specific analysis which outlines whether the IRC event/censoring was earlier or later than investigator assessment will also be provided.

The two assessments will be considered in agreement if the two time-to-event determinations do not differ by more than 30 days and both agree on whether there is disease progression or not. Note, PFS events due to death are handled separately from disease progression events within the summary table. The overall response assessments at the end of the treatment between the IRC and investigator will also be compared in the same way as disease progression events.

CR Rate and ORR

For the secondary efficacy endpoints of CR rate and ORR, an estimate of CR rate or ORR and its 95% CI will be calculated using the Clopper-Pearson method for each treatment arm. Complete response rate and ORR will be compared between treatment arms using the Cochran-Mantel-Haenszel test stratified by the randomization (IxRS recorded) stratification factors. Responses *after* initiation of NALT will not be included in the analysis of CR rate and ORR.

Duration of objective response

The methodologies detailed for the OS analysis will be used for the duration of response analysis, except that the analysis will not be stratified.

Multiplicity and Interim analysis

For the primary endpoint of OS, the stopping boundaries will be based on the O'Brien-Fleming a-spending function. At both the interim and final OS analyses, key secondary endpoints listed in this section will be evaluated in the order specified above for statistical significance only if the study primary efficacy endpoint of OS is statistically significant at the appropriate boundary level. For these key secondary endpoints, the boundaries for statistical significance will be based on a Pocock a-spending function, i.e., 0.03244. Key secondary endpoints will be tested at the appropriate significance level in the order specified in this section. If, for one endpoint in this list the null hypothesis cannot be rejected, then the results for this and all following endpoints are not statistically significant.

The hierarchical testing procedure with the boundaries determined as described above ensures that the overall type I error for the primary and key secondary endpoints will be controlled at 0.05.

The interim analysis is planned to occur at the latest of the following timepoints:

1) when 70% of the OS events have been documented (i.e., 97 events will trigger the interim analysis), and 2) when all patients are randomised.

These timepoints are expected to occur at a similar time; around 20 months *after* the first patient is randomised.

Overall survival will be tested at the significance level determined using the Lan-DeMets spending function with an O'Brien-Fleming boundary such that the overall two-sided type I error rate will be maintained at the 0.05 level. Based on the planned numbers of OS events, the O'Brien-Fleming boundary for statistical significance at the interim analysis will be p = 0.0148. If the boundary for statistical significance is achieved and supported by other efficacy and safety results, then the iDMC will recommend that the study results be released and no further hypothesis tests on the primary and key secondary end points will be performed *after* interim analysis. The interim analysis will be considered the primary analysis for this study and further analyses will be descriptive only. Otherwise, interim analysis results will be held by the iDMC until the final analysis is performed after 138 events. The boundary for efficacy at the final analysis will be adjusted to incorporate the alpha spent at the interim analysis, such that the overall two-sided type I error rate will be maintained at the 0.05 level (see Table 5).

A non-binding futility analysis consisting in an observed HR-OS ≥1.2 will be performed at the same time as the interim efficacy analysis. If the HR for OS ≥1.2, then the iDMC may consider the study as futile.

One formal interim analysis and one final analysis will be performed for OS (see Table 5). All efficacy analyses, including the interim analyses of OS, will be performed by the iDCC. In case not exactly 70%

of the total number of deaths (i.e., OS events) are observed at the time of the clinical cut off, the statistical methodology details are provided.

Table 17 projected Interim and final OS analysis

Analysis	No. of Events	% OS Information	Event to Participant Ratio	Projected Cutoff Date [a]	Projected MDD [b] HR	Projected Boundary (p-value) [c]	Cumulative Type I Error (two sided)	Cumulative Power
Interim (efficacy)	97	70%	36%	Month 20	0.59	$p \leq 0.0148$	0.0148	46.9%
Final	138	100%	51%	Month 26	0.70	$p \leq 0.0455$	0.05	80%

HR = hazard ratio; MDD = minimally detectable difference; No. = number; OS = overall survival;

Note: Assumes 2% dropout rate over 12 months for OS analyses.

[a] Study month at which required number of events are projected to occur, where Study Month 1 is the month the first participant is enrolled. Analysis results will be available after data cleaning.

[b] The largest observed HR that is projected to be statistically significant.

[c] The projected boundary for statistical significance for the number of events shown (actual boundary to be calculated at time of analysis based on actual number of events).

The purpose of the interim analysis of OS is to evaluate whether there is an overwhelming difference in the efficacy observed in the experimental arm compared with the central arm in terms of OS. If the test is not significant; the study will continue as planned. If the test is significant, the iDMC may recommend releasing the primary endpoint results before the targeted number of 138 events has been reached. In this latter situation, *after* the Data Review Board accepts the iDMC recommendation, the Sponsor will be unblinded to the study results and a full data package would be prepared for discussion with regulatory authorities.

If OS is statistically significant at the interim analysis and with reference to the Data Review Board decision, the Sponsor has to perform the remaining analyses for submission. The first key secondary endpoint at the interim and final analysis will be performed for PFS IRC.

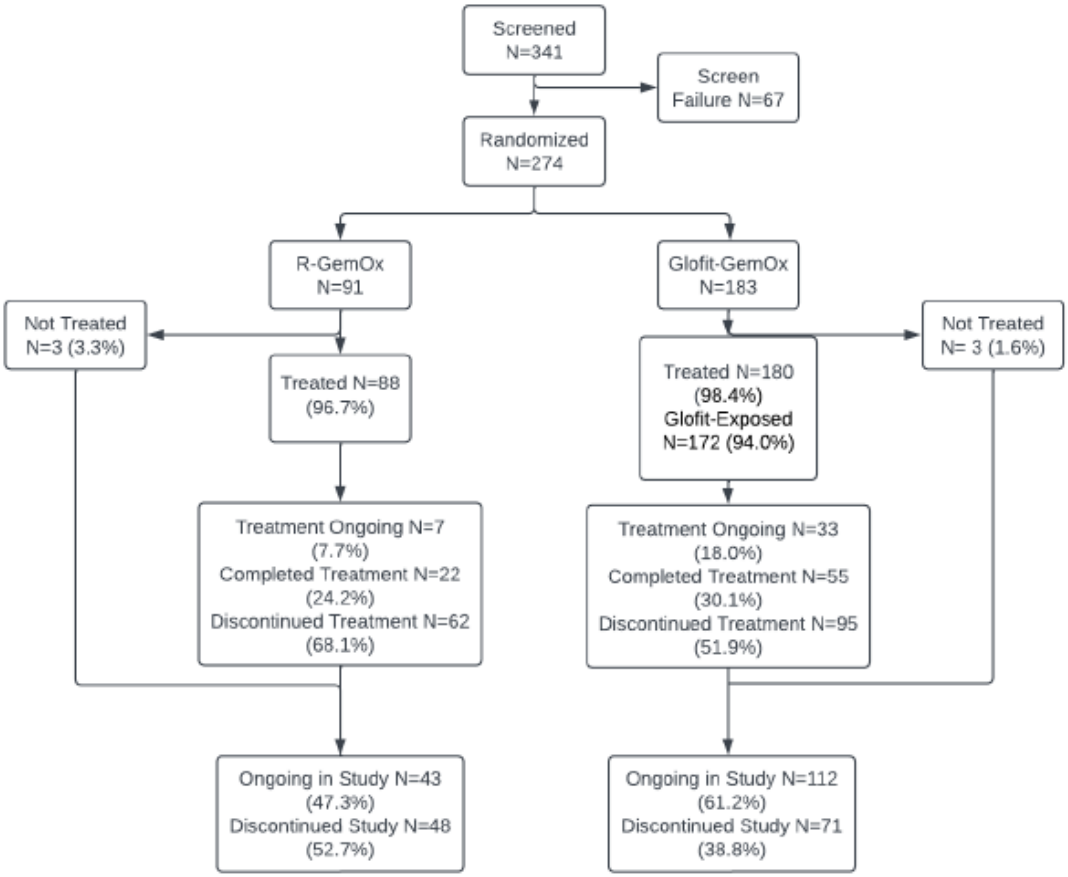
SAP amendments

No major changes were made to the planned analyses for the study. Minor adjustments were introduced to improve clarity and consistency, including additional analyses to assess the impact of the COVID-19 pandemic.

Results

Participant flow

Figure 13 Participant flow (at primary analysis)



Exposure

The median exposure to study treatment in the Glofit-GemOx arm was 162.0 days glofitamab-exposure in the Glofit-GemOx arm vs. compared to the R-GemOx arm 54.0 days rituximab-exposure in the R-GemOx arm at the time of primary analysis. Similarly, longer exposure to the chemotherapy backbone was seen in the Glofit-GemOx arm compared to the R-GemOx arm. According to the MAH, the difference in exposure was largely driven by an increased risk of progressive disease in the R-GemOx arm, so this appears to be an issue of efficacy rather than safety. The difference in risk of IRC-assessed PFS events (death or progression) supports the assertion by the MAH: at the time of primary analysis, 68/183 (37.2%) patients in the Glofit-GemOx arm and 44/91 patients (48.4%) in the R-GemOx arm had a PFS event.

Recruitment

Of the 274 patients enrolled, 183 patients were randomised to receive Glofit-GemOx, and 91 patients were randomised to receive R-GemOx. The study was conducted at 62 centers that enrolled patients: Australia (6 centers), Belgium (2 centers), Switzerland (2 centers), China (8 centers), Germany (3 centers), Denmark (2 centers), Spain (5 centers), France (5 centers), United Kingdom (5 centers), Republic of Korea (6 centers), Poland (5 centers), Taiwan (3 centers) and USA (10 centers). The number of patients enrolled per country, including their respective randomization, in descending order was as follows:

Europe:

– France (20 patients [Glofit-GemOx: N = 14, R-GemOx: N = 6])

– Poland (18 patients [Glofit-GemOx: N = 13, R-GemOx: N = 5])

– Spain (16 patients [Glofit-GemOx: N = 13, R-GemOx: N = 3])

– United Kingdom (16 patients [Glofit-GemOx: N = 11, R-GemOx: N = 5])

– Denmark (6 patients [Glofit-GemOx: N = 5, R-GemOx: N = 1])

– Germany (6 patients [Glofit-GemOx: N = 4, R-GemOx: N = 2])

– Belgium (3 patients [Glofit-GemOx: N = 1, R-GemOx: N =2])

– Switzerland (3 patients [Glofit-GemOx: N = 1, R-GemOx: N = 2])

North America:

– USA (25 patients [Glofit-GemOx: N = 15, R-GemOx: N = 10])

Rest of World:

– China (80 patients [Glofit-GemOx: N = 55, R-GemOx: N = 25])

– Republic of Korea (37 patients [Glofit-GemOx: N = 21, R-GemOx: N = 16])

– Australia (30 patients [Glofit-GemOx: N = 22, R-GemOx: N = 8])

– Taiwan (14 patients [Glofit-GemOx: N = 8, R-GemOx: N = 6])

A total of 33.9% of patients in Glofit-GemOx arm and 28.6% of patients in the R-GemOx arm were enrolled in European centers, and 8.2% of patients in Glofit-GemOx arm and 11.0% of patients in the R-GemOx arm were enrolled in North American centers. In the Rest of the World, 57.9% of patients were enrolled in the Glofit-GemOx arm and 60.4% of patients in the R-GemOx arm.

The first patient was enrolled on 23 February 2021 and the last patient enrolled on 14 March 2023. At the time of the primary analysis (CCOD 29 MAR 2023), the median duration of follow-up in the ITT population overall was 11.3 (95% CI: 9.6, 12.7) months.

Conduct of the study

Table 18 Key protocol changes for ***Study GO41944 (versions 2 to 6)***

Protocol Version	Summary of Key Changes
Global Version 2 19 November 2020	• Eligibility criteria were updated: – Definitions of refractory and relapsed were modified – Prior treatment with R-GemOx or GemOx was added to the exclusion criteria • Requirement for dexamethasone as a premedication prior to glofitamab was added • Hospitalization requirements for Cycle 1 Day 15 and Cycle 2 Day 1 were removed except in patients with an event of Grade ≥2 CRS associated with the preceding dose of glofitamab who were hospitalized at least overnight for the next dose of glofitamab. • The requirement for primary prophylaxis with G-CSF in every GemOx cycle was revised to require primary prophylaxis only in Cycles 1 and 2. In subsequent cycles, the use of G-CSF was optional in patients who did not have therapy delays due to neutropenia. • Recommendations for the management of CNS toxicity were updated so that in case of neurologic events or signs, dexamethasone, instead of methylprednisolone, was administered. • As CRS is primarily a first-dose phenomenon across glofitamab studies, the protocol was amended to allow investigators the discretion not to administer steroid premedication once patients had tolerated two 30 mg doses of glofitamab without CRS. • Additional guidelines for the management of CRS were added, including: – Recommendation to administer tocilizumab for Grade 1 CRS for patients with significant symptoms of CRS besides fever; for patients with increased risk of complications from more severe grades of CRS; and for patients with prior Grade ≥2 CRS – For Grade 2 CRS that occurs during a glofitamab infusion, the infusion was discontinued and not resumed the infusion when symptoms resolve – For CRS Grades 2, 3, or 4, hospitalize patient for next glofitamab dose • Language for benefit-risk assessment in the setting of the COVID-19 pandemic was added • As symptoms of COVID-19 and severe CRS may overlap, language was updated to recommend testing for COVID-19 infection for patients who developed severe CRS during the study course. • Recommendation regarding screening for active infections in the setting of a pandemic was added • Additional key changes specific to the Protocol, v2 (United Kingdom): – MHRA feedback incorporated to update exclusion criteria to remove wording that permits eligibility after discussion with the Medical Monitor • Adverse event reporting period was updated to 35 days based on 5 times the half-life of glofitamab • Additional key changes specific to the Protocol, v2 (Germany): – Exclusion criterion added to exclude patients who are candidates for CAR-T-cell therapy

Protocol Version	Summary of Key Changes
Global Version 3 29 March 2021	• To limit the percentage of patients enrolled with platinum-refractory disease with low likelihood of responding to the control arm, patients refractory to ICE, DHAP, DHAC, or GDP (with/without rituximab) were required to comprise <20% of the study population. • To ensure that the study enrolled an adequate number of patients with only 1 prior line of therapy, patients with 2 or more prior lines of therapy were limited to ≤65%. • Text updated to specific that at Cycle 3 and beyond, if the patient has not had CRS with prior cycles and has tolerated the preceding glofitamab infusion with no signs or symptoms of CRS, the window of observation could be shortened based on the discretion of the investigator • To monitor for a possible class-effect for bispecific antibodies, any grade pneumonitis or interstitial lung disease (excluding pneumonia of infectious etiology) was added as an AESI. • The adverse event reporting period was extended to 35 days, based on 5 times the half-life of glofitamab. • A non-binding futility analysis based on OS was added • Additional key changes specific to the Protocol, v3 (France), in response to feedback from ANSM – Exclusion criteria added to exclude patients who are candidates for CAR-T-cell therapy
Global Version 4 25 October 2021	• Eligibility criteria were updated: – The exclusion criterion for cardiovascular disease was expanded to exclude patients with extensive cardiovascular disease in the investigator's assessment. Patients with New York Heart Association Objective Assessment Class C or D were excluded, so that patients with this degree of objective evidence of heart failure independent of symptoms were not eligible. – The exclusion criteria regarding maximum corticosteroid dosage permitted and the duration and dosage of systemic steroids prior to study entry was updated. • The required primary prophylaxis with G-CSF in Cycles 1 and 2 was allowed to be omitted at the investigator's discretion for patients with a history of hyperleukocytosis. • Concomitant administration of COVID-19 vaccines with glofitamab was added as a permitted therapy and a benefit–risk assessment on concomitant administration of COVID-19 vaccines with glofitamab was added. • Potential risks of glofitamab were updated based on nonclinical and clinical evidence: – Tumor lysis syndrome (TLS) and infection were upgraded from a potential risk to an identified risk of glofitamab. – Colitis was added as a new potential risk. Colitis of any grade (excluding infectious etiology) was added as an adverse event of special interest. • Instructions added that study treatment should not be administered to patients with active infections unless the infection is considered minor by the investigator and patients did not have systemic symptoms.

Protocol Version	Summary of Key Changes
Global Version 5 16 August 2022	• Amendment to incorporate initial iDMC-recommended modifications regarding SARS-CoV-2 infections in study patients subsequent to issuance of Urgent Safety Measure Dear Investigator Letter (USM DIL). The modifications are summarized below: – Patients diagnosed with SARS-CoV-2 infection in the 6 months prior to the first dose of study treatment must have had no persistent respiratory symptoms, must have had no evidence of pneumonia on chest CT, and must have had a negative PCR – Patients diagnosed with SARS-CoV-2 infection within 30 days prior to the first dose of study treatment were not eligible – Patients who develop documented SARS-CoV-2 infection during the study must permanently discontinue study treatment • This protocol was not submitted to health authorities or sites because the iDMC issued superseding recommendations shortly after protocol publication.
Global Version 6 20 September 2022	• Amendment to incorporate changes from Protocol Version 5 (not submitted), and modifications based on additional guidance provided by the iDMC on 2 September 2022, which are summarized below: – Patients diagnosed with SARS-CoV-2 infection in the 6 months prior to the first dose of study treatment had to have no persistent respiratory symptoms, a negative PCR, and no evidence of pneumonia on chest CT. – Patients diagnosed with SARS-CoV-2 infection within 30 days prior to the first dose of study treatment were not eligible. A requirement for a negative SARS-CoV-2 antigen PCR test within 7 days prior to enrollment was added. – Patients who developed documented SARS-CoV-2 infection during the study had to permanently discontinue study treatment. – Benefit-risk assessment for SARS-CoV-2 has been amended to strengthen the caution for potential risk – Recommendations for the use of all appropriate SARS-CoV-2 prophylactic and therapeutic interventions were added The Protocol, v6 (France) and the Protocol, v6 (Germany) incorporated the same changes as the global amendment v6. Additional key changes in the Protocol, v7 (France), to incorporate safety information updates requested from the French National Agency for Medicines: • Language was modified to align vaccination status per French National guidance/recommendations • Added requirement for SARS-CoV-2 PCR testing and negative result within 48 hours before study treatment administration at each treatment cycle • Language was modified to align prophylaxis and treatment of COVID-19 infections per French National guidance/recommendations

AESI = adverse event of special interest; ANSM = Agence nationale de sécurité du médicament et des produits de santé; CAR = chimeric antigen receptor; CNS = central nervous system; COVID-19 = coronavirus disease 2019; CRS = cytokine release syndrome; HBV = hepatitis B virus; CT = computed tomography; DHAP; G-CSF = granulocyte colony-stimulating factor; GemOx = gemcitabine and oxaliplatin; OS = overall survival; PCR = polymerase chain reaction; R-GemOx = rituximab in combination with GemOx; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; TLS = tumor lysis syndrome

Table 19 Summary of major protocol deviations (ITT population)

	R-GemOx (N=91)	Glofit-GemOx (N=183)	All Intent-to-Treat Patients (N=274)
Total number of patients with at least one major protocol deviation	32 (35.2%)	90 (49.2%)	122 (44.5%)
Total number of major protocol deviations	43	164	207
Administration of glofit 30 mg dose > 7 days before or after planned next dose	0	23 (12.6%)	23 (8.4%)
>2 PK, ADA, Biomarker samples missed or out of window for a given cycle	1 (1.1%)	18 (9.8%)	19 (6.9%)
Omission of safety monitoring assessments required by protocol	9 (9.9%)	10 (5.5%)	19 (6.9%)
Failure to report SAE, AESI, pregnancy within 24 hours of knowledge of the event	2 (2.2%)	16 (8.7%)	18 (6.6%)
Failure to administer protocol-mandated premedication	3 (3.3%)	13 (7.1%)	16 (5.8%)
Omission of assessments for eligibility criteria	8 (8.8%)	7 (3.8%)	15 (5.5%)
Incorrect stratification	4 (4.4%)	8 (4.4%)	12 (4.4%)
Tumor assessment not done per protocol during screening, on treatment, or end of treatment	4 (4.4%)	8 (4.4%)	12 (4.4%)
Missed response assessment during study treatment period including end of treatment, per the SOA	3 (3.3%)	5 (2.7%)	8 (2.9%)
Administration of glofitamab step-up dose > 2 days before or after planned next dose	0	5 (2.7%)	5 (1.8%)
Failure to obtain informed consent or obtaining informed consent after initiation of study procedure	2 (2.2%)	2 (1.1%)	4 (1.5%)
More than one missed response assessment during the study follow-up period, per the SoA	2 (2.2%)	2 (1.1%)	4 (1.5%)
Use of expired, contaminated or quarantined IMP	0	4 (2.2%)	4 (1.5%)

	R-GemOx (N=91)	Glofit-GemOx (N=183)	All Intent-to-Treat Patients (N=274)
Administration of incorrect dose of study drug (deviation from planned dose >20%)	1 (1.1%)	2 (1.1%)	3 (1.1%)
Any protocol deviation from exclusion criteria	1 (1.1%)	2 (1.1%)	3 (1.1%)
Continued treatment with study drug after AE, PD, or other protocol reason to discontinue tx	0	3 (1.6%)	3 (1.1%)
Failure to take protocol required action, such as dose delays, in response to toxicity	0	3 (1.6%)	3 (1.1%)
Repeated minor deviations that present a risk to safety of the patient	1 (1.1%)	2 (1.1%)	3 (1.1%)
Use of invalid or unapproved ICF	0	3 (1.6%)	3 (1.1%)
Any protocol deviation from inclusion criteria	0	2 (1.1%)	2 (0.7%)
Loss, theft, or mishandling of IMP at site	0	2 (1.1%)	2 (0.7%)
Administration of incorrect study medication	1 (1.1%)	0	1 (0.4%)
Error in glofitamab dosing >10% above or below planned dose	0	1 (0.5%)	1 (0.4%)
Missed assessment of survival status during the follow-up period, per the SoA	1 (1.1%)	0	1 (0.4%)

Percentages are of the total number of patients in the analysis population, as given in the column headings. For frequency counts by deviation, multiple occurrences of the same deviation in an individual are counted only once. For the total number of deviations, multiple occurrences of the same deviation in an individual are counted separately.

Baseline data

Table 20 Summary of Demographic Data and Baseline Characteristics: Study GO41944 Primary Analysis (ITT Population)

	R-GemOx (N=91)	Glofit-GemOx (N=183)	All Intent-to-Treat Patients (N=274)
Age (yr)			
n	91	183	274
Mean (SD)	63.8 (14.1)	65.7 (12.3)	65.0 (13.0)
Median	68.0	68.0	68.0
Min - Max	20 - 84	22 - 88	20 - 88
Age Group			
n	91	183	274
<65	35 (38.5%)	67 (36.6%)	102 (37.2%)
>=65	56 (61.5%)	116 (63.4%)	172 (62.8%)
Sex			
n	91	183	274
Male	53 (58.2%)	105 (57.4%)	158 (57.7%)
Female	38 (41.8%)	78 (42.6%)	116 (42.3%)
Ethnicity			
n	91	183	274
Hispanic or Latino	5 (5.5%)	11 (6.0%)	16 (5.8%)
Not Hispanic or Latino	82 (90.1%)	160 (87.4%)	242 (88.3%)
Not Stated	3 (3.3%)	12 (6.6%)	15 (5.5%)
Unknown	1 (1.1%)	0	1 (0.4%)
Race			
n	91	183	274
Asian	51 (56.0%)	86 (47.0%)	137 (50.0%)
Black or African American	1 (1.1%)	2 (1.1%)	3 (1.1%)
White	33 (36.3%)	82 (44.8%)	115 (42.0%)
Unknown	6 (6.6%)	13 (7.1%)	19 (6.9%)
Weight (kg)			
n	88	180	268
Mean (SD)	68.15 (15.16)	69.48 (16.29)	69.04 (15.91)
Median	66.15	67.00	66.60
Min - Max	41.6 - 110.0	41.8 - 136.0	41.6 - 136.0
Height (cm)			
n	88	180	268
Mean (SD)	165.48 (10.24)	165.12 (9.71)	165.24 (9.87)
Median	165.85	164.25	165.00
Min - Max	140.7 - 192.0	143.0 - 195.0	140.7 - 195.0
Body Mass Index (kg/m2) at Baseline			
n	88	180	268
Mean (SD)	24.78 (4.56)	25.37 (5.00)	25.18 (4.86)
Median	24.18	24.21	24.21
Min - Max	15.2 - 44.2	16.5 - 45.7	15.2 - 45.7
Body Surface Area (m2) at Baseline			
n	88	179	267
Mean (SD)	1.75 (0.23)	1.77 (0.23)	1.76 (0.23)
Median	1.72	1.72	1.72
Min - Max	1.3 - 2.3	1.3 - 2.7	1.3 - 2.7
ECOG Status at Baseline			
0	44 (50.0%)	72 (40.0%)	116 (43.3%)
1	36 (40.9%)	89 (49.4%)	125 (46.6%)
2	8 (9.1%)	19 (10.6%)	27 (10.1%)

Table 21 Summary of baseline disease characteristics (ITT population)

	R-GemOx (N=91)	Glofit-GemOx (N=183)	All Intent-to-Treat Patients (N=274)
Number of previous lines of systemic therapy for DLBCL (IxRS)			
n	91	183	274
1	57 (62.6%)	115 (62.8%)	172 (62.8%)
>=2	34 (37.4%)	68 (37.2%)	102 (37.2%)
Relapsed/refractory to last line of therapy (IxRS)			
n	91	183	274
Refractory	54 (59.3%)	112 (61.2%)	166 (60.6%)
Relapsed	37 (40.7%)	71 (38.8%)	108 (39.4%)
Relapse or Refractory to Any Prior Therapy			
n	91	183	274
Refractory	58 (63.7%)	124 (67.8%)	182 (66.4%)
Relapse (No Refractory)	33 (36.3%)	59 (32.2%)	92 (33.6%)
Relapse or Refractory to First Line of Prior Therapy			
n	91	183	274
Refractory	47 (51.6%)	105 (57.4%)	152 (55.5%)
Relapse	44 (48.4%)	78 (42.6%)	122 (44.5%)
Relapse or Refractory to Any Prior Platinum Therapy			
n	91	183	274
Refractory	19 (20.9%)	32 (17.5%)	51 (18.6%)
Platinum Responsive	5 (5.5%)	11 (6.0%)	16 (5.8%)
No Prior Platinum	67 (73.6%)	140 (76.5%)	207 (75.5%)
Relapse or Refractory to Any Prior Anti-CD20 Therapy			
n	91	183	274
Refractory	54 (59.3%)	115 (62.8%)	169 (61.7%)
Relapse (No Refractory)	35 (38.5%)	64 (35.0%)	99 (36.1%)
Unknown	2 (2.2%)	4 (2.2%)	6 (2.2%)
Primary Refractory or Relapse within 12 months after Initial Diagnosis Date			
n	91	183	274
No	39 (42.9%)	71 (38.8%)	110 (40.1%)
Yes	52 (57.1%)	112 (61.2%)	164 (59.9%)

	R-GemOx (N=91)	Glofit-GemOx (N=183)	All Intent-to-Treat Patients (N=274)
Primary Refractory or Relapse within 12 months after 1L Therapy			
n	91	183	274
No	28 (30.8%)	49 (26.8%)	77 (28.1%)
Yes	63 (69.2%)	134 (73.2%)	197 (71.9%)
Early relapse from ASCT (PD <= 12 months from completion)			
n	91	183	274
No	1 (1.1%)	4 (2.2%)	5 (1.8%)
Yes	2 (2.2%)	4 (2.2%)	6 (2.2%)
No prior ASCT	88 (96.7%)	175 (95.6%)	263 (96.0%)
Double refractory to any prior anti-CD20 and anthracycline based regimen			
n	91	183	274
Refractory	45 (49.5%)	90 (49.2%)	135 (49.3%)
Relapse (No Refractory)	33 (36.3%)	62 (33.9%)	95 (34.7%)
Unknown	13 (14.3%)	31 (16.9%)	44 (16.1%)
Cancer Histological subtype at Initial Diagnosis			
n	83	175	258
Non-GCB	7 (7.7%)	14 (7.7%)	21 (7.7%)
Unclassified	40 (44.0%)	89 (48.6%)	129 (47.1%)
GCB	27 (29.7%)	54 (29.5%)	81 (29.6%)
ABC	7 (7.7%)	16 (8.7%)	23 (8.4%)
Unknown	2 (2.2%)	2 (1.1%)	4 (1.5%)
Ann Arbor Staging at Study Entry			
n	90	182	272
Stage I	8 (8.8%)	19 (10.4%)	27 (9.9%)
Stage II	12 (13.2%)	40 (21.9%)	52 (19.0%)
Stage III	8 (8.8%)	23 (12.6%)	31 (11.3%)
Stage IV	62 (68.1%)	100 (54.6%)	162 (59.1%)
Prior autologous SCT			
n	91	183	274
No	88 (96.7%)	175 (95.6%)	263 (96.0%)
Yes	3 (3.3%)	8 (4.4%)	11 (4.0%)

	R-GemOx (N=91)	Glofit-GemOx (N=183)	All Intent-to-Treat Patients (N=274)
Primary Reason for SCT ineligibility			
n	89	182	271
AGE	25 (27.5%)	63 (34.4%)	88 (32.1%)
AGE >= 70 YEARS	13 (14.3%)	15 (8.2%)	28 (10.2%)
CO-MORBIDITY: CARDIAC DYSFUNCTION AND NON-INSULIN DEPENDENT DIABETES	1 (1.1%)	0	1 (0.4%)
CO-MORBIDITY: CARDIAC IMPAIRMENT (IMPAIRED LV FUNCTION)	0	1 (0.5%)	1 (0.4%)
CO-MORBIDITY: CARDIOMYOPATHY	0	1 (0.5%)	1 (0.4%)
CO-MORBIDITY: COMPLICATIONS DURING INDUCTION CHEMOTHERAPY	1 (1.1%)	0	1 (0.4%)
CO-MORBIDITY: CONDITION AFTER GASTROINTESTINAL PERFORATION	0	1 (0.5%)	1 (0.4%)
CO-MORBIDITY: DEPRESSION	0	1 (0.5%)	1 (0.4%)
CO-MORBIDITY: DIABETES	1 (1.1%)	0	1 (0.4%)
CO-MORBIDITY: HYPERTENSION, DIABETES MELLITUS, ARRHYTHMIAS, SINUS NODE DISEASE WITH MAS SEIZURES.	1 (1.1%)	0	1 (0.4%)
CO-MORBIDITY: HYPERTENSION, TYPE 2 DIABETES & HISTORY OF EMBOLIC STROKES.	0	1 (0.5%)	1 (0.4%)
CO-MORBIDITY: SEVERE PRIOR COVID INFECTION & PNEUMONITIS	0	1 (0.5%)	1 (0.4%)
CO-MORBIDITY: UNDERLYING LUNG DISEASE	0	1 (0.5%)	1 (0.4%)
FAILED PRIOR TRANSPLANT	4 (4.4%)	6 (3.3%)	10 (3.6%)
INSUFFICIENT RESPONSE TO SALVAGE THERAPY	11 (12.1%)	15 (8.2%)	26 (9.5%)
LACK OF ACCESS TO TRANSPLANT CENTER	0	2 (1.1%)	2 (0.7%)
OTHER: EXPECTED INSUFFICIENT RESPONSE	1 (1.1%)	0	1 (0.4%)
OTHER: INSUFFICIENT RESPONSE TO INITIAL THERAPY	0	1 (0.5%)	1 (0.4%)
OTHER: IT RECURRED ON MAY 19, 2022 DURING FOLLOW-UP AFTER HEMATOPOIETIC STEM CELL TRANSPLANTATION IN 2018.	0	1 (0.5%)	1 (0.4%)
OTHER: NA AS >= 2 PRIOR LINES OF TREATMENT	0	1 (0.5%)	1 (0.4%)
OTHER: NON-CHEMOSENSITIVE DISEASE	0	1 (0.5%)	1 (0.4%)
OTHER: PATIENT HAD AN INSUFFICIENT RESPONSE TO INITIAL CHEMOTHERAPY.	0	1 (0.5%)	1 (0.4%)
OTHER: PATIENT HAD INSUFFICIENT RESPONSE TO PRE-TRANSPLANT CHEMOTHERAPY	1 (1.1%)	0	1 (0.4%)
OTHER: RISK OF MANY ADVERSE EVENTS	0	1 (0.5%)	1 (0.4%)
OTHER: THE PATIENT REFUSED FOR FINANCIAL REASONS	0	1 (0.5%)	1 (0.4%)
OTHER: THE PATIENT WAS NOT SUITABLE FOR HEMATOPOIETIC STEM CELL TRANSPLANTATION AND HAD PREVIOUSLY RECEIVED 4-LINE CHEMOTHERAPY	0	1 (0.5%)	1 (0.4%)
PATIENT REFUSED TRANSPLANT	30 (33.0%)	64 (35.0%)	94 (34.3%)
PERFORMANCE STATUS	0	2 (1.1%)	2 (0.7%)
Double-Expressor			
n	91	183	274
No	71 (78.0%)	157 (85.8%)	228 (83.2%)
Yes	20 (22.0%)	26 (14.2%)	46 (16.8%)

	R-GemOx (N=91)	Glofit-GemOx (N=183)	All Intent-to-Treat Patients (N=274)
Total number of risk factors for IPI			
n	90	182	272
NOT APPLICABLE	5 (5.5%)	4 (2.2%)	9 (3.3%)
0	3 (3.3%)	16 (8.7%)	19 (6.9%)
1	11 (12.1%)	25 (13.7%)	36 (13.1%)
2	18 (19.8%)	51 (27.9%)	69 (25.2%)
3	30 (33.0%)	46 (25.1%)	76 (27.7%)
4	18 (19.8%)	33 (18.0%)	51 (18.6%)
5	5 (5.5%)	7 (3.8%)	12 (4.4%)
Total number of risk factors for IPI (Derived)			
n	91	183	274
NOT APPLICABLE	6 (6.6%)	14 (7.7%)	20 (7.3%)
0	3 (3.3%)	15 (8.2%)	18 (6.6%)
1	9 (9.9%)	27 (14.8%)	36 (13.1%)
2	28 (30.8%)	41 (22.4%)	69 (25.2%)
3	29 (31.9%)	49 (26.8%)	78 (28.5%)
4	13 (14.3%)	33 (18.0%)	46 (16.8%)
5	3 (3.3%)	4 (2.2%)	7 (2.6%)
Prior CAR-T therapy			
n	91	183	274
No	83 (91.2%)	169 (92.3%)	252 (92.0%)
Yes	8 (8.8%)	14 (7.7%)	22 (8.0%)
Relapse or Refractory to Any Prior CAR-T Therapy			
n	91	183	274
Refractory	6 (6.6%)	14 (7.7%)	20 (7.3%)
Relapse (No Refractory)	2 (2.2%)	0	2 (0.7%)
Unknown	83 (91.2%)	169 (92.3%)	252 (92.0%)
Bulky Disease => 10cm			
n	90	183	273
No	76 (83.5%)	160 (87.4%)	236 (86.1%)
Yes	14 (15.4%)	23 (12.6%)	37 (13.5%)
Cell of Origin			
n	91	183	274
GCB	28 (30.8%)	56 (30.6%)	84 (30.7%)
Non-GCB (by IHC + Non GCB Unclassified)	49 (53.8%)	102 (55.7%)	151 (55.1%)
ABC	2 (2.2%)	3 (1.6%)	5 (1.8%)
Unknown	12 (13.2%)	22 (12.0%)	34 (12.4%)

	R-GemOx (N=91)	Glofit-GemOx (N=183)	All Intent-to-Treat Patients (N=274)
Category Sum of Products of Diameters Value >=3000 - Investigator			
n	86	178	264
Baseline SPD < 3000	44 (48.4%)	102 (55.7%)	146 (53.3%)
Baseline SPD >= 3000	42 (46.2%)	76 (41.5%)	118 (43.1%)
Enrollment by geographic region			
n	91	183	274
Europe	26 (28.6%)	62 (33.9%)	88 (32.1%)
North America	10 (11.0%)	15 (8.2%)	25 (9.1%)
Rest of the World	55 (60.4%)	106 (57.9%)	161 (58.8%)
Anti-CD20 monoclonal antibody therapy			
n	91	183	274
No	2 (2.2%)	4 (2.2%)	6 (2.2%)
Yes	89 (97.8%)	179 (97.8%)	268 (97.8%)

Numbers analysed

Table 22 Analysis populations (All patients)

	R-GemOx (N=91)	Glofit-GemOx (N=183)	All Patients (N=274)
Intent-to-treat Population (IT)			
Inclusion	91 (100%)	183 (100%)	274 (100%)
Safety-Evaluable Population (SE)			
Inclusion	88 (96.7%)	180 (98.4%)	268 (97.8%)
Exclusion	3 (3.3%)	3 (1.6%)	6 (2.2%)
Modified Safety-Evaluable Population (SERO)			
Inclusion	88 (96.7%)	172 (94.0%)	260 (94.9%)
Exclusion	3 (3.3%)	11 (6.0%)	14 (5.1%)
PK-Evaluable (PKP)			
Inclusion	0	165 (90.2%)	165 (60.2%)
Exclusion	91 (100%)	18 (9.8%)	109 (39.8%)
Immunogenicity (ADAP)			
Inclusion	0	156 (85.2%)	156 (56.9%)
Exclusion	91 (100%)	27 (14.8%)	118 (43.1%)

Patients are presented in the Planned Treatment group.
ITT - All randomized patients, whether or not the patient received the assigned treatment.
Safety-evaluable - Patients who receive any amount of any study treatment.
Modified Safety-evaluable - Patients who receive at least one dose of Rituximab in the R-GemOx arm and patients who receive at least one dose of Obinutuzumab plus at least one dose of Glofitamab in the Glofit-GemOx arm.
PK-evaluable - All patients who receive at least 1 dose of study treatment in the Glofit-GemOx arm and have at least 1 post-dose Glofitamab concentration result.
Immunogenicity - All patients who have at least 1 predose and 1 post-dose ADA assessment.

Outcomes and estimation

Primary endpoint – Overall survival

Table 23 Summary of Overall Survival: Study GO41944 (ITT Population)

	Primary Analysis CCOD: 29 March 2023		Updated Analysis CCOD: 16 February 2024	
	R-GemOx (N=91)	Glofit-GemOx (N=183)	R-GemOx (N=91)	Glofit-GemOx (N=183)
Primary Efficacy Endpoint: Overall Survival				
Patients with event, n (%)	40 (44.0%)	61 (33.3%)	52 (57.1%)	80 (43.7%)
Median, months (95% CI)	9.0 (7.3, 14.4)	NE (13.8, NE)	12.9 (7.9, 18.5)	25.5 (18.3, NE)
Stratified HR (95% CI)	0.59 (0.40, 0.89)		0.62 (0.43, 0.88)	
p-value (log-rank)	0.010706		0.0006366[a]	

CCOD = clinical cutoff date; CI = confidence interval; Glofit-GemOx = glofitamab in combination with gemcitabine and oxaliplatin; HR = hazard ratio; R-GemOx = rituximab in combination with gemcitabine and oxaliplatin.

[a] As the primary analysis of OS crossed the pre-specified stopping boundary, the p-value for the updated analysis is considered descriptive.

Figure 14 Kaplan-Meier Plot of Overall Survival: Study GO41944 Primary Analysis (ITT Population)

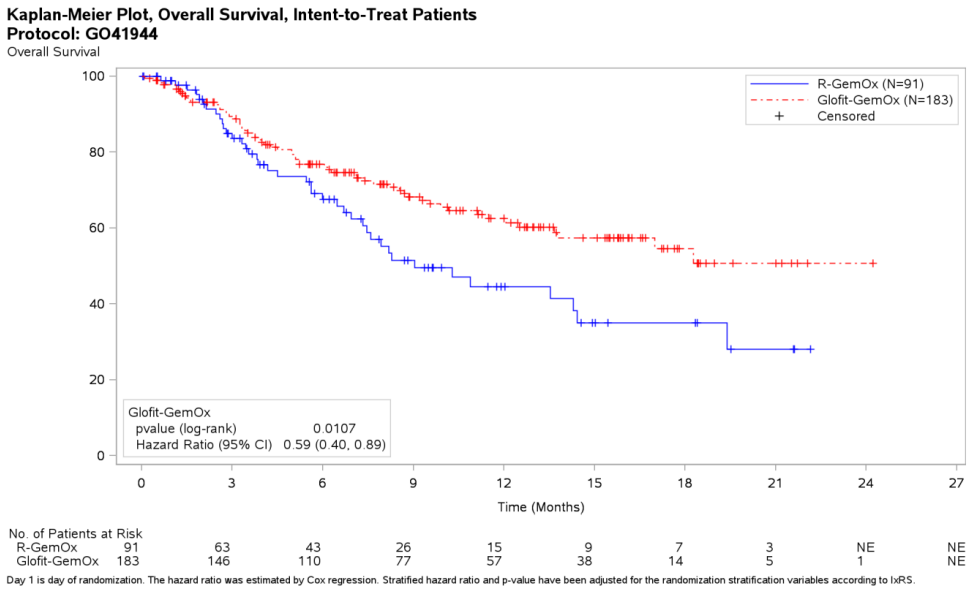
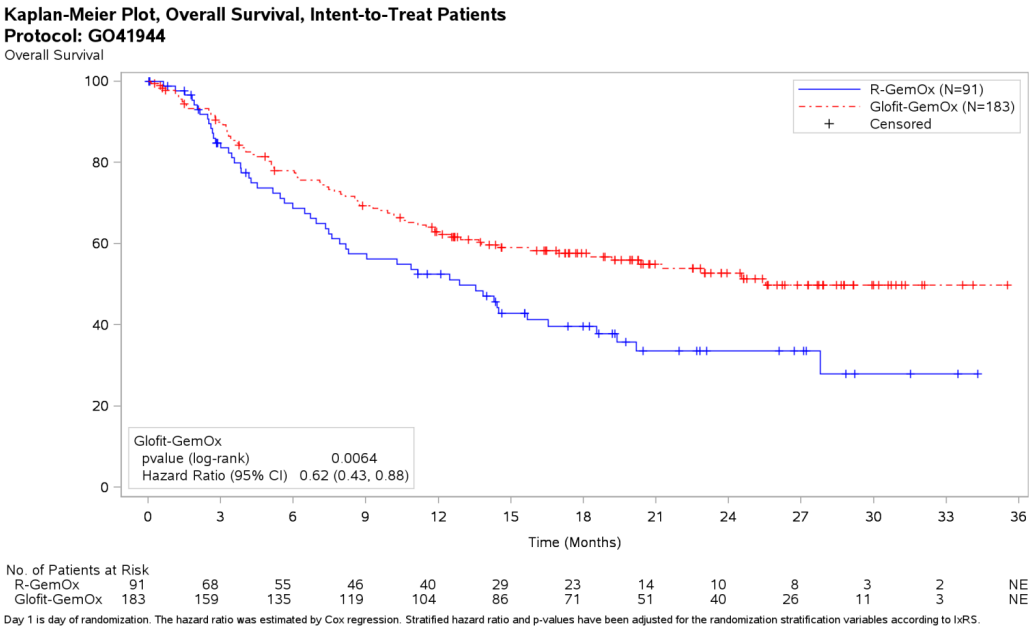


Figure 15 Kaplan-Meier Plot of Overall Survival: Study GO41944 Updated Analysis (ITT Population)



Key Secondary Endpoint - IRC-Assessed Progression-Free Survival

Table 24 Summary of IRC-Assessed Progression-Free Survival Censored Before NALT: Study GO41944 (ITT Population)

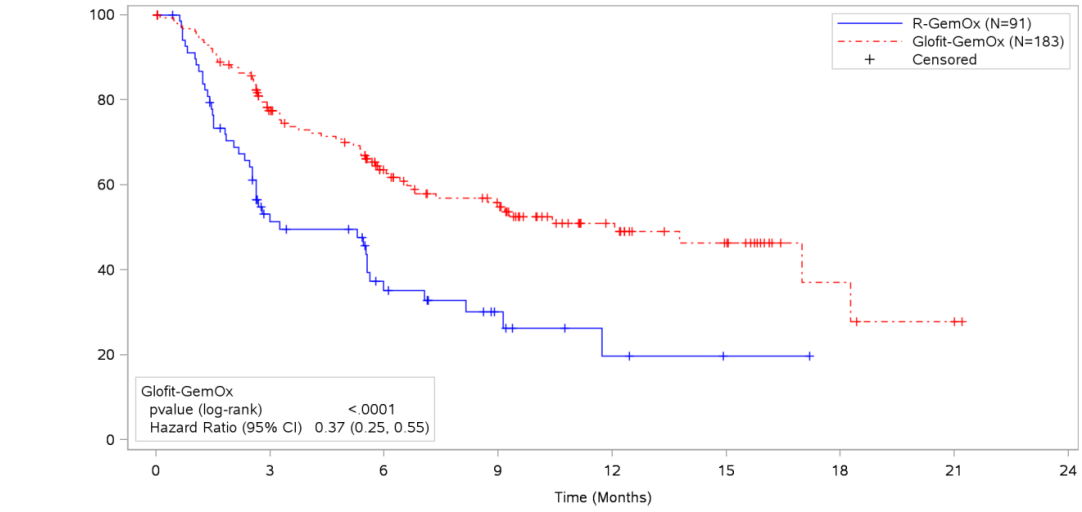
	Primary Analysis CCOD: 29 March 2023		Updated Analysis CCOD: 16 February 2024	
	R-GemOx (N=91)	Glofit-GemOx (N=183)	R-GemOx (N=91)	Glofit-GemOx (N=183)
Secondary Efficacy Endpoint: IRC-Assessed Progression Free Survival				
Patients with event, n (%)	44 (48.4%)	68 (37.2%)	54 (59.3%)	90 (49.2%)
Median, months (95% CI)	3.3 (2.5, 5.6)	12.1 (6.8, 18.3)	3.6 (2.5, 7.1)	13.8 (8.7, 20.5)
Stratified HR (95% CI)	0.37 (0.25, 0.55)		0.40 (0.28, 0.57)	
p-value (log-rank)	< 0.000001		< 0.000001[a]	

CCOD = clinical cutoff date; CI = confidence interval; Glofit-GemOx = glofitamab in combination with gemcitabine and oxaliplatin; HR = hazard ratio; IRC = Independent Review Committee; NE = not estimable; PFS = progression-free survival.

[a] As the primary analysis of IRC-assessed OS crossed the pre-specified stopping boundary, the p-value for the updated efficacy analysis is considered descriptive.

Figure 16 Kaplan-Meier Plot of Progression-Free Survival: IRC-Assessed Censored Before NALT: Study GO41944 Primary Analysis (ITT Population)

Kaplan-Meier Plot, IRC Assessed PFS Censored Before NALT, Intent-to-Treat Patients
Protocol: GO41944
Earliest Contributing Event to Progression Free Survival by IRC - Censored Before NALT



No. of Patients at Risk

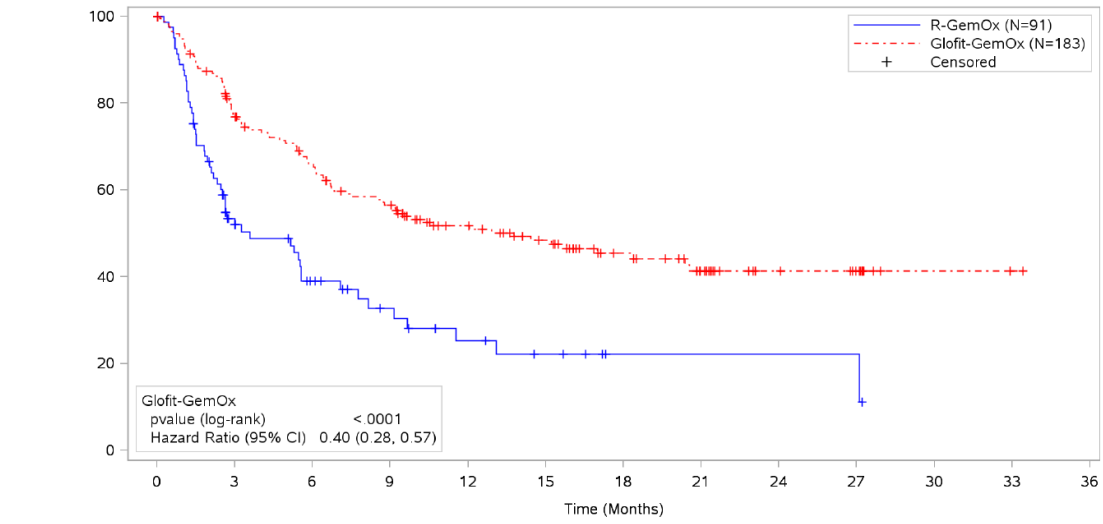
R-GemOx	91	29	16	8	3	1	NE	NE	NE
Glofit-GemOx	183	108	70	52	26	16	4	1	NE

Day 1 is day of randomization. The hazard ratio was estimated by Cox regression. Stratified hazard ratio and p-value have been adjusted for the randomization stratification variables according to IxRS

Program: root/clinical_studies/RO7082859/CDT30295/GO41944/share/data_analysis/prod/program/g_ef_km.sas
Output: root/clinical_studies/RO7082859/CDT30295/GO41944/data_analysis/Interim_Analysis_2023/prod/output/g_ef_km_IRCPFSN_IT_29MAR2023_41944.pdf
18APR2024 10:57

Figure 17 Kaplan-Meier Plot of Progression-Free Survival: IRC-Assessed Censored Before NALT: Study GO41944 Updated Analysis (ITT Population)

Kaplan-Meier Plot, IRC Assessed PFS Censored Before NALT, Intent-to-Treat Patients
Protocol: GO41944
Earliest Contributing Event to Progression Free Survival by IRC - Censored Before NALT



No. of Patients at Risk

R-GemOx	91	34	22	14	9	6	2	2	2	2	NE	NE	NE
Glofit-GemOx	183	130	107	89	66	54	37	26	14	10	2	1	NE

Day 1 is day of randomization. The hazard ratio was estimated by Cox regression. Stratified hazard ratio and p-values have been adjusted for the randomization stratification variables according to IxRS

Program: root/clinical_studies/RO7082859/CDT30295/GO41944/share/data_analysis/prod/program/g_ef_km.sas
Output: root/clinical_studies/RO7082859/CDT30295/GO41944/data_analysis/Follow_Up_Analysis_2024/prod/output/g_ef_km_IRCPFSN_IT_16FEB2024_41944.pdf
23APR2024 12:49

Table 25 ***IRC assessed PFS Censoring by geographic region (Europe, North America, Rest of the world, ITT population)***

	R-GemOx (N=91)		
	Europe (N=26)	North America (N=10)	Rest of World (N=55)
PFS Censor/Event Status			
n	26	10	55
PFS Event (Disease Progression or Death)	13 (50.0%)	3 (30.0%)	38 (69.1%)
Censoring Followed by NALT	6 (23.1%)	3 (30.0%)	10 (18.2%)
Censored to Last Tumor Assessment	5 (19.2%)	2 (20.0%)	3 (5.5%)
Censoring due to Missed Assessments	1 (3.8%)	1 (10.0%)	1 (1.8%)
Censored to Randomization	1 (3.8%)	1 (10.0%)	3 (5.5%)

	Glofit-GemOx (N=183)		
	Europe (N=62)	North America (N=15)	Rest of World (N=106)
PFS Censor/Event Status			
n	62	15	106
PFS Event (Disease Progression or Death)	35 (56.5%)	9 (60.0%)	46 (43.4%)
Censoring Followed by NALT	4 (6.5%)	1 (6.7%)	6 (5.7%)
Censored to Last Tumor Assessment	20 (32.3%)	4 (26.7%)	40 (37.7%)
Censoring due to Missed Assessments	1 (1.6%)	0	11 (10.4%)
Censored to Randomization	2 (3.2%)	1 (6.7%)	3 (2.8%)

Censoring Followed by NALT includes all patients who did not have an event but subsequently received NALT.

Table 26 **Duration of Follow up for OS and PFS (Primary and Update Analysis, ITT Population)**

	Primary Analysis CCOD: 29 March 2023		**Updated Analysis CCOD: 16 February 2024**	
	R-GemOx (N = 91)	Glofit-GemOx (N = 183)	R-GemOx (N = 91)	Glofit-GemOx (N = 183)
Median duration of follow up for OS, months (95% CI)	9.6 (7.9, 12.0)	12.0 (10.2, 13.2)	19.7 (18.0, 23.1)	22.5 (20.0, 24.5)
Median duration of follow up for PFS, months (95% CI)	6.1 (3.4, 8.8)	9.0 (6.2, 9.7)	8.6 (5.9, 14.6)	16.3 (15.3, 20.1)

Key Secondary Endpoint – IRC assessed Complete Response rate

Table 27 Summary of IRC-Assessed Complete Response Rate: Study GO41944 (ITT Population)

	Primary Analysis CCOD: 29 March 2023		**Updated Analysis CCOD: 16 February 2024**	
	R-GemOx (N=91)	**Glofit-GemOx (N=183)**	**R-GemOx (N=91)**	**Glofit-GemOx (N=183)**
Secondary Efficacy Endpoint: IRC-Assessed Complete Response Rate				
Complete Response, n (%) (95% CI)	20 (22.0%) (13.97, 31.88)	92 (50.3%) (42.80, 57.73)	23 (25.3%) (16.75, 35.47)	107 (58.5%) (50.97, 65.69)
Diff. in CR Rate (95% CI)	28.3% (16.30, 40.29)		33.2% (20.94, 45.45)	

p-value (CMH)	< 0.0001	< 0.0001[a]

CCOD = clinical cutoff date; CI = confidence interval; CMH = Cochran-Mantel-Haenszel; CR = complete response; Diff.= difference; Glofit-GemOx = glofitamab in combination with gemcitabine and oxaliplatin; IRC = Independent Review Committee; R-GemOx = rituximab in combination with gemcitabine and oxaliplatin.

[a] As the primary analysis of IRC-assessed OS crossed the pre-specified stopping boundary, the p-value for the updated efficacy analysis are considered descriptive.

Key Secondary Endpoint – Duration of IRC-assessed Complete Response

Table 28 Duration of IRC-Assessed Complete Response: Study GO41944 (Complete Responder Population)

	Primary Analysis CCOD: 29 March 2023		**Updated Analysis CCOD: 16 February 2024**	
	R-GemOx (N=91)	**Glofit-GemOx (N=183)**	**R-GemOx (N=91)**	**Glofit-GemOx (N=183)**
Secondary Efficacy Endpoint: IRC-Assessed Duration of Complete Response				
Complete Response, n (%)	20 (22.0%)	92 (50.3%)	23 (25.3%)	107 (58.5%)
(95% CI)	(13.97, 31.88)	(42.80, 57.73)	(16.75, 35.47)	(50.97, 65.69)
Responders with subsequent event, n (%)	4 (20.0%)	15 (16.3%)	7 (30.4%)	28 (26.2%)
Death	0	8	0	14
Disease Progression	4	7	7	14
Median DOCR -months (95% CI)	NE (6.4, NE)	14.4 (14.4, NE)	24.2 (6.9, NE)	NE (NE)
p-value (log rank)	0.3560		0.2040[a]	
Unstratified HR (95% CI)	0.59 (0.19, 1.83)		0.59 (0.25, 1.35)	

CCOD = clinical cutoff date; CI = confidence interval; CR = complete response; DOCR = duration of complete response; HR = hazard ratio; IRC = Independent Review Committee; NE not estimable; R-GemOx = rituximab in combination with gemcitabine and oxaliplatin.

[a] As the primary analysis of IRC-assessed OS crossed the pre-specified stopping boundary, the p-value for the updated efficacy analysis is considered descriptive.

Figure 18 Kaplan-Meier Plot of Duration of IRC-Assessed Complete Response: Study GO41944 Primary Analysis (Complete Responder Population)

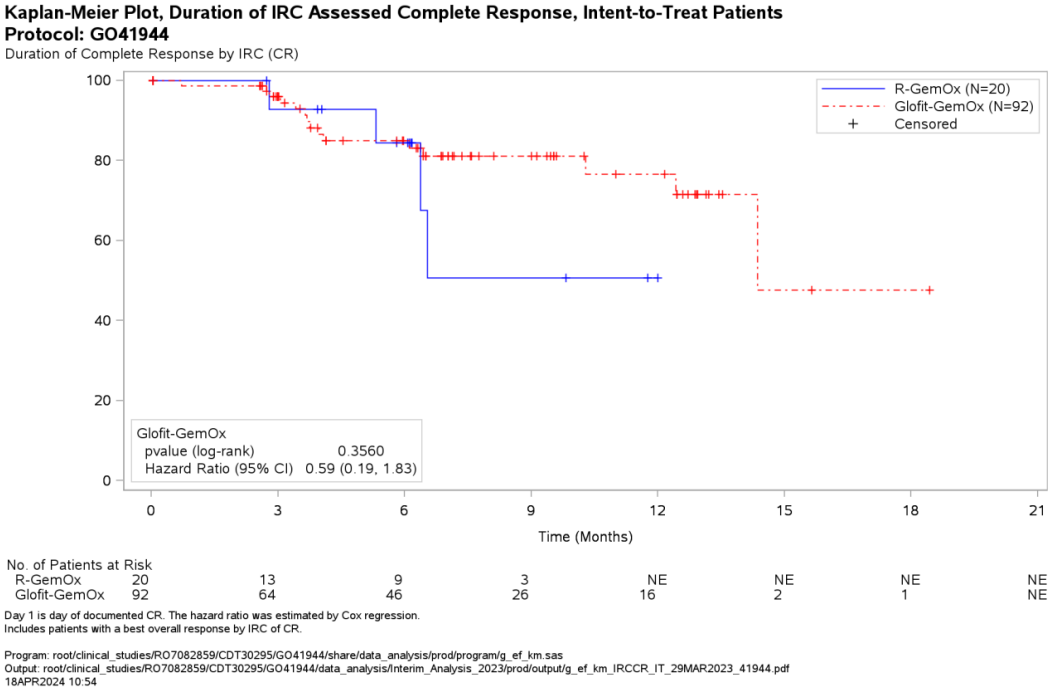
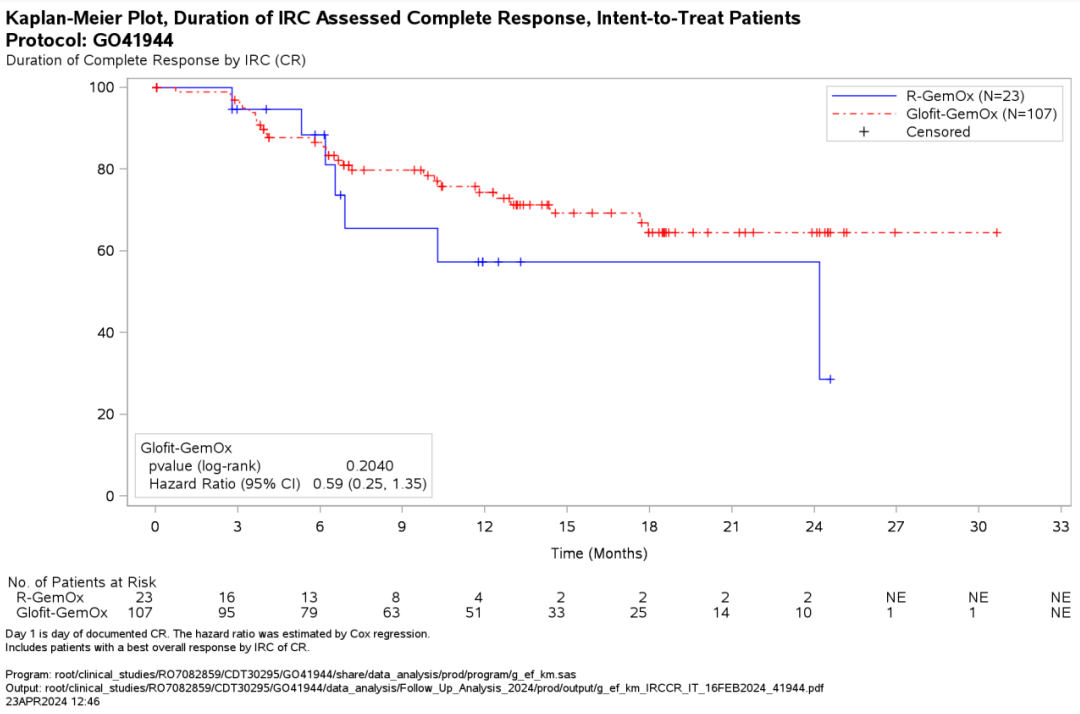


Figure 19 Kaplan-Meier Plot of Duration of IRC-Assessed Complete Response: Study GO41944 Updated Analysis (Complete Responder Population)



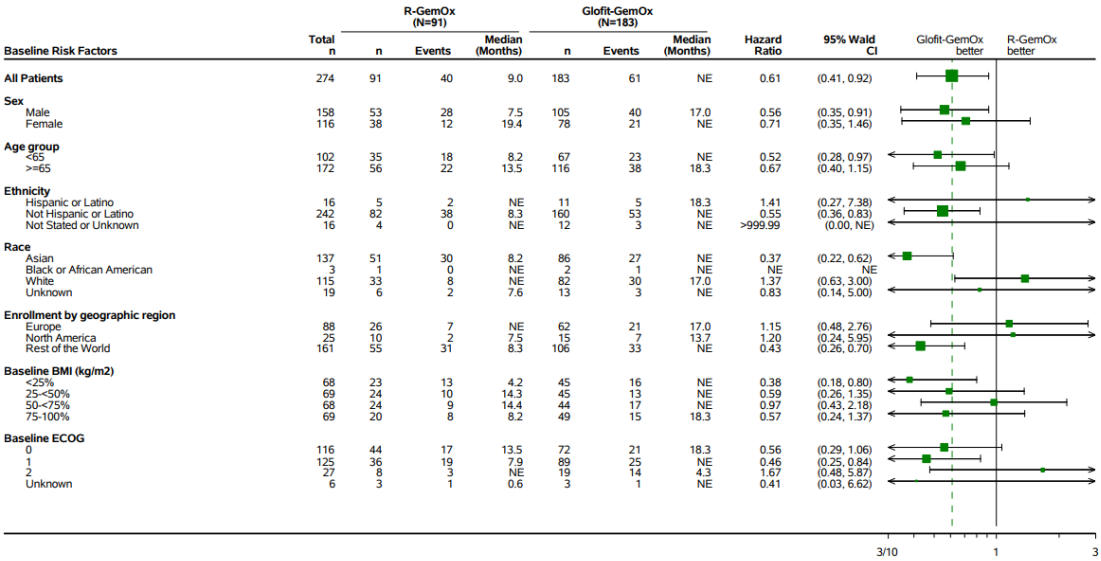
Other Secondary Efficacy Endpoints

Other endpoints tested as part of the GO41944 trial included: Investigator-Assessed Progression-Free Survival, Investigator-Assessed Complete Response Rate, Duration of INV-Assessed Complete Response, IRC-Assessed Objective Response Rate, INV-Assessed Objective Response Rate, Duration of IRC-Assessed Objective Response, Duration of INV-Assessed Objective Response and Patient-Reported Outcomes (PROs). Common to all the listed endpoints is that none of them were multiplicity protected.

Ancillary analyses

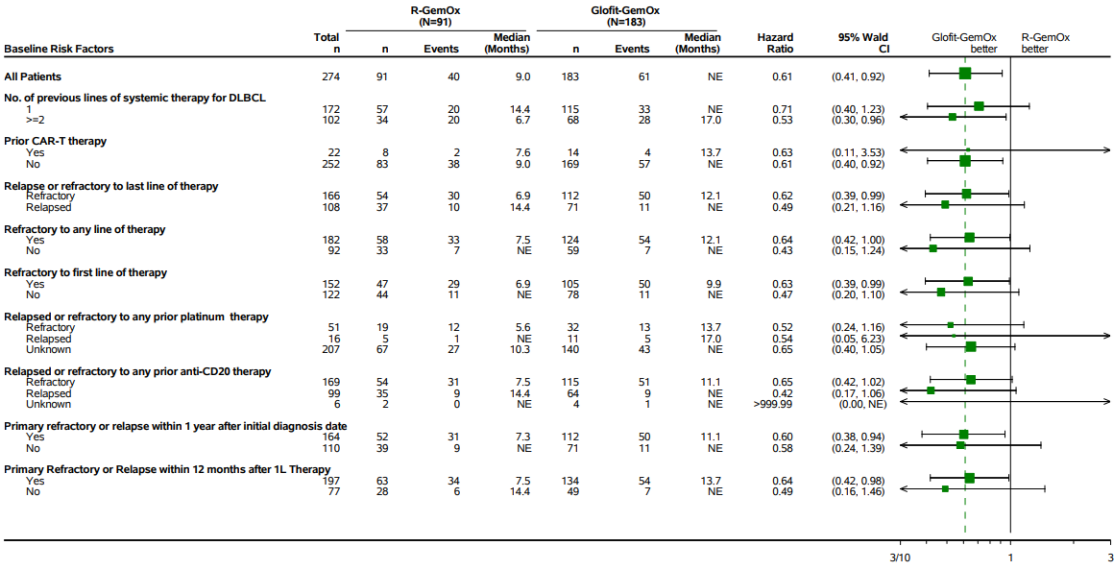
Figure 20 ***Subgroup Analysis of Overall Survival: Study GO41944 Primary Analysis (Unstratified Analysis: ITT Population)***

Forest Plot by Subgroup (Unstratified), Overall Survival, Intent-to-Treat Patients
Protocol: GO41944



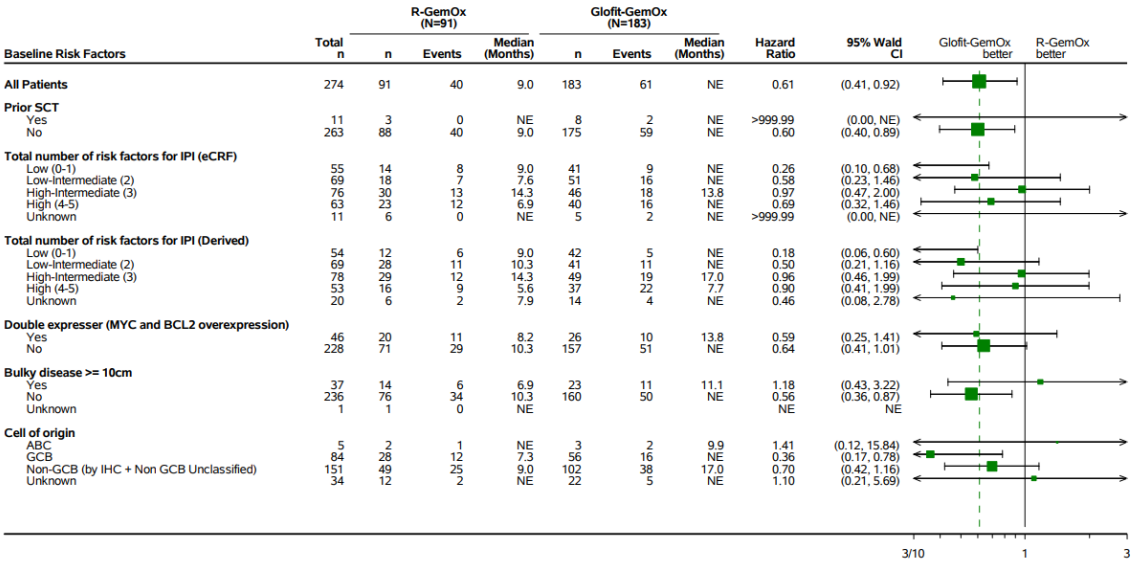
Day 1 is day of randomization. Hazard ratios and the associated Wald confidence intervals were estimated using Cox regression.
The vertical dashed line indicates the hazard ratio for all patients.

Forest Plot by Disease Characteristic Subgroup (Unstratified), Overall Survival, Intent-to-Treat Patients
Protocol: GO41944



Day 1 is day of randomization. Hazard ratios and the associated Wald confidence intervals were estimated using Cox regression.
The vertical dashed line indicates the hazard ratio for all patients.
The size of the symbol is proportional to the size of the population in the subgroup.
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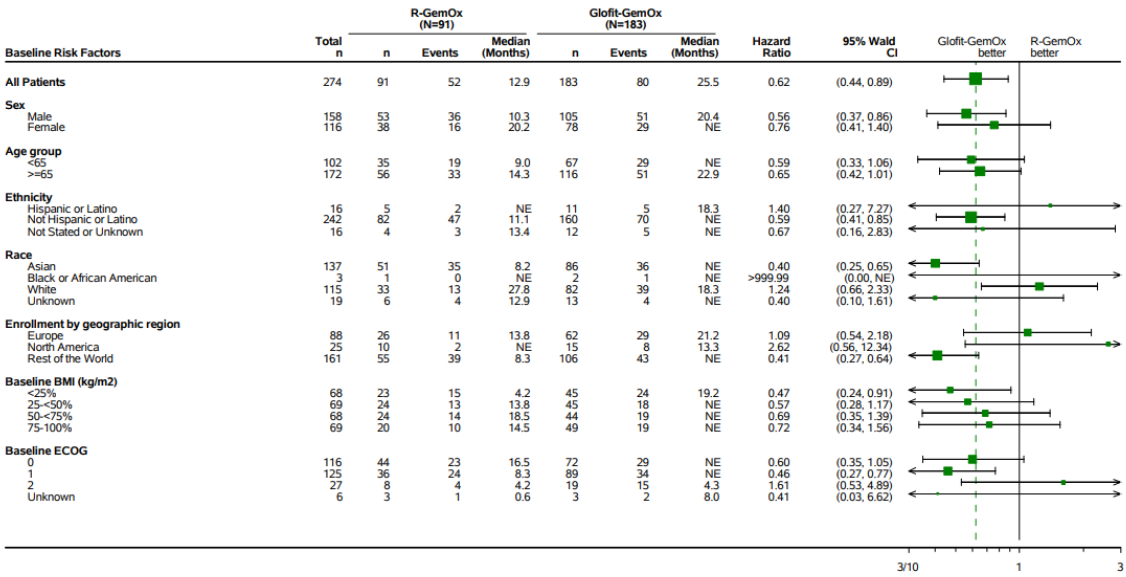
Forest Plot by Subgroup (Unstratified), Overall Survival, Intent-to-Treat Patients
Protocol: GO41944



Baseline Risk Factors	Total n	R-GemOx (N=91) n	Events	Median (Months)	Glofit-GemOx (N=183) n	Events	Median (Months)	Hazard Ratio	95% Wald CI
All Patients	274	91	40	9.0	183	61	NE	0.61	(0.41, 0.92)
Prior SCT									
Yes	11	3	0	NE	8	2	NE	>999.99	(0.00, NE)
No	263	88	40	9.0	175	59	NE	0.60	(0.40, 0.89)
Total number of risk factors for IPI (eCRF)									
Low (0-1)	55	14	8	9.0	41	9	NE	0.26	(0.10, 0.68)
Low-Intermediate (2)	69	18	7	7.6	51	16	NE	0.58	(0.23, 1.46)
High-Intermediate (3)	76	30	13	14.3	46	18	13.8	0.97	(0.47, 2.00)
High (4-5)	63	23	12	6.9	40	16	NE	0.69	(0.32, 1.46)
Unknown	11	6	0	NE	5	2	NE	>999.99	(0.00, NE)
Total number of risk factors for IPI (Derived)									
Low (0-1)	54	12	6	9.0	42	5	NE	0.18	(0.06, 0.60)
Low-Intermediate (2)	69	28	11	10.3	41	11	NE	0.50	(0.21, 1.16)
High-Intermediate (3)	78	29	12	14.3	49	19	17.0	0.96	(0.46, 1.99)
High (4-5)	53	16	9	5.6	37	22	7.7	0.90	(0.41, 1.99)
Unknown	20	6	2	7.9	14	4	NE	0.46	(0.08, 2.78)
Double expresser (MYC and BCL2 overexpression)									
Yes	46	20	11	8.2	26	10	13.8	0.59	(0.25, 1.41)
No	228	71	29	10.3	157	51	NE	0.64	(0.41, 1.01)
Bulky disease >= 10cm									
Yes	37	14	6	6.9	23	11	11.1	1.18	(0.43, 3.22)
No	236	76	34	10.3	160	50	NE	0.56	(0.36, 0.87)
Unknown	1	1	0	NE				NE	NE
Cell of origin									
ABC	5	2	1	NE	3	2	9.9	1.41	(0.12, 15.84)
GCB	84	28	12	7.3	56	16	NE	0.36	(0.17, 0.78)
Non-GCB (by IHC + Non GCB Unclassified)	151	49	25	9.0	102	38	17.0	0.70	(0.42, 1.16)
Unknown	34	12	2	NE	22	5	NE	1.10	(0.21, 5.69)

COO is investigator assessed (not centrally assessed).
Day 1 is day of randomization. Hazard ratios and the associated Wald confidence intervals were estimated using Cox regression.
The vertical dashed line indicates the hazard ratio for all patients.
The size of the symbol is proportional to the size of the population in the subgroup.
Program: root/clinical_studies/RO7082859/CDT30295/GO41944/share/data_analysis/prod/program/g_ef_forest4_unstrat.sas
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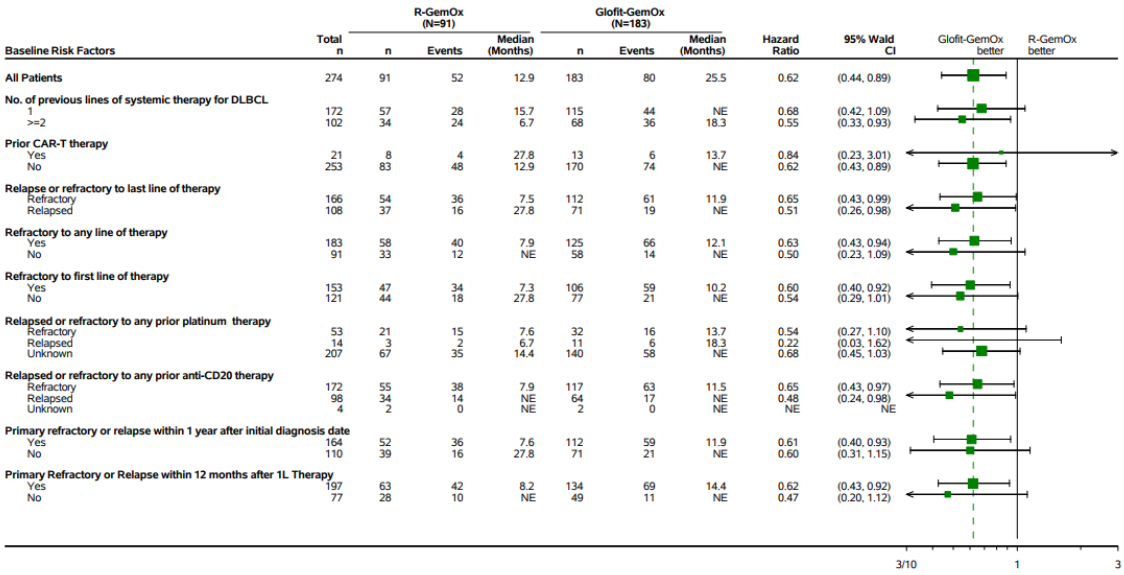
Forest Plot by Subgroup (Unstratified), Overall Survival, Intent-to-Treat Patients
Protocol: GO41944



Baseline Risk Factors	Total n	R-GemOx (N=91) n	Events	Median (Months)	Glofit-GemOx (N=183) n	Events	Median (Months)	Hazard Ratio	95% Wald CI
All Patients	274	91	52	12.9	183	80	25.5	0.62	(0.44, 0.89)
Sex									
Male	158	53	36	10.3	105	51	20.4	0.56	(0.37, 0.86)
Female	116	38	16	20.2	78	29	NE	0.76	(0.41, 1.40)
Age group									
<65	102	35	19	9.0	67	29	NE	0.59	(0.33, 1.06)
>=65	172	56	33	14.3	116	51	22.9	0.65	(0.42, 1.01)
Ethnicity									
Hispanic or Latino	16	5	2	NE	11	5	18.3	1.40	(0.27, 7.27)
Not Hispanic or Latino	242	82	47	11.1	160	70	NE	0.59	(0.41, 0.85)
Not Stated or Unknown	16	4	3	13.4	12	5	NE	0.67	(0.16, 2.83)
Race									
Asian	137	51	35	8.2	86	36	NE	0.40	(0.25, 0.65)
Black or African American	3	1	0	NE	2	1	NE	>999.99	(0.00, NE)
White	115	33	13	27.8	82	39	18.3	1.24	(0.66, 2.33)
Unknown	19	6	4	12.9	13	4	NE	0.40	(0.10, 1.61)
Enrollment by geographic region									
Europe	88	26	11	13.8	62	29	21.2	1.09	(0.54, 2.18)
North America	25	10	2	NE	15	8	13.3	2.62	(0.56, 12.34)
Rest of the World	161	55	39	8.3	106	43	NE	0.41	(0.27, 0.64)
Baseline BMI (kg/m2)									
<25%	68	23	15	4.2	45	24	19.2	0.47	(0.24, 0.91)
25-<50%	69	24	13	13.8	45	18	NE	0.57	(0.28, 1.17)
50-<75%	68	24	14	18.5	44	19	NE	0.69	(0.35, 1.39)
75-100%	69	20	10	14.5	49	19	NE	0.72	(0.34, 1.56)
Baseline ECOG									
0	116	44	23	16.5	72	29	NE	0.60	(0.35, 1.05)
1	125	36	24	8.3	89	34	NE	0.46	(0.27, 0.77)
2	27	8	4	4.2	19	15	4.3	1.61	(0.53, 4.89)
Unknown	6	3	1	0.6	3	2	8.0	0.41	(0.03, 6.62)

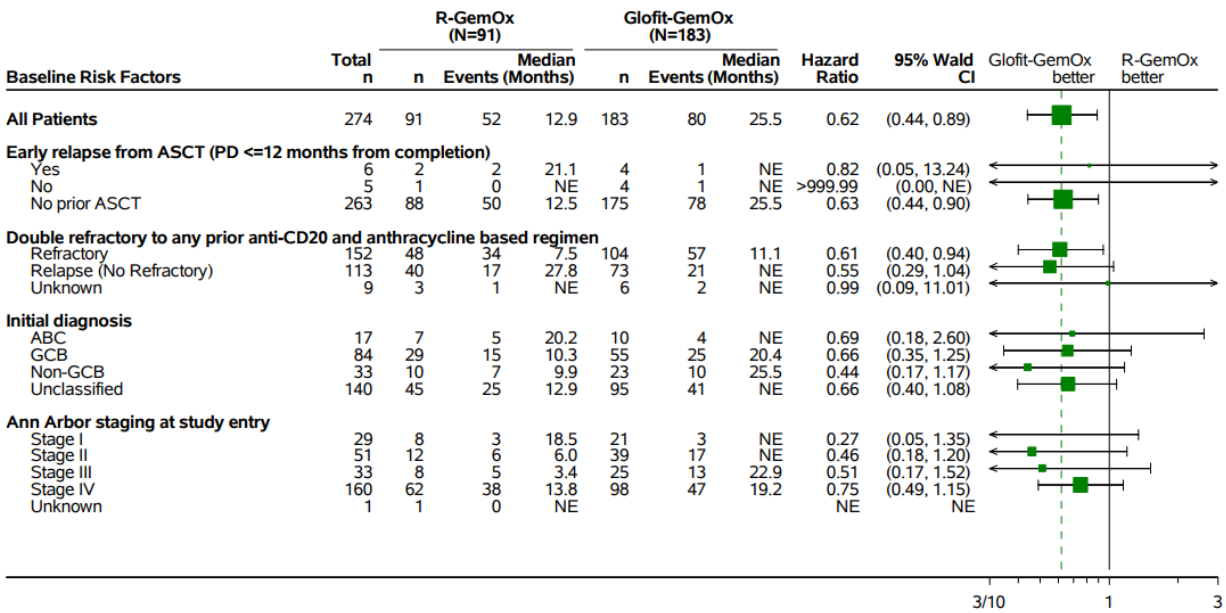
Day 1 is day of randomization. Hazard ratios and the associated Wald confidence intervals were estimated using Cox regression.
The vertical dashed line indicates the hazard ratio for all patients.
The size of the symbol is proportional to the size of the population in the subgroup.
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Forest Plot by Subgroup (Unstratified), Overall Survival, Intent-to-Treat Patients
Protocol: GO41944



Day 1 is day of randomization. Hazard ratios and the associated Wald confidence intervals were estimated using Cox regression.
The vertical dashed line indicates the hazard ratio for all patients.
The size of the symbol is proportional to the size of the population in the subgroup.
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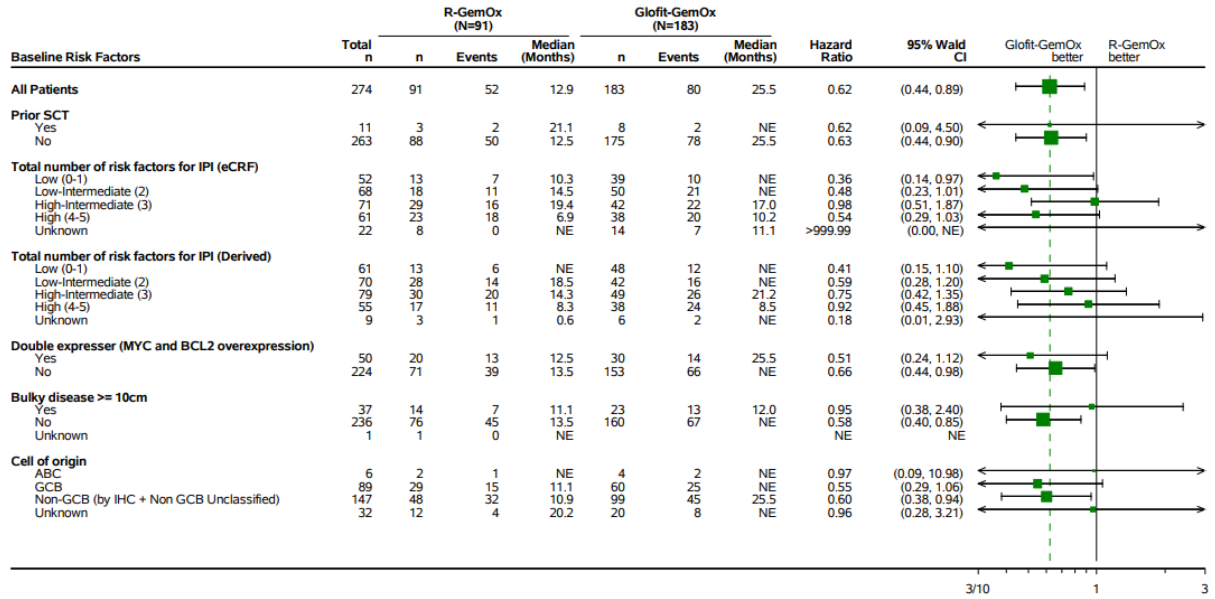
Forest Plot by Subgroup (Unstratified), Overall Survival, Intent-to-Treat Patients
Protocol: GO41944



Day 1 is day of randomization. Hazard ratios and the associated Wald confidence intervals were estimated using Cox regression.
The vertical dashed line indicates the hazard ratio for all patients.
The size of the symbol is proportional to the size of the population in the subgroup.
Any missing/unknown values for histology at initial diagnosis will be imputed with histology at study entry.
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Forest Plot by Subgroup (Unstratified), Overall Survival, Intent-to-Treat Patients
Protocol: GO41944

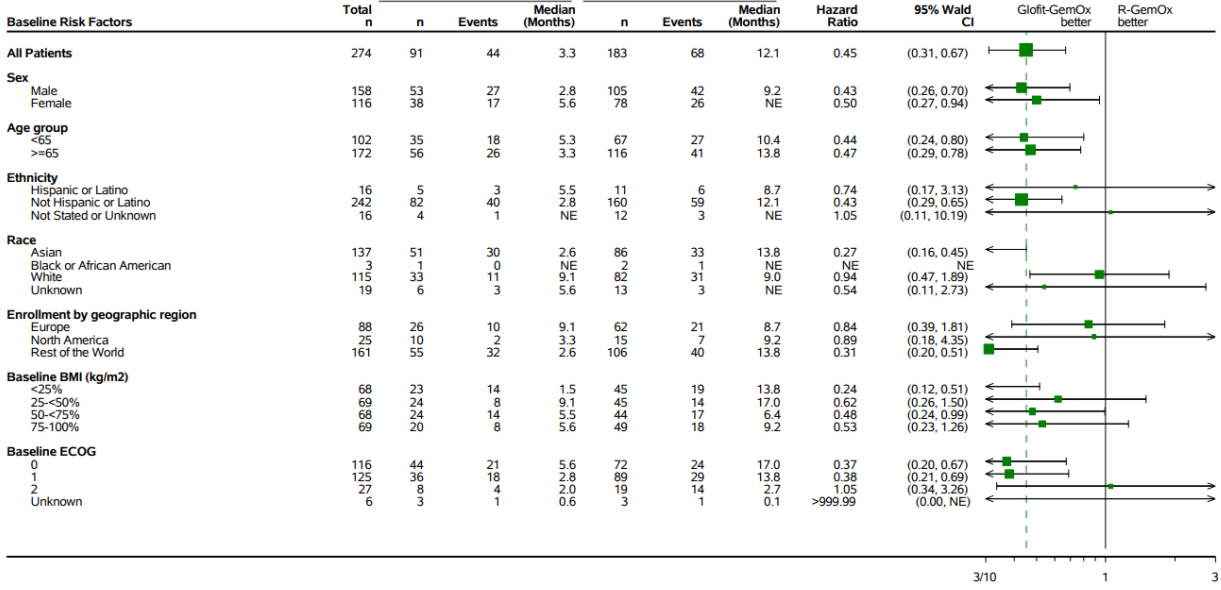
Baseline Risk Factors	Total n	R-GemOx (N=91) n	Events	Median (Months)	Glofit-GemOx (N=183) n	Events	Median (Months)	Hazard Ratio	95% Wald CI
All Patients	274	91	52	12.9	183	80	25.5	0.62	(0.44, 0.89)
Prior SCT									
Yes	11	3	2	21.1	8	2	NE	0.62	(0.09, 4.50)
No	263	88	50	12.5	175	78	25.5	0.63	(0.44, 0.90)
Total number of risk factors for IPI (eCRF)									
Low (0-1)	52	13	7	10.3	39	10	NE	0.36	(0.14, 0.97)
Low-Intermediate (2)	68	18	11	14.5	50	21	NE	0.48	(0.23, 1.01)
High-Intermediate (3)	71	29	16	19.4	42	22	17.0	0.98	(0.51, 1.87)
High (4-5)	61	23	18	6.9	38	20	10.2	0.54	(0.29, 1.03)
Unknown	22	8	0	NE	14	7	11.1	>999.99	(0.00, NE)
Total number of risk factors for IPI (Derived)									
Low (0-1)	61	13	6	NE	48	12	NE	0.41	(0.15, 1.10)
Low-Intermediate (2)	70	28	14	18.5	42	16	NE	0.59	(0.28, 1.20)
High-Intermediate (3)	79	30	20	14.3	49	26	21.2	0.75	(0.42, 1.35)
High (4-5)	55	17	11	8.3	38	24	8.5	0.92	(0.45, 1.88)
Unknown	9	3	1	0.6	6	2	NE	0.18	(0.01, 2.93)
Double expresser (MYC and BCL2 overexpression)									
Yes	50	20	13	12.5	30	14	25.5	0.51	(0.24, 1.12)
No	224	71	39	13.5	153	66	NE	0.66	(0.44, 0.98)
Bulky disease >= 10cm									
Yes	37	14	7	11.1	23	13	12.0	0.95	(0.38, 2.40)
No	236	76	45	13.5	160	67	NE	0.58	(0.40, 0.85)
Unknown	1	1	0	NE				NE	NE
Cell of origin									
ABC	6	2	1	NE	4	2	NE	0.97	(0.09, 10.98)
GCB	89	29	15	11.1	60	25	NE	0.55	(0.29, 1.06)
Non-GCB (by IHC + Non GCB Unclassified)	147	48	32	10.9	99	45	25.5	0.60	(0.38, 0.94)
Unknown	32	12	4	20.2	20	8	NE	0.96	(0.28, 3.21)



COO is investigator assessed (not centrally assessed).
Day 1 is day of randomization. Hazard ratios and the associated Wald confidence intervals were estimated using Cox regression.
The vertical dashed line indicates the hazard ratio for all patients.
The size of the symbol is proportional to the size of the population in the subgroup.
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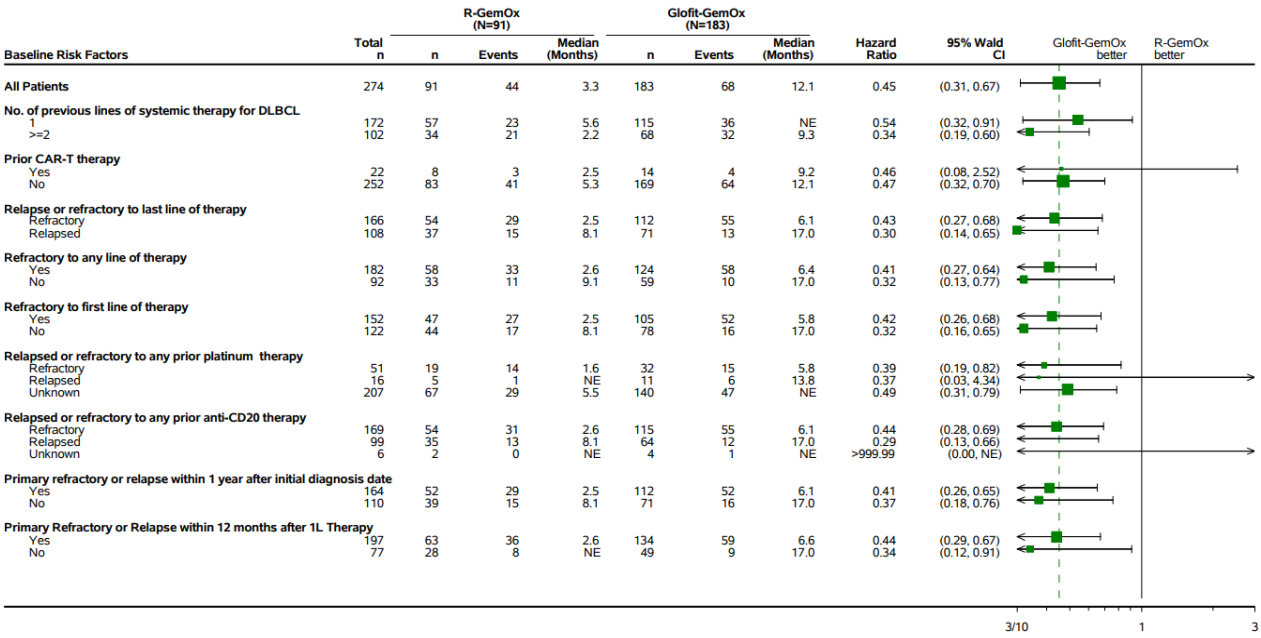
Forest Plot by Subgroup (Unstratified), IRC Assessed PFS Censored Before NALT, Intent-to-Treat Patients
Protocol: GO41944

Baseline Risk Factors	Total n	R-GemOx (N=91) n	Events	Median (Months)	Glofit-GemOx (N=183) n	Events	Median (Months)	Hazard Ratio	95% Wald CI
All Patients	274	91	44	3.3	183	68	12.1	0.45	(0.31, 0.67)
Sex									
Male	158	53	27	2.8	105	42	9.2	0.43	(0.26, 0.70)
Female	116	38	17	5.6	78	26	NE	0.50	(0.27, 0.94)
Age group									
<65	102	35	18	5.3	67	27	10.4	0.44	(0.24, 0.80)
>=65	172	56	26	3.3	116	41	13.8	0.47	(0.29, 0.78)
Ethnicity									
Hispanic or Latino	16	5	3	5.5	11	6	8.7	0.74	(0.17, 3.13)
Not Hispanic or Latino	242	82	40	2.8	160	59	12.1	0.43	(0.29, 0.65)
Not Stated or Unknown	16	4	1	NE	12	3	NE	1.05	(0.11, 10.19)
Race									
Asian	137	51	30	2.6	86	33	13.8	0.27	(0.16, 0.45)
Black or African American	3	1	0	NE	2	1	NE	NE	NE
White	115	33	11	9.1	82	31	9.0	0.94	(0.47, 1.89)
Unknown	19	6	3	5.6	13	3	NE	0.54	(0.11, 2.73)
Enrollment by geographic region									
Europe	88	26	10	9.1	62	21	8.7	0.84	(0.39, 1.81)
North America	25	10	2	3.3	15	7	9.2	0.89	(0.18, 4.35)
Rest of the World	161	55	32	2.6	106	40	13.8	0.31	(0.20, 0.51)
Baseline BMI (kg/m2)									
<25%	68	23	14	1.5	45	19	13.8	0.24	(0.12, 0.51)
25-<50%	69	24	8	9.1	45	14	17.0	0.62	(0.26, 1.50)
50-<75%	68	24	14	5.5	44	17	6.4	0.48	(0.24, 0.99)
75-100%	69	20	8	5.6	49	18	9.2	0.53	(0.23, 1.26)
Baseline ECOG									
0	116	44	21	5.6	72	24	17.0	0.37	(0.20, 0.67)
1	125	36	18	2.8	89	29	13.8	0.38	(0.21, 0.69)
2	27	8	4	2.0	19	14	2.7	1.05	(0.34, 3.26)
Unknown	6	3	1	0.6	3	1	0.1	>999.99	(0.00, NE)



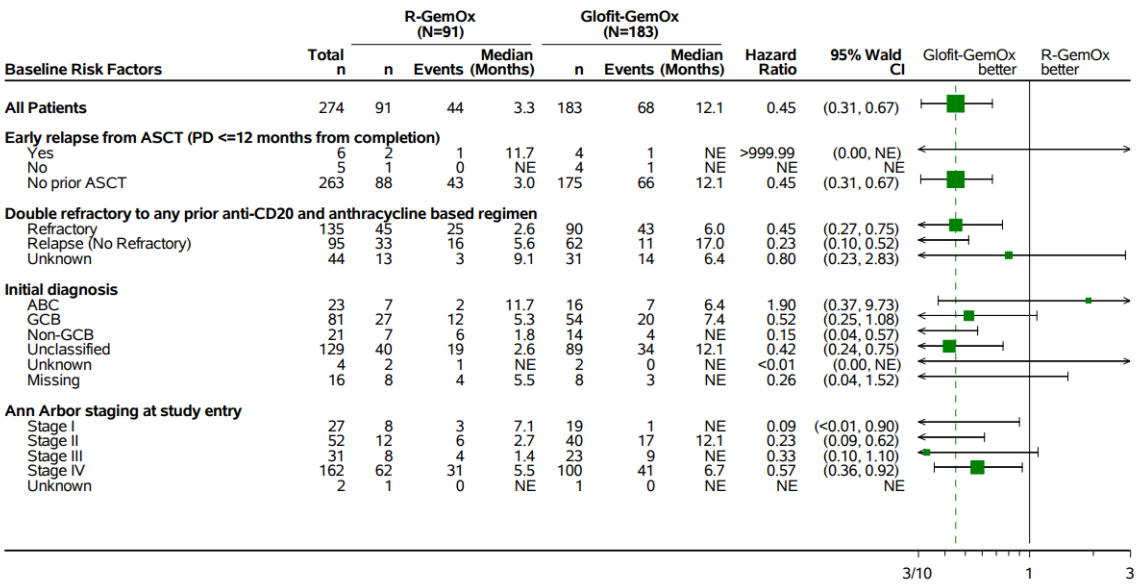
Day 1 is day of randomization. Hazard ratios and the associated Wald confidence intervals were estimated using Cox regression.
The vertical dashed line indicates the hazard ratio for all patients.
The size of the symbol is proportional to the size of the population in the subgroup.
Program: root/clinical_studies/RO7082859/CDT30295/GO41944/share/data_analysis/prod/program/g_ef_forest1_unstrat.sas
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Forest Plot by Subgroup (Unstratified), IRC Assessed PFS Censored Before NALT, Intent-to-Treat Patients
Protocol: GO41944



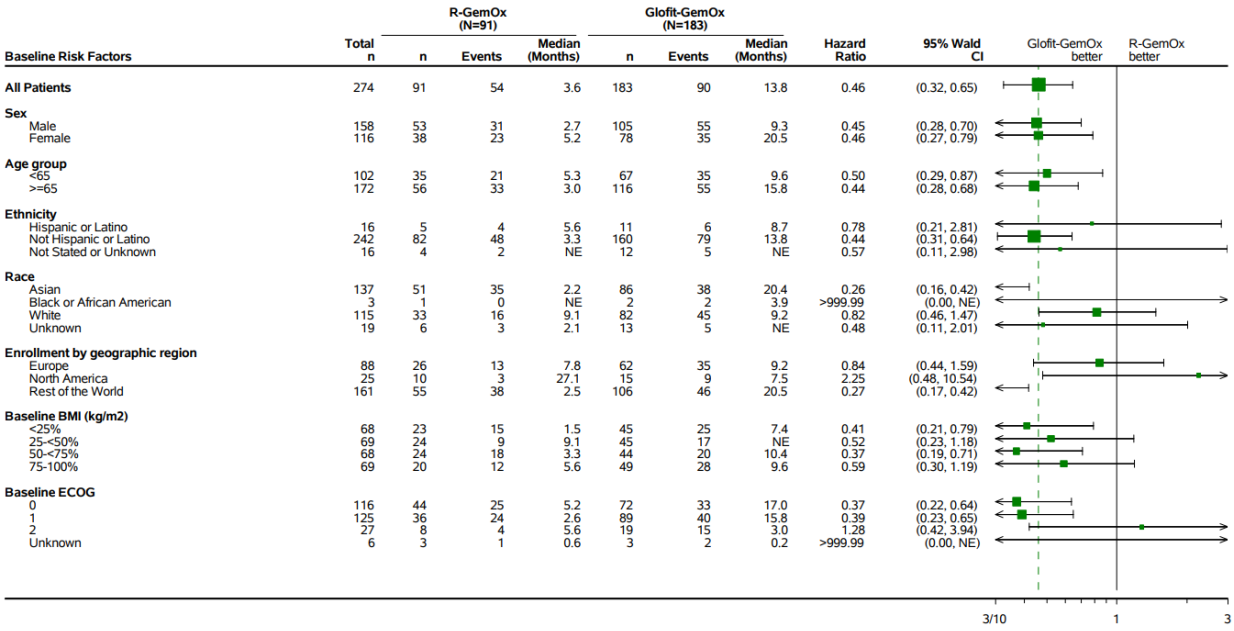
Day 1 is day of randomization. Hazard ratios and the associated Wald confidence intervals were estimated using Cox regression.
The vertical dashed line indicates the hazard ratio for all patients.
The size of the symbol is proportional to the size of the population in the subgroup.
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Output: root/clinical_studies/RO7082859/CDT30295/GO41944/data_analysis/Interim_Analysis_2023/prod/output/g_ef_forest2_unstrat_IRCPFSN_IT_29MAR2023_41944.pdf 18APR2024 10:14

Forest Plot by Subgroup (Unstratified), IRC Assessed PFS Censored Before NALT, Intent-to-Treat Patients
Protocol: GO41944



Day 1 is day of randomization. Hazard ratios and the associated Wald confidence intervals were estimated using Cox regression.
The vertical dashed line indicates the hazard ratio for all patients.
The size of the symbol is proportional to the size of the population in the subgroup.
Program: root/clinical_studies/RO7082859/CDT30295/GO41944/share/data_analysis/prod/program/g_ef_forest3_unstrat.sas
Output: root/clinical_studies/RO7082859/CDT30295/GO41944/data_analysis/Interim_Analysis_2023/prod/output/g_ef_forest3_unstrat_IRCPFSN_IT_29MAR2023_41944.pdf 20JUN2024 12:45

Forest Plot by Subgroup (Unstratified), IRC Assessed PFS Censored Before NALT, Intent-to-Treat Patients
Protocol: GO41944



Day 1 is day of randomization. Hazard ratios and the associated Wald confidence intervals were estimated using Cox regression.
The vertical dashed line indicates the hazard ratio for all patients.
The size of the symbol is proportional to the size of the population in the subgroup.
Program: root/clinical_studies/RO7082859/CDT30295/GO41944/share/data_analysis/prod/program/g_ef_forest1_unstrat.sas
Output: root/clinical_studies/RO7082859/CDT30295/GO41944/data_analysis/Follow_Up_Analysis_2024/prod/output/g_ef_forest1_unstrat_IRCPFSN_IT_16FEB2024_41944.pdf 23APR2024 14:47

Table 29 **Demographic and Baseline Characteristics of Patients by Geographic Region (Pre-Specified Subgroups)**

	Europe		North America		Rest of World		ITT Population	
	N=88		N=25		N=161		N=274	
	R-GemOx N=26	Glofit-GemOx N=62	R-GemOx N=10	Glofit-GemOx N=15	R-GemOx N=55	Glofit-GemOx N=106	R-GemOx N=91	Glofit-GemOx N=183
Median age, yrs	69.5	71.5	69.0	74.0	68.0	65.0	68.0	68.0
(range)	(50 – 82)	(32 – 84)	(20 – 83)	(62 – 85)	(27 – 84)	(22 – 88)	(20 – 84)	(22 – 88)
Age Group								
< 65 yrs	8 (30.8%)	14 (22.6%)	3 (30.0%)	2 (13.3%)	24 (43.6%)	51 (48.1%)	35 (38.5%)	67 (36.6%)
≥ 65 yrs	18 (69.2%)	48 (77.4%)	7 (70.0%)	13 (86.7%)	31 (56.4%)	55 (51.9%)	56 (61.5%)	116 (63.4%)
Male, n (%)	18 (69.2%)	35 (56.5%)	5 (50.0%)	11 (73.3%)	30 (54.5%)	59 (55.7%)	53 (58.2%)	105 (57.4%)
Race, n (%)								
Asian	0	1 (1.6%)	2 (20.0%)	0	49 (89.1%)	85 (80.2%)	51 (56.0%)	86 (47.0%)
Black or African American	0	1 (1.6%)	1 (10.0%)	1 (6.7%)	0	0	1 (1.1%)	2 (1.1%)

White	20 (76.9%)	47 (75.8%)	7 (70.0%)	14 (93.3%)	6 (10.9%)	21 (19.8%)	33 (36.3%)	82 (44.8%)
Unknown	6 (23.1%)	13 (21.0%)	0	0	0	0	6 (6.6%)	13 (7.1%)
ECOG status at baseline, n (%)								
0	13 (50.0%)	29 (48.3%)	4 (50.0%)	3 (20.0%)	27 (50.0%)	40 (38.1%)	44 (50.0%)	72 (40.0%)
1	12 (46.2%)	24 (40.0%)	3 (37.5%)	9 (60.0%)	21 (38.9%)	56 (53.3%)	36 (40.9%)	89 (49.4%)
2	1 (3.8%)	7 (11.7%)	1 (12.5%)	3 (20.0%)	6 (11.1%)	9 (8.6%)	8 (9.1%)	19 (10.6%)
Category sum of products of diameters value ≥3000/mm^2, n (%)*	12 (46.2%)	25 (40.3%)	3 (30.0%)	12 (80.0%)	27 (49.1%)	39 (36.8%)	42 (46.2%)	76 (41.5%)
Bulky disease (≥ 10cm), n (%)	6 (23.1%)	9 (14.5%)	1 (10.0%)	3 (20.0%)	7 (12.7%)	11 (10.4%)	14 (15.4%)	23 (12.6%)

Table 29Demographic and Baseline Characteristics of Patients by Geographic Region (Pre-Specified Subgroups) (Cont.)

	Europe		**North America**		**Rest of World**		**ITT Population**	
	N=88		**N=25**		**N=161**			
	R-GemOx	**Glofit-GemOx**	**R-GemOx**	**Glofit-GemOx**	**R-GemOx**	**Glofit-GemOx**	**R-GemOx**	**Glofit-GemOx**
	N=26	**N=62**	**N=10**	**N=15**	**N=55**	**N=106**	**N=91**	**N=183**
Prior lines of therapy, n (%)								
1 prior line	18 (69.2%)	41 (66.1%)	6 (60.0%)	9 (60.0%)	33 (60.0%)	65 (61.3%)	57 (62.6%)	115 (62.8%)
≥ 2 prior lines	8 (30.8%)	21 (33.9%)	4 (40.0%)	6 (40.0%)	22 (40.0%)	41 (38.7%)	34 (37.4%)	68 (37.2%)
Refractory to last line of therapy, n (%)	14 (53.8%)	32 (51.6%)	5 (50.0%)	11 (73.3%)	35 (63.6%)	69 (65.1%)	54 (59.3%)	112 (61.2%)
Primary refractory or within 12 months after 1L therapy, n (%)	16 (61.5%)	40 (64.5%)	5 (50.0%)	12 (80.0%)	42 (76.4%)	82 (77.4%)	63 (69.2%)	134 (73.2%)
Double refractory to any prior anti-CD20 and anthracycline-based regimen, n (%)	14 (53.8%)	29 (46.8%)	4 (40.0%)	12 (80.0%)	30 (54.5%)	63 (59.4%)	48 (52.7%)	104 (56.8%)

Ann Arbor staging at study entry, n (%)								
Stage I	4 (15.4%)	7 (11.3%)	2 (20.0%)	1 (6.7%)	2 (3.6%)	13 (12.3%)	8 (8.8%)	21 (11.5%)
Stage II	2 (7.7%)	9 (14.5%)	1 (10.0%)	2 (13.3%)	9 (16.4%)	28 (26.4%)	12 (13.2%)	39 (21.3%)
Stage III	5 (19.2%)	11 (17.7%)	0	3 (20.0%)	3 (5.5%)	11 (10.4%)	8 (8.8%)	25 (13.7%)
Stage IV	15 (57.7%)	35 (56.5%)	6 (60.0%)	9 (60.0%)	41 (74.5%)	54 (50.9%)	62 (68.1%)	98 (53.6%)

Table 29Demographic and Baseline Characteristics of Patients by Geographic Region (Pre-Specified Subgroups) (Cont.)

	Europe		**North America**		**Rest of World**		**ITT Population**	
	N=88		**N=25**		**N=161**			
	R-GemOx	**Glofit-GemOx**	**R-GemOx**	**Glofit-GemOx**	**R-GemOx**	**Glofit-GemOx**	**R-GemOx**	**Glofit-GemOx**
	N=26	**N=62**	**N=10**	**N=15**	**N=55**	**N=106**	**N=91**	**N=183**
Total number of risk factors for IPI (Derived), n (%)								
Not applicable	0	4 (6.5%)	2 (20.0%)	0	1 (1.8%)	2 (1.9%)	3 (3.3%)	6 (3.3%)
0	2 (7.7%)	1 (1.1%)	0	0	1 (1.8%)	15 (14.2%)	3 (3.3%)	16 (8.7%)
1	1 (3.8%)	10 (16.1%)	1 (10.0%)	1 (6.7%)	8 (14.5%)	21 (19.8%)	10 (11.0%)	32 (17.5%)
2	10 (38.5%)	17 (27.4%)	2 (20.0%)	4 (26.7%)	16 (29.1%)	21 (19.8%)	28 (30.8%)	42 (23.0%)
3	8 (30.8%)	17 (27.4%)	4 (40.0%)	6 (40.0%)	18 (32.7%)	26 (24.5%)	30 (33.0%)	49 (26.8%)
4	5 (19.2%)	11 (17.7%)	1 (10.0%)	3 (20.0%)	8 (14.5%)	20 (18.9%)	14 (15.4%)	34 (18.6%)
5	0	2 (3.2%)	0	1 (6.7%)	3 (5.5%)	1 (0.9%)	3 (3.3%)	4 (2.2%)
Prior CAR-T therapy, n (%)	4 (15.4%)	8 (12.9%)	3 (30.0%)	3 (20.0%)	1 (1.8%)	2 (1.9%)	8 (8.8%)	13 (7.1%)
Relapse or refractory to any prior CAR-T therapy								

Refractory	4 (15.4%)	8 (12.9%)	2 (20.0%)	3 (20.0%)	0	2 (1.9%)	6 (6.6%)	13 (7.1%)
Relapse	0	54 (87.1%)	7 (70.0%)	12 (80.0%)	54 (98.2%)	104 (98.1%)	83 (91.2%)	170 (92.9%)
Unknown	22 (84.6%)							

CAR-T: chimeric antigen receptor cell therapy; Glofit-GemOx = glofitamab in combination with gemcitabine and oxaliplatin; IPI = International Prognostic Index; R-GemOx = rituximab in combination with gemcitabine and oxaliplatin.

* Investigator-assessed.

Table 30 Overall Survival by Geographic Region (Pre-Specified Subgroups) (Study GO41944 Updated Analysis)

	R-GemOx	**Glofit-GemOx**
Overall Intent-to-Treat Population (N = 274)		
n	91	183
Patients with event, n (%)	52 (57.1%)	80 (43.7%)
Median OS, months (95% CI)	12.9 (7.9, 18.5)	25.5 (18.3, NE)
Median OS follow-up, months (range)	19.7 (0 - 34)	22.5 (0[a] - 36)
Stratified HR (95% CI)	0.62 (0.43, 0.88)	
Europe (N = 88)		
n	26	62
Patients with event, n (%)	11 (42.3%)	29 (46.8%)
Median OS, months (95% CI)	13.8 (11.1, NE)	21.2 (10.5, NE)
Median OS follow-up, months (range)	18.6 (1 - 27)	17.9 (0[a] - 34)
Unstratified HR (95% CI)	1.09 (0.54, 2.18)	
North America (N = 25)		
n	10	15
Patients with event, n (%)	2 (20.0%)	8 (53.3%)
Median OS, months (95% CI)	NE (7.5, NE)	13.3 (5.2, NE)
Median OS follow-up, months (range)	14.6 (0 - 27)	18.1 (1 - 26)
Unstratified HR (95% CI)	2.62 (0.56, 12.34)	
Rest of World (N = 161)		
n	55	106
Patients with event, n (%)	39 (70.9%)	43 (40.6%)
Median OS, months (95% CI)	8.3 (5.5, 14.5)	NE (20.4, NE)
Median OS follow-up, months (range)	27.2 (1[a] - 34)	24.6 (0 - 36)

	R-GemOx	Glofit-GemOx
Unstratified HR (95% CI)	0.41 (0.27, 0.64)	

CI = confidence interval; Glofit-GemOx = glofitamab in combination with gemcitabine and oxaliplatin; HR = hazard ratio; NE = not evaluable; OS = overall survival; R-GemOx = rituximab in combination with gemcitabine and oxaliplatin.

[a] Censored observation.

Figure 21 ***Kaplan-Meier Plot of Overall Survival for Patients Enrolled in Europe (Intent-to-Treat Patients) (Study GO41944, CCOD: 16 February 2024)***

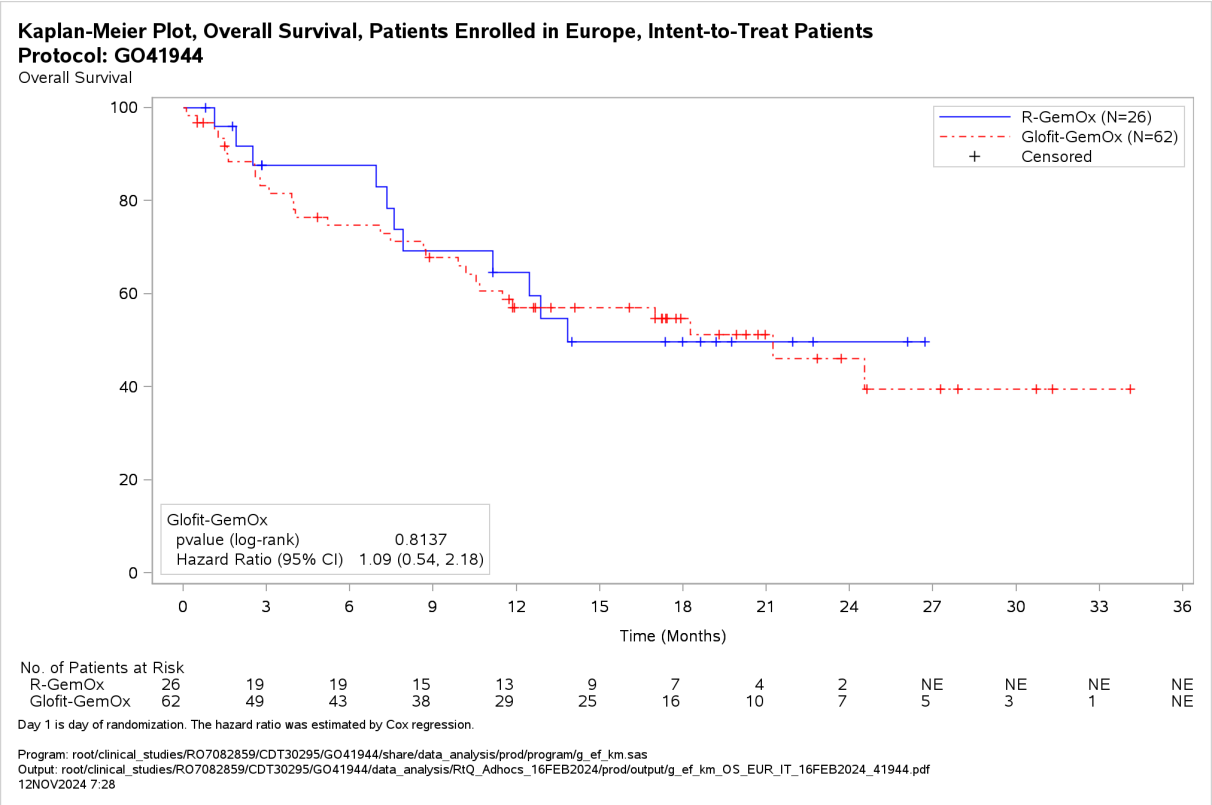


Figure 22 ***Kaplan-Meier Plot of Overall Survival for Patients Enrolled in North America (Intent-to-Treat Patients) (Study GO41944, CCOD: 16 February 2024)***

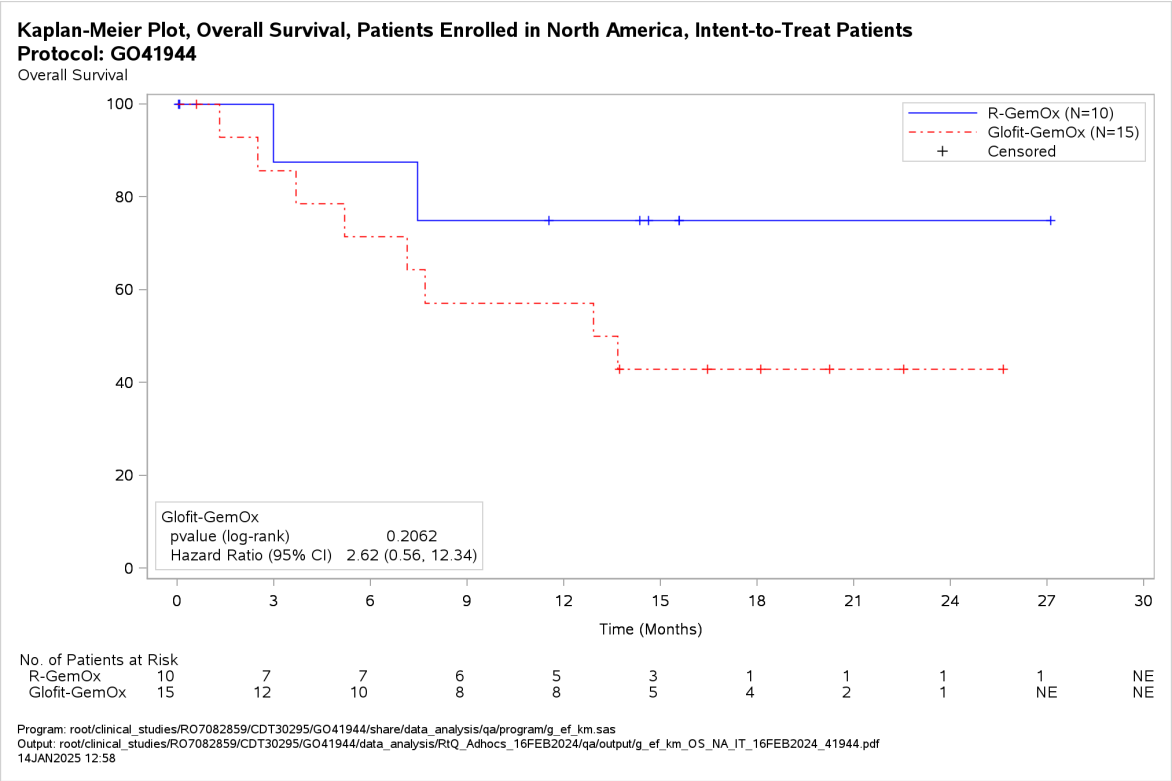


Figure 23 ***Kaplan-Meier Plot of Overall Survival for Patients Enrolled in the Rest of World (Intent-to-Treat Patients) (Study GO41944, CCOD: 16 February 2024)***

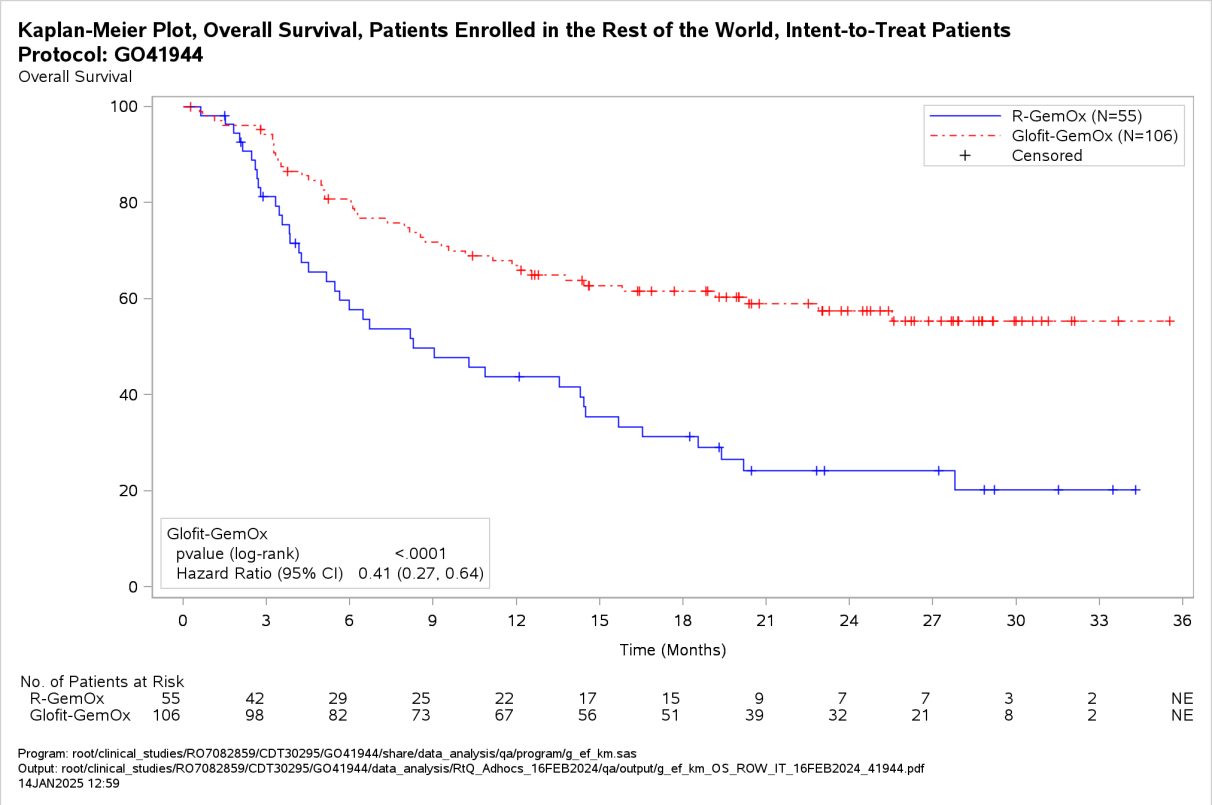


Figure 24: ***K-M OS plot – Asian patients (Study GO41944, CCOD: 16 February 2024)***

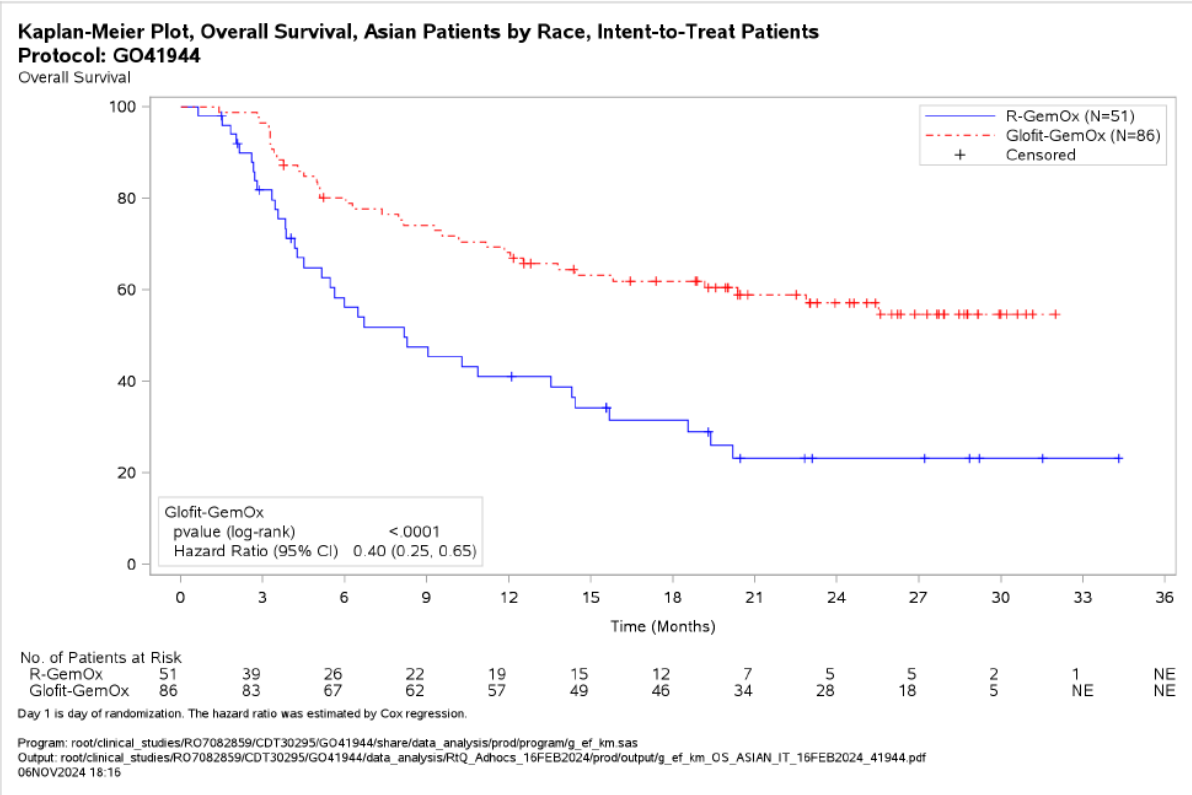


Figure 25 ***K-M OS plot – white patients by race, ITT (Study GO41944, CCOD: 16 February 2024)***

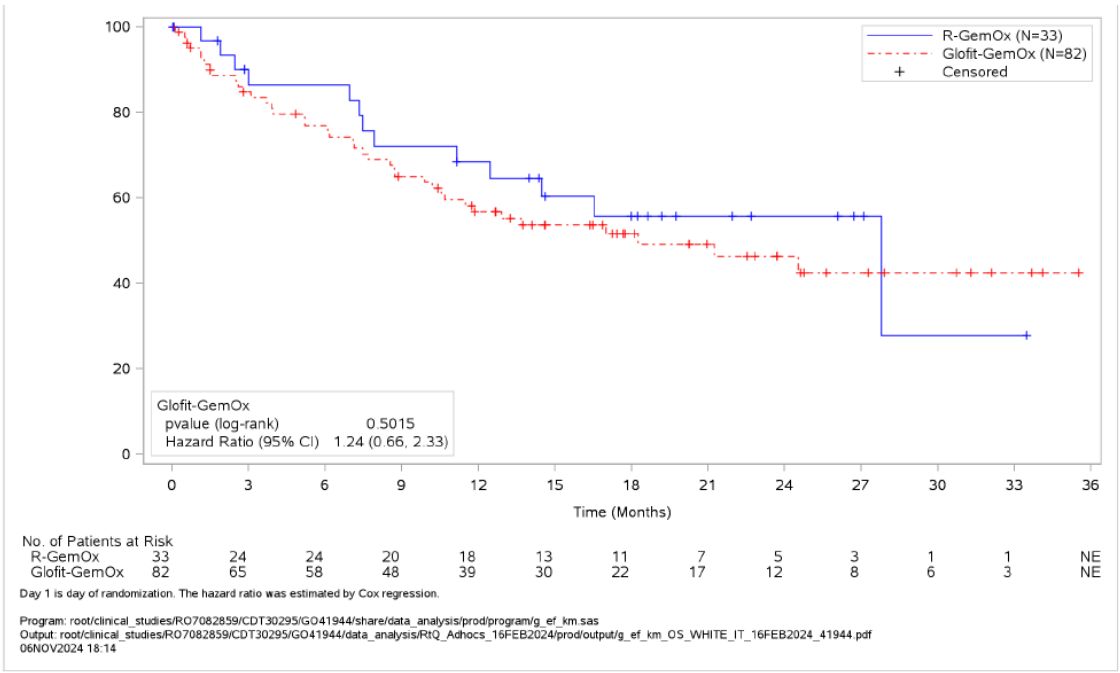


Figure 26 Swimlane Plot of Overall Survival Including all NALT, Europe (Study G041944 Updated Analysis)

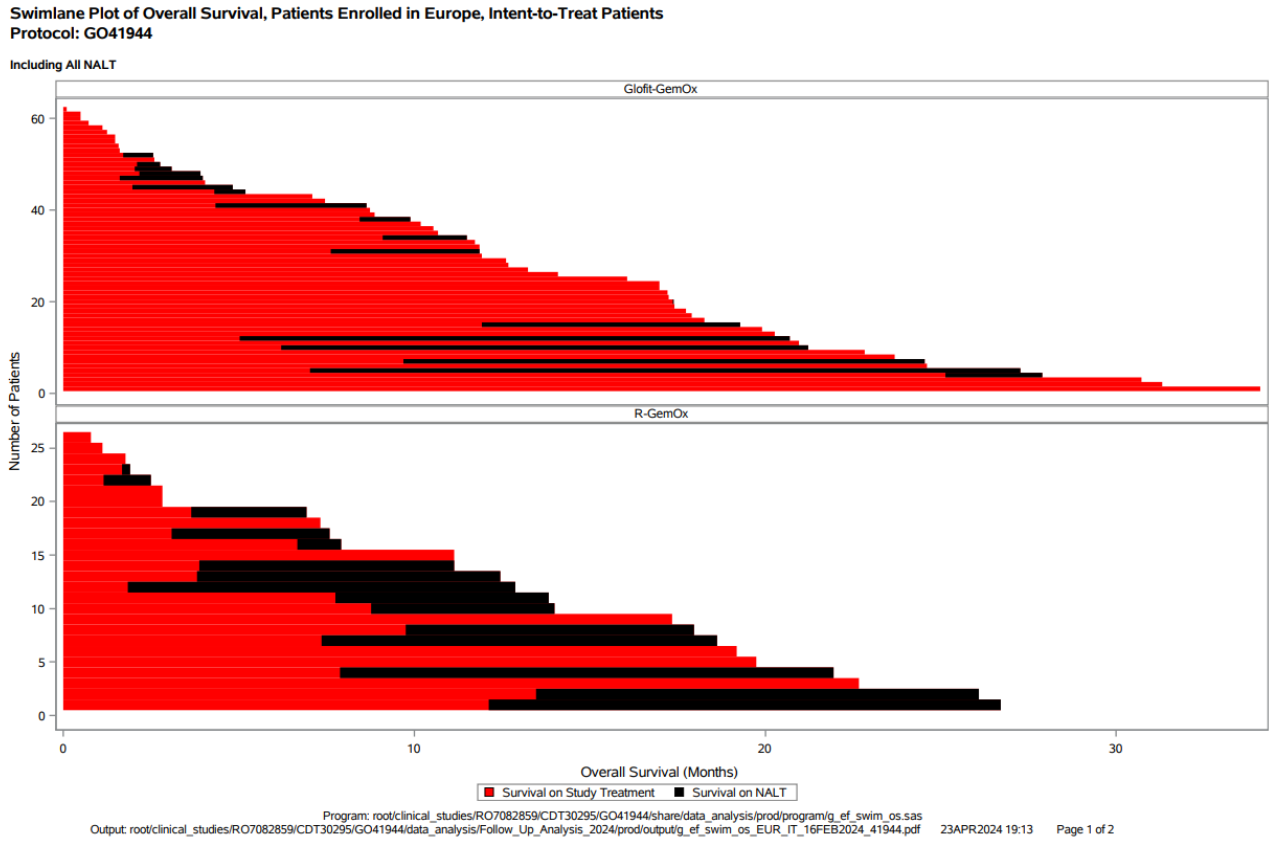


Figure 27 Swimlane Plot of Overall Survival Including all NALT, North America (Study G041944 Updated Analysis)

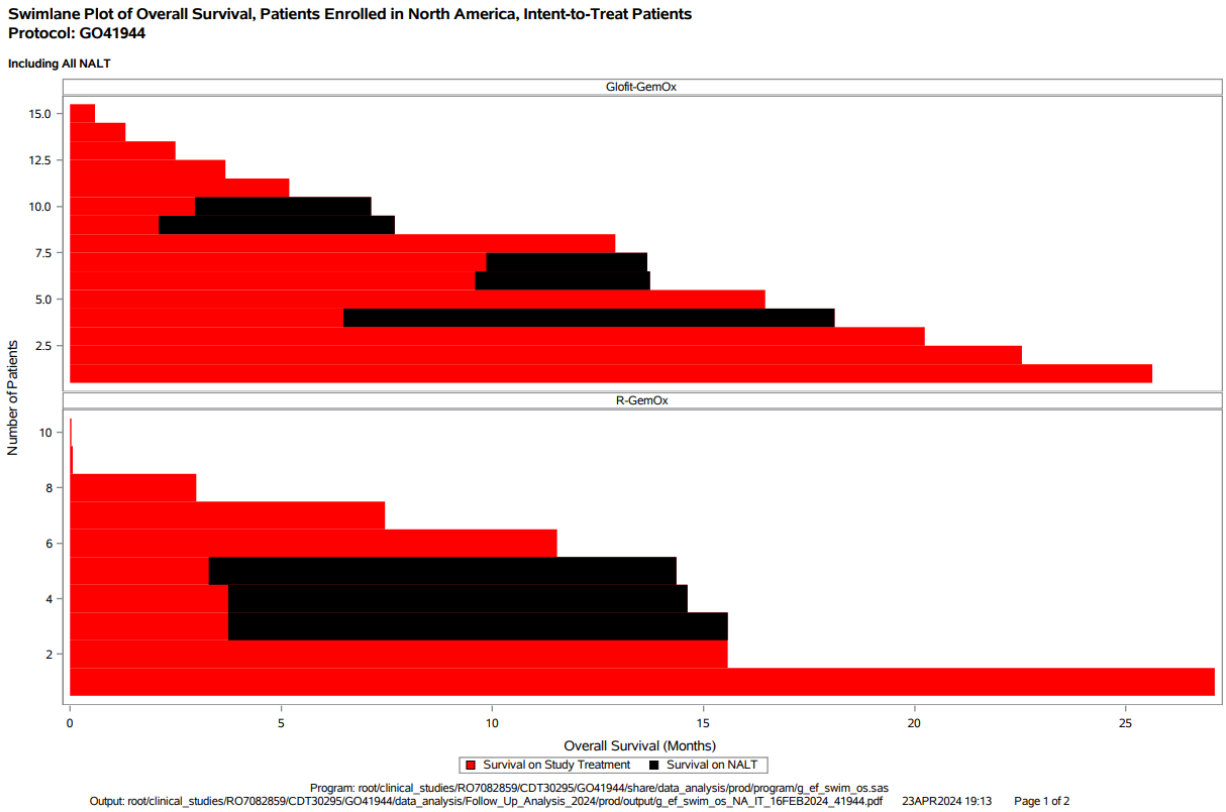


Figure 28 Swimlane Plot of Overall Survival Including all NALT, Rest of World (Study G041944 Updated Analysis)

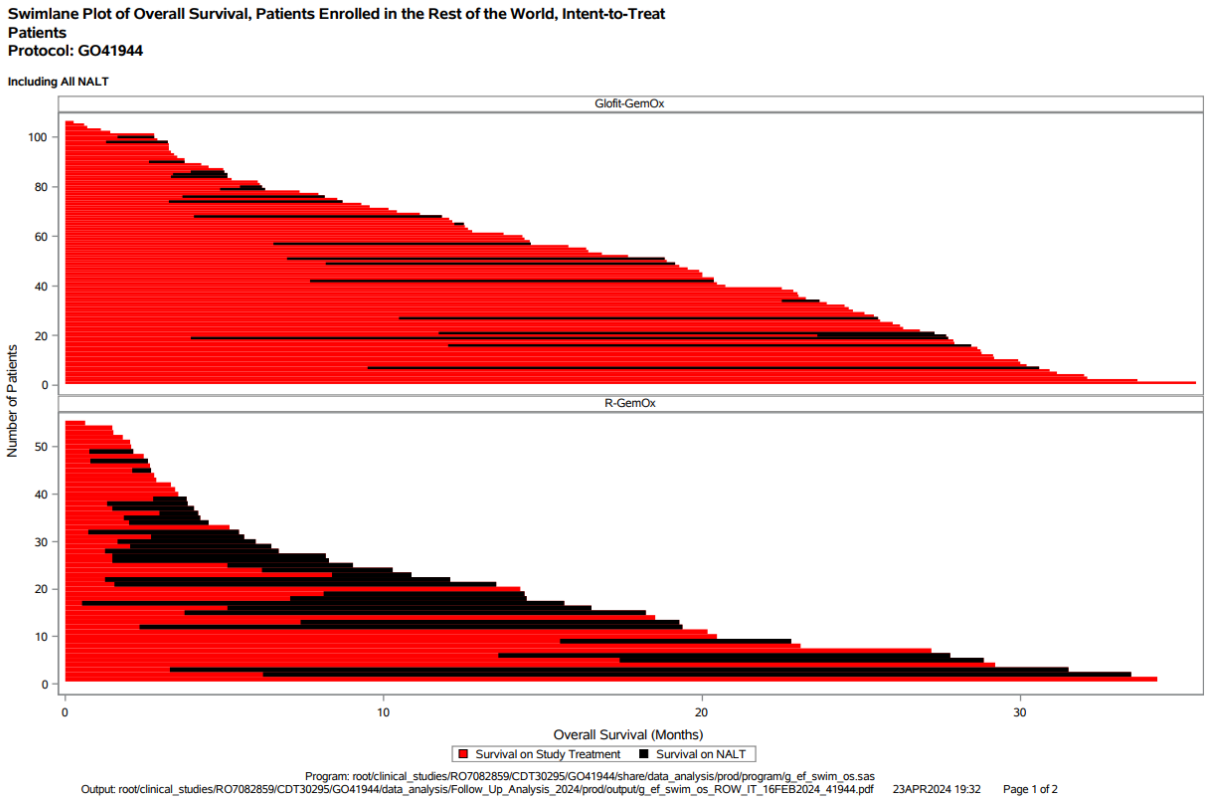


Table 31 IRC-Assessed Progression-Free Survival by Geographic Region (Study GO41944 Updated Analysis)

	R-GemOx	Glofit-GemOx
Overall Intent-to-Treat Population (N = 274)		
n	91	183
Patients with event, n (%)	54 (59.3%)	90 (49.2%)
Median PFS, months (95% CI)	3.6 (2.5, 7.1)	13.8 (8.7, 20.5)
Median PFS follow-up, months (range)	8.6 (0–27)	16.3 (0–33)
Stratified HR (95% CI)	0.40 (0.28, 0.57)	
Europe (N = 88)		
n	26	62
Patients with event, n (%)	13 (50.0%)	35 (56.5%)
Median PFS, months (95% CI)	7.8 (2.6, NE)	9.2 (6.1, 17.0)
Median PFS follow-up, months (range)	7.2 (0–17)	15.5 (0–33)
Unstratified HR (95% CI)	0.84 (0.44, 1.59)	
North America (N = 25)		
n	10	15
Patients with event, n (%)	3 (30.0%)	9 (60.0%)
Median PFS, months (95% CI)	27.1 (3.3, NE)[a]	7.5 (2.5, NE)

	R-GemOx	Glofit-GemOx
Median PFS follow-up, months (range)	3.0 (0–27[b])	17.6 (0–21)
Unstratified HR (95% CI)	2.25 (0.48, 10.54)	
Rest of World (N = 161)		
n	55	106
Patients with event, n (%)	38 (69.1%)	46 (43.4%)
Median PFS, months (95% CI)	2.5 (1.5, 5.2)	20.5 (9.3, NE)
Median PFS follow-up, months (range)	8.6 (0–27)	18.5 (0–33)
Unstratified HR (95% CI)	0.27 (0.17, 0.42)	

CI = confidence interval; Glofit-GemOx = glofitamab in combination with gemcitabine and oxaliplatin; HR = hazard ratio; IRC = Independent Review Committee; PFS = progression-free survival; R-GemOx = rituximab in combination with gemcitabine and oxaliplatin.

[a] This median PFS is considered unreliable as it was reached with one patient at risk and a median follow-up of only three months.

[b] Censored observation.

Table 32 IRC-Assessed PFS Censoring by Geographic Region (Europe, North America, Rest of World) (ITT Population)

Table 20 IRC-Assessed PFS Censoring by Geographic Region (Europe, North America, Rest of World) (ITT Population)

	R-GemOx (N=91)		
	Europe (N=26)	North America (N=10)	Rest of World (N=55)
PFS Censor/Event Status			
n	26	10	55
PFS Event (Disease Progression or Death)	13 (50.0%)	3 (30.0%)	38 (69.1%)
Censoring Followed by NALT	6 (23.1%)	3 (30.0%)	10 (18.2%)
Censored to Last Tumor Assessment	5 (19.2%)	2 (20.0%)	3 (5.5%)
Censoring due to Missed Assessments	1 (3.8%)	1 (10.0%)	1 (1.8%)
Censored to Randomization	1 (3.8%)	1 (10.0%)	3 (5.5%)
	Glofit-GemOx (N=183)		
	Europe (N=62)	North America (N=15)	Rest of World (N=106)
PFS Censor/Event Status			
n	62	15	106
PFS Event (Disease Progression or Death)	35 (56.5%)	9 (60.0%)	46 (43.4%)
Censoring Followed by NALT	4 (6.5%)	1 (6.7%)	6 (5.7%)
Censored to Last Tumor Assessment	20 (32.3%)	4 (26.7%)	40 (37.7%)
Censoring due to Missed Assessments	1 (1.6%)	0	11 (10.4%)
Censored to Randomization	2 (3.2%)	1 (6.7%)	3 (2.8%)

Censoring Followed by NALT includes all patients who did not have an event but subsequently received NALT.

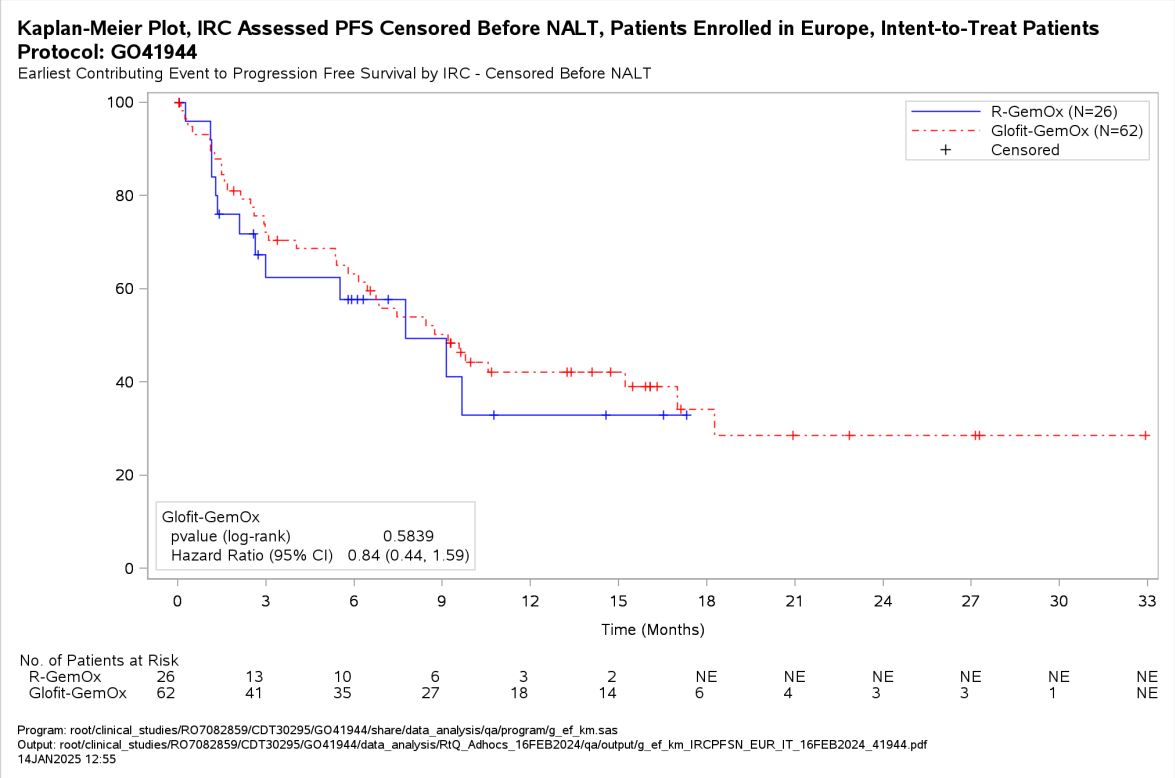
Table 21 Summary of IRC-Assessed Best Overall and Complete Response by Geographic Region

Response Assessment: Best Overall Response by IRC (confirmation not required) - WITH OR WITHOUT PET LUGANO

	Europe (N=88)		North America (N=25)		Rest of World (N=161)	
	R-GemOx (N=26)	Glofit-GemOx (N=62)	R-GemOx (N=10)	Glofit-GemOx (N=15)	R-GemOx (N=55)	Glofit-GemOx (N=106)
Responders 95% CI	14 (53.8%) (33.37, 73.41)	40 (64.5%) (51.34, 76.26)	6 (60.0%) (26.24, 87.84)	8 (53.3%) (26.59, 78.73)	17 (30.9%) (19.14, 44.81)	77 (72.6%) (63.13, 80.85)
Stratified Analysis Difference in Overall Response Rates (95% CI) p-value (Cochran-Mantel-Haenszel)	10.67 (-14.62, 35.96) 0.2962		-6.67 (-54.49, 41.16) 0.8718		41.73 (25.48, 57.99) <.0001	
Complete Response (CR) 95% CI	9 (34.6%) (17.21, 55.67)	36 (58.1%) (44.85, 70.49)	4 (40.0%) (12.16, 73.76)	6 (40.0%) (16.34, 67.71)	10 (18.2%) (9.08, 30.90)	65 (61.3%) (51.37, 70.62)
Stratified Analysis Difference in complete Response Rates (95% CI) p-value (Cochran-Mantel-Haenszel)	23.45 (-1.31, 48.21) 0.0226		0.00 (-47.53, 47.53) 0.5916		43.14 (27.98, 58.30) <.0001	
Partial Response (PR) 95% CI	5 (19.2%) (6.55, 39.35)	4 (6.5%) (1.79, 15.70)	2 (20.0%) (2.52, 55.61)	2 (13.3%) (1.66, 40.46)	7 (12.7%) (5.27, 24.48)	12 (11.3%) (5.99, 18.94)
Stable Disease (SD) 95% CI	2 (7.7%) (0.95, 25.13)	1 (1.6%) (0.04, 8.66)	0 (0.00, 30.85)	1 (6.7%) (0.17, 31.95)	2 (3.6%) (0.44, 12.53)	3 (2.8%) (0.59, 8.05)
Progressive Disease (PD) 95% CI	8 (30.8%) (14.33, 51.79)	12 (19.4%) (10.42, 31.37)	2 (20.0%) (2.52, 55.61)	4 (26.7%) (7.79, 55.10)	26 (47.3%) (33.65, 61.20)	18 (17.0%) (10.39, 25.50)
Not Evaluable (NE)	0	0	0	0	3 (5.5%)	1 (0.9%)
Missing or Not Done	2 (7.7%)	9 (14.5%)	1 (10.0%)	1 (6.7%)	6 (10.9%)	7 (6.6%)

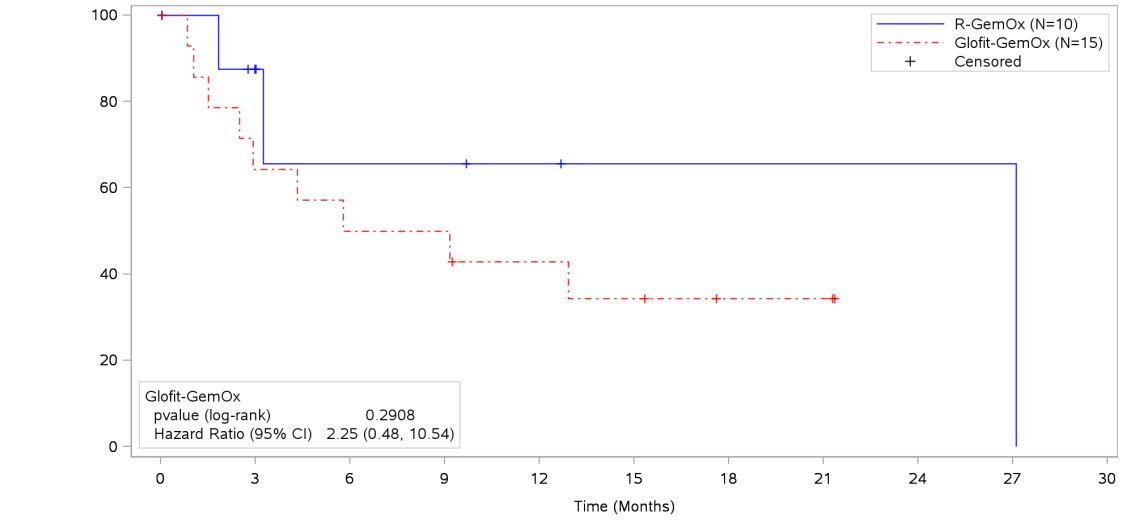
Best Overall Response is the patient's best response assessment recorded from the start of the study treatment until disease progression.
Note: All patients without response data are included in the Not Done/Missing category.
Responders refer to patients with CR or PR.
The differences in objective and complete response rates are unstratified.

Kaplan-Meier Plot of IRC-Assessed Progression Free Survival for Patients Enrolled in Europe (Intent-to-Treat Patients) (Study GO41944, CCOD: 16 February 2024)



Kaplan-Meier Plot of IRC-Assessed Progression Free Survival for Patients Enrolled in North America (Intent-to-Treat Patients) (Study GO41944, CCOD: 16 February 2024)

Kaplan-Meier Plot, IRC Assessed PFS Censored Before NALT, Patients Enrolled in North America, Intent-to-Treat Patients
Protocol: GO41944
Earliest Contributing Event to Progression Free Survival by IRC - Censored Before NALT



No. of Patients at Risk

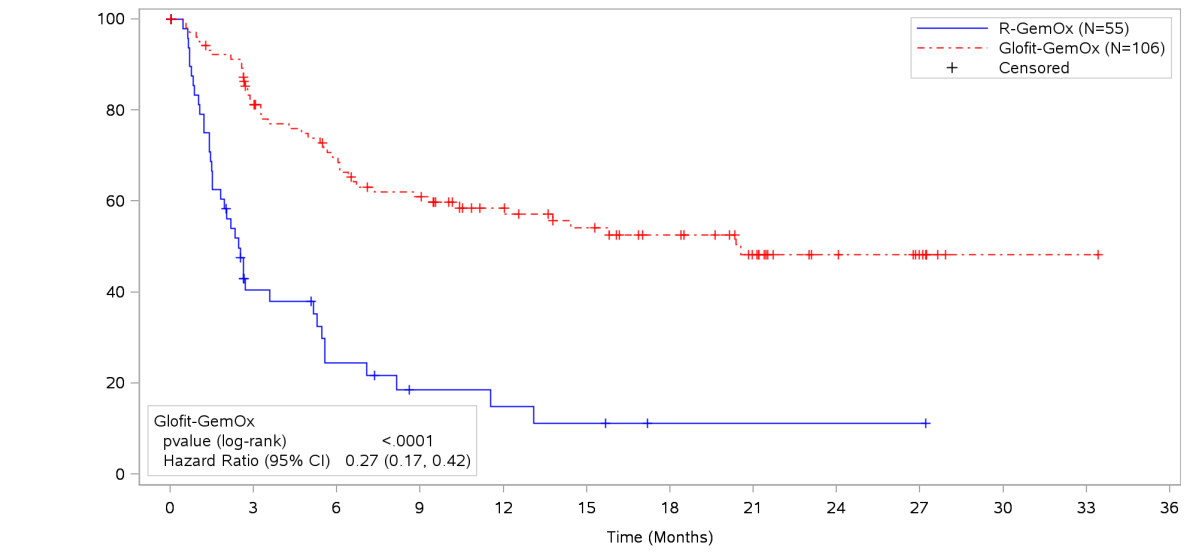
R-GemOx	10	5	3	3	2	1	1	1	1	1	NE
Glofit-GemOx	15	9	7	7	5	4	2	2	NE	NE	NE

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Kaplan-Meier Plot of IRC-Assessed Progression Free Survival for Patients Enrolled in the Rest of World (Intent-to-Treat Patients) (Study GO41944, CCOD: 16 February 2024)

Figure 29

Kaplan-Meier Plot, IRC Assessed PFS Censored Before NALT, Patients Enrolled in the Rest of the World, Intent-to-Treat Patients
Protocol: GO41944
Earliest Contributing Event to Progression Free Survival by IRC - Censored Before NALT



No. of Patients at Risk

R-GemOx	55	16	9	5	4	3	1	1	1	1	NE	NE	NE
Glofit-GemOx	106	80	65	55	43	36	29	20	11	7	1	1	NE

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Figure 30 Kaplan Meier plot IRC-Assessed Progression Free Survival Asian patients by Race
Study GO41944, CCOD: 16 February 2024

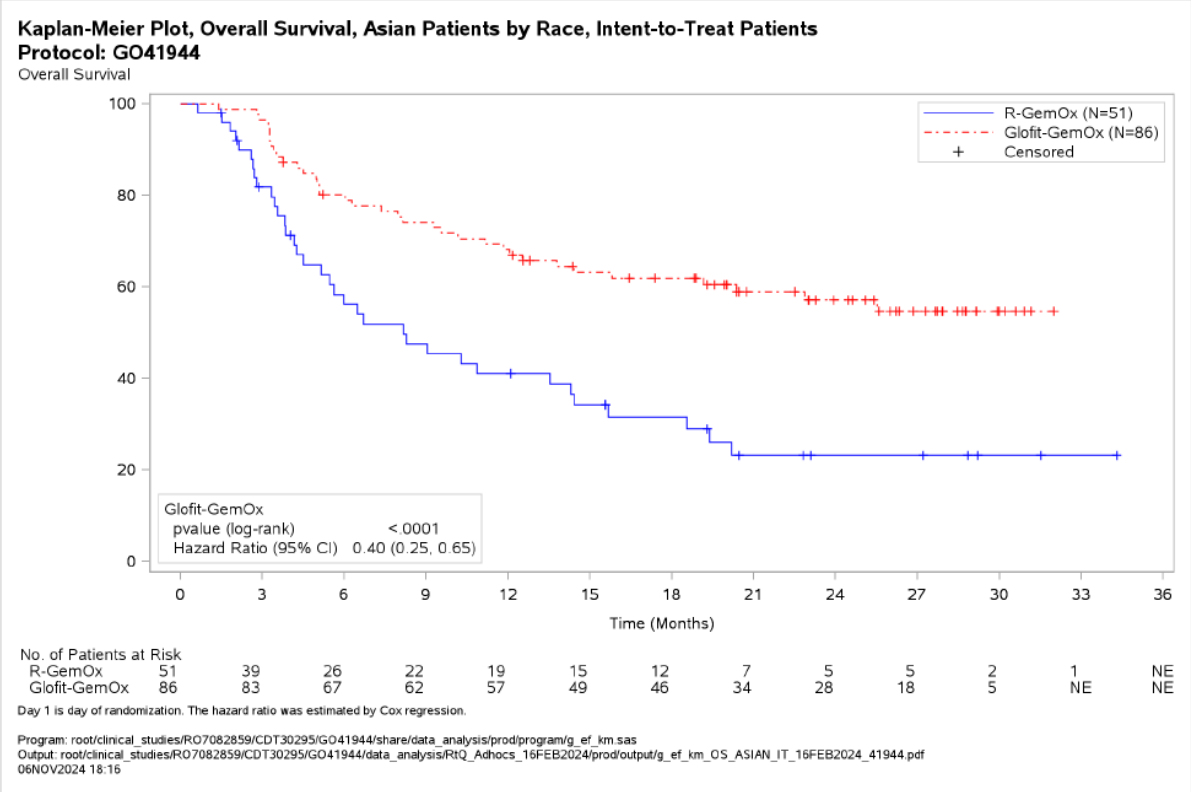
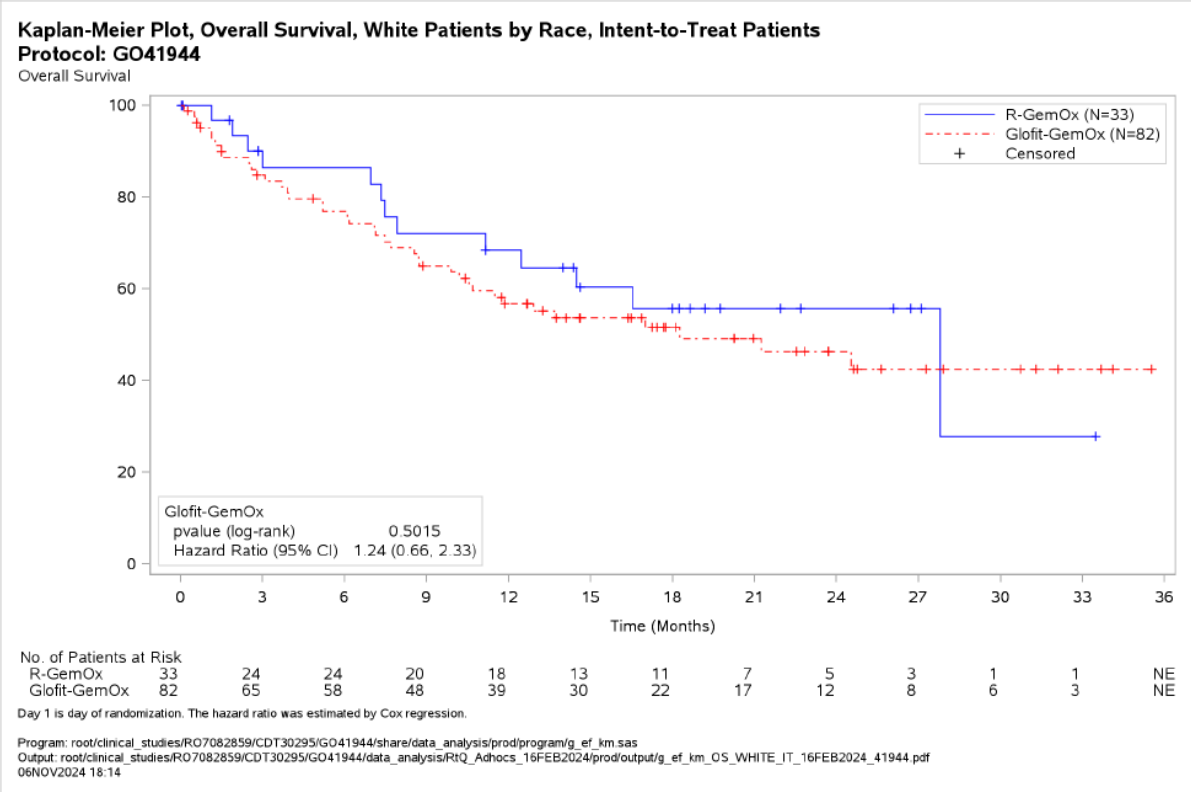
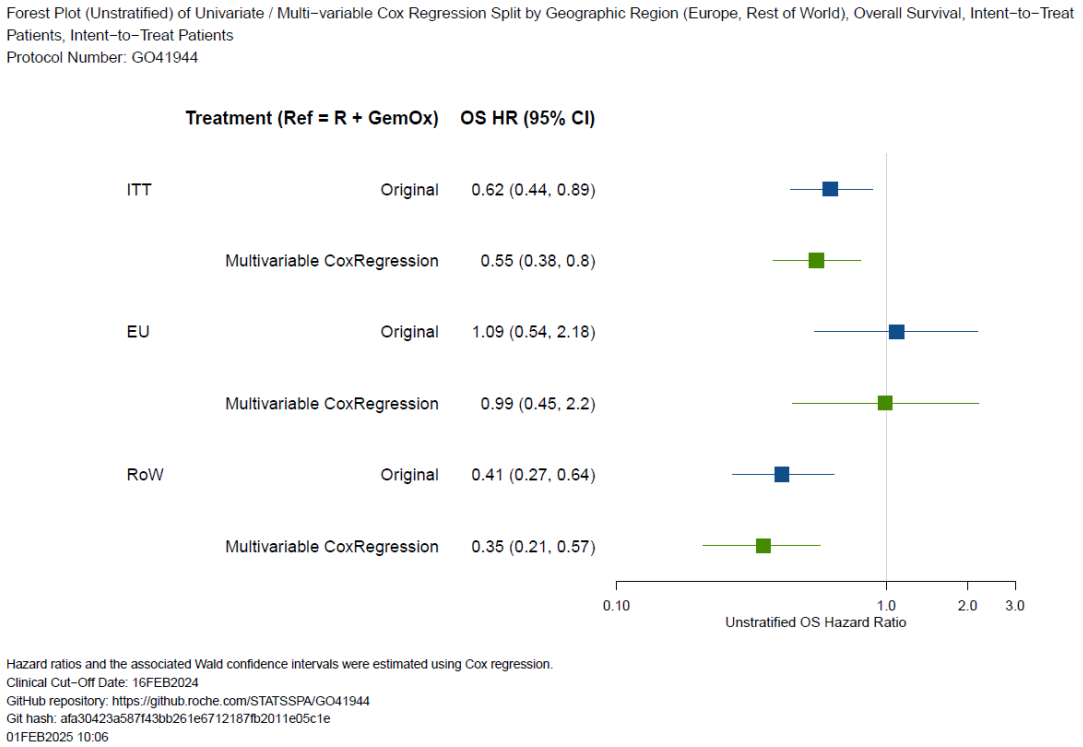


Figure 31



Multivariable Cox Regression Analysis, Glofit-GemOx vs. R-GemOx, Overall Survival, ITT Population and Europe and RoW subgroups (Study GO41944, CCOD: 16 February 2024)

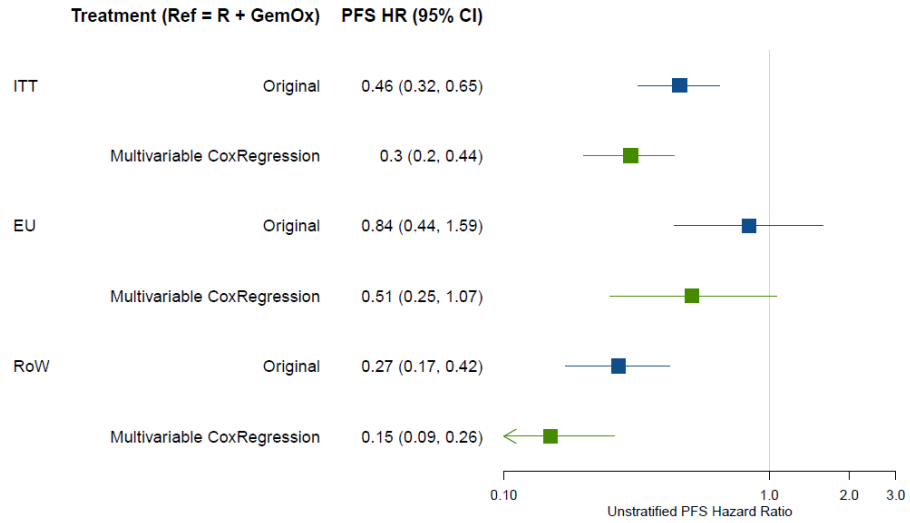
Figure 32



Multivariable Cox Regression Analysis, Glofit-GemOx vs. R-GemOx, IRC-Assessed Progression Free Survival, ITT Population and Europe and RoW subgroups (Study GO41944, CCOD: 16 February 2024)

Figure 33

Forest Plot (Unstratified) of Univariate / Multi−variable Cox Regression Split by Geographic Region (Europe, Rest of World), IRC Assessed PFS Censored Before NALT, Intent−to−Treat Patients, Intent−to−Treat Patients
Protocol Number: GO41944



Hazard ratios and the associated Wald confidence intervals were estimated using Cox regression.
Clinical Cut−Off Date: 16FEB2024
GitHub repository: https://github.roche.com/STATSSPA/GO41944
Git hash: afa30423a587f43bb261e6712187fb2011e05c1e
01FEB2025 10:06

Summary of main study

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 1. Summary of Efficacy for Trial GO41944 (STARGLO)

Title: A Phase III, Open-Label, Multicenter, Randomised Study Evaluating the Efficacy and Safety of Glofitamab in Combination with Gemcitabine Plus Oxaliplatin Versus Rituximab in Combination With Gemcitabine and Oxaliplatin in Patients With Relapsed/Refractory Diffuse Large B-Cell Lymphoma	
Study identifier	GO41944 EudraCT number: 2020-001021-31 NCT04408638
Design	A Phase III, open-label, multicenter, randomised controlled trial in patients with R/R DLBCL, designed to evaluate the efficacy and safety of glofitamab in combination with gemcitabine plus oxaliplatin (Glofit-GemOx) following pre-treatment with fixed dose of obinutuzumab (Gpt) compared with rituximab in combination with gemcitabine plus oxaliplatin (R-GemOx) in patients who have failed one line of therapy and are not candidates for transplant, as well as those patients who have failed at least two lines of therapy.

	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		Approx. 4 years (ongoing) not applicable not applicable
Hypothesis	The null hypothesis (H_o) that overall survival (OS) distribution in R/R diffuse large B-cell lymphoma not otherwise specified (DLBCL NOS) patients treated with Glofit-GemOx was equivalent to OS distribution in patients treated with R-GemOx was tested using a two-sided 0.05 level (adjusted based on the interim analysis) stratified log-rank test.		
Treatments groups	R/R DLBCL patients treated with Glofit-GemOx		A single intravenous dose of obinutuzumab pretreatment 7 days before the first dose of glofitamab, then up to 8 cycles of glofitamab in combination with gemcitabine plus oxaliplatin, followed by up to 4 cycles of glofitamab monotherapy, to complete up to a total of 12 cycles of glofitamab.
	R/R DLBCL patients treated with R-GemOx		Rituximab in combination with gemcitabine plus oxaliplatin for up to 8 cycles.
Endpoints and definitions	Primary efficacy endpoint	Overall survival (OS)	The time from randomization to date of death from any cause
	Key secondary efficacy endpoints	IRC-assessed Progression Free Survival (PFS)	The time from randomization to the first occurrence of disease progression or death from any cause, whichever occurred first as determined by the Independent Review Committee (IRC)
		IRC- assessed Complete Response (CR) rate	The proportion of patients whose best overall response was a CR on PET.CT during the study, as determined by the iRC.
		IRC-assessed Duration of Complete Response (DOCR)	The time from the first occurrence of a documented CR to disease progression, or death from any cause, whichever occurs first
Database lock	This summary is based on a clinical cut-off date of 29 March 2023 for the Primary Analysis and 16 February 2024 for the updated analysis with a database snapshot date of 25 May 2023 and 05 April 2024, respectively.		
Results and Analysis			
Analysis description	**Primary Analysis and Updated Analysis**		
Analysis population	The Intent-to-treat (ITT) population was defined as all randomised		

and time point description	patients, whether or not a patient received the assigned treatment. An interim analysis was planned to occur at the latest of the following timepoints: 1) when 70% of the OS events have been documented (i.e., 97 events will trigger the interim analysis), and 2) when all patients are randomised. These timepoints were expected to occur at a similar time; around 20 months after the first patient is randomised. Final analysis was planned to be conducted once 138 OS events are documented, which was expected to occur around 26 months after the first patient is randomised. Interim analysis took place after 101 OS events had occurred and was based on a clinical cutoff date of 29 March 2023. The independent Data Monitoring Committee (iDMC) recommended that the study be unblinded and fully analyzed because the p-value crossed the pre specified stopping boundary (0.017413). Thus, the interim analysis became the primary analysis and all subsequent updated analyses are considered descriptive. An updated analysis (CCOD of 16 February 2024) was performed in order to ensure sufficient follow-up to better characterize the overall benefit-risk assessment across all subgroups and was conducted at a time when all enrolled patients would have approximately 11 months of additional follow-up compared to the primary analysis

Descriptive statistics and estimate variability	**Analysis**	**Primary analysis CCOD: 29 Mar 2023**		**Updated analysis CCOD: 16 Feb 2024**	
	Treatment group	R-GemOx	Glofit-GemOx	R-GemOx	Glofit-GemOx
	Number of patients	91	183	91	183
	Primary Endpoint OS				
	Patients with event n (%)	40 (44.0%)	61 (33.3%)	52 (57.1%)	80 (43.7%)
	Median, months (95% CI)	9.0 (7.3, 14.4)	NE (13.8, NE)	12.9 (7.9, 18.5)	25.5 (18.3, NE)
	Stratified HR (95% CI)	0.59 (0.40, 0.89)		0.62 (0.43, 0.88)	
	p-value (log-rank)	0.010706		0.006366[c]	
Descriptive statistics and estimate variability	**Analysis**	**Primary analysis CCOD: 29 Mar 2023**		**Updated analysis CCOD: 16 Feb 2024**	
	Key Secondary Endpoint IRC-PFS (Formally tested)[a]				
	Patients with event n (%)	44 (48.4%)	68 (37.2%)	54 (59.3%)	90 (49.2%)
	Median, months	3.3	12.1	3.6	13.8

	(95% CI)	(2.5, 5.6)	(6.8, 18.3)	(2.5, 7.1)	(8.7, 20.5)
	Stratified HR (95% CI)	0.37 (0.25, 0.55)		0.40 (0.28, 0.57)	
	p-value (log-rank)	< 0.000001		< 0.000001[c]	
	Key Secondary Endpoint IRC-CR rate (Formally tested)[a, b]				
	Complete responders n (%) 95% CI	20 (22.0%) (14.0, 31.9)	92 (50.3%) (42.8, 57.7)	23 (25.3%) (16.8, 35.5)	107 (58.5%) (51.0, 65.7)
	Difference in response rate, stratified (95% CI)	28.3% (16.3, 40.3)		33.2% (20.9, 45.5)	
	p-value (Cochran-Mantel-Haenszel)	< 0.0001		< 0.0001[c]	
	Key Secondary Endpoint IRC-DOCR[a,]				
	Complete responders n (%)	20 (22.0%)	92 (50.3%)	23 (25.3%)	107 (58.5%)
	Patients with event n (%)	4 (20.0%)	15 (16.3%)	7 (30.4%)	28 (26.2%)
	Median, months (95% CI)	NE (6.4, NE)	14.4 (14.4 NE)	24.2 (6.9, NE)	NE (11.8, NE)
	Unstratified HR (95% CI)	0.59 (0.19, 1.83)		0.59 (0.25, 1.35)	
	p-value (log-rank)	0.3560		0.2040[c]	
Notes	The randomisation stratification factors used in the efficacy analyses were number of previous lines of systemic therapy for DLBCL (1 vs. ≥ 2) and outcome of last systemic therapy (relapsed vs. refractory).				

[a] These key secondary efficacy endpoints were tested according to the order shown in the table.

[b] IRC-Assessed CR rate was assessed using the Lugano Classification (Cheson et al. 2014)

[c] p-values for the updated analysis are descriptive.

CI=confidence interval; HR=hazard ratio; IRC = Independent Review Committee; NE=not evaluable;

Analysis performed across trials (pooled analyses and meta-analysis)

N/A

Clinical studies in special populations

N/A

Supportive study GO41943

Study GO41943 was a Phase Ib, open-label, multicentre study designed to evaluate the safety and preliminary efficacy of a CD20-CD3-bispecific antibody, either glofitamab or mosunetuzumab, in combination with GemOx in patients with R/R B-cell lymphoma, including patients with DLBCL, NOS; HGBCL with MYC, BCL2, and/or BCL6 rearrangements; and HGBCL, NOS.

The study was structured to allow enrolment of patients in one or both of the following two study arms:

- Arm A: Glofit-GemOx
- Arm B: Mosun-GemOx

Only the Glofit-GemOx arm (Arm A) is presented and discussed in this report.

Seventeen patients were enrolled in the Glofit-GemOx arm. Of these 17 patients, 5 patients (29.4%) completed the study. The remaining 12 patients (70.6%) discontinued the study due to death. The median duration of survival follow-up for all patients in the Glofit GemOx arm was 4.73 months (range: 0.4-12.2 months).

Demographics:

The majority of the patients in the Glofit-GemOx arm were White (15/17 patients [88.2%]) and male (13/17 patients [76.5%]), with a median age of 61 years (range: 50-78 years).

Baseline characteristics:

The most common histological cancer subtype at study entry among patients in the Glofit-GemOx arm was DLBCL germinal center B-cell (GCB) (6/17 patients [35.3%]), followed by DLBCL NOS (4/17 patients [23.5%]), HGBCL with MYC and BCL2 and/or BCL6 rearrangements (4/17 patients [23.5%]), and DLBCL activated B-cell type (ABC) (3/17 patients [17.6%]).

Patients in the Glofit-GemOx arm predominantly had Ann Arbor Stage IV (8/17 patients [47.1%]) or Ann Arbor Stage III disease (4/17 patients [23.5%]); bulky disease (11/17 patients [64.7%]), defined as tumour lesions measuring > 6 cm; and sum of the products of diameters (SPD) of ≥ 3000 mm2 (13/17 patients [76.5%]). The majority of the patients were refractory to any prior therapy (15/17 patients [88.2%]), with most also being refractory to their last line of prior therapy (14/17 patients [82.4%]) and refractory to any prior anti-CD20 therapy (12/17 patients [70.6%]).

Of the 17 patients, 11 patients (64.7%) had been treated with platinum-based therapies (such as rituximab, ifosfamide, carboplatin, and etoposide [R-ICE]) and 8 patients (47.1%) were refractory to any platinum-based therapies. The median number of prior cancer therapies was 2 (range: 1-4). The majority of patients (15/17 patients [88.2%]) had received ≥ 2 prior lines of cancer therapy and 2/17 patients (11.8%) had received 1 prior line of therapy.

Efficacy results:

All 17 patients enrolled in the Glofit-GemOx arm were included in the final efficacy analysis. Of the 17 patients who were evaluated for tumour response, 6 patients (35.3% [95% CI: 14.21, 61.67]) had an INV assessed best overall response of CR or partial response (PR), with 4 patients (23.5% [95% CI: 6.81, 49.90]) achieving CRs and 2 patients (11.8% [95% CI: 1.46, 36.44]) achieving PRs.

Patients with ECOG PS scale scores ≥ 1 (N = 11) had lower CR rates compared to patients with ECOG PS scores of zero (N = 6) (9% vs. 50%). All responses were observed in patients who had previously responded to platinum-based therapy or who had no prior platinum therapy. No responses were observed in 8 patients who were refractory to prior platinum-based regimens.

2.4.3. Discussion on clinical efficacy

The sought indication is: *COLUMVI in combination with gemcitabine and oxaliplatin is indicated for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma not otherwise specified (DLBCL NOS) who are ineligible for autologous stem cell transplant (ASCT).*

Design and conduct of clinical studies

There are several merits to the design of the pivotal trial, GO41944: The MAH has chosen to focus on a single, well-defined diagnostic entity (DLBCL NOS), and this is reflected in the sought indication. The chosen primary endpoint is overall survival, which is considered the endpoint of most interest in the population of relapsed/refractory DLBCL NOS patients. Further, the chosen chemotherapy backbone is well known and widely used, especially in the frailer population of patients not eligible for ASCT. Concerning this point, the pivotal study permitted enrolment of patients who had either failed one prior line of treatment and were ineligible for ASCT, or patients who had failed two or more lines of prior treatment. Some in the latter group of patients could in given cases conceivably tolerate ASCT, however, this treatment has historically not been recommended for those failing more than one line of treatment since the chance of success of ASCT when having failed multiple lines of (chemotherapy-containing) prior therapies is limited, while the associated burden of toxicity is high.

Along with the merits mentioned above, however, there are also a number of concerns pertaining to the submitted dossier.

Patients in Germany and France were required to have failed or be ineligible for CAR-T treatment in order to enrol in the pivotal trial. The MAH has provided additional analyses that suggest that this additional criterion did not impact the overall results of the trial.

The MAH is seeking approval for treatment in a population not eligible for ASCT. In order to select such a population for study, they have enumerated several ineligibility criteria including, for example: age, performance status and comorbidities. Most of these are fully endorsed, however, the protocol also allowed for the possibility for a patient to refuse ASCT and be considered ineligible for this treatment. This is not in line with guidelines or published reports on R-GemOx. Accepting "patient refusal" as an ineligibility criterion for ASCT might permit fitter patients than those generally fulfilling ASCT-ineligibility criteria to participate to the trial. The MAH has however provided additional information to describe the population of patients whose primary reason for ASCT ineligibility was refusal. Furthermore, the MAH provided additional evidence that a large proportion of those refusing ASCT had other characteristics that would disqualify them from this treatment. Still, it appears that OS in patients who refused ASCT was better than those who did not suggesting these patients were somehow in better condition. In addition, patient refusal of ASCT seems to be associated regional differences in prevalence and unequal distribution to treatment arms, potentially contributing significant bias to the study. Practices concerning ASCT might vary significantly between regions; yet, region was not a stratification factor (although recommended in guideline ICH-E17).

The comparator arm, R-GemOx was modified from the way it is usually administered in clinical practice (since it is not a formally approved treatment regimen but based on published reports) by extending the duration of each cycle from 2 weeks to 3 weeks, while maintaining the doses administered unaltered. This might imply undertreatment of the patients in the control arm, considering also that the trial included a fitter than average selection of relapsed patients in which there is no obvious reason to deintensify R-GemOx from a 2-week schedule to a 3-week schedule. Considering EU and international guidelines, neither ESMO nor NCCN recommendations specify the cycle duration of R-

GemOx which should be left to the physician's discretion depending on the profile of each patient even though it is generally understood that a 14-days cycle is usually preferred in fit patients who are able to tolerate shorter and intensive chemotherapy cycles. It is also acknowledged that although the trial inclusion/exclusion criteria seem to target fit patients, the addition of glofitamab could justify the choice of a less aggressive GemOx 21-days cycle regimen.

The chosen endpoints are acceptable with OS as the primary endpoint, the gold standard for a trial in R/R DLBCL NOS.

The statistical methods are acceptable. The requested RMST analysis was conducted post-hoc but is consistent with the pre-specified SAP conditions for use when PH violations are suspected. The results of additional post-hoc exploratory analyses by geographic region of enrolment indicate that several potential confounding factors, such as baseline characteristics, chance finding, NALTs, and the impact of COVID-19, have variably influenced the results in subgroups by geographic region. The RMST results showed a significant improvement in restricted mean survival time for Glofit-GemOx compared to R-GemOx, with a p-value of 0.0135. This aligns with the findings from the primary OS analysis, further supporting the benefit of Glofit-GemOx.

Baseline data:

Some baseline data seem skewed and may be of importance for the discussion on subgroups below. In terms of race, noticeably more patients of Asian race were enrolled to the control arm while more of those receiving Glofit-GemOx were White. Overall, the performance status of patients from the experimental arm was worse than the control arm at baseline. In terms of disease-severity characteristics, an imbalance in the Revised International Prognostic Index (R-IPI) was noted, with more patients treated with R-GemOx falling in the R-IPI poor risk category (3-5 points) compared to in the Glofit-GemOx arm. This imbalance is reflected in the proportions of patients with Stage III/IV disease. There were also numerically higher proportions of patients in the control arm with the adverse disease characteristics relating to tumour size (Bulky disease and SPD ≥3000) while Cell-of-Origin subtype was well balanced. Overall, the baseline characteristics of the enrolled cohort appear to favour the experimental arm. Similar proportions of patients were ineligible for ASCT due to "Patient refusal" in the two arms.

Efficacy data and additional analyses

Outcomes:

Primary endpoint - OS: At the time of the primary (interim) analysis (CCOD: 29 MAR 2023), the study demonstrated an improved HR for OS 0.59 (95% CI 0.40, 0.89) in Glofit-GemOx treated patients compared to R-GemOx treated patients. Improvement in OS was maintained at the updated analysis (HR for OS 0.62, 95% CI 0.43, 0.88). OS in the control arm falls within what has previously been published for patients treated with R-GemOx (although, OS may be influenced by later lines of treatment, many of which were not available at the time of the original R-GemOx publications). The MAH has agreed to provide an updated analysis of OS as a recommendation analysis is planned the MAH is requested to submit the analysis when the final CSR for Study GO41944 is submitted.

Key secondary endpoint – IRC-assessed PFS: At the time of primary analysis, GO41944 demonstrated improved PFS in Glofit-GemOx treated patients compared to R-GemOx treated patients (HR for PFS 0.37, 95% CI 0.25, 0.55). PFS remained improved in the experimental arm at the time of the updated analysis (HR for PFS 0.40, 95% CI 0.28, 0.57). The fact that the improvement in OS is supported by improvement in PFS is reassuring.

Key secondary endpoint – IRC-assessed CR rate: The CR rate in the Glofit-GemOx arm was higher than in the R-GemOx arm at both time points analysed. Notably, the CR rate of the Glofit-GemOx arm

increased 8 percentage points from the primary to the updated time of analysis suggesting that some late(r) responses may occur on this treatment. With all the caveats associated with cross-study comparisons in mind, it seems that the comparator arm of GO41944 performed somewhat less well than would be expected from prior reports in terms of CR rate.

Ancillary analyses: While analyses of subgroups were not adequately powered, they may still provide insight into the performance of the investigated treatment in specific populations. Most subgroups analysed aligned with the result seen in the ITT, however, white race and geographic regions of Europe and North America, as well as, patients with ECOG performance status = 2 (the highest permitted on study) all had HRs above 1. This concern was further investigated as follows:

Race: Due to the mechanism of action of glofitamab, as well as the similar pharmacology of glofitamab across racial groups, it is unlikely that race itself is a clear determinant of differential outcome to glofitamab treatment. It is noted that race and region were closely associated.

Region: In terms of regional differences, most of the benefit of the ITT population seems to be driven by the rest of the world (RoW) region while the regions of Europe and North America performed less well. When comparing Europe to the RoW, results from the primary endpoint of OS were better in the RoW for the experimental arm while the control arm performed (much) worse in RoW. Together these results yield a highly significant result in the RoW which could be argued that could be due to differences in regional baseline characteristics and/or regional availability of effective later-line treatment (NALT).

Regional differences in baseline characteristics: The European patients were older and were more likely to have received prior CAR-T than the ITT and RoW populations. The latter is potentially due to the requirement of ineligibility for CAR-T in Germany and France. Both older age and prior CAR-T (or ineligibility to this) could potentially mean that the European patients were frailer, as a group, compared to those treated in the RoW. In addition, there seem to be regional differences in the justification of ineligibility for ASCT. In Europe, the most common reason provided was age and this was well-balanced between both arms. In the RoW, the most common reason was "patient refusal", potentially selecting patients fitter than those with constitutional attributes barring them from ASCT. Furthermore, it seems that allocation to treatment was skewed among the latter group, with more patients ineligible due to "refusal" randomised to Glofit-GemOx, which could result in more fit patients in the experimental arm.

Regional differences in availability of NALT: Differences in availability of effective anti-lymphoma treatment after failure on this trial may impact OS and considering the wider availability of NALT options in the EU compared to the RoW. Furthermore, a number of patients were censored before receiving NALT, typically those not achieving CR but without definite progression either (standard practice as anything other than CR is considered a sub-optimal result). This might impact PFS so the MAH provided an analysis of EFS with death (data not shown), progression or NALT as events. Using this analysis, the hazard ratios for EFS across regions looked more favourable for the experimental arm (compared to PFS) but this was not the case in Europe. One efficacy result that should be independent of availability of NALT and censoring is CR rate. Regional differences in CR rates are present where the control arm in the RoW underperforms; the MAH however provided the treatment outcomes of R-GemOx in Study GO41944 compared with those from the NIVEAU study (Held et al, 2023) a recent study conducted almost exclusively in European countries within the same patient population. The findings of these comparisons indicate that the results of Study GO41944 from the control arm are applicable to the European population.

To further assess the generalizability of the results of Study GO41944 to the European population, an evaluation of patient characteristics in the European subgroup vs. those of the ITT population was performed. The Applicant also compared the baseline demographic and disease characteristics.

Overall, on the applicability of the results from the ITT (benefit seemingly driven by RoW) in the European context, the CHMP considers the regional differences to be explained by the rather limited size of the pivotal study, as well as the 2:1 randomisation making the overall size of the control group less than 100 patients. Further, for the evaluation of the discrepancy in the OS results between regions and race (which is highly correlated with region), ICH E17 on multi-regional trials and the *EMA guideline on subgroups* were taken into account. With the overall positive and statistically persuasive primary results and the lack of a pharmacological / biological rational why the effect should be smaller in the European population, the observed effects in the ITT population should be applicable to Europe. Taking also into account the results of multivariate analyses to account for the contribution of multiple potentially prognostic factors the CHMP considers that a benefit in a European context has been satisfactorily substantiated.

Results from a supportive study, GO41943, with 17 patients with mixed lymphoma diagnoses were included in the dossier. The main objective of the study was to assess the safety of combining glofitamab with GemOx. Due to this, as well as significant differences between the patient populations enrolled in the pivotal and supportive studies, the results could not be pooled with those from the pivotal study, GO41944. Two facts were however noted from the supportive study: platinum-exposed/-refractory patients do not seem to fare well on glofit-GemOx and patients with ECOG ≥1 may also not benefit from this treatment.

The inclusion of reference to eligibility for ASCT in the indication text is a measure of patient fitness, not a matter of patient preference or logistics. For this reason, the MAH agreed to revise the indication according to the proposal by the CHMP as: patients with relapsed or refractory diffuse large B-cell lymphoma not otherwise specified (DLBCL NOS, according to WHO 2016) who are ineligible for autologous stem cell transplant (ASCT).

Additional expert consultation

Not applicable.

Assessment of paediatric data on clinical efficacy

Not applicable.

2.4.4. Conclusions on the clinical efficacy

The pivotal trial GO41944 demonstrated an improvement in OS, IRC-assessed PFS and IRC-assessed CR rate with Glofit-GemOx compared to R-GemOx in patients with R/R DLBCL NOS who are not eligible for ASCT.

The MAH agreed to provide updated OS analysis when the final CSR for Study GO41944 (STARGLO) is available - as recommended by the CHMP.

2.5. Clinical safety

Introduction

Pivotal Study GO41944 is an ongoing Phase III, open-label, multicenter, randomised study evaluating the efficacy and safety of glofitamab in combination with gemcitabine plus oxaliplatin (Glofit-GemOx) versus rituximab in combination with gemcitabine and oxaliplatin (R-GemOx; *randomised 2:1)* in patients with relapsed or refractory (R/R) diffuse large B-cell lymphoma (DLBCL).

The updated CSR for Study GO41944 provides data based on a CCOD of 16 February 2024 by which time the last patient enrolled had approximately 11 months follow-up from treatment start.

The safety analysis comprises data from 260 patients who received at least one dose of either rituximab (R-GemOx arm) or glofitamab (Glofit-GemOx arm; *also denoted Glofit-Exposed*). This includes 88 patients in the R-GemOx arm and 172 patients in the Glofit-GemOx arm.

Supportive Study GO41943 was an open-label, multicenter, two-treatment arm Phase Ib study with non-randomised arms evaluating the safety and preliminary efficacy of Glofit-GemOx or mosunetuzumab in combination with gemcitabine plus oxaliplatin (Mosun-GemOx) in patients with R/R large B-cell lymphoma (LBCL) and high-grade large B-cell lymphoma (HGBCL).

The final CSR for Study GO41943 (last patient last visit [LPLV] date of 26 October 2021) provides data of Glofit-GemOx or Mosun-GemOx in patients with R/R DLBCL or HGBCL from the first patient enrolled (4 June 2020) up to database lock (DBL) of 2 December 2021.

In order to provide a comprehensive overview of the safety profile of Glofit-GemOx combination therapy for the treatment of R/R DLBCL, a side-by-side comparison and a pooled analysis of safety from the pivotal Study GO41944 and supportive Study GO41943 based on the following treatment groups is presented:

- GO41944 (Rituximab-GemOx arm)

1. Patients with R/R DLBCL receiving R-GemOx (N=88)

- GO41944 (Glofitamab-GemOx arm)

2. Patients with R/R DLBCL receiving Glofit- GemOx (N=172)

- GO41943 (Glofitamab-GemOx arm)

3. Patients with R/R DLBCL[a] receiving Glofit- GemOx (N=16)

- GO41944 + GO41943 (Glofitamab-GemOx arms)

4. Patients with R/R DLBCL[a] receiving Glofit-GemOx (N=188)

[a] Includes 4 patients with HGBCL in Study GO41943

There were 8 patients who discontinued study treatment following Gpt who did not receive glofitamab. Three patients experienced a Grade 5 (fatal) AE, of which 2 patients had COVID-19 associated AEs (neutropenic sepsis and COVID-19 and 1 patient experienced septic shock due to a caecal perforation and splenic rupture. Three patients discontinued from the study treatment due to adverse events: 1 patient discontinued due to COVID-19 following the implementation of the USM DIL, 1 patient discontinued due to myocardial infarction, which was unrelated to Gpt-GemOx and involved multiple cardiac risk factors (ongoing type 2 diabetes, dyslipidemia, and ischemic heart disease), and 1 patient discontinued due to cardiac failure and then had subsequent Grade 5 neutropenic sepsis which is

mentioned above. Two patients discontinued study treatment due to progressive disease or disease relapse, or symptomatic deterioration. One patient withdrew their consent from the study.

Patient exposure

Table 33 Summary of exposure GO41944, GO41943

Name of Treatment (Dose Unit)	R-GemOx (GO41944) (N=88)	Glofit-GemOx (Glofit Exposed) (GO41944) (N=172)	Glofit-GemOx (Glofit Exposed) (GO41943) (N=16)	Glofit-GemOx (Glofit Exposed) (GO41944 & GO41943) (N=188)
Gemcitabine (mg/m2)				
Number of Infusions				
n	88	172	16	188
Mean (SD)	4.4 (2.7)	6.3 (2.5)	5.6 (2.2)	6.2 (2.4)
Median	4.0	8.0	5.0	8.0
Min - Max	1 - 8	1 - 9	2 - 8	1 - 9
Glofitamab (mg)				
Number of Infusions				
n	0	172	16	188
Mean (SD)	NE (NE)	9.6 (4.1)	7.8 (3.8)	9.4 (4.1)
Median	NE	12.0	6.0	11.0
Min - Max	NE - NE	1 - 14	3 - 14	1 - 14
Oxaliplatin (mg/m2)				
Number of Infusions				
n	88	172	16	188
Mean (SD)	4.4 (2.7)	6.2 (2.5)	5.6 (2.2)	6.2 (2.4)
Median	4.0	8.0	5.0	8.0
Min - Max	1 - 8	1 - 9	2 - 8	1 - 9
Rituximab (mg/m2)				
Number of Infusions				
n	88	0	0	0
Mean (SD)	4.4 (2.7)	NE (NE)	NE (NE)	NE (NE)
Median	4.0	NE	NE	NE
Min - Max	1 - 8	NE - NE	NE - NE	NE - NE
Tocilizumab (mg/kg)				
Number of Infusions				
n	0	28	3	31
Mean (SD)	NE (NE)	1.4 (0.7)	1.7 (1.2)	1.4 (0.8)
Median	NE	1.0	1.0	1.0
Min - Max	NE - NE	1 - 4	1 - 3	1 - 4

Data Cutoff Dates: GO41943 - 08DEC2021, GO41944 - 16FEB2024.
Treatment duration is the date of the last dose of study medication minus the date of the first dose plus one day.
Dose intensity is the total dose actually received divided by the expected total dose.
The CRF Y/N tickbox for dose modifications is only available for Oxaliplatin and Tocilizumab.
A dose reduction is considered as a dose that is less than 80% of the planned dose.

Adverse events

Table 34 Overview of Adverse events, Modified Safety Evaluable patients GO41944, GO41943

	R-GemOx (GO41944) (N=88)	Glofit-GemOx (Glofit Exposed) (GO41944) (N=172)	Glofit-GemOx (Glofit Exposed) (GO41943) (N=16)	Glofit-GemOx (Glofit Exposed) (GO41944 & GO41943) (N=188)
Total number of patients with at least one AE	84 (95.5%)	172 (100%)	16 (100%)	188 (100%)
Total number of AEs	868	3299	203	3502
Total number of deaths	51 (58.0%)	74 (43.0%)	11 (68.8%)	85 (45.2%)
Total number of patients withdrawn from any treatment due to an AE	11 (12.5%)	43 (25.0%)	1 (6.3%)	44 (23.4%)
Total number of patients with an AE with fatal outcome	4 (4.5%)	12 (7.0%)	0	12 (6.4%)
Total number of patients with at least one				
AE leading to withdrawal from Glofitamab/Rituximab	11 (12.5%)	36 (20.9%)	1 (6.3%)	37 (19.7%)
AE leading to withdrawal from Obinutuzumab	0	1 (0.6%)	0	1 (0.5%)
AE leading to withdrawal from Gemcitabine	11 (12.5%)	26 (15.1%)	0	26 (13.8%)
AE leading to withdrawal from Oxaliplatin	11 (12.5%)	29 (16.9%)	0	29 (15.4%)
AE leading to dose interruption of Glofitamab/ Rituximab	14 (15.9%)	75 (43.6%)	5 (31.3%)	80 (42.6%)
AE leading to dose interruption of Obinutuzumab	0	8 (4.7%)	0	8 (4.3%)
AE leading to dose interruption of Gemcitabine	14 (15.9%)	61 (35.5%)	4 (25.0%)	65 (34.6%)
AE leading to dose modification of Gemcitabine	0	2 (1.2%)	0	2 (1.1%)
AE leading to dose interruption of Oxaliplatin	14 (15.9%)	60 (34.9%)	4 (25.0%)	64 (34.0%)
AE leading to dose modification of Oxaliplatin	6 (6.8%)	5 (2.9%)	0	5 (2.7%)
Serious AE	15 (17.0%)	90 (52.3%)	11 (68.8%)	101 (53.7%)
Serious AE leading to withdrawal from Glofitamab/ Rituximab	6 (6.8%)	21 (12.2%)	1 (6.3%)	22 (11.7%)
Serious AE leading to dose interruption of Glofitamab/Rituximab	5 (5.7%)	35 (20.3%)	2 (12.5%)	37 (19.7%)
AE related to Glofitamab/Rituximab	58 (65.9%)	149 (86.6%)	14 (87.5%)	163 (86.7%)
AE related to Obinutuzumab	0	108 (62.8%)	5 (31.3%)	113 (60.1%)
AE related to Gemcitabine	73 (83.0%)	156 (90.7%)	16 (100%)	172 (91.5%)
AE related to Oxaliplatin	79 (89.8%)	158 (91.9%)	16 (100%)	174 (92.6%)
Serious AE related to Glofitamab/Rituximab	7 (8.0%)	62 (36.0%)	4 (25.0%)	66 (35.1%)
Serious AE related to Obinutuzumab	0	15 (8.7%)	1 (6.3%)	16 (8.5%)
Serious AE related to Gemcitabine	7 (8.0%)	36 (20.9%)	6 (37.5%)	42 (22.3%)
Serious AE related to Oxaliplatin	7 (8.0%)	37 (21.5%)	6 (37.5%)	43 (22.9%)
Grade 3-5 AE	36 (40.9%)	132 (76.7%)	12 (75.0%)	144 (76.6%)
Grade 3-5 AE related to Glofitamab/Rituximab	20 (22.7%)	85 (49.4%)	5 (31.3%)	90 (47.9%)
Grade 3-5 AE related to Obinutuzumab	0	52 (30.2%)	2 (12.5%)	54 (28.7%)
Grade 3-5 AE related to Gemcitabine	28 (31.8%)	101 (58.7%)	11 (68.8%)	112 (59.6%)
Grade 3-5 AE related to Oxaliplatin	30 (34.1%)	104 (60.5%)	11 (68.8%)	115 (61.2%)

	R-GemOx (GO41944) (N=88)	Glofit-GemOx (Glofit Exposed) (GO41944) (N=172)	Glofit-GemOx (Glofit Exposed) (GO41943) (N=16)	Glofit-GemOx (Glofit Exposed) (GO41944 & GO41943) (N=188)
Glofitamab/Rituximab related AESI	9 (10.2%)	49 (28.5%)	5 (31.3%)	54 (28.7%)
Obinutuzumab related AESI	0	7 (4.1%)	1 (6.3%)	8 (4.3%)
AE related to Glofitamab/Rituximab leading to withdrawal from Glofitamab/Rituximab	3 (3.4%)	13 (7.6%)	0	13 (6.9%)
AE related to Glofitamab/Rituximab leading to dose interruption of Glofitamab/Rituximab	9 (10.2%)	43 (25.0%)	3 (18.8%)	46 (24.5%)
Outcome of adverse events				
Recovered / resolved	649	2709	154	2863
Recovering / resolving	0	0	3	3
Recovered / resolved with sequelae	6	30	1	31
Not recovered / resolved	183	528	44	572
Fatal	4	12	0	12
Unknown / missing	26	20	1	21

Data Cutoff Dates: GO41943 - 08DEC2021, GO41944 - 16FEB2024.
Investigator text for AEs encoded using MedDRA version 26.1. Percentages are based on N in the column headings. Only treatment emergent AEs are displayed.
Multiple occurrences of the same AE in one individual are counted only once except for "Total number of AEs" row in which multiple occurrences of the same AE are counted separately.
Tocilizumab not included as a study drug.

Common adverse events

Table 35 Summary of Common Adverse events, Modified Safety Evaluable patients

Table 8 Summary of Adverse Events With an Incidence Rate of ≥10% (Safety Evaluable Patients Receiving R-GemOx or Glofit-GemOx)

Summary of Adverse Events, Modified Safety-Evaluable Patients
Protocol: GO41944 & GO41943

MedDRA System Organ Class MedDRA Preferred Term	R-GemOx (GO41944) (N=88)	Glofit-GemOx (Glofit Exposed) (GO41944) (N=172)	Glofit-GemOx (Glofit Exposed) (GO41943) (N=16)	Glofit-GemOx (Glofit Exposed) (GO41944 & GO41943) (N=188)
Total number of patients with at least one adverse event	84 (95.5%)	172 (100%)	16 (100%)	188 (100%)
Overall total number of events	868	3299	203	3502
Gastrointestinal disorders				
Total number of patients with at least one adverse event	59 (67.0%)	121 (70.3%)	14 (87.5%)	135 (71.8%)
Total number of events	153	444	32	476
Nausea	35 (39.8%)	71 (41.3%)	4 (25.0%)	75 (39.9%)
Diarrhoea	24 (27.3%)	60 (34.9%)	7 (43.8%)	67 (35.6%)
Vomiting	19 (21.6%)	41 (23.8%)	3 (18.8%)	44 (23.4%)
Constipation	14 (15.9%)	32 (18.6%)	4 (25.0%)	36 (19.1%)
Abdominal pain	2 (2.3%)	17 (9.9%)	2 (12.5%)	19 (10.1%)
Investigations				
Total number of patients with at least one adverse event	48 (54.5%)	121 (70.3%)	9 (56.3%)	130 (69.1%)
Total number of events	239	1041	20	1061
Platelet count decreased	27 (30.7%)	66 (38.4%)	3 (18.8%)	69 (36.7%)
Alanine aminotransferase increased	19 (21.6%)	56 (32.6%)	2 (12.5%)	58 (30.9%)
Aspartate aminotransferase increased	17 (19.3%)	59 (34.3%)	0	59 (31.4%)
Neutrophil count decreased	18 (20.5%)	51 (29.7%)	2 (12.5%)	53 (28.2%)
Lymphocyte count decreased	12 (13.6%)	37 (21.5%)	0	37 (19.7%)
White blood cell count decreased	12 (13.6%)	37 (21.5%)	0	37 (19.7%)
Blood alkaline phosphatase increased	16 (18.2%)	31 (18.0%)	1 (6.3%)	32 (17.0%)
Serum ferritin increased	10 (11.4%)	29 (16.9%)	0	29 (15.4%)
Gamma-glutamyltransferase increased	10 (11.4%)	25 (14.5%)	0	25 (13.3%)
Weight decreased	5 (5.7%)	17 (9.9%)	3 (18.8%)	20 (10.6%)
Blood lactate dehydrogenase increased	4 (4.5%)	20 (11.6%)	0	20 (10.6%)
Metabolism and nutrition disorders				
Total number of patients with at least one adverse event	41 (46.6%)	102 (59.3%)	8 (50.0%)	110 (58.5%)
Total number of events	111	380	20	400
Decreased appetite	24 (27.3%)	50 (29.1%)	1 (6.3%)	51 (27.1%)
Hypokalaemia	6 (6.8%)	32 (18.6%)	2 (12.5%)	34 (18.1%)
Hypomagnesaemia	10 (11.4%)	13 (7.6%)	5 (31.3%)	18 (9.6%)
Hyponatraemia	5 (5.7%)	19 (11.0%)	0	19 (10.1%)

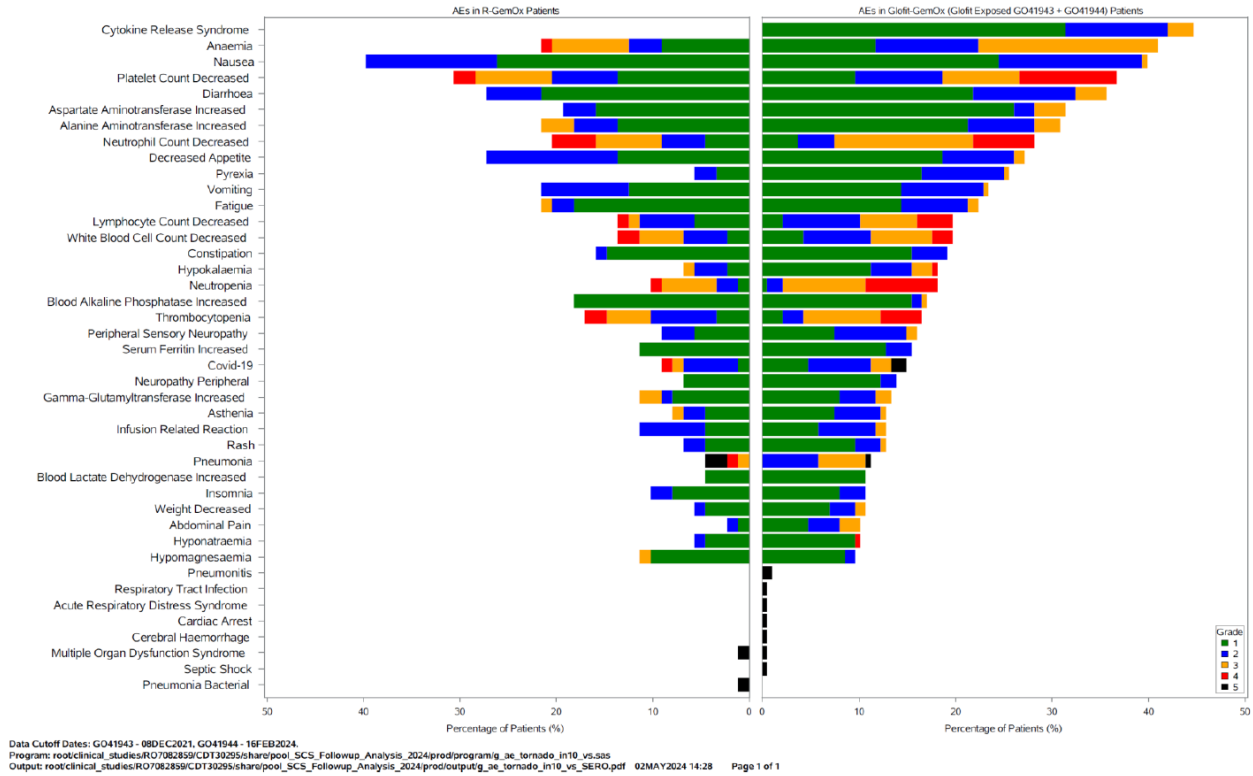
MedDRA System Organ Class MedDRA Preferred Term	R-GemOx (GO41944) (N=88)	(Glofit Exposed) (GO41944) (N=172)	(Glofit Exposed) (GO41943) (N=16)	(Glofit Exposed) (GO41944 & GO41943) (N=188)
General disorders and administration site conditions				
Total number of patients with at least one adverse event	39 (44.3%)	101 (58.7%)	8 (50.0%)	109 (58.0%)
Total number of events	53	209	12	221
Fatigue	19 (21.6%)	38 (22.1%)	4 (25.0%)	42 (22.3%)
Pyrexia	5 (5.7%)	42 (24.4%)	6 (37.5%)	48 (25.5%)
Asthenia	7 (8.0%)	24 (14.0%)	0	24 (12.8%)
Blood and lymphatic system disorders				
Total number of patients with at least one adverse event	34 (38.6%)	99 (57.6%)	10 (62.5%)	109 (58.0%)
Total number of events	81	280	29	309
Anaemia	19 (21.6%)	71 (41.3%)	6 (37.5%)	77 (41.0%)
Neutropenia	9 (10.2%)	29 (16.9%)	5 (31.3%)	34 (18.1%)
Thrombocytopenia	15 (17.0%)	26 (15.1%)	5 (31.3%)	31 (16.5%)
Infections and infestations				
Total number of patients with at least one adverse event	26 (29.5%)	95 (55.2%)	7 (43.8%)	102 (54.3%)
Total number of events	39	191	14	205
COVID-19	8 (9.1%)	28 (16.3%)	0	28 (14.9%)
Pneumonia	4 (4.5%)	21 (12.2%)	0	21 (11.2%)
Nervous system disorders				
Total number of patients with at least one adverse event	26 (29.5%)	81 (47.1%)	11 (68.8%)	92 (48.9%)
Total number of events	49	164	23	187
Peripheral sensory neuropathy	8 (9.1%)	27 (15.7%)	3 (18.8%)	30 (16.0%)
Neuropathy peripheral	6 (6.8%)	20 (11.6%)	6 (37.5%)	26 (13.8%)
Immune system disorders				
Total number of patients with at least one adverse event	1 (1.1%)	77 (44.8%)	8 (50.0%)	85 (45.2%)
Total number of events	1	155	19	174
Cytokine release syndrome	0	76 (44.2%)	8 (50.0%)	84 (44.7%)
Skin and subcutaneous tissue disorders				
Total number of patients with at least one adverse event	16 (18.2%)	54 (31.4%)	3 (18.8%)	57 (30.3%)
Total number of events	25	81	3	84
Rash	6 (6.8%)	23 (13.4%)	1 (6.3%)	24 (12.8%)

MedDRA System Organ Class MedDRA Preferred Term	R-GemOx (GO41944) (N=88)	Glofit-GemOx (Glofit Exposed) (GO41944) (N=172)	Glofit-GemOx (Glofit Exposed) (GO41943) (N=16)	Glofit-GemOx (Glofit Exposed) (GO41944 & GO41943) (N=188)
Injury, poisoning and procedural complications				
Total number of patients with at least one adverse event	12 (13.6%)	43 (25.0%)	2 (12.5%)	45 (23.9%)
Total number of events	13	61	2	63
Infusion related reaction	10 (11.4%)	23 (13.4%)	1 (6.3%)	24 (12.8%)
Psychiatric disorders				
Total number of patients with at least one adverse event	11 (12.5%)	37 (21.5%)	1 (6.3%)	38 (20.2%)
Total number of events	12	47	1	48
Insomnia	9 (10.2%)	20 (11.6%)	0	20 (10.6%)

Data Cutoff Dates: GO41943 - 08DEC2021, GO41944 - 16FEB2024.
Investigator text for AEs encoded using MedDRA version 26.1. Percentages are based on N in the column headings.
Only treatment emergent AEs are displayed. For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.

Program: root/clinical_studies/RO7082859/CDT30295/share/pool_SCS_Followup_Analysis_2024/prod/program/t_ae.sas
Adapted from Output: t_ae_SERO
02MAY2024 14:43

Figure 5 Tornado Plot of Adverse Events with ≥10% Incidence (Pooled GO41944 and GO41943 Data: Safety Evaluable Patients Receiving Glofit-GemOx or R-GemOx)



Treatment-related adverse events

The most frequently reported AEs (any grade ≥20%) by PT, excluding CRS, assessed as related to any treatment by the investigator in the Glofit-GemOx and R-GemOx arms, respectively, were:

- Platelet count decreased (38.4% vs. 28.4% patients)
- Nausea (35.5% vs. 34.1% patients)
- Anaemia (33.1% vs. 15.9% patients)
- AST increased (32.6% vs. 18.2% patients)
- ALT increased (30.2% vs. 20.5% patients)
- Neutrophil count decreased (29.7% vs. 18.2% patients)
- Decreased appetite (25.6% vs. 20.5% patients)

- Diarrhoea (25.0% vs. 20.5% patients)
- Lymphocyte count decreased (21.5% vs. 12.5% patients)
- White blood cell count decreased (21.5% vs. 12.5% patients)
- Vomiting (20.3% vs. 20.5% patients)

CRS related to treatment was reported in 44.2% of patients in the Glofit-GemOx arm, andin none of the patients in the R-GemOx arm.

Grade 3-4 Adverse Events

Table 1 Summary of Grade 3–4 Adverse Events by Preferred Term with an Incidence Rate of ≥2% in the Glofit-GemOx (Glofit Exposed) Population (Study GO41944; Safety Evaluable Population)

SOC / PT	R-GemOx (N=88)	Glofit-GemOx (Glofit Exposed) (N=172)	Glofit-GemOx (Any Treatment Exposed) (N=180)
Total no. of patients (%) with at least one AE, n (%)	35 (39.8%)	129 (75.0%)	136 (75.6%)
Investigations	20 (22.7%)	67 (39.0%)	67 (37.2%)
Neutrophil count decreased	10 (11.4%)	38 (22.1%)	38 (21.1%)
Platelet count decreased	9 (10.2%)	31 (18.0%)	31 (17.2%)
Lymphocyte count decreased	2 (2.3%)	18 (10.5%)	18 (10.0%)
White blood cell count decreased	6 (6.8%)	16 (9.3%)	16 (8.9%)
Alanine aminotransferase increased	3 (3.4%)	5 (2.9%)	5 (2.8%)
Aspartate aminotransferase increased	0	6 (3.5%)	6 (3.3%)
Blood and lymphatic system disorders	16 (18.2%)	59 (34.3%)	61 (33.9%)
Anaemia	8 (9.1%)	29 (16.9%)	29 (16.1%)
Neutropenia	6 (6.8%)	25 (14.5%)	25 (13.9%)
Thrombocytopenia	6 (6.8%)	18 (10.5%)	19 (10.6%)
Febrile neutropenia	1 (1.1%)	5 (2.9%)	6 (3.3%)
Infections and infestations	9 (10.2%)	31 (18.0%)	37 (20.6%)
Pneumonia	2 (2.3%)	9 (5.2%)	11 (6.1%)
COVID-19	2 (2.3%)	4 (2.3%)	4 (2.2%)
Metabolism and nutrition disorders	5 (5.7%)	21 (12.2%)	21 (11.7%)
Hypokalaemia	1 (1.1%)	5 (2.9%)	5 (2.8%)
Gastrointestinal disorders	0	19 (11.0%)	21 (11.7%)
Diarrhoea	0	6 (3.5%)	7 (3.9%)
Abdominal pain	0	4 (2.3%)	4 (2.2%)
Immune system disorders	0	4 (2.3%)	4 (2.2%)
Cytokine release syndrome	0	4 (2.3%)	4 (2.2%)

Table 2 Summary of Grade 3–4 Adverse Events by Preferred Term and Corresponding Grade 3–4 Adverse Reactions by Medical Concept, with an Incidence of ≥2% in the Glofit-GemOx (Glofit Exposed) Population (Study GO41944; Safety Evaluable Population)

PT/Medical Concept	Patients with at least one AE by PT, n (%)			Patients with at least one adverse reaction by medical concept, n (%)		
	R-GemOx (N = 88)	Glofit-GemOx (Glofit Exposed) (N = 172)	Glofit-GemOx (Any Treatment Exposed) (N = 180)	R-GemOx (N = 88)	Glofit-GemOx (Glofit Exposed) (N = 172)	Glofit-GemOx (Any Treatment Exposed) (N = 180)
Neutrophil count decreased*	10 (11.4%)	38 (22.1%)	38 (21.1%)	*See medical concept: neutropenia*		
Neutropenia [a]	6 (6.8%)	25 (14.5%)	25 (13.9%)	16 (18.2%)	61 (35.5%)	61 (33.9%)
Platelet count decreased*	9 (10.2%)	31 (18.0%)	31 (17.2%)	*See medical concept: thrombocytopenia*		
Thrombocytopenia [b]	6 (6.8%)	18 (10.5%)	19 (10.6%)	15 (17.0%)	46 (26.7%)	47 (26.1%)
Anaemia*	8 (9.1%)	29 (16.9%)	29 (16.1%)	8 (9.1%)	29 (16.9%)	29 (16.1%)
Lymphocyte count decreased*	2 (2.3%)	18 (10.5%)	18 (10.0%)	*See medical concept: lymphopenia*		
Lymphopenia [c]	1 (1.1%)	3 (1.7%)	3 (1.7%)	3 (3.4%)	21 (12.2%)	21 (11.7%)
White blood cell count decreased *	6 (6.8%)	16 (9.3%)	16 (8.9%)	6 (6.8%)	16 (9.3%)	16 (8.9%)
Pneumonia [d]	3 (3.4%)	9 (5.2%)	11 (6.1%)	3 (3.4%)	9 (5.2%)	11 (6.1%)
Diarrhoea *	0	6 (3.5%)	7 (3.9%)	0	6 (3.5%)	7 (3.9%)
Aspartate aminotransferase increased *	0	6 (3.5%)	6 (3.3%)	0	6 (3.5%)	6 (3.3%)
Alanine aminotransferase increased*	3 (3.4%)	5 (2.9%)	5 (2.8%)	3 (3.4%)	5 (2.9%)	5 (2.8%)
Febrile Neutropenia *	1 (1.1%)	5 (2.9%)	6 (3.3%)	1 (1.1%)	5 (2.9%)	6 (3.3%)
Hypokalaemia *	1 (1.1%)	5 (2.9%)	5 (2.8%)	1 (1.1%)	5 (2.9%)	5 (2.8%)
Abdominal Pain [e]	0	4 (2.3%)	4 (2.2%)	0	4 (2.3%)	4 (2.2%)
COVID-19 [f]	2 (2.3%)	4 (2.3%)	4 (2.2%)	2 (2.3%)	6 (3.5%)	7 (3.9%)
Cytokine Release Syndrome [g, *]	0	4 (2.3%)	4 (2.2%)	0	4 (2.3%)	4 (2.2%)
Gamma-glutamyltransferase increased [h]	2 (2.3%)	3 (1.7%)	3 (1.7%)	2 (2.3%)	4 (2.3%)	4 (2.2%)
Sepsis [i]	0	3 (1.7%)	4 (2.2%)	1 (1.1%)	5 (2.9%)	6 (3.3%)
Musculoskeletal Pain [j]	-	-	-	1 (1.1%)	4 (2.3%)	5 (2.8%)

PT = preferred term; SmPC = Summary of Product Characteristics.

* Standalone PT.

[a] Medical concept includes the following PTs: neutropenia and neutrophil count decreased.

[b] Medical concept includes the following PTs: thrombocytopenia and platelet count decreased.

[c] Medical concept includes the following PTs: lymphopenia and lymphocyte count decreased.

[d] Medical concept includes the following PTs: pneumonia, pneumonia bacterial, and pneumonia pneumococcal.

[e] Medical concept includes the following PTs: abdominal pain, abdominal discomfort, abdominal pain upper, abdominal pain lower, and gastrointestinal pain.

[f] Medical concept includes the following PTs: COVID-19, COVID-19 pneumonia, and SARS-CoV-2 test positive.

[g] Based on ASTCT consensus grading (Lee et al. 2019).

[h] Medical concept includes the following PTs: gamma-glutamyltransferase increased and gamma-glutamyltransferase abnormal.

[i] Medical concept includes the following PTs: sepsis, streptococcal sepsis, septic shock, enterococcal sepsis, and neutropenic sepsis.

[j] This is an adverse reaction/medical concept which includes the following PTs: arthralgia, musculoskeletal pain, back pain, bone pain, myalgia, neck pain, pain in extremity, musculoskeletal chest pain, and non-cardiac chest pain.

Serious adverse event/deaths/other significant events

Deaths:

Overall, the proportion of patients who died was lower in the Glofit-GemOx (74/172 patients [43.0%]) arm compared with the R-GemOx arm (51/88 patients [58.0%]) (Table 10).

The most frequent cause of death was progressive disease which accounted for fewer deaths in the Glofit-GemOx (42/74 deaths [56.8%]) arm compared with the R-GemOx arm (37/51 deaths [72.5%]). AEs were reported as the cause of death in 12/74 patients (16.2%) who died in the Glofit-GemOx arm and 4/51 patients (7.8%) who died in the R-GemOx arm (Table 11).

Deaths due to 'Other' reasons (events reported in long-term follow up period, excluding PD deaths and AEs) were reported in 20/74 patients (27.0%) who died in the Glofit-GemOx arm compared with 10/51 patients (19.6%) who died in the R-GemOx arm. Most 'other' death events were due to COVID-19 or COVID-19 associated events (Glofit-GemOx: 8 events and R-GemOx: 3 events). There were no other identifiable trends of 'other' death events.

Table 10 Summary of Deaths (Safety Evaluable Patients Receiving R-GemOx or Glofit-GemOx)

Summary of Deaths, Modified Safety-Evaluable Patients
Protocol: GO41944 & GO41943

	R-GemOx (GO41944) (N=88)	Glofit-GemOx (Glofit Exposed) (GO41944) (N=172)	Glofit-GemOx (Glofit Exposed) (GO41943) (N=16)	Glofit-GemOx (Glofit Exposed) (GO41944 & GO41943) (N=188)
Total number of deaths	51 (58.0%)	74 (43.0%)	11 (68.8%)	85 (45.2%)
Primary cause of death				
n	51	74	11	85
Adverse event	4 (7.8%)	12 (16.2%)	0	12 (14.1%)
Progressive disease	37 (72.5%)	42 (56.8%)	10 (90.9%)	52 (61.2%)
Other	10 (19.6%)	20 (27.0%)	1 (9.1%)	21 (24.7%)
ACUTE CONFUSION SYNDROME, MENINGOENCEPHALITIS, TUMOR PROGRESSION AND COVID INFECTION	0	1 (1.4%)	0	1 (1.2%)
ACUTE RESPIRATORY FAILURE	1 (2.0%)	0	0	0
CAR T- CELL THERAPY RELATED EVENTS	0	1 (1.4%)	0	1 (1.2%)
CARDIOGENIC SHOCK	0	1 (1.4%)	0	1 (1.2%)
CIRRHOSIS AND PORTAL HTN.	0	1 (1.4%)	0	1 (1.2%)
COVID-19	3 (5.9%)	7 (9.5%)	0	7 (8.2%)
LUNG INFECTION	0	1 (1.4%)	0	1 (1.2%)
MDS	0	1 (1.4%)	0	1 (1.2%)
METASTATIC POORLY DIFFERENTIATED MALIGNANT TUMOUR	1 (2.0%)	0	0	0
PNEUMONIA	0	3 (4.1%)	0	3 (3.5%)
PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY	1 (2.0%)	0	0	0
SEPSIS	0	0	1 (9.1%)	1 (1.2%)
SEPTIC SHOCK	1 (2.0%)	0	0	0
SUDDEN CARDIAC DEATH	1 (2.0%)	0	0	0
THROMBOTIC STROKE	0	1 (1.4%)	0	1 (1.2%)
UNKNOWN	2 (3.9%)	3 (4.1%)	0	3 (3.5%)
Days from last study drug administration				
n	51	73	11	84
<=30 days	4 (7.8%)	13 (17.8%)	1 (9.1%)	14 (16.7%)
>30 days	47 (92.2%)	60 (82.2%)	10 (90.9%)	70 (83.3%)
Primary cause by days from last study drug administration				
<=30 days				
n	4	13	1	14
Adverse event	3 (75.0%)	7 (53.8%)	0	7 (50.0%)
Progressive disease	1 (25.0%)	6 (46.2%)	1 (100%)	7 (50.0%)
>30 days				
n	47	60	10	70
Adverse event	1 (2.1%)	5 (8.3%)	0	5 (7.1%)
Progressive disease	36 (76.6%)	35 (58.3%)	9 (90.0%)	44 (62.9%)
Other	10 (21.3%)	20 (33.3%)	1 (10.0%)	21 (30.0%)

Data Cutoff Dates: GO41943 - 08DEC2021, GO41944 - 16FEB2024.
All study drugs are included in dose calculations.

Program: root/clinical_studies/RO7082859/CDT30295/share/pool_SCS_Followup_Analysis_2024/prod/program/t_dd.sas
Adapted from Output: t_dd_SERO
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Table 11 Summary of Fatal Adverse Events (Safety Evaluable Patients Receiving R-GemOx or Glofit-GemOx)

Summary of Adverse Events, Fatal Adverse Events, Modified Safety-Evaluable Patients
Protocol: GO41944 & GO41943

MedDRA System Organ Class MedDRA Preferred Term	R-GemOx (GO41944) (N=88)	Glofit-GemOx (Glofit Exposed) (GO41944) (N=172)	Glofit-GemOx (Glofit Exposed) (GO41943) (N=16)	Glofit-GemOx (Glofit Exposed) (GO41944 & GO41943) (N=188)
Total number of patients with at least one adverse event	4 (4.5%)	12 (7.0%)	0	12 (6.4%)
Overall total number of events	4	12	0	12
Infections and infestations				
Total number of patients with at least one adverse event	3 (3.4%)	6 (3.5%)	0	6 (3.2%)
Total number of events	3	6	0	6
COVID-19	0	3 (1.7%)	0	3 (1.6%)
Pneumonia	2 (2.3%)	1 (0.6%)	0	1 (0.5%)
Respiratory tract infection	0	1 (0.6%)	0	1 (0.5%)
Septic shock	0	1 (0.6%)	0	1 (0.5%)
Pneumonia bacterial	1 (1.1%)	0	0	0
Respiratory, thoracic and mediastinal disorders				
Total number of patients with at least one adverse event	0	3 (1.7%)	0	3 (1.6%)
Total number of events	0	3	0	3
Pneumonitis	0	2 (1.2%)	0	2 (1.1%)
Acute respiratory distress syndrome	0	1 (0.6%)	0	1 (0.5%)
General disorders and administration site conditions				
Total number of patients with at least one adverse event	1 (1.1%)	1 (0.6%)	0	1 (0.5%)
Total number of events	1	1	0	1
Multiple organ dysfunction syndrome	1 (1.1%)	1 (0.6%)	0	1 (0.5%)
Cardiac disorders				
Total number of patients with at least one adverse event	0	1 (0.6%)	0	1 (0.5%)
Total number of events	0	1	0	1
Cardiac arrest	0	1 (0.6%)	0	1 (0.5%)

MedDRA System Organ Class MedDRA Preferred Term	R-GemOx (GO41944) (N=88)	Glofit-GemOx (Glofit Exposed) (GO41944) (N=172)	Glofit-GemOx (Glofit Exposed) (GO41943) (N=16)	Glofit-GemOx (Glofit Exposed) (GO41944 & GO41943) (N=188)
Nervous system disorders				
Total number of patients with at least one adverse event	0	1 (0.6%)	0	1 (0.5%)
Total number of events	0	1	0	1
Cerebral haemorrhage	0	1 (0.6%)	0	1 (0.5%)

Data Cutoff Dates: GO41943 - 08DEC2021, GO41944 - 16FEB2024.
Investigator text for AEs encoded using MedDRA version 26.1. Percentages are based on N in the column headings.
Only treatment emergent AEs are displayed. For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.

Program: root/clinical_studies/RO7082859/CDT30295/share/pool_SCS_Followup_Analysis_2024/prod/program/t_ae.sas
Adapted from Output: t_ae_FATAL_SERO
02MAY2024 14:34

Serious Adverse Events:

Table 4 Summary of Serious Adverse Events by Preferred Term and Corresponding Serious Adverse Reaction by Medical Concept, with an Incidence Rate of ≥ 2% in the Glofit-GemOx (Glofit Exposed) Population (Study GO41944, Safety Evaluable Population)

PT / Medical Concept	Patients with at least one AE by PT, n (%)			Patients with at least one adverse reaction by medical concept, n (%)		
	R-GemOx (N = 88)	Glofit-GemOx (Glofit Exposed) (N = 172)	Glofit-GemOx (Any Treatment Exposed) (N = 180)	R-GemOx (N = 88)	Glofit-GemOx (Glofit Exposed) (N = 172)	Glofit-GemOx (Any Treatment Exposed) (N = 180)
Cytokine release syndrome *, [a]	0	35 (20.3%)	35 (19.4%)	0	35 (20.3%)	35 (19.4%)
Pyrexia *	1 (1.1%)	11 (6.4%)	11 (6.1%)	1 (1.1%)	11 (6.4%)	11 (6.1%)
Pneumonia [b]	4 (4.5%)	10 (5.8%)	12 (6.7%)	5 (5.7%)	10 (5.8%)	12 (6.7%)
Sepsis [c]	0	3 (1.7%)	4 (2.2%)	1 (1.1%)	4 (2.3%)	6 (3.3%)
COVID-19 [d]	2 (2.3%)	8 (4.7%)	9 (5.0%)	2 (2.3%)	10 (5.8%)	12 (6.7%)
Platelet count decreased*	0	6 (3.5%)	6 (3.3%)	*See thrombocytopenia medical concept*		
Thrombocytopenia [e]	0	3 (1.7%)	4 (2.2%)	0	8 (4.7%)	9 (5.0%)
Lower respiratory tract infection*	1 (1.1%)	5 (2.9%)	6 (3.3%)	*See respiratory tract infection medical concept*		
Respiratory tract infection [f]	0	1 (0.6%)	1 (0.6%)	1 (1.1%)	6 (3.5%)	7 (3.9%)
Febrile neutropenia *	1 (1.1%)	4 (2.3%)	5 (2.8%)	1 (1.1%)	4 (2.3%)	5 (2.8%)
Diarrhoea *	0	4 (2.3%)	5 (2.8%)	0	4 (2.3%)	5 (2.8%)
ICANS [g]	0	1 (0.6%)	1 (0.6%)	0	3 (1.7%)	4 (2.2%)

PT = preferred term; SmPC = Summary of Product Characteristics.

* Standalone PT.

[a] Based on ASTCT consensus grading (Lee 2019).

[b] Medical concept includes the following PTs: pneumonia, pneumonia bacterial, and pneumonia pneumococcal.

[c] Medical concept includes the following PTs: sepsis, streptococcal sepsis, septic shock, enterococcal sepsis, and neutropenic sepsis.

[d] Medical concept includes the following PTs: COVID-19, COVID-19 pneumonia, and SARS-CoV-2 test positive.

[e] Medical concept includes the following PTs: thrombocytopenia and platelet count decreased.

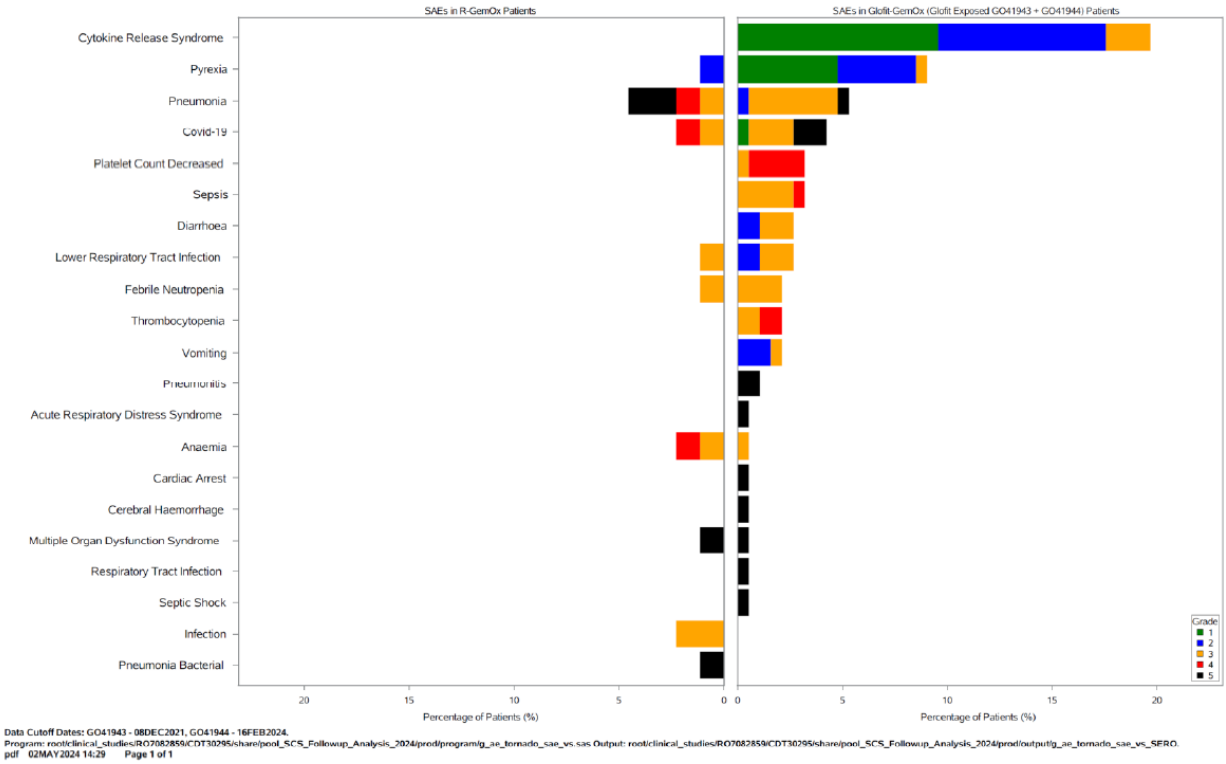
[f] Medical concept includes the following PTs: respiratory tract infection, lower respiratory tract infection, respiratory tract infection, and respiratory tract infection bacterial.

[g] Medical concept includes the following PTs: confusional state, delirium, and ICANS. It is important to note that while investigators could report ICANS as a PT, neurotoxicity in the GO41944 study was often reported as signs and symptoms of the event. To better assess the risk of events potentially consistent with ICANS associated with glofitamab, the Applicant applied an algorithmic approach which utilized the ICANS CD3 AEGT to identify events potentially consistent with ICANS occurring at any time after receiving a dose of glofitamab (see 2.7.4 SCS, Appendix 2).

Note: Multiple occurrences of a PT/PT in the pooled terms in one individual are counted once at the highest grade for that PT/medical concept.

Source: t_ae_ctc_adr2_SER_INC2PER_SE_16FEB2024_41944; Update CSR GO41944, Report No. 1130634, t_ae_ctc_SER_SE_16FEB2024_41944.

Figure 6 Tornado Plot of Serious Adverse Events with a ≥2% Incidence (Pooled GO41944 and GO41943 Data: Safety Evaluable Patients Receiving Glofit-GemOx or R-GemOx)



Adverse events of special interest

Adverse events of special interest specific for glofitamab include the following:

- Grade ≥2 CRS
- Grade ≥ 2 neurologic adverse events
- Any suspected HLH
- TLS (minimum Grade 3 by definition)
- Febrile neutropenia (minimum Grade 3 by definition)
- Grade ≥ 2 AST, ALT, or total bilirubin elevation
- Any grade disseminated intravascular coagulation (minimum Grade 2 by definition)
- Grade ≥2 tumour flare (e.g., manifestation of signs/symptoms associated with an increase in size of known nodal or extranodal lesions by clinical or radiographic assessment)
- Any grade pneumonitis, interstitial lung disease, acute respiratory distress syndrome, pulmonary fibrosis, organizing pneumonia, and/or pulmonary toxicity (excluding pneumonia of infectious etiology)
- Colitis of any grade (excluding infectious etiology)

Adverse events of special interest for obinutuzumab include the following:

- Secondary malignancies
- TLS
- Serious infections

- Serious neutropenia
- Serious IRRs

Table 7 Overview of Adverse Events of Special Interest (Safety Evaluable Patients Receiving R-GemOx or Glofit-GemOx)

	R-GemOx (GO41944) (N=88)	Glofit-GemOx (Glofit Exposed) (GO41944) (N=172)	Glofit-GemOx (Glofit Exposed) (GO41943) (N=16)	Glofit-GemOx (Glofit Exposed) (GO41944 & GO41943) (N=188)
Total number of patients with at least one AESI	68 (77.3%)	167 (97.1%)	14 (87.5%)	181 (96.3%)
Total number of events	211	1025	71	1096
Total number of patients with at least one AESI for Glofitamab				
Grade >= 2 CRS	0	22 (12.8%)	3 (18.8%)	25 (13.3%)
Grade >= 2 Neurologic Adverse Events	11 (12.5%)	52 (30.2%)	6 (37.5%)	58 (30.9%)
TLS	3 (3.4%)	3 (1.7%)	2 (12.5%)	5 (2.7%)
Febrile Neutropenia	1 (1.1%)	5 (2.9%)	0	5 (2.7%)
Grade >=2 AST, ALT, or total bilirubin elevation	7 (8.0%)	24 (14.0%)	1 (6.3%)	25 (13.3%)
Grade >=2 Tumor Flare	1 (1.1%)	1 (0.6%)	0	1 (0.5%)
Pneumonitis or ILD (excluding pneumonia of infectious etiology)	0	3 (1.7%)	0	3 (1.6%)
Colitis (excluding infectious etiology)	0	4 (2.3%)	2 (12.5%)	6 (3.2%)
Total number of patients with at least one AESI for Obinutuzumab				
Secondary Malignancies	1 (1.1%)	7 (4.1%)	2 (12.5%)	9 (4.8%)
TLS	3 (3.4%)	3 (1.7%)	2 (12.5%)	5 (2.7%)
Serious infections	11 (12.5%)	39 (22.7%)	4 (25.0%)	43 (22.9%)
Serious Neutropenia / Neutrophil Count Decrease	0	3 (1.7%)	2 (12.5%)	5 (2.7%)
Serious IRRs	0	1 (0.6%)	0	1 (0.5%)
Total number of patients with at least one selected AE				
Neutropenia / Neutrophil Count Decrease	27 (30.7%)	76 (44.2%)	7 (43.8%)	83 (44.1%)
Thrombocytopenia / Platelet Count Decreased	42 (47.7%)	86 (50.0%)	8 (50.0%)	94 (50.0%)
Liver and Pancreatic Adverse Events	26 (29.5%)	74 (43.0%)	2 (12.5%)	76 (40.4%)
Infection and Infestation Adverse Events	26 (29.5%)	95 (55.2%)	7 (43.8%)	102 (54.3%)
Immune System Disorders Adverse Events	1 (1.1%)	77 (44.8%)	8 (50.0%)	85 (45.2%)

Data Cutoff Dates: GO41943 - 08DEC2021, GO41944 - 16FEB2024.
Treatment related AEs includes Glofitamab, Rituxumab, Gemcitabine, Oxaliplatin, Obinutuzumab or Tocilizumab. Dose modified/ interrupted due to AE refers to Glofitamab and Obinutuzumab only.
Investigator text for AEs encoded using MedDRA version 26.1. Adverse Events are graded by NCI CTCAE v5.0, CRS events are graded by ASTCT 2019. AESIs not experienced by any patients are excluded. Multiple occurrences of the same AE in one individual are counted only once except for the Time to Onset, Duration and 'Total number of AEs' rows in which multiple occurrences of the same AE are counted separately. Percentages are based on N in the column headings. The count of 'Patients with treatment received for AE' is based on the AE CRF question 'Was Medication Given For AE?'
For the AESI of pneumonitis or interstitial lung disease, one event is an acute respiratory distress syndrome in the context of infection. This is captured due to the AESI search criteria including all events in the broad interstitial lung disease SMQ.

Cytokine release syndrome (CRS):

Overview of Adverse Events, Cytokine Release Syndrome AEs, Modified Safety-Evaluable Patients
Protocol: GO41944 & GO41943

	Glofit-GemOx (Glofit Exposed) (GO41944) (N=172)	Glofit-GemOx (Glofit Exposed) (GO41943) (N=16)	Glofit-GemOx (Glofit Exposed) (GO41944 & GO41943) (N=188)
Total number of patients with at least one CRS event	76 (44.2%)	8 (50.0%)	84 (44.7%)
Total number of CRS events	152	18	170
Total number of patients withdrawn from any treatment due to a CRS event	1 (0.6%)	0	1 (0.5%)
Total number of patients with a CRS event with fatal outcome	0	0	0
Total number of patients with at least one			
CRS event leading to withdrawal from Glofitamab	1 (0.6%)	0	1 (0.5%)
CRS event leading to withdrawal from Obinutuzumab	0	0	0
CRS event leading to withdrawal from Gemcitabine	1 (0.6%)	0	1 (0.5%)
CRS event leading to withdrawal from Oxaliplatin	1 (0.6%)	0	1 (0.5%)
CRS event leading to dose interruption of Glofitamab	3 (1.7%)	1 (6.3%)	4 (2.1%)
CRS event leading to dose interruption of Obinutuzumab	0	0	0
CRS event leading to dose interruption of Gemcitabine	1 (0.6%)	1 (6.3%)	2 (1.1%)
CRS event leading to dose modification of Gemcitabine	0	0	0
CRS event leading to dose interruption of Oxaliplatin	1 (0.6%)	1 (6.3%)	2 (1.1%)
CRS event leading to dose modification of Oxaliplatin	0	0	0
Serious CRS event	35 (20.3%)	2 (12.5%)	37 (19.7%)
Serious CRS event leading to withdrawal from Glofitamab	1 (0.6%)	0	1 (0.5%)
Serious CRS event leading to dose interruption of Glofitamab	3 (1.7%)	1 (6.3%)	4 (2.1%)
CRS event related to Glofitamab	76 (44.2%)	8 (50.0%)	84 (44.7%)
CRS event related to Obinutuzumab	3 (1.7%)	0	3 (1.6%)
CRS event related to Gemcitabine	14 (8.1%)	0	14 (7.4%)
CRS event related to Oxaliplatin	12 (7.0%)	0	12 (6.4%)
Serious CRS event related to Glofitamab	35 (20.3%)	2 (12.5%)	37 (19.7%)
Serious CRS event related to Obinutuzumab	1 (0.6%)	0	1 (0.5%)
Serious CRS event related to Gemcitabine	1 (0.6%)	0	1 (0.5%)
Serious CRS event related to Oxaliplatin	1 (0.6%)	0	1 (0.5%)
Grade 3-5 CRS event	4 (2.3%)	1 (6.3%)	5 (2.7%)
Grade 3-5 CRS event related to Glofitamab	4 (2.3%)	1 (6.3%)	5 (2.7%)
Grade 3-5 CRS event related to Obinutuzumab	0	0	0
Grade 3-5 CRS event related to Gemcitabine	0	0	0
Grade 3-5 CRS event related to Oxaliplatin	0	0	0
Glofitamab related AESI	22 (12.8%)	3 (18.8%)	25 (13.3%)
Obinutuzumab related AESI	0	0	0
CRS event related to Glofitamab leading to withdrawal from Glofitamab	1 (0.6%)	0	1 (0.5%)
CRS event related to Glofitamab leading to dose interruption of Glofitamab	3 (1.7%)	1 (6.3%)	4 (2.1%)
Outcome of CRS events			
Recovered / resolved	150	18	168
Recovering / resolving	0	0	0
Recovered / resolved with sequelae	1	0	1
Not recovered / resolved	1	0	1
Fatal	0	0	0
Unknown / missing	0	0	0

Data Cutoff Dates: GO41943 - 08DEC2021, GO41944 - 16FEB2024.
Investigator text for AEs encoded using MedDRA version 26.1. Percentages are based on N in the column headings. Only treatment emergent AEs are displayed.
Multiple occurrences of the same AE in one individual are counted only once except for "Total number of AEs" row in which multiple occurrences of the same AE are counted separately.
Tocilizumab not included as a study drug.
A Gemcitabine dose is considered modified if the accompanying Oxaliplatin dose was modified, the AE is related to Gemcitabine and the dose is less than 80% of the planned dose.

Table 18 Summary of Cytokine Release Syndrome Adverse Events by Highest ACTCT Grade (Safety Evaluable Patients Receiving R-GemOx or Glofit-GemOx)

Summary of Adverse Events by Highest Grade, Cytokine Release Syndrome AEs, Modified Safety-Evaluable Patients
Protocol: GO41944 & GO41943

MedDRA System Organ Class MedDRA Preferred Term	Grade	Glofit-GemOx (Glofit Exposed) (GO41944) (N=172)	Glofit-GemOx (Glofit Exposed) (GO41943) (N=16)	Glofit-GemOx (Glofit Exposed) (GO41944 & GO41943) (N=188)
- Any adverse events -	- Any Grade -	76 (44.2%)	8 (50.0%)	84 (44.7%)
	Grade 1-2	72 (41.9%)	7 (43.8%)	79 (42.0%)
	1	54 (31.4%)	5 (31.3%)	59 (31.4%)
	2	18 (10.5%)	2 (12.5%)	20 (10.6%)
	Grade 3-4	4 (2.3%)	1 (6.3%)	5 (2.7%)
	3	4 (2.3%)	1 (6.3%)	5 (2.7%)
Immune system disorders				
- Overall -	- Any Grade -	76 (44.2%)	8 (50.0%)	84 (44.7%)
	Grade 1-2	72 (41.9%)	7 (43.8%)	79 (42.0%)
	1	54 (31.4%)	5 (31.3%)	59 (31.4%)
	2	18 (10.5%)	2 (12.5%)	20 (10.6%)
	Grade 3-4	4 (2.3%)	1 (6.3%)	5 (2.7%)
	3	4 (2.3%)	1 (6.3%)	5 (2.7%)
Cytokine release syndrome	- Any Grade -	76 (44.2%)	8 (50.0%)	84 (44.7%)
	Grade 1-2	72 (41.9%)	7 (43.8%)	79 (42.0%)
	1	54 (31.4%)	5 (31.3%)	59 (31.4%)
	2	18 (10.5%)	2 (12.5%)	20 (10.6%)
	Grade 3-4	4 (2.3%)	1 (6.3%)	5 (2.7%)
	3	4 (2.3%)	1 (6.3%)	5 (2.7%)

Data Cutoff Dates: GO41943 - 08DEC2021, GO41944 - 16FEB2024.
Investigator text for AEs encoded using MedDRA version 26.1.
Only treatment emergent AEs are displayed. All counts represent numbers of Subjects. Multiple occurrences of the same preferred term in one individual are counted once at the highest grade for that preferred term. Adverse Events are graded by NCI CTCAE v5.0, CRS events are graded by ASTCT 2019. Adverse Events with missing grades are excluded from this output. Adverse Events with missing grades are excluded from this output.

Program: root/clinical_studies/RO7082859/CDT30295/share/pool_SCS_Followup_Analysis_2024/prod/program/t_ae_ctc.sas
Output: root/clinical_studies/RO7082859/CDT30295/share/pool_SCS_Followup_Analysis_2024/prod/output/t_ae_ctc_CRSAE_GLO_SERO.out
02MAY2024 15:27

Table 19 Summary of Tocilizumab Use and CRS Management (Pooled GO41944 and GO41943 Data: Safety Evaluable Patients Receiving Glofit-GemOx)

Summary of Tocilizumab Use and CRS Management, All Subjects with a CRS Event, Modified Safety-Evaluable Patients
Protocol: GO41944 & GO41943

	Glofit-GemOx (Glofit Exposed) (GO41944) (N=76)	Glofit-GemOx (Glofit Exposed) (GO41943) (N=8)	Glofit-GemOx (Glofit Exposed) (GO41944 & GO41943) (N=84)
Patients who used Tocilizumab	28 (36.8%)	3 (37.5%)	31 (36.9%)
Patients who used Corticosteroids	39 (51.3%)	3 (37.5%)	42 (50.0%)
Patients who used Tocilizumab and Corticosteroids together	18 (23.7%)	3 (37.5%)	21 (25.0%)
Patients who used ICU	4 (5.3%)	1 (12.5%)	5 (6.0%)
Patients who used fluids	10 (13.2%)	2 (25.0%)	12 (14.3%)
Patients who used a single pressor	4 (5.3%)	1 (12.5%)	5 (6.0%)
Patients who used multiple pressors	0	0	0
Patients who used low flow oxygen	9 (11.8%)	0	9 (10.7%)
Patients who used high flow oxygen	2 (2.6%)	0	2 (2.4%)
Patients who used positive pressure	0	0	0

Data Cutoff Dates: GO41943 - 08DEC2021, GO41944 - 16FEB2024.
Same CRS event has been considered to display 'Patients who used Tocilizumab and Corticosteroids together'.

Program: root/clinical_studies/RO7082859/CDT30295/share/pool_SCS_Followup_Analysis_2024/prod/program/t_crs_mngmnt.sas
Output: root/clinical_studies/RO7082859/CDT30295/share/pool_SCS_Followup_Analysis_2024/prod/output/t_crs_mngmnt_CRSPT_GLO_SERO.out
02MAY2024 15:32

Neurological Events (Any Grade)

Grade ≥2 neurologic AEs for glofitamab were reported as AESIs; however, neurologic AEs (any grade) are also summarized in this section. Neurologic AEs include PTs reported in the following SOCs: (1) nervous system disorders and (2) psychiatric disorders.

Summary of Adverse Events, Neurologic Adverse Events, Modified Safety-Evaluable Patients
Protocol: GO41944 & GO41943

MedDRA System Organ Class MedDRA Preferred Term	R-GemOx (GO41944) (N=88)	Glofit-GemOx (Glofit Exposed) (GO41944) (N=172)	Glofit-GemOx (Glofit Exposed) (GO41943) (N=16)	Glofit-GemOx (Glofit Exposed) (GO41944 & GO41943) (N=188)
Total number of patients with at least one adverse event	35 (39.8%)	102 (59.3%)	11 (68.8%)	113 (60.1%)
Overall total number of events	67	235	26	261
Nervous system disorders				
Total number of patients with at least one adverse event	26 (29.5%)	81 (47.1%)	11 (68.8%)	92 (48.9%)
Total number of events	49	164	23	187
Peripheral sensory neuropathy	8 (9.1%)	27 (15.7%)	3 (18.8%)	30 (16.0%)
Neuropathy peripheral	6 (6.8%)	20 (11.6%)	6 (37.5%)	26 (13.8%)
Headache	7 (8.0%)	15 (8.7%)	3 (18.8%)	18 (9.6%)
Dizziness	3 (3.4%)	12 (7.0%)	2 (12.5%)	14 (7.4%)
Paraesthesia	5 (5.7%)	9 (5.2%)	2 (12.5%)	11 (5.9%)
Dysgeusia	2 (2.3%)	9 (5.2%)	0	9 (4.8%)
Hypoaesthesia	3 (3.4%)	8 (4.7%)	0	8 (4.3%)
Lethargy	2 (2.3%)	2 (1.2%)	3 (18.8%)	5 (2.7%)
Polyneuropathy	3 (3.4%)	4 (2.3%)	0	4 (2.1%)
Syncope	0	4 (2.3%)	0	4 (2.1%)
Dysaesthesia	0	2 (1.2%)	0	2 (1.1%)
Taste disorder	0	2 (1.2%)	0	2 (1.1%)
Ageusia	1 (1.1%)	1 (0.6%)	0	1 (0.5%)
Peripheral motor neuropathy	1 (1.1%)	1 (0.6%)	0	1 (0.5%)
Balance disorder	0	1 (0.6%)	0	1 (0.5%)
Brain fog	0	1 (0.6%)	0	1 (0.5%)
Cerebral haemorrhage	0	1 (0.6%)	0	1 (0.5%)
Cognitive disorder	0	1 (0.6%)	0	1 (0.5%)
Extrapyramidal disorder	0	1 (0.6%)	0	1 (0.5%)
Hypotonia	0	1 (0.6%)	0	1 (0.5%)
Immune effector cell-associated neurotoxicity syndrome	0	1 (0.6%)	0	1 (0.5%)
Intention tremor	0	0	1 (6.3%)	1 (0.5%)
Loss of consciousness	0	1 (0.6%)	0	1 (0.5%)
Memory impairment	0	1 (0.6%)	0	1 (0.5%)
Metabolic encephalopathy	0	1 (0.6%)	0	1 (0.5%)
Myoclonus	0	1 (0.6%)	0	1 (0.5%)
Transient ischaemic attack	0	0	1 (6.3%)	1 (0.5%)
Tremor	0	1 (0.6%)	0	1 (0.5%)
Peroneal nerve palsy	1 (1.1%)	0	0	0
Psychiatric disorders				
Total number of patients with at least one adverse event	11 (12.5%)	37 (21.5%)	1 (6.3%)	38 (20.2%)
Total number of events	12	47	1	48
Insomnia	9 (10.2%)	20 (11.6%)	0	20 (10.6%)
Depression	0	5 (2.9%)	1 (6.3%)	6 (3.2%)
Anxiety	2 (2.3%)	4 (2.3%)	0	4 (2.1%)
Confusional state	1 (1.1%)	4 (2.3%)	0	4 (2.1%)
Delirium	0	3 (1.7%)	0	3 (1.6%)
Affective disorder	0	1 (0.6%)	0	1 (0.5%)
Bradyphrenia	0	1 (0.6%)	0	1 (0.5%)
Initial insomnia	0	1 (0.6%)	0	1 (0.5%)
Libido decreased	0	1 (0.6%)	0	1 (0.5%)
Mood altered	0	1 (0.6%)	0	1 (0.5%)
Panic attack	0	1 (0.6%)	0	1 (0.5%)
Restlessness	0	1 (0.6%)	0	1 (0.5%)

Grade ≥2 neurologic AEs were reported in a greater proportion of patients in the Glofit-GemOx arm (52/172 patients [30.2%]) compared with the R-GemOx arm (11/88 patients [12.5%]).

Table 20 Summary of Adverse Events of Special Interest for Glofitamab: Neurological Adverse Events (Grade ≥2) (Safety Evaluable Patients Receiving R-GemOx or Glofit-GemOx)

Summary of Adverse Events of Special Interest, Modified Safety-Evaluable Patients
Protocol: GO41944 & GO41943

Grade >= 2 Neurologic Adverse Events

	R-GemOx (GO41944) (N=88)	Glofit-GemOx (Glofit Exposed) (GO41944) (N=172)	Glofit-GemOx (Glofit Exposed) (GO41943) (N=16)	Glofit-GemOx (Glofit Exposed) (GO41944 & GO41943) (N=188)
Total number of pts with at least one AE	11 (12.5%)	52 (30.2%)	6 (37.5%)	58 (30.9%)
Total number of AEs	14	68	7	75
Total number of pts with at least one AE by worst grade				
Grade 2	11 (12.5%)	42 (24.4%)	5 (31.3%)	47 (25.0%)
Grade 3	0	9 (5.2%)	1 (6.3%)	10 (5.3%)
Grade 4	0	0	0	0
Grade 5 (fatal outcome)	0	1 (0.6%)	0	1 (0.5%)
Total number of pts with dose modified/interrupted due to AE	3 (3.4%)	7 (4.1%)	0	7 (3.7%)
Total number of pts with treatment received for AE	2 (2.3%)	35 (20.3%)	2 (12.5%)	37 (19.7%)
Total number of pts with all AEs resolved	3 (3.4%)	26 (15.1%)	3 (18.8%)	29 (15.4%)
Total number of pts with at least one unresolved or ongoing AE	8 (9.1%)	25 (14.5%)	3 (18.8%)	28 (14.9%)
Total number of pts with at least one serious AE	0	9 (5.2%)	2 (12.5%)	11 (5.9%)
Total number of pts with at least one related AE	7 (8.0%)	32 (18.6%)	5 (31.3%)	37 (19.7%)
Duration of AE (days)				
n	5	39	4	43
Mean (SD)	50.20 (61.13)	68.13 (106.84)	48.25 (68.52)	66.28 (103.42)
Median	40.00	14.00	15.00	14.00
Min - Max	1.0 - 151.0	1.0 - 384.0	12.0 - 151.0	1.0 - 384.0
Time to Onset (days)				
n	14	68	7	75
Mean (SD)	49.07 (54.85)	101.72 (94.38)	96.14 (95.57)	101.20 (93.85)
Median	27.50	77.50	46.00	76.00
Min - Max	1.0 - 155.0	-3.0 - 382.0	24.0 - 254.0	-3.0 - 382.0
Time to Onset from first Glofitamab/Rituximab dose (days)				
n	14	55	7	62
Mean (SD)	48.57 (54.87)	116.29 (89.45)	88.04 (94.79)	113.10 (89.71)
Median	26.99	105.62	37.57	99.52
Min - Max	0.5 - 154.5	1.5 - 374.4	16.5 - 244.7	1.5 - 374.4

Data Cutoff Dates: GO41943 - 08DEC2021, GO41944 - 16FEB2024.
Treatment related AEs includes Glofitamab, Rituximab, Gemcitabine, Oxaliplatin, Obinutuzumab or Tocilizumab. Dose modified/interrupted due to AE refers to Glofitamab, Rituximab, Gemcitabine, Oxaliplatin, Obinutuzumab or Tocilizumab.
Investigator text for AEs encoded using MedDRA version 26.1. Adverse Events are graded by NCI CTCAE v5.0, CRS events are graded by ASTCT 2019. AESIs not experienced by any patients are excluded. Multiple occurrences of the same AE in one individual are counted only once except for the Time to Onset, Duration and 'Total number of AEs' rows in which multiple occurrences of the same AE are counted separately. Percentages are based on N in the column headings. The count of 'Patients with treatment received for AE' is based on the AE CRF question 'Was Medication Given For AE?'

Haemophagocytic Lymphohistiocytosis

No suspected cases of HLH were reported in any of the treatment arms in studies GO41944 and GO41943.

Tumour Lysis Syndrome

TLS AEs (any grade) were reported in 3/172 patients (1.7%) in the Glofit-GemOx arm and in 3/88 patients (3.4%) in the R-GemOx arm. All TLS AEs were Grade 3 and all patients received treatment for the TLS AE. All TLS AEs had resolved at the time of the CCOD and all events were considered to be related to treatment.

Febrile Neutropenia

Febrile neutropenia AEs (minimum Grade 3 by definition) were reported in 5/172 patients (2.9%) in the Glofit-GemOx arm and in 1/88 patients (1.1%) in the R-GemOx arm.

Table 22 Summary of Adverse Events of Special Interest for Glofitamab: Febrile Neutropenia (Safety Evaluable Patients Receiving R-GemOx or Glofit-GemOx)

Summary of Adverse Events of Special Interest, Modified Safety-Evaluable Patients
Protocol: GO41944 & GO41943

Febrile Neutropenia

	R-GemOx (GO41944) (N=88)	Glofit-GemOx (Glofit Exposed) (GO41944) (N=172)	Glofit-GemOx (Glofit Exposed) (GO41943) (N=16)	Glofit-GemOx (Glofit Exposed) (GO41944 & GO41943) (N=188)
Total number of pts with at least one AE	1 (1.1%)	5 (2.9%)	0	5 (2.7%)
Total number of AEs	1	5	0	5
Total number of pts with at least one AE by worst grade				
Grade 3	1 (1.1%)	5 (2.9%)	0	5 (2.7%)
Grade 4	0	0	0	0
Grade 5 (fatal outcome)	0	0	0	0
Total number of pts with dose modified/interrupted due to AE	0	1 (0.6%)	0	1 (0.5%)
Total number of pts with treatment received for AE	1 (1.1%)	5 (2.9%)	0	5 (2.7%)
Total number of pts with all AEs resolved	1 (1.1%)	5 (2.9%)	0	5 (2.7%)
Total number of pts with at least one unresolved or ongoing AE	0	0	0	0
Total number of pts with at least one serious AE	1 (1.1%)	4 (2.3%)	0	4 (2.1%)
Total number of pts with at least one related AE	1 (1.1%)	5 (2.9%)	0	5 (2.7%)
Duration of AE (days)				
n	1	5	0	5
Mean (SD)	32.00 (NE)	4.40 (2.07)	NE (NE)	4.40 (2.07)
Median	32.00	4.00	NE	4.00
Min - Max	32.0 - 32.0	2.0 - 7.0	NE - NE	2.0 - 7.0
Time to Onset (days)				
n	1	5	0	5
Mean (SD)	26.00 (NE)	22.80 (9.18)	NE (NE)	22.80 (9.18)
Median	26.00	27.00	NE	27.00
Min - Max	26.0 - 26.0	7.0 - 30.0	NE - NE	7.0 - 30.0
Time to Onset from first Glofitamab/Rituximab dose (days)				
n	1	4	0	4
Mean (SD)	25.49 (NE)	18.49 (4.41)	NE (NE)	18.49 (4.41)
Median	25.49	19.59	NE	19.59
Min - Max	25.5 - 25.5	12.3 - 22.5	NE - NE	12.3 - 22.5

Data Cutoff Dates: GO41943 - 08DEC2021, GO41944 - 16FEB2024.
Treatment related AEs includes Glofitamab, Rituxumab, Gemcitabine, Oxaliplatin, Obinutuzumab or Tocilizumab. Dose modified/interrupted due to AE refers to Glofitamab, Rituxumab, Gemcitabine, Oxaliplatin, Obinutuzumab or Tocilizumab.
Investigator text for AEs encoded using MedDRA version 26.1. Adverse Events are graded by NCI CTCAE v5.0, CRS events are graded by ASTCT 2019. AESIs not experienced by any patients are excluded.
Multiple occurrences of the same AE in one individual are counted only once except for the Time to Onset, Duration and 'Total number of AEs' rows in which multiple occurrences of the same AE are counted separately. Percentages are based on N in the column headings. The count of 'Patients with treatment received for AE' is based on the AE CRF question 'Was Medication Given For AE?'

Grade ≥2 Aspartate Aminotransferase, Alanine Aminotransferase or Total Bilirubin Elevation

Table 23 Summary of Adverse Events of Special Interest for Glofitamab: Grade≥AST, ALT or Total Bilirubin Elevation (Safety Evaluable Patients Receiving R-GemOx or Glofit-GemOx)

Summary of Adverse Events of Special Interest, Modified Safety-Evaluable Patients
Protocol: GO41944 & GO41943

Grade >=2 AST, ALT, or total bilirubin elevation

	R-GemOx (GO41944) (N=88)	Glofit-GemOx (Glofit Exposed) (GO41944) (N=172)	Glofit-GemOx (Glofit Exposed) (GO41943) (N=16)	Glofit-GemOx (Glofit Exposed) (GO41944 & GO41943) (N=188)
Total number of pts with at least one AE	7 (8.0%)	24 (14.0%)	1 (6.3%)	25 (13.3%)
Total number of AEs	12	35	1	36
Total number of pts with at least one AE by worst grade				
Grade 2	4 (4.5%)	15 (8.7%)	1 (6.3%)	16 (8.5%)
Grade 3	3 (3.4%)	8 (4.7%)	0	8 (4.3%)
Grade 4	0	0	0	0
Grade 5 (fatal outcome)	0	1 (0.6%)	0	1 (0.5%)
Total number of pts with dose modified/interrupted due to AE	1 (1.1%)	5 (2.9%)	0	5 (2.7%)
Total number of pts with treatment received for AE	3 (3.4%)	9 (5.2%)	0	9 (4.8%)
Total number of pts with all AEs resolved	6 (6.8%)	18 (10.5%)	1 (6.3%)	19 (10.1%)
Total number of pts with at least one unresolved or ongoing AE	1 (1.1%)	5 (2.9%)	0	5 (2.7%)
Total number of pts with at least one serious AE	1 (1.1%)	5 (2.9%)	0	5 (2.7%)
Total number of pts with at least one related AE	7 (8.0%)	20 (11.6%)	0	20 (10.6%)
Duration of AE (days)				
n	11	29	1	30
Mean (SD)	21.27 (33.21)	29.00 (37.99)	7.00 (NE)	28.27 (37.54)
Median	8.00	15.00	7.00	15.00
Min - Max	3.0 - 120.0	1.0 - 198.0	7.0 - 7.0	1.0 - 198.0
Time to Onset (days)				
n	12	35	1	36
Mean (SD)	22.50 (21.44)	47.80 (58.78)	103.00 (NE)	49.33 (58.66)
Median	14.00	28.00	103.00	28.50
Min - Max	8.0 - 66.0	7.0 - 261.0	103.0 - 103.0	7.0 - 261.0
Time to Onset from first Glofitamab/Rituximab dose (days)				
n	12	29	1	30
Mean (SD)	22.04 (21.47)	48.78 (61.56)	95.58 (NE)	50.34 (61.09)
Median	13.75	21.62	95.58	22.06
Min - Max	7.3 - 65.6	0.4 - 253.5	95.6 - 95.6	0.4 - 253.5

Data Cutoff Dates: GO41943 - 08DEC2021, GO41944 - 16FEB2024.
Treatment related AEs includes Glofitamab, Rituxumab, Gemcitabine, Oxaliplatin, Obinutuzumab or Tocilizumab. Dose modified/interrupted due to AE refers to Glofitamab, Rituxumab, Gemcitabine, Oxaliplatin, Obinutuzumab or Tocilizumab.
Investigator text for AEs encoded using MedDRA version 26.1. Adverse Events are graded by NCI CTCAE v5.0, CRS events are graded by ASTCT 2019. AESIs not experienced by any patients are excluded. Multiple occurrences of the same AE in one individual are counted only once except for the Time to Onset, Duration and 'Total number of AEs' rows in which multiple occurrences of the same AE are counted separately. Percentages are based on N in the column headings. The count of 'Patients with treatment received for AE' is based on the AE CRF question 'Was Medication Given For AE?'

Disseminated Intravascular Coagulation

No disseminated intravascular coagulation AEs were reported in any patients who received treatment with glofitamab or rituximab in studies GO41944 and GO41943.

Grade ≥2 Tumour Flare

In the Glofit-GemOx arm, one Grade 3 suspected tumour flare event of non-serious cholestasis occurred in a patient with baseline liver lesions which had an onset prior to glofitamab infusion on Study Day 3. Study treatment was interrupted for the suspected tumour flare event of cholestasis which was considered related to treatment and was unresolved or ongoing as of the CCOD. In the R-GemOx arm, 1/88 patients (1.1%) had a Grade 2 suspected tumour flare event of non-serious thrombocytopenia on or after dosing on C1D1 and before C1D8. The Grade 2 suspected tumour flare event of thrombocytopenia was considered related to study treatment and had resolved by the CCOD.

When excluding suspected tumour flare events, there was 1/172 patients (0.6%) with Grade 2 tumour flare reported in the Glofit-GemOx arm following Gpt-GemOx. There were no Grade ≥2 tumour flare or tumour pain events on R-GemOx.

Pneumonitis or Interstitial Lung Disease Adverse Events (Excluding Pneumonia of Infectious Etiology)

Pneumonitis or interstitial lung disease (ILD; excluding pneumonia of infectious etiology) AEs were reported in 3/172 patients (1.7%) in the Glofit-GemOx arm (two Grade 5 AEs of pneumonitis and 1 Grade 5 AE of acute respiratory distress syndrome in the context of COVID-19 infection).

Table 25 Summary of Adverse Events of Special Interest for Glofitamab: Pneumonitis or Interstitial Lung Disease Excluding Pneumonia of Infectious Etiology (Safety Evaluable Patients Receiving R-GemOx or Glofit-GemOx)

Summary of Adverse Events of Special Interest, Modified Safety-Evaluable Patients
Protocol: GO41944 & GO41943

Pneumonitis or ILD (excluding pneumonia of infectious etiology)

	R-GemOx (GO41944) (N=88)	Glofit-GemOx (Glofit Exposed) (GO41944) (N=172)	Glofit-GemOx (Glofit Exposed) (GO41943) (N=16)	Glofit-GemOx (Glofit Exposed) (GO41944 & GO41943) (N=188)
Total number of pts with at least one AE	0	3 (1.7%)	0	3 (1.6%)
Total number of AEs	0	3	0	3
Total number of pts with at least one AE by worst grade				
Grade 1	0	0	0	0
Grade 2	0	0	0	0
Grade 3	0	0	0	0
Grade 4	0	0	0	0
Grade 5 (fatal outcome)	0	3 (1.7%)	0	3 (1.6%)
Total number of pts with dose modified/interrupted due to AE	0	0	0	0
Total number of pts with treatment received for AE	0	3 (1.7%)	0	3 (1.6%)
Total number of pts with all AEs resolved	0	0	0	0
Total number of pts with at least one unresolved or ongoing AE	0	0	0	0
Total number of pts with at least one serious AE	0	3 (1.7%)	0	3 (1.6%)
Total number of pts with at least one related AE	0	3 (1.7%)	0	3 (1.6%)
Duration of AE (days)				
n	0	3	0	3
Mean (SD)	NE (NE)	9.00 (5.00)	NE (NE)	9.00 (5.00)
Median	NE	9.00	NE	9.00
Min - Max	NE - NE	4.0 - 14.0	NE - NE	4.0 - 14.0
Time to Onset (days)				
n	0	3	0	3
Mean (SD)	NE (NE)	182.33 (76.26)	NE (NE)	182.33 (76.26)
Median	NE	175.00	NE	175.00
Min - Max	NE - NE	110.0 - 262.0	NE - NE	110.0 - 262.0
Time to Onset from first Glofitamab/Rituximab dose (days)				
n	0	3	0	3
Mean (SD)	NE (NE)	175.14 (76.79)	NE (NE)	175.14 (76.79)
Median	NE	167.58	NE	167.58
Min - Max	NE - NE	102.4 - 255.4	NE - NE	102.4 - 255.4

Data Cutoff Dates: GO41943 - 08DEC2021, GO41944 - 16FEB2024.
Treatment related AEs includes Glofitamab, Rituxumab, Gemcitabine, Oxaliplatin, Obinutuzumab or Tocilizumab. Dose modified/interrupted due to AE refers to Glofitamab, Rituxumab, Gemcitabine, Oxaliplatin, Obinutuzumab or Tocilizumab.
Investigator text for AEs encoded using MedDRA version 26.1. Adverse Events are graded by NCI CTCAE v5.0, CRS events are graded by ASTCT 2019. AESIs not experienced by any patients are excluded.
Multiple occurrences of the same AE in one individual are counted only once except for the Time to Onset, Duration and 'Total number of AEs' rows in which multiple occurrences of the same AE are counted separately. Percentages are based on N in the column headings. The count of 'Patients with treatment received for AE' is based on the AE CRF question 'Was Medication Given For AE?'
For the AESI of pneumonitis or interstitial lung disease, one event is an acute respiratory distress syndrome in the context of infection. This is captured due to the AESI search criteria including all events in the broad interstitial lung disease SMQ

Colitis (Excluding Infectious Etiology)

Table 26 Summary of Adverse Events of Special Interest for Glofitamab: Colitis Excluding Infectious Etiology (Safety Evaluable Patients Receiving R-GemOx or Glofit-GemOx)

Summary of Adverse Events of Special Interest, Modified Safety-Evaluable Patients
Protocol: GO41944 & GO41943

Colitis (excluding infectious etiology)

	R-GemOx (GO41944) (N=88)	Glofit-GemOx (Glofit Exposed) (GO41944) (N=172)	Glofit-GemOx (Glofit Exposed) (GO41943) (N=16)	Glofit-GemOx (Glofit Exposed) (GO41944 & GO41943) (N=188)
Total number of pts with at least one AE	0	4 (2.3%)	2 (12.5%)	6 (3.2%)
Total number of AEs	0	5	2	7
Total number of pts with at least one AE by worst grade				
Grade 1	0	0	0	0
Grade 2	0	2 (1.2%)	0	2 (1.1%)
Grade 3	0	2 (1.2%)	2 (12.5%)	4 (2.1%)
Grade 4	0	0	0	0
Grade 5 (fatal outcome)	0	0	0	0
Total number of pts with dose modified/interrupted due to AE	0	1 (0.6%)	0	1 (0.5%)
Total number of pts with treatment received for AE	0	3 (1.7%)	1 (6.3%)	4 (2.1%)
Total number of pts with all AEs resolved	0	1 (0.6%)	2 (12.5%)	3 (1.6%)
Total number of pts with at least one unresolved or ongoing AE	0	3 (1.7%)	0	3 (1.6%)
Total number of pts with at least one serious AE	0	2 (1.2%)	2 (12.5%)	4 (2.1%)
Total number of pts with at least one related AE	0	2 (1.2%)	0	2 (1.1%)
Duration of AE (days)				
n	0	2	2	4
Mean (SD)	NE (NE)	823.00 (0.00)	6.50 (3.54)	414.75 (471.41)
Median	NE	823.00	6.50	416.00
Min - Max	NE - NE	823.0 - 823.0	4.0 - 9.0	4.0 - 823.0
Time to Onset (days)				
n	0	5	2	7
Mean (SD)	NE (NE)	154.20 (32.64)	93.00 (55.15)	136.71 (45.92)
Median	NE	161.00	93.00	132.00
Min - Max	NE - NE	123.0 - 201.0	54.0 - 132.0	54.0 - 201.0
Time to Onset from first Glofitamab/Rituximab dose (days)				
n	0	5	2	7
Mean (SD)	NE (NE)	145.23 (30.29)	85.54 (55.19)	128.18 (44.36)
Median	NE	153.58	85.54	124.56
Min - Max	NE - NE	115.3 - 186.5	46.5 - 124.6	46.5 - 186.5

Data Cutoff Dates: GO41943 - 08DEC2021, GO41944 - 16FEB2024.
Treatment related AEs includes Glofitamab, Rituxumab, Gemcitabine, Oxaliplatin, Obinutuzumab or Tocilizumab. Dose modified/interrupted due to AE refers to Glofitamab, Rituxumab, Gemcitabine, Oxaliplatin, Obinutuzumab or Tocilizumab.
Investigator text for AEs encoded using MedDRA version 26.1. Adverse Events are graded by NCI CTCAE v5.0, CRS events are graded by ASTCT 2019. AESIs not experienced by any patients are excluded. Multiple occurrences of the same AE in one individual are counted only once except for the Time to Onset, Duration and 'Total number of AEs' rows in which multiple occurrences of the same AE are counted separately. Percentages are based on N in the column headings. The count of 'Patients with treatment received for AE' is based on the AE CRF question 'Was Medication Given For AE?'

Selected adverse events for glofitamab:

Neutropenia

Summary of Hematologic Adverse Events (Grouped Terms) by Highest NCI CTCAE Grade, Modified Safety-Evaluable Patients
Protocol: GO41944 & GO41943

Grouped MedDRA Preferred Term	Grade	R-GemOx (GO41944) (N=88)	Glofit-GemOx (Glofit Exposed) (GO41944) (N=172)	Glofit-GemOx (Glofit Exposed) (GO41943) (N=16)	Glofit-GemOx (Glofit Exposed) (GO41944 & GO41943) (N=188)
ANAEMIA / HAEMOGLOBIN DECREASE	- Any Grade -	19 (21.6%)	71 (41.3%)	6 (37.5%)	77 (41.0%)
	1	8 (9.1%)	22 (12.8%)	0	22 (11.7%)
	2	3 (3.4%)	20 (11.6%)	0	20 (10.6%)
	3	7 (8.0%)	29 (16.9%)	6 (37.5%)	35 (18.6%)
	4	1 (1.1%)	0	0	0
BLOOD BILIRUBIN INCREASED / HYPERBILIRUBINAEMIA	- Any Grade -	1 (1.1%)	6 (3.5%)	0	6 (3.2%)
	1	1 (1.1%)	5 (2.9%)	0	5 (2.7%)
	2	0	1 (0.6%)	0	1 (0.5%)
LEUKOPENIA / WHITE BLOOD CELL COUNT DECREASED	- Any Grade -	13 (14.8%)	39 (22.7%)	0	39 (20.7%)
	1	2 (2.3%)	8 (4.7%)	0	8 (4.3%)
	2	5 (5.7%)	13 (7.6%)	0	13 (6.9%)
	3	4 (4.5%)	14 (8.1%)	0	14 (7.4%)
	4	2 (2.3%)	4 (2.3%)	0	4 (2.1%)
LYMPHOPENIA / LYMPHOCYTE COUNT DECREASED	- Any Grade -	13 (14.8%)	42 (24.4%)	0	42 (22.3%)
	1	5 (5.7%)	4 (2.3%)	0	4 (2.1%)
	2	5 (5.7%)	17 (9.9%)	0	17 (9.0%)
	3	2 (2.3%)	11 (6.4%)	0	11 (5.9%)
	4	1 (1.1%)	10 (5.8%)	0	10 (5.3%)
NEUTROPENIA / NEUTROPHIL COUNT DECREASED	- Any Grade -	27 (30.7%)	76 (44.2%)	7 (43.8%)	83 (44.1%)
	1	5 (5.7%)	6 (3.5%)	1 (6.3%)	7 (3.7%)
	2	6 (6.8%)	9 (5.2%)	0	9 (4.8%)
	3	11 (12.5%)	40 (23.3%)	2 (12.5%)	42 (22.3%)
	4	5 (5.7%)	21 (12.2%)	4 (25.0%)	25 (13.3%)
NEUTROPENIA / NEUTROPHIL COUNT DECREASED / FEBRILE NEUTROPENIA	- Any Grade -	28 (31.8%)	78 (45.3%)	7 (43.8%)	85 (45.2%)
	1	5 (5.7%)	6 (3.5%)	1 (6.3%)	7 (3.7%)
	2	6 (6.8%)	9 (5.2%)	0	9 (4.8%)
	3	12 (13.6%)	42 (24.4%)	2 (12.5%)	44 (23.4%)
	4	5 (5.7%)	21 (12.2%)	4 (25.0%)	25 (13.3%)
THROMBOCYTOPENIA / PLATELET COUNT DECREASED	- Any Grade -	42 (47.7%)	87 (50.6%)	8 (50.0%)	95 (50.5%)
	1	15 (17.0%)	21 (12.2%)	0	21 (11.2%)
	2	12 (13.6%)	19 (11.0%)	0	19 (10.1%)
	3	11 (12.5%)	26 (15.1%)	2 (12.5%)	28 (14.9%)
	4	4 (4.5%)	21 (12.2%)	6 (37.5%)	27 (14.4%)

Data Cutoff Dates: GO41943 - 08DEC2021, GO41944 - 16FEB2024.
Investigator text for AEs encoded using MedDRA version 26.1.
Only treatment emergent AEs are displayed. All counts represent numbers of Subjects. Multiple occurrences of the same preferred term in one individual are counted once at the highest grade for that preferred term. Adverse Events are graded by NCI CTCAE v5.0, CRS events are graded by ASTCT 2019. Adverse Events with missing grades are excluded from this output.

Thrombocytopenia

Thrombocytopenia/platelet count decreased AEs (any grade) were reported in 87/172 patients (50.6%) in the Glofit-GemOx arm and in 42/88 patients (47.7%) in the R-GemOx arm.

Infections and infestation adverse events

Adverse Events by Highest Grade, Serious Adverse Events, Modified Safety-Evaluable Patients
Protocol: GO41944 & GO41943

MedDRA System Organ Class MedDRA Preferred Term	Grade	R-GemOx (GO41944) (N=88)	Glofit-GemOx (Glofit Exposed) (GO41944) (N=172)	Glofit-GemOx (Glofit Exposed) (GO41943) (N=16)	Glofit-GemOx (Glofit Exposed) (GO41944 & GO41943) (N=188)
- Any adverse events -	- Any Grade -	15 (17.0%)	90 (52.3%)	11 (68.8%)	101 (53.7%)
	Grade 1-2	0	23 (13.4%)	4 (25.0%)	27 (14.4%)
	1	0	7 (4.1%)	2 (12.5%)	9 (4.8%)
	2	0	16 (9.3%)	2 (12.5%)	18 (9.6%)
	Grade 3-4	11 (12.5%)	55 (32.0%)	7 (43.8%)	62 (33.0%)
	3	7 (8.0%)	44 (25.6%)	6 (37.5%)	50 (26.6%)
	4	4 (4.5%)	11 (6.4%)	1 (6.3%)	12 (6.4%)
	Grade 5	4 (4.5%)	12 (7.0%)	0	12 (6.4%)
Infections and infestations					
- Overall -	- Any Grade -	11 (12.5%)	39 (22.7%)	4 (25.0%)	43 (22.9%)
	Grade 1-2	0	8 (4.7%)	0	8 (4.3%)
	1	0	1 (0.6%)	0	1 (0.5%)
	2	0	7 (4.1%)	0	7 (3.7%)
	Grade 3-4	8 (9.1%)	25 (14.5%)	4 (25.0%)	29 (15.4%)
	3	6 (6.8%)	25 (14.5%)	4 (25.0%)	29 (15.4%)
	4	2 (2.3%)	0	0	0
	Grade 5	3 (3.4%)	6 (3.5%)	0	6 (3.2%)
Pneumonia	- Any Grade -	4 (4.5%)	10 (5.8%)	0	10 (5.3%)
	Grade 1-2	0	1 (0.6%)	0	1 (0.5%)
	2	0	1 (0.6%)	0	1 (0.5%)
	Grade 3-4	2 (2.3%)	8 (4.7%)	0	8 (4.3%)
	3	1 (1.1%)	8 (4.7%)	0	8 (4.3%)
	4	1 (1.1%)	0	0	0
	Grade 5	2 (2.3%)	1 (0.6%)	0	1 (0.5%)
COVID-19	- Any Grade -	2 (2.3%)	8 (4.7%)	0	8 (4.3%)
	Grade 1-2	0	1 (0.6%)	0	1 (0.5%)
	1	0	1 (0.6%)	0	1 (0.5%)
	Grade 3-4	2 (2.3%)	4 (2.3%)	0	4 (2.1%)
	3	1 (1.1%)	4 (2.3%)	0	4 (2.1%)
	4	1 (1.1%)	0	0	0
	Grade 5	0	3 (1.7%)	0	3 (1.6%)
Sepsis	- Any Grade -	0	3 (1.7%)	3 (18.8%)	6 (3.2%)
	Grade 3-4	0	3 (1.7%)	3 (18.8%)	6 (3.2%)
	3	0	2 (1.2%)	3 (18.8%)	5 (2.7%)
	4	0	1 (0.6%)	0	1 (0.5%)
Lower respiratory tract infection	- Any Grade -	1 (1.1%)	5 (2.9%)	0	5 (2.7%)
	Grade 1-2	0	2 (1.2%)	0	2 (1.1%)
	2	0	2 (1.2%)	0	2 (1.1%)
	Grade 3-4	1 (1.1%)	3 (1.7%)	0	3 (1.6%)
	3	1 (1.1%)	3 (1.7%)	0	3 (1.6%)
COVID-19 pneumonia	- Any Grade -	0	2 (1.2%)	0	2 (1.1%)
	Grade 3-4	0	2 (1.2%)	0	2 (1.1%)
	3	0	2 (1.2%)	0	2 (1.1%)
Meningitis aseptic	- Any Grade -	0	2 (1.2%)	0	2 (1.1%)
	Grade 1-2	0	1 (0.6%)	0	1 (0.5%)
	2	0	1 (0.6%)	0	1 (0.5%)
	Grade 3-4	0	1 (0.6%)	0	1 (0.5%)
	3	0	1 (0.6%)	0	1 (0.5%)

Liver and pancreatic adverse events

Adverse Events by Highest Grade, Liver and Pancreatic Adverse Events, Modified Safety-Evaluable Patients
Protocol: GO41944 & GO41943

MedDRA System Organ Class MedDRA Preferred Term	Grade	R-GemOx (GO41944) (N=88)	Glofit-GemOx (Glofit Exposed) (GO41944) (N=172)	Glofit-GemOx (Glofit Exposed) (GO41943) (N=16)	Glofit-GemOx (Glofit Exposed) (GO41944 & GO41943) (N=188)
- Any adverse events -	- Any Grade -	26 (29.5%)	74 (43.0%)	2 (12.5%)	76 (40.4%)
	Grade 1-2	22 (25.0%)	66 (38.4%)	2 (12.5%)	68 (36.2%)
	1	17 (19.3%)	54 (31.4%)	1 (6.3%)	55 (29.3%)
	2	5 (5.7%)	12 (7.0%)	1 (6.3%)	13 (6.9%)
	Grade 3-4	4 (4.5%)	8 (4.7%)	0	8 (4.3%)
	3	4 (4.5%)	8 (4.7%)	0	8 (4.3%)
Investigations					
- Overall -	- Any Grade -	26 (29.5%)	73 (42.4%)	2 (12.5%)	75 (39.9%)
	Grade 1-2	22 (25.0%)	65 (37.8%)	2 (12.5%)	67 (35.6%)
	1	17 (19.3%)	54 (31.4%)	1 (6.3%)	55 (29.3%)
	2	5 (5.7%)	11 (6.4%)	1 (6.3%)	12 (6.4%)
	Grade 3-4	4 (4.5%)	8 (4.7%)	0	8 (4.3%)
	3	4 (4.5%)	8 (4.7%)	0	8 (4.3%)
Alanine aminotransferase increased	- Any Grade -	19 (21.6%)	56 (32.6%)	2 (12.5%)	58 (30.9%)
	Grade 1-2	16 (18.2%)	51 (29.7%)	2 (12.5%)	53 (28.2%)
	1	12 (13.6%)	39 (22.7%)	1 (6.3%)	40 (21.3%)
	2	4 (4.5%)	12 (7.0%)	1 (6.3%)	13 (6.9%)
	Grade 3-4	3 (3.4%)	5 (2.9%)	0	5 (2.7%)
	3	3 (3.4%)	5 (2.9%)	0	5 (2.7%)
Aspartate aminotransferase increased	- Any Grade -	17 (19.3%)	59 (34.3%)	0	59 (31.4%)
	Grade 1-2	17 (19.3%)	53 (30.8%)	0	53 (28.2%)
	1	14 (15.9%)	49 (28.5%)	0	49 (26.1%)
	2	3 (3.4%)	4 (2.3%)	0	4 (2.1%)
	Grade 3-4	0	6 (3.5%)	0	6 (3.2%)
	3	0	6 (3.5%)	0	6 (3.2%)
Amylase increased	- Any Grade -	3 (3.4%)	5 (2.9%)	0	5 (2.7%)
	Grade 1-2	2 (2.3%)	5 (2.9%)	0	5 (2.7%)
	1	1 (1.1%)	4 (2.3%)	0	4 (2.1%)
	2	1 (1.1%)	1 (0.6%)	0	1 (0.5%)
	Grade 3-4	1 (1.1%)	0	0	0
	3	1 (1.1%)	0	0	0
Blood bilirubin increased	- Any Grade -	1 (1.1%)	5 (2.9%)	0	5 (2.7%)
	Grade 1-2	1 (1.1%)	5 (2.9%)	0	5 (2.7%)
	1	1 (1.1%)	5 (2.9%)	0	5 (2.7%)
Hepatobiliary disorders					
- Overall -	- Any Grade -	0	1 (0.6%)	0	1 (0.5%)
	Grade 1-2	0	1 (0.6%)	0	1 (0.5%)
	2	0	1 (0.6%)	0	1 (0.5%)
Hyperbilirubinaemia	- Any Grade -	0	1 (0.6%)	0	1 (0.5%)
	Grade 1-2	0	1 (0.6%)	0	1 (0.5%)
	2	0	1 (0.6%)	0	1 (0.5%)

Data Cutoff Dates: GO41943 - 08DEC2021, GO41944 - 16FEB2024.
Investigator text for AEs encoded using MedDRA version 26.1.
Only treatment emergent AEs are displayed. All counts represent numbers of Subjects. Multiple occurrences of the same preferred term in one individual are counted once at the highest grade for that preferred term. Adverse Events are graded by NCI CTCAE v5.0, CRS events are graded by ASTCT 2019.

Immune system disorders

Immune system disorder AEs (any grade) were reported in a greater proportion of patients in the Glofit-GemOx arm (77/172 patients [44.8%]) arm compared with the R-GemOx arm (1/88 patients [1.1%]) (t_ae_ctc_IMM_SERO).

In the Glofit-GemOx arm, the most commonly reported immune system disorder AE was CRS (76/77 patients).

Adverse Events by Highest Grade, Immune System Disorders, Modified Safety-Evaluable Patients
Protocol: GO41944 & GO41943

MedDRA System Organ Class MedDRA Preferred Term	Grade	R-GemOx (GO41944) (N=88)	Glofit-GemOx (Glofit Exposed) (GO41944) (N=172)	Glofit-GemOx (Glofit Exposed) (GO41943) (N=16)	Glofit-GemOx (Glofit Exposed) (GO41944 & GO41943) (N=188)
- Any adverse events -	- Any Grade -	1 (1.1%)	77 (44.8%)	8 (50.0%)	85 (45.2%)
	Grade 1-2	1 (1.1%)	73 (42.4%)	7 (43.8%)	80 (42.6%)
	1	0	54 (31.4%)	5 (31.3%)	59 (31.4%)
	2	1 (1.1%)	19 (11.0%)	2 (12.5%)	21 (11.2%)
	Grade 3-4	0	4 (2.3%)	1 (6.3%)	5 (2.7%)
	3	0	4 (2.3%)	1 (6.3%)	5 (2.7%)
Immune system disorders					
- Overall -	- Any Grade -	1 (1.1%)	77 (44.8%)	8 (50.0%)	85 (45.2%)
	Grade 1-2	1 (1.1%)	73 (42.4%)	7 (43.8%)	80 (42.6%)
	1	0	54 (31.4%)	5 (31.3%)	59 (31.4%)
	2	1 (1.1%)	19 (11.0%)	2 (12.5%)	21 (11.2%)
	Grade 3-4	0	4 (2.3%)	1 (6.3%)	5 (2.7%)
	3	0	4 (2.3%)	1 (6.3%)	5 (2.7%)
Cytokine release syndrome	- Any Grade -	0	76 (44.2%)	8 (50.0%)	84 (44.7%)
	Grade 1-2	0	72 (41.9%)	7 (43.8%)	79 (42.0%)
	1	0	54 (31.4%)	5 (31.3%)	59 (31.4%)
	2	0	18 (10.5%)	2 (12.5%)	20 (10.6%)
	Grade 3-4	0	4 (2.3%)	1 (6.3%)	5 (2.7%)
	3	0	4 (2.3%)	1 (6.3%)	5 (2.7%)
Hypersensitivity	- Any Grade -	0	1 (0.6%)	0	1 (0.5%)
	Grade 1-2	0	1 (0.6%)	0	1 (0.5%)
	1	0	1 (0.6%)	0	1 (0.5%)
Hypogammaglobulinaemia	- Any Grade -	0	1 (0.6%)	0	1 (0.5%)
	Grade 1-2	0	1 (0.6%)	0	1 (0.5%)
	2	0	1 (0.6%)	0	1 (0.5%)
Seasonal allergy	- Any Grade -	0	0	1 (6.3%)	1 (0.5%)
	Grade 1-2	0	0	1 (6.3%)	1 (0.5%)
	1	0	0	1 (6.3%)	1 (0.5%)
Drug hypersensitivity	- Any Grade -	1 (1.1%)	0	0	0
	Grade 1-2	1 (1.1%)	0	0	0
	2	1 (1.1%)	0	0	0

Data Cutoff Dates: GO41943 - 08DEC2021, GO41944 - 16FEB2024.
Investigator text for AEs encoded using MedDRA version 26.1.
Only treatment emergent AEs are displayed. All counts represent numbers of Subjects. Multiple occurrences of the same preferred term in one individual are counted once at the highest grade for that preferred term. Adverse Events are graded by NCI CTCAE v5.0, CRS events are graded by ASTCT 2019.

Laboratory findings

Haematology:

In the Glofit-GemOx and R-GemOx arms, the majority of low hemoglobin values, and low lymphocyte, neutrophil, and platelet counts were reported as NCI CTCAE Grade ≥1 or Grade ≥3 shifts from baseline. There were few patients with an NCI-CTCAE Grade 4 shift from baseline.

Table 28 Summary of Most Frequent Treatment Emergent Hematology Laboratory Abnormalities (Safety Evaluable Patients Receiving R-GemOx or Glofit-GemOx)

Summary of Most Frequent Treatment Emergent Laboratory Abnormalities, Hematology Laboratory, Modified Safety-Evaluable Patients
Protocol: GO41944 & GO41943

	R-GemOx (GO41944) (N=88)			Glofit-GemOx (Glofit Exposed) (GO41944) (N=172)		
Lab Test (Direction)	Grade >=1	Grade >=3	Grade =4	Grade >=1	Grade >=3	Grade =4
Hemoglobin (Low)						
n	88	88	88	172	172	172
Low	39 (44.3%)	7 (8.0%)	0	127 (73.8%)	34 (19.8%)	0
Hemoglobin (High)						
n	88	88	88	172	172	172
High	2 (2.3%)	1 (1.1%)	0	1 (0.6%)	1 (0.6%)	0
Lymphocytes Abs (Low)						
n	64	64	64	143	143	143
Low	39 (60.9%)	16 (25.0%)	3 (4.7%)	116 (81.1%)	72 (50.3%)	35 (24.5%)
Lymphocytes Abs (High)						
n	64	64	64	143	143	143
High	2 (3.1%)	0	0	20 (14.0%)	1 (0.7%)	0
Neutrophils, Total, Abs (Low)						
n	66	66	66	147	147	147
Low	30 (45.5%)	13 (19.7%)	3 (4.5%)	96 (65.3%)	58 (39.5%)	27 (18.4%)
Platelet (Low)						
n	88	88	88	172	172	172
Low	67 (76.1%)	15 (17.0%)	5 (5.7%)	142 (82.6%)	51 (29.7%)	22 (12.8%)
Total Leukocyte Count (Low)						
n	88	88	88	172	172	172
Low	37 (42.0%)	13 (14.8%)	4 (4.5%)	100 (58.1%)	45 (26.2%)	20 (11.6%)

Data Cutoff Dates: GO41943 - 08DEC2021, GO41944 - 16FEB2024.
The output shows any worsening Grade laboratory shifts from Baseline to 1 or higher (for High) or -1 or lower (for Low).
N shows the number of patients with a Baseline and at least one post-Baseline assessment for the lab parameter.
The "Grade>=3" column includes shifts from NCI CTCAE Grade <3 to Grade>=3 and shifts from Grade 3 to Grade 4.
The "Grade 4" column includes shifts from NCI CTCAE Grade <4 to Grade 4.

Program: root/clinical_studies/RO7082859/CDT30295/share/pool_SCS_Followup_Analysis_2024/prod/program/t_lb_freqabn.sas
Adapted from Output: t_lb_freqabn_HAELB_SERO
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Clinical chemistry:

Table 29 Summary of Most Frequent Treatment Emergent Chemistry Laboratory Abnormalities (Safety Evaluable Patients Receiving R-GemOx or Glofit-GemOx)

Summary of Most Frequent Treatment Emergent Laboratory Abnormalities, Chemistry Laboratory, Modified Safety-Evaluable Patients
Protocol: GO41944 & GO41943

Lab Test (Direction)	R-GemOx (GO41944) (N=88)			Glofit-GemOx (Glofit Exposed) (GO41944) (N=172)		
	Grade >=1	Grade >=3	Grade =4	Grade >=1	Grade >=3	Grade =4
Albumin (Low)						
n	88	88	88	171	171	171
Low	23 (26.1%)	0	0	61 (35.7%)	1 (0.6%)	0
Calcium (Low)						
n	88	88	88	172	172	172
Low	14 (15.9%)	1 (1.1%)	1 (1.1%)	62 (36.0%)	2 (1.2%)	2 (1.2%)
Calcium (High)						
n	88	88	88	172	172	172
High	6 (6.8%)	1 (1.1%)	1 (1.1%)	13 (7.6%)	2 (1.2%)	1 (0.6%)
Creatinine (High)						
n	88	88	88	172	172	172
High	10 (11.4%)	3 (3.4%)	0	29 (16.9%)	4 (2.3%)	1 (0.6%)
Glucose (Low)						
n	39	39	39	81	81	81
Low	2 (5.1%)	0	0	4 (4.9%)	2 (2.5%)	1 (1.2%)
Glucose, Fasting (Low)						
n	53	53	53	105	105	105
Low	3 (5.7%)	1 (1.9%)	0	16 (15.2%)	0	0
Magnesium (Low)						
n	88	88	88	171	171	171
Low	18 (20.5%)	1 (1.1%)	0	41 (24.0%)	1 (0.6%)	0
Magnesium (High)						
n	88	88	88	171	171	171
High	4 (4.5%)	3 (3.4%)	1 (1.1%)	9 (5.3%)	4 (2.3%)	1 (0.6%)
Potassium (Low)						
n	88	88	88	172	172	172
Low	9 (10.2%)	1 (1.1%)	0	40 (23.3%)	10 (5.8%)	2 (1.2%)

Lab Test (Direction)	R-GemOx (GO41944) (N=88)			Glofit-GemOx (Glofit Exposed) (GO41944) (N=172)		
	Grade >=1	Grade >=3	Grade =4	Grade >=1	Grade >=3	Grade =4
Potassium (High)						
n	88	88	88	172	172	172
High	9 (10.2%)	0	0	21 (12.2%)	1 (0.6%)	0
Sodium (Low)						
n	88	88	88	172	172	172
Low	19 (21.6%)	1 (1.1%)	0	77 (44.8%)	3 (1.7%)	2 (1.2%)
Sodium (High)						
n	88	88	88	172	172	172
High	3 (3.4%)	0	0	8 (4.7%)	0	0
Triglycerides (High)						
n	2	2	2	15	15	15
High	2 (100%)	0	0	5 (33.3%)	1 (6.7%)	0
Uric Acid (High)						
n	82	82	82	160	160	160
High	10 (12.2%)	10 (12.2%)	0	35 (21.9%)	35 (21.9%)	0

Data Cutoff Dates: GO41943 - 08DEC2021, GO41944 - 16FEB2024.
The output shows any worsening Grade laboratory shifts from Baseline to 1 or higher (for High) or -1 or lower (for Low).
N shows the number of patients with a Baseline and at least one post-Baseline assessment for the lab parameter.
The "Grade>=3" column includes shifts from NCI CTCAE Grade <3 to Grade>=3 and shifts from Grade 3 to Grade 4.
The "Grade 4" column includes shifts from NCI CTCAE Grade <4 to Grade 4.

Safety in special populations

Intrinsic factors:

Age:

To investigate the incidence of AEs by age, patients were categorised into two age groups; <65 years (N=110) and ≥65 years (N=166).

For the ≥65 years age group, the proportion of patients with Grade 5 (fatal) AEs was higher in the Glofit-GemOx arm (7.6%) versus the R-GemOx arm (1.8%) while for the <65 years age group the proportion of patients with Grade 5 AEs was comparable in the Glofit-GemOx (6.0%) and R-GemOx arms (9.1%).

Table 6 Summary of Grade 3–4 Adverse Events by Preferred Term by Age with an Incidence Rate of □ 2%[a] (Study GO41944; Safety Evaluable Population)

SOC / PT	R-GemOx		Glofit-GemOx (Glofit Exposed)		Glofit-GemOx (Any Treatment Exposed)	
	<65 years N=33	≥65 years N=55	<65 years N=67	≥65 years N=105	<65 years N=67	≥65 years N=113
Total no. of patients (%) with at least one AE, n (%)	13 (39.4%)	22 (40.0%)	52 (77.6%)	77 (73.3%)	52 (77.6%)	84 (74.3%)
Investigations	10 (30.3%)	10 (18.2%)	36 (53.7%)	31 (29.5%)	36 (53.7%)	31 (27.4%)
Neutrophil count decreased	5 (15.2%)	5 (9.1%)	26 (38.8%)	12 (11.4%)	26 (38.8%)	12 (10.6%)
Platelet count decreased	3 (9.1%)	6 (10.9%)	16 (23.9%)	15 (14.3%)	16 (23.9%)	15 (13.3%)
Lymphocyte count decreased	1 (3.0%)	1 (1.8%)	15 (22.4%)	3 (2.9%)	15 (22.4%)	3 (2.7%)
White blood cell count decreased	4 (12.1%)	2 (3.6%)	12 (17.9%)	4 (3.8%)	12 (17.9%)	4 (3.5%)
Alanine aminotransferase increased	1 (3.0%)	2 (3.6%)	4 (6.0%)	1 (1.0%)	4 (6.0%)	1 (0.9%)
Aspartate aminotransferase increased	0	0	5 (7.5%)	1 (1.0%)	5 (7.5%)	1 (0.9%)
Blood and lymphatic system disorders	5 (15.2%)	11 (20.0%)	20 (29.9%)	39 (37.1%)	20 (29.9%)	41 (36.3%)
Anaemia	2 (6.1%)	6 (10.9%)	8 (11.9%)	21 (20.0%)	8 (11.9%)	21 (18.6%)
Neutropenia	2 (6.1%)	4 (7.3%)	6 (9.0%)	19 (18.1%)	6 (9.0%)	19 (16.8%)
Thrombocytopenia	2 (6.1%)	4 (7.3%)	9 (13.4%)	9 (8.6%)	9 (13.4%)	10 (8.8%)
Febrile neutropenia	1 (3.0%)	0	2 (3.0%)	3 (2.9%)	2 (3.0%)	4 (3.5%)
Infections and Infestations	2 (6.1%)	7 (12.7%)	6 (9.0%)	25 (23.8%)	6 (9.0%)	31 (27.4%)
Pneumonia	1 (3.0%)	2 (3.6%)	2 (3.0%)	7 (6.7%)	2 (3.0%)	9 (8.0%)
COVID-19	0	2 (3.6%)	1 (1.5%)	3 (2.9%)	1 (1.5%)	3 (2.7%)
Lower respiratory tract infection	0	1 (1.8%)	2 (3.0%)	1 (1.0%)	2 (3.0%)	2 (1.8%)
Sepsis	0	0	0	3 (2.9%)	0	4 (3.5%)
Urinary tract infection	0	0	0	3 (2.9%)	0	3 (2.7%)
Metabolism and nutrition disorders	1 (3.0%)	4 (7.3%)	10 (14.9%)	11 (10.5%)	10 (14.9%)	11 (9.7%)
Hypokalaemia	0	1 (1.8%)	1 (1.5%)	4 (3.8%)	1 (1.5%)	4 (3.5%)
Tumour lysis syndrome	1 (3.0%)	2 (3.6%)	3 (4.5%)	0	3 (4.5%)	0
Hypertriglyceridaemia	0	0	3 (4.5%)	0	3 (4.5%)	0

SOC / PT	R-GemOx		Glofit-GemOx (Glofit Exposed)		Glofit-GemOx (Any Treatment Exposed)	
	<65 years N=33	≥65 years N=55	<65 years N=67	≥65 years N=105	<65 years N=67	≥65 years N=113
Gastrointestinal disorders	0	0	6 (9.0%)	13 (12.4%)	6 (9.0%)	15 (13.3%)
Diarrhoea	0	0	0	6 (5.7%)	0	7 (6.2%)
Abdominal pain	0	0	2 (3.0%)	2 (1.9%)	2 (3.0%)	2 (1.8%)
General disorders and administration site conditions	0	4 (7.3%)	4 (6.0%)	6 (5.7%)	4 (6.0%)	7 (6.2%)
Fatigue	0	1 (1.8%)	0	2 (1.9%)	0	3 (2.7%)
Pain	0	0	2 (3.0%)	1 (1.0%)	2 (3.0%)	1 (0.9%)
Cardiac disorders	1 (3.0%)	1 (1.8%)	0	4 (3.8%)	0	7 (6.2%)
Atrial fibrillation	0	0	0	3 (2.9%)	0	4 (3.5%)
Injury, poisoning and procedural complications	0	0	2 (3.0%)	3 (2.9%)	2 (3.0%)	4 (3.5%)
Infusion related reaction	0	0	2 (3.0%)	0	2 (3.0%)	0
Musculoskeletal and connective tissue disorders	0	1 (1.8%)	0	4 (3.8%)	0	4 (3.5%)
Back pain	0	0	0	3 (2.9%)	0	3 (2.7%)
Immune system disorders	0	0	3 (4.5%)	1 (1.0%)	3 (4.5%)	1 (0.9%)
Cytokine release syndrome	0	0	3 (4.5%)	1 (1.0%)	3 (4.5%)	1 (0.9%)
Respiratory, thoracic and mediastinal disorders	1 (3.0%)	1 (1.8%)	2 (3.0%)	2 (1.9%)	2 (3.0%)	3 (2.7%)
Renal and urinary disorders	0	0	1 (1.5%)	3 (2.9%)	1 (1.5%)	4 (3.5%)
Nervous system disorders	0	0	0	4 (3.8%)	0	4 (3.5%)
Vascular disorders	1 (3.0%)	2 (3.6%)	0	2 (1.9%)	0	3 (2.7%)
Hepatobiliary disorders	0	2 (3.6%)	0	2 (1.9%)	0	2 (1.8%)
Psychiatric disorders	0	0	1 (1.5%)	1 (1.0%)	1 (1.5%)	2 (1.8%)
Endocrine disorders	0	0	0	1 (1.0%)	0	1 (0.9%)

SOC / PT	R-GemOx		Glofit-GemOx (Glofit Exposed)		Glofit-GemOx (Any Treatment Exposed)	
	<65 years N=33	≥65 years N=55	<65 years N=67	≥65 years N=105	<65 years N=67	≥65 years N=113
Eye disorders	0	0	0	1 (1.0%)	0	1 (0.9%)
Product issues	0	0	0	1 (1.0%)	0	1 (0.9%)
Skin and subcutaneous tissue disorders	0	0	1 (1.5%)	0	1 (1.5%)	0
Reproductive system and breast disorders	0	0	0	0	0	1 (0.9%)

AE=adverse event; PT = preferred term; SOC = System Organ Class.

[a] In either the Glofit-GemOx (Glofit Exposed) < 65 years subgroup, or the Glofit-GemOx (Glofit Exposed) ≥ 65 years subgroup.

Notes: SOCs with no PTs occurring at the threshold of ≥ 2% are listed for completeness.

This table includes all patients that experienced a Grade 3–4 AE. In the summaries of Grade 3–5 AEs (t_ae_ctc_subgrp_AGEC_GA35_SE_16FEB2024_41944) and AEs of all grades (2.7.4 SCS, t_ae_ctc_subgrp_AGEC_SERO) by age, if a patient experienced both a Grade 3–4 AE and a Grade 5 AE of the same PT, they were included in the Grade 5 count. This is because multiple occurrences of the same AE by PT in a patient are counted only once at the highest grade included in each output.

Table 8 Summary of Serious Adverse Events by Preferred Term by Age with an Incidence Rate of ≥2%[a] (Study GO41944; Safety Evaluable Population

SOC / PT	R-GemOx		Glofit-GemOx (Glofit Exposed)		Glofit-GemOx (Any Treatment Exposed)	
	<65 years N=67	≥65 years N=105	<65 years N=67	≥65 years N=105	<65 years N=67	≥65 years N=113
Total no. of patients (%) with at least one AE, n (%)	4 (12.1%)	11 (20.0%)	31 (46.3%)	59 (56.2%)	31 (46.3%)	67 (59.3%)
Infections and infestations	3 (9.1%)	8 (14.5%)	10 (14.9%)	29 (27.6%)	10 (14.9%)	36 (31.9%
Pneumonia	2 (6.1%)	2 (3.6%)	3 (4.5%)	7 (6.7%)	3 (4.5%)	9 (8.0%)
COVID-19	0	2 (3.6%)	3 (4.5%)	5 (4.8%)	3 (4.5%)	6 (5.3%)
Lower respiratory tract infection	0	1 (1.8%)	2 (3.0%)	3 (2.9%)	2 (3.0%)	4 (3.5%)
Sepsis	0	0	0	3 (2.9%)	0	4 (3.5%)
Immune system disorders	0	0	8 (11.9%)	27 (25.7%)	8 (11.9%)	27 (23.9%)
Cytokine release syndrome	0	0	8 (11.9%)	27 (25.7%)	8 (11.9%)	27 (23.9%)
Gastrointestinal disorders	0	0	8 (11.9%)	7 (6.7%)	8 (11.9%)	9 (8.0%)
Diarrhoea	0	0	0	4 (3.8%)	0	5 (4.4%)
Vomiting	0	0	3 (4.5%)	0	3 (4.5%)	0
Nausea	0	0	2 (3.0%)	0	2 (3.0%)	0
Pancreatitis	0	0	2 (3.0%)	0	2 (3.0%)	0
General disorders and administration site conditions	2 (6.1%)	2 (3.6%)	5 (7.5%)	7 (6.7%)	5 (7.5%)	7 (6.2%)
Pyrexia	1 (3.0%)	0	5 (7.5%)	6 (5.7%)	5 (7.5%)	6 (5.3%)
Blood and lymphatic system disorders	2 (6.1%)	2 (3.6%)	4 (6.0%)	5 (4.8%)	4 (6.0%)	7 (6.2%)
Febrile neutropenia	1 (3.0%)	0	1 (1.5%)	3 (2.9%)	1 (1.5%)	4 (3.5%)
Thrombocytopenia	0	0	2 (3.0%)	1 (1.0%)	2 (3.0%)	2 (1.8%)
Investigations	0	1 (1.8%)	6 (9.0%)	5 (4.8%)	6 (9.0%)	(4.4%)
Platelet count decreased	0	0	4 (6.0%)	2 (1.9%)	4 (6.0%)	2 (1.8%)
Aspartate aminotransferase increased	0	0	2 (3.0%)	0	2 (3.0%)	0

SOC / PT	R-GemOx		Glofit-GemOx (Glofit Exposed)		Glofit-GemOx (Any Treatment Exposed)	
	<65 years N=67	≥65 years N=105	<65 years N=67	≥65 years N=105	<65 years N=67	≥65 years N=113
Metabolism and nutrition disorders	0	1 (1.8%)	3 (4.5%)	5 (4.8%)	3 (4.5%)	5 (4.4%)
Tumour lysis syndrome	0	1 (1.8%)	2 (3.0%)	0	2 (3.0%)	0
Cardiac disorders	1 (3.0%)	1 (1.8%)	0	6 (5.7%)	0	8 (7.1%)
Atrial fibrillation	0	0	0	3 (2.9%)	0	3 (2.7%)
Respiratory, thoracic and mediastinal disorders	1 (3.0%)	1 (1.8%)	0	4 (3.8%)	0	5 (4.4%)
Injury, poisoning and procedural complications	0	0	1 (1.5%)	3 (2.9%)	1 (1.5%)	4 (3.5%)
Nervous system disorders	0	0	1 (1.5%)	2 (1.9%)	1 (1.5%)	3 (2.7%)
Renal and urinary disorders	0	0	1 (1.5%)	2 (1.9%)	1 (1.5%)	2 (1.8%)
Vascular disorders	0	1 (1.8%)	0	2 (1.9%)	0	3 (2.7%)
Eye disorders	0	0	0	2 (1.9%)	0	2 (1.8%)
Hepatobiliary disorders	0	0	0	2 (1.9%)	0	2 (1.8%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	0	1 (1.5%)	1 (1.0%)	1 (1.5%)	1 (0.9%)
Psychiatric disorders	0	0	1 (1.5%)	1 (1.0%)	1 (1.5%)	1 (0.9%)
Product issues	0	0	0	1 (1.0%)	0	1 (0.9%)

PT = preferred term; SOC = System Organ Class.

[a] In either the < 65 years subgroup, or the ≥ 65 years subgroup in the Glofit-GemOx (Glofit Exposed) population.

Notes: SOCs with no PTs occurring at the threshold of ≥ 2% are listed for completeness.

Multiple occurrences of the same PT in one individual are counted once at the highest grade for that PT.

Source: t_ae_ctc_subgrp_AGEC_SER_SE_16FEB2024_41944.

Sex

The safety profile of Glofit-GemOx and R-GemOx in both sex subgroups was generally consistent with that in the overall safety population from Study GO41944 with a few differences.

For both males and females, the proportion of patients experiencing at least one Grade 3-5 AE in the Glofit-GemOx arm (77.8% and 75.3%, respectively) and R-GemOx arm (40.0% and 42.1%, respectively) was similar. However, a higher proportion of male patients in the Glofit-GemOx arm had a Grade 5 (fatal) AE versus the R-GemOx arm (8.1% vs. 4.0%) while for females the proportion of patients with Grade 5 AEs was comparable in the Glofit-GemOx and R-GemOx arms (5.5% and 5.3%, respectively).

For both males and females, the proportions of patients experiencing at least one SAE in the Glofit-GemOx arm (52.5% and 52.1%, respectively) and R-GemOx arm (18.0% and 15.8%, respectively) were similar.

Race

The proportion of patients in the Glofit-GemOx arm experiencing at least one SAE was higher in the White subgroup compared with the Asian subgroup (61.6% vs. 41.2%) while the proportion of R-GemOx patients experiencing at least one SAE was comparable for the two subgroups (19.4% and 16.0%, respectively).

Subgroup - Race: Asian (N=137)

	R-GemOx (GO41944) (N=50)	Glofit-GemOx (Glofit Exposed) (GO41944) (N=85)	Glofit-GemOx (Glofit Exposed) (GO41943) (N=2)	Glofit-GemOx (Glofit Exposed) (GO41944 & GO41943) (N=87)
Total number of patients with at least one AE	49 (98.0%)	85 (100%)	2 (100%)	87 (100%)
Total number of AEs	527	2082	27	2109
Total number of deaths	34 (68.0%)	36 (42.4%)	2 (100%)	38 (43.7%)
Total number of patients withdrawn from any treatment due to an AE	5 (10.0%)	24 (28.2%)	0	24 (27.6%)
Total number of patients with an AE with fatal outcome	3 (6.0%)	5 (5.9%)	0	5 (5.7%)
Total number of patients with at least one				
AE leading to withdrawal from Glofitamab/Rituximab	5 (10.0%)	20 (23.5%)	0	20 (23.0%)
AE leading to withdrawal from Obinutuzumab	0	0	0	0
AE leading to withdrawal from Gemcitabine	5 (10.0%)	10 (11.8%)	0	10 (11.5%)
AE leading to withdrawal from Oxaliplatin	5 (10.0%)	11 (12.9%)	0	11 (12.6%)
AE leading to dose interruption of Glofitamab/ Rituximab	7 (14.0%)	33 (38.8%)	0	33 (37.9%)
AE leading to dose interruption of Obinutuzumab	0	5 (5.9%)	0	5 (5.7%)
AE leading to dose interruption of Gemcitabine	7 (14.0%)	26 (30.6%)	0	26 (29.9%)
AE leading to dose modification of Gemcitabine	0	0	0	0
AE leading to dose interruption of Oxaliplatin	7 (14.0%)	26 (30.6%)	0	26 (29.9%)
AE leading to dose modification of Oxaliplatin	2 (4.0%)	1 (1.2%)	0	1 (1.1%)
Serious AE	8 (16.0%)	35 (41.2%)	2 (100%)	37 (42.5%)
Serious AE leading to withdrawal from Glofitamab/ Rituximab	4 (8.0%)	10 (11.8%)	0	10 (11.5%)
Serious AE leading to dose interruption of Glofitamab/Rituximab	3 (6.0%)	16 (18.8%)	0	16 (18.4%)
AE related to Glofitamab/Rituximab	35 (70.0%)	76 (89.4%)	2 (100%)	78 (89.7%)
AE related to Obinutuzumab	0	70 (82.4%)	1 (50.0%)	71 (81.6%)
AE related to Gemcitabine	42 (84.0%)	81 (95.3%)	2 (100%)	83 (95.4%)
AE related to Oxaliplatin	46 (92.0%)	83 (97.6%)	2 (100%)	85 (97.7%)
Serious AE related to Glofitamab/Rituximab	4 (8.0%)	25 (29.4%)	1 (50.0%)	26 (29.9%)
Serious AE related to Obinutuzumab	0	5 (5.9%)	0	5 (5.7%)
Serious AE related to Gemcitabine	4 (8.0%)	17 (20.0%)	0	17 (19.5%)
Serious AE related to Oxaliplatin	4 (8.0%)	17 (20.0%)	0	17 (19.5%)
Grade 3-5 AE	20 (40.0%)	66 (77.6%)	2 (100%)	68 (78.2%)
Grade 3-5 AE related to Glofitamab/Rituximab	13 (26.0%)	50 (58.8%)	0	50 (57.5%)
Grade 3-5 AE related to Obinutuzumab	0	37 (43.5%)	0	37 (42.5%)
Grade 3-5 AE related to Gemcitabine	17 (34.0%)	57 (67.1%)	2 (100%)	59 (67.8%)
Grade 3-5 AE related to Oxaliplatin	19 (38.0%)	59 (69.4%)	2 (100%)	61 (70.1%)
Glofitamab/Rituximab related AESI	5 (10.0%)	20 (23.5%)	0	20 (23.0%)
Obinutuzumab related AESI	0	2 (2.4%)	0	2 (2.3%)
AE related to Glofitamab/Rituximab leading to withdrawal from Glofitamab/Rituximab	1 (2.0%)	8 (9.4%)	0	8 (9.2%)
AE related to Glofitamab/Rituximab leading to dose interruption of Glofitamab/Rituximab	4 (8.0%)	23 (27.1%)	0	23 (26.4%)
Outcome of adverse events				
Recovered / resolved	383	1774	23	1797
Recovering / resolving	0	0	0	0
Recovered / resolved with sequelae	4	5	0	5
Not recovered / resolved	112	282	4	286
Fatal	3	5	0	5
Unknown / missing	25	16	0	16

Data Cutoff Dates: GO41943 - 08DEC2021, GO41944 - 16FEB2024.
Investigator text for AEs encoded using MedDRA version 26.1. Percentages are based on N in the column headings. Only treatment emergent AEs are displayed.
Multiple occurrences of the same AE in one individual are counted only once except for "Total number of AEs" row in which multiple occurrences of the same AE are counted separately.
Tocilizumab not included as a study drug.

Subgroup - Race: White (N=118)

	R-GemOx (GO41944) (N=31)	Glofit-GemOx (Glofit Exposed) (GO41944) (N=73)	Glofit-GemOx (Glofit Exposed) (GO41943) (N=14)	Glofit-GemOx (Glofit Exposed) (GO41944 & GO41943) (N=87)
Total number of patients with at least one AE	31 (100%)	73 (100%)	14 (100%)	87 (100%)
Total number of AEs	312	1021	176	1197
Total number of deaths	13 (41.9%)	34 (46.6%)	9 (64.3%)	43 (49.4%)
Total number of patients withdrawn from any treatment due to an AE	6 (19.4%)	13 (17.8%)	1 (7.1%)	14 (16.1%)
Total number of patients with an AE with fatal outcome	1 (3.2%)	6 (8.2%)	0	6 (6.9%)
Total number of patients with at least one				
AE leading to withdrawal from Glofitamab/Rituximab	6 (19.4%)	12 (16.4%)	1 (7.1%)	13 (14.9%)
AE leading to withdrawal from Obinutuzumab	0	1 (1.4%)	0	1 (1.1%)
AE leading to withdrawal from Gemcitabine	6 (19.4%)	12 (16.4%)	0	12 (13.8%)
AE leading to withdrawal from Oxaliplatin	6 (19.4%)	12 (16.4%)	0	12 (13.8%)
AE leading to dose interruption of Glofitamab/ Rituximab	6 (19.4%)	36 (49.3%)	5 (35.7%)	41 (47.1%)
AE leading to dose interruption of Obinutuzumab	0	2 (2.7%)	0	2 (2.3%)
AE leading to dose interruption of Gemcitabine	6 (19.4%)	29 (39.7%)	4 (28.6%)	33 (37.9%)
AE leading to dose modification of Gemcitabine	0	2 (2.7%)	0	2 (2.3%)
AE leading to dose interruption of Oxaliplatin	6 (19.4%)	28 (38.4%)	4 (28.6%)	32 (36.8%)
AE leading to dose modification of Oxaliplatin	4 (12.9%)	4 (5.5%)	0	4 (4.6%)
Serious AE	6 (19.4%)	45 (61.6%)	9 (64.3%)	54 (62.1%)
Serious AE leading to withdrawal from Glofitamab/ Rituximab	2 (6.5%)	7 (9.6%)	1 (7.1%)	8 (9.2%)
Serious AE leading to dose interruption of Glofitamab/Rituximab	1 (3.2%)	17 (23.3%)	2 (14.3%)	19 (21.8%)
AE related to Glofitamab/Rituximab	19 (61.3%)	60 (82.2%)	12 (85.7%)	72 (82.8%)
AE related to Obinutuzumab	0	33 (45.2%)	4 (28.6%)	37 (42.5%)
AE related to Gemcitabine	27 (87.1%)	64 (87.7%)	14 (100%)	78 (89.7%)
AE related to Oxaliplatin	29 (93.5%)	64 (87.7%)	14 (100%)	78 (89.7%)
Serious AE related to Glofitamab/Rituximab	2 (6.5%)	30 (41.1%)	3 (21.4%)	33 (37.9%)
Serious AE related to Obinutuzumab	0	9 (12.3%)	1 (7.1%)	10 (11.5%)
Serious AE related to Gemcitabine	2 (6.5%)	14 (19.2%)	6 (42.9%)	20 (23.0%)
Serious AE related to Oxaliplatin	2 (6.5%)	15 (20.5%)	6 (42.9%)	21 (24.1%)
Grade 3-5 AE	13 (41.9%)	55 (75.3%)	10 (71.4%)	65 (74.7%)
Grade 3-5 AE related to Glofitamab/Rituximab	4 (12.9%)	29 (39.7%)	5 (35.7%)	34 (39.1%)
Grade 3-5 AE related to Obinutuzumab	0	15 (20.5%)	2 (14.3%)	17 (19.5%)
Grade 3-5 AE related to Gemcitabine	8 (25.8%)	37 (50.7%)	9 (64.3%)	46 (52.9%)
Grade 3-5 AE related to Oxaliplatin	8 (25.8%)	37 (50.7%)	9 (64.3%)	46 (52.9%)
Glofitamab/Rituximab related AESI	3 (9.7%)	24 (32.9%)	5 (35.7%)	29 (33.3%)
Obinutuzumab related AESI	0	4 (5.5%)	1 (7.1%)	5 (5.7%)
AE related to Glofitamab/Rituximab leading to withdrawal from Glofitamab/Rituximab	2 (6.5%)	2 (2.7%)	0	2 (2.3%)
AE related to Glofitamab/Rituximab leading to dose interruption of Glofitamab/Rituximab	4 (12.9%)	17 (23.3%)	3 (21.4%)	20 (23.0%)
Outcome of adverse events				
Recovered / resolved	240	775	131	906
Recovering / resolving	0	0	3	3
Recovered / resolved with sequelae	2	21	1	22
Not recovered / resolved	68	218	40	258
Fatal	1	6	0	6
Unknown / missing	1	1	1	2

Data Cutoff Dates: GO41943 - 08DEC2021, GO41944 - 16FEB2024.
Investigator text for AEs encoded using MedDRA version 26.1. Percentages are based on N in the column headings. Only treatment emergent AEs are displayed.
Multiple occurrences of the same AE in one individual are counted only once except for "Total number of AEs" row in which multiple occurrences of the same AE are counted separately.
Tocilizumab not included as a study drug.

ECOG PS:

In the Glofit-GemOx population, 71 patients had ECOG PS = 0 and 101 patients had ECOG PS ≥ 1. In the R-GemOx population, 44 patients had ECOG PS=0 and 44 patients had ECOG PS ≥ 1.

Table 10 Summary of Grade 3–4 Adverse Events by Preferred Term by ECOG PS with an Incidence Rate of ≥2%[a] (Study GO41944; Safety Evaluable Population)

SOC / PT	R-GemOx		Glofit-GemOx (Glofit Exposed)		Glofit-GemOx (Any Treatment Exposed)	
	ECOG PS=0 N=44	ECOG PS ≥1 N=44	ECOG PS=0 N=71	ECOG PS ≥1 N=101	ECOG PS=0 N=72	ECOG PS ≥1 N=108
Total no. of patients (%) with at least one AE, n (%)	15 (34.1%)	20 (45.5%)	51 (71.8%)	78 (77.2%)	52 (72.2%)	84 (77.8%)
Investigations	10 (22.7%)	10 (22.7%)	24 (33.8%)	43 (42.6%)	24 (33.3%)	43 (39.8%)
Neutrophil count decreased	6 (13.6%)	4 (9.1%)	16 (22.5%)	22 (21.8%)	16 (22.2%)	22 (20.4%)
Platelet count decreased	5 (11.4%)	4 (9.1%)	9 (12.7%)	22 (21.8%)	9 (12.5%)	22 (20.4%)
Lymphocyte count decreased	1 (2.3%)	1 (2.3%)	5 (7.0%)	13 (12.9%)	5 (6.9%)	13 (12.0%)
White blood cell count decreased	4 (9.1%)	2 (4.5%)	6 (8.5%)	10 (9.9%)	6 (8.3%)	10 (9.3%)
Alanine aminotransferase increased	1 (2.3%)	2 (4.5%)	1 (1.4%)	4 (4.0%)	1 (1.4%)	4 (3.7%)
Aspartate aminotransferase increased	0	0	2 (2.8%)	4 (4.0%)	2 (2.8%)	4 (3.7%)
Gamma-glutamyltransferase increased	0	2 (4.5%)	1 (1.4%)	2 (2.0%)	1 (1.4%)	2 (1.9%)
Blood and lymphatic system disorders	5 (11.4%)	11 (25.0%)	22 (31.0%)	37 (36.6%)	23 (31.9%)	38 (35.2%)
Anaemia	3 (6.8%)	5 (11.4%)	7 (9.9%)	22 (21.8%)	7 (9.7%)	22 (20.4%)
Neutropenia	2 (4.5%)	4 (9.1%)	9 (12.7%)	16 (15.8%)	9 (12.5%)	16 (14.8%)
Thrombocytopenia	2 (4.5%)	4 (9.1%)	6 (8.5%)	12 (11.9%)	6 (8.3%)	13 (12.0%)
Febrile neutropenia	0	1 (2.3%)	2 (2.8%)	3 (3.0%)	3 (4.2%)	3 (2.8%)
Lymphopenia	1 (2.3%)	0	1 (1.4%)	2 (2.0%)	1 (1.4%)	2 (1.9%)
Leukopenia	0	0	0	2 (2.0%)	0	2 (1.9%)
Infections and infestations	3 (6.8%)	6 (13.6%)	10 (14.1%)	21 (20.8%)	11 (15.3%)	26 (24.1%)
Pneumonia	1 (2.3%)	2 (4.5%)	1 (1.4%)	8 (7.9%)	1 (1.4%)	10 (9.3%)
COVID-19	1 (2.3%)	1 (2.3%)	2 (2.8%)	2 (2.0%)	2 (2.8%)	2 (1.9%)
Lower respiratory tract infection	0	1 (2.3%)	3 (4.2%)	0	3 (4.2%)	1 (0.9%)
Sepsis	0	0	0	3 (3.0%)	1 (1.4%)	3 (2.8%)
Urinary tract infection	0	0	0	3 (3.0%)	0	3 (2.8%)

Table 10 Summary of Grade 3–4 Adverse Events by Preferred Term by ECOG PS with an Incidence Rate of ≥2%[a] (Study GO41944; Safety Evaluable Population) (cont.)

SOC / PT	R-GemOx		Glofit-GemOx (Glofit Exposed)		Glofit-GemOx (Any Treatment Exposed)	
	ECOG PS=0 N=44	ECOG PS ≥1 N=44	ECOG PS=0 N=71	ECOG PS ≥1 N=101	ECOG PS=0 N=72	ECOG PS ≥1 N=108
Metabolism and nutrition disorders	0	5 (11.4%)	6 (8.5%)	15 (14.9%)	6 (8.3%)	15 (13.9%)
Hypokalaemia	0	1 (2.3%)	0	5 (5.0%)	0	5 (4.6%)
Tumour lysis syndrome	0	3 (6.8%)	1 (1.4%)	2 (2.0%)	1 (1.4%)	2 (1.9%)
Hypertriglyceridaemia	0	0	1 (1.4%)	2 (2.0%)	1 (1.4%)	2 (1.9%)
Hypophosphataemia	0	0	1 (1.4%)	2 (2.0%)	1 (1.4%)	2 (1.9%)
Gastrointestinal disorders	0	0	6 (8.5%)	13 (12.9%)	6 (8.3%)	15 (13.9%)
Diarrhoea	0	0	2 (2.8%)	4 (4.0%)	2 (2.8%)	5 (4.6%)
Abdominal pain	0	0	0	4 (4.0%)	0	4 (3.7%)
General disorders and administration site conditions	0	4 (9.1%)	1 (1.4%)	9 (8.9%)	1 (1.4%)	10 (9.3%)
Fatigue	0	1 (2.3%)	0	2 (2.0%)	0	3 (2.8%)
Pain	0	0	0	3 (3.0%)	0	3 (2.8%)
Cardiac disorders	1 (2.3%)	1 (2.3%)	1 (1.4%)	3 (3.0%)	2 (2.8%)	5 (4.6%)
Atrial fibrillation	0	0	1 (1.4%)	2 (2.0%)	1 (1.4%)	3 (2.8%)
Musculoskeletal and connective tissue disorders	0	1 (2.3%)	1 (1.4%)	3 (3.0%)	1 (1.4%)	3 (2.8%)
Back pain	0	0	1 (1.4%)	2 (2.0%)	1 (1.4%)	2 (1.9%)
Renal and urinary disorders	0	0	3 (4.2%)	1 (1.0%)	4 (5.6%)	1 (0.9%)
Acute kidney injury	0	0	2 (2.8%)	0	2 (2.8%)	0
Immune system disorders	0	0	2 (2.8%)	2 (2.0%)	2 (2.8%)	2 (1.9%)
Cytokine release syndrome	0	0	2 (2.8%)	2 (2.0%)	2 (2.8%)	2 (1.9%)
Injury, poisoning and procedural complications	0	0	2 (2.8%)	3 (3.0%)	2 (2.8%)	4 (3.7%)
Respiratory, thoracic and mediastinal disorders	1 (2.3%)	1 (2.3%)	0	4 (4.0%)	0	5 (4.6%)
Nervous system disorders	0	0	2 (2.8%)	2 (2.0%)	2 (2.8%)	2 (1.9%)
Vascular disorders	2 (4.5%)	1 (2.3%)	1 (1.4%)	1 (1.0%)	1 (1.4%)	2 (1.9%)

Table 10 Summary of Grade 3-4 Adverse Events by Preferred Term by ECOG PS with an Incidence Rate of ≥2%[a] (Study GO41944; Safety Evaluable Population) (cont.)

SOC / PT	R-GemOx		Glofit-GemOx (Glofit Exposed)		Glofit-GemOx (Any Treatment Exposed)	
	ECOG PS=0 N=44	ECOG PS ≥1 N=44	ECOG PS=0 N=71	ECOG PS ≥1 N=101	ECOG PS=0 N=72	ECOG PS ≥1 N=108
Hepatobiliary disorders	1 (2.3%)	1 (2.3%)	0	2 (2.0%)	0	2 (1.9%)
Psychiatric disorders	0	0	1 (1.4%)	1 (1.0%)	1 (1.4%)	2 (1.9%)
Endocrine disorders	0	0	1 (1.4%)	0	1 (1.4%)	0
Eye disorders	0	0	0	1 (1.0%)	0	1 (0.9%)
Product issues	0	0	0	1 (1.0%)	0	1 (0.9%)
Skin and subcutaneous tissue disorders	0	0	1 (1.4%)	0	1 (1.4%)	0
Reproductive system and breast disorders	0	0	0	0	1 (1.4%)	0

ECOG = Eastern Cooperative Oncology Group; PS=Performance Status; PT = preferred term; SOC = System Organ Class.

[a] In either the Glofit-GemOx (Glofit Exposed) ECOG PS = 0 subgroup, or the Glofit-GemOx (Glofit Exposed) ECOG PS ≥ 1 subgroup.

Notes: SOCs with no PTs occurring at the threshold of ≥ 2% are listed for completeness.

This table includes all patients that experienced a Grade 3–4 AE. In the summary that includes AEs of all grades (t_ae_ctc_subgrp_ECOG_SE_16FEB2024_41944), if a patient experienced both a Grade 3–4 AE and a Grade 5 AE of the same PT, they were only included in the Grade 5 count. This is because multiple occurrences of the same AE by PT in a patient are counted only once at the highest grade included in each output.

Extrinsic factors:

Prior CAR-T therapy:

Overview of Adverse Events by Subgroup, Prior CAR-T Therapy, Modified Safety-Evaluable Patients
Protocol: GO41944 & GO41943

Subgroup - Prior CAR-T Therapy: Yes (N=21)

	R-GemOx (GO41944) (N=12)	Glofit-GemOx (Glofit Exposed) (GO41944) (N=8)	Glofit-GemOx (Glofit Exposed) (GO41943) (N=1)	Glofit-GemOx (Glofit Exposed) (GO41944 & GO41943) (N=9)
Total number of patients with at least one AE	12 (100%)	8 (100%)	1 (100%)	9 (100%)
Total number of AEs	73	85	6	91
Total number of deaths	8 (66.7%)	6 (75.0%)	0	6 (66.7%)
Total number of patients withdrawn from any treatment due to an AE	1 (8.3%)	0	0	0
Total number of patients with at least one				
AE leading to withdrawal from Glofitamab/Rituximab	1 (8.3%)	0	0	0
AE leading to withdrawal from Gemcitabine	1 (8.3%)	0	0	0
AE leading to withdrawal from Oxaliplatin	1 (8.3%)	0	0	0
AE leading to dose interruption of Glofitamab/ Rituximab	2 (16.7%)	0	0	0
AE leading to dose interruption of Gemcitabine	2 (16.7%)	0	0	0
AE leading to dose interruption of Oxaliplatin	2 (16.7%)	0	0	0
Serious AE	1 (8.3%)	2 (25.0%)	0	2 (22.2%)
Serious AE leading to dose interruption of Glofitamab/Rituximab	1 (8.3%)	0	0	0
AE related to Glofitamab/Rituximab	10 (83.3%)	7 (87.5%)	1 (100%)	8 (88.9%)
AE related to Obinutuzumab	0	4 (50.0%)	0	4 (44.4%)
AE related to Gemcitabine	11 (91.7%)	7 (87.5%)	1 (100%)	8 (88.9%)
AE related to Oxaliplatin	12 (100%)	7 (87.5%)	1 (100%)	8 (88.9%)
Serious AE related to Glofitamab/Rituximab	1 (8.3%)	1 (12.5%)	0	1 (11.1%)
Serious AE related to Obinutuzumab	0	1 (12.5%)	0	1 (11.1%)
Serious AE related to Gemcitabine	1 (8.3%)	1 (12.5%)	0	1 (11.1%)
Serious AE related to Oxaliplatin	1 (8.3%)	1 (12.5%)	0	1 (11.1%)
Grade 3-5 AE	2 (16.7%)	4 (50.0%)	0	4 (44.4%)
Grade 3-5 AE related to Glofitamab/Rituximab	1 (8.3%)	2 (25.0%)	0	2 (22.2%)
Grade 3-5 AE related to Obinutuzumab	0	2 (25.0%)	0	2 (22.2%)
Grade 3-5 AE related to Gemcitabine	2 (16.7%)	3 (37.5%)	0	3 (33.3%)
Grade 3-5 AE related to Oxaliplatin	2 (16.7%)	3 (37.5%)	0	3 (33.3%)
Glofitamab/Rituximab related AESI	1 (8.3%)	1 (12.5%)	0	1 (11.1%)
AE related to Glofitamab/Rituximab leading to dose interruption of Glofitamab/Rituximab	1 (8.3%)	0	0	0
Outcome of adverse events				
Recovered / resolved	54	66	1	67
Recovered / resolved with sequelae	1	0	0	0
Not recovered / resolved	18	18	5	23
Unknown / missing	0	1	0	1

Subgroup - Prior CAR-T Therapy: No (N=255)

	R-GemOx (GO41944) (N=76)	Glofit-GemOx (Glofit Exposed) (GO41944) (N=164)	Glofit-GemOx (Glofit Exposed) (GO41943) (N=15)	Glofit-GemOx (Glofit Exposed) (GO41944 & GO41943) (N=179)
Total number of patients with at least one AE	72 (94.7%)	164 (100%)	15 (100%)	179 (100%)
Total number of AEs	795	3214	197	3411
Total number of deaths	43 (56.6%)	68 (41.5%)	11 (73.3%)	79 (44.1%)
Total number of patients withdrawn from any treatment due to an AE	10 (13.2%)	43 (26.2%)	1 (6.7%)	44 (24.6%)
Total number of patients with an AE with fatal outcome	4 (5.3%)	12 (7.3%)	0	12 (6.7%)
Total number of patients with at least one				
AE leading to withdrawal from Glofitamab/Rituximab	10 (13.2%)	36 (22.0%)	1 (6.7%)	37 (20.7%)
AE leading to withdrawal from Obinutuzumab	0	1 (0.6%)	0	1 (0.6%)
AE leading to withdrawal from Gemcitabine	10 (13.2%)	26 (15.9%)	0	26 (14.5%)
AE leading to withdrawal from Oxaliplatin	10 (13.2%)	29 (17.7%)	0	29 (16.2%)
AE leading to dose interruption of Glofitamab/ Rituximab	12 (15.8%)	75 (45.7%)	5 (33.3%)	80 (44.7%)
AE leading to dose interruption of Obinutuzumab	0	8 (4.9%)	0	8 (4.5%)
AE leading to dose interruption of Gemcitabine	12 (15.8%)	61 (37.2%)	4 (26.7%)	65 (36.3%)
AE leading to dose modification of Gemcitabine	0	2 (1.2%)	0	2 (1.1%)
AE leading to dose interruption of Oxaliplatin	12 (15.8%)	60 (36.6%)	4 (26.7%)	64 (35.8%)
AE leading to dose modification of Oxaliplatin	6 (7.9%)	5 (3.0%)	0	5 (2.8%)
Serious AE	14 (18.4%)	88 (53.7%)	11 (73.3%)	99 (55.3%)
Serious AE leading to withdrawal from Glofitamab/ Rituximab	6 (7.9%)	21 (12.8%)	1 (6.7%)	22 (12.3%)
Serious AE leading to dose interruption of Glofitamab/Rituximab	4 (5.3%)	35 (21.3%)	2 (13.3%)	37 (20.7%)
AE related to Glofitamab/Rituximab	48 (63.2%)	142 (86.6%)	13 (86.7%)	155 (86.6%)
AE related to Obinutuzumab	0	104 (63.4%)	5 (33.3%)	109 (60.9%)
AE related to Gemcitabine	62 (81.6%)	149 (90.9%)	15 (100%)	164 (91.6%)
AE related to Oxaliplatin	67 (88.2%)	151 (92.1%)	15 (100%)	166 (92.7%)
Serious AE related to Glofitamab/Rituximab	6 (7.9%)	61 (37.2%)	4 (26.7%)	65 (36.3%)
Serious AE related to Obinutuzumab	0	14 (8.5%)	1 (6.7%)	15 (8.4%)
Serious AE related to Gemcitabine	6 (7.9%)	35 (21.3%)	6 (40.0%)	41 (22.9%)
Serious AE related to Oxaliplatin	6 (7.9%)	36 (22.0%)	6 (40.0%)	42 (23.5%)
Grade 3-5 AE	34 (44.7%)	128 (78.0%)	12 (80.0%)	140 (78.2%)
Grade 3-5 AE related to Glofitamab/Rituximab	19 (25.0%)	83 (50.6%)	5 (33.3%)	88 (49.2%)
Grade 3-5 AE related to Obinutuzumab	0	50 (30.5%)	2 (13.3%)	52 (29.1%)
Grade 3-5 AE related to Gemcitabine	26 (34.2%)	98 (59.8%)	11 (73.3%)	109 (60.9%)
Grade 3-5 AE related to Oxaliplatin	28 (36.8%)	101 (61.6%)	11 (73.3%)	112 (62.6%)
Glofitamab/Rituximab related AESI	8 (10.5%)	48 (29.3%)	5 (33.3%)	53 (29.6%)
Obinutuzumab related AESI	0	7 (4.3%)	1 (6.7%)	8 (4.5%)
AE related to Glofitamab/Rituximab leading to withdrawal from Glofitamab/Rituximab	3 (3.9%)	13 (7.9%)	0	13 (7.3%)
AE related to Glofitamab/Rituximab leading to dose interruption of Glofitamab/Rituximab	8 (10.5%)	43 (26.2%)	3 (20.0%)	46 (25.7%)
Outcome of adverse events				
Recovered / resolved	595	2643	153	2796
Recovering / resolving	0	0	3	3
Recovered / resolved with sequelae	5	30	1	31
Not recovered / resolved	165	510	39	549
Fatal	4	12	0	12
Unknown / missing	26	19	1	20

Data Cutoff Dates: GO41943 - 08DEC2021, GO41944 - 16FEB2024.
Investigator text for AEs encoded using MedDRA version 26.1. Percentages are based on N in the column headings. Only treatment emergent AEs are displayed.
Multiple occurrences of the same AE in one individual are counted only once except for "Total number of AEs" row in which multiple occurrences of the same AE are counted separately.
Tocilizumab not included as a study drug.

Safety related to drug-drug interactions and other interactions

No drug-drug interaction (DDI) studies were performed. Based on glofitamab popPK analysis, combination with GemOx does not have an impact on glofitamab PK. Glofitamab impact on GemOx PK was not investigated as no DDI is expected.

Discontinuation due to adverse events

AEs leading to the withdrawal of any study treatment, regardless of the specific drug withdrawn, were reported in a greater proportion of patients in the Glofit-GemOx arm (43/172 patients [25.0%]) compared with the R-GemOx arm (11/88 patients [12.5%]).

Table 14 Summary of Adverse Events Leading to Any Study Treatment Discontinuation (Safety Evaluable Patients Receiving R-GemOx or Glofit-GemOx)

Summary of Adverse Events, Adverse Events Leading to Any Study Treatment Discontinuation, Modified Safety-Evaluable Patients
Protocol: GO41944 & GO41943

MedDRA System Organ Class MedDRA Preferred Term	R-GemOx (GO41944) (N=88)	Glofit-GemOx (Glofit Exposed) (GO41944) (N=172)	Glofit-GemOx (Glofit Exposed) (GO41943) (N=16)	Glofit-GemOx (Glofit Exposed) (GO41944 & GO41943) (N=188)
Total number of patients with at least one adverse event	11 (12.5%)	43 (25.0%)	1 (6.3%)	44 (23.4%)
Overall total number of events	11	50	1	51
Infections and infestations				
Total number of patients with at least one adverse event	8 (9.1%)	24 (14.0%)	0	24 (12.8%)
Total number of events	8	24	0	24
COVID-19	5 (5.7%)	18 (10.5%)	0	18 (9.6%)
Pneumonia	2 (2.3%)	1 (0.6%)	0	1 (0.5%)
COVID-19 pneumonia	0	1 (0.6%)	0	1 (0.5%)
Herpes zoster	0	1 (0.6%)	0	1 (0.5%)
Respiratory tract infection	0	1 (0.6%)	0	1 (0.5%)
Sepsis	0	1 (0.6%)	0	1 (0.5%)
Septic shock	0	1 (0.6%)	0	1 (0.5%)
Pneumonia bacterial	1 (1.1%)	0	0	0
Nervous system disorders				
Total number of patients with at least one adverse event	0	5 (2.9%)	1 (6.3%)	6 (3.2%)
Total number of events	0	5	1	6
Peripheral sensory neuropathy	0	4 (2.3%)	0	4 (2.1%)
Cerebral haemorrhage	0	1 (0.6%)	0	1 (0.5%)
Transient ischaemic attack	0	0	1 (6.3%)	1 (0.5%)
Investigations				
Total number of patients with at least one adverse event	1 (1.1%)	5 (2.9%)	0	5 (2.7%)
Total number of events	1	7	0	7
Neutrophil count decreased	0	3 (1.7%)	0	3 (1.6%)
Platelet count decreased	1 (1.1%)	1 (0.6%)	0	1 (0.5%)
Alanine aminotransferase increased	0	1 (0.6%)	0	1 (0.5%)
Aspartate aminotransferase increased	0	1 (0.6%)	0	1 (0.5%)
SARS-CoV-2 test positive	0	1 (0.6%)	0	1 (0.5%)
Respiratory, thoracic and mediastinal disorders				
Total number of patients with at least one adverse event	0	3 (1.7%)	0	3 (1.6%)
Total number of events	0	3	0	3
Pneumonitis	0	2 (1.2%)	0	2 (1.1%)
Acute respiratory distress syndrome	0	1 (0.6%)	0	1 (0.5%)

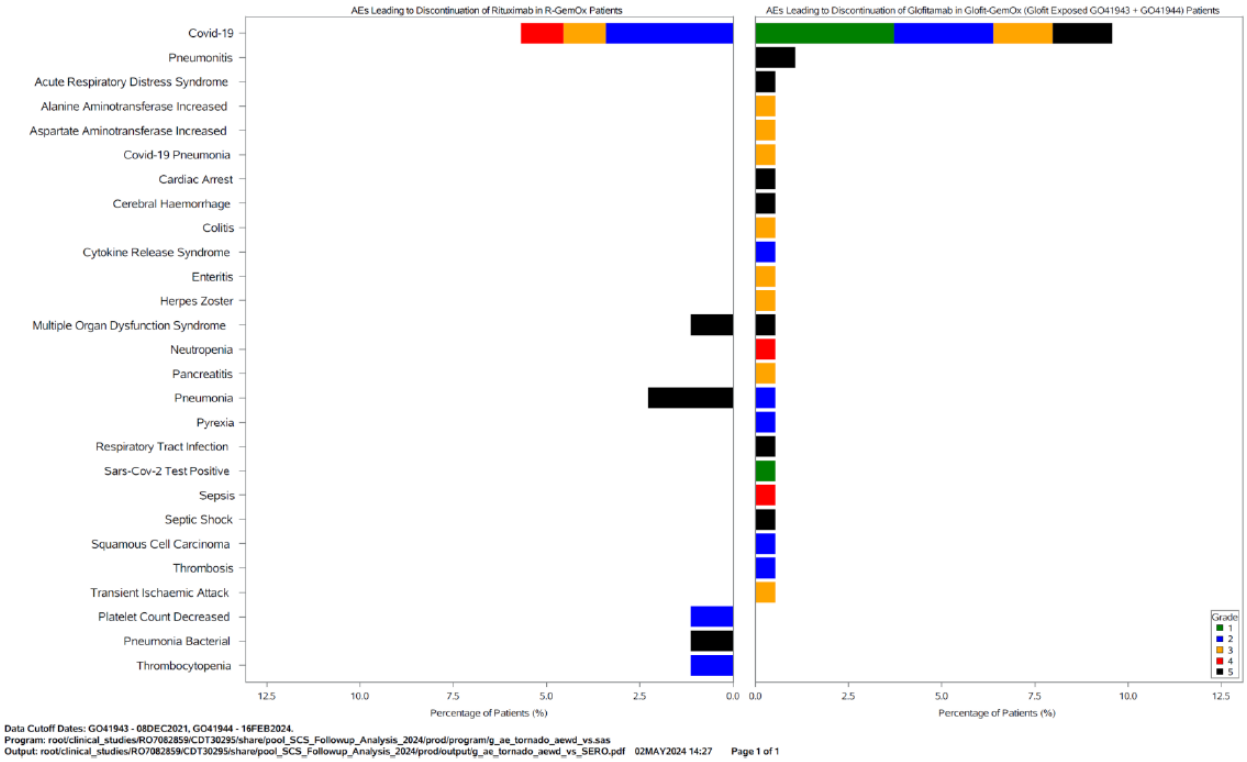
MedDRA System Organ Class MedDRA Preferred Term	R-GemOx (GO41944) (N=88)	Glofit-GemOx (Glofit Exposed) (GO41944) (N=172)	Glofit-GemOx (Glofit Exposed) (GO41943) (N=16)	Glofit-GemOx (Glofit Exposed) (GO41944 & GO41943) (N=188)
Blood and lymphatic system disorders				
Total number of patients with at least one adverse event	1 (1.1%)	2 (1.2%)	0	2 (1.1%)
Total number of events	1	2	0	2
Thrombocytopenia	1 (1.1%)	1 (0.6%)	0	1 (0.5%)
Neutropenia	0	1 (0.6%)	0	1 (0.5%)
General disorders and administration site conditions				
Total number of patients with at least one adverse event	1 (1.1%)	2 (1.2%)	0	2 (1.1%)
Total number of events	1	2	0	2
Multiple organ dysfunction syndrome	1 (1.1%)	1 (0.6%)	0	1 (0.5%)
Pyrexia	0	1 (0.6%)	0	1 (0.5%)
Gastrointestinal disorders				
Total number of patients with at least one adverse event	0	2 (1.2%)	0	2 (1.1%)
Total number of events	0	3	0	3
Colitis	0	1 (0.6%)	0	1 (0.5%)
Enteritis	0	1 (0.6%)	0	1 (0.5%)
Pancreatitis	0	1 (0.6%)	0	1 (0.5%)
Cardiac disorders				
Total number of patients with at least one adverse event	0	1 (0.6%)	0	1 (0.5%)
Total number of events	0	1	0	1
Cardiac arrest	0	1 (0.6%)	0	1 (0.5%)
Immune system disorders				
Total number of patients with at least one adverse event	0	1 (0.6%)	0	1 (0.5%)
Total number of events	0	1	0	1
Cytokine release syndrome	0	1 (0.6%)	0	1 (0.5%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)				
Total number of patients with at least one adverse event	0	1 (0.6%)	0	1 (0.5%)
Total number of events	0	1	0	1
Squamous cell carcinoma	0	1 (0.6%)	0	1 (0.5%)

MedDRA System Organ Class MedDRA Preferred Term	R-GemOx (GO41944) (N=88)	Glofit-GemOx (Glofit Exposed) (GO41944) (N=172)	Glofit-GemOx (Glofit Exposed) (GO41943) (N=16)	Glofit-GemOx (Glofit Exposed) (GO41944 & GO41943) (N=188)
Vascular disorders				
Total number of patients with at least one adverse event	0	1 (0.6%)	0	1 (0.5%)
Total number of events	0	1	0	1
Thrombosis	0	1 (0.6%)	0	1 (0.5%)

Data Cutoff Dates: GO41943 - 08DEC2021, GO41944 - 16FEB2024.
Any Study Treatment includes Glofitamab, Rituximab, Gemcitabine, Oxaliplatin, Obinutuzumab or Tocilizumab.
Investigator text for AEs encoded using MedDRA version 26.1. Percentages are based on N in the column headings.
Only treatment emergent AEs are displayed. For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.

Program: root/clinical_studies/RO7082859/CDT30295/share/pool_SCS_Followup_Analysis_2024/prod/program/t_ae.sas
Adapted from Output: t_ae_DSC_SERO
02MAY2024 14:33

Figure 7 Tornado Plot of Adverse Events Leading to Discontinuation of Glofitamab (Pooled GO41944 and GO41943 Data: Safety Evaluable Patients Receiving Glofit-GemOx or R-GemOx)



Dose interruption

No dose modifications of glofitamab, obinutuzumab, gemcitabine and rituximab were permitted, however, dose interruptions were permitted.

AEs leading to dose interruption of any study treatment were reported in a greater proportion of patients in the Glofit-GemOx arm (80/172 patients [46.5%]) compared with the R-GemOx arm (19/88 patients [21.6%]).

Post marketing experience

As of July 2024, COLUMVI is approved in more than 50 countries worldwide.

Since the International Birth Date (24 March 2023) through 23 March 2024, an estimated cumulative total of 1361 patients have received glofitamab from marketing experience (United States n=648 patients; European Union n=425 patients; Rest of the World n=288 patients). No new or unexpected safety findings have been identified in the post marketing setting.

2.5.1. Discussion on clinical safety

The presentation of safety information with combination use as a separate table in Section 4.8 of the product information is agreed: the main emphasis and comments are on the pivotal study STARGLO (172 Glofit-Exposed patients, median number of treatment cycles 11), which is also the safety pool presented in the SmPC. It is considered that the addition of 16 Glofit-GemOx (Glofit-Exposed) patients from the phase Ib study GO41943, who received a median number of treatment cycles of 5 and of which 4/16 had HGBCL, has only a minor impact on safety, and the results are presented alongside the pivotal study but not further discussed.

The median number of cycles of gemcitabine and oxaliplatin was 8.0 and 4.0 in the Glofit-GemOx and R-GemOx arms, respectively. In the Glofit-GemOx arm, the median number of cycles of glofitamab received was 11.0 (range 1-13) corresponding to a median treatment duration of 218 days (1-296). In the R-GemOx arm the median number of cycles of rituximab received was 4.0 (range 1-8) corresponding to a median treatment duration of 64 days (1-183). Thus, in the pivotal study STARGLO patients in the Glofit-GemOx arm had a longer median exposure to treatment compared to the R-GemOx arm. This was mainly due to discontinuation due to PD in the R-GemOx arm (54/91; 59.3% compared to 90/183; 49.2% in the Glofit-GemOx arm), although discontinuation due to AEs were higher in the Glofit-GemOx arm (43/172; 25.0%) compared to the R-GemOx arm (11/88; 12.5%),

The most **common AEs** occurring in the Glofit-GemOx arm compared to the R-GemOx arm with more than a 5%-point difference were CRS (44.2% vs. 0.0%), neutropenia/neutrophil count decreased (44.2% vs. 30.7%), polyneuropathy (grouped term; 41.3% vs. 29.5%), anaemia (41.3% vs. 21.6%), diarrhoea (34.9% vs. 27.3%), aspartate aminotransferase increased (34.3% vs. 19.3%), alanine aminotransferase increased (32.6 vs. 21.6%)., rash (by PT, 31.4% vs. 18.2%) lymphopenia, and pyrexia (34.4% vs. 5.7%). Nausea, thrombocytopenia/platelet count decreased, decreased appetite, vomiting, and fatigue were also frequent and comparable in both arms and thus most likely mainly related to the GemOx treatment, for which these AEs are well-known.

There were more **Grade 3-4 AEs** in the Glofit-GemOx arm (129/172 patients: 75.0%) compared to the R-GemOx arm (35/88 patients: 39.8%).

There were more **deaths** related to adverse events in the Glofit-GemOx arm (12/172; 7.0%) compared to the R-GemOx arm (4/88; 4.5%) (Table 11/SCS). Six of the deaths in the Glofit-GemOx arm and 3 deaths in the R-GemOx arm were due to events in the SOC Infections and infestations of which 3 and 0, respectively, were due to COVID-19. There were two fatal cases of pneumonitis in the Glofit-GemOx arm and none in the R-GemOx arm. Pneumonitis is an AESI for glofitamab and described in section 4.8 of the SmPC.

The frequencies of **SAE**s were higher in the Glofit-GemOx arm (90/172; 52.3%) compared to the R-GemOx arm (15/88; 17.0%) with the most frequent SAEs occurring in the SOC Infections and infestations (22.7% and 12.5%, respectively). Of note; exposure was longer in the Glofit-GemOx arm (11 cycles glofitamab, 8 cycles GemOx) compared to the R-GemOx arm (4 cycles rituximab and GemOx).

In the pivotal study 76/172 patients (44.2%) had at least one **CRS** event. 20.3% experienced an SAE and one event led to discontinuation. Grade 3 CRS AEs were reported in 4/172 patients (2.3%) and there were no Grade 4 events. 28/76 patients received tocilizumab. 22/76 patients experienced Grade ≥2 CRS and 16 of these (according to the SmPC) received tocilizumab. To reflect the need for tocilizumab treatment as well as other supportive treatments all grades CRS should be included in the SmPC, not only Grade ≥2.

Neurologic AEs (any grade) were reported in a greater proportion of patients in the Glofit-GemOx arm (59.3%) compared with the R-GemOx arm (39.8%). 9/172 in the Glofit-GemOx arm compared to 0 in the R-GemOx arm experienced any Grade 3 event. There were no Grade 4 events in either arm and 1 death in the Glofit-GemOx arm due to a cerebral haemorrhage reported in the context of myelosuppression and thrombocytopenia, and the MAH's assessment is agreed.

In the Glofit-GemOx arm, 76/172 patients (44.2%) had any grade **SAE neutropenia (grouped term)** and the corresponding number in the R-GemOx arm was 27/88 (30.7%). Grade 3-4 in the two arms were 61/172 (35.5%) and 16/88 (18.2%), respectively. Relevant for the assessment of neutropenia are also the corresponding number of **infections** overall, which by SOC was 95/172 (55.2%) and 26/88 (29.5%) in the Glofit-GemOx arm and R-GemOx arm, respectively (see Table

8/SCS). Furthermore, 22.7% in the Glofit-GemOx arm and 3.4% in the R-GemOx arm experienced an infection (by SOC) leading to treatment interruption. The frequencies of SAE COVID-19 infections were 10/172 (5.8%) in the Glofit-GemOx arm and 2/88 (2.3%) in the R-GemOx arm. Given that the median duration of treatment was significantly longer in the Glofit-GemOx-arm (11 cycles glofitamab, 8 cycles GemOx) compared to the R-GemOx arm (4 cycles rituximab and GemOx) primarily due to higher discontinuations due to PD rates in the R-GemOx arm, a clear conclusion as to the potentially higher risk of infection compared to R-GemOx is not possible.

Age: In the pivotal study GO41944 the frequencies of SAEs (any grade) were higher in the Glofit-GemOx arm compared with the R-GemOx arm (52.3% vs. 17.0%, respectively), and the corresponding frequencies for the ≥65 years age group were 56.2% and 20.0%, respectively, and 46.3% and 12.1%, respectively, in the <65 years subgroup. There was a larger difference in SAE frequency in the SOC Infections in the two age subgroups in the Glofit-GemOx arm (<65 y; 14.9%, ≥65 y; 27.6%) compared to the R-GemOx arm (<65 y; 9.1%, ≥65 y; 14.5%).

In the pivotal study GO41944 AEs leading to **discontinuation** were higher in the Glofit-GemOx arm (43/172; 25.0%) compared to the R-GemOx arm (11/88; 12.5%). The most common AEs leading to discontinuation were in the SOC Infections and infestations with 24/172 patients (14.0%) in the Glofit-GemOx arm and 8/88 patients (9.1%) in the R-GemOx arm, with the corresponding frequencies related to COVID-19 (SMQ) being 11.6% and 5.7%, respectively.

No new or unexpected safety findings have been identified in the **post marketing setting.**

All adverse reactions associated with combination use have been reflected in the PI.

Additional expert consultations

Not applicable.

Assessment of paediatric data on clinical safety

Not applicable.

2.5.2. Conclusions on clinical safety

The safety profile of Glofit-GemOx was consistent with the known risks of the individual drugs in the R/R DLBCL population. No new safety signals were observed.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The MAH submitted/was requested to submit an updated RMP version with this application.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 2.2 is acceptable.

The CHMP endorsed this advice without changes.

Safety concerns

Table SVIII.1: Summary of the Safety Concerns

Summary of safety concerns

Important identified risks	• Cytokine release syndrome • Tumour Flare • Serious Infections • Immune effector cell-associated neurotoxicity syndrome (ICANS)
Important potential risks	None
Missing information	• Long-term safety • Safety in patients with prior CAR-T therapy

The safety concerns remain unchanged.

Pharmacovigilance plan

The SOB referring to the Study GO41944 is deleted as fulfilled. The current PhV plan is considered sufficient.

Ongoing and Planned Additional Pharmacovigilance Activities

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Date(s)
Category 2—Imposed mandatory additional pharmacovigilance activities that are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
NP30179 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 (Gazyva®/Gazyvaro™) in patients with R/R B-cell NHL Ongoing	A primary objective of the study is to evaluate the safety, tolerability, and pharmacokinetics of glofitamab as single agent (and in combination with obinutuzumab) following obinutuzumab pre-treatment (Gpt) in patients with R/R CD20 + B –cell NHL. The MAH shall provide a minimum of 2 years follow-up from the end of treatment of the last patient enrolled in the primary safety population of Study NP30179, including analyses of safety in patients with prior CAR-T therapy and safety by sex.	Long-term safety Safety in patients with prior CAR-T therapy	Update CSR	Q4 2024 (Submitted)
Category 3—Required additional pharmacovigilance activities (by a competent authority such as CHMP/PRAC or NCA)—i.e., studies that investigate a safety concern or evaluate the effectiveness of risk minimization activities				
BO44309 Evaluation of the Effectiveness of the Additional Risk Minimisation Measures for Glofitamab: A Survey Among Healthcare Professionals in 10 Countries in the European Economic Area Planned	The primary objective of this study is to assess, by survey: the receipt of the educational materials, i.e., HCP brochure (for the important identified risk of TF) and Patient Card (for the important identified risks of CRS and ICANS), by the target population (glofitamab prescribers) and the distribution of the Patient Card by prescribers to their patients behavioral indicators (the level of awareness, knowledge, comprehension and adherence) of prescribers with respect to TF information included in the HCP brochure.	Cytokine release syndrome Tumor Flare ICANS [a]	Final report	4 2027

CAR-T = chimeric antigen receptor T-cell; CRS = cytokine release syndrome; CSR= clinical study report; HCP= healthcare professional; ICANS=immune effector cell-associated neurotoxicity syndrome; NHL = Non-Hodgkin's lymphoma; R/R = relapsed/refractory; TF=tumor flare.

[a]An update is planned to the design/questionnaire of this study to gather evidence on the effectiveness of the content for ICANS in addition to CRS and TF.

Risk minimisation measures

Current risk minimisation measures are considered sufficient to minimise the risks.

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

Changes are also made to the Annex II conditions in line with the deletion of Study GO41944 as a specific obligation as detailed in the recommendations section above.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons:

There is no significant impact of the new indication and associated data on the readability of the package leaflet and considers it not necessary to conduct user consultation for the Package Leaflet for this application for the following reasons:

- Key safety messages are not affected by this variation
- No significant changes to the formatting of the Package Leaflet have been introduced in this variation.
- The new information added follows the same structure and uses similar descriptions and terminology as used in the approved package leaflet.

The target group of users for the approved indication (adult patients after two or more lines of systemic therapy for DLBCL) and the proposed new indication (adult patients with R/R DLBCL not otherwise specified [DLBCL NOS] who are ineligible for autologous stem cell transplant [ASCT]) are similar, with no significant age difference.

2.7.2. Additional monitoring

Pursuant to Article 23(3) of Regulation No (EU) 726/2004, Columvi (glofitamab) is removed from the additional monitoring list as the condition(s) to the marketing authorisation/ specific obligation(s) have been fulfilled.

Therefore, the statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information, preceded by an inverted equilateral black triangle, is removed from the summary of product characteristics and the package leaflet.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The sought indication is:

Columvi in combination with gemcitabine and oxaliplatin is indicated for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma not otherwise specified (DLBCL NOS) who are ineligible for autologous stem cell transplant (ASCT).

3.1.2. Available therapies and unmet medical need

For patients with R/R DLBCL NOS who are ineligible for ASCT, multiple treatment options are available including immune-chemotherapy combinations (R-GemOx, for example), CAR-T, polatuzumab + BR, tafasitamab + lenalidomide, rituximab + lenalidomide in second line. From second relapse (3L+), bispecific CD20/CD3 monotherapy, CAR-T, loncastuximab (ADC) and pixantrone can also be used. Common to all is that they are generally not considered curative, hence an unmet medical need for new options remains.

3.1.3. Main clinical studies

The single pivotal study, GO41944, was a Phase III, open label, multiregional randomised study designed to evaluate the efficacy and safety of glofitamab in combination with GemOx (Glofit-GemOx) versus rituximab in combination with GemOx (R-GemOx) in patients with R/R DLBCL NOS who have failed one line of therapy and are ineligible for transplant, as well as those patients who have failed at least two lines of therapy. The primary efficacy endpoint of Study GO41944 was overall survival (OS), with key secondary efficacy endpoints of independent review committee (IRC)-assessed progression-free survival (PFS), IRC-assessed complete response (CR) and duration of complete response (DOCR).

The ITT constituted 274 patients randomised 2:1 so 183 patients received Glofit-GemOx while 91 received R-GemOx.

The results presented are based on an interim analysis which crossed its stopping boundary and therefore became the primary analysis (CCOD: 29 March 2023). An updated analysis providing an additional 11 months of follow up was also supplied (CCOD: 16 February 2024).

3.2. Favourable effects

Primary endpoint – OS: At the primary analysis, the pivotal study showed improved OS in Glofit-GemOx treated patients compared to R-GemOx treated patients: stratified HR = 0.59 (95% CI: 0.40, 0.89, log-rank p-value of 0.010706). Median OS in the R-GemOx arm at this time was 9.0 months (95% CI: 7.3, 14.4) and was not reached in the Glofit-GemOx arm (95% CI: 13.8, NE). OS in the

experimental arm, maintained superiority at the time of updated analysis. Median OS of 25.5 months (95% CI: 18.3, NE) vs 12.9 (95% CI: 7.9, 18.5) in the R-GemOx arm: stratified HR 0.62 (0.43, 0.88).

Key secondary endpoint – IRC-assessed PFS: At the primary analysis, the pivotal study showed improved PFS in the Glofit-GemOx arm compared to the R-GemOx arm: stratified HR = 0.37 (95% CI: 0.25, 0.55; log-rank p-value < 0.000001). Median PFS in the Glofit-GemOx arm was 12.1 months (95% CI: 6.8, 18.3) compared to 3.3 months (95% CI: 2.5, 5.6) in the R-GemOx arm. PFS in the experimental arm maintained superiority at the time of updated analysis as median PFS 13.8 months (95% CI: 8.7, 20.5) vs 3.6 months (95% CI: 2.5, 7.1) in the R-GemOx arm.

Key secondary endpoint – IRC-assessed CR rate: At the primary analysis, the pivotal study found an increase in the CR rate in the Glofit-GemOx arm (50.3%; 95% CI: 42.8, 57.7) compared to the R-GemOx arm (22.0%; 95% CI: 14.0, 31.9) with a difference of 28.3% (95% CI: 16.3, 40.3) and a Cochran-Mantel-Haenszel [CMH] p-value < 0.0001. The CR rate in the experimental arm continued to be improved at the time of updated analysis; the difference in response rate was 33.2%; 95% CI: 20.9, 45.5.

3.3. Uncertainties and limitations about favourable effects

A concern on the selection of patients relates to the requirements for ineligibility for ASCT where the MAH has allowed patients who refuse ASCT (but could potentially have tolerated it) to be considered ineligible (for ASCT and, therefore, eligible for the pivotal trial). It seems that there are regional differences in the assessment of this ineligibility criterion and imbalances in the allocation to treatment arms on the regional level. These factors were extensively discussed by the CHMP and addressed by additional analyses (see discussion on Clinical Efficacy).

A further limitation of the pivotal study is that the comparator arm, R-GemOx, has been modified from how it is usually administered. In the STARGLO trial R-GemOx was administered every three weeks and not every two weeks which is common clinical practice according to published reports. However, since neither ESMO nor NCCN recommendations specify the cycle duration of R-GemOx which should be left to the physician's discretion, the addition of glofitamab could justify the choice of a less aggressive GemOx 21-days cycle regimen.

The MAH agreed to provide updated OS analysis when the final CSR for Study GO41944 (STARGLO) is available - as recommended by the CHMP.

3.4. Unfavourable effects

There was generally a higher frequency of adverse events (all types) in the Glofit-GemOx arm.

In the pivotal study 44.2% had at least one CRS event. 20.3% experienced a CRS SAE and one event led to discontinuation. Grade 3 CRS AEs were reported in 4/172 patients (2.3%); there were no Grade 4 events.

The frequencies of SAEs were higher in the Glofit-GemOx arm (90/172; 52.3%) compared to the R-GemOx arm (15/88; 17.0%) with the most frequent SAEs occurring in the SOC Infections and infestations (22.7% and 12.5%, respectively).

There were more deaths related to adverse events in the Glofit-GemOx arm (12/172; 7.0%) compared to the R-GemOx arm (4/88; 4.5%). Six of the deaths in the Glofit-GemOx arm and 3 deaths in the R-GemOx arm were due to events in the SOC Infections and infestations of which 3 and 0, respectively,

were due to COVID-19. There were two fatal cases of pneumonitis in the Glofit-GemOx arm and none in the R-GemOx arm.

In the pivotal study GO41944 AEs leading to discontinuation were higher in the Glofit-GemOx arm (25.0%) compared to the R-GemOx arm (12.5%). The most common AEs leading to discontinuation were in the SOC Infections and infestations.

3.5. Uncertainties and limitations about unfavourable effects

Exposure was longer in the Glofit-GemOx arm compared to the R-GemOx arm (11 cycles glofitamab, 8 cycles GemOx vs. 4 cycles rituximab and GemOx) which could in part explain the unfavourable safety profile over GemOx.

3.6. Effects Table

Table 1. Effects Table for glofitamab in combination with GemOx [Indication: Columvi in combination with gemcitabine and oxaliplatin is indicated for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma not otherwise specified (DLBCL NOS) who are ineligible for autologous stem cell transplant (ASCT)]. Data cut-off: 16 FEB 2024.

Effect	Short description	Unit	Treatment Glofit-GemOx	Control R-GemOx	Uncertainties / Strength of evidence	References
Favourable Effects						
			N=183	**N=91**		
OS	Overall survival	Median, months (95% CI)	25.5 (18.3, NE)	12.9 (7.9, 18.5)	HR: 0.62 (0.43, 0.88); secondary endpoints (PFS, CR) also supportive.	**Study GO41944, CCOD: 16 February 2024**
PFS (IRC-assessed)	Progression free survival	Median, months (95% CI)	13.8 (8.7, 20.5)	3.6 (2.5, 7.1)	HR: 0.40 (0.28, 0.57)	
Unfavourable Effects						
			N=172	**N=88**		
Treatment exposure	Glofitamab vs rituximab	Cycles	11	4		
	GemOx	Cycles	8	4		

Effect	Short description	Unit	Treatment Glofit-GemOx	Control R-GemOx	Uncertainties / Strength of evidence	References
						Study GO41944, CCOD: 16 February 2024
Discontinuation due to AE		N (%)	43 (25.0)	11 (12.5)	Infections (SOC): 24/172 (14.0%) vs 8/88 (9.1%).	Study GO41944, CCOD: 16 February 2024
Infections (SOC)	Any AE SAE		95 (55.2) 13 (7.6)	26 (29.5) 4 (4.5)		Study GO41944, CCOD: 16 February 2024
CRS	Any AE SAE	N (%)	76 (44.2) 35 (20.3)	0:	Tocilizumab use: 28/76	Study GO41944, CCOD: 16 February 2024

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The results from pivotal trial STARGLO demonstrate a statistically significant and clinically relevant survival advantage for the substitution of rituximab by glofitamab to a chemotherapy backbone of gemcitabine + oxaliplatin in patients with R/R DLBCL NOS who are ineligible for ASCT. The favourable survival effects are supported by key secondary endpoints such as progression free survival and complete response rate.

Concerning safety, in particular CRS and the risk of serious infections are considered the AEs with the most impact. The GemOx regimen is considered to contribute substantially to the latter, and it is important that only patients considered fit for this chemotherapy regimen are treated.

3.7.2. Balance of benefits and risks

The benefits from Glofit-GemOx seem to outweigh its safety risks as demonstrated by an OS gain in the ITT population.

3.7.3. Additional considerations on the benefit-risk balance

Conditional marketing authorisation

Although Columvi is conditionally approved, the fact that the pivotal trial for the current procedure is a phase III randomised controlled trial is deemed as comprehensive data to substantiate the current application for an extension of indication.

As part of the specific obligations to the CMA, SOB-CLIN-002 will be considered fulfilled by the provision of the results of trial GO41944 (STARGLO); in parallel SOB-CLIN-001 is being assessed through submission II/10 and therefore a conversion from conditional to a full MA is being considered under the II/10 procedure.

3.8. Conclusions

Overall, the B/R of Columvi is considered positive in adult patients with relapsed/refractory diffuse large B-cell lymphoma not otherwise specified (DLBCL NOS) who are ineligible for autologous stem cell transplant (ASCT) subject to the conditions stated in section 'Recommendations'.

Divergent positions to the majority are appended to this report.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends, by a majority of 27 out of 31 votes, the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II, IIIA and IIIB

Extension of indication to include in combination with gemcitabine and oxaliplatin the treatment of adult patients with relapse or refractory diffuse large B-cell lymphoma not otherwise specified (DLBCL NOS) who are ineligible for autologous stem cell transplant (ASCT) for COLUMVI, based on results of primary and updated analyses from study GO41944 (STARGLO) listed as a Specific Obligation in the Annex II of the Product Information, as well supportive data from the Phase Ib study GO41943. Study GO41944 (STARGLO) is a Phase III, open-label, multicenter, randomised study of glofitamab in combination with GemOx (Glofit-GemOx) vs. rituximab in combination with GemOx (R-GemOx) in patients with R/R DLBCL. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC are updated. The Annex II and Package Leaflet are updated in accordance. Version 2.2 of the RMP has also been submitted. In addition, the MAH took the opportunity to introduce minor editorial changes to the PI and update the list of local representatives in the Package Leaflet.

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es) I, II, IIIA and IIIB and to the Risk Management Plan are recommended.

The following obligation (Study GO41944) has been fulfilled, and therefore it is recommended that is be deleted from the Annex II:

Description	Due date
In order to provide further evidence of efficacy and safety of glofitamab in DLBCL, the MAH will provide the results of Study GO41944, a phase III open-label, multicentre, randomised study evaluating the efficacy and safety of glofitamab in combination with gemcitabine plus oxaliplatin versus rituximab in combination with gemcitabine and oxaliplatin in patients with relapsed or refractory DLBCL.	~~Q3 2024~~

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk management plan (RMP)

The Marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

In addition, an updated RMP should be submitted:

At the request of the European Medicines Agency;

Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Additional risk minimisation measures

Prior to the use of Columvi in each Member State, the MAH must agree about the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The educational programme is aimed at:

- Informing physicians to provide each patient with the patient card and educate the patient on its content, which includes a list of symptoms of CRS and ICANS to prompt patient actions including to seek immediate medical attention in case of their occurrence.
- Prompting patient actions, including seeking immediate medical attention, in case of the occurrence of symptoms of CRS and/or ICANS.
- Informing physicians on the risk of tumour flare and its manifestations.

The MAH shall ensure that in each Member State where Columvi is marketed, all healthcare professionals (HCPs) who are expected to prescribe, dispense, or use Columvi have access to/are provided with a healthcare professional brochure, which will contain:

- A description of tumour flare, and information on early recognition, appropriate diagnosis, and monitoring of tumour flare.
- A reminder to provide each patient with the patient card, which includes a list of symptoms of CRS and ICANS to prompt patients to seek immediate medical attention in case of their occurrence.

All patients who receive Columvi shall be provided with a patient card, which will contain the following key elements:

Contact details of the Columvi prescriber.

- List of symptoms of CRS and ICANS to prompt patient actions including to seek immediate medical attention in case of their occurrence.
- Instructions that the patient should carry the patient card at all times and to share it with HCPs involved in their care (i.e., urgent care HCPs, etc.).
- Information for the HCPs treating the patient that Columvi treatment is associated with the risk of CRS and ICANS

Specific Obligation to complete post-authorisation measures for the conditional marketing authorisation

This being a conditional marketing authorisation and pursuant to Article 14(7) of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

Description	Due date
The MAH shall provide the updated clinical study report with a minimum of 2 years follow-up from the end of treatment of the last patient enrolled in the primary safety population of Study NP30179 in scope of procedure EMEA/H/C/005751/0000.	Q4 2024

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Columvi is not similar to Minjuvi, Polivy, Yescarta, or Kymriah within the meaning of Article 3 of Commission Regulation (EC) No. 847/200. See appendix.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion ‘Product Name-H-C-Product Number-II-Var.No’

APPENDIX

DIVERGENT POSITION DATED 27 FEBRUARY 2025

DIVERGENT POSITION DATED 27 FEBRUARY 2025

Columvi EMEA/H/C/005751/II/0005

The undersigned members of the CHMP did not agree with the CHMP's positive opinion recommending the granting of the Extension of Indication of Columvi in combination with gemcitabine and oxaliplatin is indicated for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma not otherwise specified (DLBCL NOS) who are ineligible for autologous stem cell transplant (ASCT).

The reason for divergent opinion was the following:

The pivotal phase III GO41944 randomised controlled study showed a benefit of glofitamab in combination with gemcitabine and oxaliplatin (Glofit-GemOx) over rituximab-GemOx (R-GemOx) in terms of overall survival (OS) and progression-free survival (PFS) in the intent-to-treat (ITT) population. However, there were marked regional differences in efficacy, with the benefit primarily driven by the region "Rest of the World" (RoW; Asian and Australian patients) whereas patients in the regions of "Europe" and "North America" did not show a clear benefit. In fact, the hazard ratio for OS in the European region was 1.09 (95% CI: 0.54, 2.18), indicating no benefit. Although activity for the Glofit-GemOx arm did not differ between regions, the performance of the suboptimal R-GemOx comparator arm did show different activity between regions.

These results should also be seen in the light of methodological concerns. The comparator arm in the trial was suboptimal, with a prolonged cycle duration (21 days instead of usual 14 days), which may have resulted in undertreatment. Additionally, the 2:1 randomization and lack of stratification by region make it difficult to interpret subgroup results.

The single pivotal trial results are not considered compelling, and the relative superiority of Glofit-GemOx treatment over R-GemOx is not demonstrated for the European target population. Extrapolation of the results from the overall study population to the European population is not possible due to regional differences in the clinical treatment landscape and the study populations included, such as reasons for transplant-ineligibility, treatment exposure in the control arm, and next anti-lymphoma therapy.

The burden of toxicity was noticeably increased in the Glofit-GemOx arm compared to the R-GemOx arm, which is concerning given the lack of benefit in European patients.

The differences in efficacy between the European patients compared to those from the RoW may be due to real differences in lymphoma management and no obvious benefit was shown with a more toxic regimen in European patients.

In conclusion, based on the results of the GO41944 trial the divergent members do not consider that a positive benefit-risk balance in the targeted indication has been established in a European context with reasonable certainty.

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