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Oncologic Drugs Advisory Committee (ODAC) Meeting
May 20, 2025

BLA 761309/Supplement 001
Drug name: glofitamab-gxbm
Applicant: Genentech, Inc

Combined FDA and Applicant ODAC Briefing Document

DISCLAIMER STATEMENT

The attached package contains background information prepared by the Applicant and the Food and Drug Administration (FDA) for the panel members of the advisory committee. We have brought the drug glofitamab-gxbm to this Advisory Committee in order to gain the Committee's insights and opinions, and the background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

Contents

Table of Tables

Table of Figures

Glossary

ABC-DLBCL	Activated B cell-like Diffuse Large B cell Lymphoma
AE	adverse event
AEGT	adverse event group term
AFT	accelerated failure time
ASCT	autologous stem cell transplant
BMI	body mass index
CAR-T	chimeric antigen receptor T-cell
CCOD	clinical cutoff date
COVID-19	Coronavirus disease 2019
CR	complete response
CReWE	Consortium for Real World Evidence
CRS	Cytokine Release Syndrome
DLBCL	Diffuse Large B-Cell Lymphoma
DOCR	duration of complete response
DOR	duration of response
ECOG	Eastern Cooperative Oncology Group
EFS	event-free survival
FDA	Food and Drug Administration
GCB-DLBCL	Germinal Center B-cell like Diffuse Large B cell Lymphoma
GDPR	General Data Protection Regulations
GemOx	gemcitabine and oxaliplatin
GEP	Gene Expression Profiling
Glofit-GemOx	glofitamab in combination with gemcitabine plus oxaliplatin
HR	hazard ratio
ICANS	Immune effector cell-associated neurotoxicity syndrome
IPCW	Inverse probability of censoring weighting
IPI	International Prognostic Index
IRC	Independent Review Committee
ITT	intent-to-treat
MRCT	multiregional clinical trial
MVA	multivariable analysis
NALT	new anti-lymphoma therapy
NCCN	National Comprehensive Cancer Network
NE	not estimable
NHL	Non-Hodgkin's Lymphoma
NOS	not otherwise specified
NR	not reached
ODAC	Oncologic Drugs Advisory Committee
ORR	overall response rate
OS	overall survival
PFS	progression-free survival
PK	pharmacokinetics
PRO	patient-reported outcomes
R-GemOx	rituximab in combination with gemcitabine plus oxaliplatin
RPSFT	rank preserving structural failure time
RWD	real-world data
SAE	serious adverse event
SAP	Statistical Analysis Plan
sBLA	supplemental Biologics License Application
US	United States
USPI	United States Prescribing Information

Representatives of FDA:

Nicole Sunseri, MD, PhD, Clinical Reviewer, Division of Hematologic Malignances II
Margret Merino, MD, Clinical Team Leader, Division of Hematologic Malignancies II
Bindu Kanapuru, MD, Supervisory Associate Director for Therapeutic Review, Division of Hematologic Malignancies II
Nicholas Richardson, DO, MPH, Deputy Director, Division of Hematologic Malignancies II
Nicole Gormley, MD, Director, Division of Hematologic Malignancies II
Shu Wang, PhD, Statistical Reviewer, Division of Biometrics IX
Emily Nguyen, MS, Statistical Analyst, Division of Analytics and Informatics
Zhiheng Xu, PhD, Statistical Team Leader, Division of Biometrics IX
Jonathan Vallejo, PhD, Supervisory Statistician, Division of Biometrics IX
Yuan-Li Shen, PhD, Director, Division of Biometrics IX
Yue Xiang, PharmD, Clinical Pharmacology Reviewer, Division of Cancer Clinical Pharmacology I
Xiling Jiang, PhD, Master Clinical Pharmacology Reviewer, Division of Cancer Clinical Pharmacology I
Robyn Konicki, PharmD, Pharmacometrics Reviewer, Division of Pharmacometrics
Jiang Liu, PhD, Associate Director for Therapeutic Review, Division of Pharmacometrics
Olanrewaju Okusanya, PharmD, MS, Deputy Director, Division of Cancer Clinical Pharmacology I
Brian Booth, PhD, Director, Division of Cancer Clinical Pharmacology I
Vishal Bhatnagar, MD, Associate Director for Patient Outcomes, Oncology Center of Excellence
R. Angelo de Claro, MD, Deputy Director (Acting) Oncology Center of Excellence
Richard Pazdur, MD, Director, Oncology Center of Excellence

Representatives of Genentech, Inc.
Michelle Boyer, PhD, Global Head for Lymphoma/CLL Clinical Development
Michelle Byrtek, PhD, Senior Director Biostatistics, Data & Statistical Sciences
David Carlile, PhD, Principal Leader, Late Phase Clinical Pharmacology
Charles Fuchs, MD, MPH, Senior Vice President, Global Head of Oncology & Hematology Drug Development
Huang Huang, MSc, Principal Statistical Scientist, Data & Statistical Sciences
Murali Kesavan, MD, PhD, Senior Clinical Director, Clinical Science
Bea Lavery, MSc, Vice President, Regulatory Portfolio Strategy Lead
Linda Lundberg, PhD, Global Development Lead, Clinical Science
James Relf, MD, Principal Clinical Director, Clinical Safety
Venkat Sethuraman, PhD, Senior Vice President, Global Head of Data Science & Analytics
Satyajit Shetage, PhD, Program Director, Regulatory
Ashley Weber, PharmD, Program Director, Regulatory

1. Introduction

1.1. Purpose of the Meeting:

The FDA's Position

Glofitamab-gxbm, a bispecific CD20-directed CD3 T-cell engager, received accelerated approval in June 2023 as monotherapy for the treatment of adult patients with relapsed or refractory (R/R) diffuse large B-cell lymphoma, not otherwise specified (DLBCL, NOS) or large B-cell lymphoma (LBCL) arising from follicular lymphoma, after two or more lines of systemic therapy. STARGLO (Study GO41944) was designated as the confirmatory trial to verify the anticipated clinical benefit of glofitamab-gxbm and to support approval in combination with gemcitabine and oxaliplatin in an earlier line of therapy. FDA is convening this Oncologic Drugs Advisory Committee (ODAC) meeting to discuss concerns arising from STARGLO, a randomized phase 3 trial evaluating the substitution of rituximab with glofitamab-gxbm in the R-GemOx (rituximab, gemcitabine, and oxaliplatin) regimen in patients with DLBCL, NOS, who have R/R disease following at least one line of systemic therapy and who are considered ineligible for hematopoietic stem cell transplantation. The primary issues to be discussed include:

1. Inconsistent treatment effects between regional subgroups
2. The applicability of the results to a U.S. patient population

The purpose of this meeting is to obtain the Advisory Committee's input regarding the robustness of the STARGLO study results given the inconsistent treatment effect across multiple endpoints between regional subgroups and whether the STARGLO population and the overall trial results are applicable to the proposed U.S. patient population.

1.1.1. Context for the Meeting:

The accelerated approval of glofitamab-gxbm was based on overall response rate (ORR) and duration of response (DOR) in Study NP30179, an open-label, multicenter, single-arm trial that included 132 patients with R/R disease following at least 2 prior lines of systemic therapy. The ORR was 56% (95% confidence interval [CI]: 47-65%) with an estimated median DOR of 18.4 months (95% CI: 11.4, not estimable). Cytokine release syndrome and infections were significant safety issues identified. The risks of neurologic toxicity and tumor flare were also included in the WARNINGS AND PRECAUTIONS section of the U.S. Prescribing Information (USPI).

STARGLO was designated as the confirmatory trial to verify the anticipated clinical benefit of glofitamab-gxbm. STARGLO is a multiregional, randomized, open-label trial evaluating the substitution of rituximab with glofitamab-gxbm in the R-GemOx regimen as therapy for adult patients with R/R DLBCL, NOS, who had at least one prior line of systemic therapy and who are considered ineligible for stem cell transplantation. The study randomized 274 patients in a 2:1 ratio to receive glofitamab-gxbm + GemOx (Glofit-GemOx) or R-GemOx. The primary endpoint was overall survival (OS). The key secondary endpoints were progression-free survival (PFS), best complete response (CR) rate, and duration of complete response (DOCR), all of which were assessed by blinded independent review. STARGLO met its primary endpoint and demonstrated a

statistically significant improvement in OS, PFS, and CR rate with Glofit-GemOx as compared to R-GemOx. Duration of complete response did not meet statistical significance.

Upon review of the results, notable differences were observed in OS, PFS, ORR, and CR rate based on race and region, with the results being largely driven by outcomes in the Asian region.

The inconsistent results raise concerns regarding the robustness of the efficacy and safety data and whether the results are generalizable to a U.S. patient population. An overview of the major topics for discussion is provided next.

Major Topics:

1. Inconsistent Treatment Effects

The STARGLO trial was conducted globally, in North America, Europe, Australia, and Asia (including China, Korea, and Taiwan), with patients enrolled in the Asian regions comprising 48% of the population. The Applicant's efficacy analysis demonstrated a statistically significant improvement in survival in the intention-to-treat (ITT) patient population treated with Glofit-GemOx versus those treated with R-GemOx, with a hazard ratio (HR) of 0.62 (95% CI: 0.43, 0.88) (updated analysis, CCOD 2/16/2024). However, examination of pre-specified subgroups based on race and region revealed a potential unfavorable trend in OS with hazard ratios of 1.24 (95% CI: 0.66, 2.32) in patients identifying as White race, 1.09 (95% CI: 0.54, 2.18) in patients enrolled in Europe, and 2.62 (95% CI: 0.56, 12.34) in patients enrolled in North America compared to a large treatment effect observed in patients of Asian race, OS HR of 0.40 (95% CI: 0.25, 0.65), and those treated in Asian regions ,HR 0.39 (95% CI: 0.25, 0.63). Notably, these inconsistencies were also observed in progression free survival (PFS), overall response rate (ORR), and complete response rate (CR) for these same subgroups.

To better align the population, FDA regrouped the regions into two large subgroups: "Asian region" and a "Non-Asian region." This regrouping allowed for more comparable sample sizes (n=131 in Asian region and n=143 in Non-Asian region) and better alignment based on intrinsic and extrinsic characteristics. Comparison of these two subgroups revealed a marked difference in treatment effect of Glofit-GemOx vs R-GemOx. While the benefit of Glofit-GemOx vs R-GemOx was clearly demonstrated in patients enrolled in the Asian countries with an OS HR of 0.39 (95% CI: 0.25, 0.63), the treatment effect was substantially less and potentially worse for those patients enrolled in the Non-Asian countries with an OS HR of 1.06 (95%: 0.61, 1.84). This difference in treatment effect was also observed in the other assessments of efficacy (PFS, ORR, and CR rate), which isolate the treatment effect independent of subsequent anti-lymphoma treatment.

Although data from subgroups should be interpreted with caution, subgroup analysis does provide valuable insight into the robustness of the overall efficacy results, allowing for an assessment of consistency across different populations. FDA is concerned by the lack of internal consistency observed in the STARGLO trial and how the results of the Asian region appear to be driving the overall trial results.

2. Applicability of STARGLO Results to the U.S. Patient Population

STARGLO is a multiregional trial. However, there was low enrollment of patients from the U.S., with only 25 patients, comprising 9% of the total trial population. Compared to prior studies in lymphoma, there was a large representation of patients from Asian countries, accounting for 48% of the ITT population. Of note, there was a minimum requirement for 80 patients from China. The remaining 52% of the population were enrolled in Australia, Europe, and the U.S. The low enrollment of patients in the U.S. limits the Agency's ability to assess the applicability of the study results to a U.S. patient population. Furthermore, the FDA has identified multiple differences in patient-related, disease-related, and healthcare system-related factors between the Non-Asian and Asian regional subgroup populations. Taken together, these issues raise uncertainty as to whether the results in the Asian region subgroup or the overall results are generalizable and applicable to a U.S. patient population.

Conclusion:

The results from the intended confirmatory study, STARGLO, require careful consideration to assess the robustness of the efficacy and safety data in light of the inconsistent treatment effects across multiple endpoints observed between regions and the applicability of the overall results to a U.S. patient population with R/R DLBCL following at least one line of systemic therapy, who are considered ineligible for autologous stem cell transplantation.

The Applicant's Position:

Diffuse large B-cell lymphoma (DLBCL) is a fast growing, aggressive, heterogenous disease. With the introduction of rituximab, a monoclonal antibody targeting the CD20 protein on B cells, cancer immunotherapy transformed the DLBCL therapeutic landscape enabling many patients to be cured of their disease. Nonetheless, up to 40% of patients progress following first-line therapy. Autologous stem cell transplant (ASCT), and more recently, chimeric antigen receptor T-cell (CAR-T) therapy offer potential cure for some patients after failing initial treatment. However, approximately 75% of patients in the United States (US) with relapsed/refractory (R/R) DLBCL are not eligible, cannot tolerate, or do not have access to ASCT or CAR-T therapy. Due to the rapidly progressing nature of this disease, patients often need immediate treatment to prevent a fatal outcome. Consequently, there is a pressing need for second-line therapies that can achieve an early and durable complete remission, providing patients with the best chance of potential cure and a return to life without cancer.

Glofitamab is a novel CD20 x CD3 bispecific antibody designed to target and destroy B-cell lymphoma by engaging T cells (via CD3) to kill CD20-positive malignant B cells - offering an accessible, infusion-ready treatment for patients with R/R DLBCL who are in urgent need of effective therapy. The Food and Drug Administration (FDA) granted accelerated approval to glofitamab monotherapy for the treatment of patients with R/R DLBCL after two or more lines of therapy on 15 June 2023. Prior to the accelerated approval, the STARGLO study was designed in consultation with FDA to evaluate glofitamab plus gemcitabine and oxaliplatin (Glofit-GemOx) in the second or later line therapy for transplant-ineligible R/R DLBCL compared to a relevant

standard of care, rituximab plus GemOx (R-GemOx). STARGLO was later designated as the confirmatory study to verify the clinical benefit of glofitamab in R/R DLBCL and support traditional approval by FDA.

STARGLO is the first randomized Phase 3 study in patients with transplant-ineligible R/R DLBCL that met its primary endpoint in improving overall survival (OS). The results were statistically significant and clinically meaningful. Patients treated with Glofit-GemOx had a 41% reduction in the risk of death (hazard ratio [HR] 0.59, p=0.010706) and a 63% reduction in the risk of disease progression or death (HR 0.37, $p < 0.000001$) compared to R-GemOx, along with a notable increase in complete response (CR) rate (50.3% vs. 22.0%, $p < 0.0001$). The safety of the Glofit-GemOx regimen was well characterized and consistent with established safety profiles of the individual agents in the combination. Adverse events (AEs) such as cytokine release syndrome (CRS), a commonly observed AE in patients treated with T-cell-engaging therapies, along with neurologic AEs, hematologic AEs and infections, generally resolved promptly supported by effective measures to mitigate and manage AEs.

As a multiregional clinical trial, STARGLO was designed to produce globally applicable results. The study demonstrated compelling and consistent treatment benefit across multiple clinical endpoints in a population representative of US patients. Glofit-GemOx is recognized as a Category 1 preferred treatment in the National Comprehensive Cancer Network (NCCN 2025) guidelines, underscoring its clinical utility in US medical practice and the potential to become a new standard treatment option for transplant-ineligible patients with R/R DLBCL.

1.2. Proposed Indication(s)

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 not candidates for autologous stem cell transplant (ASCT).

1.3. Regulatory History

Glofitamab, as monotherapy, was approved by the FDA via the accelerated approval pathway on 15 June 2023 for the treatment of patients with R/R DLBCL who received at least two prior lines of therapy. The initial FDA approval was granted based on the highly durable responses observed with an overall response rate (ORR) of 56% (95% CI: 47, 65) with 43% achieving complete responses and a median duration of response (DOR) of 18.4 months (95% CI: 11.4, NE) in the multicenter, open-label, single-arm Phase 1/2 Study NP30179 (Table 14; COLUMVI USPI).

Prior to the accelerated approval, the Applicant discussed the STARGLO design and registration strategy for Glofit-GemOx for the treatment of transplant ineligible patients with R/R DLBCL at a Pre-Phase 3 meeting with FDA on 20 December 2019. STARGLO completed enrollment in March 2023 and was ongoing when it was designated in June 2023 as the confirmatory study to fulfill the post marketing requirement to verify clinical benefit of glofitamab in R/R DLBCL.

On 20 September 2024, the Applicant submitted a supplemental Biologics License Application (sBLA) to the FDA. This application seeks the approval of the use of Glofit-GemOx in the proposed

indication, based on the positive results of the STARGLO trial.

Key interactions held with the FDA for the development of glofitamab in the proposed indication are summarized in Appendix 1.

The FDA's Position on Regulatory History

FDA agrees with the overall summary by the Applicant regarding the key interactions with the FDA and the issuance of the postmarketing requirement (PMR) to verify the anticipated clinical benefit of glofitamab-gxbm in R/R DLBCL.

Regarding the overall study design of STARGLO, the FDA agrees that that the Agency did not object to the study as proposed by the Applicant and its use as a potential confirmatory trial to fulfill the PMR to confirm clinical benefit of glofitamab-gxbm. The Agency did inform the Applicant that the trial population should be an appropriate population for the R-GemOx regimen.

In July 2023, the Applicant informed the Agency of the topline results after the interim analysis (IA) at 73% OS events demonstrated a statistically significant improvement in OS with an OS HR of 0.59 (95% CI: 0.40, 0.89). However, the Applicant noted the inconsistent OS results between the regional subgroups. At that time, the Applicant posited that the differential OS follow-up between the Non-Asian region (median 8.7 months) vs. Asian region (median 14.6 months) may have contributed to the differences in the subgroup results. The Applicant chose to pursue additional follow-up of 11 months to allow for longer follow-up duration in the Non-Asian regional subgroup expecting that this would result in a more consistent treatment effect. The Applicant also posited that an increase in COVID-19 related events in the Non-Asian region may also have impacted results and proposed additional follow-up to further address safety. The Agency expressed concerns regarding the inconsistency between the regional subgroups and requested additional information by region, including enrollment, safety data, discordant follow-up, and relevant intrinsic (i.e., body weight and exposure) or extrinsic factors that may impact the treatment effect.

The Applicant provided an updated analysis in April 2024 with approximately one additional year of follow-up which demonstrated similar results to the original analysis with continued inconsistency between the Asian and Non-Asian regional subgroups.

At the pre sBLA meeting in June 2024, FDA expressed significant concerns regarding the inconsistent results between Asia and Non-Asia regional subgroups and the limited U.S. representation. FDA stated that the Applicant would have to address these issues and the applicability of the STARGLO results to a U.S. population if they submitted an application based on these data.

2. Efficacy

2.1. Description of Clinical Setting

The Applicant's Position:

2.1.1. DLBCL Overview

DLBCL is a serious and aggressive life-threatening disease with significant individual and societal burden. Globally, DLBCL is the most common subtype of non-Hodgkin's lymphoma (NHL), accounting for 30-40% of all presentations (Wang 2023). In the US, approximately 19,000 people are diagnosed with DLBCL each year and it is estimated that 5,000 people with DLBCL died in 2024 alone (SEER Cancer Statistics; US Census). A typical patient diagnosed with R/R DLBCL tends to be male, older than 60 years old and often presents with advanced stage disease. Regional comparisons reveal that baseline characteristics of patients with R/R DLBCL are similar globally, with comparable responses to salvage treatments (Jacobson et al. 2024; Flowers and Odejide 2022; Duarte and Kamdar 2023; Wang et al. 2021; Crump et al. 2017).

Several critical factors influence outcomes for patients with R/R DLBCL, including response to initial therapy and time to first relapse. Prognosis is particularly poor in patients with primary refractory disease, defined as those who do not respond to or relapse within six months of first treatment (Duarte and Kamdar, 2023). The number of prior therapies also impacts prognosis, as the response to new treatments tends to diminish with each relapse. Additionally, patients with a higher International Prognostic Index (IPI) score, which considers factors such as age, performance status, and Ann Arbor disease stage, face a greater risk of disease progression and have lower survival rates compared to those with lower IPI scores (Amy, 2020).

The FDA's Position

The Agency agrees with the Applicant's description of the condition and risk factors associated with poor prognosis. In addition to the factors mentioned by the Applicant, SEER (COO) determination is also important in the classification of DLBCL and has been associated with prognosis (Rosenwald, 2002). Cell of origin considerations are discussed further in FDA's sub-section Cell of Origin Differences.

2.1.2. Unmet Need in R/R DLBCL and Current Treatment Options

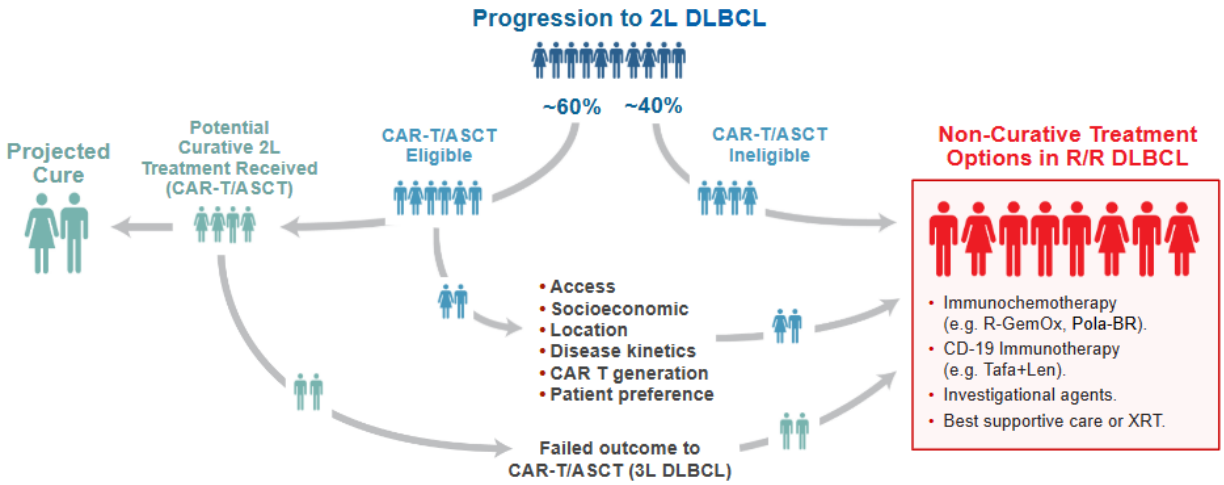
The confirmation of R/R disease is a devastating moment for patients, who face further treatment, a reduced chance of cure, and increased risks of treatment-related complications. For patients experiencing a relapse of this aggressive cancer, the disease can progress quickly, sometimes before the opportunity to start the next therapy. Thus, timely and decisive discussions between patients and physicians are essential to promptly initiate treatment following the identification of relapse.

The journey of patients with R/R DLBCL is similar across the globe (Figure 1). The principles guiding patient management, including diagnosis, first-line therapy recommendations, and treatment standards, are uniformly applied across regions, thanks to the broad alignment of regional clinical practice guidelines like the National Comprehensive Cancer Network [NCCN], the

European Society for Medical Oncology [ESMO], the Chinese Society of Clinical Oncology [CSCO], and the Australasian Lymphoma Alliance [ALA]. Although access to certain therapies may vary, the available standard-of-care regimens are consistent. The universal goal of therapy remains to achieve a durable complete remission and extend patient survival, with a chance of cure, while also minimizing toxicity and treatment burden.

Globally, the treatment options for patients with R/R disease are dependent on their response to treatment, the timing and kinetics of the disease relapse, patient-specific factors and treatment availability/accessibility. Social determinants of health also impart a critical impact on DLBCL outcomes and inform individual patient prognosis potentially due to the impact on access to care over time (Section 4.1; Battiwalla et al. 2025; Hwang et al. 2023; Mikhael et al. 2022).

Figure 1 Journey of Patients With R/R DLBCL



ASCT = autologous stem cell transplant; BR= bendamustine+rituximab; CAR-T = chimeric antigen receptor T-cell; DLBCL = diffuse large B-cell lymphoma; Len = lenalidomide; Pola = polatuzumab vedotin; R-GemOx = rituximab in combination with gemcitabine and oxaliplatin; R/R = relapsed / refractory; Tafa = tafasitamab; XRT = radiotherapy; 2L = second line; 3L = third line.
Percentages are estimated and projected based upon data from clinical trials and historical outcomes.
Source: Westin and Sehn 2022.

For the past 25 years, high-dose chemotherapy followed by ASCT has been the standard second-line treatment option for patients who are considered eligible candidates for transplant (Westin and Sehn 2022). Due to the rigorous nature of this treatment, many patients with R/R DLBCL are rendered ineligible for ASCT due to age and comorbidities or because they do not respond to chemotherapy (Figure 1; Philip et al. 1995 ; NCCN 2025; Tilly et al. 2015). Factors determining candidacy are similar across regions, but uptake varies as this is a highly personalized treatment decision. Approximately half of the patients eligible for ASCT will respond to salvage chemotherapy, but it is estimated that only 5% of all patients with second-line (2L) DLBCL will achieve a cure from ASCT (Westin and Sehn 2022).

CAR T-cell therapies have also shown curative potential (Kamdar et al. 2022; Locke et al. 2022; Yescarta USPI; Breyanzi USPI) and have started to displace ASCT as the standard second-line treatment for patients with R/R DLBCL. However, only 30-40% of eligible patients currently

benefit from these therapies (Battiwalla et al. 2025; Westin and Sehn 2022). Patient eligibility and access barriers significantly limit the broad applicability of this therapy option. Logistical barriers including failure to manufacture this bespoke product can restrict the use of CAR T-cell therapy and a high number of patients simply cannot wait for treatment because of their rapid disease progression or death (Battiwalla et al. 2025; Hwang et al. 2023). CAR-T cell therapies are generally only available at specialized facilities like academic medical centers, limiting access for patients in rural or community settings compared to those in metropolitan areas (Emole et al. 2022; Hwang et al. 2023; Auletta et al. 2023). Consequently, of the eligible patients who currently have the opportunity to benefit from CAR T-cell therapies, approximately 20% of all patients with 2L DLBCL will achieve cure from CAR-T therapy (Westin and Sehn 2022).
Despite these therapeutic options, real-world data indicates that only a small percentage of patients achieve a cure (Figure 1), with many still requiring additional interventions (Flowers and Odejide 2022; Westin and Sehn 2022). Current treatments for R/R DLBCL, apart from ASCT or CAR T-cell therapy, include R-GemOx, polatuzumab vedotin in combination with bendamustine + rituximab, and tafasitamab in combination with lenalidomide (NCCN 2025). These approaches aim to control the disease but do not utilize the immune system by engaging the T-cells with lymphoma cells and are not curative, highlighting a critical gap in their effectiveness (Sehn and Salles 2021).

There remains a significant unmet need for immediately available, effective treatment options to rapidly control this aggressive disease. Physicians treating patients with R/R DLBCL need broad access to multiple effective treatment options to offer to their patients to rapidly control this aggressive disease (Duarte and Kamdar 2023) and provide a chance of durable remission. The ideal therapy should be infusion ready, well tolerated and minimize burden on both patients and healthcare systems.

The FDA's Position
Patients with newly diagnosed DLBCL are potentially curable after standard chemoimmunotherapy. For patients that relapse, cure is still possible for those who are candidates for intensive therapy and autologous stem cell transplant. For those patients who are not candidates, there is no agreed upon standard of care; however, a variety of chemoimmunotherapy regimens, including R-GemOx, as well as targeted and immune-directed therapies are available (Appendix 10: Summary of Treatment Options for R/R DLBCL Not Eligible for Stem Cell Transplant).

Diffuse large B-cell lymphoma is a heterogenous disease with a rapidly evolving landscape in which molecular and histologic subtyping potentially impact response to and choice of therapies. The choice of therapy for patients with relapsed disease is based on patient and disease characteristics, available treatments, and treatment practices. These considerations may vary across global regions. In particular, the availability of and regional practices with regards to stem cell transplant and CAR-T therapy vary by region (Hwang, 2023) (Battiwalla, 2025) (Michael, 2022). Regional differences were observed in the STARGLO trial which will be discussed later.

2.1.3. Glofitamab

Glofitamab is a novel, T-cell engaging bispecific antibody with a 2:1 (CD20:CD3) format for bivalent binding to CD20 on B cells and monovalent binding to CD3 on T cells leading to the engagement and redirection of patients' existing T cells to eliminate malignant B cells. Glofitamab is administered as a fixed duration, infusion-ready therapy making it a widely available and accessible treatment option.

As a monoclonal antibody based on the human immunoglobulin G1 (IgG1) isotype, elimination is primarily driven by proteolytic degradation. Thus, the pharmacokinetics (PK) of glofitamab is not expected to be impacted by renal and hepatic function or routes of metabolism. In addition, there is no evidence to indicate the formation of neutralizing antibodies as a theoretical mode of tolerance or resistance to therapy.

The scientific rationale for combining glofitamab with GemOx is based on their complementary mechanisms of action, where GemOx's immune modulation (Larson et al. 2024), upregulation of CD20 (Hayashi et al. 2016), and enhancement of the tumor microenvironment (García-Domínguez et al. 2022) were hypothesized to improve the therapeutic effectiveness of glofitamab in the treatment of DLBCL. The combination is further supported by manageable toxicity profiles observed with glofitamab and GemOx.

2.2. Summary of Clinical Trials Supporting Efficacy

The Applicant's Position:

2.2.1. Study GO41944 (STARGLO) Design

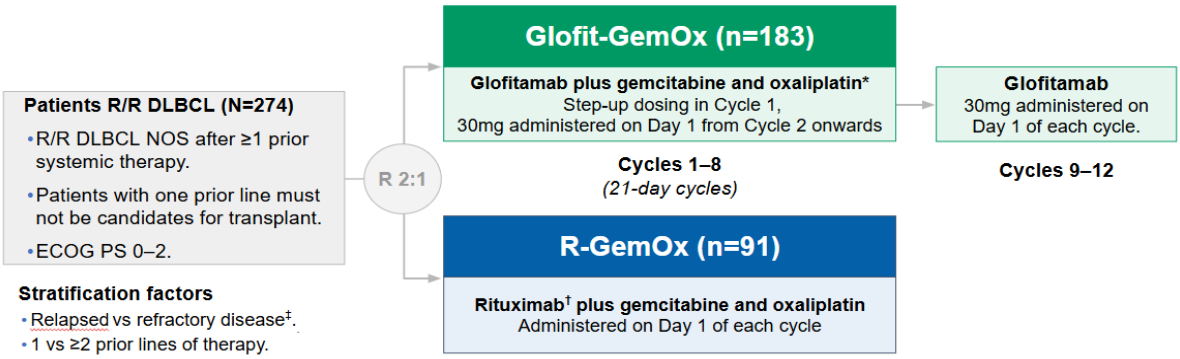
STARGLO is a randomized, open-label, Phase 3, multiregional clinical trial investigating the combination of glofitamab with GemOx compared with R-GemOx in transplant-ineligible patients with R/R DLBCL, not otherwise specified (NOS) (Figure 2).

R-GemOx is a globally accepted standard of care for patients who are not considered candidates for high-dose chemotherapy and/or transplant, as reflected by its continued endorsement in international practice guidelines (e.g. NCCN, ESMO, CSCO, ALA). Selecting R-GemOx as a comparator also enabled the demonstration of glofitamab's contribution in the Glofit-GemOx regimen, where glofitamab replaced rituximab in combination with GemOx. At the Pre-Phase 3 meeting with FDA, R-GemOx was noted to be a reasonable comparator, provided that the trial population would be adequately defined as patients for whom R-GemOx therapy was appropriate.

In accordance with treatment guidelines, R-GemOx has been consistently utilized globally as an effective immunochemotherapeutic option for many patients with transplant ineligible R/R DLBCL in recent years and during the STARGLO recruitment period (Yamshon et al. 2025, Flatiron Health RWD [2011-2024], IPSOS [2022-2024]).

STARGLO was designed based on an assumed median OS of 11 months in patients receiving R-GemOx (Mounier et al. 2013; Lopez et al. 2008; Corazzelli et al. 2009), and hypothesized an improvement of 7.3 months in median OS (HR = 0.6) in patients receiving Glofit-GemOx. A target sample size of approximately 270 patients with 138 events at the final analysis was established to provide 80% statistical power for the evaluation of OS in the intent-to-treat (ITT) population, using a 2:1 randomization to sufficiently characterize the safety profile of the Glofit-GemOx regimen. This randomization also provided more participants the chance to receive a novel agent that had shown potential efficacy and safety in later lines of therapy. Patients were randomized in a stratified manner based on two clinically relevant prognostic factors known to impact outcomes in R/R DLBCL: number of prior therapies (one vs. two or more) and whether the disease was relapsed or refractory.

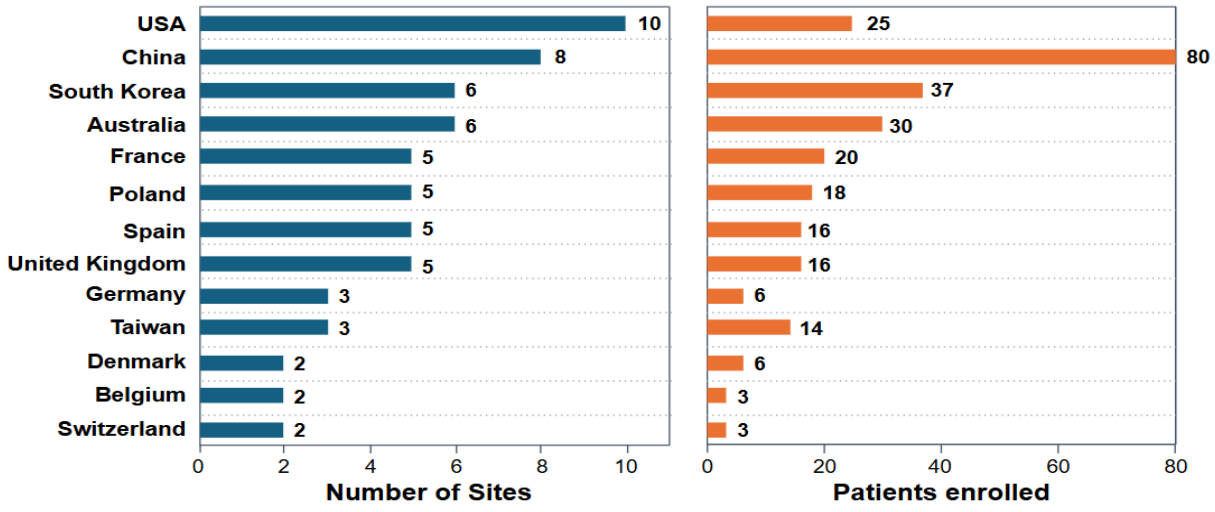
Figure 2 Study Design for STARGLO



*Gemcitabine 1000 mg/m2 and oxaliplatin 100 mg/m2. In C1, obinutuzumab pretreatment (Gpt) administered on D1, GemOx on D2, followed by glofit 2.5 mg on D8 and glofit 10 mg on D15; in C2–8, glofit 30 mg and GemOx are administered on D1. Gpt and glofitamab step up dosing with premedication are mitigation measures to reduce risk of cytokine release syndrome.
†Rituximab 375 mg/m2.
‡Relapsed disease: recurrence following a response that lasted ≥6 months after completion of the last line of therapy; refractory disease: disease that did not respond to, or that progressed <6 months after completing, the last line of therapy.
C = cycle; D = day; DLBCL = diffuse large B-cell lymphoma; ECOG PS = Eastern Cooperative Oncology Group performance status; NOS = not otherwise specified; R 2:1 = patients randomized in a 2:1 ratio.

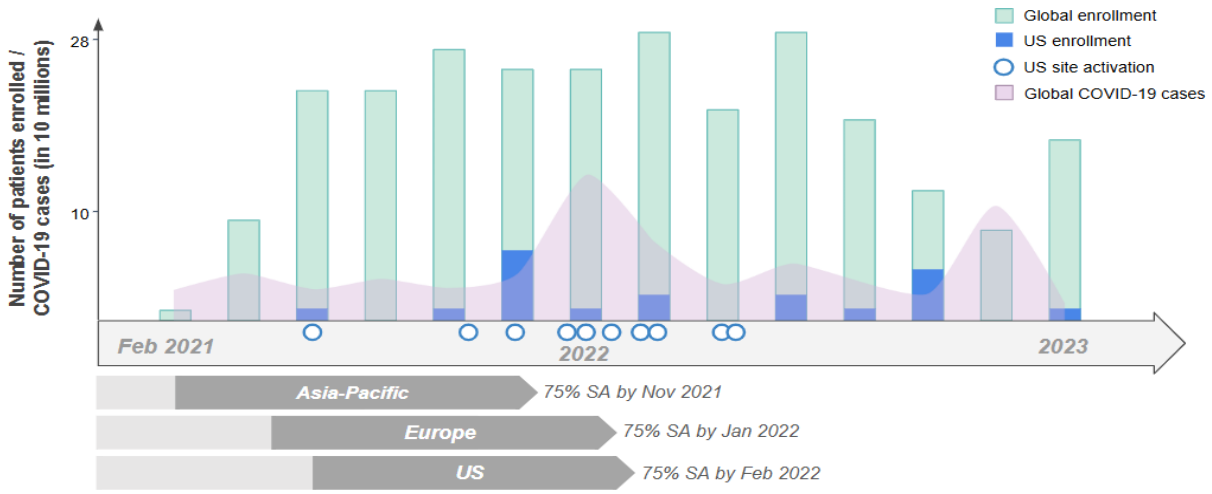
Between February 2021 and March 2023, 274 patients were enrolled globally across 62 sites in 13 countries (Figure 3). The study was initiated across all countries simultaneously however varied in country site activation timing (Figure 4). US was the country with the highest number of sites (10 enrolling sites) while the highest number of sites by region was in Europe (49% of sites, enrolling 32% of patients), followed by Asia-Pacific (China, Taiwan, South Korea, and Australia) (35% of sites, enrolling 59% of patients), and North America (16% of sites, enrolling 9% of patients).

Figure 3 Enrollment in STARGLO by Country (Sites and Patients)



Across clinical trial sites, the COVID-19 pandemic introduced resource constraints, regulatory and logistical challenges, prioritization of COVID-19 care and research, and the need to implement enhanced safety measures. Additionally, patients were unable to attend clinic visits in person due to COVID restrictions and patient fears. These challenges, common across oncology clinical trials, delayed site activations for the STARGLO trial, primarily in Europe and North America, resulting in a delayed onset for US enrollment (Figure 4) and reduction in on-study follow-up time at the primary analysis. Independent analyses across US cancer centers demonstrated a marked decrease in interventional treatment trial accruals in both 2020 and 2021 (George et al. 2023), with the lowest trial screening rates corresponding to COVID-19 mortality or case peaks (deaths in mid-April 2020, cases in December 2020, cases in August 2021 associated with the delta variant, and cases associated with the omicron variant at the end of 2021/beginning of 2022; McDonald et al. 2023). While the pandemic affected the intended regional makeup of patients enrolled in the trial, particularly in the US, a population relevant to the US was obtained (Section 2.3.1.2; Section 4.1) and nonetheless, does not compromise the validity of the overall findings.

Figure 4 STARGLO Conducted During the COVID-19 Pandemic



SA = site activation; 75% SA = timepoint when majority (75%) of sites are activated.

STARGLO utilized an independent Data Monitoring Committee (iDMC), which was established to monitor patient safety and to assess study outcomes at pre-specified analysis timepoints, including the pre-specified interim analysis for OS (Section 2.2.3).

Major protocol amendments for STARGLO are summarized in Appendix 2.

2.2.2. Study Endpoints

The primary endpoint of the study was OS, defined as time from randomization to death from any cause. Key secondary endpoints included:

- Progression-free survival (PFS): Time from randomization to the first occurrence of disease progression or relapse, or death from any cause, assessed by blinded independent review.

- Complete response (CR) rate: The percentage of patients with CR whose best overall response is a CR on PET-CT, assessed by blinded independent review.
- Duration of complete response (DOCR): time from the first occurrence of a documented CR to disease progression, or death from any cause, whichever occurs first, assessed by blinded independent review.

The response-based endpoints (PFS, CR, DOCR) were evaluated using the 2014 Lugano response criteria, and assessed by the blinded Independent Review Committee (IRC) to guard against potential bias.

Additional secondary efficacy endpoints (no formal statistical testing) included PFS by investigator (INV), CR rate by INV, best ORR by IRC and INV, DOCR by INV, DOR by IRC and INV. Event-free survival (EFS) was included as a post-hoc exploratory analysis.

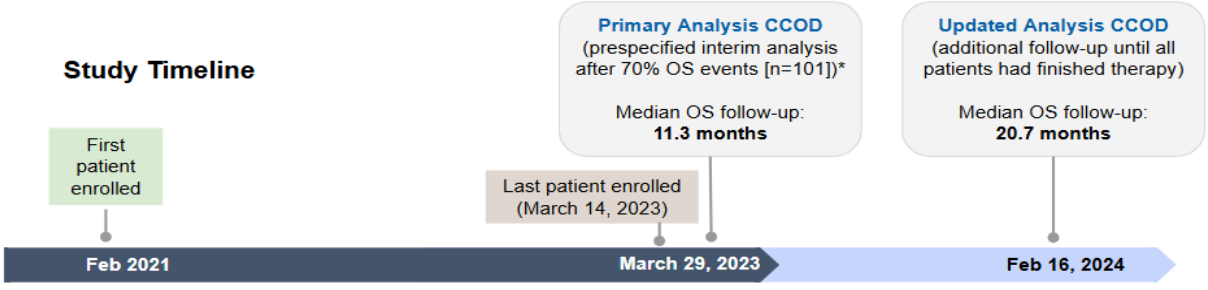
Safety data from adverse event (AE) reports, and information on new anti-lymphoma therapy (NALT) as well as patient-reported outcomes (PROs) were collected.

2.2.3. Statistical Methods

An efficacy interim analysis was pre-planned to be conducted after enrollment completion and at approximately 70% (97 events) of the total number of OS events required for the final analysis, with statistical significance if $p \leq 0.0148$, estimated using the O'Brien-Fleming method, which set a high bar for statistical significance. At the interim analysis with a clinical cutoff date (CCOD) of 29 March 2023, 101 OS events were observed, and the threshold for statistical significance was adjusted to $p \leq 0.0174$ per the statistical analysis plan (SAP) to account for the actual number of events.

The primary endpoint was met at the interim analysis and based on this data the iDMC recommended that the study be fully analyzed. Following the iDMC's recommendations, the interim analysis became the primary analysis, and data were made available by the Applicant for the formal reporting of results (Figure 5). At the primary analysis, 33 patients in the Glofit-GemOx arm and 7 patients in the R-GemOx arm were still on active study treatment.

Figure 5 STARGLO Timeline



*Study met interim threshold for significance. CCOD = clinical cut-off date; OS = overall survival.

An additional, subsequent updated analysis was conducted to allow all patients to complete study therapy and to allow longer follow-up for patients in the US and Europe due to the impact of COVID-19 pandemic (Section 2.2.1).

To ensure unbiased data collection and the integrity of the updated analysis, investigators and patients were not informed of the outcome of the primary analysis, and no analyses were conducted on the accumulating data until the updated analysis (CCOD: 16 February 2024) when all patients had completed study therapy, approximately 11 months after the primary analysis. At the updated analysis, 132 OS events (48% of the 274 patients enrolled in the study) were observed across both treatment arms.

In this briefing document, results from both the primary and updated efficacy analyses and the cumulative safety data collected up to the updated analysis (CCOD of 16 February 2024) are presented.

The major SAP amendments are summarized in Appendix 3.

The FDA's Position

There are several aspects of the STARGLO trial design and conduct that impact the interpretation of the study results.

- *Minimum Number of Patients Required for China Subpopulation:*
  The trial was designed as a multiregional trial, enrolling in North America, Europe, Australia, and Asia. The FDA notes that the total trial population was not balanced by region and had an large representation of patients enrolled in Asian countries, which accounted for almost half of the population. It is important to note that the protocol stipulated a minimum requirement for a China subpopulation. Specifically, the protocol states that patients were to be enrolled "at sites in mainland China, Hong Kong, and Taiwan that are recognized by the China's National Medical Products Administration (NMPA) to ensure a total of up to approximately 80 patients in a China subpopulation." The rationale for this requirement was "to characterize the efficacy and safety profile of glofitamab in addition to GemOx to potentially support a marketing application in China" (protocol v1)." If this number of patients was not obtained during the global enrollment phase of the protocol, additional patients could be enrolled in an extended China enrollment phase. Extended enrollment was not needed, as ultimately 80 patients were enrolled from China. No such requirements were included in the protocol for other regions to ensure equal representation.

- *Reasons for the Updated Analysis (CCOD of 16 February 2024):*
  The FDA notes that a subsequent updated analysis was not only conducted to offset the potential impact of the COVID-19 pandemic. The Applicant initially presented topline data to the Agency based on the interim analysis conducted at 73% of the estimated OS events. At that time, the inconsistent efficacy results based on race and region were observed and the Agency conveyed their concern about the robustness of the study results. The Applicant posited that the shorter follow-up in Non-Asian countries (median 8.7 months) compared to the longer follow-up in the Asian countries (median 14.6 months) was the likely reason for the inconsistent results and posited that further follow-up would reveal a more consistent treatment effect. The additional year of follow-up was proposed by the Applicant to help address the inconsistencies observed.

- *Schedule of R-GemOx in Aggressive Lymphoma: Every Three Week Dosing (Q3W) versus Every Two Week Dosing (Q2W)*
  The comparator arm is R-GemOx administered every three weeks (Q3W). While R-GemOx can be administered once every three weeks, most studies and many institutions administer the regimen more frequently, once every two weeks, due to the aggressive nature of R/R DBCL. The use of R-GemOx dosing every two weeks is recommended in clinical practice guidelines based on the literature (Gnaoui, 2007) (Mounier, 2013) (Crump, 2016) (Corazzelli, 2015)

- *Utilization of R-GemOx in a U.S. Patient Population*
  R-GemOx is not a regimen commonly used in the U.S., with reported use of 2-8% per recent RWD and utilization reports (Yamshon, 2025) (Applicant response, BLA 761309-S-001, SD 202 received 10-25-2025). When used, R-GemOx is generally reserved for patients who are not suitable for intensive therapy due to age or comorbidities (Cazelles, 2021) (Gnaoui, 2007). The observed utilization of R-Gem-Ox in the U.S. calls into question the suitability of R-Gem-Ox as a control arm for the U.S. patient population.

- *Delayed Enrollment in the U.S.*
  As noted by the Applicant, the Asian regions enrolled patients early in the study, whereas Europe and North America accrued through the mid- to late- phases of the study. The Applicant attributes the late enrollment of patients from Europe and the U.S. in part to the effects of the COVID-19 pandemic. However, the Applicant also notes that in the U.S. a higher number of sites declined participation in STARGLO. Over 50 sites were approached in the U.S. with 11 sites activated and 10 sites that enrolled patients (Applicant Submission, BLA 761309-S001, Module 2, Clinical Overview, SD 194 received 9-20-2024). Although not mentioned by the Applicant, the high rate of sites declining participation in STARGLO may reflect a lack of investigator interest.

- *2:1 Randomization:*
  In general, randomization is most efficient when utilizing a 1:1 randomization ratio. While 2:1 randomization is used in oncology, in trials with small sample sizes, this imbalanced ratio reduces the amount of information on the control arm, limiting comparative analyses. Additionally, a 2:1 randomization may introduce bias as the experimental arm may be considered a better treatment, which in an open-label trial can impact adherence and conduct between treatment arms.

- *Obinutuzumab Pre-treatment*
  To mitigate the risk of CRS, obinutuzumab pre-treatment is administered prior to the initiation of glofitamab. Obinutuzumab is a 2nd-generation CD20 monoclonal antibody that has been shown to be superior to rituximab in several non-Hodgkin lymphoma settings (Townsend, 2023) (Goede, 2015). With the use of obinutuzumab in the Glofit-GemOx arm, there may be a differential impact given the differences between obinutuzumab and rituximab.

2.2.4. Patient Selection

The STARGLO study aimed to enroll patients with a high unmet need and the eligibility criteria ensured the selection of patients with R/R DLBCL who were not candidates for high intensity chemotherapy followed by transplant.

The key inclusion and exclusion criteria are presented in Table 1. The complete eligibility criteria are provided in the protocol (Abramson et al. 2024: appendix 2 pp 232–38).

Table 1 Key Inclusion and Exclusion Criteria in STARGLO

Inclusion criteria	Exclusion criteria

• Patients aged 18 years or older
• Patients with an ECOG performance status of 0, 1 or 2
• Patients with histologically confirmed DLBCL, NOS
• Patients who had received ≥ 1 previous systemic therapies and
  - who had relapsed disease (recurrence following a response that lasted ≥6 months after completing the last line of therapy) or
  - refractory disease (disease that did not respond to, or that progressed within 6 months after completing, the last line of therapy)
• Patients enrolling after only one previous line of therapy had to be considered ASCT-ineligible based on age (≥70 years), end organ dysfunction, ECOG performance status of 2 or higher, patient refusal for ASCT, or other comorbidities that precluded the use of transplant based on local practice standards or in the investigator's opinion.
	• Patients who had failed only one prior line of therapy and were a candidate for stem cell transplantation
	• Patients with DLBCL transformed from indolent disease
	• Patients with double or triple hit lymphomas (HGBL with MYC and BCL2 and/or BCL6 rearrangements), or high-grade B-cell lymphoma, NOS
	• Prior treatment with glofitamab or other bispecific antibodies targeting both CD20 and CD3
	• Prior treatment with R-GemOx or GemOx

ASCT = autologous stem cell transplant; DLBCL= diffuse large B-cell lymphoma; ECOG = Eastern Cooperative Oncology Group; GemOx = gemcitabine and oxaliplatin; HGBL = high-grade B-cell lymphoma; NOS = not otherwise specified; R-GemOx = rituximab in combination with gemcitabine and oxaliplatin.

The FDA's Position

The FDA agrees with the Applicant's description of the eligibility criteria. The FDA does not agree with the Applicant's statement that the eligibility criteria ensured the selection of patients with R/R DLBCL who were not candidates for high-dose chemotherapy followed by transplant, see section Reasons for Transplant Ineligibility.

2.3. Efficacy Summary

The Applicant's Position:

2.3.1. Study Patients

2.3.1.1. Patient Disposition

Patient enrollment was complete (last patient enrolled 14 March 2023) at the time of primary analysis (CCOD: 29 March 2023). The ITT population comprised of a total of 274 patients randomized 2:1 (183 patients to the Glofit-GemOx arm and 91 patients to the R-GemOx arm).

At the time of the updated analysis, all patients had completed or discontinued study therapy and a total of 160 patients (58.4%) had discontinued from the study: 97 of 183 patients (53.0%) in the Glofit-GemOx arm and 63 patients (69.2%) in the R-GemOx arm; whereas 86 patients (47.0%) on the Glofit-GemOx arm and 28 patients (30.8%) on the R-GemOx arm were still being followed in the study. The primary reason for study discontinuation in both treatment arms was death (Glofit-GemOx: 80 patients [43.7%], R-GemOx: 52 patients [57.1%]).

2.3.1.2. Demographic Characteristics

The STARGLO ITT population was generally balanced between the treatment arms across the measured baseline characteristics (Table 11).
The median age was 68 years, more patients were male (58%) and 63% had received one prior line of therapy. Most patients had advanced stage disease (Ann Arbor III-IV 70%) and 49% had high or high intermediate risk IPI. The majority of patients were refractory to their most recent line of therapy (61%) with 56% of patients presenting with primary refractory disease (Table 11).

The overall ITT population in STARGLO closely mirrors the clinical profile of DLBCL patients in the US (Sineshaw et al. 2024; Koff et al. 2023; Budde et al. 2024 [Flatiron]; Yamshon et al. 2024 [LEO Consortium]).

While low enrollment of Black or African American and Hispanic or Latino patients was observed in STARGLO, the overall proportion of these patients is broadly consistent with expected incidence in the US for their respective subpopulations (~8%) (Budde et al. 2024 [Flatiron]; Yamshon et al. 2024 [LEO Consortium]). Additional Phase 1b clinical trials are in progress to further characterize safety, efficacy, PK, and PD of Glofit-GemOx in patients with R/R DLBCL in the US population (NCT06624085 and NCT06806033).

The FDA's Position on STARGLO's Patient Population

The FDA has concerns with the composition of the ITT population in terms of regional representation as well as generalizability to a U.S. patient population.

The STARGLO study is a multiregional trial as it enrolled patients from multiple countries and regions. However, distribution of the population across those regions demonstrates an large representation of patients enrolled in Asian countries (China, Taiwan, and Korea). While the combined grouping of patients from North America, Europe, and Australia resulted in 52% of the ITT population, 48% of the total population was enrolled solely from Asian countries (FDA Table 1). As noted, the protocol specified that at least 80 patients from China be enrolled "in order to characterize the efficacy and safety profile of glofitamab in addition to GemOx to potentially support a marketing application in China" (protocol v1). The protocol did not include such requirements for the Non-Asian countries to ensure a more evenly distributed population. Region was not used as a stratification factor nor pre-specified as a separate powered analysis. However, regional subgroups, which the Applicant designated as "North America," "Europe," and "Rest of World," were included in the pre-specified subgroup analyses (Figure 8 Subgroup Analysis of OS by Key Baseline Risk Factors (STARGLO Updated Analysis, ITT Population).

FDA Table 1: Number of Patients by Regions

Region		Total ITT N=274 n (%)	Glofit-GemOx N=183 n (%)	R-GemOx N=91 n (%)
US		25 (9)	15 (8)	10 (11)
Europe[a]		88 (32)	62 (34)	26 (29)
Australia		30 (11)	22 (12)	8 (9)
Asia	**Total**	131 (48)	84 (46)	47 (52)
	China	80 (29)	55 (30)	25 (27)
	Korea	37 (14)	21 (11)	16 (18)
	Taiwan	14 (5)	8 (4)	6 (7)

[a] France, Poland, Great Brittain, Spain, Denmark, Germany, Belgium, Switzerland
ITT: Intent-to-treat population; Glo-GemOx: glofitamab+gemcitabine+oxaliplatin; R-GemOx: Rituximab +GemOx
Source: FDA analysis, Data cutoff: 16 February 2024

FDA does not agree that the STARGLO population mirrors the clinical profile of the intended population of U.S. patients with R/R DLBCL. There was a limited number of patients enrolled in the U.S. and an large representation of the patients from Asian regions. While the majority of DLBCL cases do occur in patients identifying as White, the overall U.S. population with DLBCL is not homogenous. The US SEER data from 2016-2020 estimates the number of cases of DLBCL in 2024 to occur in 87% of patients identifying as White, 7.5% as Black, 4.8% as Asian or Pacific Islander, and 0.5% as American Indian/Alaska Native (SEER Cancer Statistics; US Census). In terms

of ethnicity, 11% of cases were estimated to occur in Hispanic patients, while the majority of cases (89%) were estimated to occur in patients who are not Hispanic (SEER Cancer Statistics; US Census).

The demographic profile of the overall patient population exhibits similarities to the U.S. patient population in terms of median age and gender distribution. Specifically, patients in the U.S. have a reported median age of 67 years and a slight male predominance (56%) (SEER Cancer Statistics; US Census). However, other patient characteristics appear to differ between these populations. The intended patient population are those who are considered ineligible for transplant. These patients are typically older or unfit due performance status, comorbidity, or insufficient response to prior treatment. As FDA Table 2 shows, 35% of the population was considered ineligible due to patient refusal. As discussed further in Reasons for Transplant Ineligibility, the reason for the refusal is not clear and could reflect a patient that would otherwise be a candidate for intensive chemotherapy and autologous stem cell transplantation. This difference, as well as others, appear magnified in the regional subgroup analyses. There is also uncertainty regarding potential differences in disease biology, specifically cell of origin between the regions that can play role in patient disease course and response to treatment. These considerations are further discussed in Cell of Origin Differences.

FDA Table 2: Baseline Demographics

Baseline Characteristic		ITT population N=274
Age	Median, y (range)	68 (20, 88)
	<65y, n (%)	102 (37)
	≥65 to <75y, n (%)	107 (39)
	≥75y	65 (24)
Sex, n (%)	Male	158 (58)
	Female	116 (42)
Race, n (%)	**Asian**	**137 (50)**
	Black	3 (1)
	White	**115 (42)**
	Unknown	19 (7)
Ethnicity, n (%)	Hispanic	16 (6)
	Not hispanic	242 (88)
	Not reported	15 (5)
	Unknown	1 (0)
Reason for Transplant Ineligibility n, (%)	Age	116 (42)
	Performance Status	2 (1)
	Comorbidity[a]	11 (4)
	Insufficient response to Salvage	27 (10)
	Failed Prior Transplant	12 (4)
	Lack of Access to Transplant Center	2 (1)
	Patient Refused Transplant	**95 (35)**
	Other[b]	6 (2)
	None listed	3 (1)
Cell of origin by Nanostring[c](GEP), n (%)	GEP test available	161 (59)
	ABC-DLBCL[d]	86 (53)
	GCB-DLBCL[d]	59 (37)
	Unclassified[d]	16 (10)

GEP: Gene Expression profiling; ABC: Activated B-cell like; GCB: Germinal Center B-cell like

[a] Comorbidities listed: Population (1 patient each): cardiac dysfunction/non-insulin dependent diabetes mellitus(1), cardiac impairment, cardiomyopathy, induction complications, complications after gastrointestinal perforation , depression, diabetes, hypertension/diabetes mellitus/arrhythmias/seizures, hypertension/diabetes mellitus/embolic strokes, severe COVID/pneumonitis, underlying lung disease.

[b] Other (1 patient each): Expected insufficient response, N/A:≥2 prior lines of therapy, risk of many adverse events, pre-transplant: insufficient response, non-chemosensitive disease, too chemorefractory.

[c] Not all patients tested

[d] Proportion was calculated with number of GEP testing available by central testing as the denominator

Source: FDA analysis, Data cutoff: 16 February 2024

2.3.2. Overview of Efficacy Results

2.3.2.1. Primary Efficacy Endpoint: Overall Survival

At the primary analysis, STARGLO met its primary endpoint, demonstrating a statistically significant and clinically meaningful 41% reduction in the risk of death among patients receiving Glofit-GemOx compared to those receiving R-GemOx (OS HR: 0.59 [95% CI: 0.40, 0.89]; log-rank p-value of 0.010706) in transplant-ineligible patients with R/R DLBCL (Table 2). Median OS in the R-GemOx arm was 9.0 months (95% CI: 7.3, 14.4) and was not reached in the Glofit-GemOx arm (95% CI: 13.8, NE) (Table 2).

The OS results were robust as confirmed by additional analyses (Appendix 6):

- Pre-specified sensitivity analyses (including stratification discrepancies, COVID-19-associated deaths and early discontinuations)
- Post-hoc multivariable analysis (MVA) adjusting for prognostic and clinically relevant baseline factors identified among 26 pre-specified factors, including the stratification factors (number of prior systemic therapies and refractory status to last systemic therapy), sex, IPI score, bulky disease of ≥ 10 cm, body mass index (BMI), and enrollment region.

The OS benefit was maintained in the updated analyses with an additional 11 months of follow-up where patients treated with Glofit-GemOx achieved a median OS of 25.5 months (95% CI 18.3, NE), nearly double that of the R-GemOx treatment arm, which had a median OS of 12.9 months (95% CI: 7.9, 18.5). The HR was 0.62 (95% CI: 0.43, 0.88) (Table 2; Figure 6).

Table 2 Primary Efficacy Endpoint Results from Primary and Updated Analyses (STARGLO, ITT population)

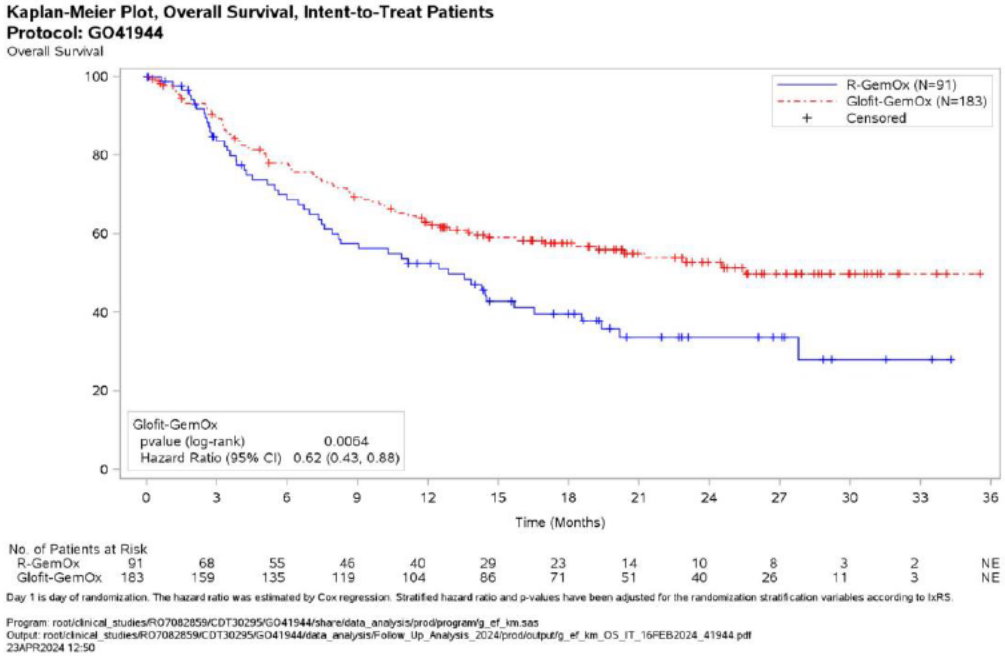
	Primary Analysis CCOD: 29 March 2023		Update Analysis CCOD: 16 February 2024	
	R-GemOx (N=91)	Glofit-GemOx (N=183)	R-GemOx (N=91)	Glofit-GemOx (N=183)
Overall Survival				
Patients with event, n (%)	40 (44.0%)	61 (33.3%)	52 (57.1%)	80 (43.7%)
Median, months (95% CI)	9.0 (7.3, 14.4)	NR[c] (13.8, NE[d])	12.9 (7.9, 18.5)	25.5 (18.3, NE[d])
Median OS follow-up, months (range)	9.6 (0-22)	12.0 (0[a]-24)	19.7 (0 – 34)	22.5 (0[a] - 36)
Stratified HR (95% CI)	0.59 (0.40, 0.89)		0.62 (0.43, 0.88)	
p-value (log-rank)	0.010706		0.006366[b]	
Overall survival rate (95% CI)				
12 month duration	44.6% (31.6, 57.6)	62.5% (54.4, 70.7)	52.5% (41.6, 63.3)	62.9% (55.7, 70.1)
Diff. in event-free rate	17.9%		10.4%	
18 month duration	35.0% (21.1, 49.0)	54.6% (44.7, 64.6)	39.7% (28.7, 50.7)	57.6% (50.2, 65.1)
Diff. in event-free rate	19.6%		18.0%	
24 month duration	NE[d]	NE[d]	33.5% (22.2, 44.9)	52.8% (44.8, 60.7)
Diff. in event-free rate	NE[d]		19.2%	

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

[a] Censored observation. [b] As the primary analysis of OS crossed the pre-specified stopping boundary, all p-values for the updated analysis are considered descriptive. [c] Not reached. [d] Not estimable.

Sources: t_ef_tte_OS_IT_29MAR2023_41944 [ADSL, ADTTE]; t_ef_tte_OS_IT_16FEB2024_41944 [ADSL, ADTTE].

Figure 6 Kaplan–Meier Estimates of OS (STARGLO Updated Analysis, ITT Population)*



Source: g_ef_km_OS_IT_16FEB2024_41944 [ADSL, ADTTE].

*Replaced by FDA for improved resolution using Figure 3 from Applicant's updated CSR page 105

In Phase 2 studies evaluating R-GemOx in R/R DLBCL, the median OS ranged from 9.1 to 11 months (Lopez et al. 2008; Mounier et al. 2013). Recent real-world data, in which more than 90% of patients had prior exposure to rituximab therapy, indicates a median OS of 8 to 13.5 months (Dhanapal et al. 2017; Cazelles et al. 2021; Budde et al. 2024; Yamshon et al. 2024) (Appendix 7). The median OS of 12.9 months observed in the R-GemOx arm in STARGLO is within the expected range for this regimen reinforcing the validity of the comparative OS findings.

2.3.2.2. Secondary Efficacy Endpoints

The OS benefit demonstrated in STARGLO was supported by consistent, clinically meaningful and statistically significant improvements in secondary endpoints (IRC-assessed PFS and CR rates) in the Glofit-GemOx arm compared to the R-GemOx arm.

At the primary analysis, the PFS analysis showed a 63% reduction in the risk of disease progression or death in patients 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), and the CR rate was 28.3% higher (p < 0.0001) 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) (Table 3). With longer follow-up, the PFS results persisted and a further improvement in CR rate was observed as all patients had completed therapy (Table 3; Figure 7).

Similar to OS, PFS results were robust, with consistent treatment effects across sensitivity analyses assessing the impact of COVID-19, across stratified subgroups as well as a post-hoc MVA adjusting for prognostic and clinically relevant baseline factors (Appendix 6).

IRC-assessed DOCR showed a 41% reduction in the risk of disease progression or death that was not statistically significant in patients who achieved CR (stratified HR = 0.59, 95% CI: 0.19, 1.83; log-rank p-value = 0.356) (Table 3).

Table 3 Key Secondary Efficacy Endpoint Results from Primary and Updated Analyses (STARGLO, ITT population)

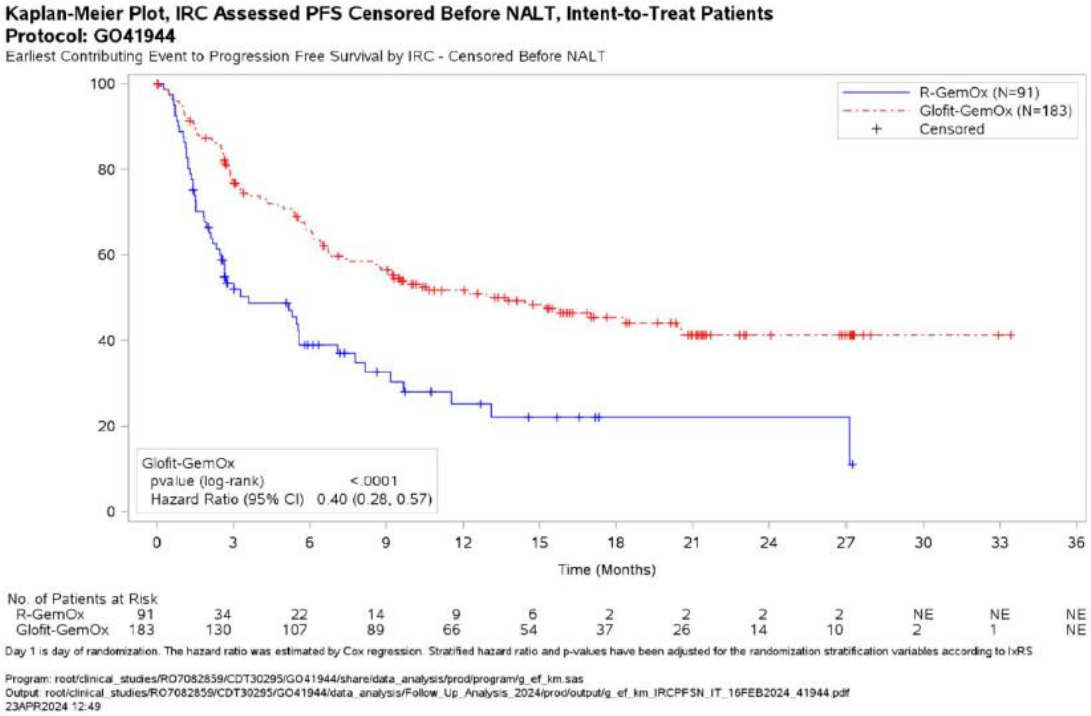
	Primary Analysis CCOD: 29 March 2023		Update Analysis CCOD: 16 February 2024	
	R-GemOx (N=91)	Glofit-GemOx (N=183)	R-GemOx (N=91)	Glofit-GemOx (N=183)
Key secondary efficacy endpoints (hierarchically tested) [b]				
IRC-assessed PFS				
Patients with event, n (%)	44 (48.4%)	68 (37.2%)	54 (59.3%)	90 (49.2%)
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)
Median PFS follow-up, months (range)	6.1 (0-17)	9.0 (0-21)	8.6 (0 – 27)	16.3 (0 – 33)
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]	
PFS rate (95% CI)				
6 month duration	35.2% (22.6, 47.7)	63.6% (55.6, 71.6)	39.0% (27.6, 50.4)	65.9% (58.7, 73.0)
Diff. in event-free rate	28.5%		26.9%	
9 month duration	30.1% (17.5, 42.7)	55.9% (47.2, 64.5)	32.7% (21.1, 44.3)	56.5% (49.0, 64.1)
Diff. in event-free rate	25.8%		23.8%	
12 month duration	19.8% (4.9, 34.6)	51.0% (41.9, 60.1)	25.2% (13.6, 36.9)	51.7% (44.0, 59.4)
Diff. in event-free rate	31.2%		26.5%	
IRC-assessed CR rate[c]				
Complete responders, n (%)	20 (22.0%)	92 (50.3%)	23 (25.3%)	107 (58.5%)
95% CI	(14.0, 31.9)	(42.8, 57.7)	(16.8, 35.5)	(51.0, 65.7)
Difference in CRR, (95% CI)	28.3% (16.3, 40.3)		33.2% (20.9, 45.5)	
p-value (CMH)	< 0.0001		< 0.0001[a]	
IRC-assessed DOCR[c, d]				
Complete responders, n	20	92	23	107
Patients with event, n (%)	4 (20.0%)	15 (16.3%)	7 (30.4%)	28 (26.2%)
Median, months (95% CI)	NR[e] (6.4, NE[f])	14.4 (14.4, NE[f])	24.2 (6.9, NE[f])	NR[e] (NE[f])
Median DOCR follow-up, months (range)	6.1 (0-12)	6.9 (0-18)	11.8 (0 – 25)	13.6 (0 – 31)
Unstratified HR (95% CI)	0.59 (0.19, 1.83)		0.59 (0.25, 1.35)	
p-value (log-rank)	0.3560		0.2040[a]	

CCOD = clinical cutoff date; CI = confidence interval; CMH = Cochran-Mantel-Haenszel; CR = complete response; DOCR = duration of complete response; Glofit-GemOx = glofitamab in combination with gemcitabine plus oxaliplatin; HR = hazard ratio; IRC = Independent Review Committee; PFS = progression-free survival; R-GemOx = rituximab in combination with gemcitabine plus oxaliplatin.

[a] As the primary analysis of OS crossed the pre-specified stopping boundary, all p-values for the updated analysis are considered descriptive. [b] For the primary analysis, these key secondary efficacy endpoints were tested according to the order shown in the table above. [c] IRC- and INV-Assessed response rates were assessed using the Lugano Classification (Cheson et al. 2014). [d] The Applicant retained DOCR as a key secondary endpoint in the hierarchical testing acknowledging the FDA would not formally assess the DOCR as a key secondary endpoint as it is a responder analysis, which is a subgroup analysis. [e] Not reached. [f] Not estimable.

Sources: t_ef_tte_IRCPFSN_IT_29MAR2023_41944 [ADSL, ADTTE]; t_ef_tte_IRCPFSN_IT_16FEB2024_41944 [ADSL, ADTTE]; t_rsp_IRC_IT_29MAR2023_41944 [ADSL, ADRS]; t_rsp_IRC_IT_16FEB2024_41944 [ADSL, ADRS]; t_ef_dor_IRCCR_IT_29MAR2023_41944 [ADSL, ADTTE]; t_ef_dor_IRCCR_IT_16FEB2024_41944 [ADSL, ADTTE]; t_ef_tte_fup_OS_T_IT_29MAR2023_41944 [ADSL, ADTTE]; t_ef_tte_fup_OS_T_IT_16FEB2024_41944 [ADSL, ADTTE]; t_ef_tte_fup_IRCPFSN_T_IT_29MAR2023_41944 [ADSL, ADTTE]; t_ef_tte_fup_IRCPFSN_T_IT_16FEB2024_41944 [ADSL, ADTTE]; t_ef_tte_fup_IRCCR_T_IT_29MAR2023_41944 [ADSL, ADTTE]; t_ef_tte_fup_IRCCR_T_IT_16FEB2024_41944 [ADSL, ADTTE].

Figure 7 Kaplan-Meier Estimates of IRC-assessed PFS, Censored Before NALT (STARGLO Updated Analysis, ITT Population)*



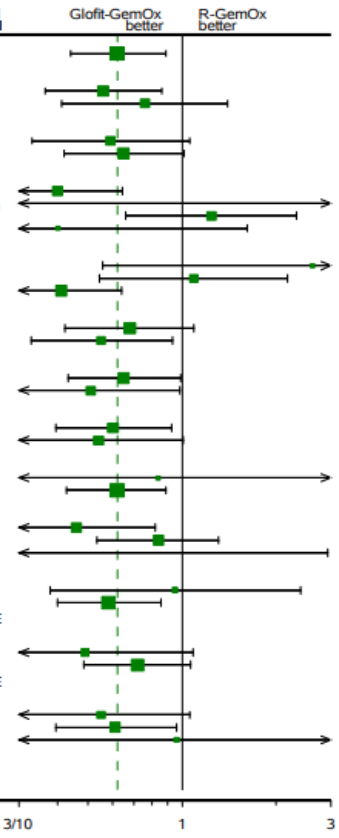
Source: g_ef_km_IRCPFSN_IT_16FEB2024_41944 [ADSL, ADTTE].
*Replaced by FDA for improved resolution using Figure 6 from Applicant's updated CSR page 124

2.3.2.3. *Exploratory Subgroup Analyses*

Subgroup analyses were conducted for 26 pre-specified factors across 77 subgroups (each factor consisted of multiple subgroups) (Figure 8).

Figure 8 Subgroup Analysis of OS by Key Baseline Risk Factors (STARGLO Updated Analysis, ITT Population)

Baseline Risk Factors	Total n	R-GemOx (N=91) n	R-GemOx (N=91) Events	R-GemOx (N=91) Median (Months)	Glofit-GemOx (N=183) n	Glofit-GemOx (N=183) Events	Glofit-GemOx (N=183) 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)
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									
North America	25	10	2	NE	15	8	13.3	2.62	(0.56, 12.34)
Europe	88	26	11	13.8	62	29	21.2	1.09	(0.54, 2.18)
Asia Pacific	161	55	39	8.3	106	43	NE	0.41	(0.27, 0.64)
No. of previous lines of systemic therapy for DLBCL									
1	172	57	28	15.7	115	44	NE	0.68	(0.42, 1.09)
>=2	102	34	24	6.7	68	36	18.3	0.55	(0.33, 0.93)
Relapse or refractory to last line of therapy									
Refractory	166	54	36	7.5	112	61	11.9	0.65	(0.43, 0.99)
Relapsed	108	37	16	27.8	71	19	NE	0.51	(0.26, 0.98)
Primary refractory									
Yes	153	47	34	7.3	106	59	10.2	0.60	(0.40, 0.92)
No	121	44	18	27.8	77	21	NE	0.54	(0.29, 1.01)
Prior CAR-T therapy									
Yes	21	8	4	27.8	13	6	13.7	0.84	(0.23, 3.01)
No	253	83	48	12.9	170	74	NE	0.62	(0.43, 0.89)
Total number of risk factors for IPI (Derived)									
0 - 2	131	41	20	18.5	90	28	NE	0.46	(0.26, 0.82)
3 - 5	134	47	31	12.9	87	50	11.1	0.84	(0.53, 1.31)
Unknown	9	3	1	0.6	6	2	NE	0.18	(0.01, 2.93)
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
Ann Arbor staging at study entry									
Stage I/II	80	20	9	18.5	60	20	NE	0.49	(0.22, 1.08)
Stage III/IV	193	70	43	12.9	123	60	21.2	0.72	(0.49, 1.07)
Unknown	1	1	0	NE				NE	NE
Cell of origin									
Germinal centre B cell	89	29	15	11.1	60	25	NE	0.55	(0.29, 1.06)
Non-Germinal centre B cell+	153	50	33	10.9	103	47	25.5	0.61	(0.39, 0.96)
Unknown	32	12	4	20.2	20	8	NE	0.96	(0.28, 3.21)



Day 1 is day of randomization. HRs and Wald CIs were estimated using Cox regression. The vertical dashed line indicates the HR for all patients. The symbol size is proportional to the subgroup size. COO is investigator assessed.

CAR-T = chimeric antigen receptor T-cell; Glofit-GemOx = glofitamab in combination with gemcitabine plus oxaliplatin; HR = hazard ratio; IPI = International Prognostic Index; NE = not estimable; R-GemOx = rituximab in combination with gemcitabine plus oxaliplatin.

Source: g_ef_forest_unstrat_odac_OS_IT_16FEB2024_41944 (ADSL, ADSUB, ADTTE).

When examining the subgroup analyses for OS, the great majority of subgroups showed a benefit consistent with the treatment effect in the overall population with few exceptions notably in the exploratory subgroups of race and region. In North America (n=25), an OS HR of 2.62 (95% CI: 0.56, 12.34), PFS HR of 2.25 (95% CI: 0.48, 10.54) and equal CR rates (40%) between the arms were observed (Table 4). In Europe, an OS HR of 1.09 (95% CI: 0.54, 2.18) was observed, with a directionally consistent benefit in favor of Glofit-GemOx in key secondary endpoints of PFS and CR when compared with the overall population. Of note, the OS HR of 0.62 in the overall population (ITT) falls within the 95% CIs for the OS/PFS HRs in North America and Europe.

Table 4 Efficacy Overview in Pre-specified Regional Subgroups (STARGLO Updated Analysis)

	North America N=25		**Europe N=88**		**Asia Pacific[a] N=161**		**ITT N=274**	
	R-GemOx N=10	**Glofit-GemOx N=15**	**R-GemOx N=26**	**Glofit-GemOx N=62**	**R-GemOx N=55**	**Glofit-GemOx N=106**	**R-GemOx N=91**	**Glofit-GemOx N=183**
OS								
Median, months (95% CI)	NR (7.5, NE)	13.3 (5.2, NE)	13.8 (11.1, NE)	21.2 (10.5, NE)	8.3 (5.5, 14.5)	NR (20.4, NE)	12.9 (7.9, 18.5)	25.5 (18.3, NE)
HR (95% CI)	2.62 (0.56, 12.34)		1.09 (0.54, 2.18)		0.41 (0.27, 0.64)		0.62 (0.43, 0.88)	
IRC-assessed PFS								
Median, months (95% CI)	27.1[b] (3.3, NE)	7.5 (2.5, NE)	7.8 (2.6, NE)	9.2 (6.1, 17.0)	2.5 (1.5, 5.2)	20.5 (9.3, NE)	3.6 (2.5, 7.1)	13.8 (8.7, 20.5)
HR (95% CI)	2.25 (0.48, 10.54)		0.84 (0.44, 1.59)		0.27 (0.17, 0.42)		0.40 (0.28, 0.57)	
IRC-assessed CR								
CR, n (%)	4 (40.0%)	6 (40.0%)	9 (34.6%)	36 (58.1%)	10 (18.2%)	65 (61.3%)	23 (25.3%)	107 (58.5%)
95% CI	(12.2, 73.8)	(16.3, 67.7)	(17.2, 55.7)	(44.9, 70.5)	(9.1, 30.9)	(51.4, 70.6)	(16.8, 35.5)	(51.0, 65.7)
Difference	0%		23.5%		43.1%		33.2%	

CI= confidence interval; CR=complete response; Glofit-GemOx= glofitamab in combination with gemcitabine plus oxaliplatin; HR = hazard ratio; NE = not evaluable; NR = not reached; PFS = progression-free survival; R-GemOx = rituximab in combination with gemcitabine plus oxaliplatin. OS= overall survival.

[a] Asia Pacific: China, Taiwan, South Korea, and Australia. [b] This median PFS is considered unreliable as it was reached with one patient at risk and a median follow-up of only three months.

Sources: t_ef_tte_OS_IT_16FEB2024_41944 [ADSL, ADTTE]; t_ef_tte_IRCPFSN_IT_16FEB2024_41944 [ADSL, ADTTE]; t_rsp_IRC_IT_16FEB2024_41944 [ADSL, ADRS]; t_ef_tte_subgrp_REG3_OS_IT_16FEB2024_41944 [ADSL, ADTTE]; t_ef_tte_subgrp_REG3_IRCPFSN_IT_16FEB2024_41944 [ADSL, ADTTE]; t_rsp_subgrp_REG3_IRC_IT_16FEB2024_41944 [ADSL, ADRS].

In prior glofitamab monotherapy studies that included 185 patients worldwide, no differences in clinical efficacy were observed by geographical region as demonstrated by consistent CR rates ranging from 40%-47% (Appendix 5: Table 15). The safety profile for glofitamab monotherapy shows similar results across regions noting differences in COVID-19 events reflecting recruitment during the pandemic and the varied COVID-19 policies across the regions (Appendix 5: Table 16). The PK profile of glofitamab was also comparable across regions (Appendix 5: Figure 11). Efficacy outcomes in trials evaluating R-GemOx in R/R DLBCL did not show regional differences across various countries in Europe, China, and the US (Appendix 7).

To better understand the variations in the regional subgroups observed in STARGLO, further interrogation and additional analyses were conducted in accordance with ICH E17 guidance. A high association between race and region was observed, as to be expected, with 83.2% of patients in the Asia Pacific region being Asian, and the majority of patients in Europe (76.1%) and North America (84.0%) being White (Appendix 5: Table 17). Given this correlation, additional analyses focused on geographical regions.

Among the 25 patients enrolled in North America, an imbalance in prognostic factors between the arms was identified, with notably more high-risk patients in the Glofit-GemOx arm vs. the R-GemOx arm. More patients in the Glofit-GemOx arm were primary refractory (80.0% vs. 40.0%), had higher IPI scores (66.6% vs. 50.0%), and more advanced stage disease (80.0% vs. 66.7%) (Appendix 5: Table 18). This imbalance underscores the difficulties with interpreting data from small subgroups, where the effectiveness of randomization in terms of balancing prognostic factors between treatment arms was essentially lost. Consequently, in North America, the Glofit-GemOx arm includes a higher proportion of patients with poorer prognoses and higher likelihood of worse OS outcomes compared to R-GemOx, potentially independent of the treatment administered. The inherent challenges associated with exploratory analyses in small groups, such as reduced sample sizes and lack of statistical power, exacerbate uncertainties. This issue is particularly evident in the North American subgroup, with n = 15 patients in the Glofit-GemOx arm versus n = 10 in the R-GemOx arm. In these small groups, observed heterogeneity in treatment effects can arise from chance alone (Wittes 2013; Alosh et al. 2016), further complicating the interpretation of any findings.

To further assess regional subgroups, an alternative grouping for regions with larger sample sizes was applied, as recommended by ICH E17. Countries of enrollment were grouped based on expected similarities in intrinsic and extrinsic factors: NA/EUR/AUS (n = 143, includes US, European countries, and Australia) and Asia (n = 131, includes China, South Korea and Taiwan). In Asia, all patients identify as Asian race, while all patients identifying as White race were enrolled in the NA/EUR/AUS subgroup, which also includes unknown race[1] from France (13%); Asian (4%); and Black or African American (2%). In NA/EUR/AUS the OS HR = 1.06, 95% CI (0.61, 1.84), while in Asia, the OS HR = 0.39, 95% CI (0.25, 0.63). In both the NA/EUR/AUS and Asia subgroups, key secondary endpoints of PFS and CR showed directionally consistent benefit in favor of Glofit-GemOx when compared to the overall population (Table 5).

[1] This data is unknown due to the local regulations related to the General Data Protection Regulations (GDPR) that prevent the collection of data related to protected subgroups like race.

Table 5 Efficacy Overview in NA/EUR/AUS and Asia Subgroups (STARGLO Updated Analysis)

	NA/EUR/AUS[a] (N=143)		Asia[b] (N=131)		ITT (N=274)	
	R-GemOx N=44	Glofit-GemOx N=99	R-GemOx N=47	Glofit-GemOx N=84	R-GemOx N=91	Glofit-GemOx N=183
OS						
Median, months (95% CI)	27.8 (12.5, NE)	21.2 (11.9, NE)	8.2 (4.5, 14.3)	NR (19.2, NE)	12.9 (7.9, 18.5)	25.5 (18.3, NE)
HR (95% CI)[3]	1.06 (0.61, 1.84)		0.39 (0.25, 0.63)		0.62 (0.43, 0.88)	
IRC-assessed PFS						
Median, months (95% CI)	7.8 (3.6, NE)	9.2 (6.4, 18.3)	2.0 (1.4, 2.7)	20.4 (9.3, NE)	3.6 (2.5, 7.1)	13.8 (8.7, 20.5)
HR (95% CI)[c]	0.81 (0.48, 1.35)		0.25 (0.15, 0.40)		0.40 (0.28, 0.57)	
IRC-assessed CR						
CR, n (%) (95% CI)	15 (34.1%) (20.5, 49.9)	56 (56.6%) (46.2, 66.5)	8 (17.0%) (7.7, 30.8)	51 (60.7%) (49.5, 71.2)	23 (25.3%) (16.8, 35.5)	107 (58.5%) (51.0, 65.7)
Difference	22.5%		43.7%		33.2%	

CI = confidence interval; CR = complete response; Glofit-GemOx = glofitamab in combination with gemcitabine plus oxaliplatin; HR = hazard ratio; NE = not evaluable; PFS = progression-free survival; R-GemOx = rituximab in combination with gemcitabine plus oxaliplatin. OS = overall survival. [a] US, Europe and Australia. [b] China, Taiwan, and South Korea. [c] Stratified HR reported for ITT and unstratified HR reported for the subgroups.

Sources: t_ef_tte_OS_IT_16FEB2024_41944 [ADSL, ADTTE]; t_ef_tte_IRCPFSN_IT_16FEB2024_41944 [ADSL, ADTTE]; t_rsp_IRC_IT_16FEB2024_41944 [ADSL, ADRS]; t_ef_tte_subgrp_REG2_OS_IT_16FEB2024_41944 [ADSL, ADTTE]; t_ef_tte_subgrp_REG2_IRCPFSN_IT_16FEB2024_41944 [ADSL, ADTTE]; t_rsp_subgrp_REG2_IRC_IT_16FEB2024_41944 [ADSL, ADRS].

In the analyses below, outcomes in the larger sample size subgroups of NA/EUR/AUS and Asia were examined by various factors, including baseline characteristics, PK, and New Anti-Lymphoma Therapy (NALT) use to further understand the observed regional differences.

Baseline Characteristics in NA/EUR/AUS and Asia Subgroups

Compared to the three regional subgroups, the baseline characteristics including prognostic factors between the R-GemOx vs. Glofit-GemOx arms in NA/EUR/AUS were not as evidently imbalanced (Appendix 5: Table 19) as in the North American subgroup (Appendix 5: Table 18).

Pharmacokinetics (PK) in NA/EUR/AUS and Asia Subgroups

Glofitamab PK was characterized across NA/EUR/AUS and Asia in STARGLO. PK analyses indicated that the following factors were predictors of glofitamab PK characteristics: baseline weight, baseline CRP, baseline tumor size, baseline obinutuzumab concentration and tumor histopathology. Factors that had no significant impact on glofitamab PK included age, sex, race and region, hepatic impairment, renal impairment. Similar glofitamab PK exposures in NA/EUR/AUS and Asia were observed, illustrated by the overlapping individual time concentration profiles (Appendix 5: Figure 12).

Glofitamab PK exposure was not a significant predictor of achieving a CR in a univariate logistic regression model (Appendix 5: Figure 13). As illustrated in Figure 13, an increase in glofitamab PK exposure (plotted on X axis), does not result in a significant increase of probability of CR (plotted on Y axis). In addition, race and region were not identified as predictors of CR in a multivariate logistic regression model. Glofitamab PK exposure as well as race and region were also not identified as predictors of all other tested efficacy endpoints, including OS, PFS and ORR.

Impact of NALT in NA/EU/AUS and Asia Subgroups

Notably, in Asia, the median OS of 8.2 months in the R-GemOx control arm fell within the anticipated range of 8 - 13.5 months. However, in NA/EUR/AUS, the median OS of 27.8 months for R-GemOx was higher than expected. This high median OS in NA/EUR/AUS far exceeds that observed for prior R-GemOx studies (Appendix 7) and a similar trend was observed with PFS, which prompted further investigation into factors that had the potential to influence efficacy outcomes, including the impact of NALT.

Patients in the R-GemOx arm received more NALT compared to those in the Glofit-GemOx arm in both NA/EUR/AUS (54.5% vs. 27.3%) and Asia (59.6% vs. 22.6%) (Table 6). Although the overall incidence of NALT was similar across regions, the type of NALT, most notably the use of highly effective NALT, varied by arm and region. In NA/EUR/AUS, a greater proportion of patients on the R-GemOx arm received CAR-T therapy (20.5%) or bispecific regimens (18.2%) compared to patients on the Glofit-GemOx arm. In contrast, in Asia, although some patients on the R-GemOx arm received CAR-T therapy (6.4%) or bispecific regimens (14.9%), there was higher utilization of more standard treatments like radiotherapy (19.1%) and other systemic therapy (38.3%). In general, CAR-T therapy was more frequently utilized in the R-GemOx arm within NA/EUR/AUS with 38% of the NALT as CAR-T therapy compared to 11% of the NALT in Asia.

Table 6 Summary of New Anti-Lymphoma Therapy (NALT) by NA/EUR/AUS and Asia Subgroups (STARGLO Updated Analysis)

	NA/EUR/AUS[a] (N=143)		Asia[b] (N=131)		ITT (N=274)	
	R-GemOx N=44	Glofit-GemOx N=99	R-GemOx N=47	Glofit-GemOx N=84	R-GemOx N=91	Glofit-GemOx N=183
Patients with at least one NALT, n (%)	24 (54.5%)	27 (27.3%)	28 (59.6%)	19 (22.6%)	52 (57.1%)	46 (25.1%)
Cellular Therapy/Novel agents						
CAR-T	9 (20.5%)	7 (7.1%)	3 (6.4%)	1 (1.2%)	12 (13.2%)	8 (4.4%)
Bispecific regimens	8 (18.2%)	2 (2.0%)	7 (14.9%)	0	15 (16.5%)	2 (1.1%)
CD19 immunotherapy	3 (6.8%)	8 (8.1%)	2 (4.3%)	1 (1.2%)	5 (5.5%)	9 (4.9%)
SCT	1 (2.3%)	0	0	2 (2.4%)	1 (1.1%)	2 (1.1%)

Table 6 Summary of New Anti-Lymphoma Therapy (NALT) by NA/EUR/AUS and Asia Subgroups (STARGLO Updated Analysis) (cont.)

	NA/EUR/AUS[a] (N=143)		Asia[b] (N=131)		ITT (N=274)	
	R-GemOx N=44	Glofit-GemOx N=99	R-GemOx N=47	Glofit-GemOx N=84	R-GemOx N=91	Glofit-GemOx N=183
Standard Treatments						
Other systemic therapy	14 (31.8%)	21 (21.2%)	18 (38.3%)	14 (16.7%)	32 (35.2%)	35 (19.1%)
Radiotherapy/procedures[c]	5 (11.4%)	2 (2.0%)	9 (19.1%)	4 (4.8%)	14 (15.4%)	6 (3.3%)
EFS						
Median, months (95% CI)	5.1 (3.6, 7.8)	9.2 (6.1, 17.0)	1.9 (1.5, 2.6)	13.8 (7.4, NE)	2.8 (2.2, 3.9)	10.4 (7.4, 17.0)
HR (95% CI)[d]	0.58 (0.38, 0.91)		0.23 (0.15, 0.36)		0.34 (0.25, 0.46)	

CAR-T = chimeric antigen receptor T-cell therapy; Glofit-GemOx = glofitamab in combination with gemcitabine plus oxaliplatin; NALT = new anti-lymphoma therapy; R-GemOx = rituximab in combination with gemcitabine plus oxaliplatin; SCT = stem cell transplant.

[a]US, Europe and Australia. [b] China, Taiwan, and South Korea. [c]Includes radiotherapy, excision of tumor, and lysis of intestinal adhesions. [d] Stratified HR reported for ITT and unstratified KR reported for the subgroups.

Notes: Patients could have received more than one NALT. Multiple uses of a specific medication for a patient were counted once in the frequency for the medication. For frequency counts in "Total number of treatments", multiple uses of the same medication for a patient were counted separately. Different therapies started on the same date have been included.

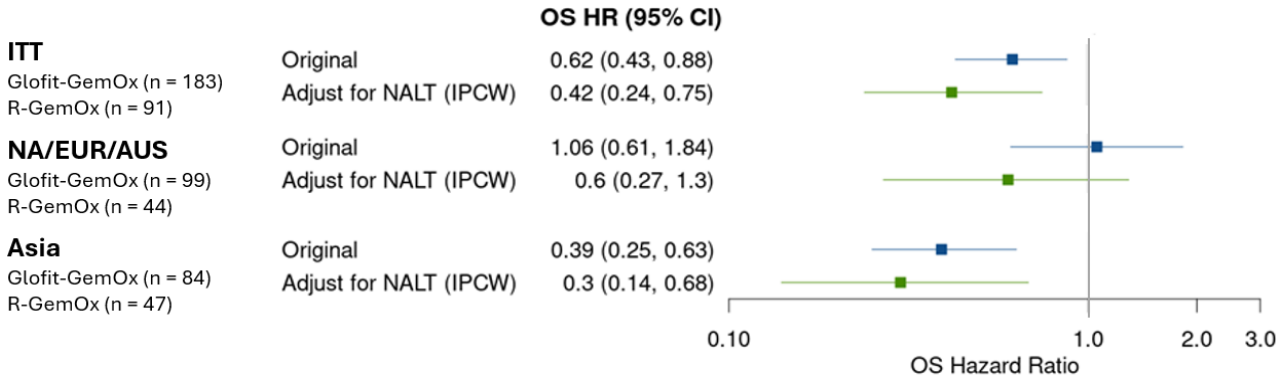
Sources: t_cm_nalt3_subgrp_REG2_T_IT_16FEB2024_41944 [ADSL, ADCM]; t_cm_nalt3_T_IT_16FEB2024_41944 [ADSL, ADCM]; t_ef_tte_subgrp_REG2_IRCTTNE_IT_16FEB2024_41944 [ADSL, ADCM]. t_ef_tte IRCTTNE_IT_16FEB2024_41944 [ADSL, ADCM].

The more frequent use of highly efficacious NALT such as CAR-T therapy and bispecific regimens may explain the unusually high median OS of 27.8 months observed in patients randomized to receive R-GemOx in NA/EUR/AUS compared to the overall population median OS of 12.9 months, which is similar to contemporary studies evaluating R-GemOx performance (Yamshon et al. 2024; Budde et al. 2024).

Event-free survival (EFS), a clinically relevant endpoint in R/R DLBCL, was examined by considering NALT as an event in addition to disease progression and death. The EFS analyses showed directionally consistent benefit in favor of Glofit-GemOx in both NA/EUR/AUS (HR = 0.58, 95% CI: 0.38, 0.91) and Asia (HR=0.23, 95% CI: 0.15, 0.36) when compared with the overall population (Table 6).

The EFS findings suggest varying impact of NALT between the treatment arms and across the two regions. To further understand this, additional post-hoc analyses were conducted using inverse probability of censoring weighting (IPCW) to adjust for NALT and re-estimate the OS and PFS HRs in a scenario where NALT would not have had an impact (Figure 9, Figure 10). Additional details on the rationale and methodology of IPCW are provided in Appendix 4. Since EFS can also be considered an adjustment for NALT in relation to PFS, the consistent results between EFS and IPCW reinforce the findings on the impact of NALT (Figure 10).The varied impact of NALT on OS was seen in Figure 9, where a larger decrease in HR (from 1.06 to 0.6) was observed in NA/EUR/AUS compared to a smaller decrease (from 0.39 to 0.3) in Asia. This indicates that NALT primarily impacted the R-GemOx arm in NA/EUR/AUS.

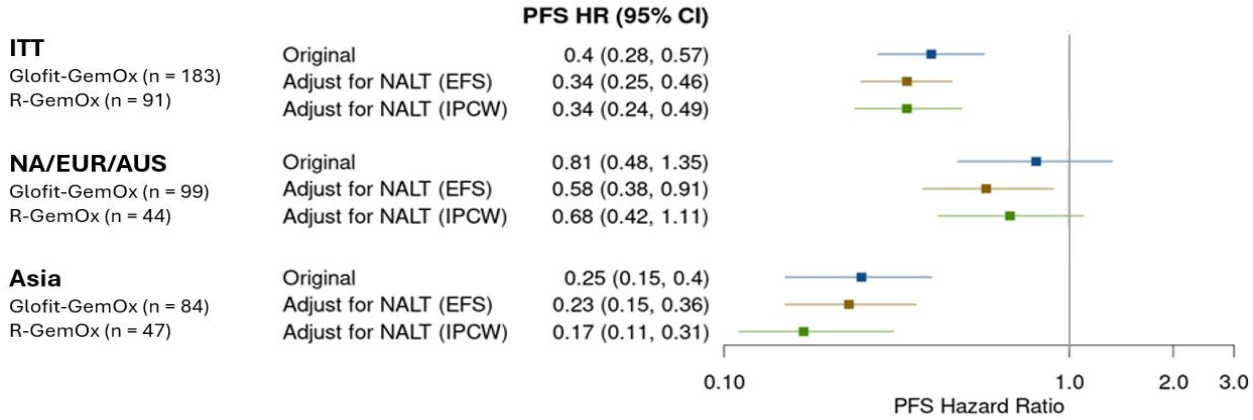
Figure 9 Summary of OS HRs Before and After Adjusting for NALT by NA/EUR/AUS and Asia (STARGLO Updated Analysis)



Glofit-GemOx = glofitamab in combination with gemcitabine plus oxaliplatin; IPCW = Inverse Probability of Censoring Weighting; NALT = new anti-lymphoma therapy; R-GemOx = rituximab in combination with gemcitabine plus oxaliplatin.

Sources: t_ipcw_os_ASIA_IT_16FEB2024_GO41944 [ADSL, ADSUB, ADSPD, ADRS, ADTTE]; t_ipcw_os_NASIA_IT_16FEB2024_GO41944 [ADSL, ADSUB, ADSPD, ADRS, ADTTE]; t_ipcw_os_IT_16FEB2024_GO41944 [ADSL, ADSUB, ADSPD, ADRS, ADTTE]; t_ef_tte_OS_IT_16FEB2024_41944 [[ADSL, ADTTE]; t_ef_tte_subgrp_REG2_OS_IT_16FEB2024_41944 [ADSL, ADTTE].

Figure 10 Summary of PFS HRs Before and After Adjusting for NALT by NA/EUR/AUS and Asia (STARGLO Updated Analysis)



Glofit-GemOx = glofitamab in combination with gemcitabine plus oxaliplatin; EFS = event-free survival; IPCW = Inverse Probability of Censoring Weighting; R-GemOx = rituximab in combination with gemcitabine plus oxaliplatin.
Sources: t_ipcw_pfs_ASIA_IT_16FEB2024_GO41944 [ADSL, ADSUB, ADSPD, ADRS, ADTTE]; t_ipcw_pfs_NASIA_IT_16FEB2024_GO41944 [ADSL, ADSUB, ADSPD, ADRS, ADTTE]; t_ipcw_pfs_IT_16FEB2024_GO41944 [ADSL, ADSUB, ADSPD, ADRS, ADTTE]; t_ef_tte_IRCPFSN_IT_16FEB2024_41944 [ADSL, ADTTE]; t_ef_tte_subgrp_REG2_IRCTTNE_IT_16FEB2024_41944 [ADSL, ADTTE]; t_ef_tte_IRCTTNE_IT_16FEB2024_41944 [ADSL, ADTTE]; t_ef_tte_subgrp_REG2_IRCPFSN_IT_16FEB2024_41944 [ADSL, ADTTE].

In summary, to understand the observed racial and regional differences in treatment effect, various factors, including the inherent high variability of subgroup findings, baseline characteristics, PK, and the impact of NALT, were examined. Imbalances in baseline prognostic factors heavily impacted the OS analysis for the smaller North American subgroup (n=25). Variations in PK did not influence outcomes in any of the regional groupings. However, detailed analyses revealed that the use of NALT in the R-GemOx arm influenced the observed OS HR in NA/EUR/AUS and adjusting for NALT resulted in directionally consistent improvements across regions, aligning with the overall population data. Challenges with subgroup analyses include a lack of appropriate statistical power and susceptibility to multiplicity (i.e. chance finding), resulting in high variability that can be misleading.

Based on the totality of data presented, the Applicant concludes that the observed differences in OS HR among certain racial and regional subgroups do not indicate true deviations in treatment effect from the overall population and can be attributed to a multitude of factors including subgroup variability, baseline imbalances, and the influence of NALT. Therefore, the overall conclusions should be elicited from the overall population (ITT), for which STARGLO was designed and powered, where a statistically significant and clinically meaningful treatment effect was observed for OS, PFS, and CR.

2.3.3. Overall Efficacy Conclusions

STARGLO met its primary endpoint, demonstrating a statistically significant and clinically meaningful 41% reduction in the risk of death with Glofit-GemOx compared to R-GemOx, for transplant-ineligible patients with R/R DLBCL. Substantial benefit was supported by secondary endpoints of IRC-assessed PFS, with a 63% reduction in the risk of a PFS event, and a higher CR

rate (50.3% vs. 22.0%).

The treatment benefit of Glofit-GemOx for OS and PFS endpoints persisted in an updated analysis with more mature data and longer follow-up. CR rates also improved in the updated analysis after all patients had completed therapy. The robustness of OS and PFS results were further demonstrated via the pre-specified sensitivity analyses, the post-hoc multivariable analyses, and the benefit of Glofit-GemOx observed across clinically relevant subgroups.

Based on the available PK, safety and efficacy evidence from glofitamab monotherapy data and STARGLO, there is no biological or clinical explanation to indicate that race and/or region are relevant determinants of outcome to glofitamab treatment. Additional analyses of geographical region indicate that NALT likely played a significant role in the OS subgroup results. This demonstrates that any variation in treatment outcomes across racial and regional subgroups was not due to inherent differences related to race or geography, but likely due to external factors such as the inherent high variability in subgroup findings, imbalances in baseline characteristics, and the impact of NALT. As a result, the Applicant finds no evidence that the observed results are indicative of an actual difference in treatment effect across these subgroups compared to the overall population. Thus, the OS HR based on the overall trial population is considered the best estimate of the treatment effect because it is based on the most robust and comprehensive analysis available, minimizing the influence of statistical noise/fluctuations and increasing the reliability of the findings.

Overall, the clinically meaningful OS, PFS, and CR benefits in the ITT population support the use of Glofit-GemOx. The study population is representative of typical transplant-ineligible patients with R/R DLBCL across geographies, making the STARGLO results applicable to US patients. See Section 4.1 for further discussion on the totality of data and applicability to the US population.

The FDA's Position on Efficacy:

There were substantial inconsistencies in the efficacy results of STARGLO based on region. The inconsistencies identified in the results of STARGLO are broadly summarized in the table below and these issues require further consideration and are outlined below.

FDA Table 3: Inconsistences Identified Between Subgroups Defined by Region in STARGLO

Factors	Notable Differences
Differential treatment effect on outcomes	• OS • PFS • CR • ORR
Patient and disease-related factors	• Demographics • Disease burden and histology • Treatment history
Treatment and data capture	• Exposure • Concordance in response assessments • Timing of efficacy assessments • Use of New Anti-Lymphoma Therapy

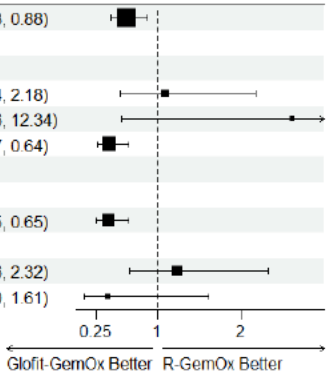
Inconsistent Treatment Effects Between Subgroups

Although the primary analysis of OS was statistically significant in the ITT population, the differential treatment effects across multiple endpoints in subgroups defined by race and region raise substantial uncertainty. There are limitations of subgroup analyses, yet the evaluation of subgroups provides valuable information about the consistency of the treatment effect and overall benefit-risk to support that the treatment benefit observed applies to the entire patient population studied. It is important to note that adequate interpretation of the treatment effect based on the ITT population can only be made if the treatment effect is consistent across subgroups.

As depicted in the figure below, the hazard ratios for overall survival based on enrollment from Europe and North America, or identification as White race were all above 1.0 with upper bounds far above 1.0, suggesting outcomes favoring the R-GemOx comparator over Glofit-GemOx but also the potential for a detriment in overall survival with Glofit-GemOx. These survival results differed substantially from those observed for patients identifying as Asian race or being enrolled from the Rest of the World, the latter of which mostly consisted of patients enrolled in Asian countries. For these patients, the point estimate of the hazard ratio was 0.40 and 0.41, respectively, and the upper bounds of the associated 95% confidence intervals below 1.0, favoring the Glofit-GemOx regimen.

FDA Figure 1: Forest Plot of OS Subgroup Analyses by Region and Race

		R-GemOx (N=91)			Glofit-GemOx (N=183)				
Baseline Risk Factors	**Total N**	**n**	**Events**	**Median (Months)**	**n**	**Events**	**Median (Months)**	**Hazard Ratio**	**95% Wald CI**
All Patients	274	91	52	12.9	183	80	25.5	0.62	(0.43, 0.88)
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)
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	NE	NE
White	115	33	13	27.8	82	39	18.3	1.24	(0.66, 2.32)
Unknown	19	6	4	12.9	13	4	NE	0.40	(0.10, 1.61)



Source: FDA Analysis, Data cutoff: 16 February 2024.

The FDA focused further subgroup analysis using region as opposed to race. To assess for a potential regional treatment difference following exposure to either Glofit-GemOx or R-GemOx, the FDA regrouped the ITT population into two large regional subgroups: "Asian Region" and "Non-Asian Region." These FDA groupings combined patients who were enrolled and treated in the Asian countries China, Taiwan, and Korea into the "Asian Region" and those patients enrolled and treated in North America, Europe, and Australia into the "Non-Asian Region" (FDA Table 4: FDA's Definition of Regional Subgroups). This new subgrouping differed slightly from the initial pre-specified subgrouping by the Applicant by including Australia with the Non-Asian Region. Given the racial and ethnic demographics of Australians, the similar medical practices and available therapies, and longstanding participation in global clinical research, it was deemed reasonable to group Australia with Europe and North America in the Non-Asian region. Furthermore, this revised subgrouping was considered to yield groups of patients with likely similar intrinsic and extrinsic factors.

FDA Table 4: FDA's Definition of Regional Subgroups

Region		**ITT Population N=274 n (%)**	**Prespecified Subgroup[b]**	**FDA-Defined Subgroups**
US		25 (9%)	North America	Non-Asian Region
Europe[a]		88 (32%)	Europe	
Australia		30 (11%)	Rest of World	
Asia	**Total**	**131 (48%)**		Asian Region
	China	80 (29%)		
	Korea	37 (14%)		

	Taiwan	14 (5%)		

[a] France, Poland, Great Brittain, Spain, Denmark, Germany, Belgium, Switzerland
[b] Pre-specified regional subgroups by the Applicant. Used for initial exploratory subgroup analysis.
ITT: Intent-to-treat population;
Source: FDA analysis, Data cutoff: 16 February 2024

Differential Treatment Effects between Patients Enrolled in Asian Region Versus Non-Asian Region

With the updated data (data cutoff: 2/16/2024), the efficacy results in FDA regional subgroups are shown in FDA Table 5: Efficacy Summary in Regional Subgroups . Kaplan-Meier curves of OS and PFS per IRC are shown in FDA Figure 2 and FDA Figure 3, respectively.

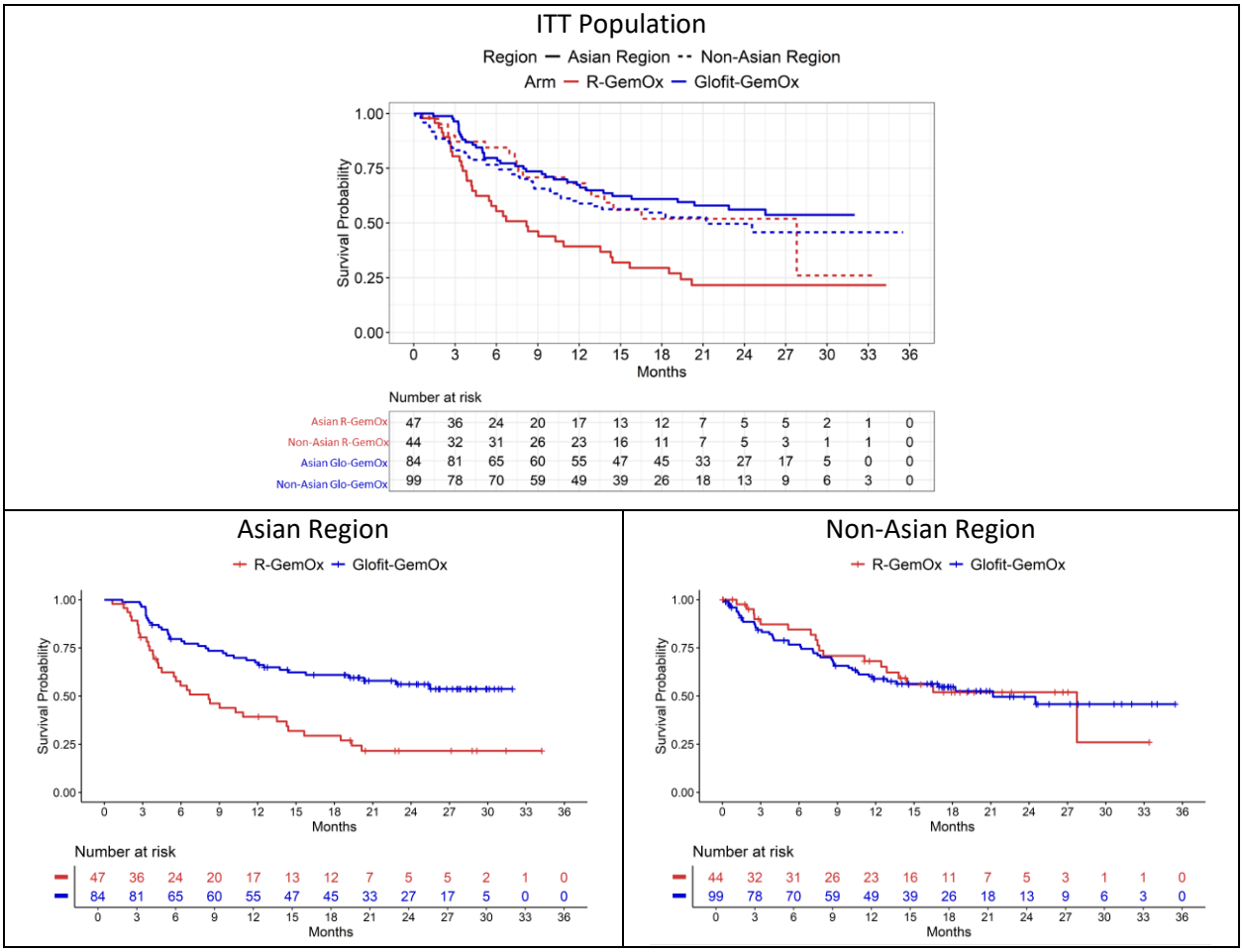
FDA Table 5: Efficacy Summary in Regional Subgroups

	Asian Region		Non-Asian Region	
	Glofit-GemOx N=84	R-GemOx N=47	Glofit-GemOx N=99	R-GemOx N=44
OS				
Events, n (%)	36 (42.9%)	34 (72.3%)	44 (44.4%)	18 (40.9%)
Median OS (95% CI), months	NE (19.2, NE)	8.2 (4.5, 14.3)	21.2 (11.9, NE)	27.8 (12.5, NE)
HR (95% CI)[a]	0.39 (0.25, 0.63)		1.06 (0.61, 1.84)	
PFS per IRC				
Events, n (%)	37 (44.0%)	33 (70.2%)	53 (53.5%)	21 (47.7%)
Median PFS (95% CI), months	20.4 (9.3, NE)	2.0 (1.4, 2.7)	9.2 (6.4, 18.3)	7.8 (3.6, NE)
HR (95% CI)[a]	0.25 (0.15, 0.41)		0.81 (0.48, 1.35)	
CR per IRC				
n (%)	51 (60.7%)	8 (17.0%)	56 (56.6%)	15 (34.1%)
95% CI	(49.5%, 71.2%)	(7.6%, 30.8%)	(46.2%, 66.5%)	(20.5%, 49.9%)
Difference (95% CI)	43.7% (27.0%, 60.3%)		22.5% (3.8%, 41.2%)	
ORR per IRC[b]				
n (%)	60 (71.4%)	12 (25.5%)	65 (65.7%)	25 (56.8%)
95% CI	(60.5%, 80.8%)	(13.9%, 40.3%)	(55.4%, 74.9%)	(41.0%, 71.7%)
Difference (95% CI)	45.9% (28.5%, 63.3%)		8.8% (-10.2%, 27.8%)	

[a] Estimated from unstratified Cox regression
[b] Not pre-specified for formal hypothesis testing
Source: FDA Analysis, Data cutoff: 16 February 2024

The FDA's overall survival results by region demonstrated a differential treatment effect between the Asian and Non-Asian regions. The Glofit-GemOx arm demonstrated a benefit in survival outcomes for the 48% of the population enrolled in Asian regions with an OS HR of 0.39 (95% CI: 0.25, 0.63) (FDA Figure 2). However, in the remaining 52% of patients enrolled outside of Asian regions, the OS benefit was markedly different, with an OS hazard ratio of 1.06 (95% CI: 0.61, 1.84) (FDA Figure 2: Kaplan-Meier Curves of OS in Regional Subgroups).

FDA Figure 2: Kaplan-Meier Curves of OS in Regional Subgroups

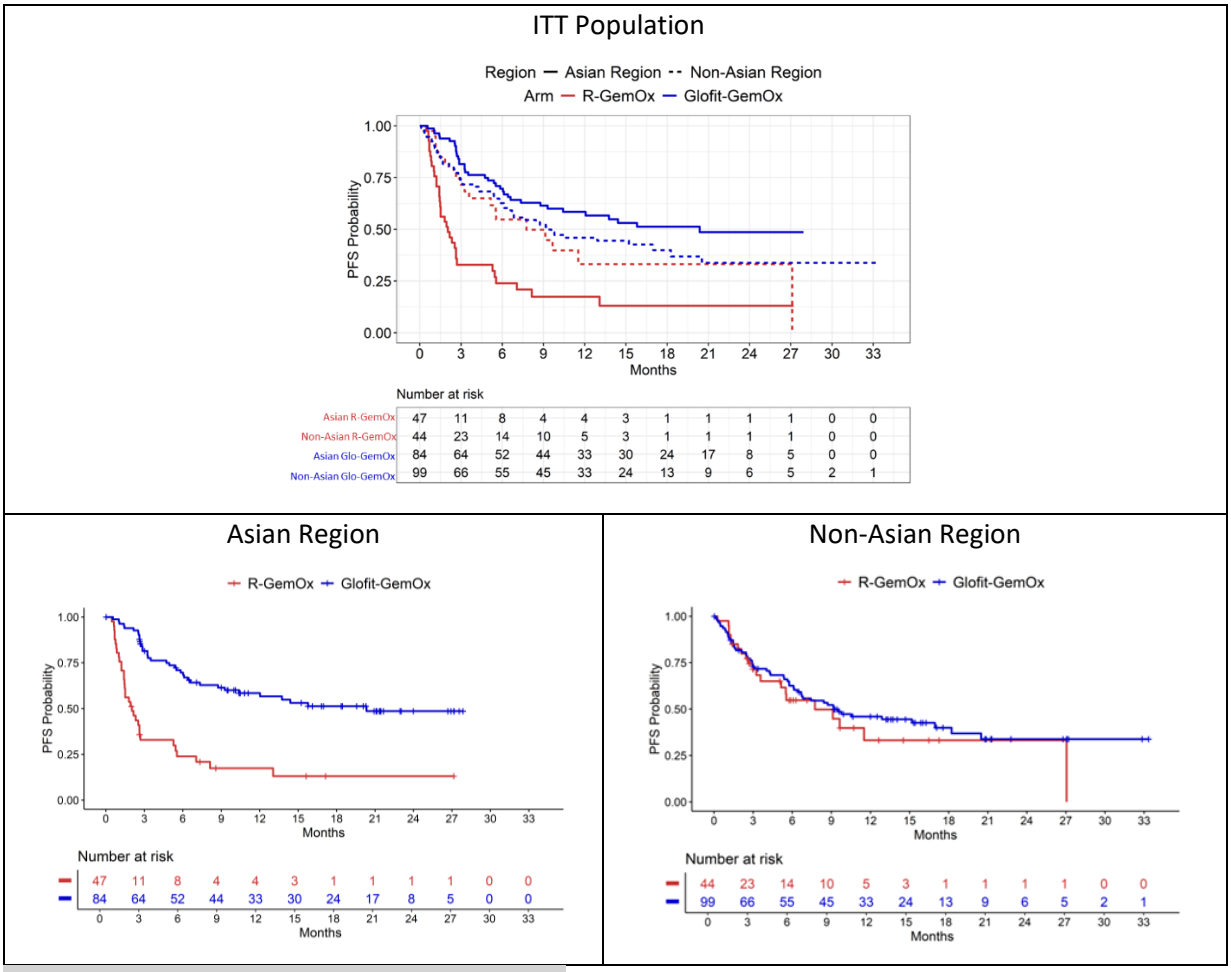


Source: FDA Analysis, Data cutoff: 16 February 2024

This differential treatment effect by region was also observed in progression-free survival (PFS), overall response rate (ORR), and complete response (CR) rate (FDA Table 5, FDA Figure 3, and

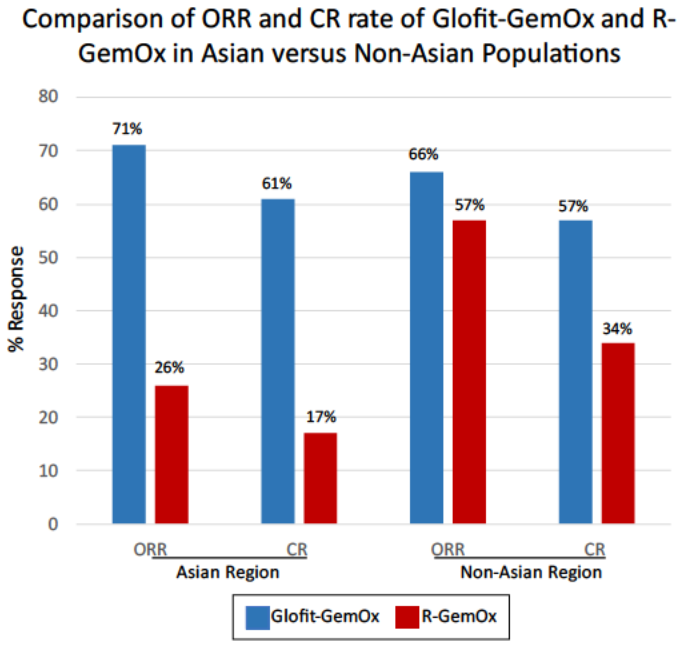
FDA Figure 4). A PFS improvement was demonstrated in patients who were treated with Glofit-GemOx versus R-GemOx in Asian regions with a median PFS increase of approximately 18.4 months and a PFS HR of 0.25 (95%CI: 0.15, 0.41) (FDA Figure 3). The improvement in median PFS was limited to about 1.4 months for patients treated in the Non-Asian regions, resulting in a PFS HR of 0.81 with a 95% confidence interval that includes 1.0 (95% CI: 0.48, 1.35) (FDA Figure 3). A similar trend was observed for the comparison of response rates between regions. While patients treated with Glofit-GemOx versus R-GemOx in Asian regions demonstrated improved responses, both overall and complete responses, this difference was decreased for those treated in Non-Asian regions (FDA Figure 4).Taken together, these observations for PFS, ORR, and CR rate suggest that there is a potential regional regimen-specific effect.

FDA Figure 3: Kaplan-Meier Curves of PFS in Regional Subgroups



Source: FDA Analysis, Data cutoff: 16 February 2024

FDA Figure 4: Bar Plots of ORR and CR by Region



Source: FDA Analysis; Data cutoff: 16 February 2024

Assessment of Treatment Effect Consistency across Regions

FDA conducted an exploratory, post-hoc analysis using interaction tests to assess the treatment effect consistency across efficacy endpoints. Interaction tests are intended to test for the presence of differential treatment effects among two or more subgroups. In an analysis of two subgroups, a significant interaction test indicates that the treatment effect is different for the two subgroups tested. A significant interaction ($p<0.05$) between treatment arms and regions was identified for the time-to-event endpoints of OS and PFS and response endpoint of ORR suggesting that the treatment effect is significantly different between Asian and Non-Asian regions regarding these endpoints, as shown in the table below.

FDA Table 6: The Treatment Effect by Regions and Results of Interaction Tests

Endpoint Summary Measure	Asian Region (Glofit-GemOx vs R-GemOx)	Non-Asian Region (Glofit-GemOx vs R-GemOx)	p-value[a]
OS Hazard Ratio (95% CI)	0.39 (0.25, 0.63)	1.06 (0.61, 1.84)	0.0081
PFS Hazard Ratio (95% CI)	0.25 (0.15, 0.41)	0.81 (0.48, 1.35)	0.0006
CR Risk Difference (95% CI)	44% (27%, 60%)	22% (4%, 41%)	0.0612
ORR[b] Risk Difference (95% CI)	46% (28%, 63%)	9% (-10%, 28%)	0.0036

[a] Cox regressions with randomized treatment arm (Glofit-GemOx vs. R-GemOx), region (Asia region vs. Non-Asia region), and the interaction term between arm and region as covariates were used for OS and PFS per IRC, respectively. Logistic regressions with the same covariates were used for ORR per IRC and CR per IRC, respectively.

[b] Not pre-specified for formal hypothesis testing

Source: FDA Analysis, Data cutoff: 16 February 2024

Outcomes with R-GemOx in Patients with R/R DLBCL

To provide context for the differential treatment effect observed by region in the STARGLO trial, a review of the expected outcomes with R-GemOx is important. The available literature for R-GemOx in patients with R/R DLBCL is provided in Appendix 7. Briefly, the reported CR rate with R-GemOx ranges from 13% to 58% across studies; in studies of 100 patients or more, the reported CR rate range is 22% to 33% (Appendix 7). In the STARGLO trial, the CR rate with R-GemOx was 17% in the Asian region vs 34% in the Non-Asian region. The data with CR rate is informative as it is a direct measure of the activity of the regimen, whereas the data with the time-to-event endpoints of PFS and OS are limited in availability and may be subject to other limitations as reported in the literature.

Major Regional Differences in STARGLO and Uncertain Applicability of Overall STARGLO Study Results to a U.S. Patient Population and U.S. Medical Practice.

Given the differential treatment effects observed in the STARGLO regional subgroups (Asian Region vs Non-Asian Region), the FDA examined potential intrinsic and extrinsic factors including patient- and disease-related factors and healthcare system factors that could have impacted the results. These factors, which are discussed below, were identified as being different between the Asian Region and the Non-Asian Region, raising uncertainty about the robustness of the efficacy results and whether the overall study result is applicable to a U.S. patient population.

Regional Differences in Baseline Patient and Disease Characteristics:

Age

The patients enrolled in the Asian region were younger than those enrolled in the Non-Asian region with median ages of 62 years old and 71 years old, respectively (FDA Table 7). The younger age distribution was even more pronounced when evaluating the age subgroups. For example, only 21% of the patients were 65 years or younger in the Non-Asian Region compared to 55% in the Asian region.

Age is a prognostic factor in DLBCL with poorer prognosis in those patients over 60 years of age (Mauer, 2021). Thus, this noted difference in age between the regions is important in projected treatment outcomes. Furthermore, the younger age distribution of the population in the Asian region is unlike that observed in the U.S. patient population. Specifically, per the US SEER data from 2016-2020, the median age of patients was 67 years old and over two-thirds of the DLBCL cases in the U.S. in 2024 were estimated to be in patients 65 years or older (SEER Cancer Statistics; US Census). The intended patient population in the U.S for Glofit-GemOx, those with R/R disease and considered transplant ineligible, would be older than that estimated from the SEER database as the database is based on prevalence of newly diagnosed and R/R DLBCL. Importantly, age plays a role in the determination of whether a patient is not eligible for transplant. Thus, the outcomes of the younger Asian Region population, which comprises almost half of the ITT population, may not be applicable to the intended U.S. patient population.

FDA Table 7: Regional Difference in the Baseline Demographics

	Non-Asian Region N=143	Asian Region N=131
Age		
Median Age, y (range)	**71 (20, 88)**	**62 (22, 82)**
<65y, n (%)	**30 (21)**	**72 (55)**
≥65 to <75y, n (%)	66 (46)	41 (31)
≥75y, n (%)	47 (33)	18 (14)
Sex, n (%)		
Male	86 (60)	72 (55)
Female	57 (40)	59 (45)
Race, n (%)		
Asian	6 (4)	131 (100)
Black	3 (2)	0
White	115 (80)	0
Unknown	19 (13)	0
Ethnicity, n (%)		
Hispanic	13 (9)	3 (2)
Non-Hispanic	114 (80)	128 (98)
Not reported	15 (10)	0
Unknown	1 (1)	0

Y: years
Source: FDA Analysis, Data cutoff: 16 February 2024.

Reasons for Transplant Ineligibility

Transplant ineligibility is a key eligibility criterion for the intended patient population in STARGLO. The exact reason for this ineligibility, such as older age or multiple comorbidities, may impact response to or tolerability of the type of treatment. In the STARGLO protocol, allowable reasons for transplant ineligibility were the following: Age (≥70 years), end organ dysfunction, ECOG performance status of 2 or higher, patient refusal, or other comorbidities that precluded the use of transplant based on local practice standards or in the opinion of the investigator.

In trials conducted in the U.S or similar populations, the most common reasons for transplant ineligibility in patients with DLBCL are usually older age, comorbidities, or insufficient response

to salvage chemotherapy (Tilly, 2015) (Lazarus, 2008). This pattern was reflected in those patients enrolled in the Non-Asian region (FDA Table 8). However, fewer patients were enrolled based on these categories in the Asian Region. Instead, 65% or the majority of patients in the Asian region refused a transplant compared to only 7% in the Non-Asian region. The exact reasons for the refusals were not captured, precluding a full characterization of the fitness of these patients and the appropriateness of the transplant ineligible determination. However, one potential reason may be the regional differences in utilization of stem cell transplantation, which appears to be used less frequently in countries in the Asian Region compared to those in the Non-Asian Region (Appendix 11: Regional Differences in Utilization of Stem Cell Transplantation). Nevertheless, the 85 patients in the Asian region that refuse transplant may represent a different population than those that are transplant ineligible in the U.S.

FDA Table 8: Regional Difference in the Reasons for Transplant Ineligibility

Reason for Transplant Ineligibility	Non-Asian Region N=143 n (%)	Asian Region N=131 n (%)
Age	86 (60%)	30 (23%)
Performance Status	2 (1%)	0
Comorbidity	11 (8%)	0
Insufficient response to salvage	19 (13%)	8 (6%)
Failed prior transplant	9 (6%)	3 (2%)
Lack of access to transplant center	0	2 (2%)
Patient refused transplant	**10 (7%)**	**85 (65%)**
Other[a]	4 (3%)	2 (2%)
None listed	2 (1%)	1 (0.8%)

[a] Other reasons listed: non-chemotherapy sensitive disease, too chemotherapy refractory, risk of many adverse events, expected insufficient response, not 2 or more prior lines of treatment, patient had insufficient response to pre-transplant chemotherapy
Source: FDA analysis, Data cutoff: 16 February 2024.

Cell of Origin Differences

DLBCL is a heterogenous disease but can be characterized into subtypes based on the cell of origin (COO), which refers to the type of B-cell from which the lymphoma develops. Classification of DLBCL COO using gene expression profiling (GEP), which is the preferred method, divides the lymphoma into three main groups: (1) Germinal center B-cell like (GCB), (2)

Activated B-cell like (ABC) and (3) "unclassified" (Alizadeh, 2000). DLBCL COO has prognostic implications and regional differences in prevalence.

The ABC versus GCB-DLBCL distinction provides a biologic classification with associated prognostic implications. In the frontline setting, patients with ABC-DLBCL have inferior outcomes following treatment with standard chemoimmunotherapy treatment (i.e., R-CHOP) when compared to those with GCB-DLBCL with 5-year OS rates of approximately 50% and 80%, respectively (Lenz 2008). The prognostication of cell of origin is less well-defined in the relapsed/refractory setting, but does appear to still have significance with differential outcomes based on the type of treatment received. For instance, GCB-type demonstrated better responses to R-DHAP in the Phase 3 CORAL Study, while ABC-type had higher responses in another study with bortezomib combined with chemotherapy (Thieblemont, 2011) (Dunleavy 2009)

The type of DLBCL based on cell of origin also appears to vary by region, which could contribute to regional differences in responses to treatment. There is a higher proportion of ABC-DLBCL (per GEP) or non-GCB DLBCL (per immunohistochemistry) in Asian countries. In the ROBUST study, a global Phase 3 study in frontline DLBCL, 60% of patients were found to be ABC-DLBCL in China, Japan, Korea, and Taiwan compared to 40% in Russia, Europe, and the Middle East and 37% in North America, Australia, and New Zealand (Nowakowski, 2020) (Nowakowski, 2021). Similar distributions of ABC-DLBCL or non-GCB-DLBCL were observed in other studies (Scott, 2014) (Yoon, 2017) (Shiozawa, 2007).

Given that cell of origin has prognostic significance with the potential for differential treatment responses, along with regional differences in prevalence, there is potential that COO contributed to the differences observed by region in the STARGLO trial.

Cell of origin (COO) classification, using gene expression profiling performed centrally via NanoString technology, was included as an exploratory endpoint in STARGLO. The COO determination per Nanostring testing occurred in 59% of patients in the STARGLO trial (FDA Table 9). Notably, of the 49% of the patients in the Asian Region with testing performed, 70% of the patients were characterized as ABC-DLBCL. This percentage was much lower in those patients enrolled in the Non-Asian region with 42% ABC-DLBCL identified (FDA Table 10). Although 41% of the patient results remain unknown, the regional difference observed in STARGLO demonstrates a predominance of ABC-DLBCL in Asian countries compared to Non-Asian countries, consistent with the findings in the literature. (Nowakowski, 2020). This regional difference in prevalence of ABC-DLBCL may have implications in the patient responses to either R-GemOx or Glofit-GemOx in the STARGLO trial and may have contributed to the differential treatment effects observed by region.

FDA Table 9: Cell of Origin (COO) GEP Testing Performed

Population	GEP Tested n (%)	Unknown n (%)
Total Population, n=274	161 (59%)	113 (41%)
Asian Region, n=131	64 (49%)	67 (51%)
Non-Asian Region, n=143	97 (68%)	46 (32%)

GEP: gene expression profiling using Nanostring technology
Source: FDA Analysis, Data cutoff: 16 February 2024

FDA Table 10: Cell of Origin based on by GEP Testing

Population	ABC-DLBCL n (%)	GCB-DLBCL n (%)	Unclassified DLBCL n (%)
Total Population, n=161	**86 (53%)**	59 (37%)	16 (10%)
Asian Region, n=64	**45 (70%)**	15 (23%)	4 (6%)
Non-Asian Region, n=97	**41 (42%)**	44 (45%)	12 (12%)

GEP: gene expression profiling; ABC: activated B-cell like; GCB: Germinal cell B-Cell like
Source: FDA Analysis, Data cutoff: 16 February 2024

As noted, patients with high-risk histologic DLBCL subtypes, including ABC subtype, have worse outcomes with chemoimmunotherapy compared to GBC subtypes (Nowakowski, 2015) (Rosenwald, 2002). R-GemOx administered on a de-intensified Q3week schedule, as done in the STARGLO trial may not be a preferred option for patients with aggressive disease. Patients enrolled in Asian regions were overall younger, with a high percentage of patients refusing transplant versus having functional comorbidities precluding transplant. This, in addition to the potential for more aggressive disease (ABC subtype and higher percentage of early relapsed patients), raises concerns that an R-GemOx comparator arm may have been suboptimal for this group of patients.

Prior Therapy Exposure

The intended patient population in the STARGLO trial was those patients with R/R DLBCL after at least 1 prior systemic therapy. The regional subgroups were similar with regards to the number of prior lines of therapy (FDA Table 11). Despite most patients being exposed to CD20-based and/or anthracycline based therapy, there were regional differences in other types of agents administered. While more patients in the Non-Asian Region had exposure to CAR-T therapy (13% Non-Asian Region versus 2% Asian Region), more patients in the Asian Region had exposure to lenalidomide-containing regimens (13% Asian Region versus 3% Non-Asian Region) and "other" therapies (15% Asian Region versus 2% Non-Asian Region). The exposure to therapy with lenalidomide and the multitude of other therapies in the Asian Region is not consistent with the therapies used in a U.S. patient population.

FDA Table 11: Regional Difference in Prior Lines of Therapy

Prior Lines of Therapy[a]	Non-Asian Region N=143 n (%)	Asian Region N=131 n (%)
Median lines (range)	1 (1,5)	1 (1,5)
Component of Prior Therapy (n %)		
Anthracycline	139 (97)	129 (98)
CD20 or CD19[b]	142 (99)	128 (98)
Platinum	31 (22)	36 (27)
Lenalidomide	**5 (3)**	**22 (13)**
Polatuzimab[c]	8 (6)	2 (2)
Radiotherapy	33 (23)	15 (11)
CAR-T	**19 (13)**	**2 (2)**
Stem Cell Transplant	7 (5)	4 (3)
Other[d]	**3 (2)**	**19 (15)**

[a] Radiotherapy not counted as separate line.

[b] CD19 immunotherapy: tafasitamab, which was in combination with lenalidomide

[c] Polatuzumab was in combination with Bendamustine and rituximab: Pola-BR

[d] Other regimens included: "clinical trial", PD1 inhibitors, BTK inhibitors, Selinexor, enzastaurin, BCL2 inhibitors, HDAC inhibitors, VEGR2 inhibitors, unknown

Source: FDA Analysis, Data cutoff: 16 February 2024

Baseline Disease Characteristics

Most other baseline disease characteristics that may influence response to treatment were generally similar with only small differences noted between patients enrolled in the Non-Asian and Asian regions as depicted in FDA Table 12. However, one notable exception was the percentage of patients who relapsed within 12 months of the first line of therapy. Over 80% of patients enrolled in the Asian Region as opposed to 64% in the Non-Asian Region had disease that was considered an early relapse. These patients may have disease that is more aggressive or harder-to-treat and associated with a poorer prognosis (Gisselbrecht, 2010).

FDA Table 12: Regional Difference in Baseline Disease Characteristics

Baseline Disease Characteristic	Non-Asian Region N=143 n (%)	Asian Region N=131 n (%)
Double Expressor: *MYC, BCL2*	22 (15)	28 (21)
Stage III-IV[a]	106 (74)	87 (66)
Bulky Disease	24 (17)	13 (10)
IPI score 4-5[a]	33 (23)	22 (17)
Primary Refractory Disease	76 (53)	77 (59)
Double Refractory[b]	75 (52)	77 (59)
Relapsed or Refractory within 12 months of first line therapy	**91 (64)**	**106 (81)**

[a] International prognostic index (IPI) factors in stage in addition to age>60 years, LDH, ECOG performance status, extranodal sites
[b] Refractory to both CD20 and anthracycline therapies
Source: FDA Analysis, Data cutoff: 16 February 2024

Taken together, the differences in patient and disease characteristics are concerning in terms of applicability of the trial results to a U.S. patient population. Forty-eight percent of the ITT population is comprised of patients enrolled in the Asian Region. This population is a younger, racially homogenous DLBCL patient population with higher rates of ABC-type DLBCL, and early relapsed disease than that observed in a U.S patient population. Importantly, a high number of these patients (65%) refused transplant. It is unclear if these patients would have qualified as "transplant ineligible" in the U.S., where transplant is utilized more and patient ineligibility is typically due to older age and comorbidites. Thus, these patients may not represent appropriate candidates for R-GemOx and may not be representative of the intended use population in the U.S.

Regional Differences in Trial Conduct and Processes

New Anti-Lymphoma Therapy (NALT)

In treatment for lymphoma, subsequent therapy following discontinuation of study treatment is termed "new anti-lymphoma therapy" or NALT. Ideally, the types of NALT available to patients are similar in all regions included in a trial, so that the impact of NALT reflects its availability relative to the disease and patient status as opposed to whether the therapy is available in that region due to differences in healthcare practices. The primary endpoint of the STARGLO trial is OS, which is an endpoint that incorporates the receipt of subsequent anti-lymphoma therapy. In assessing the applicability of the STARGLO trial OS results to a U.S patient

population and medical practice, the FDA assessed for regional differences in the frequency and type of NALT received.

Overall, a higher percentage of patients treated with R-GemOx proceeded onto at least one line of NALT (FDA Table 13). While the percentage of patients exposed to NALT was similar between regions, the type of NALT regimen received was different between regions. Examination of the components of NALT regimens revealed that novel therapies, such as CAR-T, bispecific T-cell Engagers (TCE), tafasitamab combined with lenalidomide (Taf+len), and polatuzumab vedotin combined with bendamustine and rituximab (Pola-BR), were utilized more frequently in the Non-Asian region. In this regard, the Non-Asian Region as opposed to the Asian Region is more similar to a U.S. patient population as these agents are available and commonly employed as part of U.S. standard of care for treatment in the R/R DLBCL setting. The differences in NALT regimens received suggests there are differences in the available treatments in these regions and raises uncertainty in the applicability of the results to a U.S. population.

Of note, the regional difference in NALT regimens was observed for both the R-GemOx and the Glofit-GemOx arms (FDA Table 13), suggesting the impact of these NALT regimens should affect both treatment arms.

FDA Table 13: Regional Difference in the Number and Type of NALTs Received per Arm

	Asian Region		Non-Asian Region	
	Glofit-GemOx N=83	R-GemOx N=46	Glofit-GemOx N=89	R-GemOx N=42
Number of patients with at least one NALT, n (%)[a]	19 (23%)	28 (61%)	27 (30%)	23 (55%)
Number of patients with at least one "novel" NALT, n(%)[ab]	5 (6%)	11 (24%)	17 (19%)	17 (40%)
ADC[c]	2 (2%)	2 (4%)	10 (11%)	4 (10%)
Taf + Len[d]	1 (1%)	0	3 (3%)	2 (5%)
CAR-T	1 (1%)	3 (7%)	7 (8%)	9 (21%)
TCE[e]	0	8 (17%)	2 (2%)	8 (19%)
SCT[f]	2 (2%)	0	0	1 (2%)

[a] Includes all treated patients (except obinutuzumab-only patients in Glofit-GemOx arm)
[b] More effective NALTs include ADC, Taf + Len, CAR-T, TCE, and SCT
[c] ADC: Antibody drug conjugate alone or in combination
[d] Taf+len: Tafasitamab and lenalidomide
[e] TCE: CD20 or CD19-directed CD3 T cell engager
[f] SCT: Stem cell transplantation (autologous or allogeneic)
Source: FDA Analysis, Data cutoff: 16 February 2024

Importantly, while FDA acknowledges that NALT may impact OS, NALT has minimal impact on PFS (via censoring) and does not impact ORR or CR. The observed differential treatment effects between regions remain for these endpoints, indicating that regional differences in NALT do not explain the study results.

Exploratory Analysis with Inverse Probability of Censoring Weights (IPCW)

The Applicant presents analyses using inverse probability of censoring weights (IPCW) to assess the impact of NALT on OS and PFS. The IPCW method is an observational-based approach which attempts to reweight patient data at time points based on the probability of receiving NALT. For each time point, higher weights are assigned to patients who have not received NALT relative to similar patients who have received NALT by that time point. The goal of IPCW is to estimate an alternative treatment effect under a hypothetical scenario in which NALT does not exist. That is, it targets a hypothetical estimand. This is in contrast to an ITT analysis of OS, which estimates the treatment effect in the presence of various NALTs. These differences are broadly described in FDA Table 14.

FDA Table 14: Estimands Targeted by the ITT and IPCW Analysis Approaches of OS

Analysis Approach	Estimand Targeted (Clinical Question Answered by Analysis)	Relevant Assumptions[a]
ITT	"What is the effect of Glo-GemOx vs. R-GemOx on OS, **regardless of NALT received**?"	The NALTs administered in the trial are representative of those administered in the proposed population.
IPCW	"What is the effect of Glo-GemOx vs. R-GemOx on OS, **in a hypothetical scenario where NALT is not available/cannot be given**?"	The probability of NALT can be correctly modeled.

[a] Not exhaustive. Assumptions summarized are those relevant to how NALT is handled in each analysis approach.

As noted in FDA Table 14, IPCW relies on correctly modeling the probability of being censored. Thus, the IPCW method requires stronger assumptions than the ITT method. In general, the IPCW method may not be able to completely overcome initial selection bias and cannot control for unobserved confounders. As a result, unmeasured confounding may still be present in the weighted observations as the weights may be biased. In addition, due to the imbalance on the percentage of patients receiving NALT between arms (56% in GemOx vs. 25% in Glofit-GemOx), the IPCW method may become less stable and confidence intervals may become wider, as shown in the Applicant's analysis (Figure 9 and Figure 10).

The clinical relevance of the IPCW analysis is marginal. In the context of STARGLO, IPCW allows for the estimation of treatment effects as if NALTs were absent. However, patients with

relapsed or refractory DLBCL who are transplant ineligible are likely to receive other subsequent therapies, thus NALT is a relevant part of a patient's overall treatment. In addition, the differential NALT received between Asian and Non-Asian regions in STARGLO suggest differences in available treatments. The inconsistent treatment effects observed in STARGLO could be indicative of differential treatment effects, which may be due in part to these differences.

The ITT analyses of OS remain the standard primary analysis in oncology. This is due to the minimal assumptions required and its ability to estimate the treatment effect in a treatment setting which includes elements of intended practice such as use of subsequent therapy.

Response Assessments: Frequency of Unscheduled, Early Assessments

The first protocol-specified tumor assessment was scheduled to occur between Day 15 to Day 21 of Cycle 4 for both arms. The Agency categorized patients into 3 groups based on the timing of their first post-screening tumor assessment: before Cycle 4, within Cycle 4, after Cycle 4. Among 274 patients in ITT, 234 had post-screening tumor assessments by IRC. The distribution of these groups is shown in FDA Table 15. The distribution of the first post-screening assessments is shown in FDA Figure 5, relative to the pre-specified Cycle 4 assessment (horizontal bar).

The Glofit-GemOx arm had a similar proportion of patients who had earlier tumor assessments across regions (17% vs. 20%). In contrast, the R-GemOx arm in the Asian Region had a much higher proportion of earlier tumor assessments compared to the Non-Asian Region R-GemOx arm (56% vs. 22%). Note that these percentages are of only the n=234 patients who had at least one post-screening tumor assessment. An analysis utilizing the ITT population (FDA Figure 10: Time to First Observed Efficacy Outcome per IRC) as well as other time-to-event analyses are provided in Appendix 19: Time to First Efficacy Assessment. The results are consistent with those presented in FDA Table 15 and FDA Figure 5.

FDA Table 15: Regional Difference in the Assessment Timing per Arm

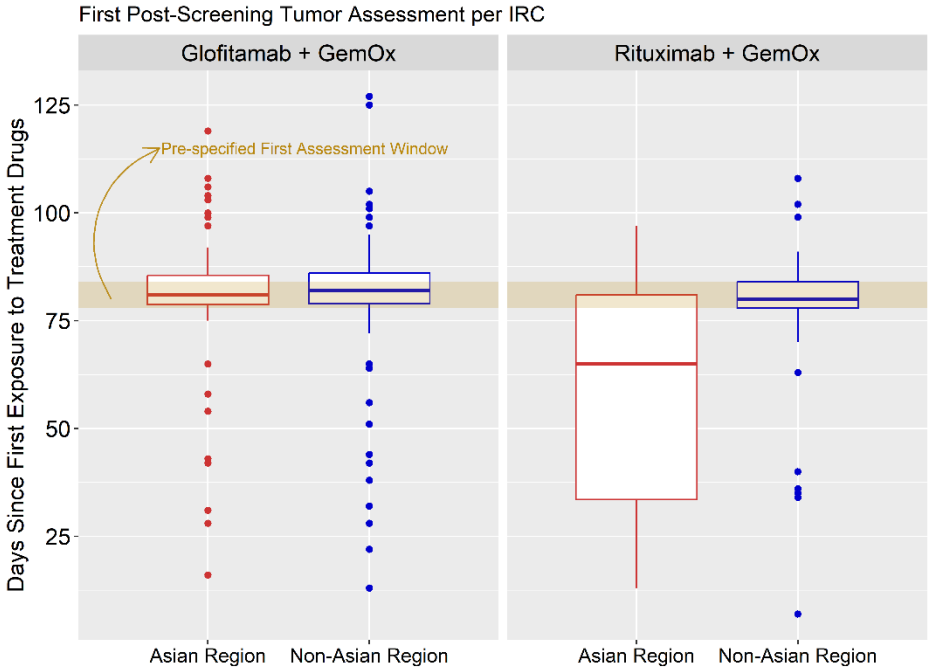
Assessment Timing[a]	Glofit-GemOx n (%)		R-GemOx n (%)	
	Asian Region (N=76)	Non-Asian Region (N=82)	Asian Region (N=39)	Non-Asian Region (N=37)
Earlier	13 (17%)	16 (20%)	**22 (56%)**	**8 (22%)**
Cycle 4[b]	41 (54%)	39 (48%)	12 (31%)	21 (57%)
Later	22 (29%)	27 (33%)	5 (13%)	8 (22%)

[a] 234 patients with post-screening tumor assessments

[b] Cycle 4 Interim Response per protocol: Day 15-21 of cycle 4: corresponds to approximately Study day 78-84

Source: FDA analysis, Data cutoff: 16 February 2024

FDA Figure 5: Regional Difference in the first Tumor Assessment Timing per Arm



Source: FDA Analysis, Data cutoff: 16 February 2024

To address this concern, the Applicant submitted reasons that triggered early tumor assessments that occurred before the pre-specified Cycle 4 assessment. Most of the early tumor assessments were triggered by progression symptoms. It is unclear why signs or symptoms of progression might have manifested so much earlier in the R-GemOx arm of the Asian region. Potential reasons include the open-label trial design and bias prompting early tumor assessments based on the knowledge of assignment to the control arm or the patients from the Asian region exhibiting high-risk intrinsic factors (e.g., early relapse, COO) leading to increased risk of progression. Taken together, these observations raise concern that the efficacy outcomes, especially of the R-GemOx arm, in the Asian region may not adequately reflect efficacy outcomes of those in the Non-Asian region.

Concordance of Tumor Assessments Between IRC and INV

FDA examined the concordance of tumor assessments across regions. Concordance is used to assess the overall agreement of IRC and investigator assessments. Low concordance or differential concordance may suggest that these assessments are poorly captured either due to inaccurate methodology or bias in data capture. The overall concordance rates of ORR, CR, and PFS are shown in FDA Table 16. The concordance rates are generally high in all subgroups

across various endpoints. However, in the Asian R-GemOx regional subgroup, a lower concordance rate of PFS assessments is observed compared to other subgroups.

FDA Table 16: Regional Difference on the Concordance of Tumor Assessment between IRC and Investigator per Arm

	ITT	Asian Region		Non-Asian Region	
		Glofit-GemOx N=84	R-GemOx N=47	Glofit-GemOx N=99	R-GemOx N=44
ORR	93%	94%	94%	96%	82%
CR	94%	93%	96%	94%	95%
PFS (status)[a]	95%	99%	**85%**	98%	93%
PFS (PFS time)[b]	82%	86%	**68%**	85%	84%

[a] Discordance only includes cases whose PFS event indicator is different between IRC and INV assessments
[b] Discordance includes cases whose (1) IRC indicates PFS event while INV indicates PFS censoring, vice versa; and (2) both IRC and INV indicate the same PFS status, but different PFS times
Source: FDA analysis, Data cutoff: 16 February 2024

This observation is noteworthy given the discrepancies observed in time to first response assessments in the Asian regional subgroup. These findings suggest that trial processes may have been different for the Asian R-GemOx subgroup and a concern for bias in the estimation of the associated treatment effects.

Treatment Exposure

The exposure to GemOx was generally shorter than the protocol specified 8 cycles (~5.5 months) in the R-GemOx arm compared to the Glofit-GemOx arm. While GemOx exposure in the Glofit-GemOx arm was similar between regions at a median exposures of 4.8 (Non-Asian Region) and 4.9 (Asian Region) months, it was substantially different between regions in the R-GemOx arm. The exposure for patients treated with R-GemOx in the Asian region was much shorter with a median exposure of 1.1 months compared to the median exposure of 3.1 months for those in the Non-Asian Region (FDA Table 17).

FDA Table 17: Regional Difference in the Treatment Exposure of GemOx Component per Arm

GemOx Component of Regimen		Glofit-GemOx		R-GemOx	
		Non-Asian Region N=97	Asian Region N=83	Non-Asian Region N=42	Asian Region N=46
Gemcitabine	Median Months Q1, Q3	4.8 0.9, 5.0	4.9 2.2, 5.2	**3.1** 1.2, 4.8	**1.1** 0.7, 2.5
Oxaliplatin	Median Months Q1, Q3	4.8 0.9, 5.0	4.8 2.2, 5.1	**3.1** 1.2, 4.8	**1.1** 0.7, 2.5

Q1: First quartile: 25th percentile; Q3: Third quartile: 75th percentile
Source: FDA Analysis, Data cutoff: 16 February 2024

Treatment Discontinuation

The discordant treatment exposure may also be reflected in the rate of discontinuation observed for patients in the R-GemOx Arm. There was a higher rate of discontinuation of R-GemOx for patients treated in the Asian Region at 78% compared to those patients treated in the Non-Asian region at 62%. For both regions, progressive disease was the most common reason for discontinuation. However, more patients discontinued R-GemOx due to progressive disease in the Asian Region than in Non-Asian region, accounting for 72% and 46% of the patients who discontinued study treatment, respectively (FDA Table 18). Again, it is unclear the exact reasons for the increase in progression in the patients in the Asian region, but it may potentially be related to the increased early response assessments due to bias and/or more aggressive underlying disease. Regardless, the differential outcome is of importance in generalizing these results to a U.S patient population.

FDA Table 18: Regional Difference in the Reasons for Treatment Discontinuation per Arm

	Glofit-GemOx N=180[a]		R-GemOx N=88[a]	
	Non-Asian Region n=97	Asian Region N=83	Non-Asian Region N=42	Asian Region N=46
Discontinued Treatment, n (%)	52 (54)	51 (61)	**26 (62)**	**36 (78)**
Reason for Discontinuation (n, % of discontinued)				
Progressive Disease	**20 (38)**	**20 (39)**	**12 (46)**	**26 (72)**
Adverse Event	**12 (23)**	**16 (31)**	**6 (23)**	**1 (3)**
Death	9 (17)	5 (10)	2 (8)	1 (3)
Withdrawal by Patient	3 (6)	4 (8)	1 (4)	3 (8)
Symptomatic Deterioration	4 (8)	0	2 (8)	2 (6)
Physician Decision	3 (6)	4 (8)	0	0
Lack of Efficacy	0	1 (2)	2 (8)	2 (6)
Other[b]	1 (2)	1 (2)	0	0
Protocol Deviation	0	0	1 (4)	0
Lost to Follow-up	0	0	0	1 (3)

[a] Actually treated (includes obinutuzumab only exposed)
[b] Other: CNS disease before treatment, toxicity.
Source: FDA Analysis, Data cutoff: 16 February 2024

Note that FDA Table 18 does not include patients who were randomized but not treated. There were 3/91 (3.3%) patients randomized-not-treated in the R-GemOx arm and 3/183 (1.6%) patients randomized-not-treated in the Glofit-GemOx arm. Further, Appendix 14: End of Treatment Disposition presents the end of treatment disposition by region and arm in the ITT population. Patients who are randomized-not-treated are counted as "Withdrawal by Subject". In the ITT population, 7/91 (7.7%) patients were considered withdrawn in the R-GemOx as compared to 7/183 (3.8%) in the Glofit-GemOx arm. Imbalances in patients who are randomized-not-treated or who withdrew from therapy may reflect differences in adherence stemming from knowledge of treatment assignment. Such differences in adherence can lead to biased estimation of the treatment effects observed.

Efficacy Conclusion:

The inconsistencies in the treatment effect between the Asian and Non-Asian regions of STARGLO are substantial. All major efficacy endpoints demonstrated inconsistent treatment effects between Asian and Non-Asian regions in the STARGLO trial. Multiple intrinsic and extrinsic factors related to outcomes have been identified in the FDA's analyses, including

regional differences in the baseline demographics and disease characteristics, and trial conduct and processes. These inconsistencies are summarized in FDA Table 19. Such regional differences and the associated factors could impact the generalizability of the STARGLO results to the U.S. population.

FDA Table 19: Summary of Evidence of Inconsistences Identified Between Subgroups Defined by Region in STARGLO

Factors	Notable Differences		Asian Region	Non-Asian Region
Differential treatment effect	OS Hazard ratio		0.39 (0.25, 0.63)	1.06 (0.61, 1.84)
	PFS Hazard ratio		0.25 (0.15, 0.41)	0.81 (0.48, 1.35)
	CR Risk Difference		43.7% (27.0%, 60.3%)	22.5% (3.8%, 41.2%)
	ORR Risk Difference		45.9% (28.5%, 63.3%)	8.8% (-10.2%, 27.8%)
	Interaction Test		p-value <0.05 for OS, PFS, and ORR	
Patient and disease-related factors	Demographics	Median Age	62	71
		Race (Asian)	100%	4%
		Ethnicity (Hispanic)	2%	9%
	Disease burden and histology	R/R within 12 months of 1L therapy	81%	64%
		COO (ABC-DLBCL)	70%	42%
	Treatment history	Prior therapy (CAR-T))	2%	13%
		Refused transplant	65%	7%
Treatment and Assessments	Exposure (in R-GemOx arm), median		1.1 months	3.1 months
	Concordance in response assessments		Concordance in PFS assessments lowest in R-GemOx arm of Asia region	
	Timing of efficacy assessments (earlier than scheduled for the first assessment in R-GemOx arm)		56%	22%
	Use of NALT (CAR-T) in R-GemOx		3 (7%)	9 (21%)
	Use of NALT (CAR-T) in Glofit-GemOx		1 (1%)	7 (8%)

Source: FDA summary

The specific reasons for the substantial difference in the treatment effect across multiple endpoints between patients treated in Asian Regions compared to Non-Asian regions is likely due to the culmination of multiple intrinsic and extrinsic factors. The differences in patient and disease characteristics and healthcare system factors identified suggest that the population enrolled in the Asian region, predominantly in China, represents a different and distinct

population than a U.S population with R/R DLBCL who are transplant ineligible. These differences likely led to the differential treatment effect observed between patients treated in Asian vs Non-Asian regions, raising uncertainty as to whether the results of the STARGLO trial are applicable to the intended U.S. patient population and U.S. medical practice.

3. Safety

The Applicant's Position:

3.1. Safety Overview

STARGLO was designed to compare the safety and tolerability of Glofit-GemOx compared with R-GemOx and importantly to be able to characterize the safety profile of the glofitamab combination to support the benefit/risk profile in patients with R/R DLBCL.

The safety risks with glofitamab monotherapy, GemOx and the control arm combination R-GemOx are shown in Table 7. For both the Glofit-GemOx and R-GemOx arms the AE profiles of the component parts of the combinations are well understood, expected and routinely managed by oncologists. The safety management plan as conducted in STARGLO provides clear guidance in the management of potential AEs by physicians and patients.

Table 7 Safety Risks for Glofitamab, GemOx and R-GemOx

Glofitamab	GemOx	R-GemOx
Cytokine Release Syndrome	Infusion related reactions	Infusion related reactions
Neurologic toxicity including ICANS	Neurologic toxicity (neuropathy)	Neurologic toxicity (neuropathy)
Neutropenia and Febrile Neutropenia	Hematological toxicity	Hematological toxicity
Serious Infections	Infections	Infections
Tumor Flare	Gastrointestinal side effects	Gastrointestinal side effects
Tumor Lysis Syndrome	Renal/Lung toxicity	Renal/Lung toxicity

ICANS=immune effector cell-associated neurotoxicity syndrome.
Source: Glofitamab USPI; Gemcitabine USPI; Oxaliplatin USPI; Rituximab USPI; Lopez et al. 2008; Mounier et al. 2013.

The overview of safety in STARGLO is presented in Table 8 for the glofitamab exposed population (all patients who received obinutuzumab pretreatment, GemOx and at least one dose of glofitamab). The glofitamab exposed population of the STARGLO study provides results that offer a comprehensive assessment of the safety profile of Glofit-GemOx. Importantly, patients remained on Glofit-GemOx therapy more than three times longer compared to R-GemOx (Table 9).

As expected, based on the known AEs for the regimen components, CRS is the most common AE reported with Glofit-GemOx. It is predominantly low grade and most frequently a first dose phenomenon following treatment with glofitamab (Appendix 9). Effective mitigation measures include the use of obinutuzumab pre-treatment 7 days before the first dose of glofitamab, step

up dosing regimen, and premedications including dexamethasone (Section 3.3). Nausea is the second most common AE with Glofit-GemOx which, with the exception of a single Grade 3 event, was Grade 1 or 2 in severity (Appendix 9). Other side effects described included infection, neurologic and hematologic AEs which are expected and routinely managed by oncologists (Section 3.3).

Overall, based on the review of the safety data from the STARGLO study as well as the extensive clinical program and post-marketing experience to date with glofitamab, the safety profile of Glofit-GemOx is well-characterized and consistent with established safety profiles of the individual agents (glofitamab, gemcitabine and oxaliplatin).

Table 8 Overview of Safety (STARGLO Updated Analysis)

	R-GemOx (N=88)	Glofit-GemOx (Glofit Exposed)[a] (N=172)
Total number of patients with at least one		
Grade 5 AE	4 (4.5%)	12 (7.0%)
COVID-19	0	3 (1.7%)[b]
Pneumonia	2 (2.3%)	1 (0.6%)
Septic shock	0	1 (0.6%)
Respiratory tract infection	0	1 (0.6%)[b]
Pneumonia bacterial	1 (1.1%)	0
Pneumonitis	0	2 (1.2%)
Acute respiratory distress syndrome	0	1 (0.6%)[b]
Multiple organ dysfunction syndrome	1 (1.1%)	1 (0.6%)
Cardiac arrest	0	1 (0.6%)
Cerebral hemorrhage	0	1 (0.6%)
Serious AE	15 (17.0%)	90 (52.3%)
Common Grade 3-4 AEs [c] (≥10%)	35 (39.8%)	129 (75.0%)
Anemia	8 (9.1%)	29 (16.9%)
Neutropenia	16 (18.2%)	61 (35.5%)
Febrile neutropenia	1 (1.1%)	5 (2.9%)
Thrombocytopenia	15 (17.0%)	47 (27.3%)
AE leading to withdrawal from Glofitamab/Rituximab	11 (12.5%)	36 (20.9%)
Other AEs of Interest		
CRS (ASTCT grading)	0	76 (44.2%)
Grade 1	0	54 (31.4%)
Grade 2	0	18 (10.5%)
Grade 3	0	4 (2.3%)
Neurological AEs	35 (39.8%)	102 (59.3%)
ICANS (clinically adjudicated) [d]	NA	4 (2.3%)
Infection and infestations AEs	26 (29.5%)	95 (55.2%)
Serious infections	11 (12.5%)	39 (22.7%)

Table 8 Overview of Safety (STARGLO Updated Analysis) (cont.)

AE = adverse event; AEGT = adverse event group term; ALT = alanine aminotransferase; AST = aspartate aminotransferase; ASTCT = American Society for Transplantation and Cellular Therapy; CRS = cytokine release syndrome; ICANS = immune effector cell-associated neurotoxicity syndrome; N/A = not applicable.

[a]"Glofitamab exposed population" = all patients who received obinutuzumab pretreatment, GemOx and at least one dose of glofitamab ("Glofit Exposed" population [n = 172]). 180 patients received any study treatment with 8 patients not going on to receive glofitamab (5 patients experienced adverse events, 2 died due to progressive disease and 1 patient withdrew) [b] These fatal AEs were identified as COVID-19 associated events defined as AEs occurring 7 days before a confirmed COVID-19 AE and up to 30 days after or anytime during the COVID-19 infection (Glofit-GemOx [Glofit Exposed]: 5 events; Glofit-GemOx [Any Treatment Exposed]: 7 events). [c]Anemia includes events with preferred terms of 'Anemia' and 'Hemoglobin decrease'. Neutropenia includes events with preferred terms of 'Neutropenia' and 'Neutrophil count decreased'. Thrombocytopenia includes events with preferred terms of 'Thrombocytopenia' and 'Platelet count decreased'. [d] Potential cases were identified using the ICANS adverse event group term (AEGT). Those cases were then clinically adjudicated to identify suspected or confirmed ICANS cases in the updated analysis.

Sources: t_ae_FATAL_SE_16FEB2024_41944 [ADSL, ADAE]; t_ae_COVAS2_FATAL_SE_16FEB2024_41944 [ADSL, ADAE]; l_ae_covas2_SE_16FEB2024_41944 [ADSL, ADAE]; t_ae_ctc_GA34_SE_16FEB2024_41944 [ADSL, ADAE] ; t_ae_DSC_SE_16FEB2024_41944 [ADSL, ADAE]; t_ae_ctc_heme_GA34_SE_16FEB2024_41944 [ADSL, ADAE].

3.2. Exposure

The median duration of treatment was notably different between the two arms (Glofit-GemOx: 218 days vs. R-GemOx: 64 days) (Table 9), primarily due to higher discontinuations due to disease progression in the R-GemOx arm. Discontinuations due to disease progression leading up to and including the first response assessments were 15.0% in the Glofit-GemOx arm vs. 40.9% in the R-GemOx arm.

Table 9 Treatment Exposure in Patients who Received at least One Dose of Study Drug (STARGLO Updated Analysis)

Median (range)	R-GemOx (n = 88)			Glofit-GemOx (n = 172)		
	Rituximab	Gemcitabine	Oxaliplatin	Glofitamab	Gemcitabine	Oxaliplatin
Number of infusions	4.0 (1–8)	4.0 (1–8)	4.0 (1–8)	12.0[a] (1–14)	8.0 (1–9)	8.0 (1–9)
Total cumulative dose [b]	1488.2 (366.7–3379.0)	3997.7 (1000–8314.7)	396.2 (99.0–810.5)	303.8 (2.5–355.0)	7882.75 (465.1–9000.0)	788.53 (97.8–900.0)
Total duration, days	64.0 (1–183)	63.0 (1–183)	63.0 (1–183)	218 (1–296)	147.0 (1–241)	147.0 (1–241)
Number of treatment cycles	4.0 (1–8)	4.0 (1–8)	4.0 (1–8)	11.0 (1–13) [c]	8.0 (1–9) [d]	8.0 (1–9) [d]

[a] During step-up dosing in Cycle 1, multiple infusions of glofitamab were administered, thus the median number of glofitamab cycles and infusions was not equal. [b] Dose units: rituximab/gemcitabine/oxaliplatin: mg/m^2; glofitamab: mg. [c]For one patient, the first step-up dosing cycle was repeated and reported in an unscheduled visit, which was counted as an additional cycle. [d] For one patient an extra GemOx infusion was reported. Source: t_ex_SE_16FEB2024_41944 [ADSL, ADEX].

3.3. Summary of AEs

The incidence of AEs was higher with Glofit-GemOx than with R-GemOx (Table 8), however, this needs to be contextualized with the longer treatment exposure to Glofit-GemOx (Table 9). In addition, some AEs such as CRS are specific to glofitamab while others such as peripheral neuropathy reflect cumulative toxicity associated with longer treatment with chemotherapy components (GemOx) of Glofit-GemOx compared to the R-GemOx arm.

Grade 5 AEs

Grade 5 (fatal) AEs were reported in a greater proportion of patients in the Glofit-GemOx arm compared with the R-GemOx arm (12 patients [7.0%] versus 4 patients [4.5%]). Fatal events in both arms were primarily due to infections. In the Glofit-GemOx arm, 5 out of 12 fatal events were related to COVID-19. No COVID-19-related deaths occurred in the US. The observed fatal COVID-19 associated events all occurred in 2021-2022 during changing COVID-19 pandemic policies (Hale et al. 2021) with the majority occurring prior to the widespread use of effective COVID-19 therapies such as nirmatrelvir/ritonavir and varying COVID-19 vaccination uptake in recruiting countries (The New York Times 2025). All fatal events also occurred prior to changes to study conduct in 2022 as recommended by independent Data Monitoring Committee (iDMC) mandating patients with COVID-19 need to discontinue treatment

Serious Adverse Events (SAEs)

SAEs were reported in a greater proportion of patients in the Glofit-GemOx arm compared with the R-GemOx arm (Table 8). The most common SAE was CRS, a recognized risk with glofitamab,

which was mostly low grade, reversible and most frequently a first dose phenomenon that reduces in frequency with subsequent doses (Appendix 8; Appendix 9). The management of CRS with bispecific antibodies such as glofitamab is well-understood (Crombie et al. 2024). With appropriate HCP education and detection of early signs and symptoms of CRS, AEs in patients can be managed quickly and appropriately to reduce the potential for more severe events.

Grade 3-4 AEs

While Grade 3-4 AEs were reported in a greater proportion of patients in the Glofit-GemOx arm compared with the R-GemOx arm (Table 8), the majority of Grade 3-4 events reported were primarily hematologic abnormalities consistent with glofitamab in combination with GemOx (Table 8) and the low withdrawal rate (0.6%) with glofitamab indicates hematologic AEs with the Glofit-GemOx regimen are expected, tolerable and effectively managed.

Neurologic AEs

Neurological AEs are a known risk associated with CD20-CD3 antibodies and with GemOx. Neurologic AEs were reported in a greater proportion of patients in the Glofit-GemOx arm compared with the R-GemOx arm, of which 10 (5.8%) and 0 (0.0%), respectively, were Grade ≥3. The primary neurologic AE reported in both arms was peripheral sensory neuropathy (including neuropathy peripheral; Glofit-GemOx: 26.2% vs. R-GemOx: 15.9%).
All peripheral neuropathy events except two (both Grade 3) were Grade 1-2 in severity. Peripheral neuropathy is expected with GemOx and higher rates for Glofit-GemOx may be a consequence of a higher median duration of treatment compared to R-GemOx (218 days versus 64 days). Events consistent with immune effector cell-associated neurotoxicity syndrome (ICANS) were reported rarely in the Glofit-GemOx arm with 4 events, predominantly of low grade, which all occurred with CRS events and resolved (Appendix 9). As such the neurologic toxicity profile with Glofit-GemOx is well understood.

Infections

Infection AEs (any grade) were reported in a greater proportion of patients in the Glofit-GemOx arm compared with the R-GemOx arm (Table 8). COVID-19 was the most commonly reported infection: Glofit-GemOx (28/172 patients [16.3%]) compared with R-GemOx (8/88 patients [9.1%]). Aside from COVID-19, in both the Glofit-GemOx and R-GemOx arms, pneumonia (12.2% vs. 4.5%), upper respiratory tract infections (9.3% vs. 2.3%) and lower respiratory tract infections (4.1% vs. 1.1%) were the next most commonly reported infection AEs. Grade 3-4 infection AEs were reported more frequently in the Glofit-GemOx arm compared to R-GemOx arm (16.9% vs. 9.1%).

The infection risk profile of Glofit-GemOx is consistent with that of the individual study drugs considering overlapping toxicity and the impacts of COVID-19 (Appendix 9). Kyvsgaard et al (2024) show that with appropriate and effective COVID-19 management, patients can be treated relatively safely with glofitamab. In addition, existing management guidelines for glofitamab outlines that dosing in the presence of an active infection is contraindicated and provide recommendations on antimicrobial prophylaxis to further mitigate risk and overlapping toxicity. As such infection risk is monitorable and well understood.

AEs leading to withdrawal

AEs leading to withdrawal from glofitamab/rituximab were reported in a greater proportion of patients in the Glofit-GemOx arm (36/172 patients: 20.9%) compared with the R-GemOx arm (11/88 patients: 12.5%) (Table 8).

These withdrawals were mostly due to COVID-19, as the iDMC overseeing the trial required in August 2022 that patients who developed COVID-19 were to discontinue any study treatment. This requirement was implemented during evolving understanding of management of COVID-19. Following the iDMC recommendation, no patients on treatment with either Glofit-GemOx (n=106) or R-GemOx (n=34) experienced a fatal COVID-19 event. Considering the impacts of the COVID-19 pandemic and the cumulative exposure to chemotherapy on the Glofit-GemOx arm, due to a higher proportion of patients remaining on study treatment for longer, the AEs leading to any treatment discontinuation are consistent with the expected risks of Glofit-GemOx.

Safety by Subgroups

Due to the small sample size of North America and in accordance with ICH E17, the safety profile is presented as NA/EUR/AUS vs. Asia. Similar total number of deaths, Grade 5, Grade 3-5 AEs, CRS and ICANS were noted between NA/EUR/AUS and Asia (Table 10).
SAEs were more frequent in NA/EUR/AUS than in Asia, primarily due to serious CRS events and infections. Only one patient in Europe discontinued treatment due to a CRS event.

While higher numbers of serious infections were noted in NA/EUR/AUS in the Glofit-GemOx arm (27.0% vs. 18.1%), treatment discontinuations due to an infection were lower compared to Asia (11.2% vs. 16.9%) which were driven by COVID-19 discontinuations (11.2% vs. 15.7%), mainly due to an iDMC mandate requiring discontinuation for any COVID-19 event (5.6% vs. 10.8%).

Grade 3-4 hematological AEs were more frequent in Asia, though this may be influenced by the trend of increased reporting of laboratory abnormalities as AEs in the region. Notably, with these higher rates of hematologic AEs, there were no observed trends correlating excessive hematologic related AEs (e.g. infections with neutropenia or bleeding events with thrombocytopenia) to higher rates of hematologic abnormalities in Asia (Table 10).

Table 10 Safety in NA/EUR/AUS and Asia Subgroups (STARGLO Updated Analysis)

	R-GemOx		Glofit-GemOx (Glofit Exposed)	
	NA/EUR/AUS[d] N=42	Asia[e] N=46	NA/EUR/AUS[d] N=89	Asia[e] N=83
Total number of deaths, n (%)	18 (42.9%)	33 (71.7%)	38 (42.7%)	36 (43.4%)
Grade 5 AEs	2 (4.8%)	2 (4.3%)	7 (7.9%)	5 (6.0%)
Grade 3-5 AE	18 (42.9%)	18 (39.1%)	68 (76.4%)	64 (77.1%)
Serious AE	8 (19.0%)	7 (15.2%)	57 (64.0%)	33 (39.8%)
AE leading to withdrawal from glofitamab/rituximab	8 (19.0%)	3 (6.5%)	16 (18.0%)	20 (24.1%)

	R-GemOx		Glofit-GemOx (Glofit Exposed)	
	NA/EUR/AUS[d] N=42	Asia[e] N=46	NA/EUR/AUS[d] N=89	Asia[e] N=83
CRS (ASTCT grading)	-	-	41 (46.1%)	35 (42.2%)
Neurological AEs[a]	21 (50.0%)	14 (30.4%)	61 (68.5%)	41 (49.4%)
ICANS (clinically adjudicated)[b]	-	-	2 (2.2%)	2 (2.4%)
Infection and infestations AEs	16 (38.1%)	10 (21.7%)	51 (57.3%)	44 (53.0%)
Serious infections	5 (11.9%)	6 (13.0%)	24 (27.0%)	15 (18.1%)
COVID-19 Infections	6 (14.3%)	2 (4.3%)	14 (15.7%)	16 (19.3%)
COVID-19 fatal AEs	0	0	3 (3.4%)	2 (2.4%)
COVID-19 treatment discontinuations	4 (9.5%)	1 (2.2)	10 (11.2%)	13 (15.7%)
COVID-19 discontinuations due to iDMC mandate	4 (9.5%)	1 (2.2)	5 (5.6%)	9 (10.8%)
Hematological adverse events (HAEs)[c]				
Anemia (Any Grade) Grade 3-4	 10 (23.8%) 5 (11.9%)	 9 (19.6%) 3 (6.5%)	 29 (32.6%) 18 (20.2%)	 42 (50.6%) 11 (13.3%)
Neutropenia (Any Grade) Grade 3-4	 12 (28.6%) 7 (16.7%)	 15 (32.6%) 9 (19.6%)	 27 (30.3%) 24 (27.0%)	 49 (59.0%) 37 (34.5%)
Febrile Neutropenia (Any Grade) Grade 3-4	 0 0	 1 (2.2%) 1 (2.2%)	 3 (3.4%) 3 (3.4%)	 2 (2.4%) 2 (2.4%)
Thrombocytopenia (Any Grade) Grade 3-4	 14 (33.3%) 8 (19.0%)	 28 (60.9%) 7 (15.2%)	 29 (32.6%) 23 (25.8%)	 58 (69.9%) 24 (29.0%)
HAE Leading to withdrawal of Rituximab or Glofitamab	2 (4.8%)	0	0	1 (1.2%)

AE = adverse event; AEGT = adverse event group term; ASTCT = American Society for Transplantation and Cellular Therapy; CRS = cytokine release syndrome; Glofit-GemOx = glofitamab in combination with gemcitabine plus oxaliplatin; HAE = hematological adverse events; ICANS = immune effector cell-associated neurotoxicity syndrome; iDMC = independent Data Monitoring Committee; R-GemOx = rituximab in combination with gemcitabine plus oxaliplatin; SOC = system organ class. [a] AEs from Nervous system disorder SOC and Psychiatric disorder SOC. [b] Events from ICANS AEGT and post-clinical adjudication. [c] Includes anemia, hemoglobin decreased, neutropenia, neutrophil count decreased, thrombocytopenia, and platelet count decreased. [d] North America, Europe, and Australia. [e] China, Taiwan, and South Korea.

Sources: t_ae_ctc_subgrp_REG2_WD_SE_16FEB2024_41944 [ADSL, ADAE]; t_ae_ctc_heme_subgrp_REG2_SE_16FEB2024_41944 [ADSL, ADAE]; t_ae_ctc_subgrp_REG2_COVAS2_SE_16FEB2024_41944 [ADSL, ADAE; t_ae_ctc_subgrp_REG2_SER_SE_16FEB2024_41944 [ADSL, ADAE]; t_ae_ctc_subgrp_REG2_SE_16FEB2024_41944 [ADSL, ADAE; t_ae_oview_subgrp_REG2_SE_16FEB2024_41944 [ADSL, ADAE]; t_ae_ctc_subgrp_REG2_FATAL_SE_16FEB2024_41944 [ADSL, ADAE; t_ae_ctc_subgrp_REG2_NEUR_16FEB2024_41944 [ADSL, ADAE]; t_ae_ctc_subgrp_REG2_COV_ADIL_ENADIL_SE_16FEB2024_41944 [ADSL, ADAE]; t_ae_ctc_subgrp_REG2_COVAS2_DSC_SE_16FEB2024_41944 [ADSL, ADAE].

3.4. Safety Conclusions

The data from STARGLO allows for a thorough assessment of the safety profile of glofitamab in combination with GemOx in the intended patient population, including characterization of common AEs and SAEs, and informing labeling and risk management strategies. This profile is consistent with the known risks for glofitamab monotherapy (as outlined in the USPI) and the individual study drugs (Keshishyan et al. 2018, Devanabanda 2024). Differences in the safety profile of Glofit-GemOx compared to R-GemOx reflect a number of factors including drug specific risks such as CRS with glofitamab, the timing of conduct of STARGLO study during the COVID-19 pandemic (with evolving understanding COVID-19 management), overlapping toxicity or cumulative toxicity from the GemOx backbone expected due to a larger median number of cycles of treatment received with Glofit-GemOx. Glofit-GemOx has a well-characterized safety profile and is supported by robust safety management guidance.

The FDA's Position on Safety:

Overall, the FDA agrees with the Applicant's position pertaining to the safety of the Glofit-GemOx and R-GemOx regimens. The FDA independently reviewed the safety profiles of the regimens in both the ITT population as well as by region (FDA Table 20).

FDA Table *20*: The Safety Profile of the Regimens per Arm

	Glofit-GemOx n (%)			**R-GemOx n (%)**		
	ITT N=172	Non-Asian Region N=89	Asian Region N=83	ITT N=88	Non-Asian Region N=42	Asian Region n=46
All Grade AE	172 (100)	89 (100)	83 (100)	84 (95)	39 (93)	45 (98)
Serious AE	90 (52)	57 (64)	33 (40)	15 (17)	8 (19)	7 (15)
Grade 3-4 AE	120 (70)	61 (69)	59 (71)	32 (36)	16 (38)	16 (35)
Grade 5 AE	12 (7)	7 (8)	5 (6)	4 (5)	2 (5)	2 (4)

ITT: Intent-to-treat population; AE: Adverse event
Source: FDA Analysis, Data cutoff: 16 February 2024

The only regional differences the FDA noted were in infections and neurotoxicity rates (FDA Table 20 and FDA Table 21). Generally, the infection and neurotoxicity differences were small or differed for low grade events. Thus, these differences likely did not impact the outcomes of the overall study.

FDA Table 21: Regional Difference on the Infection Rates by Arm

		Glofit-GemOx n (%)		R-GemOx n (%)	
		Non-Asian Region N=89	Asian Region N=83	Non-Asian Region N=42	Asian Region N=46
Infections and Infestations (SOC)	Any Grade	51 (57)	44 (53)	16 (38)	10 (22)
	Grade 3-4	19 (21)	12 (14)	5 (12)	4 (9)
	Grade 5	4 (5)	1 (2)	1 (2)	2 (4)
COVID-19 (GT)	Any Grade	13 (15)	16 (19)	6 (14)	2 (4)
	Grade 3-4	3 (3)	3 (4)	1 (2)	1 (2)
	Grade 5	1 (1)	2 (2)	0	0
Pneumonia (GT)	Any Grade	11 (12)	13 (16)	1 (2)	4 (9)
	Grade 3-4	4 (5)	7 (8)	0	2 (4)
	Grade 5	1 (1)	0	1 (2)	2 (4)
Opportunistic Infections (GT)	Any Grade	1 (1)	20 (24)	0	2 (4)
	Grade 3-4	0	3 (4)	0	1 (2)
	Grade 5	0	0	0	0

SOC: System Organ Class; GT: FDA Grouped Term
Source: FDA Analysis, Data cutoff: 16 February 2024

FDA Table 22: Regional Difference on the Neurotoxicity Rates by Arm

		Glofit-GemOx n (%)		R-GemOx n (%)	
		Non-Asian Region N=89	Asian Region N=83	Non-Asian Region N=42	Asian Region N=46
Neurotoxicity (GT)	Any Grade	41 (46)	14 (17)	16 (38)	3 (7)
	Grade 3-4	2 (2)	3 (4)	0	0
	Grade 5	0	0	0	0
Peripheral neuropathy and paresthesia (GT)	Any Grade	44 (49)	17 (20)	15 (36)	5 (11)
	Grade 3-4	1 (1)	1 (1)	0	0
	Grade 5	0	0	0	0

GT: FDA Grouped Term
Source: FDA Analysis, Data cutoff: 16 February 2024

The STARGLO trial is a "substitution trial" where rituximab in R-GemOx is substituted with glofitamab-gxbm (Glofit-GemOx). Comparing the two arms demonstrated increased overall adverse events, specifically serious, severe, and fatal events in the Glofit-GemOx arm compared to the comparator. The increased AEs, such as CRS, neurotoxicity, infections, and cytopenias are known side effects following treatment with glofitamab. Yet, it is notable that the substitution of glofitamab-gxbm yields an increase in acute risk with CRS and neurotoxicity along with increased rates of serious infections and Grade 3-4 cytopenias compared to R-GemOx. Further, because of the exposure differences between arms, a safety analysis based on cycle cutoffs was conducted (

FDA Table 23), which suggests a higher AE rate with Glofit-GemOx compared to R-GemOx independent of the exposure difference.

FDA Table 23: The Safety Profile of Regimens per Arm by Cycle Cutoffs

	Glofit-GemOx n (%)			R-GemOx n (%)		
	Any AE	Grade 3-4 AE	Grade 5 AE	Any AE	Grade 3-4 AE	Grade 5 AE
Cycle 1-2[a] n=160; n=75	155 (97)	84 (53)	3 (3)	73 (97)	22 (29)	1 (1)
Cycle 1-4[a] n=145; n=49	144 (99)	87 (60)	2 (1)	48 (98)	22 (45)	1 (2)
Cycle 1-6[a] n=121; n=31	120 (99)	77 (64)	0	30 (97)	12 (39)	1 (3)
Cycle 1-8[a] n=111; n=26	111 (100)	74 (67)	1 (1)	26 (96)	10 (38)	0
Cycle 1-12[a] n=77; n=0	77 (100)	56 (73)	0	n/a	n/a	n/a

AE: Adverse Event; n/a: not applicable
[a] Based on patients who received treatment for that duration (n=Glo-GemOx; n=R-GemOx). AEs counted are those up to 30 days after the last cycle listed.
Source: FDA Analysis, Data cutoff: 16 February 2024

Patient-reported outcomes (PROs) were collected in STARGLO which could have informed tolerability, however the data quality was not adequate to yield meaningful interpretation of results. There were too few patients in the R-GemOx arm at many assessment timepoints to make any comparison between arms due to the study design (2:1 randomization), attrition, and poor PRO compliance in the follow-up phase. For example, the number of patients in the R-GemOx arm at Cycles 5 and 7 were 35 and 28, respectively. Furthermore, there was high and asymmetric missingness in post-treatment phase, preferentially in the R-GemOx arm. For example, only 55% of patients treated with R-GemOx expected to complete a PRO assessment at follow-up month 3, 6, and 9 actually did so. At the same timepoints, >70% of eligible patients in the Glofit-GemOx arm completed PROs. Therefore, FDA urges caution in making conclusions based on PRO data given these significant data quality issues.

4. Other Significant Issues Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Applicability of STARGLO Study Results to US patients

The Applicant's Position:

DLBCL is a global disease and the incidence rates across regions are comparable (Wang 2023). Medical practices, including pathological classification, diagnosis, staging, initial treatment and relapse management, are similarly approached worldwide (NCCN 2025; ESMO; CSCO; ALA). The consistency of a patient's journey across geographic regions supports the generalizability of the STARGLO results to US patients and US medical practice.

STARGLO was designed as a multiregional clinical trial (MRCT) to provide globally applicable results by generating robust evidence across various geographic regions. Developed in consultation with the FDA, the study aligns with global standards for well-designed and executed MRCTs (ICH E17). Clinical trial sites across regions were selected with investigators who have extensive experience conducting Phase 3 trials in NHL. Importantly, STARGLO is a randomized study with a comparator arm relevant to the US and it utilizes OS as its primary endpoint, which is a reliable and unbiased measure of both efficacy and safety.

Notably, the overall population (ITT) median OS of the R-GemOx control arm was highly consistent with real-world outcomes in the US (Budde et al. 2024 (Flatiron) mOS 12.7 months; Yamshon et al. 2024 (LEO Consortium) mOS 13.5 months; Appendix 7). Furthermore, the compelling benefit observed with Glofit-GemOx in the overall study population is considered relevant to US patients, as baseline disease characteristics in the overall study closely resemble those of US patients with R/R DLBCL who currently receive R-GemOx in both the community and academic settings (Table 11).

Table 11 Comparison of Baseline Characteristics of ITT Population from STARGLO and US Real World Data Sources for R-GemOx

	Study GO41944 (STARGLO)			GO45305 Flatiron RWD Budde et al. 2024	LEO CReWE RWD Yamshon et al. 2024
Characteristic	R-GemOx (N = 91)	Glofit-GemOx (N = 183)	ITT (N = 274)	R-GemOx (N = 281)	R-GemOx (N = 183)
Age in years (median, range)	68 (20 – 84)	68 (22 – 88)	68 (20-88)	71 (22-85)	68 (21-88)
Elderly patients	62% (age≥ 65)	63% (age≥ 65)	63% (age ≥ 65) 43% (age ≥ 70)	68% (age ≥ 65)	39% (age ≥ 70)
White race	36%	45%	42%	78%	NR
Histology (DLBCL NOS)	100%	100%	100%	86%[a]	87%
Transformed lymphoma	NA	NA	NA	22%[a]	13%
ECOG 0-1	88%	88%	88%	71%	79%
IPI score 3-5	52%	48%	49%	NR	38%
Stage III/IV	77%	67%	70%	NR	83%
Prior lines of therapy (median, range)[b]	1 (1-4)	1 (1-4)	1 (1-4)	1 (1-7)	2 (1-7)
Prior anti-CD20	98%	99%	99%	99%	NR
Prior anthracycline	99%	98%	98%	89%	98%
Primary refractory	69%[c]	73%[c]	72%[c]	69%[c]	72%[d]
Refractory to last prior line	59%	61%	61%	77%	NR
Prior SCT	3%	4%	4%	10%	19%
Prior CAR T-cell therapy	9%	7%	8%	1%	5%

DLBCL = diffuse large B-cell lymphoma; ECOG = Eastern Cooperative Oncology Group; CAR-T = chimeric antigen receptor T-cell; Glofit-GemOx = glofitamab in combination with gemcitabine plus oxaliplatin; IPI = International Prognostic Index; NA = not applicable; NOS = not otherwise specified; NR = not reported; R-GemOx = rituximab in combination with gemcitabine plus oxaliplatin; RWD = real world data; SCT = stem cell transplant.

[a]DLBCL NOS histology the Flatiron database is reported independent of transformed disease status. [b] Indicates lines of therapy for DLBCL i.e. lines of therapy after transformation in patients with transformed disease. [c] Primary refractory is defined as no CR to first-line of therapy or relapse within 6 months following a CR to first-line of therapy. [d] Primary refractory is defined as no CR to first-line of therapy or relapse within 12 months following a CR to first-line of therapy.

Sources (STARGLO): t_cm_prior_T_IT_16FEB2024_41944 [ADSL, ADCM]; t_dm_T_IT_16FEB2024_41944 [ADSL, ADSUB]; t_mh_char_T_IT_16FEB2024_41944 [ADSL, ADSUB, ADCM].

Based on extensive subgroup assessment (Section 2.3.2.3; Appendix 5), the Applicant did not identify any reason to believe there is a true underlying difference in the treatment effect across regional subgroups. The North America subgroup poses substantial limitations in interpretation due to a small sample size (n=25) making the findings most likely driven by the imbalance in prognostic factors at baseline in this subgroup and/or by chance. In larger regional subgroups, the observed results were more consistent with the global population but were influenced by varied use of highly effective NALT (including CAR-T therapy and bispecific agents). The use of highly-effective NALT in NA/EUR/AUS led to an unprecedented median OS for the R-GemOx arm (mOS = 27.8 months; Section 2.3.2.3) that has not been observed in any prior clinical trial or real world data.

Despite the consistent availability of highly effective NALT across the global study regions, utilization varied primarily due to access barriers, including socioeconomic determinants. Access to potentially curative salvage therapies clearly has the potential to impact outcomes such as OS. However, the varying utilization of these therapies by region supports published data indicating that access barriers faced by US patients are similarly encountered in other countries across the globe such as China (Battiwalla et al. 2025; Hwang et al. 2023; Mikhael et al. 2022). This underscores the need for more effective treatment options for patients with transplant-ineligible R/R DLBCL both in the US and globally.

Patients have multiple dimensions; specifically, no single, individual characteristic is indicative of their treatment benefit. While exploratory subgroup analyses are an established methodology to interrogate clinical trial results, univariate subgroup analyses fail to adequately capture the holistic situation of a patient with DLBCL because treatment effects are impacted by the interplay of multiple patient factors (ICH E5).

MRCTs enable the assessment of heterogeneity in genetic, physiological, cultural, and environmental factors (e.g. healthcare systems) on dosing, safety, and efficacy in the overall trial population and across different regions (ICH E17). For this reason, MRCTs are recognized as the most valuable clinical research tool, providing a robust framework for testing specific hypotheses and extrapolating study results. The FDA's recent oncology MRCT guidance (FDA 2024) emphasizes the importance of US patient representativeness, investigator site selection, and considerations of disease, available treatments and medical products for applicability to US patients and US medical practice.

Applicability of the STARGLO results to US patients and US medical practice rests on the reliability of this well-designed and conducted trial with established and clinically relevant endpoints evaluating a patient population representative of US patients with R/R DLBCL. Despite lower-than-expected enrollment of US patients primarily due to COVID-19 restrictions, the comprehensive PK, safety and efficacy data from STARGLO confirm the positive benefit/risk of Glofit-GemOx for transplant-ineligible patients with R/R DLBCL, including those in the US.

The FDA's Position on Applicability of STARGLO Results to a U.S. Patient Population and U.S. Medical Practice:

The FDA's draft guidance on "Generating Clinical Evidence from Oncology Multiregional Clinical Development Programs" emphasizes that the primary consideration for the FDA when assessing multiregional oncology trials is the applicability of results to the intended use population in the United States and to U.S. standard oncological medical care. Evidence generated from these studies should be derived from study populations that allow for interpretation of results within the context of U.S. patients with the disease or condition and U.S. medical practice standards.

In trials where an adequate proportion of the population is enrolled in the United States or regions similar to the United States, the generalizability of the overall study results is less

concerning. However, in the case of the STARGLO trial, given the limited U.S. patient enrollment (9% of the Intent-to-Treat population, with 15 patients treated on the Glofit-GemOx arm and 10 patients on the R-GemOx arm) and the observed differential treatment effect between regional subgroups, the extrapolation of study results to the U.S. patient population and U.S. medical practice is less certain. The STARGLO trial presents a notable imbalance in its distribution of patient enrollment, with nearly half of the Intent-to-Treat (ITT) population recruited from the Asian Region. Specifically, 48% of the ITT population consisted of patients enrolled in China, Taiwan, and Korea with 29% of patients enrolling from China. As previously noted, the protocol specified that at least 80 patients from China be enrolled "in order to characterize the efficacy and safety profile of glofitamab in addition to GemOx to potentially support a marketing application in China" (protocol v1). The protocol did not include such requirements for the Non-Asian countries to ensure a more evenly distributed population.

Efficacy outcomes observed in patients from the Asian Region demonstrated marked improvements in survival and disease response. In contrast, the remaining half of the population, comprising patients enrolled in Australia, North America, and Europe, showed markedly different efficacy outcomes. The efficacy measures observed in the patients enrolled from the Asian Region seemed to have exerted a strong influence on the overall STARGLO trial results. Notably, the presence of such significant inconsistencies between these two large regional subgroups in the STARGLO trial raises concerns about the robustness of the overall study results.

Given the potential substantial impact of the results from patients enrolled in the Asian Region on the overall outcomes, the Agency conducted a thorough assessment of key factors characterizing this population. This evaluation aimed to determine whether these results could be applicable to the U.S. patient population and align with U.S. standard oncological care practices in the treatment of relapsed/refractory diffuse large B-cell lymphoma (R/R DLBCL). The STARGLO Trial revealed significant differences between the patient population enrolled in the Asian Region based on intrinsic and extrinsic factors to what would be expected in a comparable U.S. patient population with relapsed/refractory diffuse large B-cell lymphoma (R/R DLBCL) following one prior line of therapy and considered ineligible for autologous stem cell transplantation.

5. Points for the Advisory Committee to Consider

The Applicant's Position:

DLBCL is an aggressive disease that can advance rapidly. It is the most common subtype of NHL and leads to death within months if left untreated. While a proportion of patients with DLBCL can be cured with first-line therapy, up to 40% will experience relapsed or refractory disease, reducing their chances of long-term survival. The confirmation of relapse is a devastating life event for patients as they are faced with the realization of a diminishing chance of cure and the prospect of further treatment related burden.

Even intensive therapies with curative potential, such as ASCT and CART-cell therapy, face limitations in eligibility, accessibility and patient preference, potentially leaving up to 75% of patients with R/R DLBCL dependent on non-curative treatments focused on disease management. This highlights the ongoing need for a variety of accessible treatment options to address individual needs of patients with R/R DLBCL that can improve long-term survival prospects.

For more than two decades, starting with the development of rituximab, Genentech/Roche has conducted rigorous multiregional Phase 3 trials in NHL. The STARGLO study, designed in 2019 in consultation with FDA, is a multiregional, randomized, open-label, Phase 3 trial. It aims to produce globally applicable results in a representative population of patients with R/R DLBCL who are ineligible for transplant. The study evaluates the benefit-risk profile of Glofit-GemOx compared to R-GemOx in these patients.

The robust design of the STARGLO study included OS as the primary endpoint, the most reliable and preferred endpoint in oncology (FDA 2018), with PFS, CR rate and DOCR as clinically relevant key secondary endpoints. Patients were randomized 2:1 and stratified by previous therapies and disease status, factors known to influence treatment outcome in DLBCL.

Glofitamab is the first CD20xCD3 bispecific antibody, and the first therapy for transplant-ineligible patients with R/R DLBCL, to confer a survival benefit in transplant-ineligible R/R DLBCL in a randomized Phase 3 trial.

STARGLO showed that Glofit-GemOx reduced the risk of death by 41% (HR 0.59, p=0.010706), the risk of progression by 63% (HR 0.37, p<0.000001), and more than doubled the CR rate (50.3% vs. 22.0%, p<0.0001) compared to a US relevant control arm, R-GemOx. With an additional 11 months of follow-up, benefits were maintained, reaching a median OS of 25.5 months, nearly doubling what was seen for patients treated with R-GemOx at a median OS of 12.9 months. Sensitivity analyses further confirmed the robustness of these results.

Exploratory subgroup analyses generally showed a benefit consistent with the overall treatment effect across most subgroups, including the clinically relevant stratification factors. However, subgroups based on region and race exhibited higher hazard ratios. Given the consistent PK, efficacy and safety by region demonstrated in glofitamab monotherapy studies, similar outcomes were expected for Glofit-GemOx across different geographical regions. This was supported by the STARGLO study's PK and exposure-response analyses, which showed similar glofitamab PK characteristics and exposure-response profile across regions.

Further exploration of STARGLO data indicated that the observed outcomes in the NA/EUR/AUS subgroup were primarily influenced by NALT. Adjustments to account for the impact of NALT resulted in numerical reductions in HR estimates for OS and PFS, bringing them closer in line with the overall population results. Importantly, the totality of data shows that there is no consistent evidence suggesting true underlying difference in treatment effects across region

and race. The subgroup analyses are not powered to show differences and are not considered to be representative of the true clinical benefit of glofitamab. The most relevant assessment of the treatment effect should be based on the results from the overall study population.

STARGLO demonstrated compelling and consistent clinical benefit across multiple clinical endpoints with Glofit-GemOx, along with an AE profile that is consistent with the known risks for the individual drugs that form the Glofit-GemOx regimen. Glofit-GemOx has a well-characterized safety profile which is supported by robust safety management guidance. The study represents a critical advancement in treating patients with R/R DLBCL. Importantly, the trial was designed to be globally applicable and enrolled a patient population resembling a typical DLBCL population in the US. The trial was executed with adherence to global standards and sensitivity and post hoc analyses further support the robustness of the findings, reinforcing that the overall study's conclusions remain valid. The totality of evidence underscores the applicability and reliability of its outcomes, promising a positive impact on patient care in the US.

Reflecting the clinical relevance of these findings and potential utility in US medical practice, Glofit-GemOx has also been recognized as a Category 1 preferred treatment in the 2025 NCCN guidelines, based on the results from the STARGLO study (NCCN 2025).

Glofit-GemOx is an accessible T cell engaging therapy for patients with R/R DLBCL who face a poor prognosis and are ineligible for transplant. It provides a transformative treatment that leverages the patient’s own immune system to fight lymphoma. This therapy ensures that all relapsing patients and their physicians have the choice of an important novel treatment modality with proven and meaningful efficacy. The availability of multiple treatment options with curative potential allows for truly personalized care, addressing the individual complexities of relapsed disease and ultimately improving patient outcomes. For patients in the US who do not benefit from or lack access to other potentially curative therapies, Glofit-GemOx can be quickly initiated in any setting and meaningfully addresses the urgent needs of an aggressive and life-threatening disease.

The FDA's Position:

Multiregional trials have numerous advantages, such as allowing rapid accrual and more efficient clinical development by generating evidence to support use of a drug in multiple regions. One additional benefit of multiregional clinical trials is the potential to identify factors that may predict regional treatment differences. However, typically this regional difference is identified prior to implementation of the trial and measures are taken to ensure that the trial will still produce statistically robust and clinically meaningful results that are applicable to the intended use population. Per the ICH E17 guidance, multiregional clinical trials should be "planned under the assumption that the treatment effect applies to the entire target population, particularly to the regions included in the trial." (ICH E17). This guidance also stipulates that intrinsic and/or extrinsic factors could be present that may have an impact on patients' response to therapies differently across regions. Therefore, these factors should be considered with planning multiregional trials. Studies should ensure an effective assessment of the consistency of a treatment. In cases where a major difference is expected in treatment effects, the ICH E17 guidance notes that multiregional trials can still be conducted but may require exclusion of some regions or a defined subgroup within a region.

The STARGLO trial exhibited a notable regional effect, potentially amplified by the disproportionate representation of Asian regional participants in the ITT population. The study was characterized by limited enrollment from the United States and significant regional disparities in overall survival, progression-free survival, and response rate/complete response outcomes. Multiple patient-specific factors were identified as potential contributors to these regional differences, including patient age, reasons for transplant ineligibility, exposure to types of prior therapies, cell of origin characterization, and discontinuation rate due to progressive disease. Additionally, aspects of trial conduct and analyses may have further influenced the divergent results observed between Asian and Non-Asian regions, including the timing of disease assessments, differences in exposure and treatment discontinuation, and potential bias. These observed differences and their potential contributing factors raise substantial concerns regarding both the robustness of the trial results and their applicability to the intended United States patient population. Consequently, these findings warrant careful consideration in the interpretation and generalizability of the STARGLO trial results

6. References

Applicant References:

Abramson JS, Ku M, Hertzberg M, et al. Glofitamab plus gemcitabine and oxaliplatin (GemOx) versus rituximab-GemOx for relapsed or refractory diffuse large B-cell lymphoma (STARGLO): a global phase 3, randomised, open-label trial. Lancet. 2024 Nov 16;404(10466):1940-1954.

Alosh M, Huque M, Bretz F, et al. Tutorial on statistical considerations on subgroup analysis in confirmatory clinical trials. Stat Med. 2016;36:1334–60.

Amy S. Ruppert, Jesse G. et al. International prognostic indices in diffuse large B-cell lymphoma: a comparison of IPI, R-IPI, and NCCN-IPI. *Blood* 2020; 135 (23): 2041–2048.

Auletta JJ, Khera N, DeMartino P, et al. Assessing Medicaid Coverage for Hematopoietic Cell Transplantation and Chimeric Antigen Receptor T Cell Therapy: A Project from the American Society for Transplantation and Cellular Therapy and the National Marrow Donor Program ACCESS Initiative. Transplant Cell Ther. 2023 Nov;29(11):713-720.

Battiwalla M, Tees M, Flinn I, et al. Access barriers to anti-CD19+ CART therapy for NHL across a community transplant and cellular therapy network. Blood Adv. 2025 Jan 28;9(2):429-435.

Breyanzi (lisocabtagene maraleucel) United States Prescribing Information. Available at: https://www.fda.gov/media/145711/download?attachment.

Budde E, Olszewski J, Hu Bei, et al. Characterizing the US Patient Population Receiving Rituximab with Gemcitabine and Oxaliplatin (R-GemOx) for Relapsed or Refractory Diffuse Large B-cell Lymphoma Using Real-World Data [abstract]. American Society of Hematology. 2024;1-3; Flatiron Health RWD data on file (2011-2024).

Cazelles C, Belhadj K, Vellemans H, et al. Rituximab plus gemcitabine and oxaliplatin (R-GemOx) in refractory/relapsed diffuse large B-cell lymphoma: a real-life study in patients ineligible for autologous stem-cell transplantation. Leuk Lymphoma 2021;62(9):2161-8.

Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for initial evaluation, staging and response assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification. J Clin Oncol 2014;32(27):3059–68.

Columvi (glofitamab-gxbm) United States Prescribing Information. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/761309s000lbl.pdf.

Corazzelli G, Capobianco G, Arcamone M, et al. Long-term results of gemcitabine plus oxaliplatin with and without rituximab as salvage treatment for transplant-ineligible patients with refractory/relapsing B-cell lymphoma. Cancer chemotherapy and pharmacology. 2009;64:907-16.

Crombie JL, Graff T, Falchi L et al. Consensus recommendations on the management of toxicity associated with CD3×CD20 bispecific antibody therapy. Blood. 2024 Apr 18;143(16):1565-1575.

Crump M, Neelapu SS, Farooq U, et al. Outcomes in refractory diffuse large B-cell lymphoma: results from the international SCHOLAR-1 study. Blood. 2017 Oct 19;130(16):1800-1808.

Devanabanda B, Kasi A. Oxaliplatin. StatPearls Publishing, 2024.

Dhanapal V, Gunasekara M, Lianwea C, et al. Outcome for patients with relapsed/refractory aggressive lymphoma treated with gemcitabine and oxaliplatin with or without rituximab; a retrospective, multicentre study. Leukemia & Lymphoma. 2017;58(9):2051-6.

Dickinson MJ, Carlo-Stella C, Morschhauser F, et al. Glofitamab for Relapsed or Refractory Diffuse Large B-Cell Lymphoma. N Engl J Med. 2022 Dec 15;387(24):2220–31.

Duarte C, Kamdar M. Management Considerations for Patients with Primary Refractory and Early Relapsed Diffuse Large B-Cell Lymphoma. Am Soc Clin Oncol Educ Book. 2023 Jan;43:e390802.

El Gnaoui T, Dupuis J, Belhadj K, et al. Rituximab, gemcitabine and oxaliplatin: an effective salvage regimen for patients with relapsed or refractory B-cell lymphoma not candidates for high-dose therapy. Ann Oncol. 2007 Aug; 18(8):1363–8.

Emole J, Lawal O, Lupak O, et al. Demographic differences among patients treated with chimeric antigen receptor T-cell therapy in the United States. Cancer Med. 2022 Dec;11(23):4440-4448.

Flowers CR, Odejide OO. Sequencing therapy in relapsed DLBCL. Hematology Am Soc Hematol Educ Program. 2022 Dec 9;2022(1):146-154.

Food and Drug Administration (FDA). Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics Guidance for Industry. December 2018. Available at: https://www.fda.gov/media/71195/download.
Food and Drug Administration (FDA). Considerations for Generating Clinical Evidence from Oncology Multiregional Clinical Development Programs Guidance for Industry Draft Guidance. September 2024. Available at: https://www.fda.gov/media/181824/download.
García-Domínguez DJ, Hontecillas-Prieto L, et al. Tumor Immune Microenvironment in Lymphoma: Focus on Epigenetics. Cancers. 2022; 14(6):1469.
Gemcitabine United States Prescribing Information. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/209604s003lbl.pdf.
George TJ, Lin TL, Adrales Bentz T, et al. Quantifying the impact of the COVID-19 pandemic on cancer center clinical trial operations. JNCI Cancer Spectr. 2023 Jul 3;7(4):pkad048.
Hale T, Angrist N, Goldszmidt R, et al. A global panel database of pandemic policies (Oxford COVID-19 Government Response Tracker). Nat Hum Behav. 2021 Apr;5(4):529-38.
Hayashi K, Nagasaki E, Kan S, et al. Gemcitabine enhances rituximab-mediated complement-dependent cytotoxicity to B cell lymphoma by CD20 upregulation. Cancer Sci. 2016 May;107(5):682-9. Epub 2016 Apr 7.
Held G, Altmann B, Kerkhoff A, et al. R-GemOx plus Nivolumab vs R-GemOx as second-line therapy for transplant-ineligible patients: interim analysis of the Niveau Trial, an international, randomized Phase 3 study of the AGMT, GLA, HOVON, Lysa and PLRG. Blood 142 (Supp 1): 435. 2 Nov 2023.
Hwang WY, Takahashi S, Choi B, et al. Challenges in Global Access to CAR-T cells: an Asian Perspective. Blood Cell Ther. 2023 Dec 28;7(1):10-13.
ICH E5. Ethnic Factors in the Acceptability of Foreign Clinical Data., 1998. Available at: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/e5-ethnic-factors-acceptability-foreign-clinical-data.
ICH E17. General Principles for Planning and Design of Multi-regional Clinical Trials, 2018. Available at: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/e17-general-principles-planning-and-design-multi-regional-clinical-trials.
IPSOS Global Oncology Monitors. Available at: https://www.ipsos.com/en/healthcare/global-oncology-monitors; IPSOS Therapy Monitor data on file (2022-2024).
Jacobson CA, Munoz J, Sun F, et al. Real-World Outcomes with Chimeric Antigen Receptor T Cell Therapies in Large B Cell Lymphoma: A Systematic Review and Meta-Analysis. Transplant Cell Ther. 2024 Jan;30(1):77.e1-77.e15. Epub 2023 Oct 27.
Kamdar M, Solomon SR, Arnason J, et al. Lisocabtagene maraleucel versus standard of care with salvage chemotherapy followed by autologous stem cell transplantation as second-line treatment in patients with relapsed or refractory large B-cell lymphoma (TRANSFORM): results from an interim analysis of an open-label, randomised, phase 3 trial. Lancet 2022;399(10343):2294–308. Erratum in: Lancet 2022;400(10347):160.
Keshishyan S, Nguyen HL, Afolabi OD, et al. Chapter 45 - cytostatic agents. In: Ray SD, ed. Side effects of drugs annual. Elsevier, 2018: 569–77. 35.
Koff JL, Larson MC, Martin P et al. LEO Consortium for Real World Evidence (CReWE): Outcomes after Second-Line Therapy in Large B-Cell Lymphoma by Treatment Era. *Blood* (2023) 142 (Supplement 1): 307.
Kyvsgaard ER, Riley C, Clausen MR, et al. Low mortality from COVID-19 infection in patients with B-cell lymphoma after bispecific CD20xCD3 therapy. Br J Haematol. 2024 Jan;204(1):356-360.
Larson AC, Doty KR, Solheim JC. The double life of a chemotherapy drug: Immunomodulatory functions of gemcitabine in cancer. Cancer Med. 2024 May;13(10):e7287.
Latimer, Nicholas R, and Keith R Abrams. NICE DSU technical support document 16: adjusting survival time estimates in the presence of treatment switching. An update to TSD 16 (2024).
Locke FL, Miklos DB, Jacobson CA, et al. All ZUMA-7 Investigators and Contributing Kite Members. Axicabtagene Ciloleucel as Second-Line Therapy for Large B-Cell Lymphoma. N Engl J Med. 2022 Feb 17;386(7):640–54.
Lopez A, Gutierrez A, Palacios A et al. GEMOX-R regimen is a highly effective salvage regimen in patients with refractory/relapsing diffuse large-cell lymphoma: a Phase II study. Eur J Haematol 2008;80(2):127–32.
McDonald K, Seltzer E, Lu M, et al. Quantifying the impact of the COVID-19 pandemic on clinical trial screening rates over time in 37 countries. Trials. 2023 Apr 4;24(1):254.

Mikhael J, Fowler J, Shah N. Chimeric Antigen Receptor T-Cell Therapies: Barriers and Solutions to Access. JCO Oncol Pract. 2022 Dec;18(12):800-807.
Mounier N, El Gnaoui T, Tilly H, et al. Rituximab plus gemcitabine and oxaliplatin in patients with refractory/relapsed diffuse large B-cell lymphoma who are not candidates for high-dose therapy. A Phase II Lymphoma Study Association trial. Haematologica 2013;98:1726-31.
National Cancer Institute, SEER. Cancer Stat Facts: NHL — Diffuse Large B-Cell Lymphoma (DLBCL). Available at: https://seer.cancer.gov/statfacts/html/dlbcl.html.
National Comprehensive Cancer Network (NCCN). Clinical practice guidelines in oncology (NCCN Guidelines) B-cell lymphomas (Version 2.2025).
New York Times. Tracking Coronavirus Vaccinations Around the World. Available at https://www.nytimes.com/interactive/2021/world/covid-vaccinations-tracker.html.
Oxaliplatin United States Prescribing Information. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/022160s010lbl.pdf.
Philip T, Guglielmi C, Hagenbeek A, et al. Autologous bone marrow transplantation as compared with salvage chemotherapy in relapses of chemotherapy-sensitive non Hodgkins lymphoma. N Engl J Med 1995;333:1540–5.
Rituximab United States Prescribing Information. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/103705s5311lbl.pdf.
Rongshuang Z, Mingzhi Z. Clinical comparative study of R-GemOx regimen and R-GDP regimen as second-line regimens for patients with relapsed or refractory diffuse large B-cell lymphoma. Journal of Basic and Clinical Oncology. 2021:(3). Abstract in English.
Sehn L and Salles G. Diffuse large B cell lymphoma. N Engl J Med. 2021 Mar 4; 384(9): 842–58.
Sineshaw HM, Zettler CM, Prescott J, et al. Real-world patient characteristics, treatment patterns, and treatment outcomes of patients with diffuse large B-cell lymphoma by line of therapy. Cancer Med. 2024 Apr;13(7):e7173.
Song YQ, Zhang HL, Huang HQ, et al. Glofitamab monotherapy induces high complete response rates and manageable safety in Chinese patients with heavily pretreated relapsed or refractory diffuse large B-cell lymphoma. Haematologica. 2024 Apr 1;109(4):1269-1273.
Tilly H, Gomes da Silva M, Vitolo U, et al. Diffuse large B-cell lymphoma (DLBCL): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2015;26:v116-25.
United States Census Bureau. Available at: https://www.census.gov/library/stories/2024/12/population-estimates.html.
Wang S, Wang L, Hu J, et al. Outcomes in refractory diffuse large B-cell lymphoma: results from a multicenter real-world study in China. Cancer Commun (Lond). 2021 Mar;41(3):229-239.
Wang SS. Epidemiology and etiology of diffuse large B-cell lymphoma. Semin Hematol. 2023 Nov;60(5):255-266.
Westin J and Sehn L. CAR T cells as a second-line therapy for large B-cell lymphoma: a paradigm shift? Blood 2002;139(18)2737-2746.
Wight J, Hamad N, Campbell BA, et al. Diffuse large B-cell lymphoma: a consensus practice statement from the Australasian Lymphoma Alliance. Intern Med J. 2022 Sep;52(9):1609-1623.
Wittes, Janet Turk. “Why Is This Subgroup Different from All Other Subgroups? Thoughts on Regional Differences in Randomized Clinical Trials.” (2013).
Yamshon S, Koff JL, Larson MC, et al. Outcomes of Relapsed or Refractory Diffuse Large B-Cell Lymphoma Treated with R-GemOx: A Multi-Center Cohort Study, 2024 (abstract).
Yescarta (axicabtagene ciloleucel). United States Prescribing Information. Available at: https://www.fda.gov/media/108377/download?attachment.
Zhang H, Wang H, Fu K, et al. Comparative study of R-GemOx and RICE regimens as second-line treatments for refractory or relapsed DLBCL. Chinese Journal of Clinical Oncology. 2011;38(18):1107-10.
Zhu J, Ma J; Union for China Lymphoma Investigators of Chinese Society of Clinical Oncology. Chinese Society of Clinical Oncology (CSCO) diagnosis and treatment guidelines for malignant lymphoma 2021 (English version). Chin J Cancer Res. 2021 Jun 30;33(3):289-301.

Additional FDA References:

Alizadeh, A. A., Eisen, M. B., Davis, R. E., et al. (2000). Distinct types of diffuse large B-cell lymphoma identified by gene expression profiling. Nature, 403(6769), 503-511. https://doi.org/10.1038/35000501

BLA 761309 S-001, Applicant Submission 9/20/2024. Module 2, Clinical Summary page 36, and Updated CSR GO41944 Report, COVID-19 Appendix, Section 3.2.1.

Corazzelli, G., et al. (2015). Long-term results of gemcitabine plus oxaliplatin with and without rituximab as salvage treatment for transplant-ineligible patients with refractory/relapsing B-cell lymphoma. Cancer Chemotherapy and Pharmacology, 76(1), 169-177.

Crump, M. (2016). Management of Relapsed Diffuse Large B-cell Lymphoma. Hematol Oncol Clin North Am, 30(6), 1195-1213. https://doi.org/10.1016/j.hoc.2016.07.004

Cusatis R, Litovich C, et al. (2024) Current Trends and Outcomes in Cellular Therapy Activity in the United States, Including Prospective Patient-Reported Outcomes Data Collection in the Center for International Blood and Marrow Transplant Research Registry. Transplant Cell Ther. 30(9):917.e1-917.e12.

Dunleavy K, Pittaluga S, Czuczman MS, et al. (2009). Differential efficacy of bortezomib plus chemotherapy within molecular subtypes of diffuse large B-cell lymphoma. Blood. Jun 11;113(24):6069-76. doi: 10.1182/blood-2009-01-199679. Epub 2009 Apr 20. PMID: 19380866; PMCID: PMC2699229.

Flannelly C, Tan BE, et al. Barriers to Hematopoietic Cell Transplantation for Adults in the United States: A Systematic Review with a Focus on Age. Biol Blood Marrow Transplant. 2020;26(12):2335-2345.

Gisselbrecht C, Glass B, Mounier N, et al. (2010). Salvage regimens with autologous transplantation for relapsed large B-cell lymphoma in the rituximab era. J Clin Oncol 28:4184-4190.

Goede, V., Fischer, K., Engelke, A., et al. (2015). Obinutuzumab as frontline treatment of chronic lymphocytic leukemia: updated results of the CLL11 study. Leukemia, 29(7), 1602-1604. https://doi.org/10.1038/leu.2015.14

Lazarus, H. M., Carreras, J., Boudreau, C., et. al. (2008). Influence of age and histology on outcome in adult non-Hodgkin lymphoma patients undergoing autologous hematopoietic cell transplantation (HCT): a report from the Center For International Blood & Marrow Transplant Research (CIBMTR). Biol Blood Marrow Transplant, 14(12), 1323-1333.
https://doi.org/10.1016/j.bbmt.2008.09.008

Lenz, G., Wright, G. W., Emre, N. C., et al. (2008). Molecular subtypes of diffuse large B-cell lymphoma arise by distinct genetic pathways. Proc Natl Acad Sci U S A, 105(36), 13520-13525.

Maurer MJ, Jakobsen LH, Mwangi R, et al. (2021), Relapsed/Refractory International Prognostic Index (R/R-IPI): an international prognostic calculator for relapsed/refractory diffuse large B-cell lymphoma. Am J Hematol;96(5):599-605.

Nowakowski, G. S., Chiappella, A., Gascoyne, R. D., et al. (2021). ROBUST: A Phase III Study of Lenalidomide Plus R-CHOP Versus Placebo Plus R-CHOP in Previously Untreated Patients With ABC-Type Diffuse Large B-Cell Lymphoma. J Clin Oncol, 39(12), 1317-1328.
https://doi.org/10.1200/JCO.20.01366

Nowakowski, G. S., Chiappella, A., Witzig, et al. (2020). Variable global distribution of cell-of-origin from the ROBUST phase III study in diffuse large B-cell lymphoma. Haematologica, 105(2), e72-e75. https://doi.org/10.3324/haematol.2019.220475

Nowakowski, G. S., & Czuczman, M. S. (2015). ABC, GCB, and Double-Hit Diffuse Large B-Cell Lymphoma: Does Subtype Make a Difference in Therapy Selection? Am Soc Clin Oncol Educ Book, e449-457. https://doi.org/10.14694/EdBook_AM.2015.35.e449

Passweg, J. R., Baldomero, H., Alexander, T., et al. (2025). Utilization of hematopoietic cell transplantation and cellular therapy technology in Europe and associated Countries. Using the 2022 activity survey data to correlate with economic and demographic factors. A report from the EBMT. Bone Marrow Transplant, 60(2), 227-236. https://doi.org/10.1038/s41409-024-02459-0

Phillips AA, Smith DA. (2017). Health Disparities and the Global Landscape of Lymphoma Care Today. Am Soc Clin Oncol Educ Book; 37:526-534.

Rosenwald, A., et al. (2002). The use of molecular profiling to predict survival after chemotherapy for diffuse large-B-cell lymphoma. N Engl J Med, 346(25), 1937-1947. https://doi.org/10.1056/NEJMoa012914

Scott, D. W., Mottok, A., Ennishi, D., et al. (2015). Prognostic Significance of Diffuse Large B-Cell Lymphoma Cell of Origin Determined by Digital Gene Expression in Formalin-Fixed Paraffin-Embedded Tissue Biopsies. J Clin Oncol, 33(26), 2848-2856. https://doi.org/10.1200/JCO.2014.60.2383

Shiozawa, E., Yamochi-Onizuka, T., Takimoto, M., et al. (2007). The GCB subtype of diffuse large B-cell lymphoma is less frequent in Asian countries. Leuk Res, 31(11), 1579-1583. https://doi.org/10.1016/j.leukres.2007.03.017

Townsend, W., Hiddemann, W., Buske, et al. (2023). Obinutuzumab Versus Rituximab Immunochemotherapy in Previously Untreated iNHL: Final Results From the GALLIUM Study. Hemasphere, 7(7), e919. https://doi.org/10.1097/HS9.0000000000000919

Thieblemont C, Briere J, Mounier N, et. al. (2011). The germinal center/activated B-cell subclassification has a prognostic impact for response to salvage therapy in relapsed/refractory diffuse large B-cell lymphoma: a bio-CORAL study. J Clin Oncol. Nov 1;29(31):4079-87.

Vaughn JL, Soroka O, et al. (2021). Racial and ethnic differences in the utilization of autologous transplantation for lymphoma in the United States. Cancer Med. 10(20):7330-7338.

Yoon, N., Ahn, S., Yong Yoo, et al. (2017). Cell-of-origin of diffuse large B-cell lymphomas determined by the Lymph2Cx assay: better prognostic indicator than Hans algorithm. Oncotarget, 8(13), 22014-22022. https://doi.org/10.18632/oncotarget.15782

7. Appendix

Appendix 1: Regulatory History of Key Interactions with FDA Regarding the Development of Glofit-GemOx in R/R DLBCL

Date	Type of Interaction/Meeting	Purpose of Interaction/Meeting
20 December 2019	Type B End of Phase 2/ Pre-Phase 3 (Teleconference)	To discuss the development program and registration strategy for glofitamab in R/R B-cell lymphoma after one line of systemic therapy (Reference ID: 4541080). FDA noted the proposed design of the Phase 3 study including the primary endpoint of OS was acceptable. Additionally, the Agency acknowledged the secondary endpoints, the patient population, the use of R-GemOx as comparator, and the stratification factors are reasonable. The nonclinical package and proposed clinical pharmacology plan appeared sufficient and reasonable. The proposed safety monitoring plan and safety database with the majority of patients having at least 6 months of follow-up appeared reasonable. FDA provided additional comments and guidance regarding the PRO measurement strategy. FDA provided feedback on the proposed statistical considerations, noting the proposed interim analyses appeared reasonable and requesting a competing risk sensitivity analysis.
04 January 2023	Type C Content and Format (Written Responses Only)	To obtain feedback regarding the proposed content and format of the sBLA to enable regular approval for the proposed indication in R/R DLBCL (Reference ID: 5104274). FDA recommended removing DOR as a key secondary endpoint due to it being a subgroup analysis. The Applicant chose to retain DOR and acknowledged FDA will not formally assess it. FDA noted the precision of OS results from the interim analysis may be affected due to immature data and differential enrollment across sites. While the interim analysis for efficacy is at the Sponsor's discretion, FDA emphasized continued patient follow-up for efficacy and safety if the trial stops early. FDA requested pooled datasets for analysis, including subject level data, adverse event data, lab data, and summary exposure, along with an integrated death dataset. FDA found the proposed safety narrative categories acceptable and suggested additional considerations. The proposed plan for population PK and exposure-response analyses for safety and efficacy appeared reasonable to FDA. FDA requested justification for the glofitamab dosing regimen with GemOx. The proposed follow-up plan and assessment of COVID-19's impact on STARGLO were deemed reasonable by FDA.
27 July 2023	STARGLO Primary Analysis Results	To provide FDA topline results from the primary analysis of STARGLO as well as a supporting document including interpretation of results and additional context regarding next steps stating the Applicant's plan to conduct a follow-up analysis in a pre-identified manner to ensure sufficient follow-up to better characterize the overall benefit-risk assessment.
17 April 2024	STARGLO Update Analysis Results	To provide FDA topline results from the update analysis of STARGLO which includes an additional 11 months of follow-up from primary analysis.
05 June 2024	Type B Pre-sBLA (Videoconference)	To discuss the results from the primary and updated analyses from pivotal STARGLO as well as the final results from supportive Study GO41943 and obtain feedback on the acceptability of the results to form the basis of an sBLA for approval of COLUMVI in the proposed indication (Reference ID: 5394610). FDA advised the Applicant that the sBLA should address the applicability of the data to the US patient population and include a comprehensive assessment of safety.

FDA = Food and Drug Administration; OS = overall survival; PRO = patient-reported outcome, sBLA = supplemental Biologics License Application; R/R = relapsed or refractory; DLBCL = diffuse large B-cell lymphoma; DOR = duration of response; PK = Pharmacokinetics; R-GemOx = rituximab in combination with gemcitabine plus oxaliplatin.

FDA Position

The following additional interactions occurred after the interim analysis in July of 2023:
The Agency expressed concerns regarding the inconsistent treatment results and requested that the Applicant provide additional analysis of efficacy and safety per Asian and Non-Asian regions. The Agency also requested justification for the planned additional analysis time.
The Applicant indicated the proposed additional analysis time was to provide adequate follow-up for the later enrolling Non-Asian regions to allow for additional OS follow-up and for additional safety data collection given COVID-related safety concerns. Refer to section The FDA's Position on Regulatory History.

Appendix 2: Major Protocol Amendments

The original global protocol dated 9 April 2020 was amended seven times. The key changes to the protocol are summarized below in Table 12.

Table 12 Summary of Select Key Changes to the Protocol

Protocol Amendment Version, Date	**Summary of Key Changes**
Version 2, 19 November 2020	Amended to require dexamethasone as a premedication prior to glofitamab in Cycles 1-3, to clarify the definition of patients with relapsed vs refractory disease, and to provide additional instructions for the prevention and management of CRS.
Version 3, 29 March 2021	Amended to limit the percentage of patients enrolled with platinum-refractory disease to 20% of randomized patients; to limit the percentage of patients enrolled who have had ≥2 lines of prior therapy; to establish a non-binding futility analysis at the time of interim analysis; and to clarify inclusion/exclusion criteria, duration of AE monitoring, and study rationale.
Version 4, 23 October 2021	Amended to incorporate safety information updates from the Investigator's Brochure for glofitamab. Additional changes include guidance for the use of COVID-19 vaccines for study patients.
Version 5, 16 August 2022 (not submitted)	Amended to incorporate initial iDMC-recommended modifications regarding SARS-CoV-2 infections in study patients subsequent to issuance of a USM-DIL. Modifications are summarized below: • Patients diagnosed with SARS-CoV-2 infection within 30 days prior to the first dose of study treatment were not eligible • 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 who develop documented SARS-CoV-2 infection during the study must permanently discontinue study treatment This protocol version was not submitted to health authorities or sites because the iDMC issued superseding recommendations shortly after protocol publication.
Version 6, 20 September 2022	Amended to incorporate changes from Protocol Version 5 (not submitted), updated COVID-19 guidance, and modifications based on additional guidance provided by the iDMC on 2 September 2022, which are as follows: • 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 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 who developed documented SARS-CoV-2 infection during the study had to permanently discontinue study treatment.
Version 7, 22 September 2023	Amended to incorporate v7 (France) and v6 (Germany) into v7 (Global) to harmonize under the Common Technical Document ahead of the switch to submission under the EU Clinical Trials Regulation which included a section describing Country-Specific Stipulations. Additional key changes included alignment with SAP v4.

AE = adverse event; CRS = cytokine release syndrome; coronavirus disease 2019 = COVID-19; CT = computed tomography; iDMC = independent Data Monitoring Committee; OS=overall survival; PCR = Polymerase Chain Reaction; SAE: Serious Adverse Event; SAP = statistical analysis plan; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; USM-DIL = Urgent Safety Memo-Dear Investigator Letter.

Appendix 3: Statistical Analysis Plan (SAP) Amendments

SAP Amendments

The original SAP dated 26 April 2022 was amended six times. The key changes to the SAP are summarized below in Table 13.

Table 13 Summary of Key SAP Changes

SAP Version	Summary of Key SAP Changes
SAP v2 28 July 2022	• Additional sensitivity analysis for primary endpoint added for patients who discontinued study treatment due to drug supply issues caused by COVID-19 pandemic. • Missing response data handling strategy added for patients who have already achieved complete response by PET/CT scans while follow-up response assessments were missing for PET scan only.
SAP v3 11 November 2022	• CRS risk score added as an exploratory safety endpoint. • Additional sensitivity analysis for primary endpoint added for patients who discontinued study treatment due to COVID-19 AE. • Detailed censoring rules for OS and PFS added. • Additional sensitivity analyses added on PFS without censoring for NALT and censoring for NALT except for ASCT. • Additional supportive analysis for PFS by RMST method added in the event that proportional hazard assumption is violated. • Table of Thresholds of P-values for OS Among Information Fraction at the Time of Efficacy Interim Analysis updated based on code-based trial design software such as rpact. A reproduceable code-based trial design program has been utilized for P-value thresholds calculation. • The key secondary endpoint of DOCR clarified to be based on IRC.
SAP v4 19 February 2023	• Enrollment by region added as a new subgroup analysis category and cell type of origin clarified to be based on IHC or gene expression. • Best ORR and DOR removed from hierarchical testing. • PFS censoring rules updated to censor patients who have two or more consecutive missing visits. • Additional sensitivity analysis for PFS added for patients who missed more than two consecutive response assessments due to COVID-19 pandemic. • Table of thresholds of p-values for OS among information fraction at the time of efficacy interim analysis expanded based on code-based trial design software such as rpact. • Clarification added that the same PFS censoring rules will be applied to DOR and DOCR.
SAP v5 11 May 2023	• Handling strategy for NALT for DOCR and DOR updated to hypothetical strategy to align with the same censoring rules for PFS which also apply hypothetical strategy for intercurrent event like NALT. • IRC will also be used to evaluate study endpoints including DOR and DOCR. • Additional approach for sensitivity analysis on death due to COVID-19 added. • New subgroup (primary refractory disease or relapse within one year of first-line therapy) added for subgroup analysis for the primary endpoint. • Clarifications have been provided for patient-reported outcome endpoints.
SAP v6 14 December 2023	• Additional follow-up analysis added approximately 11 months after the last patient enrolled.

AE = adverse event; ASCT = autologous stem cell transplant; CR = complete response; CT = computed tomography; CRS = cytokine release syndrome; coronavirus disease 2019 = COVID-19; DOR = duration or response; DOCR = duration of complete response; iDMC = independent Data Monitoring Committee; IHC = Immunohistochemistry; IRC = independent review committee; NALT = new anti-lymphoma therapy; ORR = Overall Response Rate; OS = overall survival; PET = positive-electron tomography; PFS = progression-free survival; RMST = Restricted Mean Survival Time; SAP = statistical analysis plan.

Appendix 4: Statistical Details on Post-Hoc Analyses

Multivariable analysis (MVA)

The MVA was aimed to assess the robustness of the OS and PFS results observed in the overall population by adjusting for prognostic and clinically relevant baseline factors. These factors were selected from the 26 factors pre-specified for the subgroup analysis of OS, based on their individual association with OS and PFS, and correlation among themselves. Factors selected for the MVA included the stratification factors (number of prior systemic therapies and refractory status to last systemic therapy), sex, IPI, bulky disease (≥ 10 cm), BMI, and enrollment region.

Inverse propensity censoring weighting (IPCW)

While there is no perfect method to adjust for NALT for OS, the IPCW method was chosen, as despite its complexity, IPCW provides a fairly unbiased way to adjust for NALT (Latimer et al. 2024). The IPCW method adjusts for the impact of NALT for both OS and PFS, and is considered a less biased approach compared to naïve approaches such as censoring at NALT, by allowing some patients to represent more and others less through reweighting in order to create a pseudo-population that would have been observed if censoring at NALT had not occurred. In addition to IPCW, two additional methods for adjusting treatment switching were also considered, including the rank preserving structural failure time (RPSFT) and the two-stage accelerated failure time (AFT). However, RPSFT is used to adjust for treatment switch from one arm to the other (i.e. crossover) and therefore not applicable for NALT. On the other hand, the two-stage AFT required defining a second baseline prior to switching to NALT, which was challenging to establish, as patient baseline characteristics were only recorded once. As a result, the IPCW was chosen to investigate the impact of NALT for STARGLO. The IPCW method conducted was in accordance with the recently updated NICE DSU technical support document 16 (Latimer et al. 2024). Results of the IPCW should be interpreted with some caution due to the key statistical assumption that there are no unmeasured confounders in the model used to estimate weights. Event-free survival (EFS), an endpoint that also adjusts for NALT by treating NALT as an additional event to disease progression and death in PFS, served as a consistency check for IPCW, where consistent EFS and IPCW results for PFS would indicate that the IPCW method was appropriate, and by extension, also indicate that the IPCW results for OS were reasonable.

Appendix 5: Supplementary Data Module – Further Exploration of Subgroup Results

5.1 Introduction

The goal of the data included in this appendix is to supplement the data supporting the exploration of subgroup results by race and region, as presented in Section 2.3.2.3. The additional analyses were performed to gain a deeper understanding of the outcomes in these specific subgroups by examining several factors.

5.2 Glofitamab Monotherapy Data Evaluated Across Regions

Glofitamab PK, efficacy, and safety in different geographic regions based on data from various clinical studies with glofitamab monotherapy (Table 14) was examined.

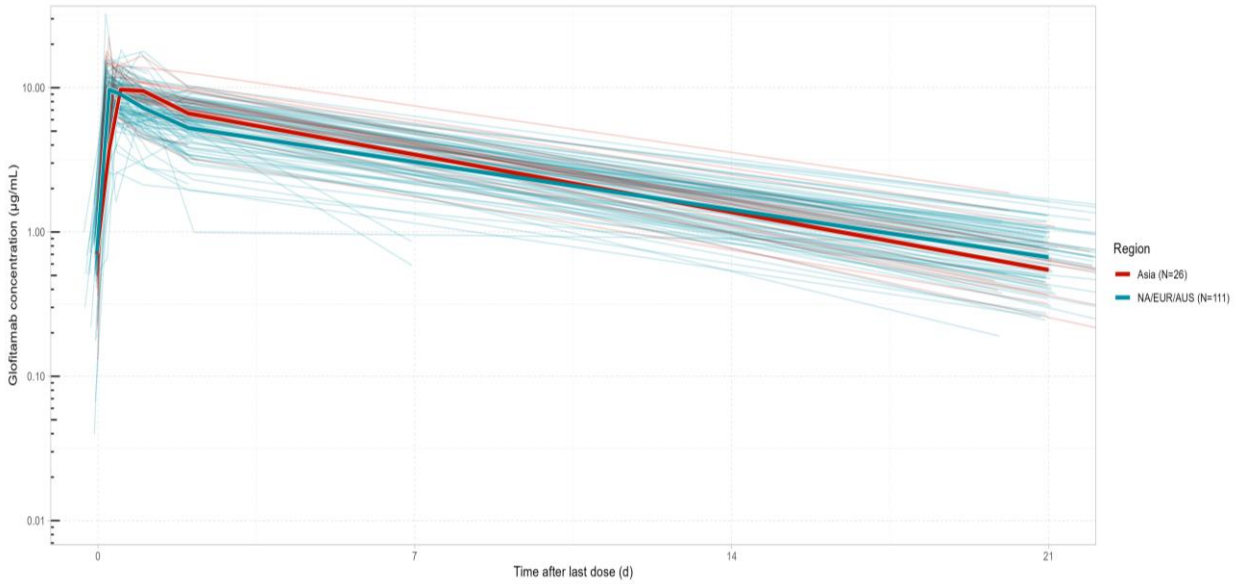
Table 14 Summary of Studies Evaluating Glofitamab Monotherapy in Patients with R/R NHL and DLBCL

Study Number	Overall Design	Primary Endpoint	Participating countries	Status
NP30179	Phase I/II study of glofitamab as a single agent and in combination with obinutuzumab in patients with R/R NHL	Safety, tolerability, ADA, PK, CR rate by IRC	Australia, Belgium, Canada, Czech, Denmark, Finland, France, Italy, New Zealand, Poland, Spain, Taiwan, US	Ongoing Enrollment of DLBCL patients completed
YO42610	Phase I, single-arm study of glofitamab IV infusion in Chinese patients with R/R DLBCL	Safety, tolerability, ADA, PK, CR rate by IRC	China	Completed LPLV: 12 January 2024

ADA = anti-drug antibody; CR = complete response; DLBCL = diffuse large B-cell lymphoma; LPLV = last patient last visit; NHL = non-Hodgkin's lymphoma; PK = pharmacokinetics; R/R = relapsed/refractory; USA = United States.
Study NP30179: Multicenter, open-label, Phase 1/2 study to evaluate the safety, efficacy, tolerability and pharmacokinetics of glofitamab monotherapy administered after a fixed, single dose pre- treatment of obinutuzumab (Gpt) in patients with R/R B-cell NHL (Dickinson et al. 2022; Clinical Trials Identifier NCT03075696).
Study YO42610: A Study to Evaluate Glofitamab as Single Agent Administered After Pretreatment with Obinutuzumab in Chinese Patients With R/R DLBCL (Yu-Qin Song et al. 2023; Clinical Trials Identifier NCT04657302).

Experience across the glofitamab clinical development program has not demonstrated meaningful differences in clinical outcomes (Table 15) and has demonstrated similarities in safety profile (Table 16) across geographic regions. In particular, the glofitamab monotherapy trials (NP30179 and YO42610) showed similar clinical activity (CR rates ranged 40%-47% with ITT 41%) (Table 15) and similar PK profile of glofitamab across geographic regions (Figure 11).

Figure 11 Individual and Median Glofitamab Concentration-Time Profiles at the 30 mg Target Dose by Region at Cycle 2 in Monotherapy Studies NP30179 and YO42610



Study NP30179 CCOD: 15 June 2022. Study YO42610 CCOD: 2 December 2022.
Sources: p.regionasia.mono11.png [PPK30179]. Study YO42610 (data on file)
The bold lines represent the median by nominal time. The thin lines are individual patients.

Table 15 Study NP30179 and Study YO42610: Efficacy Results in Regional Subgroups (Glofitamab Monotherapy)

	Study NP30179[a]+YO42610[b] Glofitamab Monotherapy		
	NA/EUR/AUS/NZ[c] (N=149)	**Asia[d] (N=36)**	**ITT[e] (N=185)**
Complete response (by IRC) n (%) (95% CI)	59 (40%) (32, 48)	17 (47%) (30, 65)	76 (41%) (34, 49)

[a] Study NP30179 CCOD: 15 June 2022.
[b] Study YO42610 CCOD: 2 December 2022.
[c] North America, Europe, Australia, New Zealand.
[d] Taiwan, China.
[e] Study NP30179 (ITT population): Glofitamab 2.5/10/30 mg in the Primary Efficacy Population Cohorts D2[Sub. 2] + D3 + D5 (R/R DLBCL Patients, ≥2 Prior Lines of Systemic Therapy). Study YO42610 (ITT population): Glofitamab 2.5/10/30 mg in Chinese patients (R/R DLBCL Patients, ≥2 Prior Lines of Systemic Therapy.
Sources: Study NP30179: t_rsp_IRC_PIV_I_SCE_IT_15JUN2022_30179 [ADSL, ADRS], t_rsp_subgrp_IRC_REG1_PIV_RP2D_I_IT_15JUN2022_30179 [ADSL, ADRS]. Study YO42610 (data on file): t_ef_bor_AP_irc_02DEC2022_42610 [ADSL, ADRS].

Table 16 Study NP30179 and Study YO42610: Safety Results in Regional Subgroups (Glofitamab Monotherapy)

	NP30179 (3L+ Glofit Mono[a]) + YO42610 (3L+ Glofit Mono China[b])		
	NA/EUR/AUS/NZ[c] N=139	Asia[d] N=33	Glofit Exposed N=172
Grade 5 AEs	8 (5.8%)	0	8 (4.7%)
COVID-19	3 (2.2%)	0	3 (1.7%)
COVID-19 Pneumonia	2 (1.4%)	0	2 (1.2%)
Sepsis	2 (1.4%)	0	2 (1.2%)
Delirium	1 (0.7%)	0	1 (0.6%)
Patients with at least one Grade 3-4 AE	81 (58.3%)	25 (75.8%)	106 (61.6%)
Common Grade 3-4 AEs (>5%)			
Anemia	11 (7.9%)	4 (12.1%)	15 (8.7%)
Neutropenia	40 (28.8%)	11 (33.3%)	51 (29.7%)
Thrombocytopenia	10 (7.2%)	2 (6.0%)	12 (7.0%)
Hypophosphatemia	9 (6.5%)	1 (3.0%)	10 (5.8%)
Patients with at least one SAE	67 (48.2%)	14 (42.4%)	81 (47.1%)
Total number of patients withdrawn from any treatment due to an AE	9 (6.5%)	3 (9.0%)	12 (6.9%)
Known Risks with Glofitamab			
CRS (ASTCT grading) [e]	93 (66.9%)	24 (72.7%)	117 (68.0%)
Grade 1	69 (49.6%)	21 (63.6%)	90 (52.3%)
Grade 2	19 (13.7%)	1 (3.0%)	20 (11.6%)
Grade 3	4 (2.9%)	1 (3.0%)	5 (2.9%)
Grade 4	1 (0.7%)	1 (3.0%)	2 (1.2%)
Neurological AEs	54 (38.8%)	11 (33.3%)	65 (37.8%)
ICANS (clinically adjudicated) [f]	7 (5.0%)	0	7 (4.1%)
Serious infections	22 (15.8%)	6 (18.2%)	28 (16.3%)

AE = adverse event; ASTCT = American Society for Transplantation and Cellular Therapy; CRS = cytokine release syndrome; Glofit-GemOx = glofitamab in combination with gemcitabine plus oxaliplatin; ICANS = immune effector cell-associated neurotoxicity syndrome; R-GemOx = rituximab in combination with gemcitabine plus oxaliplatin; SAE = serious adverse event.

[a]Study NP30179 CCOD: 15 June 2022.
[b]Study YO42610 CCOD: 2 December 2022.
[c]North America, Europe, Australia, New Zealand.
[d]Taiwan, China.
[e] No Grade 5 CRS events were reported.
[f]Potential cases were identified using the ICANS adverse event group term (AEGT). Those cases were then clinically adjudicated to identify true or likely ICANS cases in the updated analysis.

Sources: Study NP30179: l_ae_ICANS_PIV_RP2D_I_SERO_15JUN2022_30179 [ADSL, ADAE];
t_ae_ctc_heme_subgrp_REG1_PIV_RP2D_I_SERO_15JUN2022_30179 [ADSL, ADAE];
t_ae_ctc1_subgrp_NEUR_REG1_PIV_RP2D_I_SERO_15JUN2022_30179 [ADSL, ADAE];
t_ae_ctc1_subgrp_REG1_PIV_RP2D_I_SERO_15JUN2022_30179 [ADSL, ADAE];
t_ae_ctc1_subgrp_SER_REG1_PIV_RP2D_I_SERO_15JUN2022_30179 [ADSL, ADAE];
t_ae_ctc1_subgrp_WD_REG1_PIV_RP2D_I_SERO_15JUN2022_30179 [ADSL, ADAE];
t_ae_oview_subgrp_REG1_PIV_RP2D_I_SERO_15JUN2022_30179 [ADSL, ADAE]; Study YO42610 (data on file):
t_ae_oview_I_SERO_02DEC2022_42610 [ADSL, ADAE]; t_ae_ctc1_I_SERO_neur_02DEC2022_42610 [ADSL, ADAE];
t_ae_ctc1_I_SERO_ICANS_02DEC2022_42610 [ADSL, ADAE]; t_ae_ctc_all_I_SERO_ser_02DEC2022_42610 [ADSL, ADAE];
t_ae_ctc_all_I_SERO_NEUT_02DEC2022_42610 [ADSL, ADAE]; t_ae_ctc_all_I_SERO_HEMO_02DEC2022_42610 [ADSL, ADAE];
t_ae_ctc_all_I_SERO_HAEM_02DEC2022_42610 [ADSL, ADAE]; t_ae_ctc_all_I_SERO_dsc_02DEC2022_42610 [ADSL, ADAE];
t_ae_ctc_all_I_SERO_02DEC2022_42610 [ADSL, ADAE].

5.3 Additional Subgroup Analyses in STARGLO

Based on a high association observed between race and region in STARGLO (Table 17) the exploratory analyses presented in this section are based on the regional subgroups. The potential differences by race are primarily considered to be a reflection of geographic enrollment region as opposed to having a true biological underpinning.

Table 17 Association between Race and Geographic Region of Enrollment

	North America (N = 25)	Europe (N = 88)	Asia Pacific[a] (N = 161)
White	21 (84.0%)	67 (76.1%)	27 (16.8%)
Asian	2 (8.0%)	1 (1.1%)	134 (83.2%)
Black / African American	2 (8.0%)	1 (1.1%)	0
Unknown[b]	0	19 (21.6%)	0

[a] Asia Pacific: China, Taiwan, South Korea, and Australia.

[b] Patients with unknown race were enrolled in France only.

Source: t_dm_subgrp_REG3_T_IT_16FEB2024_41944 [ADSL, ADSUB].

Thus, initial assessments examined the results within pre-specified geographical region subgroups:

- North America (US), N=25
- Europe (Belgium, Denmark, France, Germany, Poland, Spain, Switzerland, UK), N=88
- Asia Pacific (China, Taiwan, South Korea, and Australia), N=161.

5.3.1 Baseline Characteristics by Pre-specified Region (by Arm)

Baseline prognostic factors were not balanced in North America, with notably more high-risk patients in Glofit-GemOx vs. R-GemOx (Table 18).

Table 18 Demographic and Baseline Characteristics in the ITT Population and Pre-specified Regional Subgroups by Arm (STARGLO Updated Analysis)

	North America N=25		Europe N=88		Asia Pacific[a] N=161		ITT Population N=274	
	R-GemOx N=10	Glofit-GemOx N=15	R-GemOx N=26	Glofit-GemOx N=62	R-GemOx N=55	Glofit-GemOx N=106	R-GemOx N=91	Glofit-GemOx N=183
Age, ≥65yrs, n (%)	**7 (70.0%)**	**13 (86.7%)**	**18 (69.2%)**	**48 (77.4%)**	**31 (56.4%)**	**55 (51.9%)**	**56 (61.5%)**	**116 (63.4%)**
Male, n (%)	5 (50.0%)	11 (73.3%)	18 (69.2%)	35 (56.5%)	30 (54.5%)	59 (55.7%)	53 (58.2%)	105 (57.4%)
≥ 2 prior lines of therapy, n (%)	4 (40.0%)	6 (40.0%)	8 (30.8%)	21 (33.9%)	22 (40.0%)	41 (38.7%)	34 (37.4%)	68 (37.2%)
Primary refractory disease[b], n (%)	4 (40.0%)	12 (80.0%)	13 (50.0%)	31 (50.0%)	30 (54.5%)	63 (59.4%)	47 (51.6%)	106 (57.9%)
Refractory to last line of therapy[c], n (%)	5 (50.0%)	11 (73.3%)	14 (53.8%)	32 (51.6%)	35 (63.6%)	69 (65.1%)	54 (59.3%)	112 (61.2%)
IPI score 3-5 (Derived), n (%)	5 (50.0%)	10 (66.6%)	13 (50.0%)	30 (48.4%)	29 (52.7%)	47 (44.3%)	47 (51.6%)	87 (47.5%)
Ann Arbor stage III-IV, n (%)	6 (60.0%)	12 (80.0%)	20 (76.9%)	46 (74.2%)	44 (80.0%)	65 (61.3%)	70 (76.9%)	123 (67.2%)
Bulky disease (≥ 10cm), n (%)	1 (10.0%)	3 (20.0%)	6 (23.1%)	9 (14.5%)	7 (12.7%)	11 (10.4%)	14 (15.4%)	23 (12.6%)

Glofit-GemOx = glofitamab in combination with gemcitabine plus oxaliplatin; IPI = International Prognostic Index; R-GemOx = rituximab in combination with gemcitabine plus oxaliplatin.

[a] Asia Pacific: China, Taiwan, South Korea, and Australia. [b] Primary Refractory disease: disease that did not respond to, or that progressed <6 months after completing the first-line of therapy. [c] Refractory disease: disease that did not respond to, or that progressed <6 months after completing the last line of therapy.

Sources: t_dm_AA_T_IT_16FEB2024_41944 [ADSL, ADSUB], t_mh_char_T_IT_16FEB2024_41944 [ADSL, ADSUB, ADCM], t_dm_subgrp_REG3_T_IT_16FEB2024_41944 [ADSL, ADSUB], t_mh_char_subgrp_REG3_IT_16FEB2024_41944 [ADSL, ADSUB, ADCM].

5.3.2 Baseline Characteristics NA/EUR/AUS and Asia (by Arm)

When examining these larger regional subgroups, the baseline prognostic factors were more balanced between the arms in both NA/EUR/AUS and Asian populations (Table 19).

Table 19 Demographic and Baseline characteristics in the ITT population and NA/EUR/AUS and Asia (STARGLO Updated Analysis)

	NA/EUR/AUS[b] (N=143)		Asia[a] (N=131)		ITT population (N=274)	
	R-GemOx N=44	Glofit-GemOx N=99	R-GemOx N=47	Glofit-GemOx N=84	R-GemOx N=91	Glofit-GemOx N=183
Age ≥ 65yrs, n (%)	31 (70.5%)	82 (82.8%)	25 (53.2%)	34 (40.5%)	56 (61.5%)	116 (63.4%)
Male, n (%)	27 (61.4%)	59 (59.6%)	26 (55.3%)	46 (54.8%)	53 (58.2%)	105 (57.4%)
≥ 2 prior lines of therapy, n (%)	15 (34.1%)	31 (31.3%)	19 (40.4%)	37 (44.0%)	34 (37.4%)	68 (37.2%)
Primary refractory disease[c], n (%)	21 (47.7%)	55 (55.6%)	26 (55.3%)	51 (60.7%)	47 (51.6%)	106 (57.9%)
Refractory to last therapy[d], n (%)	24 (54.5%)	56 (56.6%)	30 (63.8%)	56 (66.7%)	54 (59.3%)	112 (61.2%)
IPI score 3-5 (Derived), n (%)	25 (56.8%)	51 (51.5%)	22 (46.8%)	36 (42.9%)	47 (51.6%)	87 (47.5%)
Ann Arbor stage III-IV, n (%)	34 (77.3%)	72 (72.7%)	36 (76.6%)	51 (60.7%)	70 (76.9%)	123 (67.2%)
Bulky disease (≥ 10cm), n (%)	9 (20.5%)	15 (15.2%)	5 (10.6%)	8 (9.5%)	14 (15.4%)	23 (12.6%)

Glofit-GemOx = glofitamab in combination with gemcitabine plus oxaliplatin; IPI = International Prognostic Index' R-GemOx = rituximab in combination with gemcitabine plus oxaliplatin.

[a] China, Taiwan, and South Korea.

[b] US, Europe and Australia.

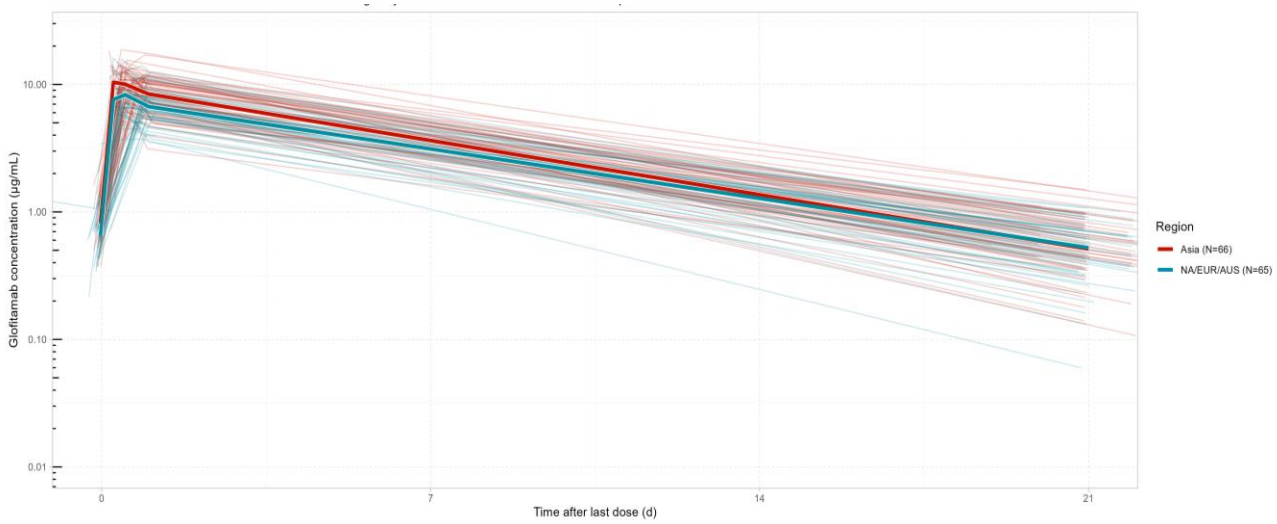
[c] Primary Refractory disease: disease that did not respond to, or that progressed <6 months after completing the first-line of therapy.

[d] Refractory disease: disease that did not respond to, or that progressed <6 months after completing the last line of therapy.

Sources: t_dm_AA_T_IT_16FEB2024_41944 [ADSL, ADSUB], t_mh_char_T_IT_16FEB2024_41944 [ADSL, ADSUB, ADCM], t_dm_subgrp_REG2_T_IT_16FEB2024_41944 [ADSL, ADSUB], t_mh_char_subgrp_REG2_IT_16FEB2024_41944 [ADSL, ADSUB, ADCM].

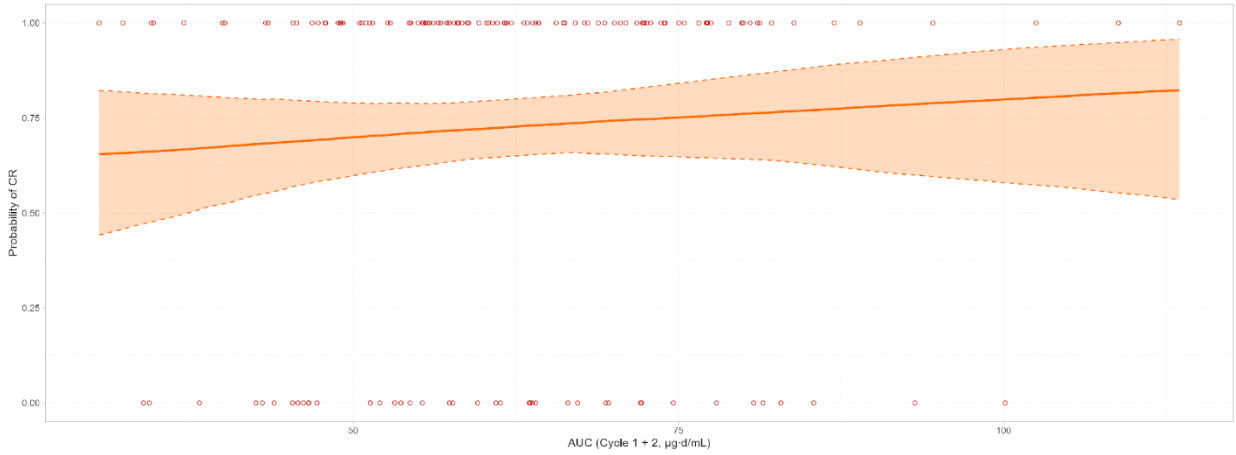
5.3.3 Exposure by NA/EUR/AUS and Asia

Figure 12 Individual and Median Glofitamab Concentration-Time Profiles at the 30 mg Target Dose by Region at Cycle 2 in STARGLO



The bold lines represent the median by nominal time. The thin lines are individual patients. CCOD of 16 February 2024.
Source: p.regionasia.starglo11.png [PPK41944]

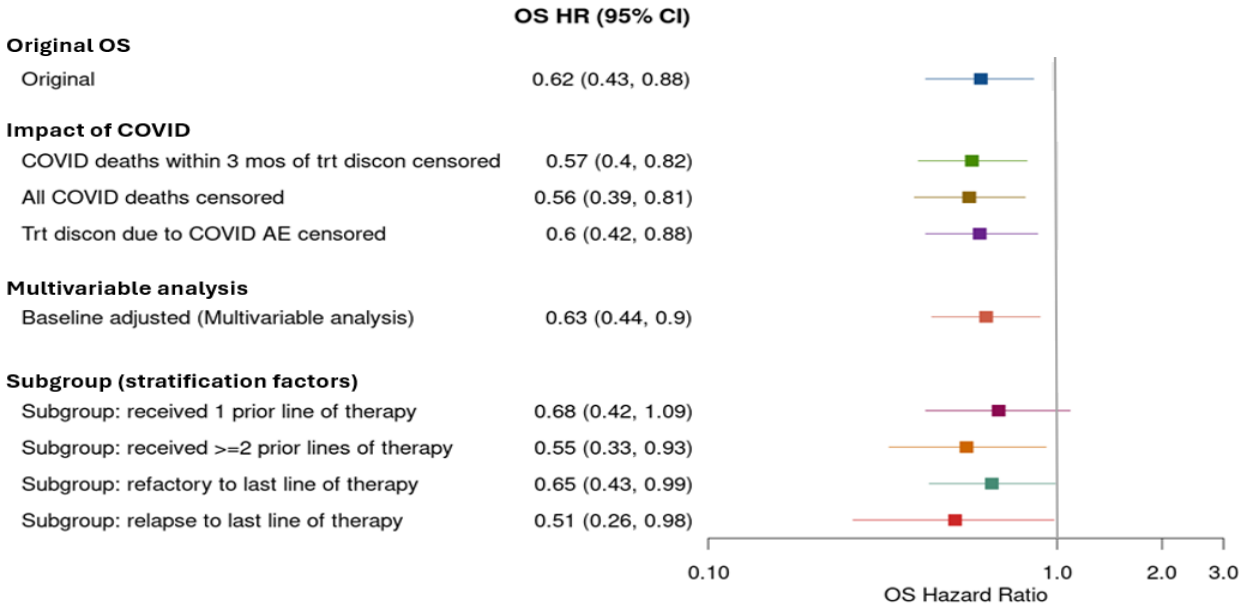
Figure 13 Univariate Model for CR Using AUC Cycle 1 – Cycle 2 Exposure Metric and Population of STARGLO



Line and shaded area represent predicted response and associated 95% prediction interval. CCOD of 16 February 2024.
Source: p.crr.reionasia.1curve.med.noanno.png [PPK41944].

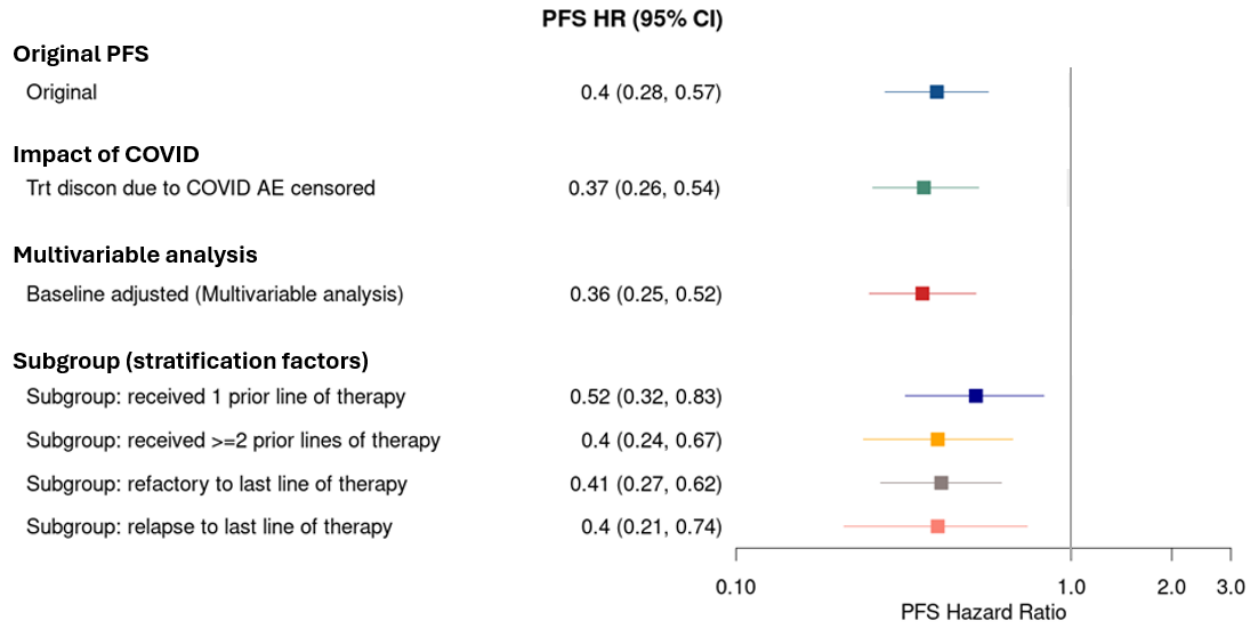
Appendix 6: Analyses Demonstrating Robustness of Efficacy Outcomes

Figure 14 Analyses Demonstrating Robustness of Efficacy Outcomes (OS)



AE = adverse event; OS = overall survival.
Sources: t_ef_tte_OS_IT_16FEB2024_41944 [ADSL, ADTTE]; t_ef_tte_OSCOVDTH_IT_16FEB2024_41944 [ADSL, ADTTE]; t_ef_tte_OSCOVCEN_IT_16FEB2024_41944 [ADSL, ADTTE]; t_ef_tte_OSCOVAE_IT_16FEB2024_41944 [ADSL, ADTTE]; g_ef_forest2_unstrat_OS_IT_16FEB2024_41944 [ADSL, ADSUB, ADTTE]; t_ef_cox_OS_IT_16FEB2024_41944 [ADSL, ADSUB, ADTTE].

Figure 15 Analyses Demonstrating Robustness of Efficacy Outcomes (PFS)



AE = adverse event; PFS = progression-free survival.
Sources: t_ef_tte_IRCPFSN_IT_16FEB2024_41944 [ADSL, ADTTE]; t_ef_cox3_IRCPFSN_IT_16FEB2024_41944 [ADSL, ADSUB, ADTTE]; g_ef_forest2_unstrat_IRCPFSN_IT_16FEB2024_41944 [ADSL, ADTTE]; t_ef_tte_IRCPFSNC_IT_16FEB2024_41944 [ADSL, ADTTE].

Appendix 7: R-GemOx Outcomes in Available Literature

Table 20 Overview of Efficacy Results for R-GemOx Regimen in the Available Literature

Publication Author, year	Patients treated with R-GemOx (n)	Type of Study, country	Histologies	Prior anti-CD20-containing therapy	CRR	PFS	OS
						mPFS (months)	mOS (months)
El Gnaoui et al. 2007	33	Ph2 France	R/R DLBCL unsuitable for HDT	57%	58%[a]	NA	NA
López A et al. 2008	32	Ph2 Spain	R/R DLBCL	78%	34%	NA	9.1
Corazzelli et al. 2009	32	Ph2 Italy	R/R B-cell lymphoma unsuitable for HDT	66%	50%	NA	NA
Zhang et al. 2011	32	RCT China	R/R DLBCL	Unk.	13%	NA	NA
Rongshuang and Mingzhi 2021	47	R China	R/R DLBCL	Unk.	23%	NA	NA
Mounier et al. 2013	49	Ph2 France	R/R DLBCL unsuitable for HDT	63%	38%	5	11
Dhanapal et al. 2017	44	R UK	R/R aggressive lymphoma	90%	30%	NA	8
Cazelles et al. 2021	196	R France	R/R DLBCL not eligible for ASCT	100%	33%	5	10
Held et al. 2023	90	RCT, MCT Europe	R/R LBCL not eligible for HDCT/HSCT	100%[b]	20%	NA	NA
Budde et al. Flatiron 2024	281	RWD US	R/R DLBCL (both eligible and ineligible for transplant)	99%	22%	2.8	12.7
Yamshon et al. 2024 LEO Consortium	183	RWD US	R/R LBCL (both eligible and ineligible for transplant)	100%	29%	2.3[c]	13.5
GO41944 (STARGLO)	91	RCT, MCT Global	R/R DLBCL ASCT ineligible	98%	25%	3.6	12.9

CR = complete response rate; DLBCL = diffuse LBCL; HDT = high-dose therapy; ITT = intent-to-treat; m = median; LBCL = large B-cell lymphoma; MCT=multicenter trial; PFS= progression-free survival; R = retrospective; RCT = randomized controlled trial; R/R = relapsed or refractory; OS = overall survival; RWD = real-world data; Unk = unknown.

[a] Responses after R-GemOx induction phase therapy (N = 33).

[b] As per study protocol eligibility criteria, rituximab must be part of the first-line regimen in case of B-cell lymphoma (Held et al. 2023).

[c] Event-free survival.

Appendix 8: Summary of Serious Adverse Events in ≥ 5% of patients

Table 21 Summary of Serious Adverse Events in ≥ 5% of patients (STARGLO Updated Analysis)

MedDRA System Organ Class MedDRA Preferred Term	R-GemOx N=88	Glofit-GemOx (Glofit Exposed) N=172
Total number of patients with at least one AE	5 (5.7%)	59 (34.3%)
Total number of events	9	75
Immune system disorders		
Total number of patients with at least one AE	0	35 (20.3%)
Total number of events	0	46
Cytokine release syndrome	0	35 (20.3%)
Infections and infestations		
Total number of patients with at least one AE	5 (5.7%)	18 (10.5%)
Total number of events	7	18
Pneumonia	4 (4.5%)	10 (5.8%)
COVID-19	2 (2.3%)	8 (4.7%)
General disorders and administration site conditions		
Total number of patients with at least one AE	1 (1.1%)	11 (6.4%)
Total number of events	2	11
Pyrexia	1 (1.1%)	11 (6.4%)

AE = adverse event ; Glofit-GemOx = glofitamab in combination with gemcitabine plus oxaliplatin; R-GemOx = rituximab in combination with gemcitabine plus oxaliplatin.

Sources: t_ae_INC5PER_SER_SE_16FEB2024_41944 [ADSL, ADAE].

Appendix 9: CRS, Gastrointestinal AEs, Neurological AEs and Infections

Table 22 CRS, Gastrointestinal AEs, Neurological AEs and Infections (STARGLO Updated Analysis)

n (%) of patients with ≥1 CRS AE[a]	Glofit-GemOx N=172*
Any grade[b]	76 (44.2)
Grades 1-3 Grade 1 Grade 2 Grade 3	54 (31.4) 18 (10.5) 4 (2.3)[c]
SAE	20.3%
CRS by Dose	C1D1 (N=172): 1 (0.6%) C1D8 (N=172): 59 (34.3%) C1D15 (N=167): 24 (14.4%) C2 (N=161): 15 (9.3%) C3 (N=149): 10 (6.7%) C4+ (N=145): 16 (11.0%)

Gastro intestinal AEs	R-GemOx N=88	Glofit-GemOx N=172*
Nausea Any Grade Grade 3-4	35 (39.8%) 0 (0%)	71 (41.3%) 1 (0.6%)
Diarrhea (Any Grade) Grade 3-4	24 (27.3%) 0	60 (34.9%) 6 (3.5%)
Vomiting (Any Grade) Grade 3-4	19 (21.6%) 0	41 (23.8%) 1 (0.6%)
Constipation Any Grade Grade 3-4	14 (15.9%) 0	32 (18.6%) 0

Neurological AEs	R-GemOx N=88	Glofit-GemOx N=172*
Neurological AEs Any grade Grade 3-4 Grade 5	35 (39.8) 0 0	102 (59.3%) 9 (5.2%) 1 (0.6%)[f]
ICANS (Any Grade) **Grade 3-4**	0[e] 0	4 (2.3%)[h] 1 (0.6%)
Neurological AEs >10% **Peripheral sensory neuropathy** Any Grade Grade 3-4	8 (9.1%) 0	27 (15.7%) 2 (1.2%)
Neuropathy peripheral Any Grade[h] Grade 3-4	6 (6.8%) 0	20 (11.6%) 0

Infections	R-GemOx N=88	Glofit-GemOx N=172*
Infections Any Grade Grade 3-5	26 (29.5%) 11 (12.5%)	95 (55.2%) 35 (20.3%)
Infections >10% **COVID-19 associated AE** Any Grade Grade 3-4 Grade 5	8 (9.1%) 3(3.4%) 0	30 (17.4%) 9 (5.2%) 5 (2.9%)
Pneumonia Any Grade Grade 3-4 Grade 5	4 (4.5%) 2 (2.3%) 2(2.3%)	21 (12.2%) 9 (5.2%) 1 (0.6%)

n (%) of patients with ≥1 CRS AE[a]	Glofit-GemOx N=172*		Gastro intestinal AEs	R-GemOx N=88	Glofit-GemOx N=172*	Neurological AEs	R-GemOx N=88	Glofit-GemOx N=172*	Infections	R-GemOx N=88	Glofit-GemOx N=172*
	2.5 mg glofit (C1D8)	10 mg glofit (C1D15)	**AE Leading to withdrawal of Rituximab or Glofitamab**	0	2 (1.2%)[d]	**Insomnia** Any Grade Grade 3-4	 9 (10.2%) 0	 20 (11.6%) 0			
Median time to CRS onset, hours (range)	13.5 (4.4–134.9)	32.4 (7.4–564.3)									
Median CRS duration, hours (range)	22.7 (0.0–168.0)	24.0 (0.0–248.5)									
Tocilizumab for CRS management, n, n (%)	28 / 76 (36.8)										
Corticosteroids for CRS management, n, n (%)	39 / 76 (51.3)										

AE = adverse event; CRS = cytokine release syndrome; Glofit-GemOx = glofitamab in combination with gemcitabine plus oxaliplatin; R-GemOx = rituximab in combination with gemcitabine plus oxaliplatin.

*Glofitamab-Exposed population. Dexamethasone premedication was mandated to prevent/mitigate CRS prior to step-up doses and prior to at least two 30 mg doses of glofitamab, until no additional CRS was observed.

[a] Unless otherwise specified.

[b] No Grade 4 or 5 CRS events were reported.

[c] One patient had a Grade 3 CRS event confounded by a concurrent Grade 5 Septic Shock that required multiple pressors.

[d] Colitis and pancreatitis. Includes any patient who received any study treatment including obinutuzumab pretreatment, rituximab, glofitamab, gemcitabine, or oxaliplatin.

[e] ICANS is not a risk identified for R-GemOx. ICANS, immune effector cell-associated neurotoxicity syndrome; NA, not applicable.

[f] Grade 5 NAE of suspected cerebral hemorrhage.

[g] Total incidence of peripheral neuropathy (peripheral sensory neuropathy [PSN] and neuropathy peripheral [NP] was 15.9% for R-GemOx and 26.2% for G-GemOx. [h]Potential cases were identified using the ICANS adverse event group term (AEGT). Those cases were then clinically adjudicated to identify suspected or confirmed ICANS cases in the updated analysis.

Sources: t_ae_oview_CRSAE_GLO_SE_16FEB2024_41944 [ADSL, ADAE]; t_ae_ctc_CRSAE_GLO_SE_16FEB2024_41944 [ADSL, ADAE]; t_ae_aestat_dose123_CRSAE_GLO_SE_16FEB2024_41944 [ADSL, ADAE, ADEX]; t_ae_aestat_dose123_CRSAE_GLO_SE_16FEB2024_41944 [ADSL, ADAE, ADEX]; t_crs_mngmnt_CRSPT_GLO_SE_16FEB2024_41944 [ADSL, ADAE, ADEX, ADCM]; t_ae_ctc_NEUR_SE_16FEB2024_41944 [ADSL, ADAE]; l_ae_NEUR_SE_16FEB2024_41944 [ADSL, ADAE]; l_ae_ICANS_GLO_SE_16FEB2024_41944 [ADSL, ADAE]; l_ae_ICANS_CCRS_GLO_SE_16FEB2024_41944 [ADSL, ADAE]; t_ae_ctc_SE_16FEB2024_41944 [ADSL, ADAE]; t_ae_DSC_SE_16FEB2024_41944 [ADSL, ADAE]; t_ae_ctc_INFEST_SE_16FEB2024_41944 [ADSL, ADAE]; t_ae_ctc_covas2_SE_16FEB2024_41944 [ADSL, ADAE].

Appendix 10: Summary of Treatment Options for R/R DLBCL Not Eligible for Stem Cell Transplant

FDA Table 24: Summary of Treatment Options for R/R DLBCL Not Eligible for Stem Cell Transplant

Drug/Combination	Approval	Indication
Chemoimmunotherapy **R-GemOx, GDP, CEOP** **GDP, ICE, ESHAP, MINE**	**Standard of Care Treatments**	Based on prior therapy, patient co-morbidities, DLBCL subtype and high-risk features
Axicabtagene ciloleucel	Regular Approval – 2022	R/R LBCL (DLBCL NOS, PMBL, HGBCL, trDLBCL) after at least 2 prior lines LBCL refractory to 1L therapy or relapse within 12 months of 1L therapy
Tisagenlecleucel	Regular Approval 2018	R/R LBCL (DLBCL NOS, HGBCL, trDLBCL) after at least 2 prior lines
Polatuzumab vedotin + BR	Regular Approval – 2023	R/R DLBCL NOS after at least 2 prior therapies
Selinexor	Accelerated Approval - 2020	R/R DLBCL NOS, trDLBCL after at least 2 prior lines
Tafasitamab + Lenalidomide	Accelerated Approval 2020	R/R DLBCL NOS, trDLBCL not eligible for SCT
Loncastuximab teserine	Accelerated Approval - 2021	R/R DLBCL NOS, trDLBCL, HGBCL
Lisocabtagene maraleucel	Regular Approval – 2022	LBCL refractory to 1L therapy or relapse within 12 months of 1L chemoimmunotherapy, or relapse after 1L therapy and not eligible for HSCT
Epcoritamab	Accelerated Approval - 2023	R/R DLBCL NOS, trDLBCL, HGBCL after at least 2 prior therapies
Glofitamab	Accelerated Approval - 2023	R/R DLBCL NOS, trDLBCL after at least 2 prior therapies
Brentuximab vedotin + R2	Regular Approval – 2025	R/R LBCL including DLBCL NOS, trDLBCL, HGBCL after 2 prior and not eligible for auto-HSCT or CAR-T

Appendix 11: Regional Differences in Utilization of Stem Cell Transplantation

Given the observed imbalance in transplant refusal between the Non-Asia and Asia regions, the Agency requested additional information from the Applicant on the utilization of stem cell transplantation in the regions enrolled in the STARGLO study. The Applicant stated that autologous stem cell transplantation (ASCT) was not uniformly available across all countries or regions due to health infrastructure demands, noting variation in availability and degree of insurance coverage and access limitations driven by number of centers and geographic distribution of patients (Phillips, 2017; Flannelly, 2020; Vaughn, 2021; Cusatis, 2024; Passewag, 2024). Using data obtained via the region-specific registries Asia Pacific Blood and Marrow transplantation group (APBMT), European Group for Blood and Marrow Transplantation (EBMT) and Center for International Blood and Marrow Transplant Research (CIBMTR), the Applicant estimated that the percent utilization of ASCT for the treatment of lymphoid malignancies ranged from 15% to 51% depending on the region as shown below:

The Applicant stated that the direct comparisons between regions should be limited since the data was not specific to only R/R DLBCL and each registry had different data capture methods and reporting standards. Keeping these limitations in mind, the FDA notes that the differences in stem cell transplantation utilization are substantial with far less transplants employed for treatment of lymphoid malignancies in the Asia-Pacific regions than the North America Region. Thus, the identification of ineligibility due to "patient refusal" may in fact not be due to a patient being unfit or considered inappropriate for treatment with intensive chemotherapy followed by autologous stem cell transplant but rather due to access and availability issues. These "fit" patients may have different responses to treatment than the intended patient population in the U.S. population.

FDA Table 25: Autologous Stem Cell Transplant Utilization by Region and Country Included in the STARGLO Study

Region	Country	Registry	Year of Most Recent Registry Report	Estimated ASCT Utilizaton per 10 million Population for all Indications[1]	% of reported ASCT utilized for the treatment of lymphoid malignancies
Asia-Pacific	China	APBMT	2019	1-50	15%[2]
	Taiwan			50-150	
	South Korea			150-300	
	Australia			>300	
Europe	Poland	EBMT	2022	221	24%
	Denmark			296	
	France			385	
	Belgium			410	
	United Kingdom			435	
	Spain			449	
	Switzerland			511	
	Germany			538	
North America	United States	CIBMTR	2022	~330[3]	51%

[1]Includes plasma cell disorders, malignant lymphoma, and others.
[2]Includes combined data for allogeneic/autologous hematopoietic stem cell transplantation (HSCT)
[3]Estimate of ASCT utlizatino per 10 million population for all indications is not reported in US. The reported value has been calculated by the Applicant using the number of ASCT reported in 2022 in the CIBMTR registry (n=11139) and an approximation of the 2022 US population (334 million people).
Source: Applicant Response BLA 761309 S-001, SD 224 received 12-16-2024

Appendix 12: Regional Differences in NALT Categories

FDA Table 26: Regional Differences in NALT Categories

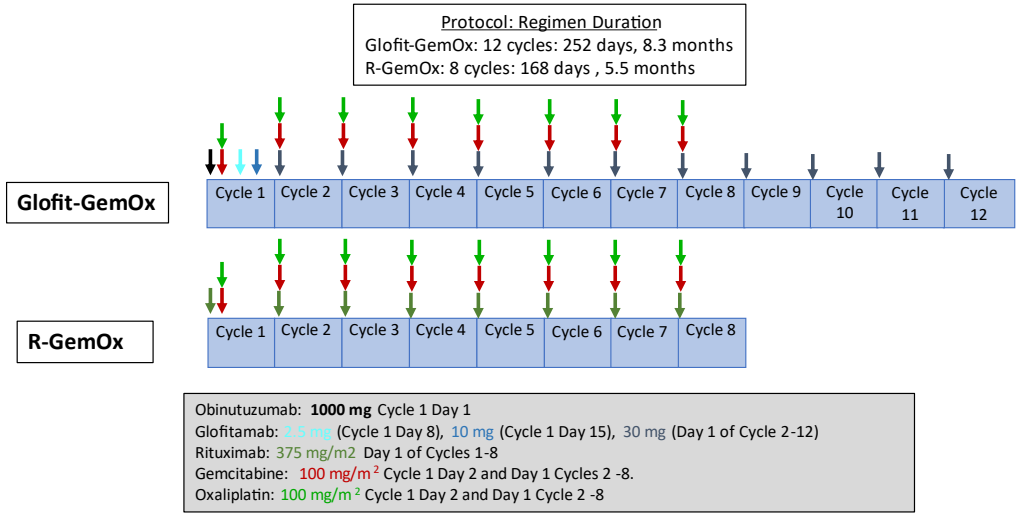
	Chemo Alone[c]	CD20± Chemo[d]	Lenalidomide or similar	Other[e]	Novel Treatment Regimens					
					ADC[f]	Taf+ len[g]	CAR-T	TCE[h]	SCT[i]	CAR-T, SCT, TCE, ADC, Taf+len
R-GemOx Arm n (%)										
Non-Asian Region (n=42)[a]	1 (2)	7 (17)	5 (12)	4 (10)	4 (10)	2 (5)	9 (21)	8 (19)	1 (2)	**17 (40)**
Asian Region (n=46)[a]	8 (17)	4 (9)	6 (13)	9 (20)	2 (4)	0	3 (7)	8 (17)	0	11 (24)
Difference[b]	-7	+3	-1	-5	+2	+2	+6	0	1	**+6**
Glofit-GemOx Arm n (%)										
Non-Asian Region (n=89)[a]	2 (2)	6 (7)	5 (6)	4 (4)	10 (11)	3 (3)	7 (8)	2 (2)	0	**17 (19)**
Asian Region (n=83)[a]	4 (5)	3 (4)	4 (5)	8 (10)	2 (2)	1 (1)	1 (1)	0	2 (2)	5 (6)
Difference[b]	-2	+3	+1	-4	+8	+2	+6	+2	-2	**+12**

[a]Includes all treated patients (except obinutuzumab-only treated in Glofit-GemOx arm).
[b]Non-Asian minus Asian Region: difference is number of patients
[c]Chemo alone: chemotherapy alone
[d]CD20 ± chemo: CD20 mAb with or without chemotherapy but not combined with lenalidomide or "novel" agent

[e]Other: anti-CD47 mAb, PI3K inhihitor + chemotherapy, BTK inhibitor, MALT inhibitor, VIPOR regimen, acalabrutnib, CDK9 inhibitor, PD-1 inhibitors and combinations, chidamide, venetoclax, HTK inhibitor, clinical trial; can not be combined with TCE
[f]ADC: Antibody drug conjugate alone or in combination
[g]Taf+len: Tafasitamab and lenalidomide
[g]TCE: CD20 or CD19-directed CD3 T cell engager
[i]SCT: Stem cell transplantation (autologous or allogeneic)
Source: FDA Analysis; Data cut-off: 16 February 2024

Appendix 13: Summary of Exposure Differences between Treatment Arms in ITT Population

FDA Figure 6: Glofit-GemOx and R-GemOx Treatment Schedules



Appendix 14: End of Treatment Disposition

FDA Table 27: Summary of Patients Treatment Status (ITT Population)

	Glofit-GemOx N=183		R-GemOx N=91	
	Non-Asian Region n=99	Asian Region N=84	Non-Asian Region N=44	Asian Region N=47
Completed Treatment	44 (44.9)	32 (38.1)	16 (36.4)	10 (21.3)
Discontinued Treatment	54 (54.5)	52 (61.9)	28 (63.6)	37 (78.7)
Adverse Event	12 (12.2)	16 (19.0)	6 (13.6)	1 (2.1)
Death	10 (10.2)	5 (6.0)	2 (4.5)	1 (2.1)
Lack of Efficacy	0 (0.0)	1 (1.2)	2 (4.5)	2 (4.3)
Lost to Follow-Up	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.1)
Other[a]	1 (1.0)	1 (1.2)	0 (0.0)	0 (0.0)
Physician Decision	3 (3.1)	4 (4.8)	0 (0.0)	0 (0.0)
Progressive Disease or Disease Relapse	21 (21.4)	20 (23.8)	12 (27.3)	26 (55.3)
Protocol Deviation	0 (0.0)	1 (1.2)	1 (2.3)	0 (0.0)
Symptomatic Deterioration	4 (4.1)	0 (0.0)	2 (4.5)	2 (4.3)
Withdrawal by Subject	3 (3.1)	4 (4.8)	3 (6.8)	4 (8.5)
Ongoing	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)

[a] Other: CNS disease before treatment, toxicity.
Source: FDA Analysis, Data cutoff: 16 February 2024

Appendix 15: Treatment Exposure by Component

FDA Table 28: Treatment Exposure Difference on Components of GemOx

Component of Regimen	Duration Measure	Glofit-GemOx N=180	R-GemOx N=88
Glofitamab or Rituximab	Median Months (range)	7.2 (0.03, 9.7)	2.1 (0.03, 6.0)
	Median Cycles (range)	11 (1, 13)	4 (1, 8)
Gemcitabine	Median Months (range)	**4.8** (0.03, 7.9)	**2.1** (0.03, 6.02)
	Median Cycles (range)	8 (1, 9)	4 (1, 8)
Oxaliplatin	Median Months (range)	**4.8** (0.03, 7.9)	**2.1** (0.03, 6.02)
	Median Cycles (range)	8 (1, 9)	4 (1, 8)
Source: FDA Analysis; Data Cut-off: 16 February 2024			

Appendix 16: Sensitivity Analysis Excluding the North America Subgroup

FDA acknowledges that US subgroup has imbalanced prognostic factors between arms, and this imbalance could pose challenges in interpreting results in US subgroup. FDA notes that these treatment effects appear to be replicated in other Non-Asian countries, such that the imbalance in prognostic factors may not be the sole reason for the inconsistent results.

FDA conducted exploratory analysis excluding US patients in the Non-Asia region. Efficacy summary by regions excluding US patients is shown in the table below. The OS HR (95% CI) is 0.39 (0.25, 0.63) vs. 0.90 (0.50, 1.63) in Asia and Non-Asia Regions; PFS HR (95% CI) is 0.25 (0.15, 0.41) vs. 0.69 (0.39, 1.21) in Asian and Non-Asian Region. The CR rate difference is 43.7% vs. 27.2% and ORR difference is 45.9% vs. 12.0%. The inconsistent treatment effects across regions still exist after excluding US patients. Therefore, the imbalanced prognostic factors among US patients could not explain the observed differential treatment effects.

FDA Table 29: Efficacy Summary by Region, Excluding US (DCO: 2/16/2024)

	Asian Region		Non-Asian Region (no US)	
	Glofit-GemOx N=84	R-GemOx N=47	Glofit-GemOx N=84	R-GemOx N=34
OS				
Events, n (%)	36 (42.9)	34 (72.3)	36 (42.9%)	16 (47.1%)
Median OS (95% CI), months	NE (19.2, NE)	8.2 (4.5, 14.3)	24.5 (11.5, NE)	16.5 (11.1, NE)
HR (95% CI) [a]	0.39 (0.25, 0.63)		0.90 (0.50, 1.63)	
PFS per IRC				
Events, n (%)	37 (44.0)	33 (70.2)	44 (52.4%)	18 (52.9%)
Median PFS (95% CI), months	20.4 (9.3, NE)	2.0 (1.4, 2.7)	9.6 (6.4, 20.5)	7.8 (3.6, 11.5)
HR (95% CI) [a]	0.25 (0.15, 0.41)		0.69 (0.39, 1.21)	
CR per IRC				
N (%)	51 (60.7%)	8 (17.0%)	50 (59.5%)	11 (32.4%)
95% CI	(49.5%, 71.2%)	(7.6%, 30.8%)	(48.3%, 70.1%)	(17.4%, 50.5%)
Difference (95% CI)	43.7% (27.0%, 60.3%)		27.2% (6.2%, 48.1%)	
ORR per IRC				
N (%)	60 (71.4%)	12 (25.5%)	57 (67.9%)	19 (55.9%)
95% CI	(60.5%, 80.8%)	(13.9%, 40.3%)	(56.8%, 77.6%)	(37.9%, 72.8%)
Difference (95% CI)	45.9% (28.5%, 63.3%)		12.0% (-9.5%, 33.5%)	

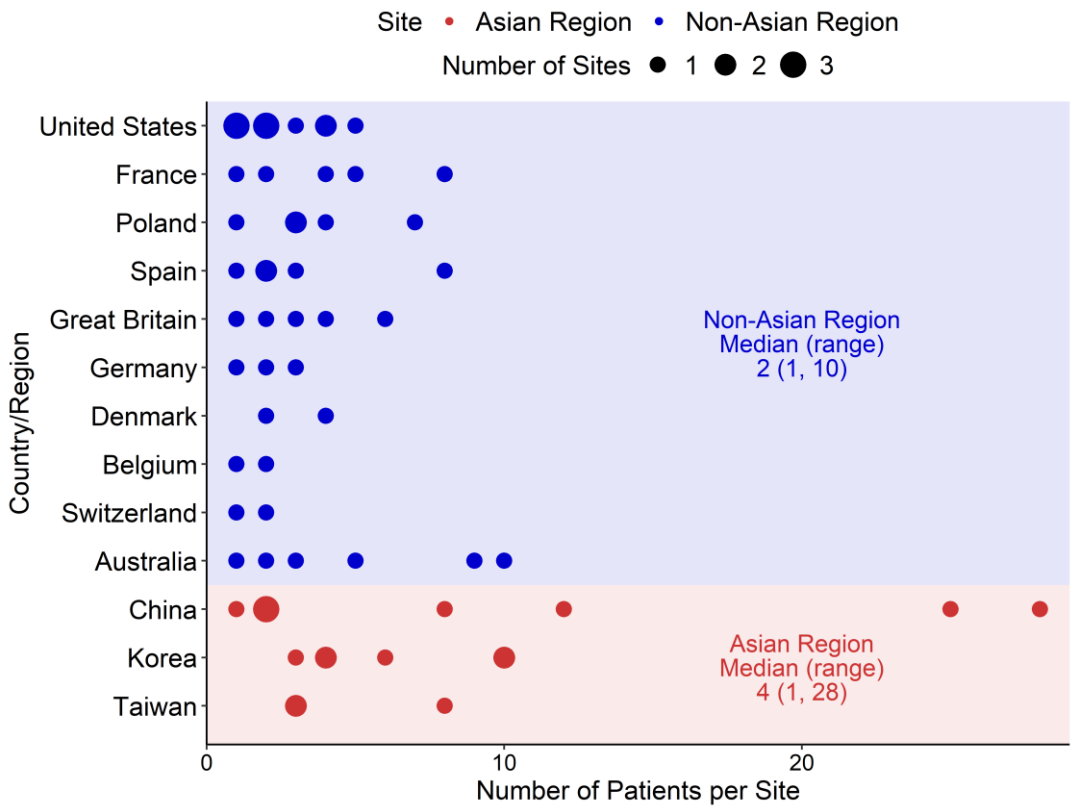
[a] Estimated from unstratified Cox regression
Source: FDA analysis, Data cutoff: 16 February 2024

Appendix 17: Study Enrollment

FDA Table 30: Patient Enrollment per Site

	Number of Sites	Number of enrolled Patients	Number of Patients per Site median (range)
Non-Asian Region	**45**	**143**	**2 (1, 10)**
US	10	25	2 (1, 5)
Europe	29	88	2 (1, 8)
France	5	20	4 (1, 8)
Poland	5	18	3 (1, 7)
Spain	5	16	2 (1, 8)
UK	5	16	3 (1, 6)
Germany	3	6	2 (1, 3)
Denmark	2	6	3 (2, 4)
Belgium	2	3	1.5 (1, 2)
Switzerland	2	3	1.5 (1, 2)
Australia	6	30	4 (1, 10)
Asian Region	**17**	**131**	**4 (1, 28)**
China	8	80	5 (1, 28)
Korea	6	37	5 (3, 10)
Taiwan	3	14	3 (3, 8)
Source: FDA analysis, Data cutoff: 16 February 2024			

FDA Figure 7: Enrollment per Site by Country/Region



Source: FDA analysis, Data cutoff: 16 February 2024

Appendix 18: Safety Profile of Glofit-GemOx and R-GemOx based on Cycle Cutoffs

FDA Table 31: The Safety Profile of Glofit-GemOx per Region by Cycle Cutoffs

	Non-Asian Region Glofit-GemOx n (%)			Asian Region Glofit-GemOx n (%)		
	Any AE	Grade 3-4 AE	Grade 5 AE	Any AE	Grade 3-4 AE	Grade 5 AE
Cycle 1-2[a] n=80; n=80	76 (95)	40 (50)	2 (2.5)	79 (99)	44 (55)	2 (2.5)
Cycle 1-4[a] n=71; n=74	70 (99)	40 (56)	2 (2.8)	74 (100)	47 (64)	0
Cycle 1-6[a] n=60; n=61	59 (98)	37 (62)	0	61 (100)	40 (66)	0
Cycle 1-8[a] n=56; n=55	56 (100)	37 (66)	0	55 (100)	37 (67)	1 (1.8)
Cycle 1-12[a] n=45 n=32	45 (100)	33 (73)	0	32 (100)	23 (72)	0

AE: Adverse Event; n/a: not applicable

[a] Based on patients who received treatment for that duration (n=Non-Asian Region; n=Asian Region). AEs counted are those up to 30 days after the last cycle listed.

Source: FDA Analysis, Data cutoff: 16 February 2024

FDA Table 32: The Safety Profile of R-GemOx per Region by Cycle Cutoffs

	Non-Asian Region R-GemOx n (%)			Asian Region R-GemOx n (%)		
	Any AE	Grade 3-4 AE	Grade 5 AE	Any AE	Grade 3-4 AE	Grade 5 AE
Cycle 1-2[a] n=39; n=36	37 (95)	13 (33)	0	36 (100)	9 (25)	1 (2.8)
Cycle 1-4[a] n=31; n=18	30 (97)	15 (48)	0	18 (100)	7 (39)	1 (6)
Cycle 1-6[a] n=21; n=10	20 (95)	8 (38)	1 (5)	10 (100)	4 (40)	0
Cycle 1-8[a] n=16; n=10	15 (94)	6 (38)	0	10 (100)	4 (40)	0
Cycle 1-12[a] n=0; n=0	N/A	N/A	N/A	N/A	N/A	N/A

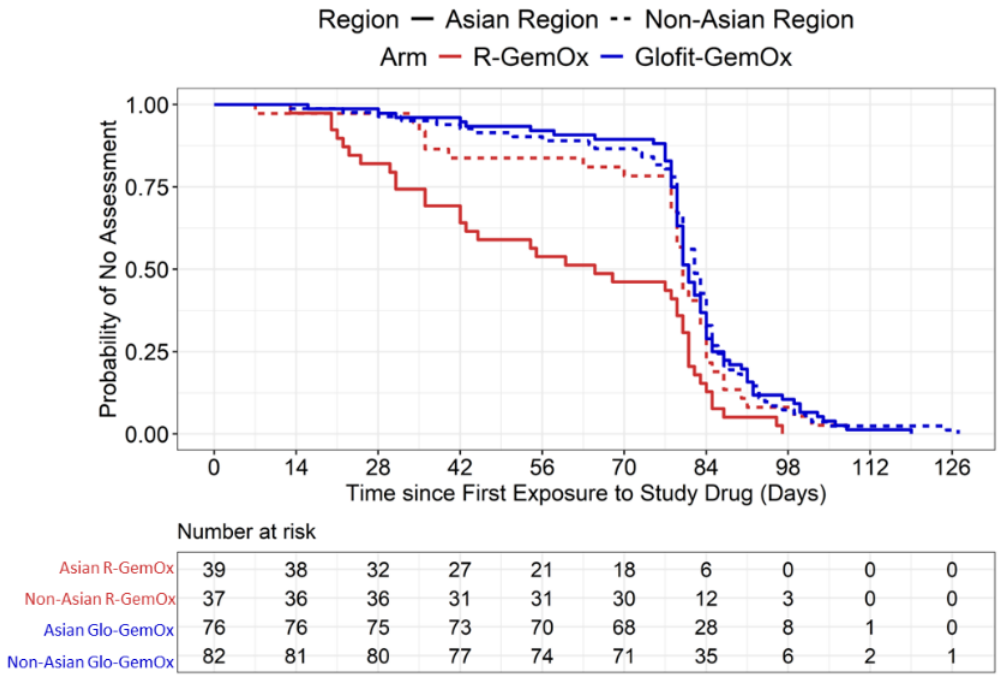
AE: Adverse Event; n/a: not applicable

[a] Based on patients who received treatment for that duration (n=Non-Asian Region; n=Asian Region). AEs counted are those up to 30 days after the last cycle listed.

Source: FDA Analysis, Data cutoff: 16 February 2024

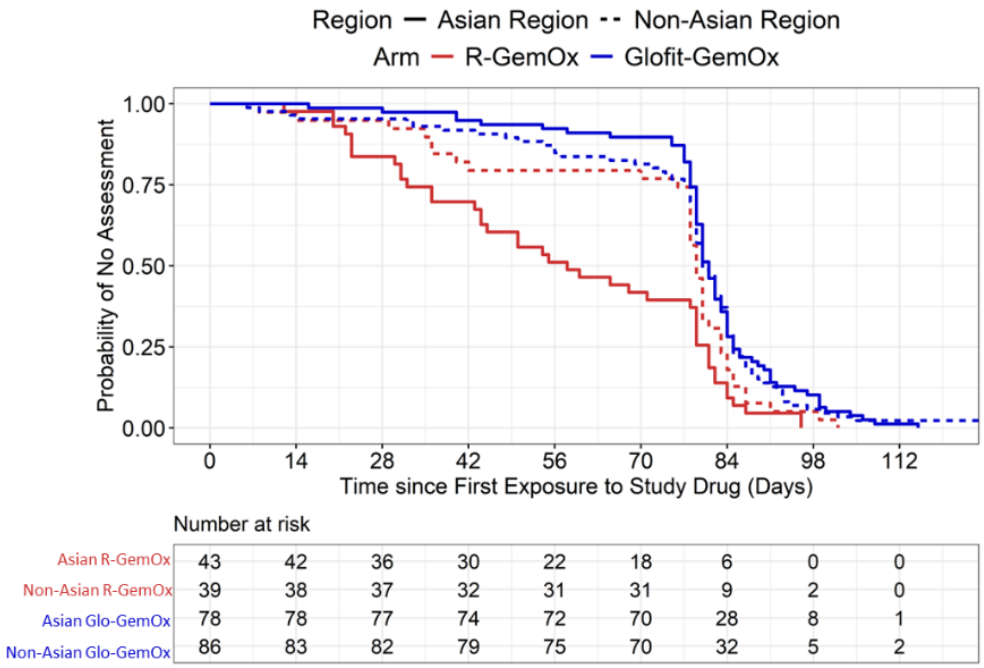
Appendix 19: Time to First Efficacy Assessment

FDA Figure 8: Time to First Efficacy Assessment per IRC



Source: FDA Analysis, Data cutoff: 16 February 2024

FDA Figure 9: Time to First Efficacy Assessment per Investigator



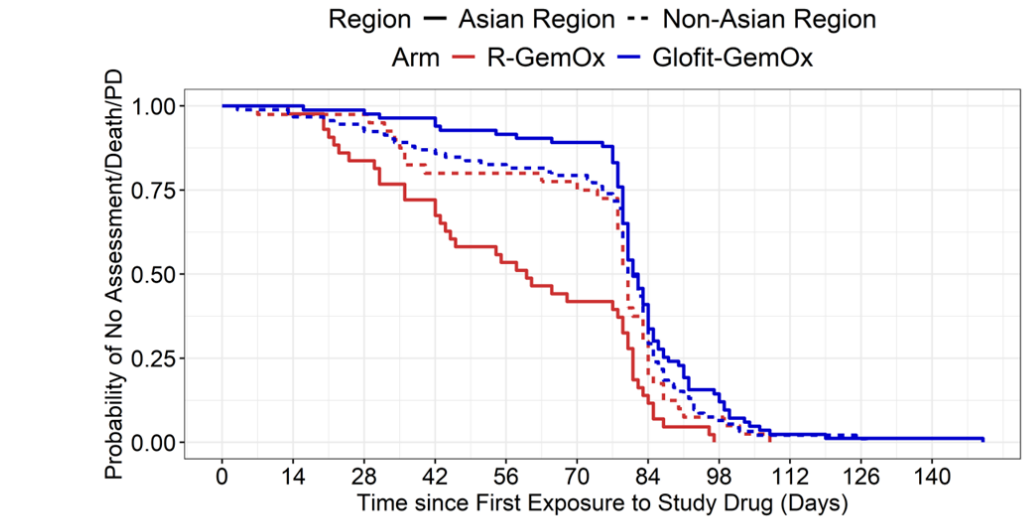
Source: FDA Analysis, Data cutoff: 16 February 2024

FDA Figure 10 presents "Time to First Observed Efficacy Outcome per IRC" by region. An event is defined as the first occurrence of:

- A response assessment
- Progression
- Death

Patients who do not have an efficacy outcome observed are censored according to PFS per IRC rules. As demonstrated in FDA Table 33, all patients who were censored had PFS per IRC observations censored at the time of randomization.

FDA Figure 10: Time to First Observed Efficacy Outcome per IRC



Note: Patients who were not treated (N=6) were censored at Day 1.

Source: FDA Analysis, Data cutoff: 16 February 2024

FDA Table 33: Outcome Breakdown of First Efficacy Outcome in ITT

	Asian Region		Non-Asian Region	
	Glofit-GemOx N=84	R-GemOx N=47	Glofit-GemOx N=99	R-GemOx N=44
Efficacy Outcome, n (%)				
Censored at randomization	1 (1%)	3 (6%)	5 (5%)	4 (9%)
Death	4 (5%)	3 (6%)	8 (8%)	1 (2%)
Progression	3 (4%)	2 (4%)	4 (4%)	2 (5%)
Efficacy Assessment per IRC	76 (90%)	39 (83%)	82 (83%)	37 (84%)
Source: FDA analysis, Data cutoff: 16 February 2024				