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- **ODAC@fda.hhs.gov**

Glofitamab-gxbm

FDA Opening Remarks

Oncologic Drugs Advisory Committee Meeting

May 20, 2025

Nicole Gormley, MD
Division of Hematologic Malignancies II
Office of Oncologic Diseases

Outline

- STARGLO Trial Results
- Regulatory Considerations
  - Foreign Data
  - Applicability of Results to a U.S. Patient Population

Glofitamab-gxbm

- Bispecific CD20-directed CD3 T-cell engager
- Granted Accelerated Approval on June 15, 2023
  - For the treatment of adult patients with relapsed or refractory 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
  - Approval was based on the results of a single-arm trial, NP30179
    - Overall response rate of 56% and median duration of response of 18.4 months
  - STARGLO was intended as the confirmatory trial

STARGLO Trial

Eligibility

- R/R DLBCL
- At least ≥ 1 line of prior therapy
- Not eligible for transplant
- Stratification factors: Relapsed vs. refractory disease, 2nd line vs 3 or more lines

N=274

2:1

Glofitamab x 12 cycles

GemOx x 8 cycles

N=183

Rituximab x 8 cycles

GemOx x 8 cycles

N=91

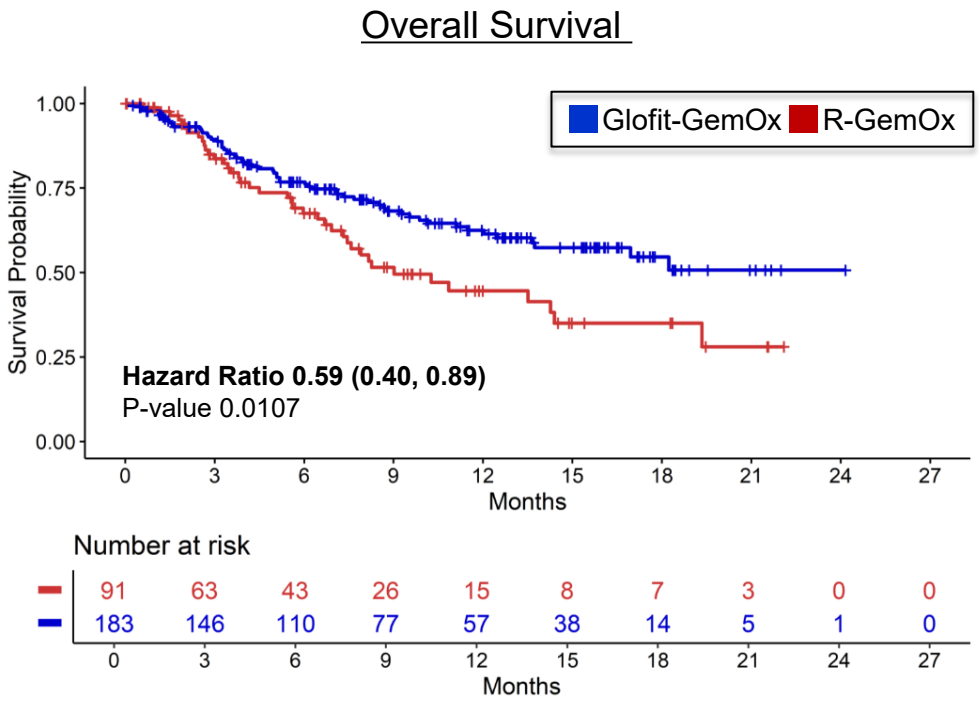
Endpoints

Primary:
Overall Survival

Key Secondary:
- PFS by IRC
- Best CR by IRC
- DOCR by IRC

Abbreviations: R/R: Relapsed/Refractory; DLBCL: Diffuse Large B-cell Lymphoma; GemOx: Gemcitabine and Oxaliplatin; IRC: Independent Review Committee; PFS: Progression-Free Survival; CR: Complete Response; DOCR: Duration of Complete Response

STARGLO Trial Results



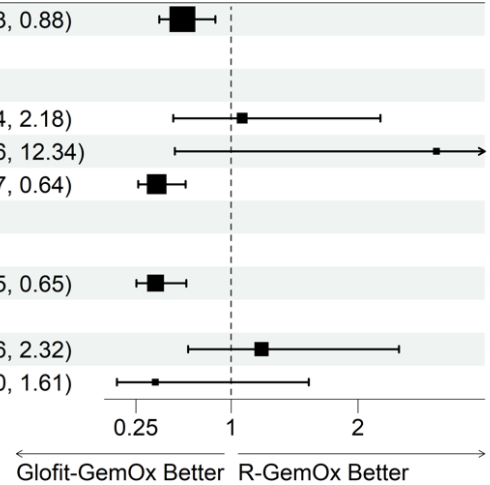
Key Secondary	Glofit-GemOx N=183	R-GemOx N=91
PFS per IRC		
Median PFS (95% CI)	12.1 (6.8, 18.3)	3.3 (2.5, 5.6)
Stratified HR (95% CI)	0.37 (0.25, 0.55)	
2-sided *p*-value	<0.001	
CR per IRC		
CR per IRC (95% CI)	50.3%	22.0%
Difference (95% CI)	28.3% (16.3%, 40.3%)	
2-sided *p*-value	<0.001	
DOCR per IRC	N = 92	N = 20
Event, n (%)	15 (16.3%)	4 (20.0%)
Median DOCR (95% CI)	14.3 (14.3, NE)	NE (6.4, NE)

Abbreviations: Glofit-GemOx: Glofitamab, Gemcitabine and Oxaliplatin; R-GemOx: Rituximab, Gemcitabine and Oxaliplatin; HR: Hazard Ratio; CI: Confidence Interval; PFS: Progression-Free Survival; CR: Complete Response; DOCR: Duration of Complete Response

Source: FDA analysis
Data Cut-off: 2023

STARGLO Overall Survival Results

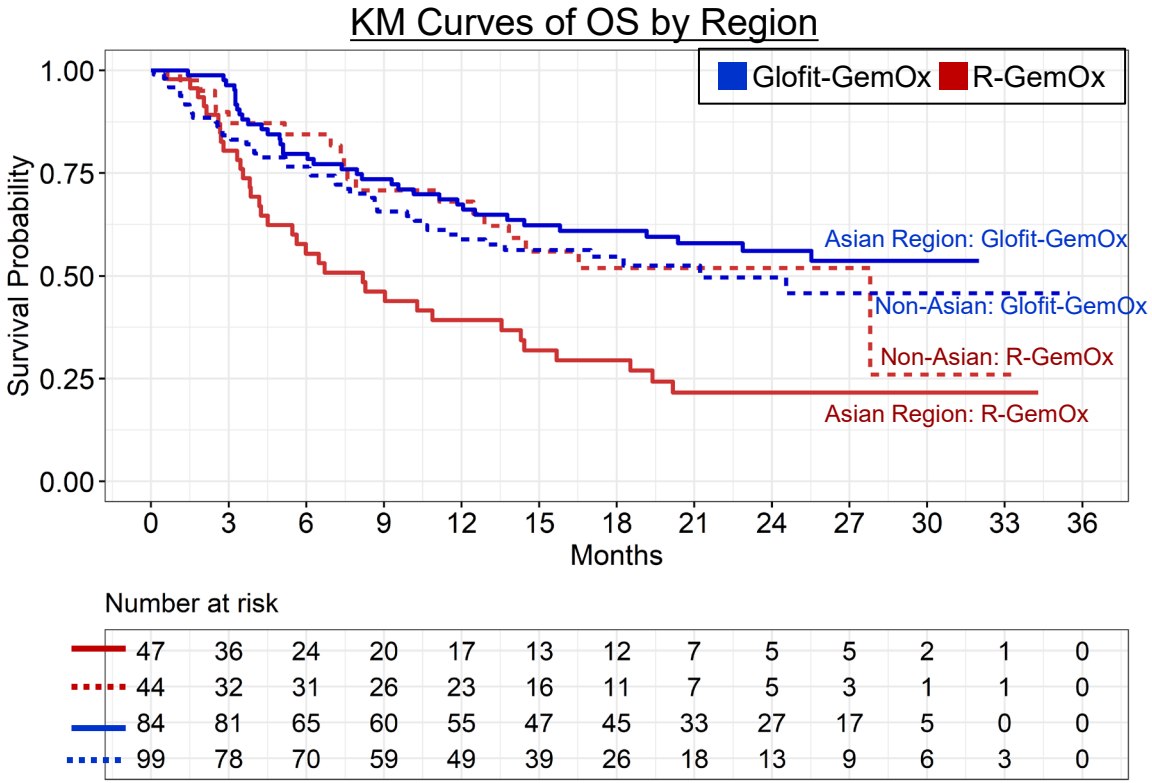
Baseline Risk Factors	Total N	R-GemOx (N=91) n	R-GemOx (N=91) Events	R-GemOx (N=91) Median (Months)	Glofit-GemOx (N=183) n	Glofit-GemOx (N=183) Events	Glofit-GemOx (N=183) Median (Months)	Hazard Ratio	95% Wald CI
All Patients	274	91	52	12.9	183	80	25.5	0.62	(0.43, 0.88)
Geographic Region									
Europe	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)



Abbreviations: R-Gem-Ox: Rituximab, Gemcitabine and Oxaliplatin; Glofit-Gem-Ox: Glofitamab, Gemcitabine and Oxaliplatin; CI: Confidence Interval

Source: FDA analysis
Data Cut-off: 2024

Differential OS Effects Across Regions



OS	Non-Asian Region	
	Glofit-GemOx N=99	R-GemOx N=44
Median OS	21.2 mo	27.8 mo
HR (95%CI)	**1.06 (0.61, 1.84)**	

U.S. HR 2.62 (0.56, 12.34)

OS	Asian Region	
	Glofit-GemOx N=84	R-GemOx N=47
Median OS	NE	8.2 mo
HR (95%CI)	**0.39 (0.25, 0.63)**	

Abbreviations: Glofit-GemOx: Glofitamab, Gemcitabine and Oxaliplatin; R-GemOx: Rituximab, Gemcitabine and Oxaliplatin; HR: Hazard Ratio; CI: Confidence Interval; NE: Not estimable

Source: FDA analysis
Data Cut-off: 2024

STARGLO PFS and Response Rate Results

	Asian Region		Non-Asian Region	
	Glofit-GemOx N=84	R-GemOx N=47	Glofit-GemOx N=99	R-GemOx N=44
PFS per IRC				
Median PFS	20.4 mo	2.0 mo	9.2 mo	7.8 mo
HR (95% CI)	0.25 (0.15, 0.41)		0.81 (0.48, 1.35)	
CR per IRC				
n (%)	51 (60.7)	8 (17)	56 (56.6)	15 (34.1)
Difference	43.7%		22.5%	
ORR per IRC				
n (%)	60 (71.4)	12 (25.5)	65 (65.7)	25 (56.8)
Difference	45.9%		8.8%	

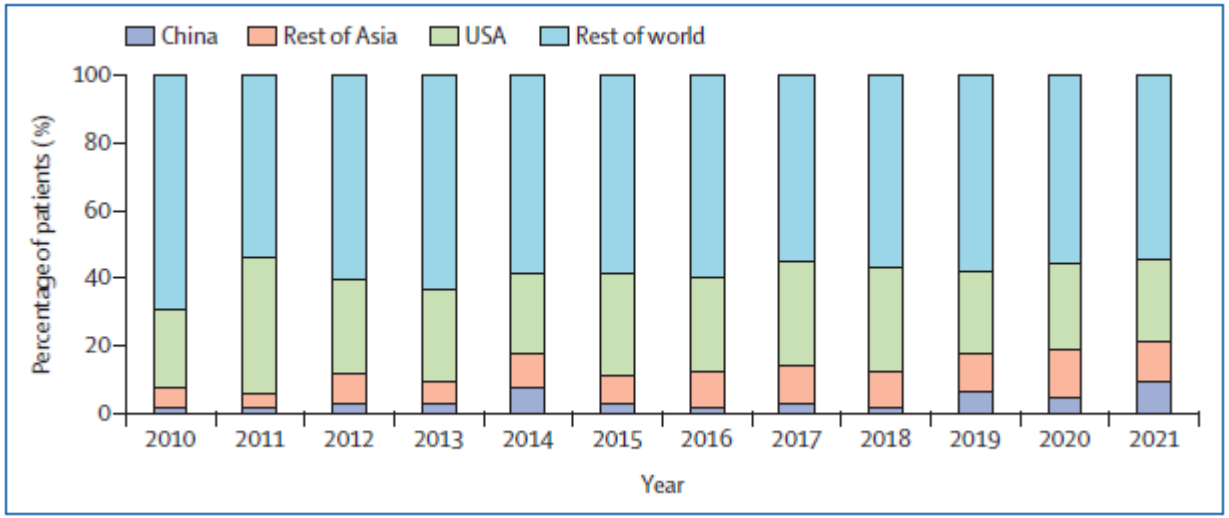
Abbreviations: Glofit-GemOx: Glofitamab, Gemcitabine and Oxaliplatin; R-GemOx: Rituximab, Gemcitabine and Oxaliplatin; PFS: Progression-Free Survival, IRC: Independent Review Committee, HR: Hazard Ratio; CI: Confidence Interval, CR: complete response, ORR: overall response rate

Source: FDA analysis
Data Cut-off: 2024

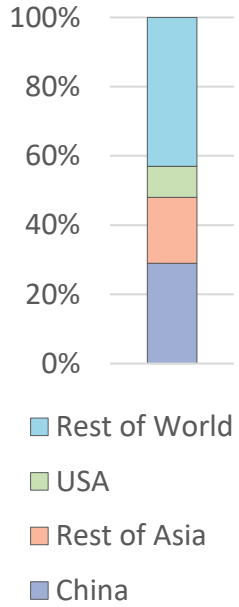
Foreign Data

- An application based solely on foreign clinical data meeting U.S. criteria for marketing approval may be approved if:
  - Foreign data are applicable to the U.S. population and U.S. medical practice
  - Studies have been performed by clinical investigators of recognized competence
  - FDA is able to validate the data through an on-site inspection or other appropriate means
- FDA will apply this policy in a flexible manner according to the nature of the drug and the data being considered

Global Drug Development



STARGLO



Singh Lancet Oncol 2022

STARGLO Demographics

Parameter		ITT Population, N= 274
Age	Median (range), years	68 (20-88)
Sex, n(%)	Male	158 (58)
	Female	116 (42)
Race, n(%)	Asian	137 (50)
	White	115 (42)
	Unknown	19 (7)
	Black or African American	3 (1)
	American Indian	0
	Native Hawaiian or Pacific Islander	0
Ethnicity, n(%)	Hispanic	16 (6)
	Not Hispanic	242 (88)
	Not Stated or Unknown	16 (6)

Initiatives to Address U.S. Representation

- Food and Drug Omnibus Reform Act (FDORA)
  - Section 3601 of FDORA requires that sponsors submit a Diversity Action Plan for a Phase III study or other pivotal study
    - Sponsor's goals for enrollment in the clinical study
      - Disaggregated by age, sex, race, and ethnicity
    - Sponsor's rationale for such goals
    - Explanation of how the sponsor intends to meet such goals

Food and Drug Omnibus Reform Act of 2022 (FDORA) included as part of the Consolidated Appropriations Act (dec 2022) (P.L. 117-328)

Initiatives to Address U.S. Representation

- Multiregional clinical trial
  - Trial conducted in multiple countries, geographical regions, or regulatory regions
  - Strengths
    - Rapid accrual
    - Generation of evidence to support use of the drug in multiple regions
    - Identification of factors that may predict regional difference
    - Improve the ability to conduct trials in rare diseases
    - Promote clinical development efficiencies

FDA Guidance for Industry: Considerations for Generating Clinical Evidence from Oncology Multiregional Clinical Development Programs

ICH E17 General Principles for Planning and Design of Multiregional Clinical Trials

"Sponsors planning a MRCT intended to support approval of an oncologic drug should plan to enroll a sufficient number of U.S. participants in the trial to help ensure that the evidence generated supports a robust assessment of the safety and effectiveness of the drug in U.S. patients with the disease and in the context of U.S. standard of care practices and treatments"

Abbreviations: MRCT: Multiregional Clinical Trial

FDA Guidance for Industry: Considerations for Generating Clinical Evidence from Oncology Multiregional Clinical Development Programs

Applicability of Foreign Data to U.S.

- Intrinsic Factors
  - Genetic polymorphism, age, gender, height, weight, organ dysfunction, etc.
- Extrinsic Factors
  - Medical practice, diet, environmental exposures, socio-economic factors, use of tobacco or alcohol, etc.

ICH E5 Ethnic Factors in the Acceptability of Foreign Clinical Data

Applicability of Foreign Data to U.S.

- Patient-related Factors
  - Genetic ancestral background, exposure to disease risk factors
- Disease-related Factors
  - Prevalence of disease subtypes, frequency and distribution of molecular drivers of oncogenesis
- Healthcare system Factors
  - Access to health care, cancer screening practices, availability and affordability of cancer treatments
- Socio-cultural factors
  - Diets, cultural beliefs, use of alternative treatments

FDA Guidance for Industry: Considerations for Generating Clinical Evidence from Oncology Multiregional Clinical Development Programs

STARGLO Trial Applicability

- Patient-related factors
  - Age, Race/Ethnicity, Transplant Ineligibility
- Disease-related factors
  - Cell of Origin, Prior Therapy
- Healthcare Systems
  - Subsequent therapies, Transplant Refusal
  - Trial Related
    - Shorter drug exposure, Early Response assessments

Subgroups

- Subgroups must be interpreted with caution
- Provide valuable information about the consistency of the benefit risk profile
- A consistent benefit-risk assessment across subgroups provides assurances that the treatment benefit observed applies to the entire patient population studied

STARGLO: Asian subgroup represents approximately 50% of the population

Evidentiary Criteria for Approval

- Safety
  - Sufficient information to determine that the drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling
- Effectiveness
  - Substantial evidence of effectiveness
    - Based on adequate and well-controlled investigations
    - The drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling

Guidance for Industry: Expedited Programs for Serious Conditions - Drugs and Biologics.
FD&C Act Section 505(d) (21 U.S.C. § 355(d))

Evidentiary Criteria for Approval

- Safety
- Effectiveness
  - Substantial evidence of effectiveness
    - Historically, based on **Two** adequate and well-controlled trials
    - If **One** trial is used, the trial should demonstrate a clinically meaningful effect of sufficient magnitude and robustness with demonstration of internal consistency

Guidance for Industry: Expedited Programs for Serious Conditions - Drugs and Biologics
FD&C Act Section 505(d) (21 U.S.C. § 355(d))

Discussion

- FDA is not seeking the advice of the Committee as to whether STARGLO should be used to convert the accelerated approval of glofitamab to traditional approval, rather we are asking the committee to discuss if the results of the STARGLO trial are applicable to a U.S. patient population

Discussion Topic

- Discuss how the differential results observed in the Asian and Non-Asian regions impact the overall interpretation of the STARGLO trial results and the generalizability to a U.S. patient population


FDA
U.S. FOOD & DRUG
ADMINISTRATION

Glofitamab-gxbm (COLUMVI)
BLA 761309

Oncologic Drugs Advisory Committee Meeting
May 20, 2025

Margret Merino, MD
Division of Hematologic Malignancies II
Office of Oncologic Diseases

Outline

- Treatment Landscape
- STARGLO Trial
- Inconsistent Treatment Effects Across Endpoints
  - Patient and Disease-related factors
  - Study and Healthcare system factors
- Applicability to the U.S. Patient Population

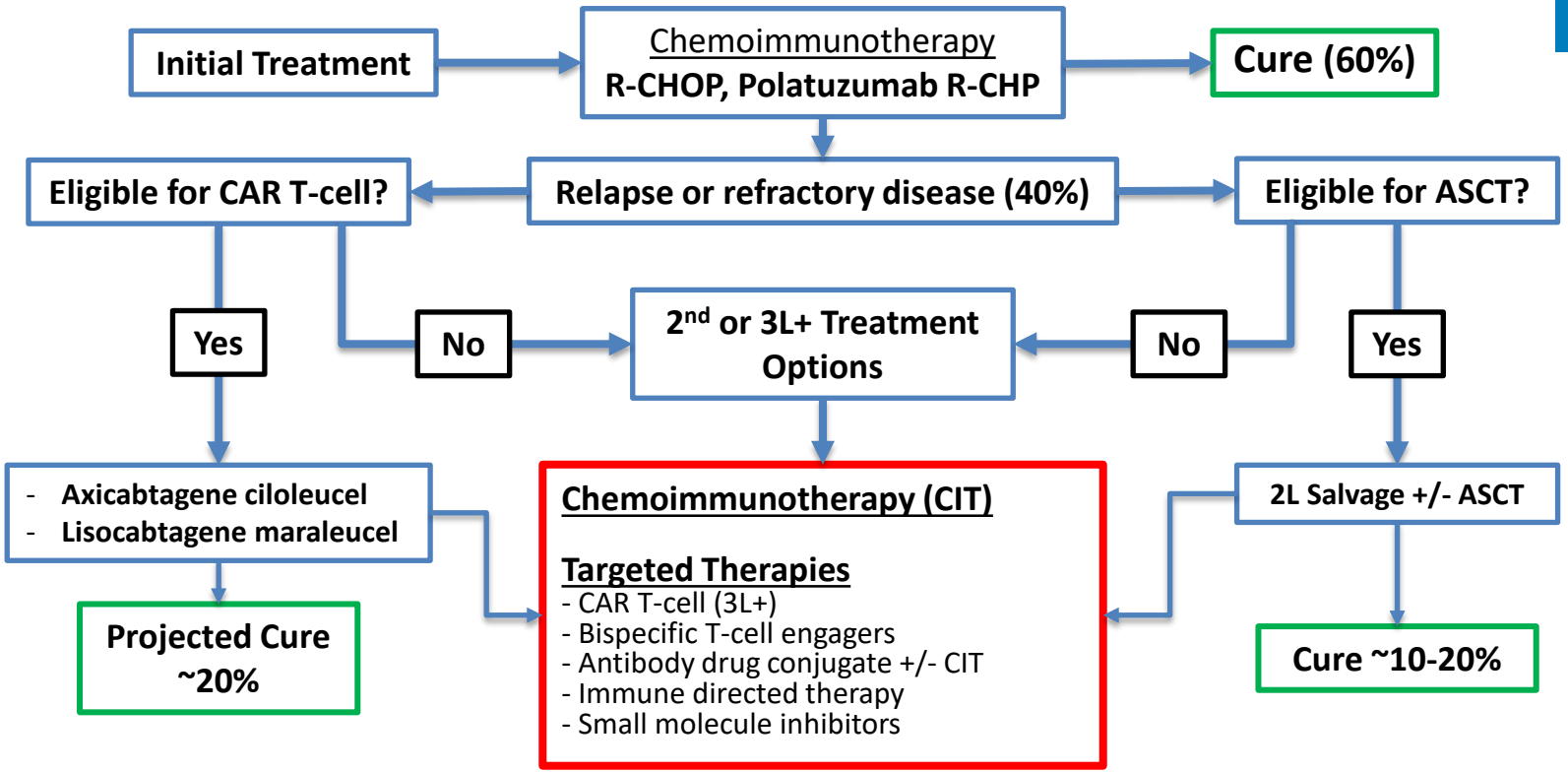
Diffuse Large B-cell Lymphoma, Not Otherwise Specified (DLBCL, NOS)

- Subtype of Large B-cell Lymphoma - heterogenous
- Diagnosis and subtyping is based on histology and/or molecular analysis
- Within DLBCL – further heterogeneity and subtypes
- Poor prognostic features
  - Age > 60 years, ECOG Performance Score ≥ 2
  - Advanced disease
  - MYC, BCL2, BCL6 rearrangements and abnormalities
  - Cell of origin (COO) – ABC subtype

Abbreviations: ABC – Activated B cell

Ziepert Journal of Clinical Oncology (JCO) 2010
Rosenwald N Engl Journal Med, 2002, Scott JCO 2015

Initial Treatment for DLBCL



Abbreviations: DLBCL: Diffuse large B-cell lymphoma; ASCT: autologous stem cell transplant; CAR T: chimeric antigen receptor T-cell therapy; R-CHOP: Rituximab, Cyclophosphamide, Adriamycin, Vincristine, Prednisone; R-CHP: Rituximab, Cyclophosphamide, Adriamycin

Westin Blood 2022, Fabbri Semin Hematol 2023

FDA Approved and SOC Treatments for R/R LBCL

Drug/Combination Class	Agent/Regimen	Indication
Chemoimmunotherapy	**R-GemOx,** GDP, CEOP, ICE, ESHAP, MINE	Considered SOC options*
T-cell Engager	Epcoritamab**	≥ 2 prior lines
	Glofitamab**	
Antibody Drug Conjugate +/- chemoimmunotherapy	Polatuzumab vedotin + BR	
	Brentuximab vedotin + R2	
	Loncastuximab teserine**	
Immune Directed Therapy	Tafasitamab + Lenalidomide**	
Small molecule inhibitor	Selinexor**	≥ 3 prior lines
CD-19 directed CAR T-cell	Lisocaptagene maraleucel	Early relapse or refractory or ≥ 2 prior lines
	Axicaptagene autoleucel	
	Tisagenlecleucel	≥ 2 prior lines

*May not be approved for R/R LBLC after 1 prior therapy but are commonly used
**Accelerated approval

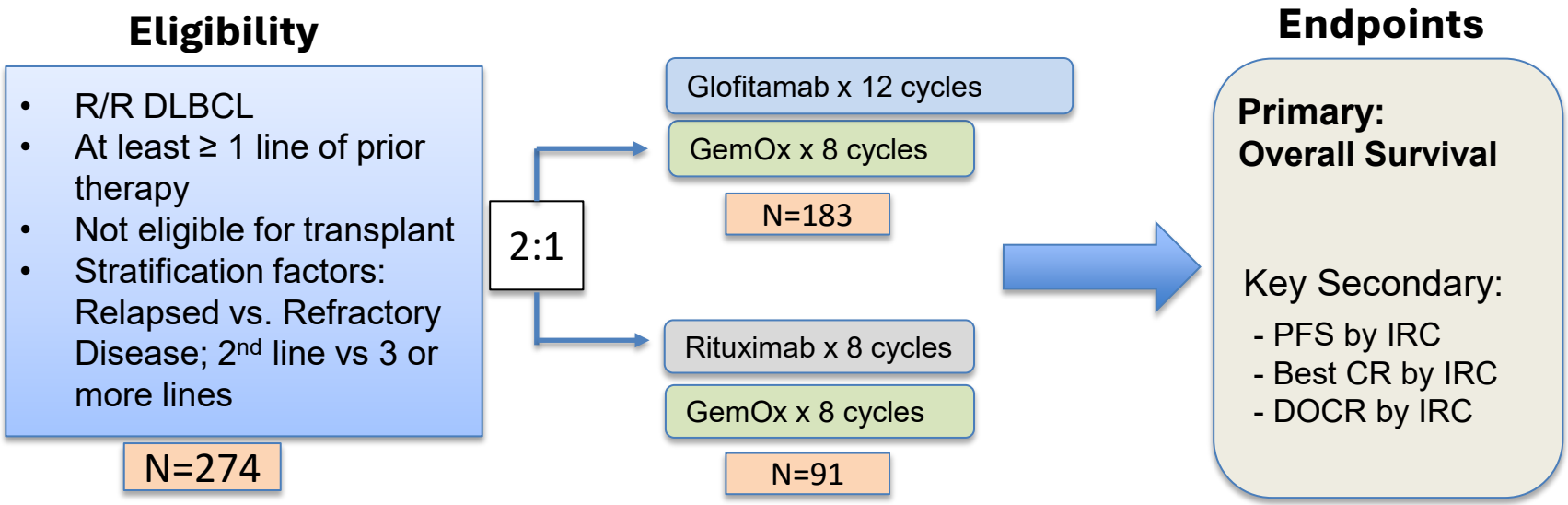
Abbreviations: R/R: Relapsed, refractory; LBCL: Large B-cell lymphoma; R-GemOx: Rituximab, Gemcitabine Oxaliplatin; GDP: Gemcitabine, Dexamethasone, Cisplatin; CEOP: Cyclophosphamide, Etoposide, Vincristine, Prednisone; ICE: Ifosphamide, Carboplatin, Etoposide; ESHAP: Etoposide, Methylprednisolone, Cytarabine, Cisplatin; MINE: Mesna, Ifosphamide Mitoxantrone, Etoposide, BR: Bendamustine, Rituximab; R2: Rituximab, Lenalidomide; SOC: Standard of Care; CAR T: Chimeric Antigen Receptor T-cell therapy

Glofitamab-gxbm

- Accelerated Approval
  - *Treatment of adult patients with relapsed or refractory DLBCL, NOS or large B-cell lymphoma (LBCL) arising from follicular lymphoma, after 2 or more lines of systemic therapy*
  - Obinutuzumab pretreatment and a glofitamab step-up regimen are used for the mitigation of CRS

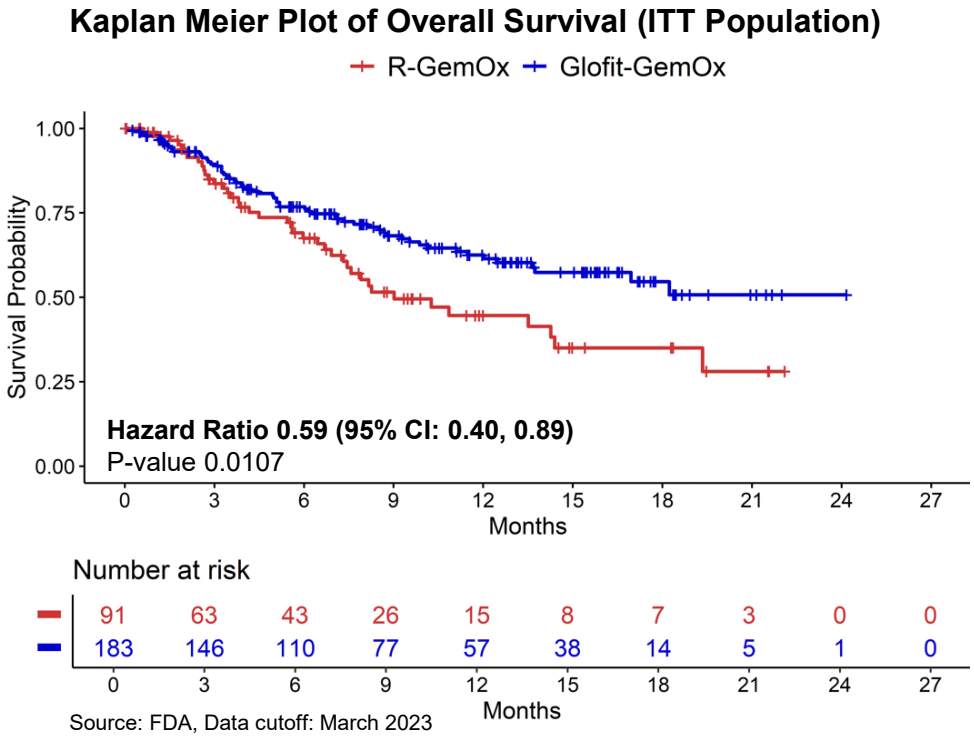
Abbreviations: DLBCL, NOS: Diffuse large B-cell lymphoma, not otherwise specified; CRS: Cytokine release syndrome

STARGLO Trial



Abbreviations: R/R: Relapsed/Refractory; GemOx: Gemcitabine and Oxaliplatin; IRC: Independent Review Committee; PFS: Progression-Free Survival; CR: Complete Response; DOCR: Duration of Complete Response

STARGLO – ITT Results (Interim Analysis)



Source: FDA, Data cutoff: March 2023

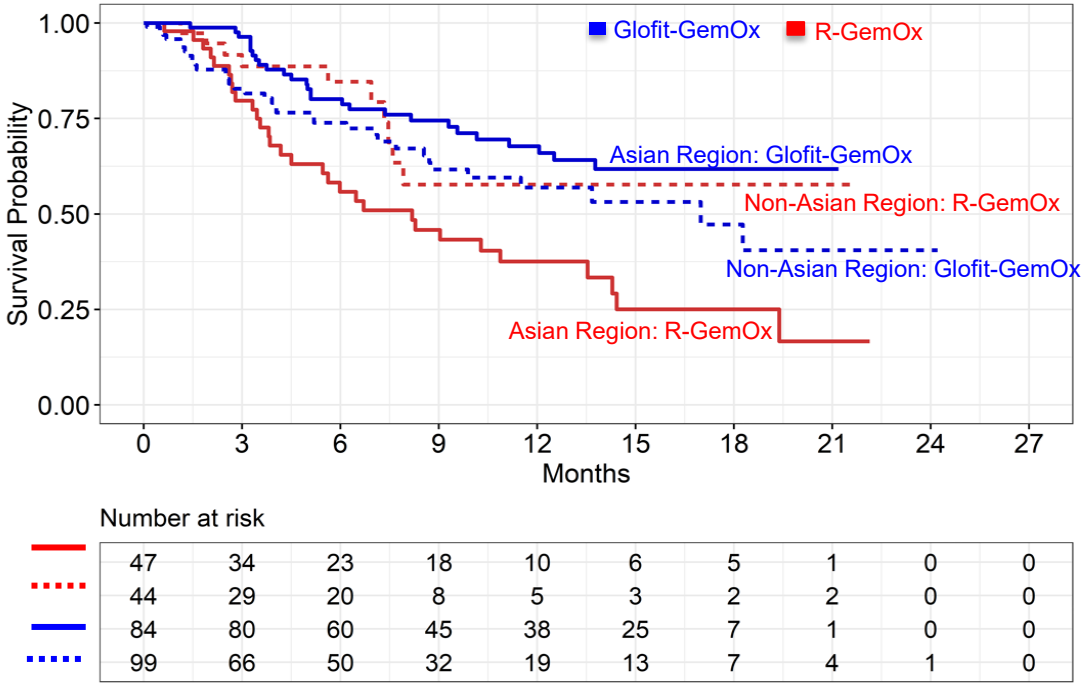
Key Secondary	Glofit-GemOx N = 183	R-GemOx N = 91
✓ Progression-free survival (PFS) per IRC		
Event, n (%)	68 (37.2%)	44 (48.4%)
Median PFS (95% CI)	12.1 (6.8, 18.3)	3.3 (2.5, 5.6)
Stratified HR (95% CI)	**0.37 (0.25, 0.55)**	
2-sided *p*-value	<0.001	
✓ Complete Response (CR) per IRC		
CR per IRC (95% CI)	50.3% (42.8%, 57.7%)	22.0% (14.0%, 31.9%)
Difference (95% CI)	**28.3% (17.1%, 39.5%)**	
2-sided *p*-value	<0.001	
✗ DOCR per IRC	N = 92	N = 20
Event, n (%)	15 (16.3%)	4 (20.0%)
Median DOCR (95% CI)	14.3 (14.3, NE)	NE (6.4, NE)

Source: FDA, Data cutoff: March 2023

Abbreviations: CI: Confidence interval; DOCR: Duration of complete response; HR: Hazard ratio; IRC: Independent Review Committee; ITT: Intention-to-treat; NE: Not estimable; Glofit: Glofitamab; R: Rituximab; GemOx: Gemcitabine, Oxaliplatin

Differential OS Effects Across Regions (IA)

Kaplan Meier Curve of Overall Survival by Region



Source: FDA, Data cutoff: March 2023

OS Results and Follow-up by Region (IA)

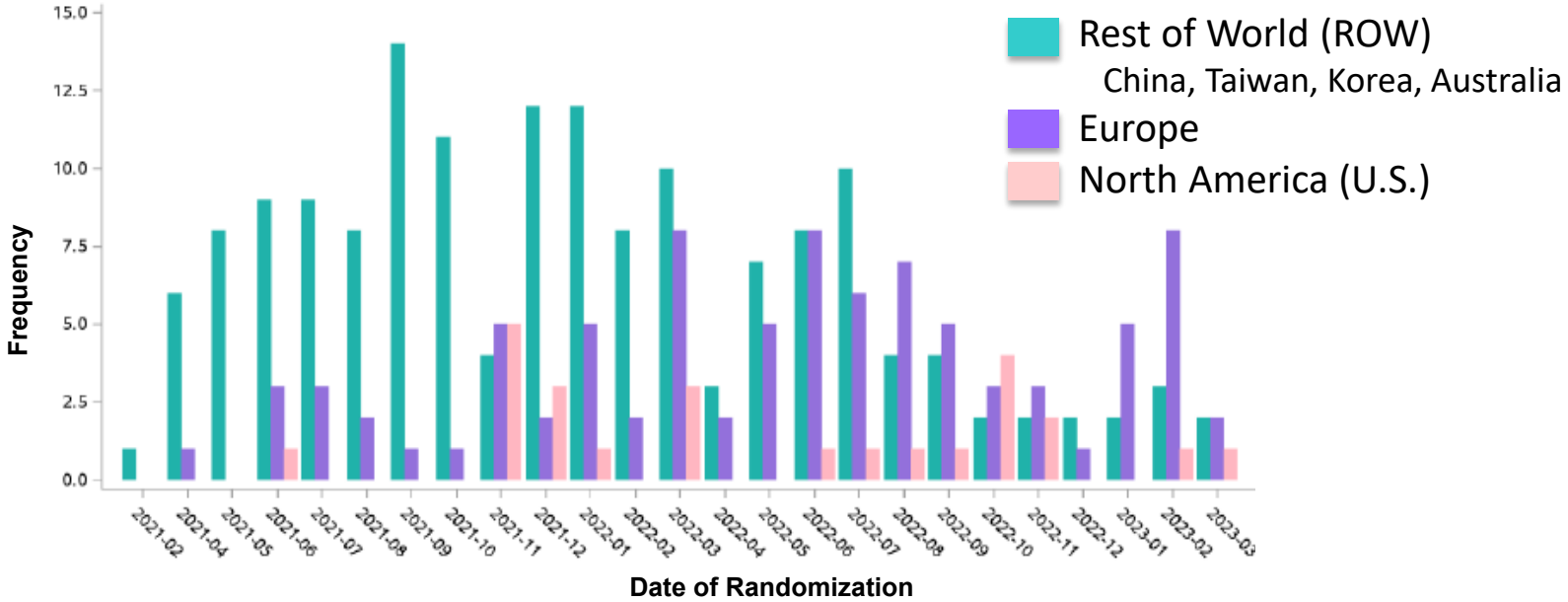
	Asian Region N = 131		Non-Asian Region N = 143	
	Glofit-GemOx	R-GemOx	Glofit-GemOx	R-GemOx
Events, (%)	32%	64%	34%	23%
Median OS (months) (95% CI)	NE (13.8,NE)	8.2 (4.5,13.5)	17.0 (9.9, NE)	NE (7.5, NE)
HR (95% CI)	**0.37 (0.22, 0.62)**		**1.3 (0.64, 2.65)**	
Median OS follow-up (months)	**14.6**		**8.7**	

Source: FDA, Data cutoff: March 2023

Abbreviations: OS: Overall survival; IA: Interim analysis; Glofit: Glofitamab; R: Rituximab; GemOx: Gemcitabine, Oxaliplatin; CI: confidence interval; NE: Not estimable; CCOD: Clinical cutoff date

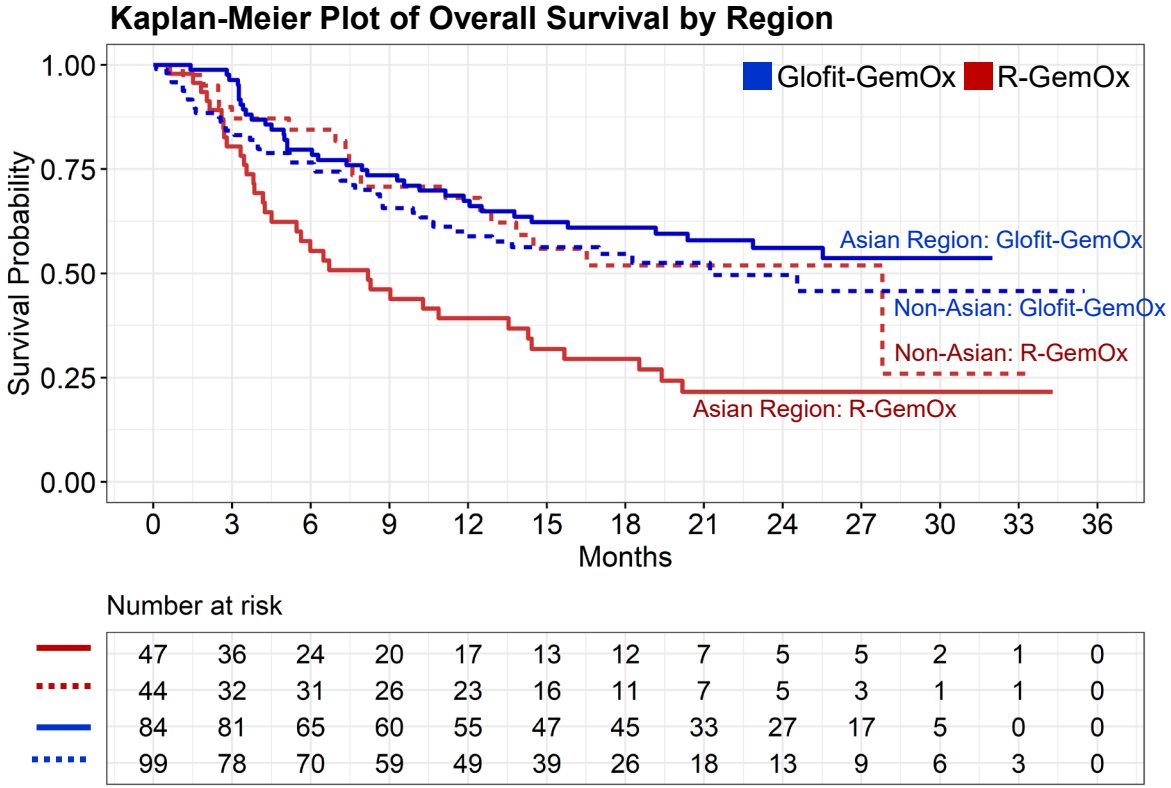
Applicant Assessment – Interim Analysis

- Inconsistent results related to differential follow-up and COVID-19
- Plan for additional analysis after **9 months** of follow-up



Source: Applicant Submission

Differential OS Effects Across Regions (Updated Analysis)



OS	Non-Asian Region	
	Glofit-GemOx N=99	R-GemOx N=44
Median OS	21.2 mo	27.8 mo
HR (95% CI)	**1.06 (0.61, 1.84)**	

OS	Asian Region	
	Glofit-GemOx N=84	R-GemOx N=47
Median OS	NE	8.2 mo
HR (95% CI)	**0.39 (0.25, 0.63)**	

Source: FDA analysis; Data cutoff: FEB 2024

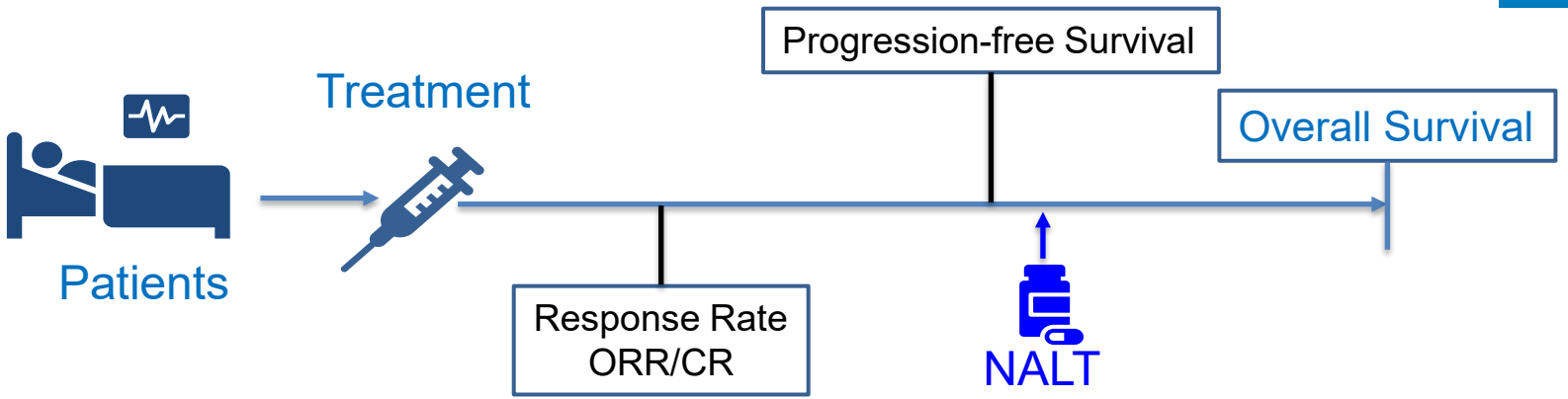
Abbreviations: HR: Hazard ratio; mo: Months

Source: FDA analysis; Data cutoff: FEB 2024

Applicant's Assessment – Updated Analysis

- Differences in new anti-lymphoma therapy (NALT)
- Limitations of subgroup analysis
- Disease characteristics of U.S. patients

New Anti-Lymphoma Therapy (NALT)



- Treatment received after discontinuing study therapy
  - After a PFS event (either IRC or investigator assessed)
  - Independent of a PFS event for other reasons (i.e., toxicity)
- Can impact OS
  - Regional differences in NALT availability and effectiveness

NALT does not impact PFS or ORR/CR

Abbreviations: ORR: Overall response rate; CR: Complete response; PFS: Progression-free survival; IRC: Independent review committee; OS: Overall survival

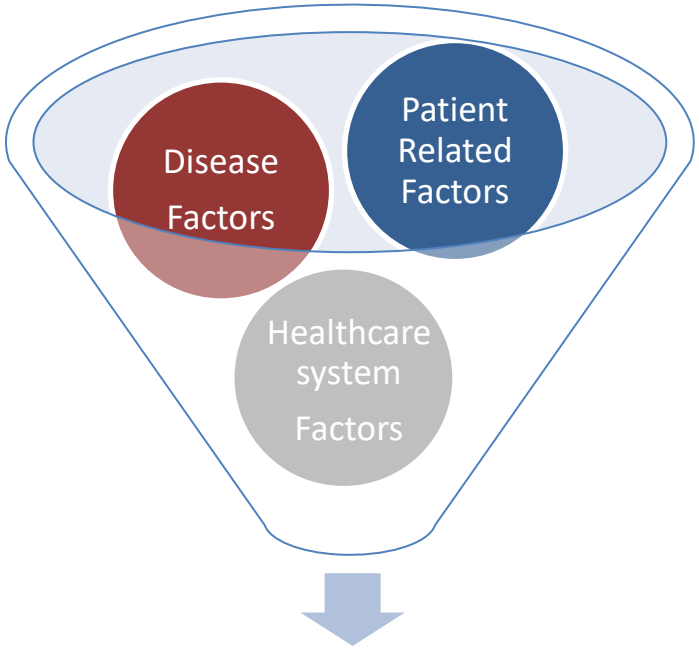
Inconsistent Results Across Multiple Endpoints

Endpoint	ITT (Glofit-GemOx vs R-GemOx)	Asian Region (Glofit-GemOx vs R-GemOx)	Non-Asian Region (Glofit-GemOx vs R-GemOx)
OS	HR: 0.62 (95% CI: 0.43, 0.88)	HR: **0.39** (95% CI: 0.25, 0.63)	HR: **1.06** (95% CI: 0.61, 1.84)
PFS	HR: 0.40 (95% CI: 0.28, 0.57)	HR: **0.25** (95% CI: 0.15, 0.41)	HR: **0.81** (95% CI: 0.48, 1.35)
ORR difference	68% vs 41% 27%	71% vs 26% **46%**	66% vs 57% **9%**
CR difference	58% vs 25% 33%	61% vs 17% **44%**	57% vs 34% **22%**

Source: FDA analysis, CCOD Feb 2024

Abbreviations: ITT: Intention-to treat; OS: Overall survival; HR: Hazard ratio; CI: Confidence interval; PFS: Progression-free survival; ORR: Overall response rate; CR: Complete response

Intrinsic and Extrinsic Factors:



Patient Related Factors
- Age
- Race/ethnicity
- Transplant ineligibility

Disease factors
- Timing of Relapse
- Cell of Origin
- Prior Therapy

Healthcare System Factors
- *Transplant eligibility*
- NALT Availability
- Trial Assessments

Applicability to U.S. Patient Population

- Limited U.S. enrollment – 9% of the trial population
- High representation of patients from Asian Region
  - 48% of total study population enrolled in Asian region
    - 34% in China and Taiwan
- Protocol specified a minimum number of patients from China

Applicability to U.S. Patient Population

- R-GemOx comparator arm
  - Limited use in the U.S. (2-8%) based on utilization and claims data
  - Generally reserved for patients unable to tolerate intensive therapy
  - Administered on a less frequent schedule in STARGLO trial

Yamshon American Journal of Hematology 2025
Applicant Submission, Flatiron Real World Database Longitudinal Access and Adjudication Data (LAAD)

Summary

- Inconsistent treatment effect by region across multiple endpoints
- Patient/Disease differences
  - Age, transplant ineligibility, disease characteristics
- Healthcare System differences
  - Response assessment timing, NALT
- Low U.S. enrollment

Discussion Topics

- Discuss how the differential results observed in the Asian and Non-Asian regions impact the overall interpretation of the STARGLO trial results and the generalizability to a U.S. patient population

Voting Question

Question:

Are the STARGLO population and trial results applicable to the proposed U.S. patient population?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ADMINISTRATION

Glofitamab-gxbm (COLUMVI)
BLA 761309

FDA Presentation

Oncologic Drugs Advisory Committee Meeting

May 20, 2025

Nicole Sunseri, MD, PhD
Division of Hematologic Malignancies II
Office of Oncologic Diseases

FDA Review Team

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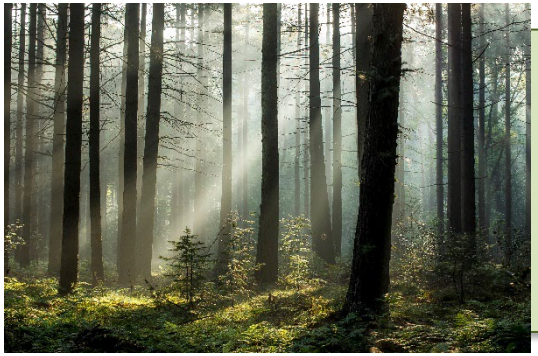
Concerns with STARGLO

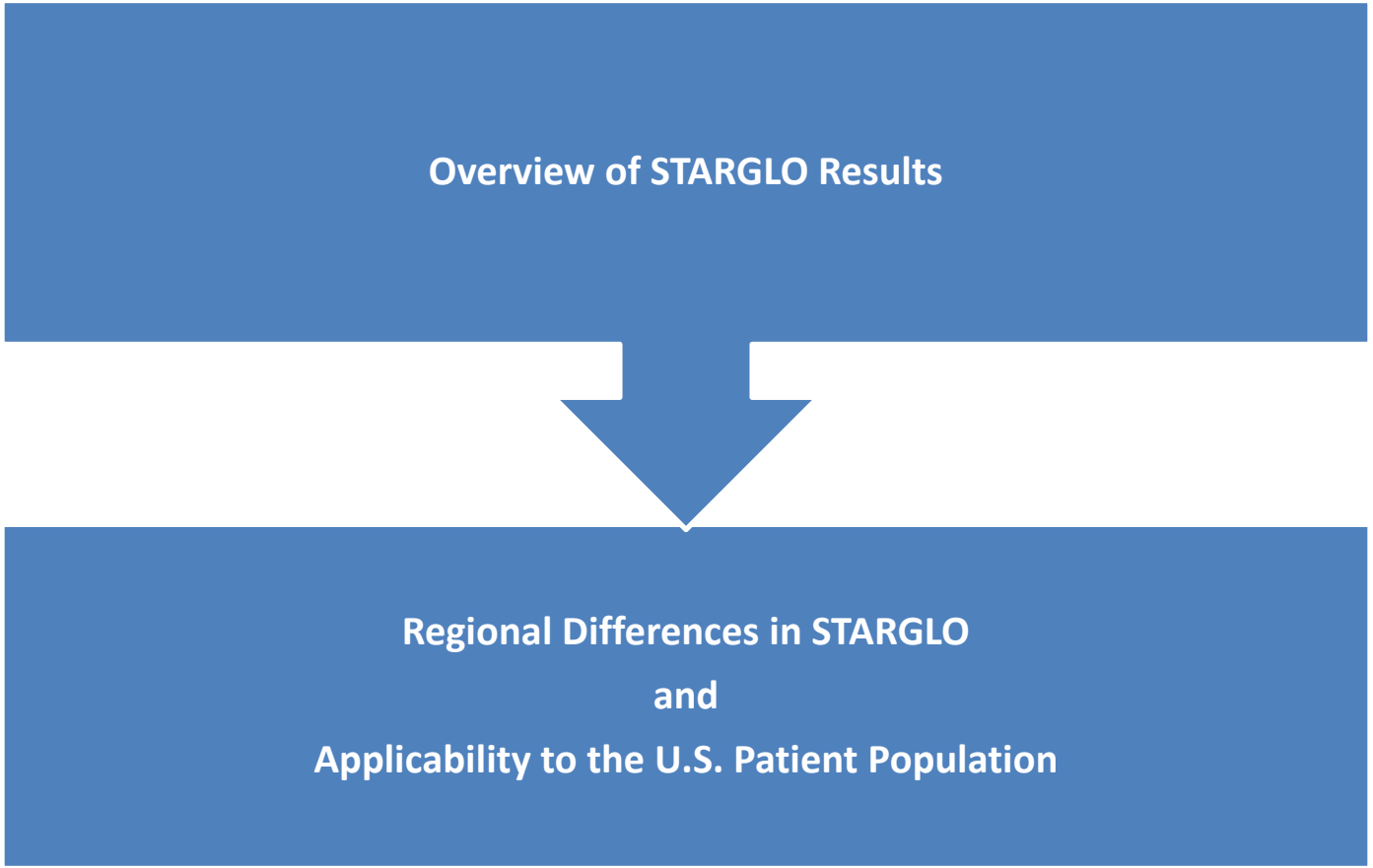
- Multiregional trial but large Asia population and little U.S. representation
- Inconsistent efficacy results in subgroups
- STARGLO Trial Population: Strong Regional Differences: Asian Subgroup vs Non-Asian Subgroup

Concerns with STARGLO



- Multiregional trial but large Asia population and little U.S. representation
- Inconsistent efficacy results in subgroups
- STARGLO Trial Population: Strong Regional Differences: Asian Subgroup vs Non-Asian Subgroup

- Trial with regional differences and inconsistent treatment effect → Trial results not robust
- Applicability of trial results to a U.S. patient population and medical practice


Overview of STARGLO Results
Regional Differences in STARGLO
and
Applicability to the U.S. Patient Population

Overview of STARGLO Results

Summary of STARGLO Efficacy Results

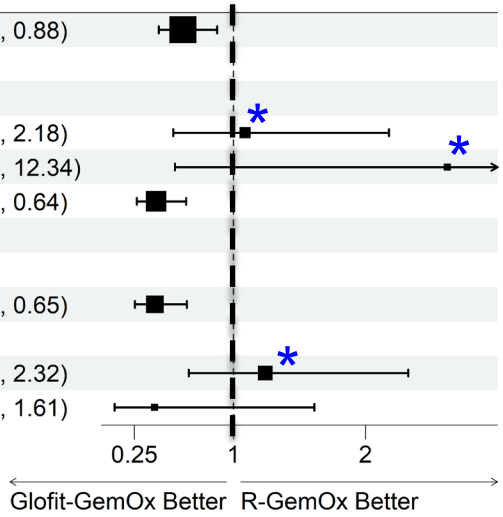
Efficacy in ITT Population: Glofit-GemOx vs R-GemOx

- Primary Endpoint → Statistically Significant improvement in OS
- 2 of 3 Key Secondary Endpoints→ Statistically significant improvement in PFS and CR rate

Abbreviations: ITT: Intention-to-treat; Glofit: Glofitamab; GemOx: Gemcitabine, Oxaliplatin; R: Rituximab; OS: Overall Survival; PFS: Progression-free Survival; CR: Complete Response Rate

Inconsistent OS by Subgroup

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	(0.43, 0.88)
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)



Differential OS trend: White Race and North American and European Regional Subgroups

Data Cut-off: 2024

Abbreviations: OS: Overall survival; Glofit: Glofitamab; GemOx: Gemcitabine, Oxaliplatin; R: Rituximab; CI: Confidence interval; NE: Not estimable

STARGLO: Large Subgroup of Patients Enrolled in Asia

Region		Prespecified Subgroup[b]	ITT Population N=274 n (%)
US		North America	**25 (9%)**
Europe[a]		Europe	88 (32%)
Australia		Rest of World	30 (11%)
Asia	**Total**		**131 (48%)**
	China		80 (29%)
	Korea		37 (14%)
	Taiwan		14 (5%)

48% of total population

↓

Enrolled in Asia

[a]France, Poland, Great Britain, Spain, Denmark, Germany, Belgium, Switzerland
[b]Region was not a stratification factor

Abbreviations: ITT: Intention-to-treat

STARGLO Asian Region Enrollment

GO41944 Protocol Version 1.0

3.1.1 Extended China Enrollment

This study will initially enroll approximately 270 patients across all sites in a global enrollment phase. After completion of the global enrollment phase, additional patients may be enrolled in an extended China enrollment phase at sites in mainland China, Hong Kong, and Taiwan that are recognized by China's National Medical Products Administration (NMPA) to ensure a total of up to approximately 80 patients in a China subpopulation. The global population will include all patients enrolled during the global enrollment phase (including patients enrolled at NMPA-recognized sites during that phase), and the China subpopulation will include all patients enrolled at NMPA-recognized sites (i.e., during both the global enrollment phase and the extended China enrollment phase).

48% ITT population enrolled in Asia → 34% of ITT population enrolled in China and Taiwan

Abbreviations: NMPA: (China's) National Medical Product Administration; ITT: Intention-to-treat

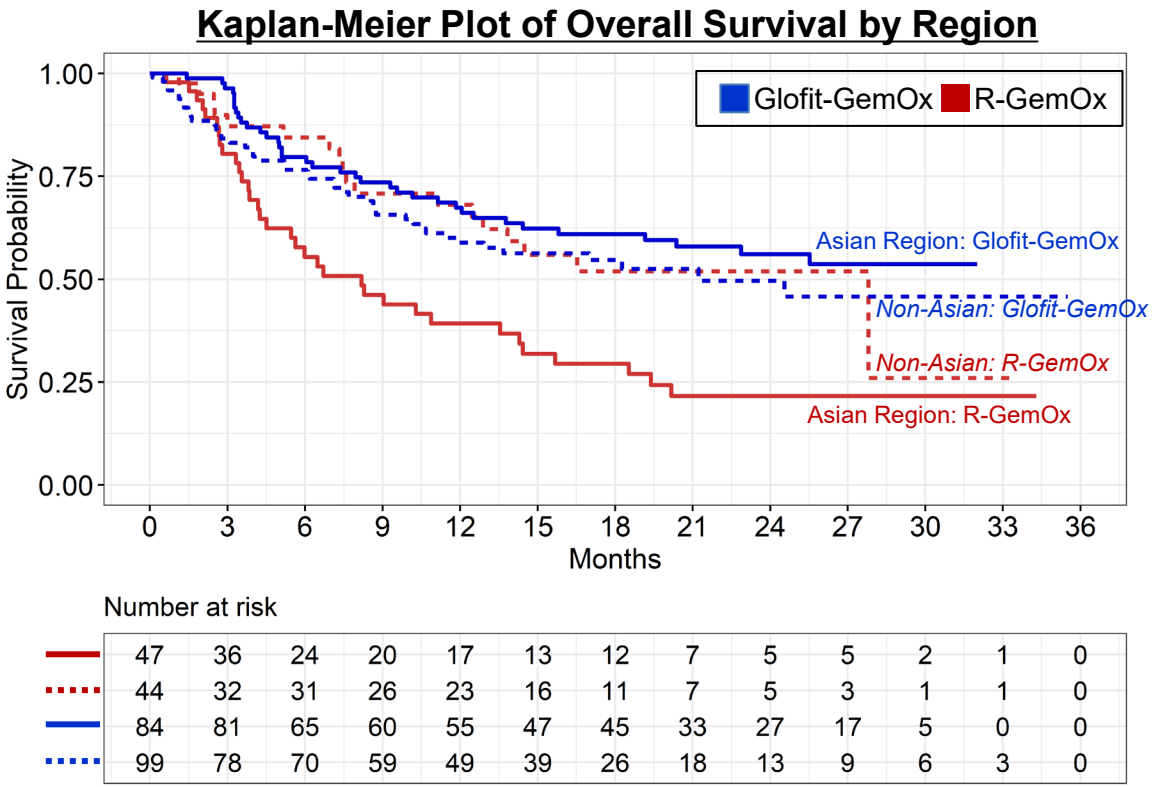
STARGLO: Regrouped FDA Regional Subgroups

Region		ITT Population N=274 n (%)	Prespecified Subgroup[b]	FDA 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 Britain, Spain, Denmark, Germany, Belgium, Switzerland
[b]Region was not a stratification factor

Abbreviations: ITT: Intention-to-treat

Differential OS Effects Across Regions



OS	Non-Asian Region	
	Glofit-GemOx N=99	R-GemOx N=44
Median OS	21.2 mo	27.8 mo
HR (95%CI)	**1.06 (0.61, 1.84)**	

OS	Asian Region	
	Glofit-GemOx N=84	R-GemOx N=47
Median OS	NE	8.2 mo
HR (95%CI)	**0.39 (0.25, 0.63)**	

Source: FDA analysis; Data Cutoff: Feb 2024

Abbreviations: OS: Overall survival; mo: Months; HR: Hazard ratio; CI: Confidence interval; NE: Not estimable

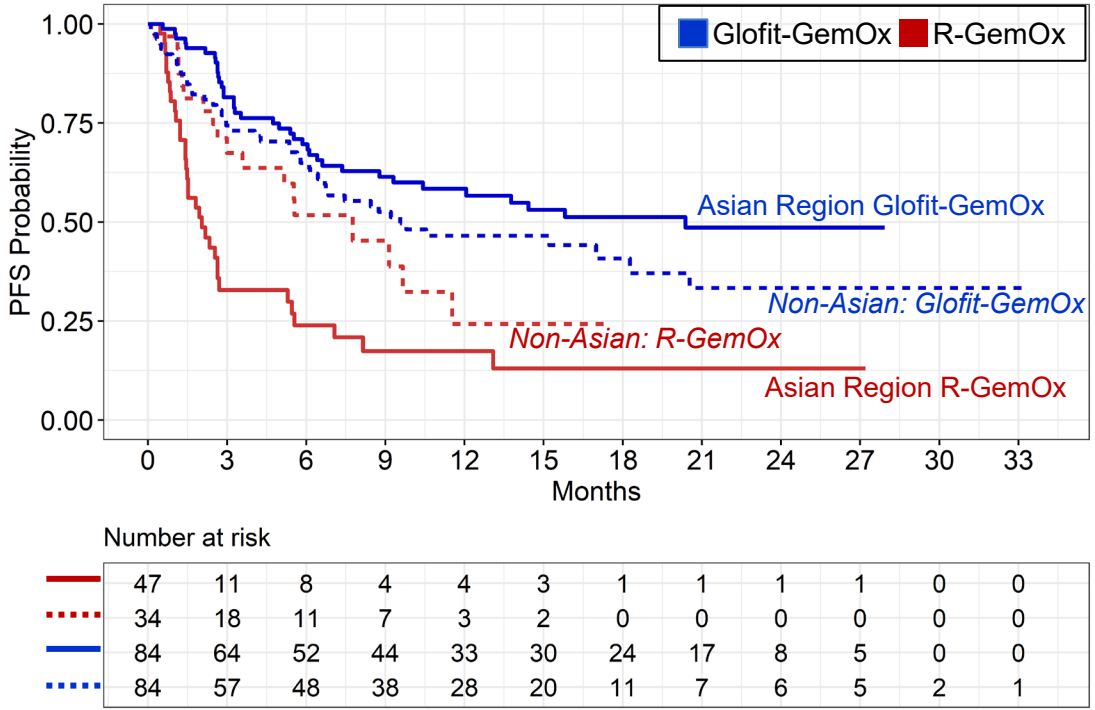
Differential PFS Effects Across Regions

PFS	Non-Asian Region	
	Glofit-GemOx N=99	R-GemOx N=44
Median PFS	9.2 mo	7.8 mo
HR (95%CI)	**0.81 (0.48, 1.35)**	

PFS	Asian Region	
	Glofit-GemOx N=84	R-GemOx N=47
Median PFS	20.4 mo	2.0 mo
HR (95%CI)	**0.25 (0.15, 0.41)**	

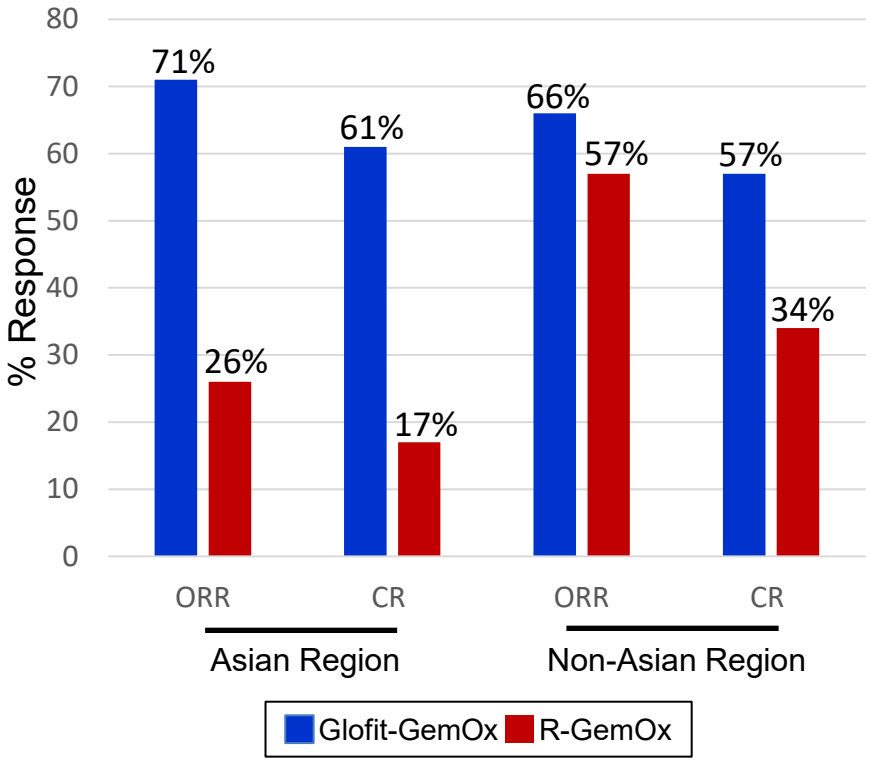
Source: FDA analysis; Data Cutoff: Feb 2024

Kaplan-Meier Plot of PFS by Region



Abbreviations: PFS: Progression-free survival; mo: Months; HR: Hazard ratio; CI: Confidence interval

Differential ORR/CR Rates Across Regions



	Asian Region N=143		Non-Asian Region N=131	
	Glofit-GemOx N=84	R-GemOx N=47	Glofit-GemOx N=99	R-GemOx N=44
CR rate[a], n (%)	51 (61)	8 (17)	56 (57)	15 (34)
[95% CI]	[49,71]	[8,31]	[46,67]	[20,50]
ORR, n (%)	60 (71)	12 (26)	65 (66)	25 (57)
[95% CI]	[61,81]	[14,40]	[55,75]	[41,72]

[a]Key secondary endpoint
Source: FDA Analysis; Data cutoff: Feb 2024

Abbreviations: ORR: Overall response rate; CR: Complete response; CI: Confidence interval

Subgroup Interpretation

- Role of Subgroups[a]:
  - Valuable information on benefit-risk profile across important populations
  - Consistent subgroup benefit-risk assessment→ assurance treatment benefit to entire population

- Asian Region and Non-Asian Region:
  - Large subgroups, ~50% of ITT each

- **All** efficacy assessments (OS, PFS, ORR, CR) with regional inconsistency

[a]Amatya et al. Clin Cancer Res 2022

Abbreviations: ITT: Intention-to-treat; OS: Overall survival; PFS: Progression-free survival; ORR: Overall response rate; CR: Complete response

Statistical Evidence of Inconsistent Treatment Effect between Asian and Non-Asian Regional Subgroups

Regression model with Arm*region interaction term

Endpoint	Asian Region (Glofit-GemOx vs R-GemOx)	Non-Asian Region (Glofit-GemOx vs R-GemOx)	p-value[a]
OS	HR: 0.39 (95% CI: 0.25, 0.63)	HR: 1.06 (95% CI: 0.61, 1.84)	0.0081
PFS	HR: 0.25 (95% CI: 0.15, 0.41)	HR: 0.81 (95% CI: 0.48, 1.35)	0.0006
CR Rate	61% vs 17%	57% vs 34%	0.0612
ORR	71% vs 26%	66% vs 57%	0.0036

[a]Limitations of testing for interaction term: study not designed/powered to test interaction, post-hoc analysis not adjusted for multiplicity and/or does not account for testing of other subgroups

Source: FDA Analysis, Data cutoff: Feb 2024

"Significant" interaction term → different treatment effect

Abbreviations: OS: Overall survival; PFS: Progression-free survival; ORR: Overall response rate; CR: Complete response; HR: Hazard ratio; CI: Confidence interval

Summary of STARGLO Efficacy Results

Efficacy in ITT Population: Glofit-GemOx vs R-GemOx

- Primary Endpoint → Statistically significant improvement in OS
- 2 of 3 Key Secondary Endpoints→ Statistically significant improvement in PFS and CR rate

Notable Findings

- Non-Asian Regional Subgroup accounts for 48% of ITT population: multiregional trial with **large representation of single region**
- **Inconsistent treatment effects** between Asian and Non-Asian regional subgroups **across multiple endpoints**
- **Large treatment effect in Asian regional subgroup: appears to "drive" ITT results**

Abbreviations: ITT: Intention-to-treat; OS: Overall survival; PFS: Progression-free survival; CR: Complete response; Glofit: Glofitamab; GemOx: Gemcitabine, Oxaliplatin; R: Rituximab

FDA Assessment of Multiregional Clinical Trials (MRCT)[a]

"The paramount consideration for FDA when evaluating such oncology trials is whether the results are applicable to the intended use population in the U.S. and to the U.S. standard oncological care"[a]

[a]Draft Guidance for Industry: *Considerations for Generating Clinical Evidence from Oncology Multiregional Clinical Development Programs* (September 2024)

FDA Assessment of Multiregional Clinical Trials (MRCT)[a]

"The paramount consideration for FDA when evaluating such oncology trials is whether the results are applicable to the intended use population in the U.S. and to the U.S. standard oncological care"

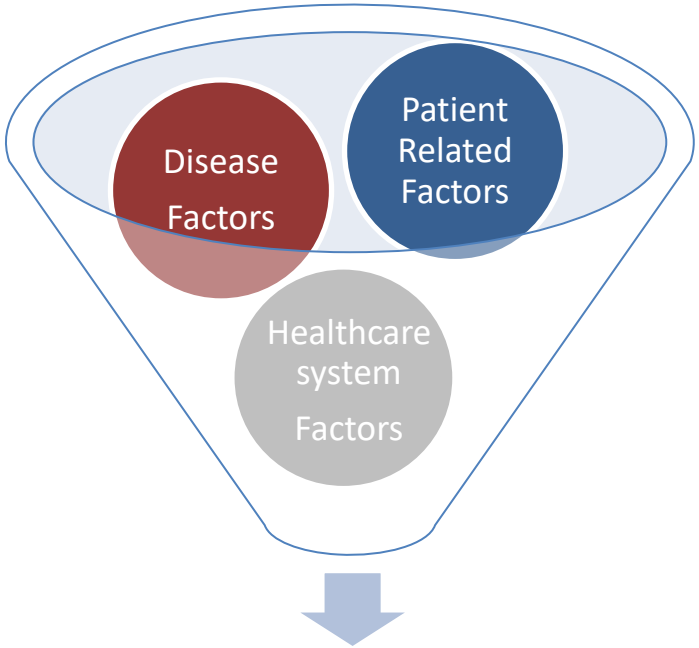
- Evidence generated should be derived from study populations that enable the results to be interpretable in the context of U.S. patients with the disease or condition and U.S. medical practice

- FDA's determination of the applicability of the data to U.S. patients in the context of U.S. medical practice includes an assessment of the impact of both intrinsic and extrinsic factors on study outcomes[b]

[a]Draft Guidance for Industry: *Considerations for Generating Clinical Evidence from Oncology Multiregional Clinical Development Programs* (September 2024);[b]Guidance for industry: *E5 – Ethnic Factors in the Acceptability of Foreign Clinical Data – Questions and Answers* (September 2006)

Regional Differences in STARGLO
and
Applicability to the U.S. patient population

Intrinsic and Extrinsic Factors:



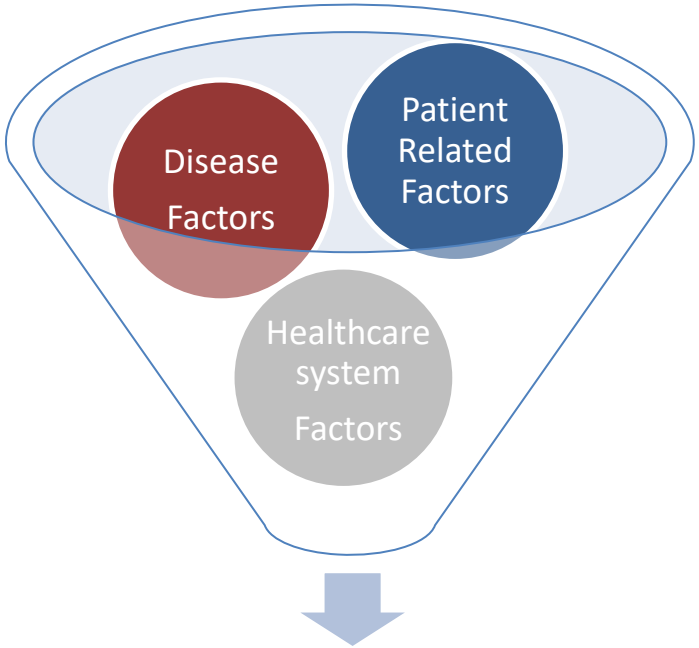
Patient Related Factors
- Age
- Race/ethnicity
- Transplant ineligibility

Disease factors
- Timing of Relapse
- Cell of Origin
- Prior Therapy

Healthcare System Factors
- *Transplant eligibility*
- NALT Availability
- Trial Assessments

Abbreviations: NALT: New Anti-Lymphoma Therapy

Intrinsic and Extrinsic Factors: Patient and Disease Factors



Patient Related Factors

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Disease factors

- Timing of Relapse
- Cell of Origin
- Prior Therapy

Different Regional 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)
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)

- **Age:**
  - Asian Region overall younger
- **Race:**
  - Majority of Non-Asian Region White
- **DLBCL in U.S. (SEER data 2017-2021)**
  - Older population: Median age of 69 → >60% of cases over 65 years
  - *More diverse race and ethnicity*:

Race: 83% White, 8% Black, 8% Asian
Ethnicity: 17% Hispanic

Abbreviations: DLBCL: Diffuse Large B-cell Lymphoma; SEER: Surveillance, Epidemiology, and End Results Program

Reasons for Transplant Ineligibility

Reason for Transplant Ineligibility	Non-Asian Region N=143 n (%)	Asian Region N=131 n (%)
Age		
Performance status		
Comorbidity		
Insufficient response to salvage		
Failed prior transplant		
Lack of access to transplant center		
Patient refused transplant		
Other*		
None listed		

*other: non-chemosensitive disease, too chemo refractory, risk of many adverse events, expected insufficient response; not ≥2 prior lines of treatment, insufficient response to pre-transplant chemotherapy

Transplant Refusal:
Primary Reason for Asian Region 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*	4 (3%)	2 (2%)
None listed	2 (1%)	1 (0.8%)

*other: non-chemosensitive disease, too chemo refractory, risk of many adverse events, expected insufficient response; not ≥2 prior lines of treatment, insufficient response to pre-transplant chemotherapy

Different Regional Baseline Disease Characteristics

Baseline Characteristic	Non-Asian Region N=143 (%)	Asian Region N=131 (%)
Double Expressor: *MYC*, *BCL2*	15	21
Stage III-IV[a]	74	66
Bulky Disease	17	10
IPI score 4-5[a]	23	17
Primary Refractory	53	59
Relapse within 12 months of 1st line	**64**	**81**

Disease Characteristic Differences:

- Asian Region: More relapsed disease within 12 months ("early relapse") after front-line treatment in Asia

[a]IPI includes stage with age, ECOG, LDH, extranodal sites

Abbreviations: MYC: MYC proto-oncogene; BCL2: BCL2 apoptosis regulator; IPI: International Prognostic Index

DLBCL and Characterization by Cell of Origin

Classification

- Immunohistochemistry (IHC)[a]
  - Germinal Center B-cell Like (GCB) vs non-GCB
- Gene Expression Profiling (GEP)[a]
  - Activated B-cell like (ABC) vs GCB vs "unclassified"

[a]Alizadeh et al. 2000

Abbreviations: ABC: Activated B-cell like; DLBCL: Diffuse Large B-cell Lymphoma

DLBCL and Characterization by Cell of Origin

Classification

- Immunohistochemistry (IHC)[a]
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  - Activated B-cell like (ABC) vs GCB vs "unclassified"

Prognostic Factor

- Frontline Setting: Prognostic
  - Chemoimmunotherapy (R-CHOP) 3y-OS: 80% GCB vs 45% ABC[b]
  - Required by WHO Classification of Lymphoid Neoplasms[c]
- R/R Setting: Less clear and therapy dependent
  - R-DHAP: GCB higher response[d]
  - Bortezomib + chemotherapy: ABC higher response[e]

[a]Alizadeh et al. 2000; [b]Lenz et al. 2008.; [c]Kurz et al 2023;[d]Thieblemont et al 2011; [e]Dunleavy et al. 2009

Abbreviations: ABC: Activated B-cell like; DLBCL: Diffuse Large B-cell Lymphoma; R-CHOP: Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, Prednisone; WHO: World Health Organization; R-DHAP: Rituximab, Dexamethsone, High-dose Cytarabine, Cisplatin

Regional Difference of Cell of Origin: ABC-DLBCL Higher in Asia Countries

Non-Asian Countries

- North America, Australia, New Zealand[a]
  - 37% ABC-DLBCL
- Russia, Europe, Middle East[a]
  - 40%
- Canada[c]
  - 32%

Asian Countries

- China, Japan, Korea, Taiwan[a,b]
  - ***~60% ABC-DLBCL***

[a]Nowakowski et al. *Haematologica* 2020.; [b]Yoon et al *Oncotarget* 2017; [c]Scott et al. *J Clin Oncol.* 2015

Abbreviations: ABC: Activated B-cell like; DLBCL: Diffuse Large B-cell Lymphoma

ABC-DLBCL High Overall Representation in STARGLO and Highest in Asia Regional Subgroup

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

- Gene Expression Profiling (GEP via Nanostring) performed centrally

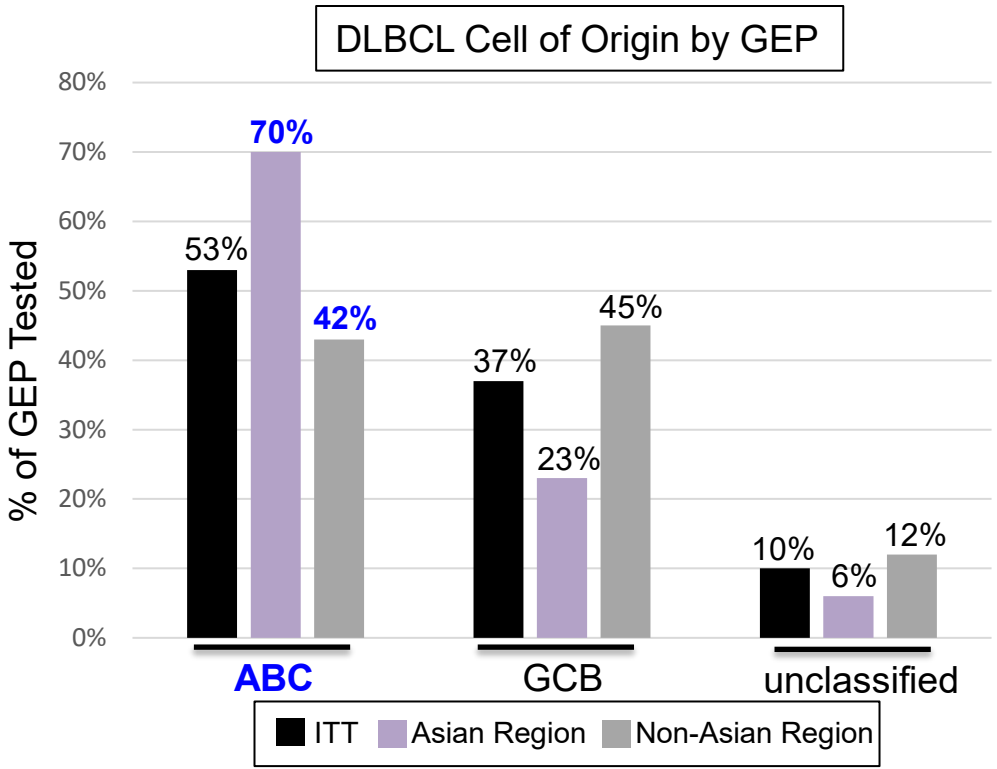
Abbreviations: ABC: Activated B-cell like; GCB: Germinal Center B-cell Like; GEP: Gene Expression Profiling; ITT: Intention-to-treat

ABC-DLBCL High Overall Representation in STARGLO and Highest in Asia Regional Subgroup

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

[a]Gene Expression Profiling centrally by NanoString

- **Only 49% of Asian region population tested but 70% ABC-subtype vs 42% of non-Asian subgroup**
- Limitation: Large % unknown



 Abbreviations: ABC: Activated B-cell like; GCB: Germinal Center B-cell Like; GEP: Gene Expression Profiling; ITT: Intention-to-treat

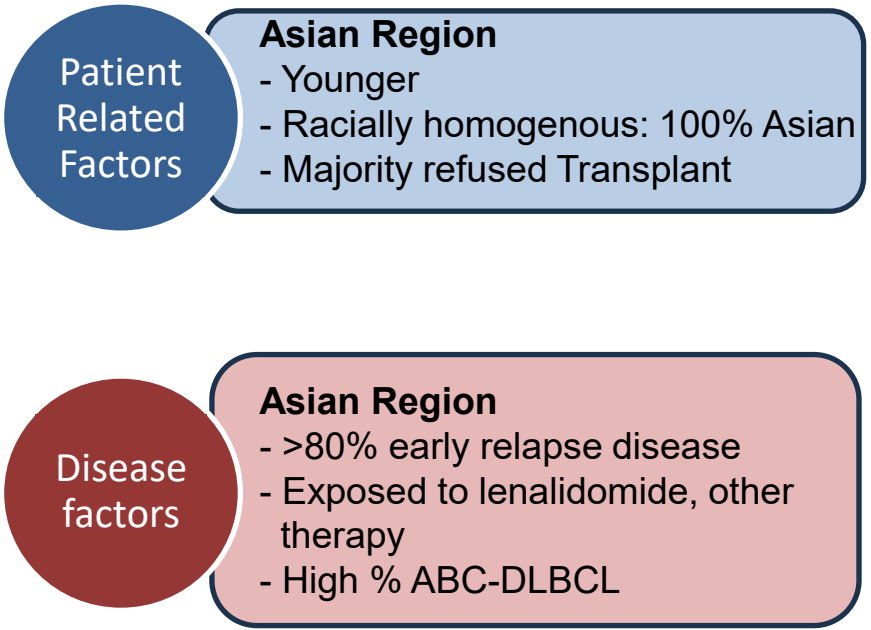
Prior Therapy Characteristics: Different Prior Treatment Exposures

Prior Therapy	Non-Asian Region N=143 n (%)	Asian Region N=131 n (%)
Median lines (range)	1 (1-5)	1 (1-5)
Component of Prior therapy		
Anthracycline	139 (97)	129 (98)
CD20 (ritux, obinu) or taf [CD19]	142 (99)	128 (98)
Platinum	31 (22)	36 (27)
Lenalidomide	**5 (3)**	**22 (13)**
Polatuzumab (pola-BR)	8 (6)	2 (2)
Radiotherapy	33 (23)	15 (11)
CART	**19 (13)**	**2 (2)**
ASCT	7 (5)	4 (3)
Other (PD1i, BTKi, Selinexor, etc)	**3 (2)**	**19 (15)**

- **Asian-enrolled** patients: higher % exposed to lenalidomide-containing regimens and "other therapy"
- **Non-Asian enrolled** patients: higher % CAR-T

Abbreviations: Ritux: Rituximab; Obinu: Obinutuzumab; Taf: Tafasitamab; Pola-BR: polatuzumab+bendamustine+ritixumab; ASCT: autologous or allogeneic stem cell transplantation; BTKi: Bruton Tyrosine Kinase inhibitor; PD1i: Programmed-cell Death inhibitor

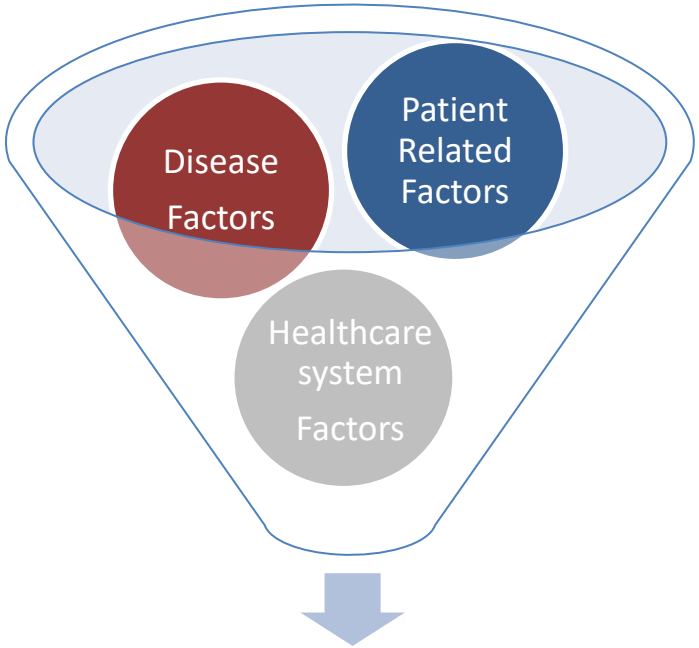
Intrinsic and Extrinsic Factors: Patient and Disease Factors Major Regional Differences



- **Patient in Asian Region: potential different "fitness" and underlying disease than U.S. patient**
- Younger age and "transplant refusal" indicate differences in fitness and suitability for R-GemOx regimen
- Early relapse and ABC-DLBCL signal different disease characteristics
- Prior treatment differences compared with standard U.S. treatments

Abbreviations: ABC: Activated B-cell like; DLBCL: Diffuse Large B-cell Lymphoma; GemOx: Gemcitabine, Oxaliplatin; R: Rituximab

Intrinsic and Extrinsic Factors: Healthcare System Factors



Healthcare System Factors

- *Transplant eligibility*
- NALT Availability
- Trial Assessments

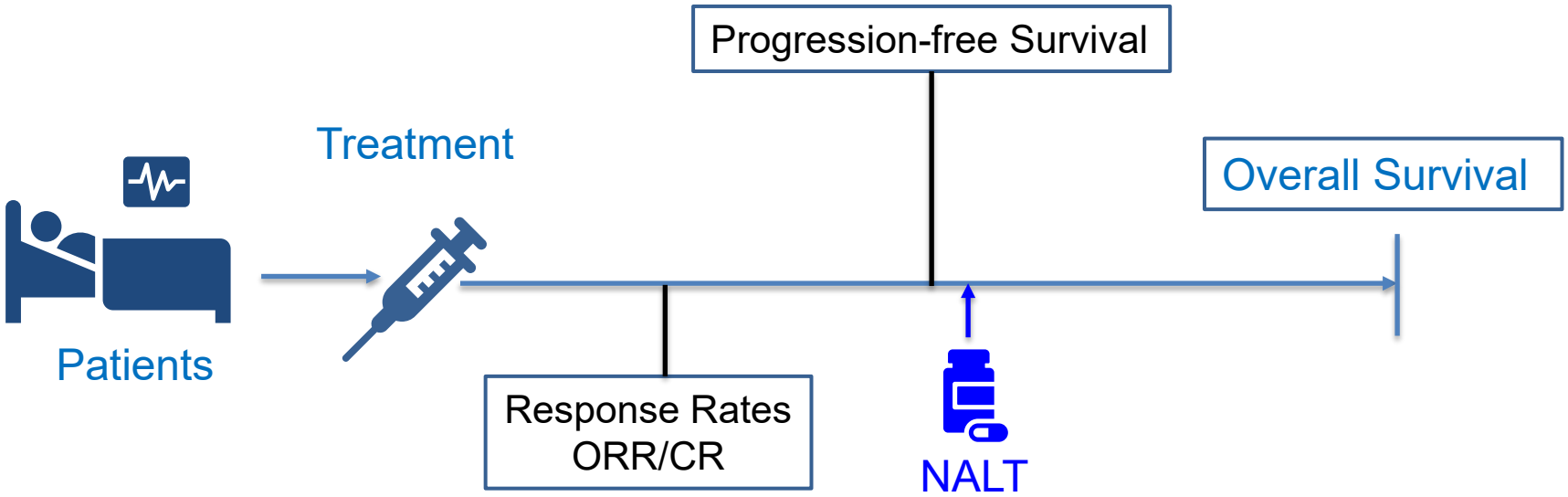
Abbreviations: NALT: New Anti-Lymphoma Therapy

The Role of NALT

- NALT = new anti-lymphoma therapy
- Subsequent therapy will typically impact a patient's overall survival
- The analysis of OS, assesses the time from randomization to death (regardless of NALT)
- The presence of and types of available subsequent therapies should be similar across regions

Abbreviations: NALT: New Anti-Lymphoma Therapy; OS: Overall Survival

New Anti-lymphoma Therapy Should Not Affect PFS and **Does Not Affect** ORR/CR Results



Abbreviations: PFS: Progression-free Survival; ORR: Overall Response Rate; CR: Complete Response Rate; NALT: New Anti-Lymphoma Therapy

Regional Assessment of NALT Frequency and Type

Total Population *Any* NALT Received:	R-GemOx: 51 patients (58%) Glofit-GemOx: 46 patients (27%)

	NALT received[a]
R-GemOx Arm	
Non-Asian Region: (n=42)	23 (55)
Asian Region: (n=46)	28 (61)
Glofit-GemOx Arm	
Non-Asian Region: (n=89)	27 (30)
Asian Region: (n=83)	19 (23)

Similar rates of NALT *within* each arm by region

[a]all treated patients (excluding obinutuzumab-only)

Source: FDA analysis
Data Cut-off: 2024

Abbreviations: NALT: New Anti-Lymphoma Therapy; Glofit: Glofitamab; GemOx: Gemcitabine, Oxaliplatin; R: Rituximab

Regional Difference in NALT Regimens Received

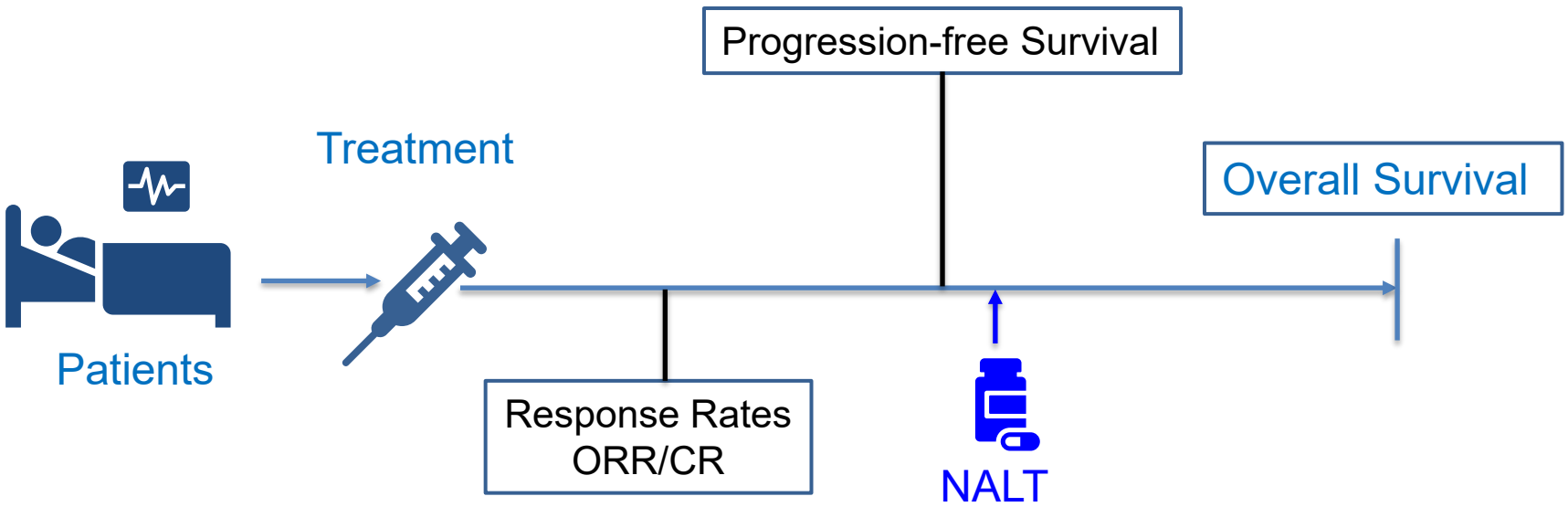
	NALT Therapeutic Categories					
	ADC	Tafasitamab+ lenalidomide	CAR-T	TCE	SCT	CAR-T, SCT, TCE, ADC, Tafasitamab+lenalidomide
R-GemOx Arm						
Non-Asian Region (n=42)[a]	4 (10%)	2 (5%)	9 (21%)	8 (19%)	1 (2%)	**17 (40%): +6 patients**
Asian Region (n=46)[a]	2 (4%)	0	3 (7%)	8 (17%)	0	11 (24%)
Glofit-GemOx Arm						
Non-Asian Region (n=89)[a]	10 (11%)	3 (3%)	7 (8%)	2 (2%)	0	**17 (19%): +12 patients**
Asian Region (n=83)[a]	2 (2%)	1 (1%)	1 (1%)	0	2 (2%)	5 (6%)

[a]all treated patients (excluding obinutuzumab-only)

Source: FDA analysis
Data Cut-off: 2024

Abbreviations: NALT: New Anti-lymphoma Therapy; SCT: Stem Cell Transplant, TCE: CD20 or CD19-directed CD3 T-cell engager, ADC: Antibody Drug Conjugate alone or in combo, CD20+chemo: anti-CD20 mAb and chemotherapy but not with lenalidomide or novel agent; Other: anti-CD47, PI3Ki+chemotherapy, BTKi+MALTi, ViPOR, acalabrutinib, CDK9i, Pembrolizumab and other PD-1 inhibitor, Chidamide, etc. not in combination with TCE.

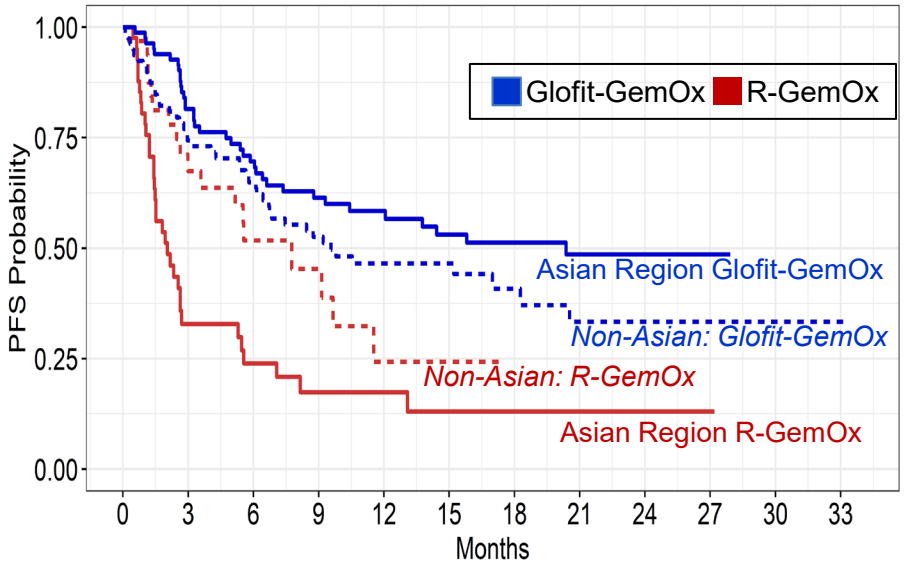
New Anti-lymphoma Therapy Should Not Affect PFS and **Does Not Affect** ORR/CR Results



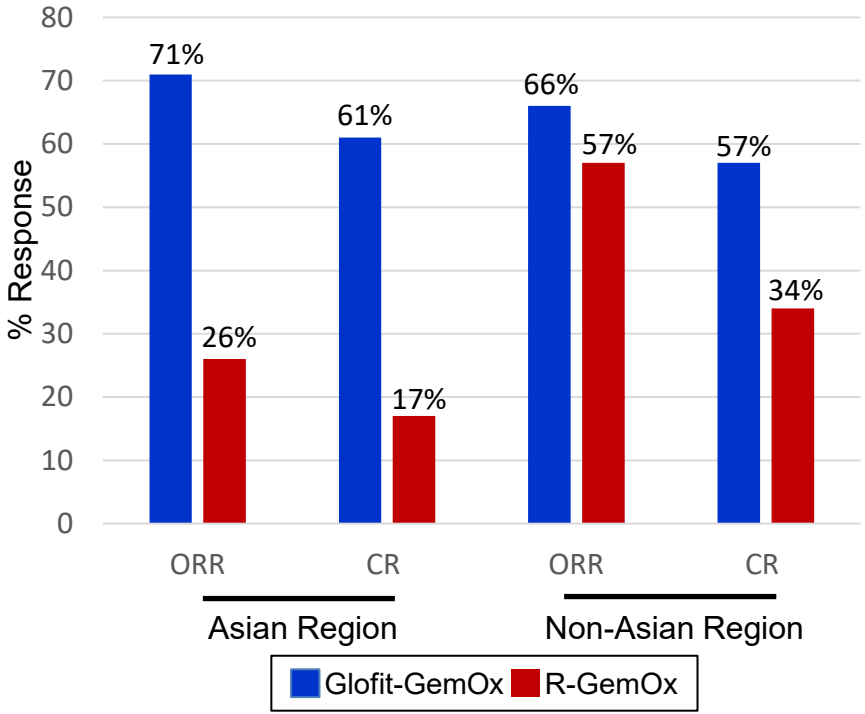
Abbreviations: PFS: Progression-free Survival; ORR: Overall Response Rate; CR: Complete Response Rate; NALT: New Anti-Lymphoma Therapy

New Anti-lymphoma Therapy Should Not Affect PFS and **Does Not Affect** ORR/CR Results

KM Curves of PFS by Region



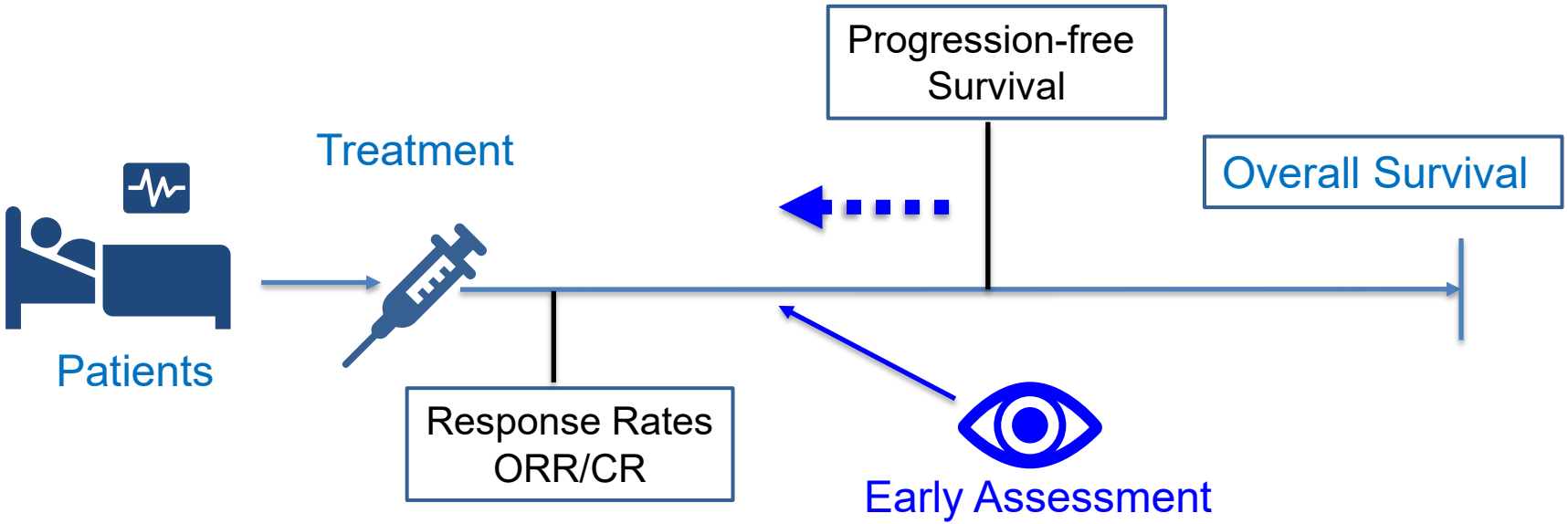
Response Rates by Region



Source: FDA analysis
Data Cut-off: 2024

Abbreviations: PFS: Progression-free Survival; ORR: Overall response rate; CR: Complete response; KM: Kaplan-Meier; Glofit: Glofitamab; GemOx: Gemcitabine, Oxaliplatin; R: Rituximab

Earlier Unscheduled Responses Assessments May Affect PFS and Introduce Bias

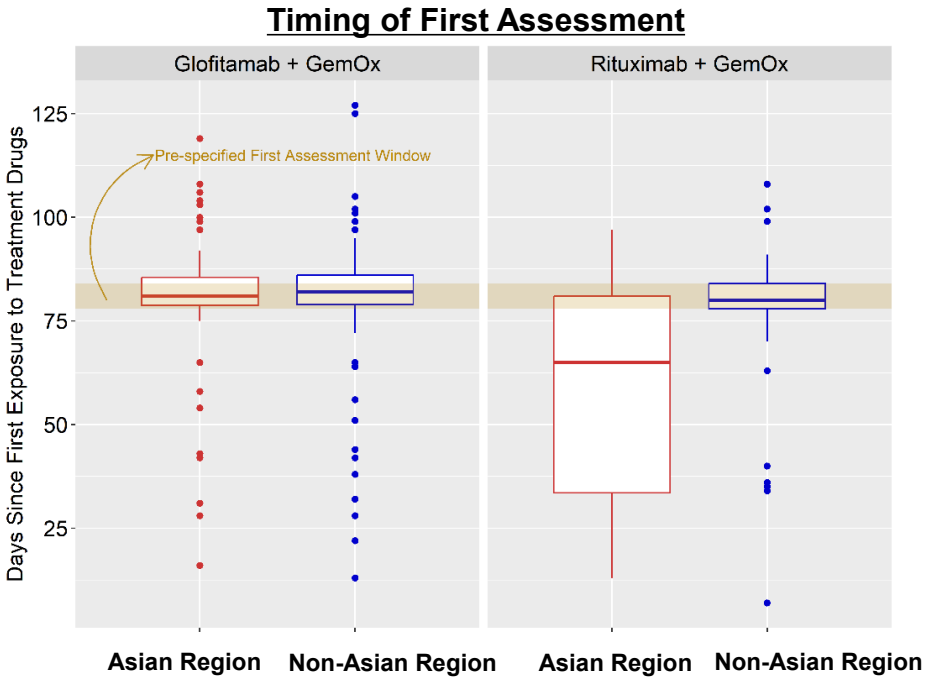


Abbreviations: PFS: Progression-free Survival; ORR: Overall Response Rate; CR: Complete Response Rate

Response Assessments: Earlier Unscheduled Assessments Overall Higher in R-GemOx in Asia Region

Assessment Timing	Glofit-GemOx		R-GemOx	
	Asian Region (N=76)	Non-Asian Region (N=82)	Asian Region (N=39)	Non-Asian Region (N=37)
Earlier	17%	20%	**56%**	**22%**
Cycle 4 IR	54%	48%	31%	57%
Later	29%	33%	13%	22%

- Among 274 subjects in ITT, 234 had post-screening tumor assessments
- Cycle 4 Interim Response (IR): Day 15-21 of cycle 4 → ~Study day 78-84



Source: FDA analysis
Data Cut-off: 2024

Abbreviations: Glofit: Glofitamab; GemOx: Gemcitabine, Oxaliplatin; R: Rituximab; IR: Interim Response; ITT: Intention-to-treat

Intrinsic and Extrinsic Factors: Healthcare System Factors Major Regional Differences

Healthcare System Factors

Asian Region
- Different NALT available
- R-GemOx arm: more unscheduled early response assessments
- *Transplant refusal: transplant less utilized**

- Medical Practice different:
  - U.S. NALT standard of care in R/R disease: CAR-T, SCT, TCE→ *may have impacted OS in U.S.*
  - **NALT should not impact PFS and does not impact response rate**
- Earlier assessments: bias with open-label trial or early progression

* Discussed previously under disease related factors

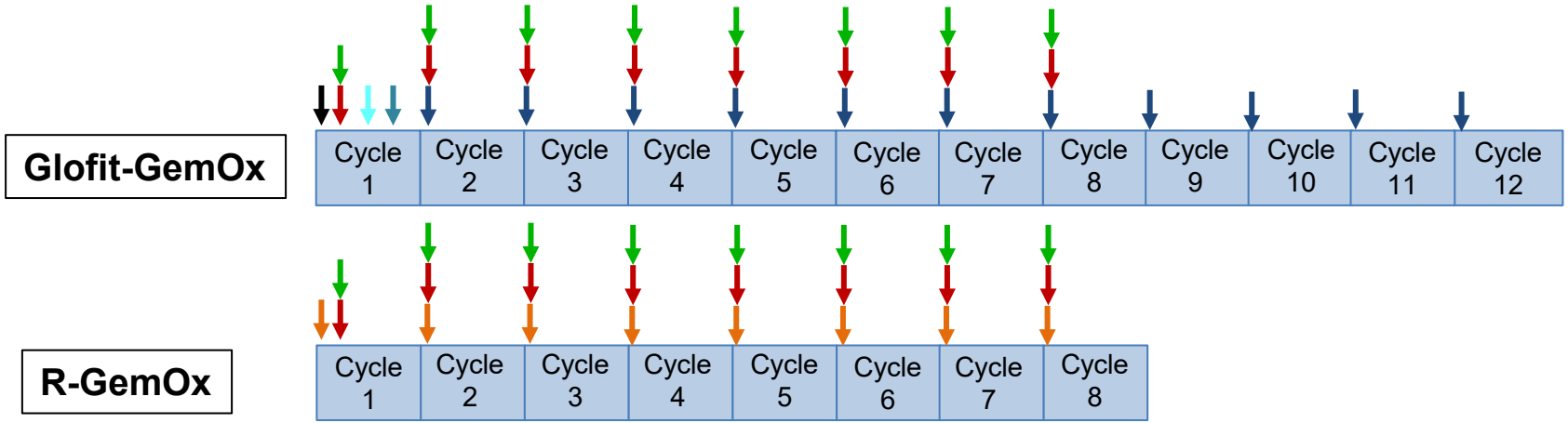
Abbreviations: NALT: New Anti-Lymphoma Therapy; Glofit: Glofitamab; GemOx: Gemcitabine, Oxaliplatin; R: Rituximab; SCT: Stem Cell Transplantation; TCE: Bispecific T-cell Engager; OS: Overall Survival; PFS: Progression-free Survival

Other Notable Regional Differences

- Treatment Duration
- Treatment Discontinuation

Protocol-Specified Treatment Regimen: Imbalanced

Protocol: Regimen Duration
Glofit-GemOx: 12 cycles: 8.3 months
R-GemOx: 8 cycles: 5.5 months



Obinutuzumab: **1000 mg** Cycle 1 Day 1
Glofitamab: 2.5 mg (Cycle 1 Day 8), 10 mg (Cycle 1 Day 15), 30 mg (Day 1 of Cycle 2-12)
Rituximab: 375 mg/m2 Day 1 of Cycles 1-8
Gemcitabine: 100 mg/m^2 Cycle 1 Day 2 and Day 1 Cycles 2-8.
Oxaliplatin: 100 mg/m^2 Cycle 1 Day 2 and Day 1 Cycle 2-8

Abbreviations: Glofit: Glofitamab; GemOx: Gemcitabine, Oxaliplatin; R: Rituximab

Treatment Regimen: GemOx Treatment Duration

		Glofit-GemOx N=172	R-GemOx N=88
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)

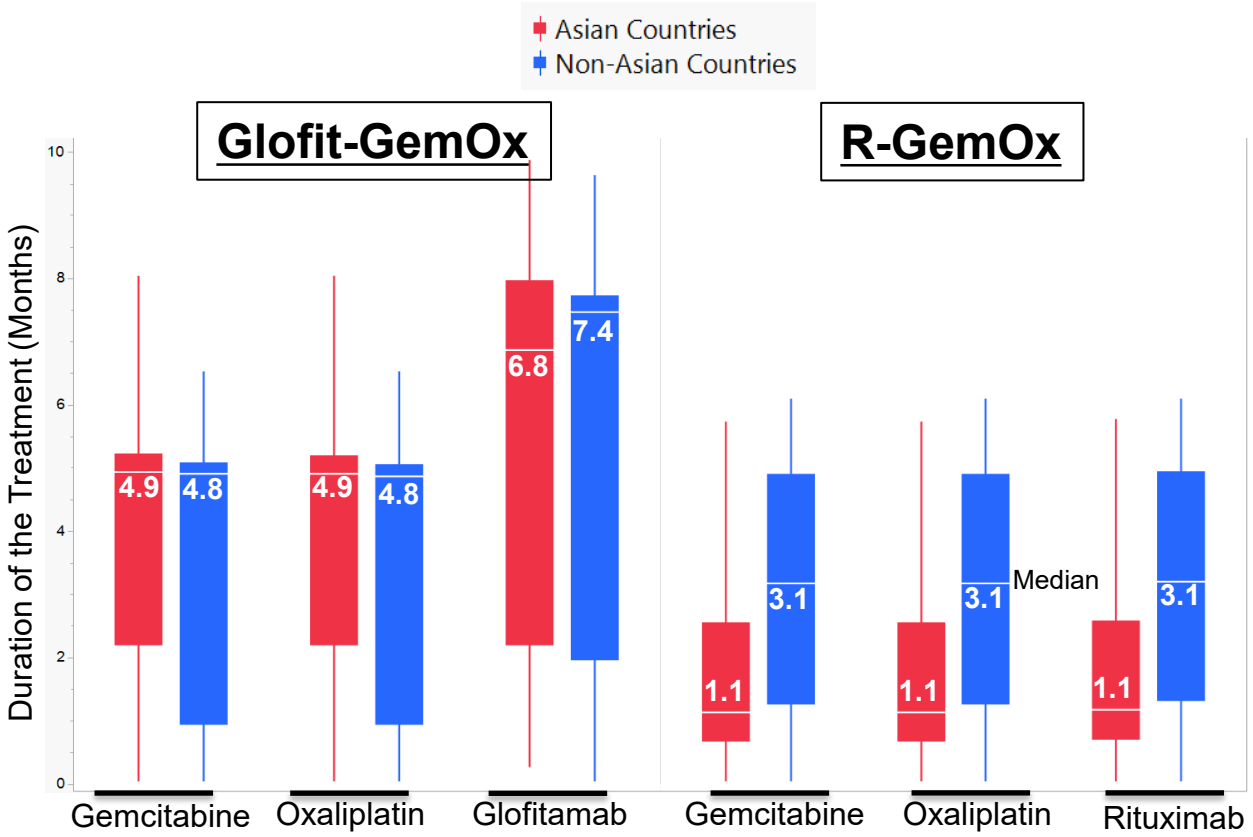
Protocol-Specified in both Arms:
GemOx: 8 cycles: 5.5 months

R-GemOx with markedly shorter exposure than protocol specified

*Based on Actually Treated (excluding obinutuzumab only), DCO: 2024

Abbreviations: Glofit: Glofitamab; GemOx: Gemcitabine, Oxaliplatin; R: Rituximab

GemOx Treatment Duration Shorter in Asia Population



Protocol-Specified:
GemOx: 8 cycles: 5.5 months

R-*GemOx*: median
ITT: 2.1 mo
Asia: 1.1 mo
Non-Asia: 3.1 mo

Glofit-*GemOx*: median
ITT: 4.8 mo
Asia: 4.9 mo
Non-Asia: 4.8 mo

Data cut-off: 2024

Abbreviations: Glofit: Glofitamab; GemOx: Gemcitabine, Oxaliplatin; R: Rituximab; mo: months

Higher Discontinuation in Asia R-GemOx versus Non-Asia R-GemOx

	Glofit-GemOx N=180*		R-GemOx N=88*	
	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)**

*Based on Actually Treated (including obinutuzumab only), Data cut-off: 2024

Abbreviations: Glofit: Glofitamab; GemOx: Gemcitabine, Oxaliplatin; R: Rituximab

Discontinuation due to Progressive Disease Higher in Asia Population Treated with R-GemOx

	Glofit-GemOx N=180*		R-GemOx N=88*	
	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 (% of discontinued)				
Progressive Disease	**38**	**39**	**46**	**72**
Adverse Event	**23**	**31**	**23**	**3**
Death	17	10	8	3
Withdraw by Patient	6	8	4	8
Symptomatic Deterioration	8	0	8	6
Physician Decision	6	8	0	0
Lack of Efficacy	0	2	8	6
Other	2	2	0	0
Protocol Deviation	0	0	4	0
Lost to Follow-up	0	0	0	3

*Based on Actually Treated (including obinutuzumab only), Data Cut-off: 2024

- Progressive Disease #1 cause for discontinuation
- **Asian Region higher % discontinued due to progression vs Non-Asian Region**

Abbreviations: Glofit: Glofitamab; GemOx: Gemcitabine, Oxaliplatin; R: Rituximab

Other Factors the FDA Assessed in the Asian and Non-Asian Regional Subgroups

- Exposure differences due to body weight
- Quality verification of locally sourced products: Gemcitabine and Oxaliplatin, where applicable
- Delayed regional enrollment
- Safety profile differences

Summary: Other Regional Factors Examined in STARGLO

No Marked Difference

- Exposure based on body weight
- Quality of GemOx
- Delayed enrollment and differential follow-up impact on efficacy
- Safety profile

Regional Differences Noted

- **Shorter GemOx exposure** for R-GemOx in Asian Region vs Non-Asian Region (median 1.1 months vs 3.1 months)
- Higher % of discontinuations of R-GemOx **due to progressive disease** in Asian Region vs Non-Asian Region (46% vs 72%)

Abbreviations: GemOx: Gemcitabine, Oxaliplatin; R: Rituximab; mo: Months

Summary of Regional Differences

Abbreviations: OS: Overall survival; PFS: Progression-free Survival; Complete Response Rate ; ORR: Overall Response Rate; GemOx: Gemcitabine, Oxaliplatin; R: Rituximab; y: Years; ABC-DLBCL: Activated B-cell Like Diffuse Large B-cell Lymphoma

Summary of Regional Differences

Factors	Difference	Asian Region (48% ITT)	Non-Asian Region (52% ITT)
Treatment effect on outcomes	**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 difference	44% (27, 60)	22% (4, 41)
	ORR difference	46% (28, 63)	9% (-10, 28)
	Interaction test	p-value <0.05 for OS, PFS, ORR	

Abbreviations: OS: Overall survival; PFS: Progression-free Survival; Complete Response Rate ; ORR: Overall Response Rate; GemOx: Gemcitabine, Oxaliplatin; R: Rituximab; y: Years; ABC-DLBCL: Activated B-cell Like Diffuse Large B-cell Lymphoma

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	Interaction test		p-value <0.05 for OS, PFS, ORR	
Patient and Disease factors	Demographics	Age	Median age 62y, 21%>65y	Median age 71y, 55%>65y
		Race/ethnicity	100% Asian/2% Hispanic	80% White/4% Asian/9%Hispanic
	Disease	Early relapse	81%	64%
		ABC-DLBCL	70% (49% tested)	42% (68% tested)
	Treatment history	Prior therapy	2% CART,13% lenalidomide, 15%other	13% CART,3% lenalidomide, 2% other
		Transplant refusal	65%	7%

Abbreviations: OS: Overall survival; PFS: Progression-free Survival; Complete Response Rate ; ORR: Overall Response Rate; GemOx: Gemcitabine, Oxaliplatin; R: Rituximab; y: Years; ABC-DLBCL: Activated B-cell Like Diffuse Large B-cell Lymphoma

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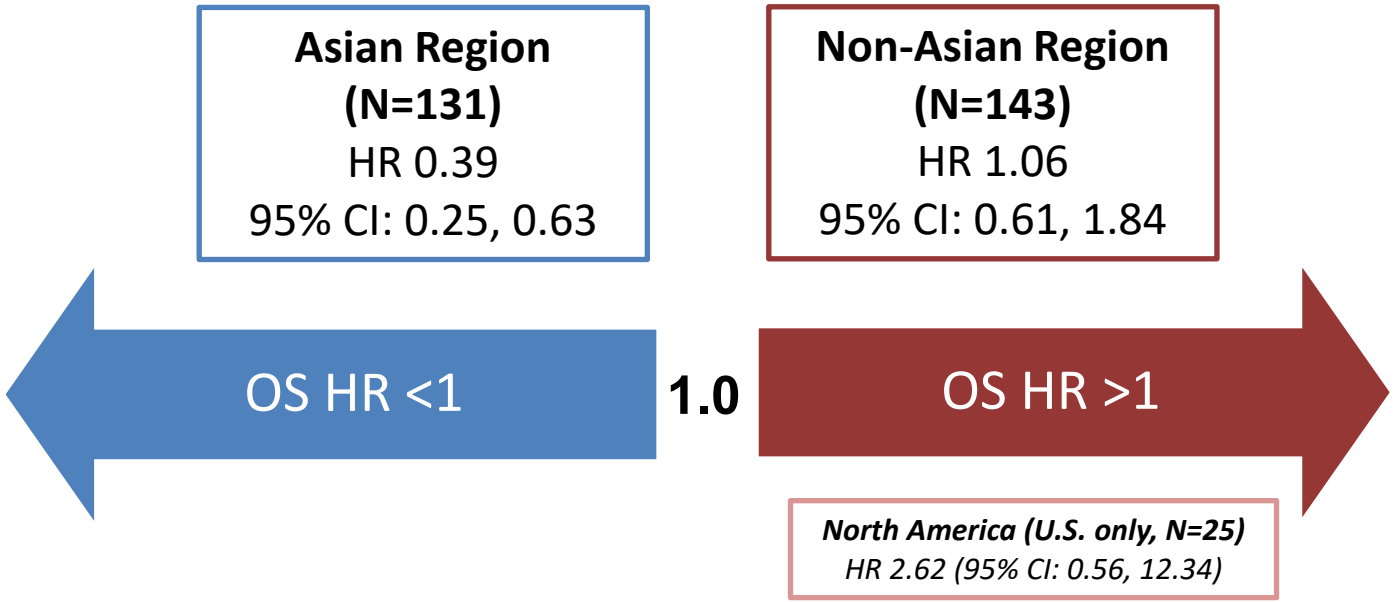
		Transplant refusal	65%	7%
Healthcare System and Trial Factors	Treatment Duration (R-GemOx)		1.1 months	3.1 months
	Early Assessments (R-GemOx)		56%	22%
	"Novel" NALT (R-GemOx)		24% (7% CAR-T)	40% (21% CAR-T)

Abbreviations: OS: Overall survival; PFS: Progression-free Survival; Complete Response Rate ; ORR: Overall Response Rate; GemOx: Gemcitabine, Oxaliplatin; R: Rituximab; y: Years; ABC-DLBCL: Activated B-cell Like Diffuse Large B-cell Lymphoma

Residual Uncertainty of Treatment Effect
STARGLO Regional OS HR: Glofit-GemOx vs R-GemOx



Source: FDA analysis; Data Cutoff: Feb 2024

Abbreviations: OS: Overall survival; Glofit: Glofitamab; GemOx: Gemcitabine, Oxaliplatin; R: Rituximab; HR: Hazard Ratio; CI: Confidence interval

Discussion Topic

Discuss how the differential results observed in the Asian and Non-Asian regions impact the overall interpretation of the STARGLO trial results and the generalizability to a U.S. patient population

Voting Question for the Committee

Are the STARGLO population and trial results applicable to the proposed U.S. patient population?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Backup Slides Displayed

Inverse Probability of Censoring Weights (IPCW)

Purpose (in the context of STARGLO)

To estimate an alternative treatment effect under a hypothetical scenario in which NALT does not exist.

Limitations of IPCW

- Assumes no unmeasured confounding.
  - Cannot verify this assumption with observed data.
  - Cannot capture every prognostic factor predicting receiving NALT.
- IPCW may become less stable with small sample sizes.
- IPCW was not pre-specified in STARGLO.
  - Selection of prognostic factors are post-hoc.

IPCW may not be relevant for STARGLO:
NALTs are realistic parts of a patient's treatment pathway → should be captured in the assessment of OS.

Inverse Probability of Censoring Weights (IPCW)

Unstable with small numbers of subjects who received NALTs

- ITT: 97 subjects received NALT
- Asian region: 47 subjects received NALT
- Non-Asian region: 50 subjects received NALT

Selection of prognostic factors are post-hoc

→ Results are highly dependent on selected factors in the model.

OS results:

- ITT could range from 0.38 (0.24, 0.59) to 0.76 (0.45, 1.28)
- Asian region could range from 0.19 (0.09, 0.37) to 0.45 (0.19, 1.03)
- Non-Asian region could range from 0.58 (0.28, 1.22) to 1.05 (0.51, 2.17)

Note: inclusion/exclusion of covariates included in these models were varied.

- List of baseline covariates considered: number of prior systemic therapies, R/R to last systemic therapy, ECOG, Ann Arbor Stage, IPI score, derived IPI score, age, and sex.
- Time-varying covariate considered: response by Investigator.

Source: FDA Analysis, Data cut-off: 16 February 2024