BITE-Sized Breakthroughs: Bispecific Antibodies in Hematologic and Solid Tum

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Disclosures

- The planner(s) and speaker(s) have indicated that there are no relevant financial relationships with any ineligible companies to disclose.

Learning objectives

Upon completion of this presentation, participants will be able to:

- Describe the mechanisms of action of bispecific T cell engagers
- Review the pathophysiology and treatment of CRS and ICANS
- Outline the efficacy of bispecific T cell engagers in the treatment of lymphoma
- Explain the efficacy of bispecific T cell engagers in the treatment of small cell lung cancer

Table of contents

01

bispecific Antibodies

Bispecific Antibodies

- Bispecific antibodies (BsAbs) have two distinct binding domains that are directed at two different antigens or epitopes of an antigen simultaneously
- BsAbs are divided into three categories
  - Antibodies targeting two different tumor antigens
  - Antibodies targeting one tumor antigen and one immune-related molecule
  - Antibodies targeting two immune-related molecules
- Structures of BsAbs are divided into two categories
  - Immunoglobulin G (IgG)-based antibodies
  - Two single chain variable fragments (scFv)-based antibodies

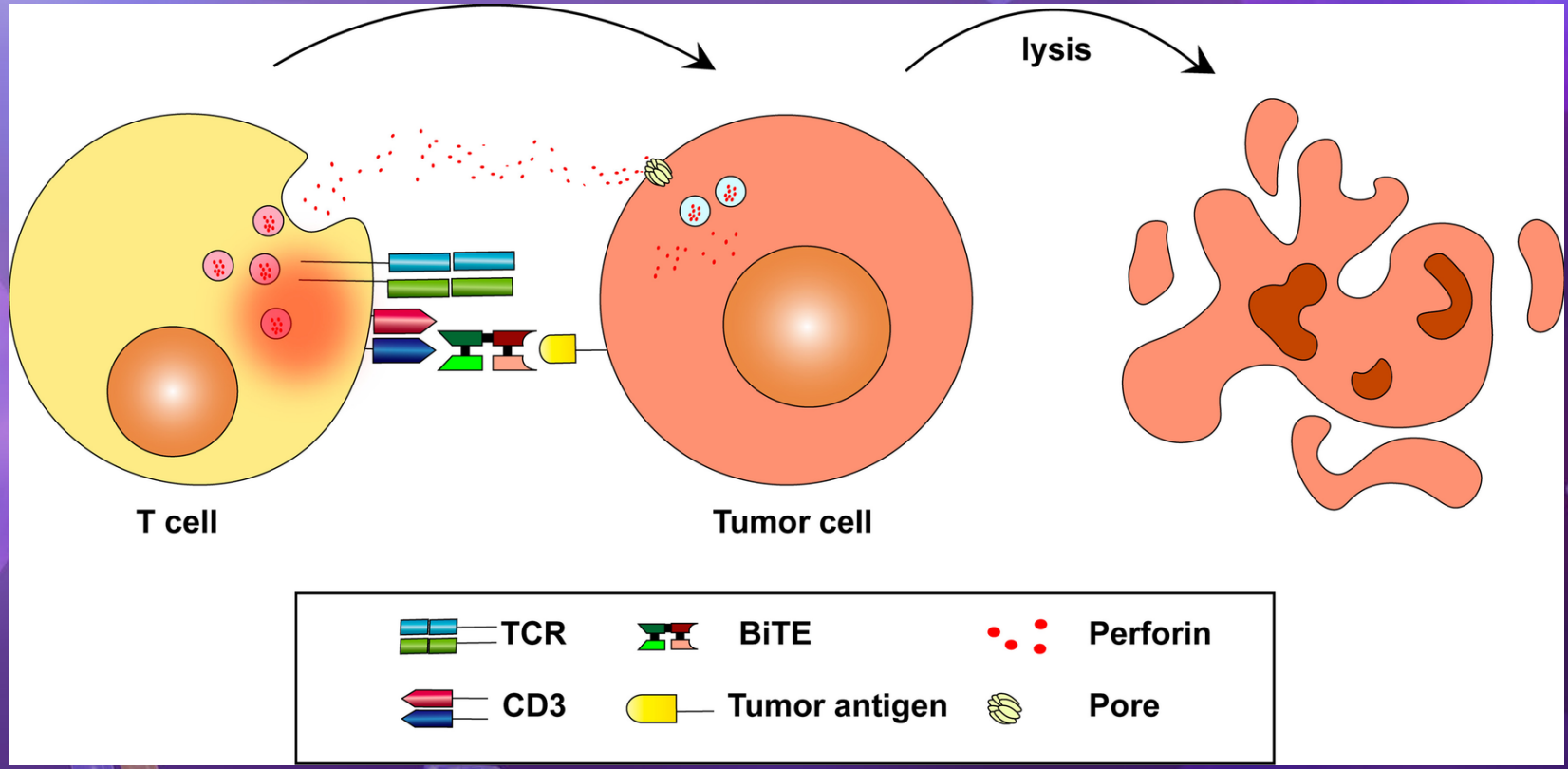
Ma J, et al. *Front Immunol* 2021;12:626616.
Tian Z, et al. *J Hematol Oncol* 2021;14(1):75.

Bispecific T Cell engagers

- Bispecific T cell engagers belong to the second type of BsAbs and enhance patients' immune response to tumors by focusing T cells to tumor cells
- T cell engagers consist of two scFv connected by a flexible linker
  - One scFv binds to a T cell-specific molecule, usually CD3
  - Second scFv binds to a tumor-associated antigen
  - This structure allows T cell engagers to physically link a T cell to a tumor cell
  - The immunological synapse between the T cell and tumor cell is essential to assemble and amplify the T cell engager-mediated tumor lysis
- The CD3 molecule associates with the T cell receptor (TCR) and participates in antigen-specific signals transduction to activate T cells
  - T cells are activated without costimulatory signals like CD28 and IL-2
  - In the presence of T cell engagers, both CD8+ and CD4+ T cells are activated

Ma J, et al. *Front Immunol* 2021;12:626616.
Tian Z, et al. *J Hematol Oncol* 2021;14(1):75.

T Cell engager Mechanism



Tian Z, et al. *J Hematol Oncol* 2021;14(1):75.

Bispecific T Cell engagers

Generic	Brand	Targets	Indications
Catumaxomab (withdrawn in 2017)	Removab	CD20/ EpCAM	Malignant ascites
Blinatumomab	Blincyto	CD3/CD19	R/R precursor B-cell ALL
Amivantamab-vmjw	Rybrevant	EGFR/cMet	NSCLC
Tebentafusp-tebn	Kimmtrak	CD3/GP100	Unresectable or metastatic uveal melanoma
Mosunetuzumab	Lunsumio	CD3/CD20	R/R follicular lymphoma
Cadonilimab	Kaitanni	PD1/CTLA4	Hepatocellular carcinoma
Teclistamab	Tecvayli	CD3/BCMA	R/R multiple myeloma
Glofitamab	COLUMVI	CD3/CD20	DLBCL
Epcoritamab	Epkinly	CD3/CD20	DLBCL
Elranatamab	Elrexfio	CD3/BCMA	R/R multiple myeloma
Talquetamab	Talvey	CD3/GPRC5D	R/R multiple myeloma
Tarlatamab-dlle	Imdelltra	CD3/DLL3	ES-SCLC

Klein C, Brinkmann, et al..*Nat Rev DrugDiscov* 2024;23(4):301-319.

Bispecific T Cell engagers

BsAb	Target	Indication
Epcoritamab	CD3/CD20	DLBCL
Glofitamab	CD3/CD20	DLBCL
Tarlatamab	CD3/DLL3	ES-SCLC

02

CrsandCANS

Cytokine Release Syndrome (CRS)

Pathophysiology

- CRS is a systemic inflammatory response that results from the rapid release of large amounts of cytokines into the blood from immune cells
- Excessive cytokine release can lead to widespread inflammation and multi-organ dysfunction
- Key cytokines involved include IL-6, IL-1, IFN-γ, and TNF-α

Signs and Symptoms:

- Fever
- Fatigue
- Headache
- Myalgia
- Nausea
- Hypotension
- Tachycardia
- Dyspnea
- Elevated LFTs
- Organ dysfunction

Shimabukuro-Vornhagen A, et al. *J Immunother Cancer*. 2018;6(1):56.
Cytokine release syndrome (CRS). In: UpToDate [database online].
Lee DW, et al. *Biol Blood Marrow Transplant*. 2019;25(4):625-638.

CRS Classification

American Society for Transplantation and Cellular Therapy Grading System of CRS

Grade	Toxicity
Grade 1	Fever (Temperature ≥38°C/100.4°F)
Grade 2	Fever (Temperature ≥38°C/100.4°F) with either: • Hypotension not requiring vasopressors • Hypoxia requiring low-flow nasal cannula (NC) or blow-by
Grade 3	Fever (Temperature ≥38°C/100.4°F) with either: • Hypotension requiring a vasopressor with or without vasopressin • Hypoxia requiring high-flow NC, facemask, nonrebreather mask, or Venturi mask
Grade 4	Fever (Temperature ≥38°C/100.4°F) with either: • Hypotension requiring multiple vasopressors (excluding vasopressin) • Hypoxia requiring positive pressure (CPAP, BiPAP, intubation, mechanical ventilation)
Grade 5	Death

Shimabukuro-Vornhagen A, et al. *J Immunother Cancer*. 2018;6(1):56.
Cytokine release syndrome (CRS). In: UpToDate [database online].
Lee DW, et al. *Biol Blood Marrow Transplant*. 2019;25(4):625-638.

CRS Treatment

ASTCT Recommendations for CRS Treatment by Grade

- Grade 1: Analgesics and antipyretics. Consider tocilizumab if > 3 days
- Grade 2:
  - 500-1000 mL IV fluid bolus and tocilizumab
  - Add dexamethasone 10 mg IV Q6H if hypotension persists
- Grade 3: Admission to ICU
  - Administer tocilizumab and dexamethasone 10 mg IV Q6H
  - If refractory, increase dexamethasone to 20 mg IV Q6H
  - If unresponsive, add anakinra 2 mg/kg daily for 3–5 days
- Grade 4: Admission to ICU
  - Administer tocilizumab and high-dose methylprednisolone 1 g/day IV
  - If unresponsive, add anakinra 2 mg/kg daily for 3–5 days
  - If unresponsive, consider anti-TNF-α agents

Shimabukuro-Vornhagen A, et al. *J Immunother Cancer*. 2018;6(1):56.
Cytokine release syndrome (CRS). In: UpToDate [database online].
Lee DW, et al. *Biol Blood Marrow Transplant*. 2019;25(4):625-638.

Immune effector-associated neurotoxicity syndrome (ICANS)

Pathophysiology

- ICANS is believed to be caused by an inflammatory response that affects the blood-brain barrier (BBB), leading to the leakage of cytokines and immune cells into the CNS resulting in neurotoxicity.

Signs and Symptoms:

- Encephalopathy with confusion and behavioral changes
- Visual and auditory hallucinations
- Language dysfunction, speech alterations, and apraxia
- Headache, fatigue, and tremors
- Dysgraphia and other fine motor impairment
- Clinical or subclinical seizures, including status epilepticus
- Cerebral edema with coma
- Death secondary to cerebral edema

Shimabukuro-Vornhagen A, et al. *J Immunother Cancer* 2018;6(1):56.
Suarez Montero JC, et al. *Med Intensiva (Engl Ed)* 2022;46(4):201-212.
Immune effector cell-associated neurotoxicity syndrome (ICANS). In: UpToDate [database online].

ICANS Classification

ASTCT ICANS Consensus Grading for Adults

Grade	ICE score	Depressed level of consciousness	Seizure	Motor findings	Elevated ICP/cerebral edema
Grade 1	7-9	Awakens spontaneously	N/A	N/A	N/A
Grade 2	3-6	Awakens to voice	N/A	N/A	N/A
Grade 3	0-2	Awakens only to tactile stimulus	Any clinical seizure	N/A	Focal/local edema on neuroimaging
Grade 4	0: unarousable to perform	Unarousable or requires vigorous	Life-threatening prolonged seizure	Deep focal motor weakness	Diffuse cerebral edema on neuroimaging; decerebrate or decorticate posturing; or cranial nerve VI palsy; or papilledema; or Cushing's triad

Shimabukuro-Vornhagen A, et al. *J Immunother Cancer* 2018;6(1):56.
Suarez Montero JC, et al. *Med Intensiva (Engl Ed)* 2022;46(4):201-212.
Immune effector cell-associated neurotoxicity syndrome (ICANS). In: UpToDate [database online].

ICANS Treatment

ASTCT Recommendations for ICANS Treatment by Grade

- Grade 1: Haloperidol or lorazepam if agitated. Dexamethasone in high-risk patients. Non-sedating anti-epileptics
- Grade 2: Dexamethasone 10 mg IV Q12H. If no change in 48 hrs, increase to 20 mg IV Q6H
  - Tocilizumab or anakinra if concomitant CRS
  - Non-sedating anti-epileptics
- Grade 3: Dexamethasone 10 mg IV Q6H. If no change in 48 hrs, increase to 20 mg IV Q6H or methylprednisolone 1-2 g/day
  - Tocilizumab or anakinra if concomitant CRS
  - Non-sedating anti-epileptics
- Grade 4: Dexamethasone 20 mg IV Q6H. If dex refractory, methylprednisolone 2 g Q12H
  - If steroid refractory, consider alternative therapies including lymphodepletion with cyclophosphamide and other drugs

Shimabukuro-Vornhagen A, et al. *J Immunother Cancer* 2018;6(1):56.
Suarez Montero JC, et al. *Med Intensiva (Engl Ed)* 2022;46(4):201-212.
Immune effector cell-associated neurotoxicity syndrome (ICANS). In: UpToDate [database online].

03

Epcoritamab in lymphoma

Epcoritamab: A Novel, Subcutaneous CD3xCD20 Bispecific T-Cell Engaging Antibody, in Relapsed or Refractory Large B-Cell Lymphoma: Dose Expansion in a Phase I/II Trial

Published in the *Journal of Clinical Oncology*
April 20, 2023

Epcoritamab for R/R LBCL

Study Design: Phase I/II, single-arm, multicenter, open-label, dose-escalation/dose-expansion study

Study Objective: Evaluated the efficacy and safety of subcutaneous epcoritamab in patients with relapsed or refractory LBCL

Patient Population

- Between June 19, 2020 - January 31, 2022, 157 patients were enrolled and treated with epcoritamab

Primary Endpoint

- The primary end point was overall response rate (ORR) by the independent review committee

Results

- Overall response rate was 63.1% (95% CI, 55.0 to 70.6)
- Complete response rate was 38.9% (95% CI, 31.2 to 46.9).
- Median duration of response was 12.0 months (not reached in complete responders)
- Most common tr adverse events were CRS (49.7%) pyrexia (23.6%), and fatigue (22.9%)

Thieblemont C, et al. *J Clin Oncol* 2023;41(12):2238-2247.

EPCORE FULL: Epcoritamab monotherapy in patients w relapsed or refractory follicular lymphoma

Published in *The Lancet Hematology*
August 11, 2024

EPCORE FL: Epcoritamab in R/

Study Design: Phase 2 part of a single-arm, multicohort, international trial

- Pivotal dose optimization cohort
- Cycle 1 optimization cohort

Study Objective: Investigate the safety and activity of subcutaneous epcoritamab in the relapsed or refractory follicular lymphoma setting

Patient Population

- From June 19, 2020 – April 21,2023, 214 patients were enrolled
  - Pivotal: 128 patients; Optimization: 86 patients
- Before study entry
  - Primary refractory disease: 54%; 44%
  - Refractory to previous anti-CD20 therapy: 79%; 78%
  - Double refractory disease: 70%; 63%

Linton KM, et al. *LancetHaematol* 2024;11(8):e593-e605.

EPCORE FL-1: Epcoritamab in R/

Key Inclusion/Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
• ≥ 18 years of age • Histologically confirmed CD20+ follicular lymphoma • R/R to ≥2 prior therapies, including anti-CD20 mAb and alkylator or lenalidomide • ECOG status ≤ 2	• Primary CNS lymphoma • HIV infection, significant cardiovascular disease • Current autoimmune disease • Previous therapy with an investigational bispecific targeting CD3 and CD20 • CAR T-cell therapy within 30 days before treatment

Intervention

- Epcoritamab subcutaneous injection 48 mgper 28-day cycle:
  - Weekly cycles 1–3; biweekly cycles 4–9; every 4 weeks until progression or toxicity
- CRS Mitigation
  - Pivotal: Step-up doses in cycle 1 (0.16 mg day 1, 0.80 mg day 8, then full dose day 15+) plus 100 mg prednisolone
  - Optimization: Additional 3 mg dose day 15, aggressive hydration, and 15 mg dexamethasone

Linton KM, et al. *LancetHaematol* 2024;11(8):e593-e605.

EPCORE NHL: Epcoritamab in R/

Primary Endpoints

- Pivotal: The primary efficacy endpoint was the overall response rate (ORR), independently reviewed
- Optimization: The primary safety endpoint was the incidence of CRS of grade 2 or worse and the rate of any-grade CRS within 7 days on administration

Secondary Endpoints

- Pivotal: Complete response rate, time to response, time to complete response, duration of response, duration of complete response, progression-free survival, overall survival
- Optimization: Incidence of CRS of grade 2 or worse and the rate of any-grade CRS after the first 48 mg dose and overall adverse events

Linton KM, et al. *LancetHaematol* 2024;11(8):e593-e605.

EPCORE FL: Epcoritamab in R/

Statistical Analysis

- 128 patients in the pivotal cohort gave about 90% power to detect an ORR > 50% (two-sided significance level 0.05).
- 80 patients in the optimization cohort gave >80% power to detect a true event rate of grade 2+ CRS of at least 2%.
- Time-to-event endpoints (e.g., PFS, OS) were analyzed in the full analysis set using Kaplan–Meier estimates for median time and 95% CI
- All enrolled patients who received at least one dose of study treatment were included in the efficacy analysis
- Safety endpoints were summarized using frequency and percentages based on all patients who received at least one dose of epcoritamab.

Linton KM, et al. *LancetHaematol* 2024;11(8):e593-e605.

EPCORE FL: Epcoritamab in R/

Efficacy

- ORR pivotal cohort: 82.0% (105/128, 95% CI 74.3–88.3)
- Complete response rate: 62.5% (80/128, 95% CI 53.5–70.9)

Safety

- Most common Grade 3–4 AE: Neutropenia (25%)

CRS:

- Pivotal: Any grade 65%, grade 3 in 2%
- Optimization: Any grade 49%, grade 2 in 9%,no grade 3 or higher

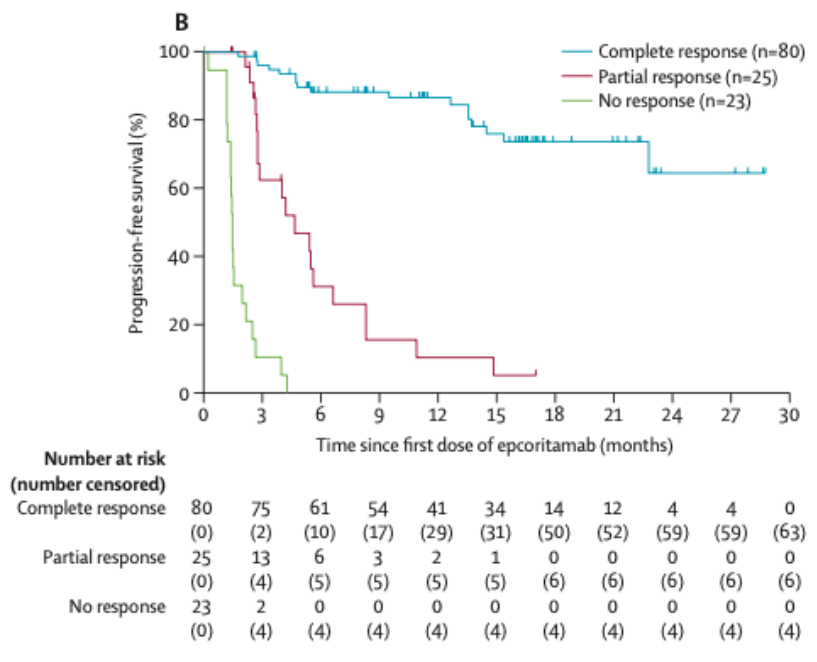
ICANS (neurotoxicity):

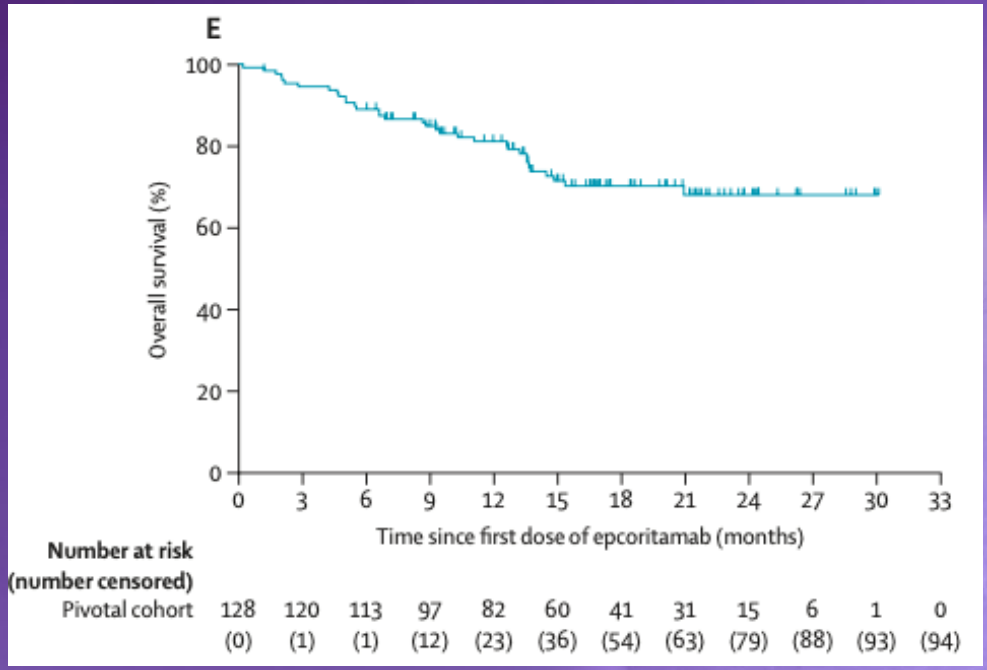
- Pivotal: 6% (5% grade 1, 2% grade 2)
- Optimization: 0% reported

Linton KM, et al. *LancetHaematol* 2024;11(8):e593-e605.

EPCORE R/R LBCL: Epcoritamab in R/

Efficacy





Linton KM, et al. *LancetHaematol* 2024;11(8):e593-e605.

EPCORE NHL-1: Epcoritamab in R/

Author's Conclusion

"Results from EPCORE NHL-1 showed robust, clinically meaningful efficacy, including deep and durable responses and high rates of MRD negativity in the largest known analysis of T-cell-engaging therapies in patients with relapsed or refractory follicular lymphoma. Cycle 1 optimization further improved the safety profile, in addition to removing mandatory hospitalization. These results indicate that epcoritamab has the potential to be an important therapy for the treatment of relapsed or refractory follicular lymphoma."

Linton KM, et al. *LancetHaematol* 2024;11(8):e593-e605.

EPCORE FL: Epcoritamab in R/

Strengths and Weaknesses

Strengths	Weaknesses
• Large, multinational population • Robust independent efficacy review • Detailed safety monitoring • Robust response	• Single-arm study design • Lack of long-term follow -up • Excluding previous BsAb • Results may not generalize to patients with less refractory disease or to front-line settings

Linton KM, et al. *LancetHaematol* 2024;11(8):e593-e605.

EPCORE FL: Epcoritamab in R/

Presenter's Conclusion

Epcoritamab monotherapy demonstrated clinically meaningful activity in heavily pretreated FL patients and deliveried a high rate of complete and overall responses. The safety profile was manageable, with CRS being the most common immune-related event, which was further lowered with cycle 1 dosing optimization. These results suggest a clinically meaningful role for epcoritamab in later-line FL therapy, especially for patients who have exhausted traditional options and addressing an unmet need.

Linton KM, et al. *LancetHaematol* 2024;11(8):e593-e605.

Long-term follow-up from EPCORE D

Updated Results Published November 5, 2024

- Median follow-up at 37.1 months:
  - 41% of patients achieved complete response
    - At 36 months, an estimated 63% of complete responders remained alive
  - 59% of of patients achieved objective response
  - Median duration of response was 20.8 months (95% CI, 13–32)
  - Median duration of CR 36.1 months (95% CI, 20.2–NE)
  - Median overall survival was 18.5 mo (95% CI, 11.7-27.7)

Epcoritamab continued to show deep and durable responses, with more than half of complete responders remaining in remission at 3 years

Vose JM, etal. *Blood* 2024; 144 (Supplement 1): 4480.

Epcoritamab (Epkinly)

FDA approval: May 19, 2023

Dosing:

Cycle	Day	Epcoritamab Dose
Cycle 1	Day 1	0.16 mg SC
	Day 8	0.8 mg SC
	Day 15	3 mg SC
	Day 22	48 mg SC
Cycle 2 and 3	Day 1, 8, 15, 22	48 mg SC
Cycles 4 to 9	Day 1 and 15	48 mg SC
Cycle 10+	Day 1	48 mg SC

Premedications: 30-120 min prior to treatment with glofitamab

- Cycle 1: Dexamethasone 15 mg; diphenhydramine 50 mg; acetaminophen 650-1,000 mg
- Cycle 2+ if CRS grade 2 or 3 with previous dose: Dexamethasone 15 mg

UpToDate Lexidrug

04

Glofitamab in lymphoma

Glofitamab for Relapsed or Refractory Diffuse Large Cell Lymphoma

Published in *New England Journal of Medicine*
December 11, 2022

Glofitamab for R/R DLBCL

Study Design: Phase 2 part of an open-label phase 1–2 clinical trial

Study Objective: Assessthe efficacy and safety of glofitamab monotherapy in patients with relapsed or refractory DLBCL who had received at least two lines of therapy previously

Patient Population

- 154 patients received at least one dose of any study treatment

Primary Endpoint

- Primary efficacy end point was complete response as assessed by independent review committee

Results

- 39% of patients had a complete response
- Median time to a complete response was 42 days
- 78% of complete responses were ongoing at 12 months
- Most common adverse event was CRS (63% of the patients)

Dickinson MJ, et al. *N Engl J Med* 2022;387(24):2220-2231.

STARGLO: Glofitamab plus gemcitabine and oxaliplatin versus rituximab plus gemcitabine and oxaliplatin for relapsed or refractory diffuse large B-cell lymphoma

Published in *The Lancet*
November 16, 2024

STARGLO: Glofitamab + GEMOX in R

Study Design: Global phase 3, open-label, randomized trial

Study Objective: Investigate the efficacy and safety of Glofit-GemOx compared with R-GemOx in patients with relapsed or refractory diffuse large B-cell lymphoma after one or more previous therapies

Patient Population

- From Feb 23, 2021, to March 14, 2023 , 274 were enrolled and randomized 2:1 to receive either Glofit-GemOx or R-GemOx
  - 183 patients were assigned to the Glofit-GemOx group
  - 91 patients were assigned to the R-GemOx group
- Before the study
  - 63% patients had received a median of 1 previous line of therapy
  - 67% relapsed/refractory to any previous therapy
  - 21 patients had previously received CAR-T cell therapy
  - 11 patients had previously received ASCT

Abramson JS, et al. *Lancet* 2024;404(10466):1940-1954.

STARGLO: Glofitamab + GEMOX in R

Key Inclusion/Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
• ≥18 years of age • Histologically confirmed DLBCL who received 1 or more previous systemic therapies with relapsed or refractory disease • ECOG status of 0-2 • Patients with only one previous line of therapy had to be considered ASCT-ineligible	• Patients with DLBCL transformed from indolent lymphoma, double or triple hit lymphomas, or high-grade B-cell lymphoma

Intervention

Glofit-GemOx	R-GemOx

• Glofitamab was administered for up to 12 cycles.
• Obinutuzumab 1,000 mg IV on day 1 of cycle 1
• Glofitamab IV by step-up dosing during cycle 1
  ○ Day 8: 2·5 mg; day 15: 10 mg
  ○ Glofitamab 30 mg on day 1 of cycles 2-12
	• Rituximab 375 mg/m^2 IV on day 1 of each cycle up to 8 cycles

• GemOx: IV gemcitabine 1000 mg/m^2 and oxaliplatin 100 mg/m^2 given on day 2 of cycle 1, then day 1 of subsequent cycles • Prophylactic GCSF required during cycles 1-2 in both groups and was optional thereafter	

Abramson JS, et al *Lancet* 2024;404(10466):1940-1954.

STARGLO: Glofitamab + GEMOX in R

Primary Endpoint

- The primary end point was overall survival assessed by site investigators

Secondary Endpoints

- Key secondary end points included progression-free survival, complete response rate, and duration of complete response assessed by the IRC in a masked manner

Statistical Analysis

- A sample size of 270 patients (138 events) provided 80% power to detect a difference in median overall survival of 7.3 months
- Efficacy analyses conducted in the intention-to-treat population
- OS, PFS, DCR, and DOR were compared between groups with a two-sided log-rank test
- Kaplan–Meier method was used to estimate survival, including median survival, 24-month overall survival rate, and 12-month progression-free survival
- Safety was assessed in all patients that received any study treatment

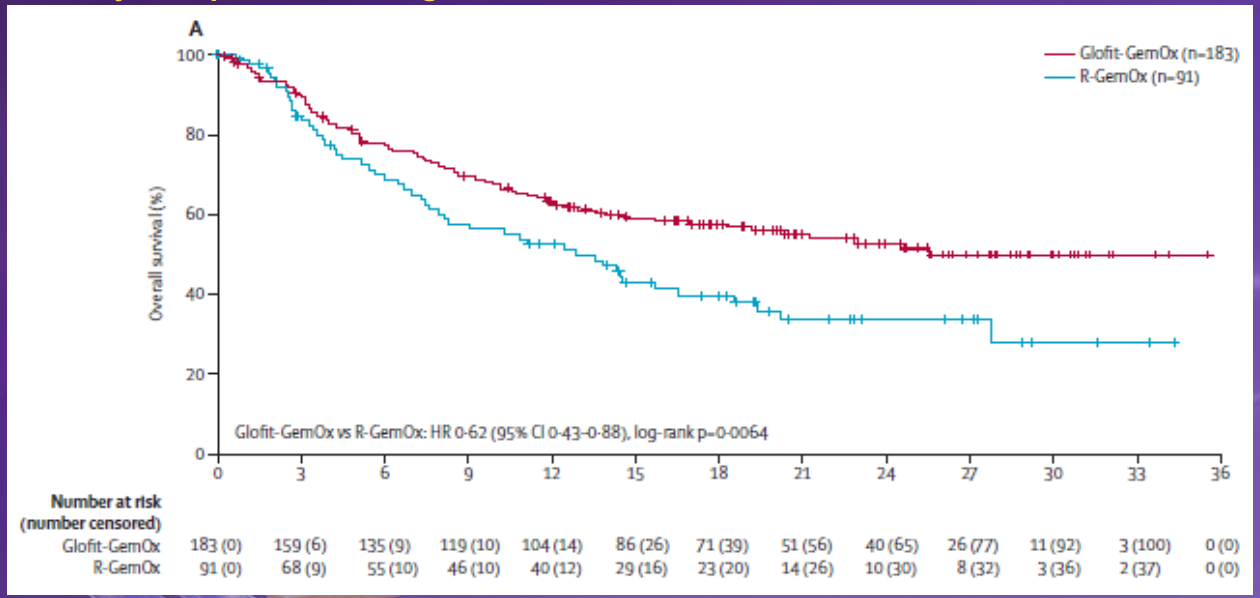
Abramson JS, et al *Lancet* 2024;404(10466):1940-1954.

STARGLO: Glofitamab + GEMOX in R

Efficacy

- 172 (94%) of 183 patients were exposed to glofitamab
- 88 (97%) of 91 patients were exposed to rituximab

Primary Endpoint: Investigator -assessed overall survival



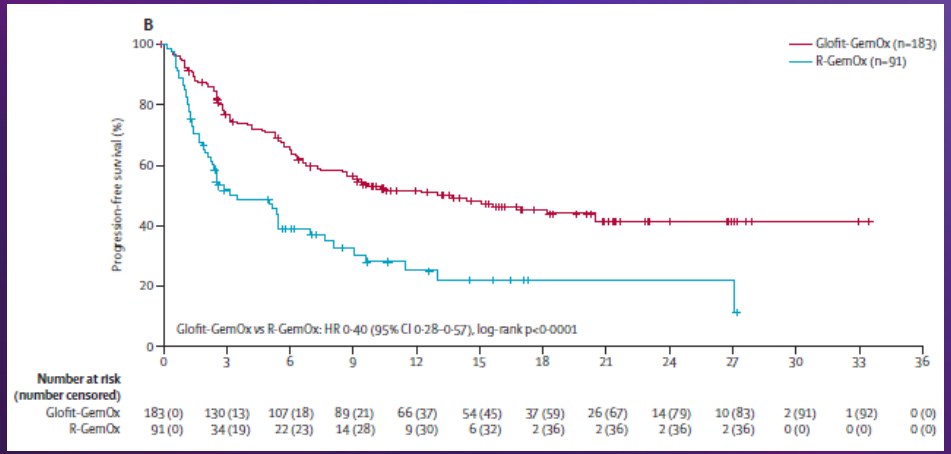
- Glofit-GemOx: 25.5 months (95% CI 18.3–NE)
- R-GemOx: 12.9 months (95% CI 7.9–18.5)
- HR: 0.62 (95% CI 0.43–0.88)
- p = 0.0064

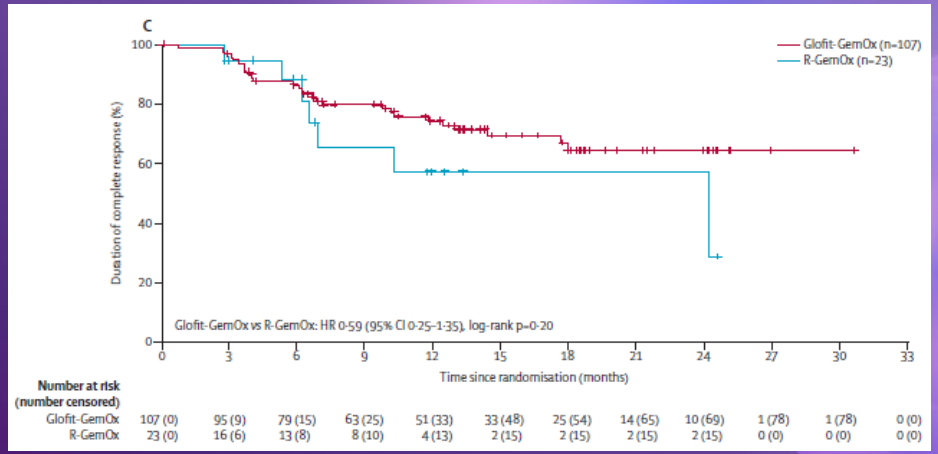
Abramson JS, et al *Lancet* 2024;404(10466):1940-1954.

STARGLO: Glofitamab + GEMOX in R

Secondary Endpoints

IRC-assessed complete response: Glofit-GemOx 58.5% vs R-GemOx 25.3%; p < 0.0001





IRC-assessed progression-free survival

- Glofit-GemOx: 13.8 months (95% CI 8.7–20.5)
- R-GemOx: 3.6 months (95% CI 2.5–7.1)
- p < 0.0001

IRC-assessed duration of complete response

- Glofit-GemOx: NE (95% CI NE–NE)
- R-GemOx: 24.2 months (95% CI 9.9–NE)
- p = 0.205

Abramson JS, et al. *Lancet* 2024;404(10466):1940-1954.

STARGLO: Glofitamab + GEMOX in R

Safety

- 180 (100%) of Glofit-GemOx patients and 84 of 88 (96%) R-GemOx patients had at least one adverse event
  - Thrombocytopenia occurred in 48% of Glofit-GemOx patients and 48% of R-GemOx patients
  - Neutropenia occurred in 42% of Glofit-GemOx patients and 31% of R-GemOx patients
- CRS occurred in 76 of 172 glofitamab-exposed patients (44%) and predominantly occurred after the initial 2.5 mg glofitamab dose
- ICANS was reported in 4 (2%) Glofit-GemOx recipients

Abramson JS, et al *Lancet* 2024;404(10466):1940-1954.

STARGLO: Glofitamab + GEMOX in R

Author's Conclusion

"STARGLO met its primary endpoint, with a statistically significant and clinically meaningful overall survival benefit with Glofit-GemOx compared with R-GemOx in relapsed or refractory diffuse large B-cell lymphoma…The results showed a significant benefit with Glofit-GemOx versus R-GemOx for overall survival, progression-free survival, and complete response rate in ASCT-ineligible patients with relapsed or refractory diffuse large B-cell lymphoma, with a safety profile consistent with the known risks of the individual agents."

Abramson JS, et al *Lancet* 2024;404(10466):1940-1954.

STARGLO: Glofitamab + GEMOX in R

Strengths and Weaknesses

Strengths	Weaknesses
• Global, multi-center design • Masked independent endpoint assessment • Comprehensive efficacy endpoints, including OS and PFS	• Open-label design • Under-representation of Black patients and possible regional heterogeneity • Exclusion of double/triple -hit lymphomas • Duration of follow -up is relatively limited (~21 months)

Abramson JS, et al *Lancet* 2024;404(10466):1940-1954.

STARGLO: Glofitamab + GEMOX in R

Presenter's Conclusion

The findings of STARGLO demonstrate a substantial, statistically significant benefit in OS, PFS, and response rates for Glofit-GemOx. The OS benefit exceeds that previously achieved by the current standard of R-GemOx in a comparable real-world population. Glofitamab's relative ease of administration compared to CAR T-cell therapy could expand access to cellular therapies which is important for patients that are ineligible for transplant/CAR T or lack access.The evidence strongly supports Glofit-GemOx as a new standard in transplant-ineligible, relapsed/refractory DLBCL.

Abramson JS, et al *Lancet* 2024;404(10466):1940-1954.

FDA Statement on StarGlo

The FDA issued a complete response letter (CRL) rejecting Glofit-GemOx for the treatment of R/R DLBCL in the U.S. due to insufficient evidence from the STARGLO trial for the U.S. patient population.

Key Points of the FDA's Decision

- Low U.S. Participation in STARGLO:
  - Only a small percentage (9%) of patients in the STARGLO trial were from the U.S., raising concerns about how well the trial's findings apply to the American patient population.
- Lack of Survival Benefit in North America:
  - The survival benefit seen in Asian patients within the STARGLO trial did not translate to non-Asian regions, including North America and Europe.

Long-term follow-up For Glofitamab

Updated Results Published November 5, 2024

- Median follow-up at 37.7 months:
  - Median time on study was 41.0 months, with all patients with ongoing remission being treatment-free for ≥ 2 years following end of treatment (EOT)
  - Patients with a CR
    - Median duration of CR: 29.8 months (95% CI: 22.0-NE]).
    - PFS rate 2 years after EOT was 57%
    - OS rate 2 years after EOT was 77%

Extended follow-up of over 3 years shows durable and continued response with glofitamab in patients with R/R DLBCL

Dickinson MJ, et al. *Blood* 2024; 144 (Supplement 1): 865.

Glofitamab (COLUMVI)

FDA approval: June 15, 2023

Dosing:

- Pretreat with a single dose of obinutuzumab on cycle 1, day 1

Cycle	Day	Glofitamab Dose
Cycle 1	Day 8	2.5 mg over 4 hours
	Day 15	10 mg over 4 hours
Cycle 2	Day 1	30 mg over 4 hours
Cycles 3 to 12	Day 1	30 mg over 2 hours

Premedications: 1 hr prior to treatment with glofitamab

- Acetaminophen 500-1,000 mg orally
- Diphenhydramine 50 mg orally or IV
- Dexamethasone 20 mg IV
  - Required for cycles 1-3 but only in those who experienced CRS in cycles 4+

05

Tarlatamab in Small Cell Lung Cance

DeLLphi-301: a First-in-Class DLL3-Targeted Bispecific T Cell Engager, in Recurrent Small Cell Lung Cancer: An Open-Label, Phase I Study

Published in *Journal of Clinical Oncology*
January 23, 2023

DeLLphi-301: Tarlatamab for SCLC

Study Design: Phase I, international, open-label, dose-escalation study

Study Objective: Evaluate the safety, PK, and preliminary efficacy of tarlatamab in SCLC patients

Patient Population

- 107 patients received tarlatamab in dose escalation (0.003-100 mg) and expansion (100 mg)

Primary/Secondary Endpoints

- The primary endpoint was safety including dose-limiting toxicities, AEs during the treatment period, TEAEs possibly related to tarlatamab
- The secondary endpoints were: objective response , duration of response, PFS, and OS

Results

- Objective response was 23.4% (2 CR, 23 PR)
- Responses were seen starting with the 0.3 mg. Higher rates at doses ⩾ 3 mg
- 78% of complete responses were ongoing at 12 months
- Most common ADEs were CRS (56 patients) pyrexia (43) and constipation (33)

Paz-Ares L, et al. *J Clin Oncol* 2023;41(16):2893-2903.

DeLLphi-301 Tarlatamab for Patients with Previously Tr Small-Cell Lung Cancer

Published in the *New England Journal of Medicine*
November 30, 2023

DeLLphi-301: Tarlatamab for SCLC

Study Design: Phase 2, open-label, international trial

Study Objective: Evaluate the antitumor activity, safety, side effect profile, and pharmacokinetics (PK) of tarlatamab in patients with advanced SCLC previously treated with 2 or more lines of therapy

Trial Design: Consisted of 3 parts

- Part 1: Dose-comparison of 10 mg or 100 mg of tarlatamab IV infusion
- Part 2: Enrolled 100 patients (parts 1 and 2 combined) at selected dose
- Part 3: Evaluated the safety when inpatient monitoring during cycle 1 was reduced from 48 to 24 hours after the infusion

Ahn MJ, et al. *N Engl J Med*. 2023;389(22):2063-2075.

DeLLphi-301: Tarlatamab Efficacy

Key Inclusion/Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
• ≥18 years of age • Histologically/cytological confirmed SCLC R/R to one platinum-based regimen and at least 1 other line • ECOG 0-1 • Measurable lesions within 21 days prior to first dose	• Interstitial lung disease or active, non-infectious pneumonitis • Prior anti-cancer therapy within 28 days of first dose • History of other malignancy within the past 2 years

Patient Population

- From December 2021- May 2023, 222 patients were enrolled and randomized 1:1 to 10 mg (N=100, parts 1+2) or 100 mg (N=88) tarlatamab.
  - Median age: ~64 years; majority male (70–72%)
  - Median prior therapies: 2 (range 1–8). Most had extensive-stage, platinum-R/R disease
  - 70% had prior PD-1/PD-L1 inhibitor

Ahn MJ, et al. *N Engl J Med* 2023;389(22):2063-2075.

DeLLphi-301: Tarlatamab Schedule

Intervention

- Step-up dosing was used in all 3 parts of the study
  - 1 mg IV on day 1
  - Followed by target dose on day 8, day 15,
  - Every 2 weeks in 28-day cycles
- Pre-medications
  - 8 mg dexamethasone before tarlatamab on day 1 and 8 of cycle 1
  - IV hydration after infusion after each dose in cycle 1
- Dose-selection committee independent of the trial team analyzed the data and recommended the 10 mg target dose for parts 2 and 3
- Tarlatamab administration was continued until disease progression, unacceptable side effects, or consent withdrawal

Ahn MJ, et al. *N Engl J Med* 2023;389(22):2063-2075.

DeLLphi-301: Tarlatamab Efficacy

Primary Endpoint

- The primary end point was confirmed objective response

Secondary Endpoints

- Duration of objective response
- Disease control
- Duration of disease control
- Progression-free survival
- Overall survival
- Adverse events during the treatment period

Ahn MJ, et al. *N Engl J Med* 2023;389(22):2063-2075.

DeLLphi-301: Tarlatamab Efficacy

Statistical Analysis

- To detect an expected ORR of 30% vs the 15% historical control, 100 patients at the selected dose were needed to give a 92% probability that the lower bound of the 97.5% CI would exceed 15%
- All patients enrolled in parts 1 and 2 included in intention-to-treat analysis
  - Patients in part 3 were excluded due to immature data
- All patients who received at least one dose of tarlatamab (from parts 1-3) were included in the safety analysis
- ORR and other response rates were estimated using the Clopper–Pearson method
- Median duration of response, progression-free survival (PFS), and overall survival (OS) were estimated using the Kaplan–Meier method

Ahn MJ, et al. *N Engl J Med* 2023;389(22):2063-2075.

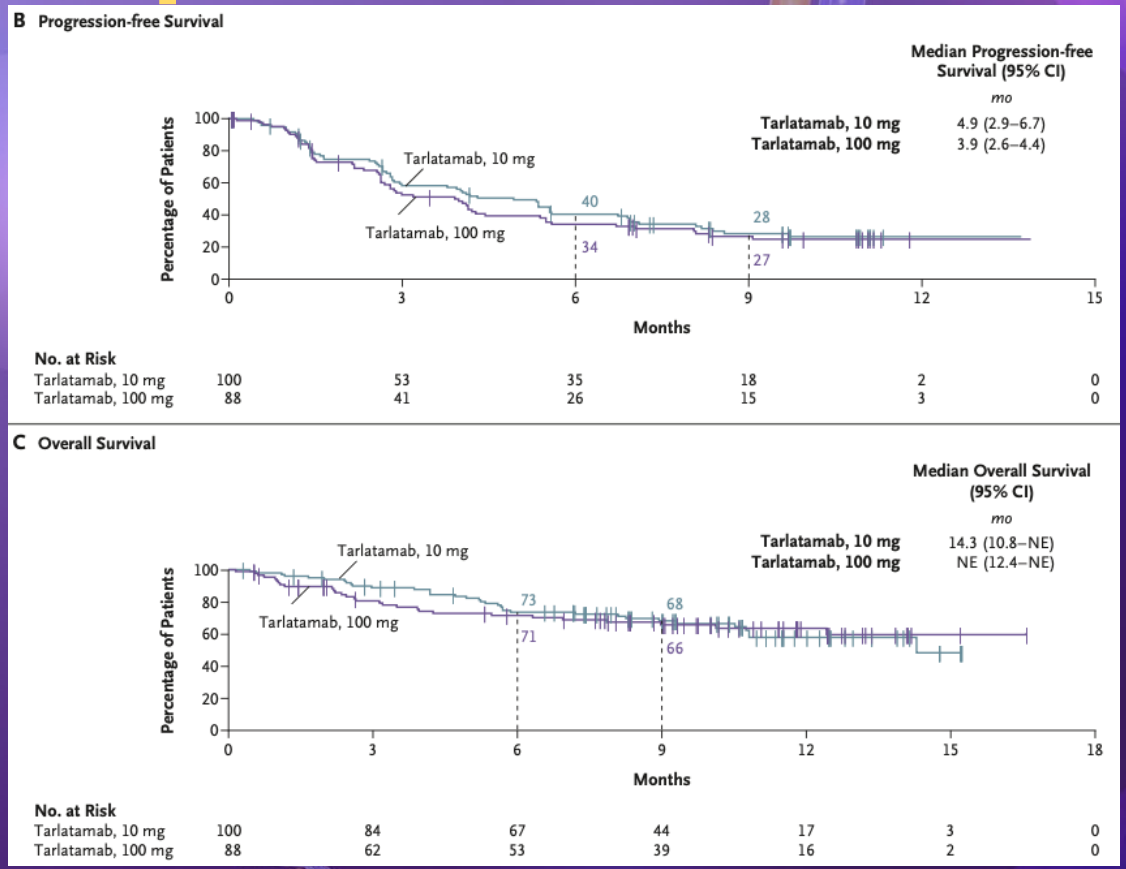
DeLLphi-301: Tarlatamab Efficacy

Efficacy

Outcome	Tarlatamab 10 mg	Tarlatamab 100 mg
Objective Response Rate (ORR)	40% (29–52%) [N=100]	32% (21–44%) [N=88]
Complete Responses	1%	8%
Partial Responses	39%	24%
Disease Control Rate	70% (60–79%)	63% (52–73%)
Median DOR	Not Estimable (≥6 mo in 58%)	Not Estimable (≥ 6 mo in 61%)
Median PFS	4.9 mo (2.9–6.7)	3.9 mo (2.6–4.4)
Median OS	14.3 mo (10.8–NE)	Not Estimable (NE [≥12.4])
Ongoing responses at cutoff	55%	57%

Ahn MJ, et al. *N Engl J Med* 2023;389(22):2063-2075.

DeLLphi-301: Tarlatamab Efficacy



Ahn MJ, et al. *N Engl J Med* 2023;389(22):2063-2075.

DeLLphi-301: Tarlatamab Efficacy

Safety

- Any adverse event: 97% (10 mg arm), 100% (100 mg arm)
- Grade ≥3 events: 59% (10 mg), 64% (100 mg)
- CRS:
  - Any grade: 51% (10 mg), 61% (100 mg)
  - Grade ≥3: 1% (10 mg), 6% (100 mg)
  - Most CRS cases were grade 1–2, occurred in cycle 1, and were managed supportively
- ICANS/neurologic events: 8% (10 mg), 28% (100 mg)
  - Mostly low grade; no grade ≥ 3 in the 10 mg group
- Other common AEs: Decreased appetite, pyrexia, constipation, anemia

Ahn MJ, et al. *N Engl J Med* 2023;389(22):2063-2075.

DeLLphi-301: Tarlatamab Efficacy

Author's Conclusion

"In this phase 2 DeLLphi-301 trial, tarlatamab had durable antitumor activity in patients with heavily pretreated small-cell lung cancer…The 10-mg dose was selected for subsequent tarlatamab trials because it had a more favorable benefit-to-risk profile than the 100-mg dose, with an objective response in 40% of the patients and a median overall survival of 14.3 months."

Ahn MJ, et al. *N Engl J Med* 2023;389(22):2063-2075.

DeLLphi-301: Tarlatamab Efficacy

Strengths and Weaknesses

Strengths	Weaknesses
• Rigorous and blinded efficacy assessment • Adequate size and international • Novel mechanism/unmet need • Robust antitumor activity	• Open-label design • Lack of Control Arm • Sponsor Involvement • Long-term benefit/risks remain uncertain

Ahn MJ, et al. *N Engl J Med* 2023;389(22):2063-2075.

DeLLphi-301: Tarlatamab for SCLC

Presenter's Conclusion

Tarlatamab 10 mg IV every two weeks demonstrated significant antitumor activity in heavily pretreated SCLC patients. The safety profile was manageable with most CRS and neurotoxicity events being low grade. Given the lack of approved third-line therapies and historically poor outcomes in this setting, tarlatamab represents a promising and innovative immunotherapeutic option for R/R SCLC.

Ahn MJ, et al. *N Engl J Med* 2023;389(22):2063-2075.

Long-term follow-up from DeLLphi-301

Updated Results Published August 2024

- No new safety signals on longer follow-up
- Overall follow-up at 12.1 months (N=152):
  - ORR: 25.0% (4 CR, 34 PR)
  - Median DOR: 11.2 months (95% CI 6.6–22.3).
  - Median PFS: 3.5 months (95% CI 2.7–3.8).
  - Median OS: 17.5 months (95% CI 11.4–NE).
- 10 mg Q2W Cohort (Phase 2 dose, N =17)
  - ORR: 35.3%
  - Median DOR: 14.9 months (95% CI 3.0–NE)
  - Median OS: 20.3 months (95% CI 5.1–NE)

Demonstrated durable responses and clinically meaningful survival outcomes in relapsed SCLC with longer median OS than other second-line agents

Dowlati A, et al. *J Clin Oncol* 2024;42(29):3392-3399.

Tarlatamab (Imdelltra)

FDA approval: May 16, 2024

Dosing:

Cycle	Day	Tarlatamab Dose
Cycle 1	Day 1	1 mg
	Day 8	10 mg
	Day 15	10 mg
Cycles 2+	Day 1 and 15	10 mg

Premedications:

Cycle	Day	Dose
Cycle 1: Days 1 and 8	Dexamethasone 8 mg IV 1 hour prior to administration	
Cycle 1: Days 1, 8, 15	NS 1 L IV over 4 to 5 hours immediately after completion	

UpToDate Lexidrug

06

Future of Bispecific Antibo

Future Studies in Bispecifics

Epcoritamab (Epkinly)

- Safety and Efficacy Study of Epcoritamab in Subjects With R/R Chronic Lymphocytic Leukemia and Richter's Syndrome
- Epcoritamab and Rituximab for First-line Follicular Lymphoma
- Epcoritamab With Dose Adjusted EPOCH-R for the Treatment of Aggressive B-Cell Non-Hodgkin Lymphoma

Glofitamab (Columvi)

- A Study Evaluating the Safety and Efficacy of Glofitamab + Gemcitabine + Oxaliplatin in U.S. Patients With R/R DLBCL
- A Study of Glofitamab and Lenalidomide in People With Mantle Cell Lymphoma
- A Study of Axicabtagene Ciloleucel and Glofitamab as Second-Line Therapy for R/R Patients With LBCL

Clinicaltrials.gov

Future Studies in Bispecifics

Tarlatamab (Imdelltra)

- First-Line Tarlatamab in Combination With Carboplatin, Etoposide, and PD-L1 Inhibitor in Subjects With Extensive Stage Small Cell Lung Cancer (ESCLC)
- A Study of Tarlatamab for People With Prostate Cancer
- Tarlatamab in Advanced Delta-like 3 (DLL3)-Expressing Tumors Including Neuroendocrine Neoplasms

Clinicaltrials.gov

Future Concepts in Bispecifics

More than 200 BsAbs in > 300 clinical trials:

- ~75% for solid tumors, 25% for hematologic cancers

New Modalities

- **Dual receptor/ligand inhibition:** Blocking multiple tumor growth or angiogenesis pathways (Ex: VEGF + PD1/PDL1 BsAbs)
- **Targeted payload delivery:** BsAb–drug conjugates to deliver payloads such as cytotoxic agents or radioactivity
- **Checkpoint modulation:** Dual checkpoint inhibitors (Ex: PD1/CTLA4) and costimulatory BsAbs enhance antitumor immunity with potentially fewer autoimmune toxicities
- **Conditional/prodrug BsAbs:** Activated only in the tumor microenvironment to reduce toxicity

Klein C, Brinkmann, et al..*Nat Rev Drug Discov* 2024;23(4):301-319.

Future Concepts in Bispecifics

New Modalities

- **BsAb-based proteolysis targeting chimeras (PROTACs):** Promote internalization and degradation of tumor-driving surface proteins
- **Cytokine mimetic BsAbs:** Deliver immune-boosting signals like IL-2 or IL-15 selectively to tumor-reactive cells.
- **Novel delivery:** mRNA, viral vectors, and CART cells engineered to secrete BsAbs
- **Trispecific antibodies:** Combine a tumor cell antigen, checkpoint modulation, and co-stimulatory molecule. The simultaneous engagement of multiple immune cell receptors can lead to a stronger and more robust immune response.

Klein C, Brinkmann, et al..*Nat Rev DrugDiscov* 2024;23(4):301-319.

Self-Assessment Questions

Self-Assessment Questions

1. Which of the following best describes the mechanism of bispecific T-cell engagers (BiTEs)?
   A. They activate T cells by binding CD28 and IL-2 directly
   B. They connect T cells to tumor cells via CD3 and a tumor-associated antigen
   C. They block PD-1 and CTLA-4 simultaneously to enhance immune response
   D. They deliver cytotoxic payloads to tumor cells through antibody–drug conjugates

Ahn MJ, et al. *N Engl J Med* 2023;389(22):2063-2075.

Self-Assessment Questions

2. What is the most common treatment -emergent adverse event associated with epcoritamab in lymphoma trials?

A. Neutropenia
B. Fatigue
C. Cytokine release syndrome (CRS)
D. Peripheral neuropathy

Ahn MJ, et al. *N Engl J Med* 2023;389(22):2063-2075.

Self-Assessment Questions

3. According to the STARGLO trial, what was the primary endpoint when evaluating glofitamab plus GemOx in relapsed/refractory DLBCL?
   A. Overall survival
   B. Progression-free survival
   C. Complete response rate
   D. Duration of response

Dowlati A, et al. *J Clin Oncol* 2024;42(29):3392-3399.

Self-Assessment Questions

4. In the DeLLphi-301 trial of tarlatamab for small cell lung cancer, why was the 10 mg dose selected for further studies instead of 100 mg?

A. The FDA mandated use of the 10 mg dose for all bispecific antibody studies

B. The 10 mg dose demonstrated significantly higher complete response rates

C. The 100 mg dose caused excessive hematologic toxicity

D. The 10 mg dose had a more favorable safety profile with similar efficacy

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Thank You

Do you have any questions?

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