The evolving role for bispecific antibodies in B-cell lymphoma

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Disclosures

Honoraria

Seattle Genetics

Bispecific antibodies in B-cell lymphoma

- Review of US FDA-approved agents
  - Mosunetuzumab
  - Glofitamab
  - Epcoritamab
- Forecasting bispecifics
  - Emerging CD20 x CD3: Odronextamab, imvotamab
  - Novel targets
  - New strategies: Combinations, earlier lines of therapy, other histologies

Background

- **FL is the most common indolent subtype of NHL**[1]
  - Most patients experience relapse and face a risk of transformation to aggressive lymphoma
- **Phase II study (NCT02500407; GO29781)**
  - Fixed-duration mosunetuzumab demonstrated a high rate of CRs and durable responses in patients with R/R FL and ≥2 prior lines of therapy[5]

Mosunetuzumab: first-in-class, CD20xCD3 T-cell engaging bispecific antibody that redirects T cells to engage and eliminate malignant B cells2–4

CR, complete response; EOT, end-of-treatment; FL, follicular lymphoma; NHL, non-Hodgkin lymphoma; R/R, relapsed/refractory.

1. Freedman A, et al. Am J Hematol 2020;95:316–327; 2. Sun LL, et al. Sci Transl Med 2015;7:287ra70;

3. Budde LE, et al. J Clin Oncol 2022;40:481–491; 4. Hernandez G, et al. ASH 2019; poster presentation (P-1585.);

5. Budde LE, et al. Lancet Oncol 2022;23:1055–1065.

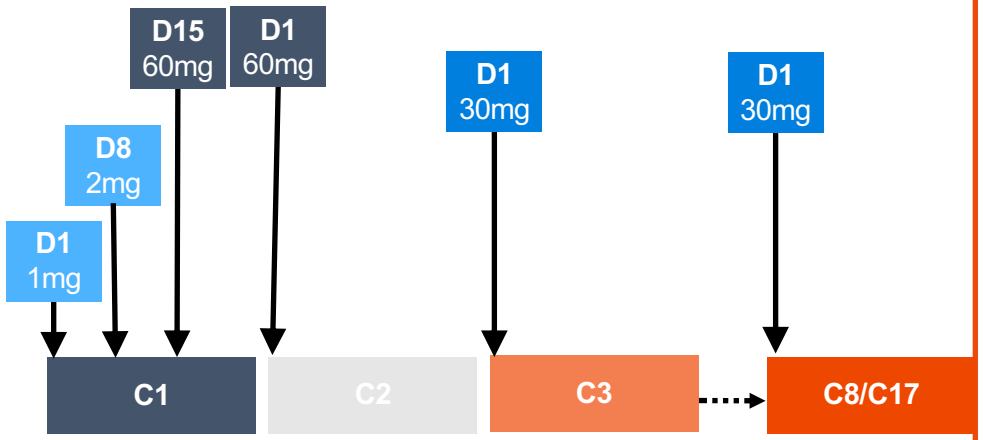
Mosunetuzumab: Study design (GO29781)

Key inclusion criteria

- R/R FL (Grade 1–3a)
- ≥2 prior therapies, including an anti-CD20 antibody and an alkylating agent
- ECOG PS 0–1

Mosunetuzumab administration

- IV mosunetuzumab (21-day cycles) with step-up dosing in C1
- Hospitalization for monitoring following mosunetuzumab infusion was not required
- Fixed-duration treatment: 8 cycles (CR after C8) / 17 cycles (PR/SD after C8)*
- As of July 8, 2022, 90 pts had received ≥1 dose of mosunetuzumab



Data analysis

- **Primary endpoint:** IRC-determined CR rate (as best response), by Cheson 2007 criteria[1]
- CRS was graded using ASTCT criteria[2]
- Exploratory analyses assessed the association between TMTV at baseline, and clinical efficacy and safety
- TMTV was derived from PET images at study entry using an artificial intelligence-based model[3]

*Premedication with corticosteroids (IV dexamethasone 20mg or IV methylprednisolone 80mg) was administered 1 hour before each dose of mosunetuzumab in C1 and C2, and was optional from C3 onwards.

ASTCT, American Society for Transplantation and Cellular Therapy; C, cycle; CRS, cytokine release syndrome; D, day; ECOG PS, Eastern Cooperative Oncology Group performance status; IRC, independent review committee; IV, intravenous; Pts, patients; PR, partial response; PET, positron emission tomography; SD, stable disease; TMTV, total metabolic tumour volume.

1. Cheson BD, et al. J Clin Oncol 2007;25:579–586;

2. Lee DW, et al. Biol Blood Marrow Transplant 2019;25:625–638;

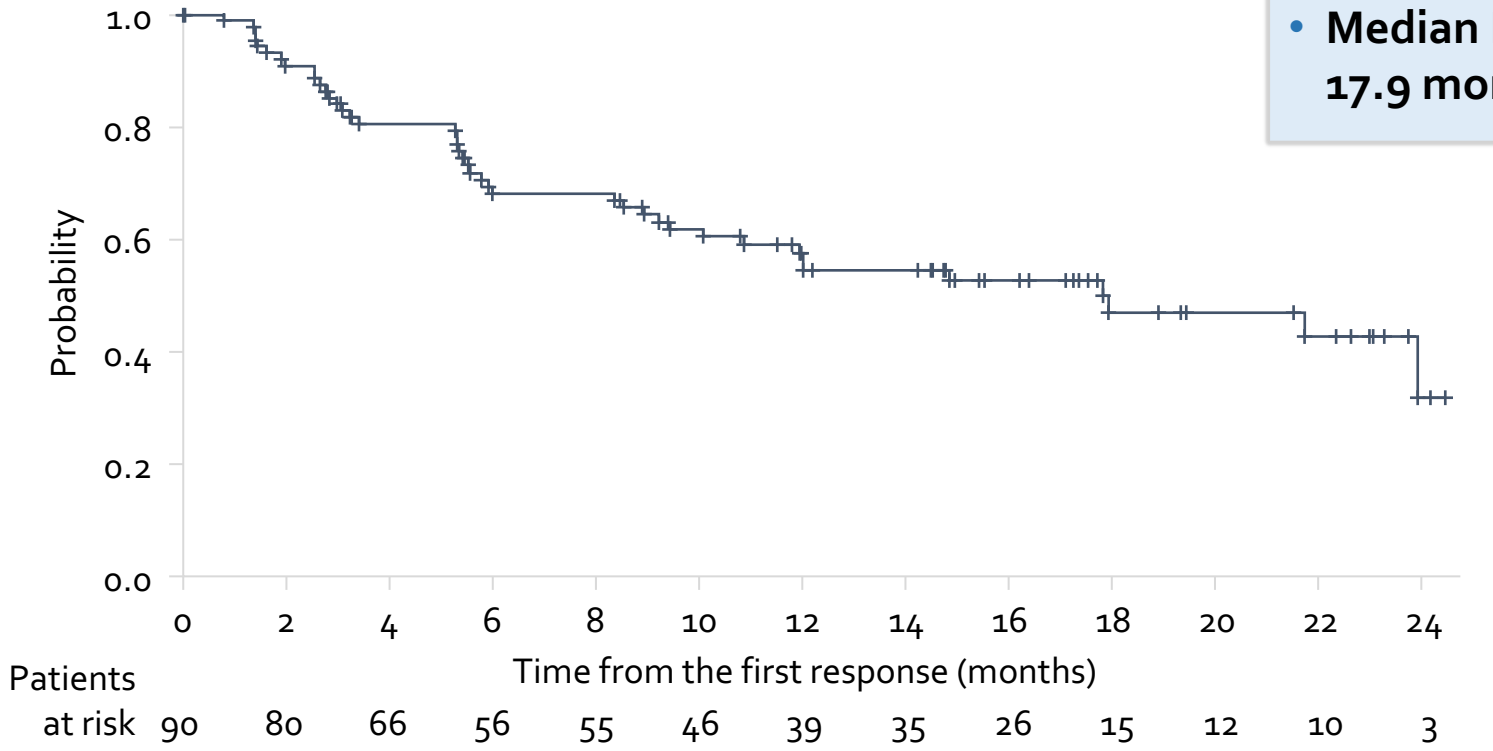
3. Jemaa S, et al. Cancer Imaging 2022;22:39.

Mosunetuzumab: Antitumor Efficacy in FL

Efficacy Endpoints	Mosunetuzumab	Last prior therapy
ORR	77.8%	55.6%
CR	60.0%	35.6%
Median DOR, months	NR	11.8
Median DOCR, months	NR	15.1
Median PFS	NR	12.6
Median TTNT	NR	16.8

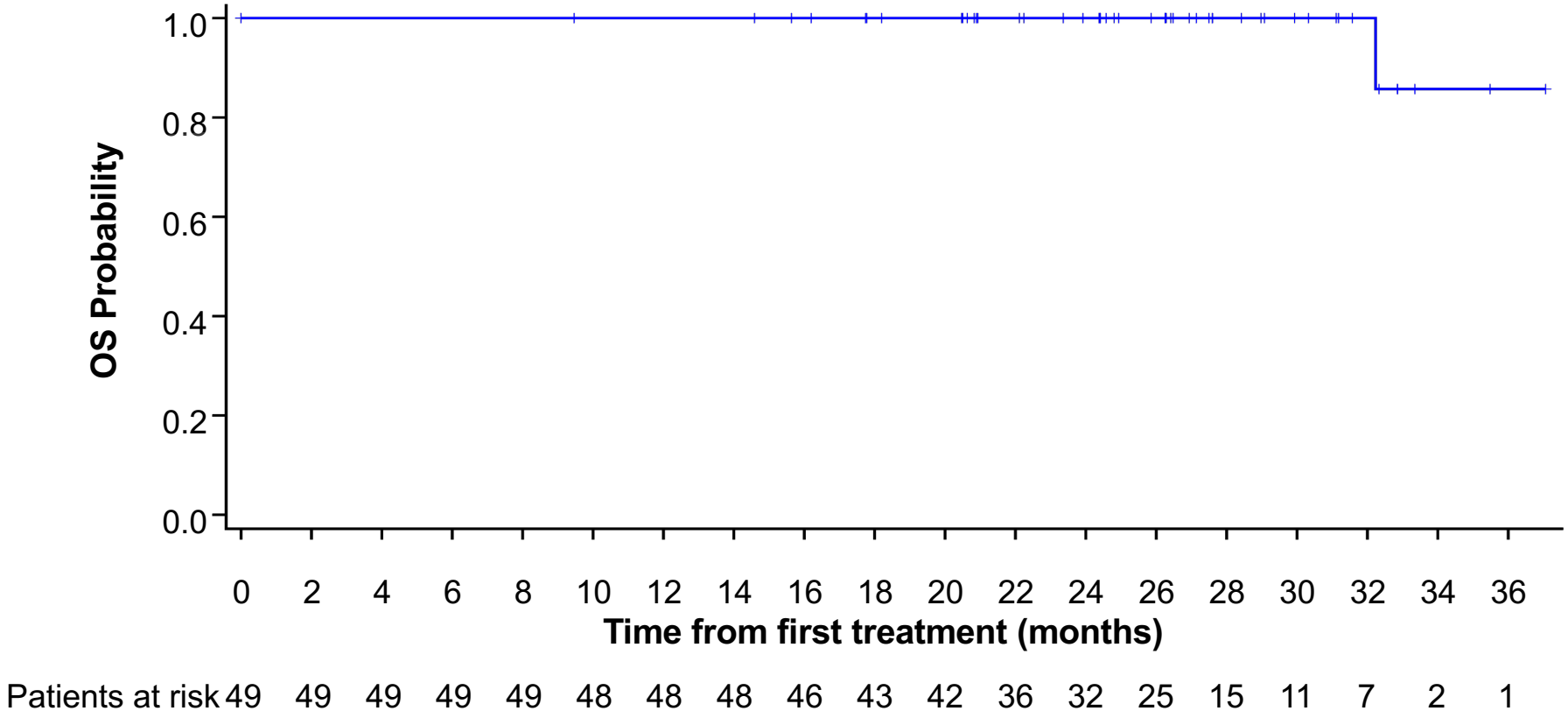
Mosunetuzumab: Progression-Free Survival

Progression-Free Survival (N = 90)



- **Median PFS:**
  17.9 months (95% CI: 10.1, NE)

OS in patients with a CR at EOT from time of first treatment



	n=49
Median, months (95% CI)	NE (NE–NE)
24-month OS, % (95% CI)	100 (100–100)

Data cut-off date: July 8, 2022.

Glofitamab

- Bispecific antibody (CD20 x CD3) indicated 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.
- Granted accelerated FDA approval in June 2023 based results from the phase 1/2 NP30179 (NCT03075696) trial[1,2]
- Administered as an intravenous infusion with step-up dosing schedule in cycle 1
- Boxed warning for Cytokine Release Syndrome (CRS)
  - Patients should be pretreated with a single 1,000 mg dose of obinutuzumab administered as an intravenous infusion on cycle 1 day 1, 7 days prior to initiation of glofitamab
  - Due to the risk of CRS, patients should be hospitalized for 24 hours after completion of the step-up dose 1 on cycle 1 day 8

1. COLUMVI (glofitamab concentrate) [prescribing information]. South San Francisco, CA: Genentech, Inc.; 2023. 2. Dickinson MJ, Carlo-Stella C, Morschhauser F, et al. Glofitamab for Relapsed or Refractory Diffuse Large B-Cell Lymphoma. N Engl J Med. 2022;387(24):2220-2231. doi:10.1056/NEJMoa2206913

NP30179: Glofitamab for Relapsed or Refractory Diffuse Large B-Cell Lymphoma

Study population

R/R DLBCL

- Aged 18 years or older
- ECOG performance status of 0-1
- ≥ 2 previous lines of therapy including an anti-CD20 regimen and an anthracycline-containing regimen

n = 155

IV glofitamab

Cycle 1
- 2.5 mg on day 8*
- 10 mg on day 15

Cycles 2-12
- 30 mg on day 1

Pretreatment
- Obinutuzumab 1000 mg IV 7 days before first dose
- Dexamethasone

*Hospitalization required for first dose of glofitamab

Study endpoints

Primary endpoint:
- Complete response by IRC

Secondary endpoints:
- Objective response
- Duration of response
- Duration of complete response
- Time to response
- Progression-free survival
- Overall survival

Safety and Tolerability

Abbreviations: DLBCL, diffuse large B-cell lymphoma; ECOG, Eastern Cooperative Oncology Group; IRC, independent review committee; R/R, relapsed or refractory.

1. Dickinson MJ, Carlo-Stella C, Morschhauser F, et al. Glofitamab for Relapsed or Refractory Diffuse Large B-Cell Lymphoma. N Engl J Med. 2022;387(24):2220-2231. doi:10.1056/NEJMoa2206913

Glofitamab: Efficacy Results

- Median age: 66 years (range: 21-90)
- 75% of patients had stage III/IV disease
- Median of 3 prior lines of therapy
- 33% had received prior CAR T-cell therapy
- 58% had primary refractory disease, 86% were refractory to the last line of therapy
- Median follow-up: 10.7 months

Efficacy Endpoints by IRC	Glofitamab
CR, %	39%
ORR, %	52%
DOCR, months	NR
Duration of Objective Response, months	18.4
Median time to first CR, days	42
Median PFS, months	4.9

Abbreviations: CR, complete response; DOCR, duration of complete response; NR, not reached; ORR, objective response rate; PFS, progression-free survival; TTNT, time to next therapy or death.

1. Dickinson MJ, Carlo-Stella C, Morschhauser F, et al. Glofitamab for Relapsed or Refractory Diffuse Large B-Cell Lymphoma. N Engl J Med. 2022;387(24):2220-2231. doi:10.1056/NEJMoa2206913

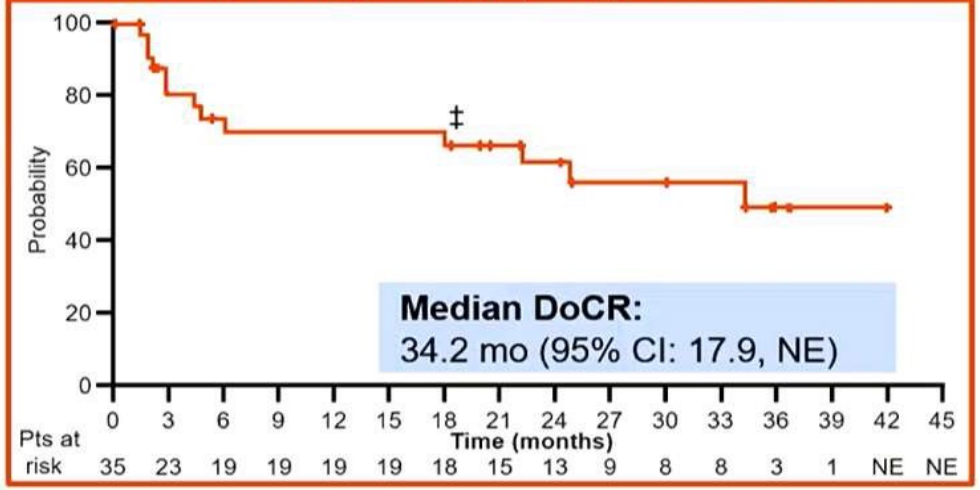
Glofitamab in DLBCL

DoCR in earlier cohorts show durable responses beyond 24 months

Supporting cohort

- **Patients in earlier cohorts have extended follow up for duration of response**
  - R/R DLBCL, HGBCL, trFL and PMBCL ≥2 prior lines (n=101)
  - Doses ≥10mg* (RP2D not included) for a fixed treatment duration of 8–12 cycles (6–9 months)
  - CR rate: 35/101 (35%)†

Duration of complete response by IRC



	N=35
Median DoCR follow-up, mo (range)	**24.8 (0, 42)**
24-months DoCR, % (95% CI)	61.4 (43.1, 79.7)
CRs ongoing at CCOD, n (%)	22 (62.9)

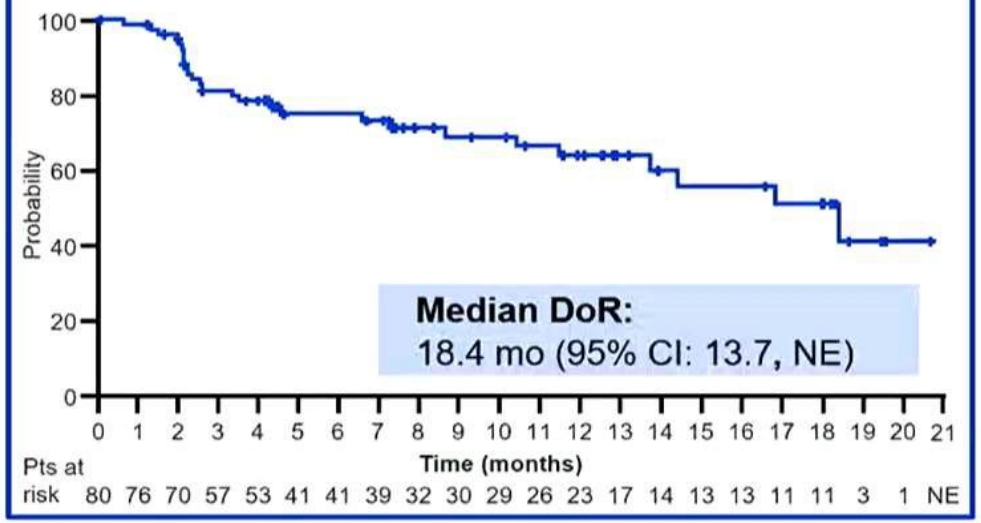
Durable responses beyond 24 months achieved after fixed-duration treatment; median: 34.2 months

*10mg, 16mg, 25mg, 10/16mg, 2.5/10/16mg; †intent-to-treat population; RP2D, recommended Phase II dose;
‡DOCR: 17.9 months PD, 22.1 months PD re-treatment (remission), 24.7 months death (unknown reason), 34.2 months death (AML).

Glofitamab in DLBCL

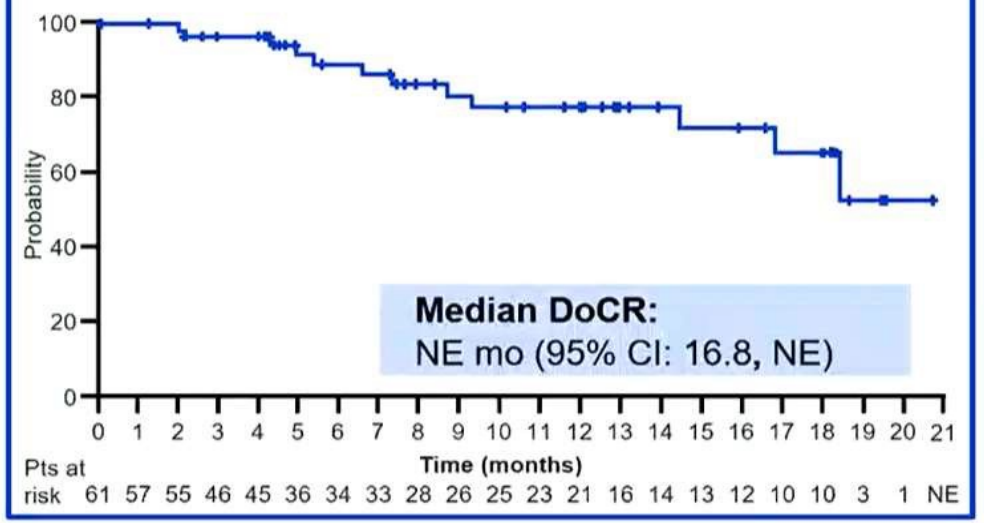
Durable responses maintained after cessation of therapy

Duration of overall response by IRC



	N=80
Median DoR follow-up, mo (range)	10.6 (0–21)
12-months DoR, % (95% CI)	**63.6 (51.1, 76.2)**
ORs ongoing at CCOD, n (%)	53 (66.3)

Duration of complete response by IRC



	N=61
Median DoCR follow-up, mo (range)	10.6 (0–21)
12-months DoCR, % (95% CI)	**77.6 (64.3, 90.8)**
CRs ongoing at CCOD, n (%)	49 (80.3)

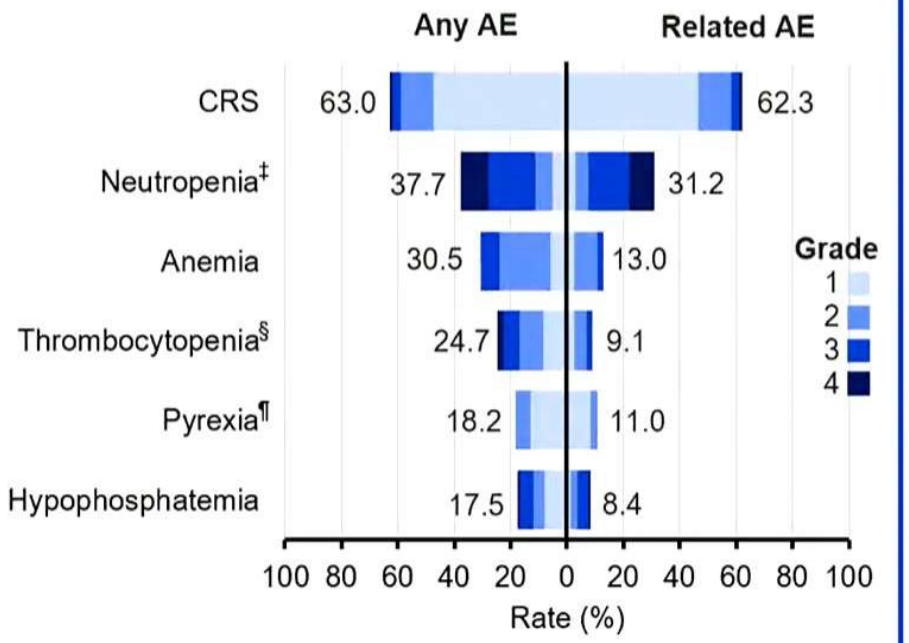
CCOD, clinical cut-off date; mo, months; NE, not estimable.

Glofitamab in DLBCL

Glofitamab safety profile

n (%)*	N=154
Median no. of cycles received (range)	5 (1–13)
Median relative dose intensity, % (range)	100 (94–100)
AE	152 (98.7)
Related AE	140 (90.9)
Grade 3–4 AE	87 (56.5)
Related AE	64 (41.6)
Serious AE	73 (47.4)
Related AE	46 (29.9)
Grade 5 (fatal AE)	8 (5.2)†
Related AE	0
AE leading to treatment discontinuation	14 (9.1)
Related AE	5 (3.2)

AEs (≥15%) by grade and relationship with glofitamab



Glofitamab was well tolerated, with a favorable safety profile

*unless otherwise specified; †COVID-19/COVID-19 pneumonia (n=5); sepsis (n=2); delirium (n=1);
‡includes neutrophil count decreased; §includes platelet count decreased; ¶pyrexia events separate from CRS.

Glofitamab in DLBCL: Safety Summary

- Cytokine release syndrome was the most common adverse event (63% of patients) and primarily associated with the first three doses of glofitamab
  - Most events were low grade (47% of all patients grade 1 and 12% grade 2) and high-grade events were uncommon (3% grade 3 and 1% grade 4)
- The most common grade 3-4 adverse events were neutropenia (27%), anemia (6%), and thrombocytopenia (8%)
- Serious adverse events occurred in 47% of patients
- Rate of adverse events leading to discontinuation was 9%, including one event of CRS-related discontinuation
- Grade 5 (fatal) adverse events occurred in 8 patients (5%; COVID-19-related pneumonia in 5, sepsis in 2, delirium in 1)

Abbreviation: CRS, cytokine release syndrome.

1. Dickinson MJ, Carlo-Stella C, Morschhauser F, et al. Glofitamab for Relapsed or Refractory Diffuse Large B-Cell Lymphoma. N Engl J Med. 2022;387(24):2220-2231. doi:10.1056/NEJMoa2206913

Epcoritamab

- Bispecific antibody (CD20 x CD3) indicated for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), not otherwise specified, including DLBCL arising from indolent lymphoma, and high-grade B-cell lymphoma after two or more lines of systemic therapy[1]
- Granted accelerated FDA approval in May 2023 based the results of the phase 1/2 EPCORE NHL-1 (NCT03625037) trial[1,2]
- Administered as a subcutaneous injection with step-up dosing schedule in cycle 1
- Boxed warning for Cytokine Release Syndrome (CRS) and Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS)
  - Due to the risk of CRS and ICANS, patients should be hospitalized for 24 hours after administration of the cycle 1 day 15 dosage of 48 mg

1. EPKINLY (epcoritamab-bysp injection) [prescribing information]. Plainsboro, NJ: Genmab US, Inc.; 2023. 2. Thieblemont C, Phillips T, Ghesquieres H, et al. Primary results of subcutaneous epcoritamab dose expansion in patients with relapsed or refractory large B-cell lymphoma: a phase 2 study. Presented at: 2022 EHA Congress; June 9-12, 2022; Vienna, Austria. Abstract LB2364

EPCORE NHL-1: Epcoritamab for R/R Large B-Cell Lymphoma[1]

Study population

R/R LBCL

- Aged 18 years or older
- ECOG performance status of 0-2
- Documented CD20+ mature B-cell neoplasm
- ≥ 2 previous lines of therapy including anti-CD20 regimen
- Prior failure/ineligibility for autologous stem cell transplantation

n = 157

SQ epcoritamab

Cycle 1
- 0.16 mg on day 1
- 0.8 mg on day 8
- 48 mg on days 15* and 22

Cycles 2-3
- 48 mg on days 1, 8, 15, 22

Cycle 4-9
- 48 mg on days 1 and 15

Cycle 10 and onwards
- 48 mg on day 1

Premedication

Corticosteroid, diphenhydramine, and acetaminophen

Study endpoints

Primary endpoint:
- Overall response rate by IRC

Secondary endpoints:
- Duration of response
- Complete response rate
- Duration of complete response
- Progression-free survival
- Time to response per IRC
- Overall survival

Safety and Tolerability

*24-hour inpatient monitoring required for first 48 mg dose

Abbreviations: ECOG, Eastern Cooperative Oncology Group; IRC, independent review committee; LBCL, large B-cell lymphoma; R/R, relapsed or refractory.

1. Thieblemont C, Phillips T, Ghesquieres H, et al. 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. J Clin Oncol. 2023;41(12):2238-2247. doi:10.1200/JCO.22.01725

EPCORE NHL-1: Results[1]

- Median age: 64 years (range: 20-83)
- Median of 3 prior lines of therapy
- Median of 1.6 years from initial diagnosis
- 38.9% had received prior CAR T-cell therapy and 19.7% had prior ASCT
- 61% had primary refractory disease, 83% were refractory to the last line of therapy
- Median follow-up: 10.7 months

Efficacy Endpoints	Epcoritamab
ORR	63%
CR	39%
Median DOR, months	12

Abbreviations: ASCT, autologous stem cell transplant; CR, complete response; DOCR, duration of complete response; DOR, duration of response in all responders; NR, not reached; ORR, objective response rate; PFS, progression-free survival; TTNT, time to next therapy or death.

1. Thieblemont C, Phillips T, Ghesquieres H, et al. Primary results of subcutaneous epcoritamab dose expansion in patients with relapsed or refractory large B-cell lymphoma: a phase 2 study. Presented at: 2022 EHA Congress; June 9-12, 2022; Vienna, Austria. Abstract LB2364

Future directions

- Additional bispecific antibodies undergoing ongoing development
  - Odronextamab: FL, DLBCL BLA submitted to FDA, review 2024
  - Plamotamab, imvotamab: TBD
- Other histologies – e.g. glofitamab in mantle cell lymphoma
- Combination approaches

Combination strategies

- Multiple strategies being pursued across lines of therapy and histologies
    - BsAb + immunomodulatory therapy
    - BsAb + chemotherapy
    - BsAb + immunotherapy

Future Directions

- DLBCL
  - 1L
    - BsAb + CHOP
    - BsAb + miniCHOP
    - BsAb + pola
    - BsAb consolidation
  - 2L
    - BsAb + chemo
    - BsAb + pola
    - BsAb + tafa+len
  - Pre/Post CAR-T
  - 3L+ in various combinations
- FL
  - 1L
    - Monotherapy
    - BsAb + len
  - 2L+
    - BsAb + len
    - BsAb + tafa+len
    - BsAb + PI3K
    - BsAb + EZH2

Key Questions:

Duration:
Fixed duration vs. continuous
Intermittent therapy
Retreatment

Selection:
Biomarkers predicting response
Role of MRD in guiding rx

Optimal combinations

Optimal sequencing
(Including BsAb vs CAR-T)

How to broaden access