RTP Live from Chicago: Investigator Perspectives on the Role of Bispecific Antibodies in the Management of Lymphoma

Tuesday, June 4, 2024
7:00 AM – 8:00 AM CT (8:00 AM – 9:00 AM ET)

Faculty

Joshua Brody, MD
Ian W Flinn, MD, PhD
Tycel Phillips, MD

Moderator

Neil Love, MD

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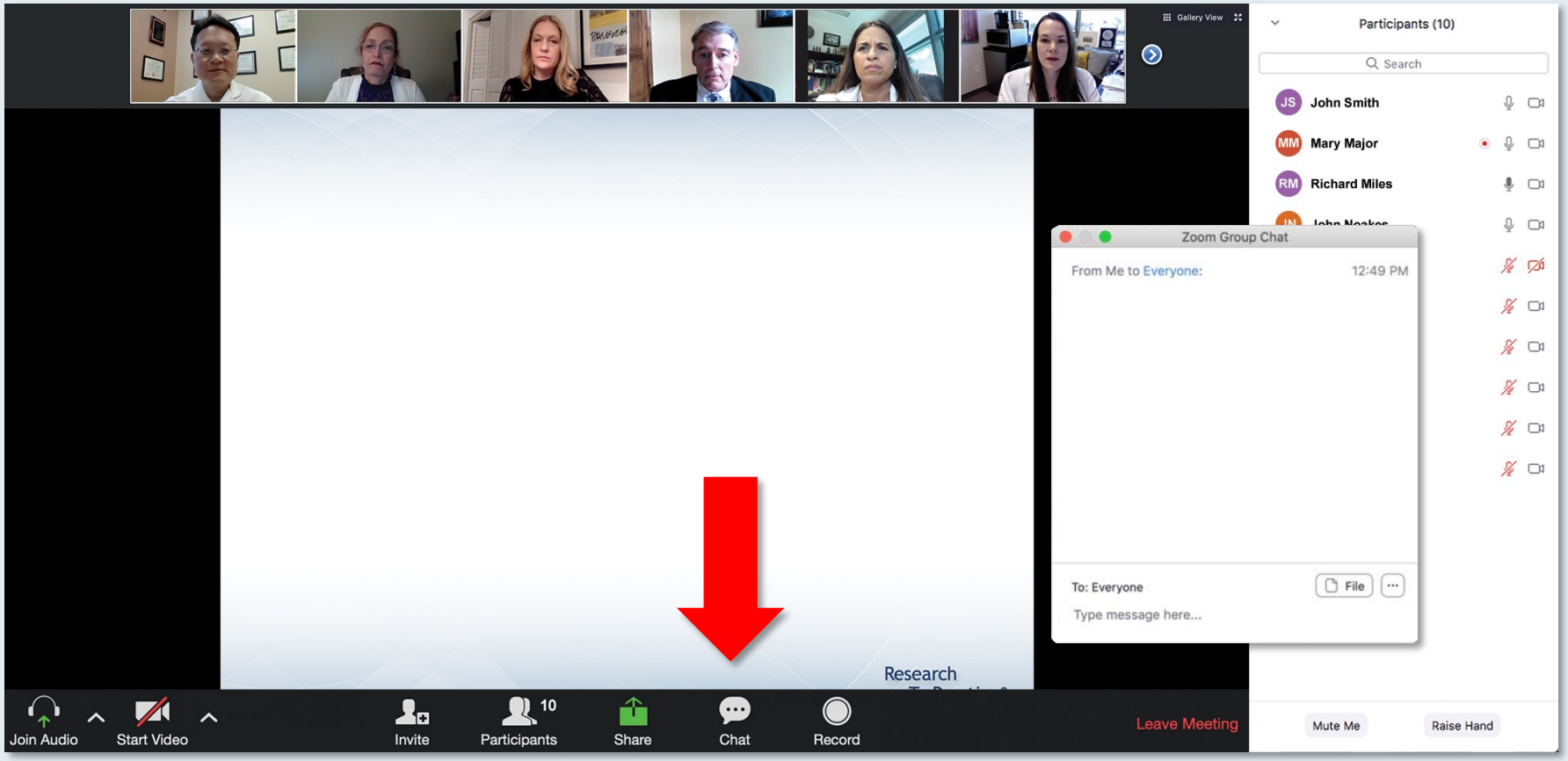
We Encourage Clinicians in Practice to Submit Questions



Feel free to submit questions now before the program begins and throughout the program.

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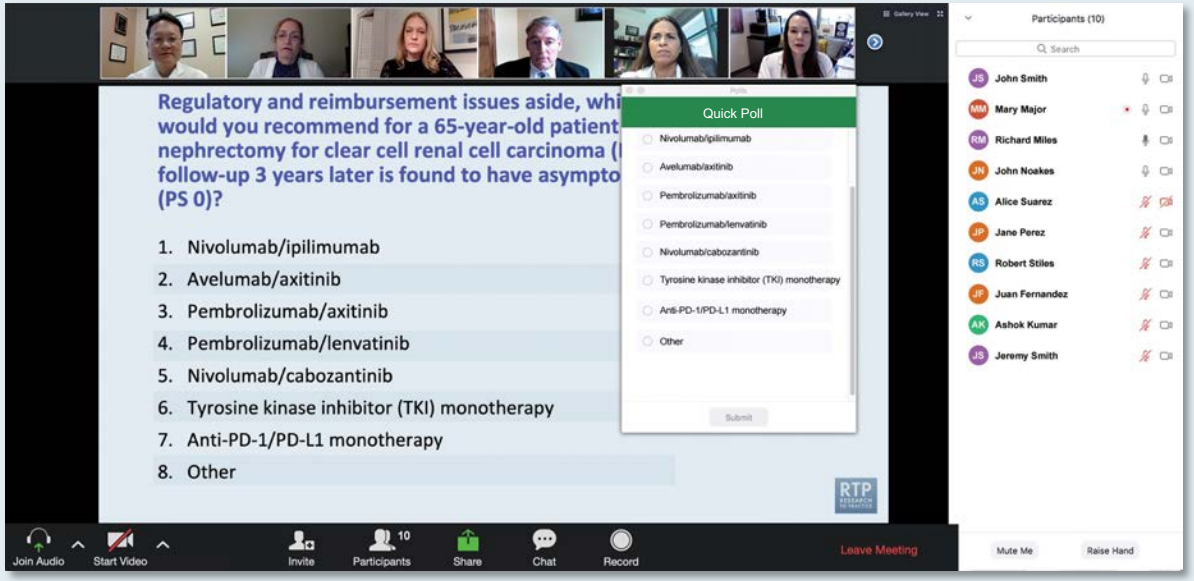
Clinicians in the Audience, Please Complete the Pre- and Postmeeting Surveys



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WITH DR NEIL LOVE

Key Presentations on Lymphoma from Recent Major Conferences

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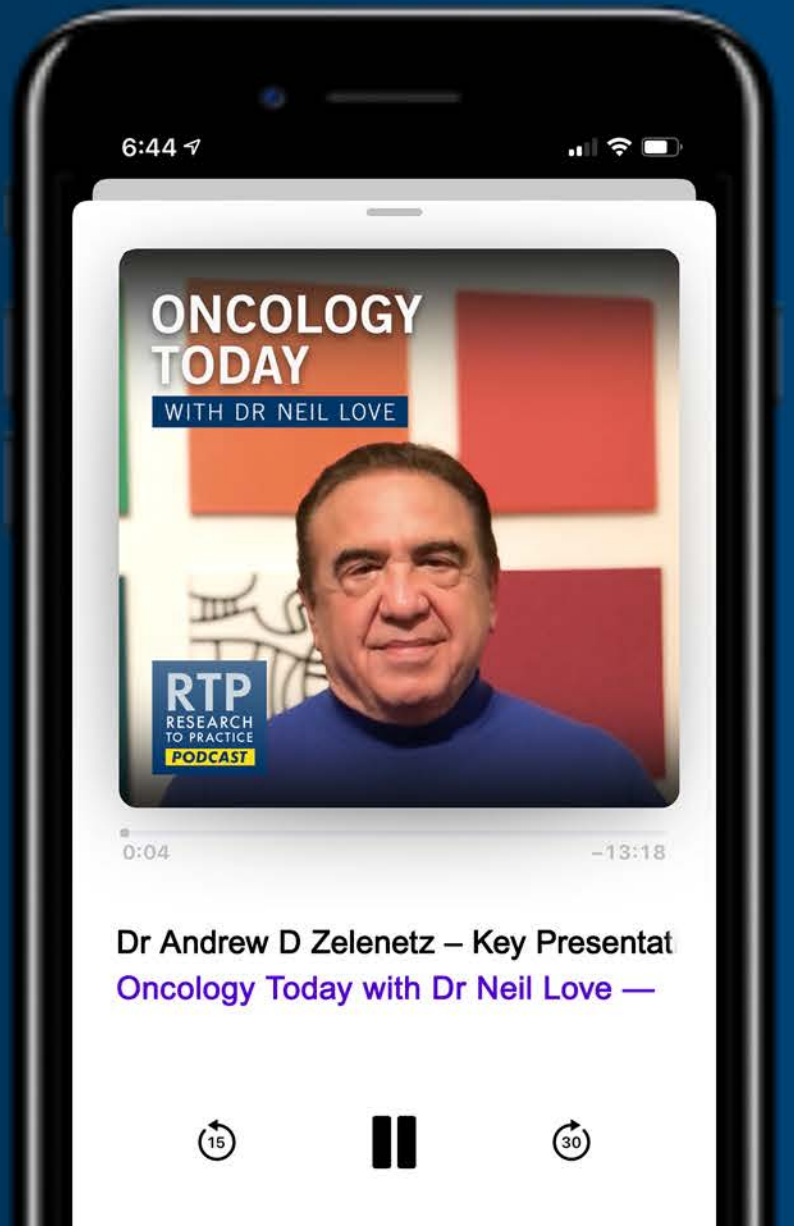

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Dr Brody — Disclosures
Faculty

No relevant conflicts of interest to disclose.

Dr Flinn — Disclosures

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Nonrelevant Financial Relationships	CALGB, Calibr-Skaggs Institute for Innovative Medicines, City of Hope National Medical Center

Dr Phillips — Disclosures

Advisory Committees	AbbVie Inc, Genentech, a member of the Roche Group, Genmab US Inc, Merck
Consulting Agreements	AbbVie Inc, ADC Therapeutics, AstraZeneca Pharmaceuticals LP, Bayer HealthCare Pharmaceuticals, BeiGene Ltd, Bristol Myers Squibb, Epizyme Inc, Genentech, a member of the Roche Group, Genmab US Inc, Gilead Sciences Inc, Incyte Corporation, Lilly, Pharmacyclics LLC, an AbbVie Company, Seagen Inc, TG Therapeutics Inc
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Agenda

Introduction: CD3 Bispecific Antibodies in the Community Oncology Setting

Module 1: ASCO and EHA 2024

Module 2: Integration of Bispecific Antibody Therapy into the Management of Diffuse Large B-Cell Lymphoma — Dr Phillips

Module 3: Current and Future Role of Bispecific Antibodies in Follicular Lymphoma and Other B-Cell Lymphomas — Dr Flinn

Module 4: Tolerability and Other Practical Considerations with the Use of Bispecific Antibody Therapy — Dr Brody

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RTP RESEARCH TO PRACTICE

FDA grants accelerated approval to tarlatamab-dlle for extensive-stage small cell lung cancer

Press release: May 16, 2024

"The Food and Drug Administration granted accelerated approval to tarlatamab-dlle for extensive stage small cell lung cancer (ES-SCLC) with disease progression on or after platinum-based chemotherapy.

Efficacy was evaluated in 99 patients with relapsed/refractory ES-SCLC with disease progression following platinum-based chemotherapy enrolled in DeLLphi-301 [NCT05060016], an open-label, multicenter, multi-cohort study. Patients received tarlatamab until disease progression or unacceptable toxicity.

ORR was 40% (95% CI: 31, 51) and median DOR was 9.7 months (range 2.7, 20.7+). Of the 69 patients with available data regarding platinum sensitivity status, the ORR was 52% (95% CI 32, 71) in 27 patients with platinum-resistant SCLC (defined as progression < 90 days after last dose of platinum therapy) and 31% (95% CI 18, 47) in 42 patients with platinum-sensitive SCLC (defined as progression ≥ 90 days after last dose of platinum therapy)."

https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-tarlatamab-dlle-extensive-stage-small-cell-lung-cancer

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ASCO 2024 Oral Abstracts on Bispecifics in Lymphoma

Phillips et al. Glofitamab monotherapy in patients with heavily pretreated relapsed/refractory (R/R) mantle cell lymphoma (MCL): Updated analysis from a phase I/II study. ASCO 2024;Abstract 7008.

Lori et al. Epcoritamab with rituximab + lenalidomide (R2) in previously untreated (1L) follicular lymphoma (FL) and epcoritamab maintenance in FL: EPCORE NHL-2 arms 6 and 7. ASCO 2024;Abstract 7014.

Vose et al. EPCORE NHL-1 follicular lymphoma (FL) cycle (C) 1 optimization (OPT) cohort: Expanding the clinical utility of epcoritamab in relapsed or refractory (R/R) FL. ASCO 2024;Abstract 7015.

ASCO 2024 Posters on Bispecifics in Lymphoma

Koh et al. Glofitamab combined with poseltinib and lenalidomide for relapsed/refractory diffuse large B cell lymphoma: Interim analysis of GPL study. ASCO 2024;Abstract 7066.

Bartlett et al. Glofitamab monotherapy retreatment in patients with heavily pre-treated relapsed or refractory (R/R) non-Hodgkin lymphoma (NHL): Results from a phase I/II study. ASCO 2024;Abstract 7020.

Andorsky et al. Subcutaneous epcoritamab (SC epcor) administered outpatient (outpt) for relapsed or refractory (R/R) diffuse large B-cell lymphoma (DLBCL) and follicular lymphoma (FL): Results from phase 2 EPCORE NHL-6. ASCO 2024;Abstract 7029.

Brody et al. Subcutaneous epcoritamab + GemOx in patients with relapsed or refractory DLBCL: Updated results from EPCORE NHL-2. ASCO 2024;Abstract 7037.

Linton et al. EPCORE FL-2: Phase 3 trial of epcoritamab with rituximab and lenalidomide (R2) vs chemoimmunotherapy or R2 in previously untreated follicular lymphoma. ASCO 2024;Abstract TPS7084.

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ASCO 2024 Posters on Bispecifics in Lymphoma (Continued)

Assouline et al. Mosunetuzumab with polatuzumab vedotin: Subgroup analyses in patients (pts) with primary refractory or early relapsed large B-cell lymphoma (LBCL). ASCO 2024;Abstract 7021.

Hawkes et al. Phase 3 trial evaluating the efficacy and safety of odronextamab versus standard-of-care (SOC) therapy in relapsed/refractory (R/R) aggressive B-cell non-Hodgkin lymphoma (B-NHL; OLYMPIA-4). ASCO 2024;Abstract TPS7093.

Hardin et al. Phase 3 trial evaluating the efficacy and safety of odronextamab plus chemotherapy versus rituximab plus chemotherapy in previously untreated follicular lymphoma (OLYMPIA-2). ASCO 2024;Abstract TPS7099.

Vitolo et al. Phase 3 trial of odronextamab plus lenalidomide versus rituximab plus lenalidomide in relapsed/refractory (R/R) follicular lymphoma (FL) and marginal zone lymphoma (MZL; OLYMPIA-5). ASCO 2024;Abstract TPS7094.

EHA 2024 Abstracts on Bispecifics in Lymphoma

Lavie et al. First data from subcutaneous epcoritamab + polatuzumab vedotin, rituximab, cyclophosphamide, doxorubicin, and prednisone (POLA-R-CHP) for first-line diffuse large B-cell lymphoma (DLBCL): EPCORE NHL-5. EHA 2024;Abstract S239.

Abramson et al. Glofitamab plus gemcitabine and oxaliplatin (GLOFIT-GEMOX) for relapsed/refractory (R/R) diffuse large B-cell lymphoma (DLBCL): Results of a global randomized phase III trial (STARGLO). EHA 2024;Abstract LB3438.

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General Medical Oncologist: Diffuse Large B-Cell Lymphoma (DLBCL) Case Presentation

Age: 64

Sex: Male

Previous treatments: R-hyperCVAD induction for double-hit DLBCL, WBC 22K, LDH 5000, 9-cm mediastinal mass, splenomegaly, abnormal rearrangements MYC, BCL6, and variant t(8;14). Pericardial effusion. Good response, changed in second month to R-DA-EPOCH, total 6 cycles followed by 3 cycles HD MTX. 1 month later, submandibular/cervical massive adenopathy. R-GDP salvage therapy with partial decrease in tumors.

2 months later had CAR-T. Grade 2 CRS and ICANS. 5 months later, new adenopathy. Minimal response to bendamustine with rituximab. Polatuzumab vedotin and rituximab no response. Developed extensive extranodal masses on legs, trunk, neck.

Started epcoritamab 3-week ramp-up 14 months ago. Continues on q 2 week dosing, still in remission.

Treatment: Continues on epcoritamab, IVIG prophylaxis, antibiotic and antifungal prophylaxis.

Side effects and/or tolerability issues: None significant

Cases from General Medical Oncologists: Potential Role of Bispecific Antibodies in the Management of Relapsed/Refractory DLBCL

- **55-year-old man, Richter's transformation, has received multiple lines of therapy including transplant**
- **59-year-old woman, previously treated with R-CHOP and ISRT and with axicabtagene ciloleucel, currently on surveillance, has developed neuropathy**
- **56-year-old man, double-hit DLBCL and PD on R-DA-EPOCH and CAR T-cell therapy, currently in remission with epcoritamab x 14 months**

Survey of US-based general medical oncologists, May 2024.

Questions from General Medical Oncologists

- **My patient with double-hit DLBCL has relapsed s/p CAR T-cell therapy. What is the best choice of therapy now? Do we try a different CAR T-cell therapy or move to transplant?**
- **The response rate to bispecifics in the real world does not match what is expected from the clinical trials. How do we predict which patients will respond to these treatments?**
- **What therapy would you recommend to bridge a patient to CAR T-cell therapy?**

Survey of US-based general medical oncologists, May 2024.

Tycel J. Phillips, MD

Associate Professor of Medicine

City of Hope Comprehensive Cancer Center

Integration of Bispecific Antibodies into R/R DLBCL

EPCORE NHL-1: LBCL Expansion Cohort

Dose escalation

Dose expansion data cutoff: January 31, 2022
Median follow-up: 10.7 mo

B-NHL:

- ✓ No DLTs
- ✓ MTD not reached
- ✓ RP2D identified
- ✓ Manageable safety profile
- ✓ Encouraging antitumor activity

Key inclusion criteria:

- R/R CD20+ mature B-cell neoplasm
- ECOG PS 0–2
- ≥2 prior lines of antineoplastic therapy, including ≥1 anti-CD20 mAb
- FDG PET–avid and measurable disease by CT/MRI
- Prior CAR T allowed

Step-up dosing[a]

Epcoritamab SC RP2D 48 mg
QW C1–3,
Q2W C4–9,
Q4W C10+

→

Treatment until PD[b,c] or unacceptable toxicity

→

LBCL Cohort N=157
DLBCL, HGBCL, PMBCL, and FL Gr3B

- To ensure patient safety and better characterize CRS, inpatient monitoring was required at first full dose for 24 h in this part of the study
- **Primary endpoint:** ORR by independent review committee (IRC)
- **Key secondary endpoints:** DOR, TTR, PFS, OS, CR rate, and safety/tolerability

[a]Step-up dosing (priming 0.16 mg and intermediate 0.8 mg dosing before first full dose) and corticosteroid prophylaxis were used to mitigate CRS. [b]Radiographic disease evaluation was performed every 6 wk for the first 24 wk (6, 12, 18, and 24 wk), then every 12 wk (36 and 48 wk), and every 6 mo thereafter. [c]Measurable disease with CT or MRI scan with involvement of ≥2 lesions/nodes with a long axis >1.5 cm and short axis >1.0 cm (or 1 lesion/node with a long axis >2.0 cm and short axis ≥1.0 cm) and FDG PET scan that demonstrates positive lesion(s) compatible with CT-defined (or MRI-defined) anatomical tumor sites for FDG-avid lymphomas. ClinicalTrials.gov: NCT03625037. EudraCT: 2017-001748-36.

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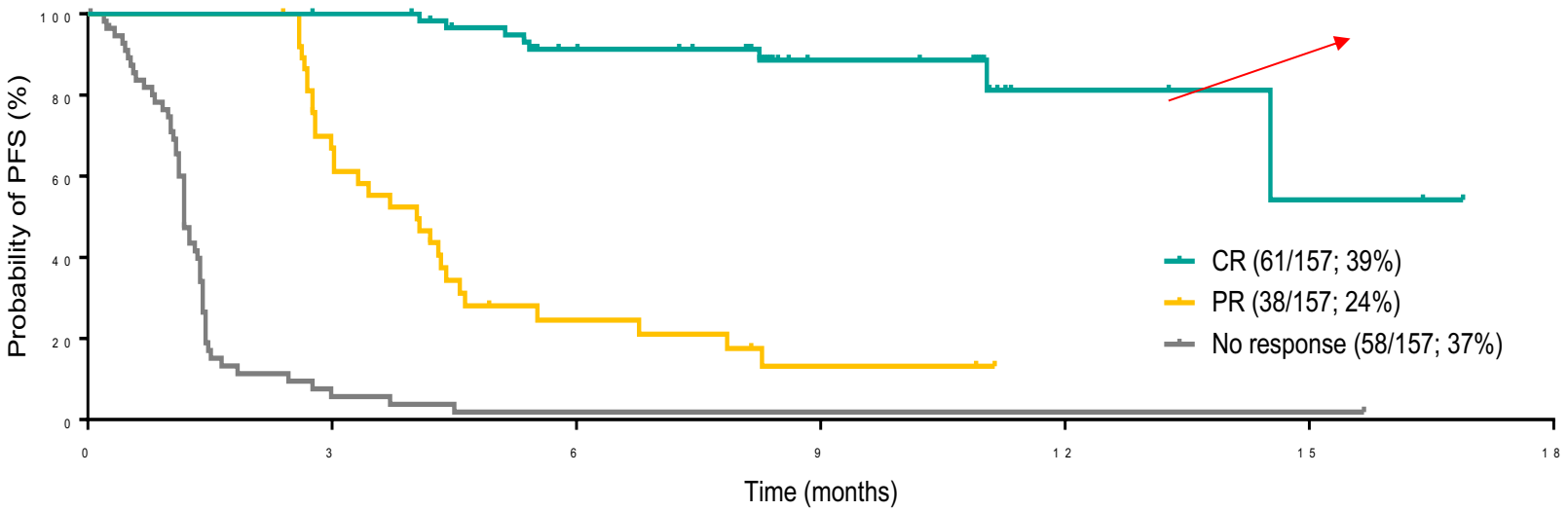
PFS by Best Response per IRC



Patients at risk

61	60	43	24	4	2	0
38	23	7	3	0	0	0
58	3	1	1	1	1	0

Kaplan–Meier Estimate	
Median PFS for complete responders	**Not reached**
Complete responders remaining in complete response at 9 mo	**89%**
Median PFS, mo (95% CI)	4.4 (3.0–7.9)
PFS at 6 mo, % (95% CI)	43.9 (35.7–51.7)

A correlation between depth of response and PFS was observed

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

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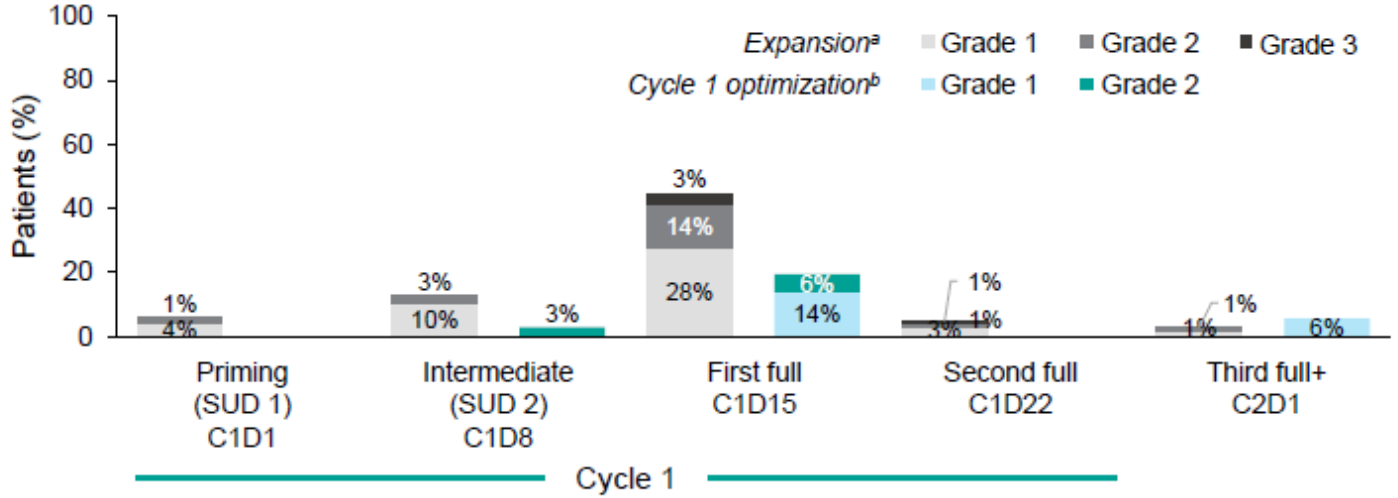
Optimization

	Expansion[a] N=157	CRS-Evaluable[b] DLBCL Cycle 1 Optimization[c] n=36
CRS, n (%)[d]	80 (51)	8 (22)
Grade 1	50 (32)	5 (14)
Grade 2	25 (16)	3 (8)
Grade 3	5 (3)	0
Signs and symptoms of CRS, n (%)[e]	**n=80**	**n=8**
Fever	79 (99)	7 (88)
Hypotension	24 (30)	3 (38)
Hypoxia	14 (18)	0
Other	15 (19)	1 (13)
Median time to onset after first full dose, h[e]	20	27
Treated with tocilizumab, n/n (%)[e]	23/80 (29)	3/8 (38)
Treated with corticosteroid, n/n (%)[e]	17/80 (21)	2/8 (25)
Leading to treatment discontinuation, n (%)	1 (0.6)	0
CRS resolution, n/n (%)[e]	79/80 (99)	8/8 (100)
Median time to resolution, d (range)[e]	2 (1–27)	2.5 (1–6)

[a]Data cutoff: November 18, 2022. [b]CRS-evaluable population was defined as patients treated with epcoritamab who either met the minimum exposure criterion and completed the CRS-evaluation period with sufficient safety evaluations or experienced a grade ≥2 CRS event during the CRS-evaluation period. [c]Data cutoff: July 17, 2023. [d]Graded by Lee et al 2019 criteria.[9] [e]Among patients with CRS.

CRS Events by Dosing Period

Most Events Following First Full Dose; Lower Rates With Cycle 1 Optimization



SUD 1, first step-up dose; SUD 2, second step-up dose. [a]Data cutoff: November 18, 2022. [b]Data cutoff: July 17, 2023. Based on the CRS-evaluable population (n=36), which consists of patients treated with epcoritamab who either met the minimum exposure criterion and completed the CRS-evaluation period with sufficient safety evaluations or experienced a grade ≥2 CRS event during the CRS-evaluation period.

- Preliminary efficacy data were comparable to data observed in the dose-expansion cohort

- **Cycle 1 optimization recommendations:**
  - Dexamethasone 15 mg premedication on D1, D8, D15, and D22 and prophylaxis on D2–4, D9–11, D16–18, and D23–25
  - 2–3 L of fluid intake during 24 h prior to each dose
  - Hold antihypertensive medications for 24 h prior to each dose
  - Administer 500 mL of isotonic IV fluids on the day of each dose prior to administration
  - 2–3 L of fluid intake during 24 h following each dose
  - Self-monitoring of temperature 3 times daily for 4 d following each dose
  - Hospitalization not required but patients must remain in close proximity to treatment facility for 24 h following first full dose
- **Primary endpoint:** Rate of grade ≥2 CRS events and all-grade CRS events from first dose through 7 d following second full dose

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

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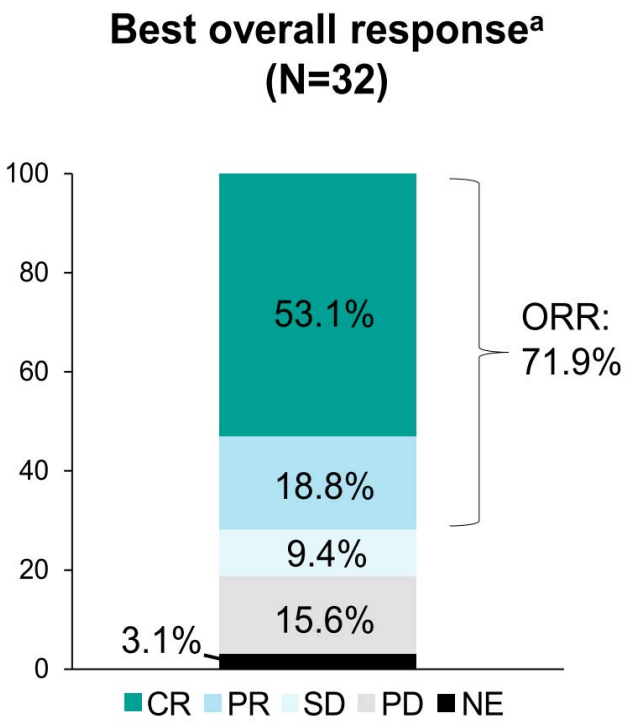
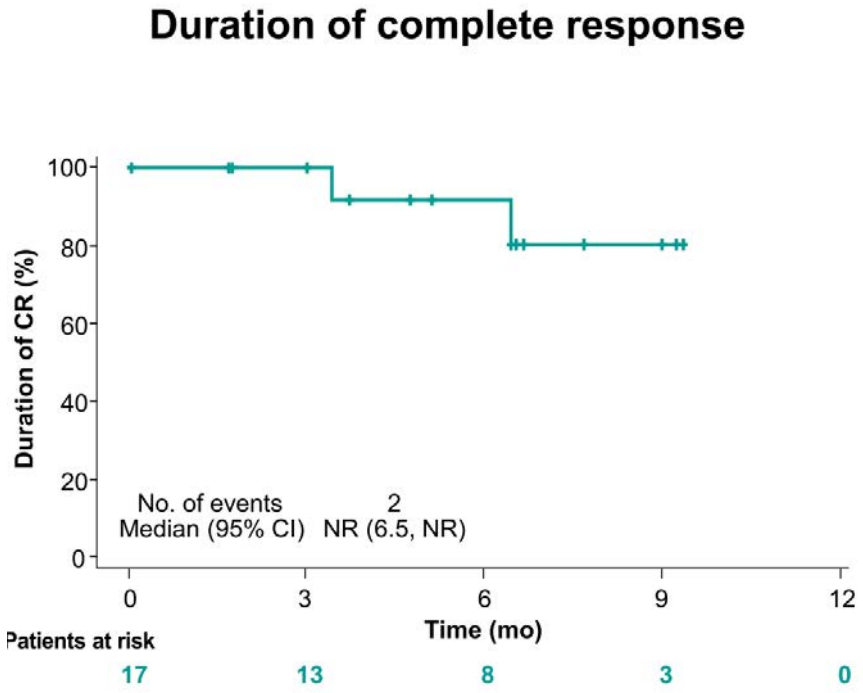
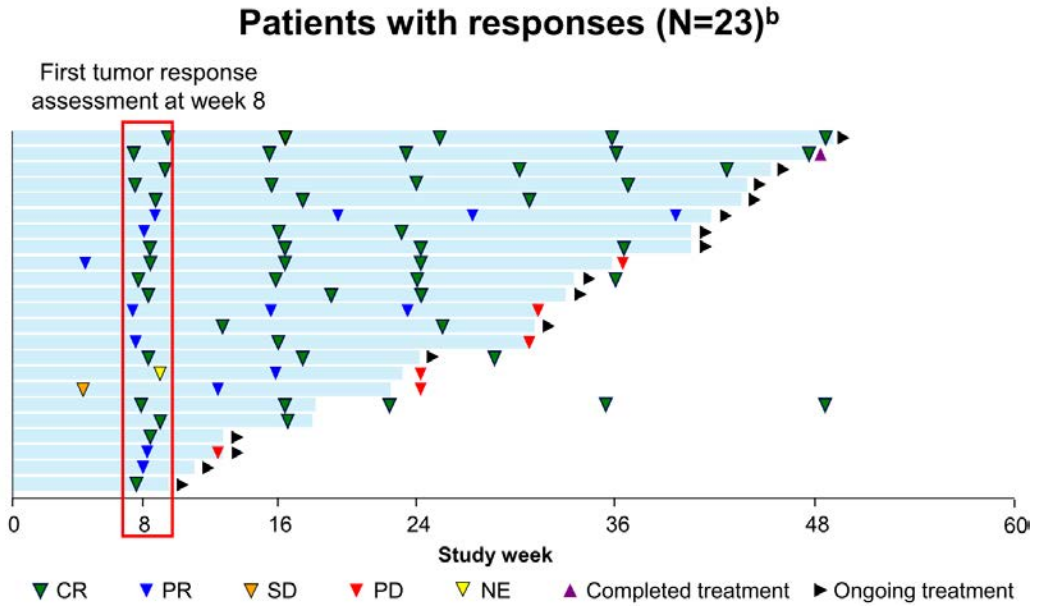
Epco-Len







Mazza IA et al. ASH 2023;Abstract 438.

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Epco-GEMOX

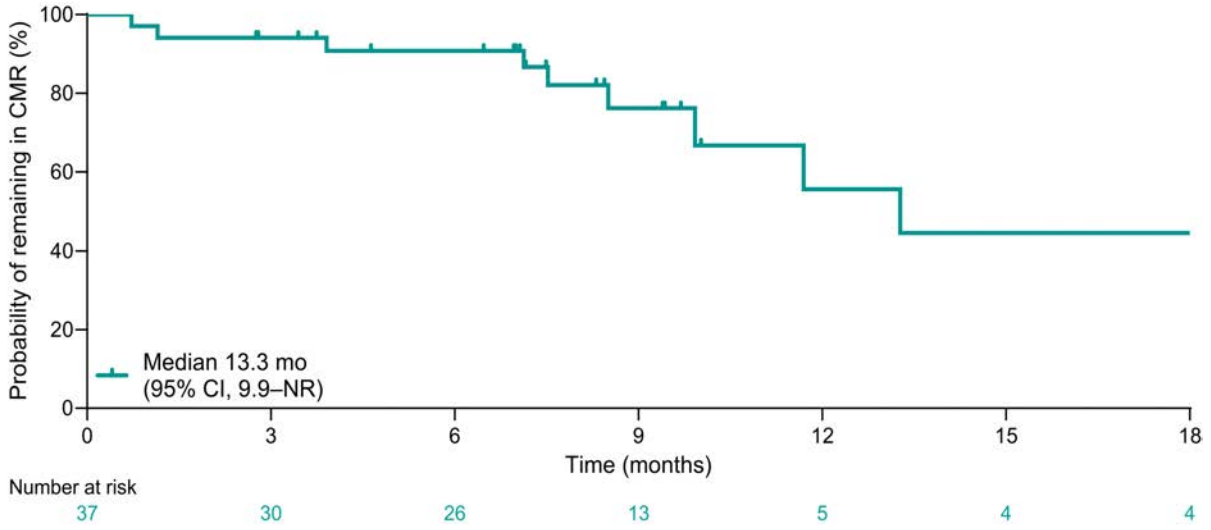
Responses Occurred Early and Rates Were High

Best Overall Response, n (%)	N=65[a]
Overall response rate	52 (80)
Complete metabolic response	37 (57)
Partial metabolic response	15 (23)
Stable disease	4 (6)
Progressive disease	4 (6)

[a]5 patients were not evaluable for response.

- Median time to response was 1.5 mo (range, 0.9–3.0)
- Median time to complete metabolic response was 1.8 mo (range, 1.3–10.7)

Durable Complete Metabolic Responses



Brody J et al. ASH 2023;Abstract 3092. Brody J et al. ASCO 2024;Abstract 7037.

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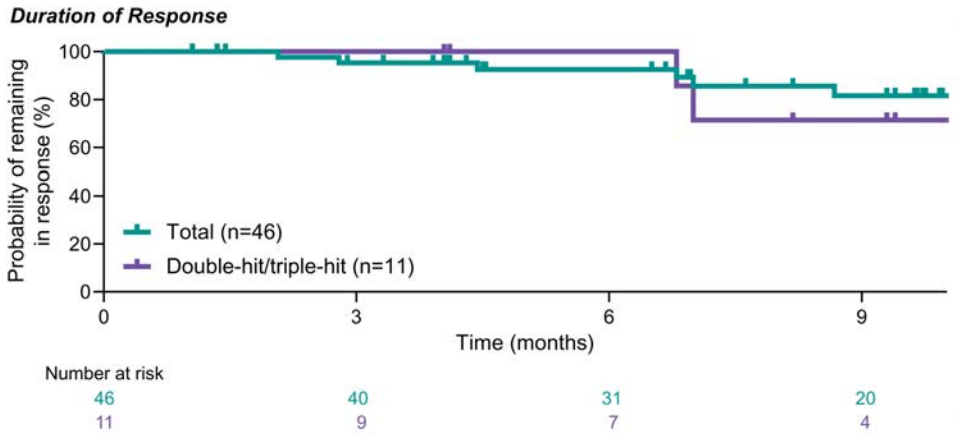
Epco-R-CHOP

High Rates of Complete Response

Best Response[a]	Efficacy Evaluable n=46	Double-Hit/ Triple-Hit n=11	Patients Who Completed 6C R-CHOP With Concomitant Epcoritamab n=44	Patients Who Completed 6C R-CHOP With 1 y Epcoritamab n=19
Overall response	100%	100%	100%	100%
CMR	80%	82%	84%	89%
PMR	20%	18%	16%	11%
Stable disease	0	0	0	0
Progressive disease	0	0	0	0

Median Duration of Response Not Reached



Responses were durable; 95% of those who completed therapy achieved and remain in complete response[a]

Falchi L et al. ASCO 2023;Abstract 7519.

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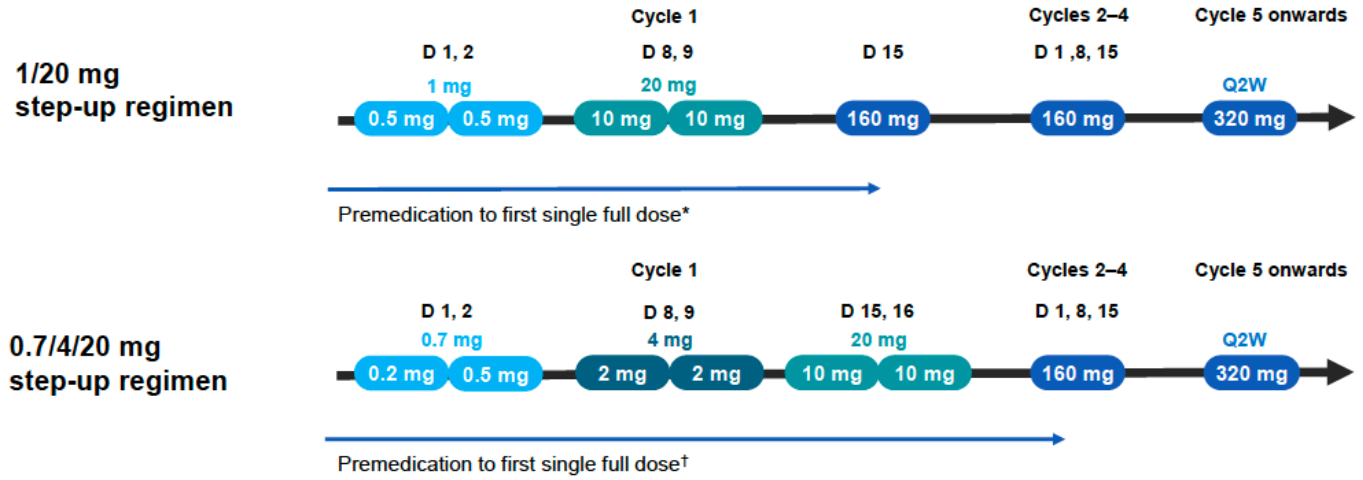
Odronextamab DLBCL Dosing

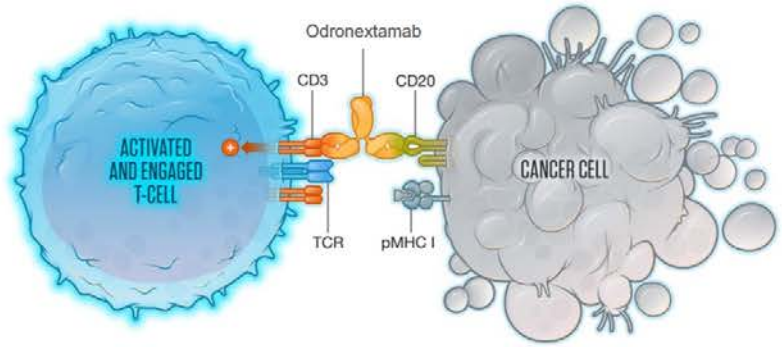
Cycle 1 step-up regimen optimized to mitigate the risk for cytokine release syndrome

- The study initiated with a Cycle 1 step up regimen of 1/20 mg
- This was modified to 0.7/4/20 mg during Cycle 1 to further mitigate the risk of CRS



Updated guidelines for tocilizumab and steroids introduced with 0.7/4/20 mg regimen.
*20 mg IV dexamethasone 1 to 3 hours prior to each split or initial single infusion. †10 mg dexamethasone orally 12 to 24 hours prior to the first split infusion. On each day of split or single infusion: dexamethasone 20 mg IV 1 to 3 hours before infusion; diphenhydramine 25 mg IV or orally and acetaminophen 650 mg orally 30 to 60 minutes before infusion.
CRS, cytokine release syndrome; D, day; IV, intravenous; Q2W, every 2 weeks.

Odronextamab
Hinge-stabilized CD20×CD3 bispecific antibody



Binds CD20 on malignant B-cells and CD3 on T cells, to elicit T-cell-mediated cytotoxicity

Kim WS et al. ASH 2022;Abstract 444.

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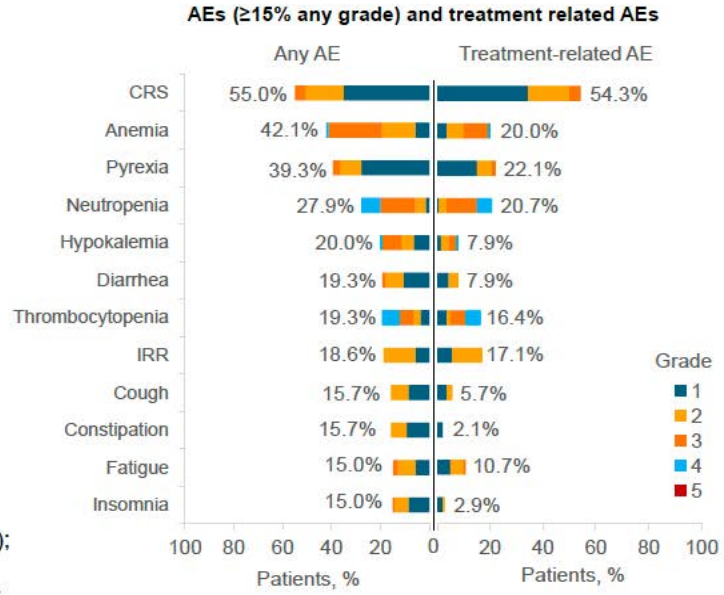
CRS

Treatment-emergent adverse events, n (%)	Patients N=140 Any event	Treatment-related
Any TEAE	139 (99.3%)	123 (87.9%)
Grade ≥3 TEAE	110 (78.6%)	74 (52.9%)
Serious AE	85 (60.7%)	64 (45.7%)
Grade 5 TEAE Related to COVID-19 Other grade 5 events	20 (14.3%) 5 (3.6%) 15 (10.7%)	5 (3.6%) 1 (0.7%) 4 (2.9%)
TEAE leading to treatment discontinuation	14 (10.0%)	11 (7.9%)



- Grade 5 TRAEs: pneumonia (n=3), COVID-19 (n=1) and pseudomonal sepsis (n=1)
- TRAEs leading to treatment discontinuation: encephalopathy (n=2); aphasia; CRS; sclerosing cholangitis; SVT; CMV reactivation (n=1 each); cough and pneumonia (n=1); PJP pneumonia and neutrophil count decreased (n=1); pancreatitis, tachycardia, septic shock and CRS (n=1); interstitial pneumonia and fungal pneumonia (n=1);

Data cut-off date: Sep 15, 2022.
AEs per NCI-CTCAE v5.0. CRS per Lee 2019 criteria.
adverse event; CMV, cytomegalovirus; CRS, cytokine release syndrome; IRR, infusion related reaction; PJP, pneumocystis jirovecii pneumonia; SVT, supraventricular tachycardia; TEAE, treatment-emergent AE; TRAE, treatment-related AE.

n, (%)	1/20 regimen N=67	0.7/4/20 regimen N=73
CRS any Grade	38 (56.7%)	39 (53.4%)
Grade 1	21 (31.3%)	28 (38.4%)
Grade 2	12 (17.9%)	10 (13.7%)
Grade 3	5 (7.5%)	1 (1.4%)
Grade 4	0	0
Grade 5	0	0
Received corticosteroids	13 (19.4%)	15 (20.5%)
Received tocilizumab	10 (14.9%)	19 (26.0%)
Received vasopressors	5 (7.5%)	1 (1.4%)

- 0.7/4/20 mg step-up regimen reduced the incidence of grade 2 and grade 3 CRS
- Approximately half of R/R DLBCL patients had CRS, mostly grade 1
- Only 1 case of grade 3 CRS with 0.7/4/20 mg step-up regimen (in the setting of acute pancreatitis at week 6) and no grade 4 or higher CRS events
- All CRS events resolved within a median time to resolution of 2 days (range 1–133)
- No patients required mechanical ventilation or ICU admission for the management of CRS

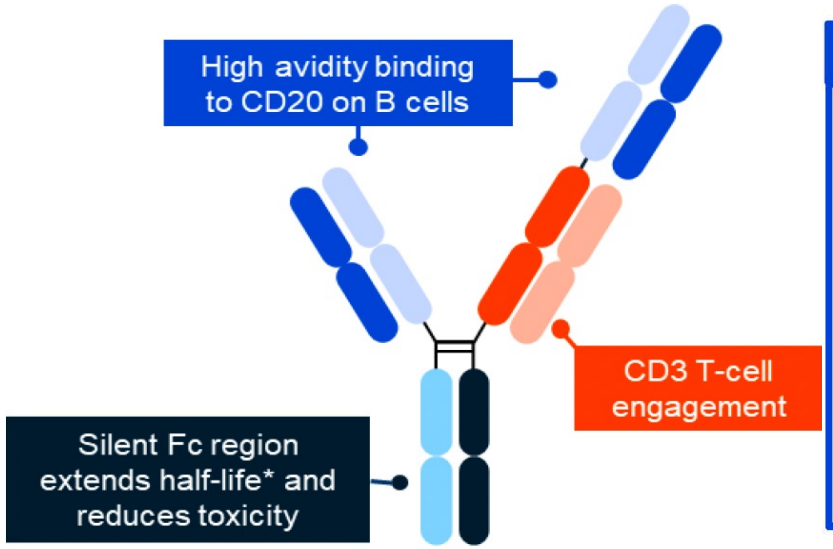
Kim WS et al. ASH 2022;Abstract 444.

Questions?

RTP
RESEARCH
TO PRACTICE

Glofitamab

Glofitamab: *CD20xCD3 bispecific antibody with 2:1 format for increased potency vs 1:1 format*[5]



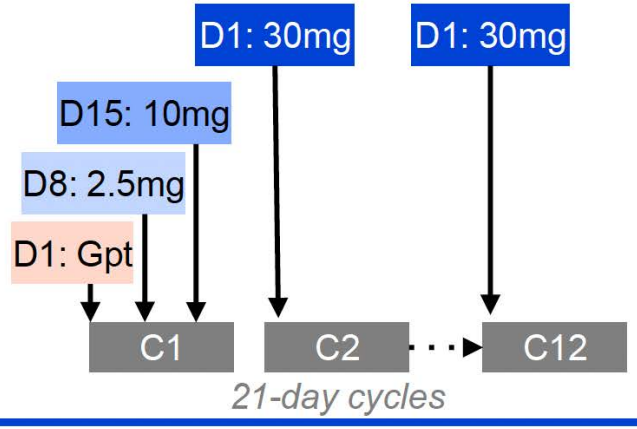
Glofitamab IV administration

Fixed-duration treatment:

- Up to 12 cycles (8.3 months)

CRS mitigation:

- Obinutuzumab IV pre-treatment (1000mg)
- C1 step-up dosing
- Monitoring after first glofitamab dose (2.5mg)



Hutchings M et al. ASH 2023; Abstract 433.

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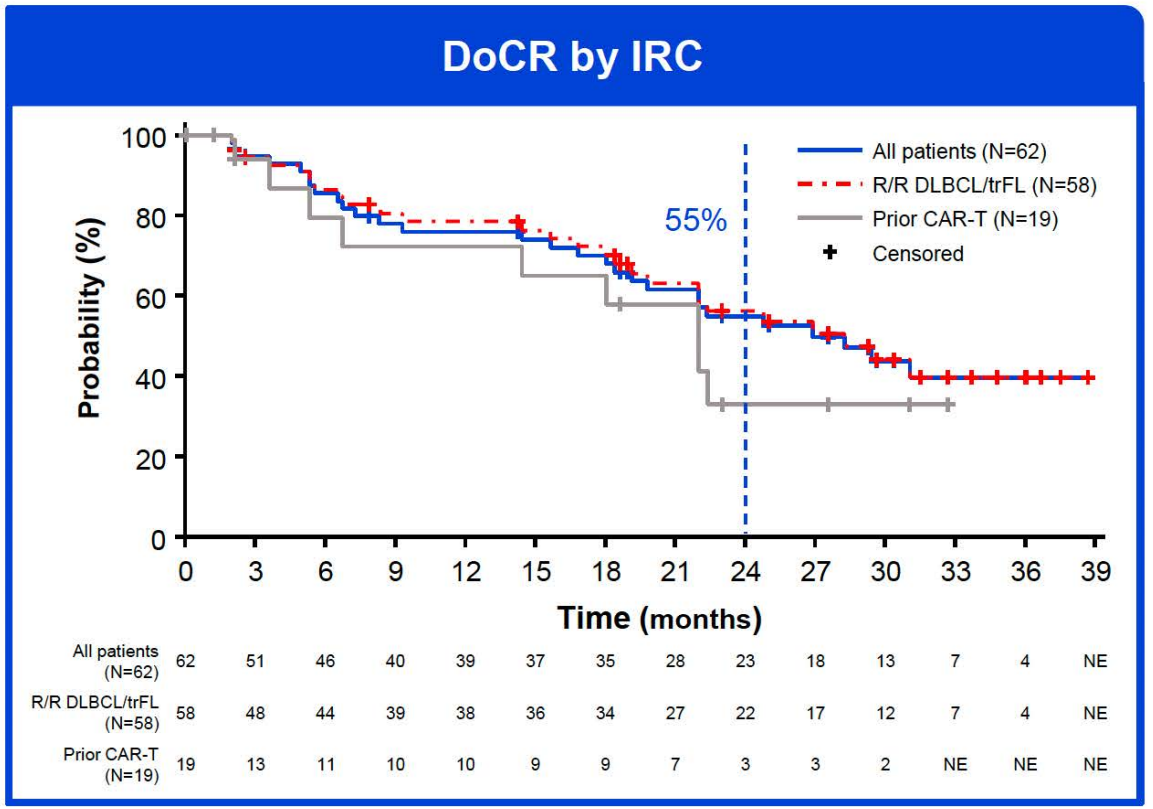
Response Rates

	All patients (N=155)*	R/R DLBCL/ trFL (N=132)[1†‡]	Prior CAR-T (N=52)[†]
ORR, n (%) [95% CI]	80 (52) [43.5–59.7]	74 (56) [47.2–64.7]	26 (50) [35.8–64.2]
CR rate, n (%) [95% CI]	62 (40) [32.2–48.2]	58 (44) [35.3–52.8]	19 (37) [23.6–51.0]
Median DoCR, months (95% CI)	26.9 (19.8–NR)	28.3 (19.8–NR)	22.0 (6.7–NR)
24-month DoCR, % (95% CI)	55.0 (41.1–68.8)	56.2 (41.9–70.4)	33.1 (7.2–59.0)
Median CR follow-up, months (range)	29.6 (0–39)	29.6 (0–39)	23.0 (0–33)
Ongoing CRs, n/N (%)	34/62 (55)	32/58 (55)	10/19 (53)



- Median time on study: 32.1 months (range: 0–43)

With 32 months median follow-up, glofitamab showed high response rates

Hutchings M et al. ASH 2023; Abstract 433.

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Adverse Events

Safety summary

- **CRS* remained the most common AE**
  - CRS occurred in 64% of patients
  - CRS events were mostly Grade 1 (48%) or Grade 2 (12%); Grade 3 (3%) and Grade 4 (1%) events were uncommon
- **The incidence of AEs and SAEs was stable compared with earlier analyses[1,2]**
  - No new AEs were reported, including ICANS, CRS, infections, or Grade 5 AEs

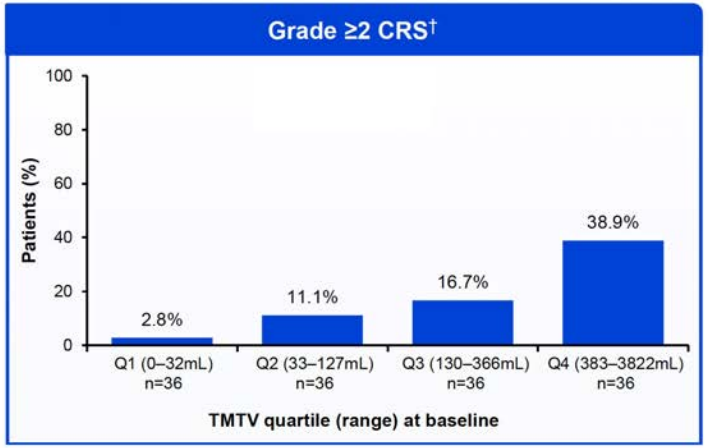
N (%)	N=154
AE Glofitamab-related	152 (99) 140 (91)
Grade ≥3 AE Glofitamab-related	100 (65) 69 (45)
SAE Glofitamab-related	75 (49) 46 (30)
Grade 5 (fatal) AE Glofitamab-related	11 (7) 0
AE leading to treatment discontinuation Glofitamab-related	14 (9) 5 (3)
AE leading to dose modification/interruption of glofitamab Glofitamab-related	29 (19) 16 (10)

The safety profile was consistent with previous analyses, with no new AEs reported[1,2]

*By ASTCT grade. AE, adverse event; ASTCT, American Society for Transplantation and Cellular Therapy criteria; ICANS, immune effector cell-associated neurotoxicity syndrome; SAE, serious adverse event.

1. Dickinson M, et al. N Engl J Med 2022;387:2220–31;
2. Dickinson M, et al. ICML 2023; Oral 095.

Association between baseline TMTV* and CRS



- Most Grade ≥2 CRS events occurred with the first dose of glofitamab (C1D8, 2.5mg) and resolved before the next dose (C1D15, 10mg)

Higher baseline TMTV was associated with an increased risk of experiencing a Grade ≥2 CRS event

*Baseline TMTV (n=144) was derived from baseline PET images using a semi-automated method with a threshold for TMTV of 2x the SUV_{mean} of the liver; †Chi-square=16.273; degrees of freedom=1; p<0.0001. Q, quartile.

Hutchings M et al. ASH 2023; Abstract 433.

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Efficacy DLBCL

Drug	N	ORR	CR	PFS (median)	DOR	Approved
Epcoritamab	157	63%	39%	4.4 m	15.6 m	Yes
Glofitamab	291	52.6%	35%	4.9 m*	18.4 m	Yes
Odronextamab	130	49.2%*	30.8%*	4.4 m	10.2 m	No

Week 12 response assessment by independent central review	1/20 step-up regimen N=67	0.7/4/20 step-up regimen N=63
ORR	46.3% [95% CI: 34.0–58.9%]	42.9% [95% CI: 30.5–56.0%]
Complete response	26.9%	20.6%

- Median opportunity of follow-up: 21.3 months (range 2.6–29.8)

Drug	post CAR-T patients	Refractory (*R*)	ORR	CR	CR (*R*)
Epcoritamab	61	46	54%	34%	28%
Glofitamab	52	N/A	N/A	35%	N/A
Odronextamab	31		48.4%*	32.3%	N/A

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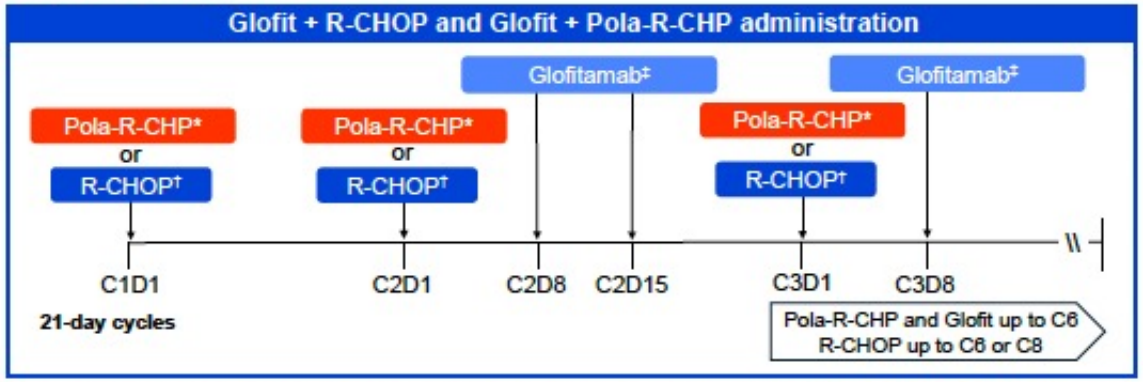
Glofitamab-R-CHOP or Glofitamab-Pola-R-CHP

Study design (NCT03467373)

- NP40126 is an ongoing Phase Ib trial evaluating Glofit + R-CHOP and Glofit + Pola-R-CHP in 1L DLBCL (**Figure 1**).

Figure 1. Study overview.



*Pola-R-CHP was administered on D1 of each 21-day cycle (maximum six cycles); †R-CHOP was administered for six to eight 21-day cycles; ‡Glofitamab IV was administered in C2–C6, with SUD during C2 (2.5mg C2D8, 10mg C2D15) and at the target dose (30mg) from C3D8 onwards. Glofitamab maintenance was allowed for up to 1 year, and hospitalization was not mandated. C, cycle; D, day; IV, intravenous; SUD, step-up dosing.

- Efficacy was analyzed in the intent-to-treat population.
- Safety was analyzed in patients who received at least one dose of any study drug.
- Circulating tumor DNA (ctDNA) dynamics were measured using linked somatic variances with the AVENIO NHL ctDNA assay (for additional details see poster 2999).

Patient characteristics were similar between the two cohorts

- As of July 14, 2023, 56 and 24 patients were enrolled to receive Glofit + R-CHOP and Glofit + Pola-R-CHP, respectively (**Table 1**).

Table 1. Summary of patient demographic and baseline characteristics.

n (%)*		Glofit + R-CHOP N=56	Glofit + Pola-R-CHP N=24
Median age, years (range)		68.0 (21–84)	65.0 (32–85)
Male		27 (48.2)	12 (50.0)
ECOG PS	0	28 (50.0)	9 (37.5)
	1	19 (33.9)	13 (54.2)
	2	8 (14.3)	2 (8.3)
	3	1 (1.8)	0 (0.0)
Ann Arbor stage	I/II	2 (3.6)	1 (4.2)
	III/IV	54 (96.4)	23 (95.8)
IPI score	1	2 (3.6)	1 (4.2)
	2	19 (33.9)	8 (33.3)
	3	20 (35.7)	10 (41.7)
	4	13 (23.2)	5 (20.8)
	5	2 (3.6)	0 (0.0)
Bulky disease	>6cm	34 (60.7)	15 (62.5)
Cell of origin†‡	GCB	24 (42.9)	8 (33.3)
	Non-GCB	11 (19.6)	9 (37.5)
Extranodal disease		42 (75.0)	17 (70.8)

*Unless otherwise specified; †Eleven and three patients were unclassified in the Glofit + R-CHOP and Glofit + Pola-R-CHP cohorts, respectively; ‡Ten and three patients were classified as unknown in the Glofit + R-CHOP and Glofit + Pola-R-CHP cohorts, respectively. ECOG PS, Eastern Cooperative Oncology Group performance status; GCB, germinal center B cell; IPI, International Prognostic Index.

Topp MS et al. ASH 2023; Abstract 3085.

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Response and Safety

- Median follow-up was 20.3 (range: 0–29) months in the Glofit + R-CHOP cohort and 12.1 (range: 5–14) months in the Glofit + Pola-R-CHP cohort.

Table 2. Investigator-assessed best overall response.

n (%) [95% CI]	Glofit + R-CHOP N=56	Glofit + Pola-R-CHP N=24
Best overall response rate*†	52 (92.9) [82.71–98.02]	24 (100.0) [85.75–100.00]
CMR	47 (83.9) [71.67–92.38]	22 (91.7) [73.00–98.97]
PMR	5 (8.9) [2.96–19.62]	2 (8.3) [1.03–27.00]
PMD	2 (3.6) [0.44–12.31]	0 (0.0) [0.00–14.25]
Missing or not done	2 (3.6)	0 (0.0)

*Response was assessed by PET-CT using Lugano criteria;[8] †Investigator-assessed best overall response rate at EOT. CI, confidence interval; EOT, end-of-treatment; PET-CT, positron emission tomography-computed tomography; PMD, progressive metabolic disease; PMR, partial metabolic response.

Glofit + R-CHOP and Glofit + Pola-R-CHP had manageable safety profiles

- The safety profiles were highly consistent with earlier analyses of the NP40126 study evaluating both cohorts (**Table 3**).[6,7]
- Median dose intensity was 100% for all Glofit + R-CHOP and Glofit + Pola-R-CHP components.

Table 3. Safety overview.

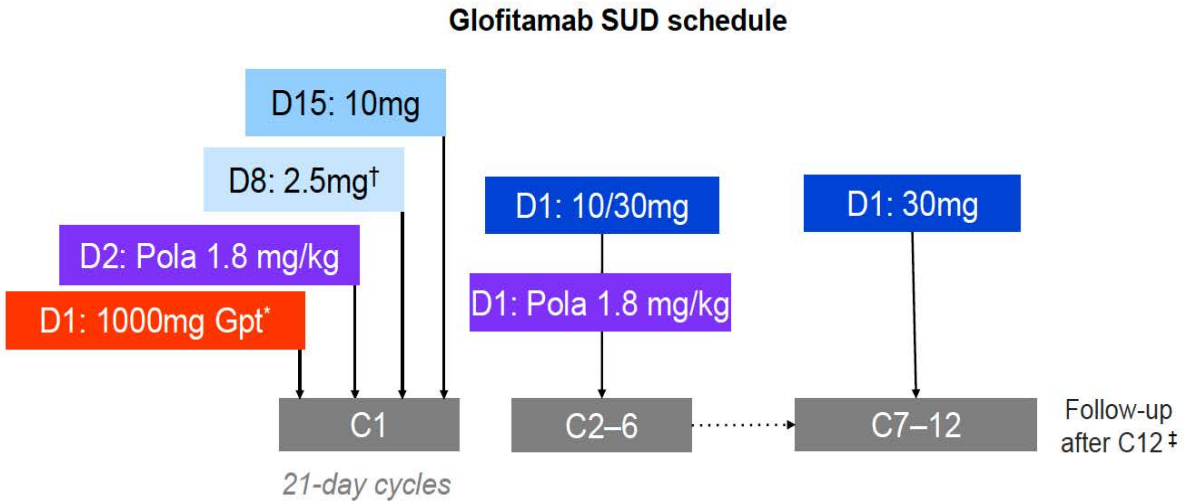
Summary of AEs*, n (%)	Glofit + R-CHOP N=56	Glofit + Pola-R-CHP N=24
Any AE	56 (100.0)	24 (100.0)
Related to glofitamab	33 (58.9)	17 (70.8)
Grade ≥3 AE	43 (76.8)	17 (70.8)
Related to glofitamab	15 (26.8)	10 (41.7)
Grade 5 (fatal) AE	4 (7.1)†	1 (4.2)‡
Related to glofitamab	0 (0.0)	0 (0.0)
SAE	20 (35.7)	13 (54.2)
Related to glofitamab	6 (10.7)	6 (25.0)
AEs leading to dose interruption of glofitamab	12 (21.4)	5 (20.8)
AEs leading to discontinuation of glofitamab	1 (1.8)	2 (8.3)
AEs of interest		
CRS[9]	6 (10.7)	2 (8.3)
Grade ≥3	0 (0.0)	0 (0.0)
Neutropenia	29 (51.8)	15 (62.5)
Grade ≥3	27 (48.2)	15 (62.5)
Infections and infestations	29 (51.8)	9 (37.5)
Grade ≥3	12 (21.5)	4 (16.7)
ICANS§	0 (0.0)	0 (0.0)

*CRS events were graded using American Society for Transplantation and Cellular Therapy criteria,[9] and other AEs were graded using Common Terminology Criteria for Adverse Events (v4.0). †COVID-19 pneumonia (n=3 [5.4%]) and infusion-related reaction associated with rituximab (n=1 [1.8%]); ‡Acute respiratory distress syndrome; §Tocilizumab was used in two (33.3%) patients with CRS in the Glofit + R-CHOP cohort; ¶ICANS after the glofitamab dose. ICANS, immune effector cell-associated neurotoxicity syndrome.

Topp MS et al. ASH 2023; Abstract 3085.

Glofitamab/Polatuzumab

Figure 1. Glofit-Pola administration in R/R DLBCL.



*Patients received obinutuzumab 1000mg on D1 of the first 21-day cycle to mitigate risk of CRS. †Mandatory 24-hour hospitalization for first glofitamab infusion. ‡Patients with CR, PR or SD were followed until disease progression, those with PD had an end of study visit then were followed for survival.
CR, complete response; CRS, cytokine release syndrome; PD, progressive disease; PR, partial response; SD, stable disease.

Table 1. Baseline patient and disease characteristics.

n (%) unless stated	N=125
Median age (range), years	67 (23–84)
Male	79 (63.2)
ECOG PS	
0–1	118 (94.4)
2	7 (5.6)
Histology	
DLBCL NOS	56 (44.8)
trFL	26 (20.8)
HGBCL	41 (32.8)
PMBCL	2 (1.6)
IPI score	
0/1	23 (18.4)
2/3	68 (54.4)
4/5	34 (27.2)

n (%) unless stated	N=125
Ann Arbor stage	
I/II	29 (23.2)
III/IV	96 (76.8)
Bulky disease	
>6cm	52 (41.6)
>10cm	19 (15.2)
Median prior lines of therapy (range)	2 (1–7)
Number of prior lines of therapy	
1	50 (40.0)
≥2	75 (60.0)
Prior CAR T-cell therapy	28 (22.4)
Refractory to any prior therapy	100 (80.0)
Refractory to last prior therapy	90 (72.0)

ECOG PS, Eastern Cooperative Oncology Group performance status; IPI, International Prognostic Index; NOS, not otherwise specified; PMBCL, primary mediastinal large B-cell lymphoma; trFL, transformed follicular lymphoma.

Hutchings M et al. ASH 2023; Abstract 4460.

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Response

Table 2. Best overall response (INV assessment).

n (%)	All patients (n=121)*	Prior CAR-T (n=27)	DLBCL NOS (n=56)	HGBCL (n=37)	trFL (n=26)	PMBCL (n=2)
Objective response	**97 (80.2)**	**21 (77.8)**	**48 (85.7)**	**27 (73.0)**	20 (76.9)	2 (100)
Complete response	**72 (59.5)**	**13 (48.1)**	**35 (62.5)**	**21 (56.8)**	14 (53.8)	2 (100)
Partial response	25 (20.7)	8 (29.6)	13 (23.2)	6 (16.2)	6 (23.1)	0
Stable disease	5 (4.1)	1 (3.7)	1 (1.8)	2 (5.4)	2 (7.7)	0
Progressive disease	16 (13.2)	4 (14.8)	6 (10.7)	7 (18.9)	3 (11.5)	0
Not determined†	3 (2.5)	1 (3.7)	1 (1.8)	1 (2.7)	1 (3.8)	0

*121/125 efficacy-evaluable population: patients who had been on the study long enough to have at least one response assessment. †Missing or not done.

Figure 2. Best overall response by histology (INV assessment).

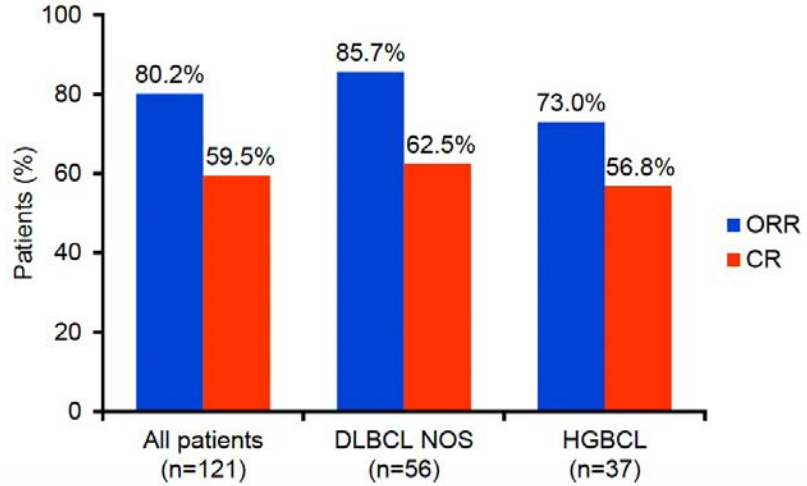


Figure 3. DoCR.

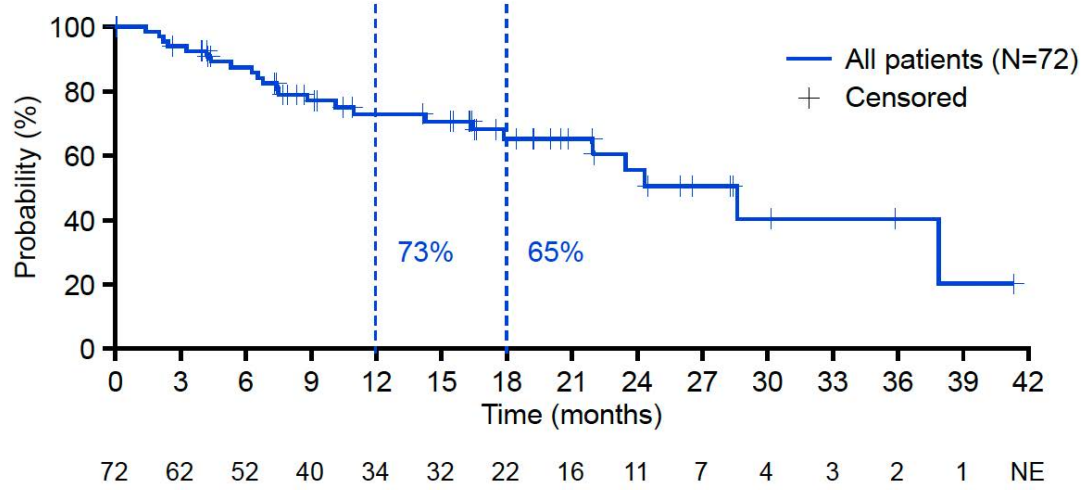
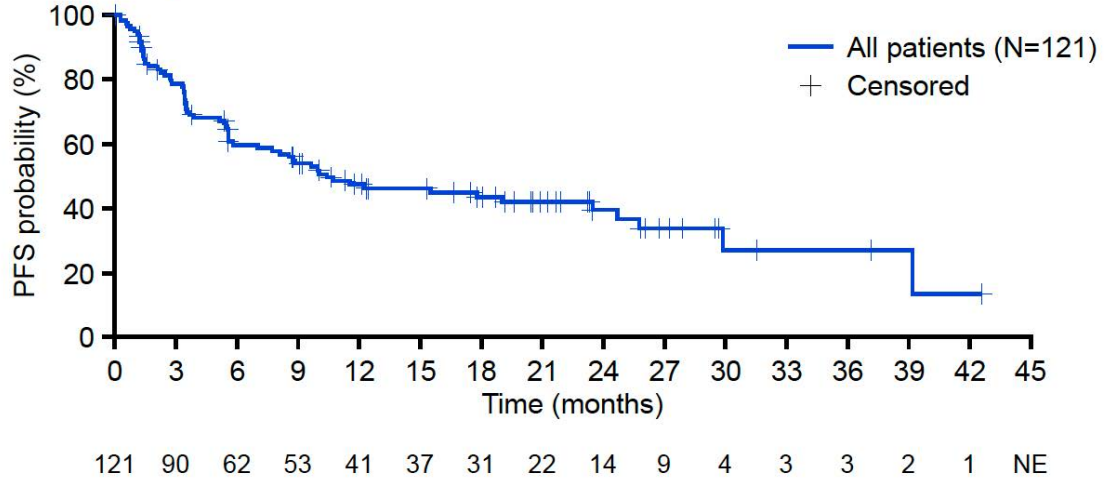


Figure 4. PFS in all patients.



Hutchings M et al. ASH 2023; Abstract 4460.

Safety

Table 3. Safety summary.

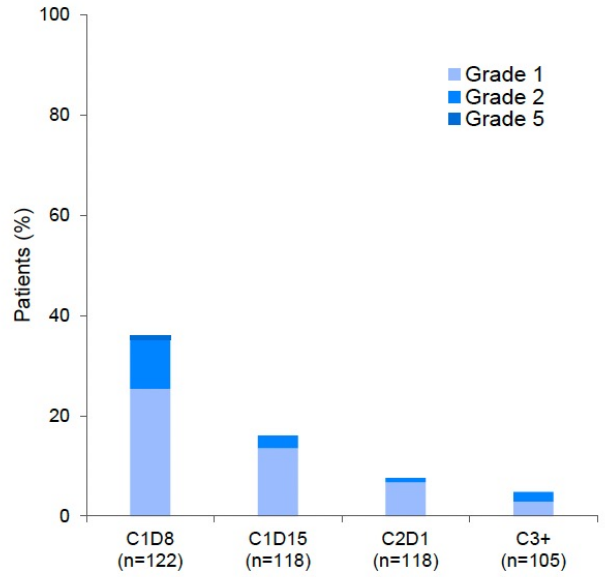
n (%) of patients with ≥1 AE	N=125
Any AEs	124 (99.2)
Grade 3–4 AEs	75 (60.0)
Grade 5 AEs	9 (7.2)
Serious AEs	75 (60.0)
AEs leading to treatment discontinuation	13 (10.4)
Glofitamab discontinuation	10 (8.0)
Polatuzumab vedotin discontinuation	8 (6.4)

Table 4. CRS summary.*

	n=122*
CRS, n (%)	
Any grade	56 (45.9)
Grade 1	36 (29.5)
Grade 2	19 (15.6)
Grade 5†	1 (0.8)
Serious AE (any grade)	37 (30.3)
Median time to CRS onset after glofitamab dose, hours (range)	
2.5mg	16.2 (5.4–42.1)
10mg	35.9 (8.9–129.5)
30mg	36.2 (18.5–55.9)

*122/125 patients who received ≥1 dose of glofitamab.
†Patient (aged 73, with advanced HGBCL and multiple CRS risk factors) developed Grade 3 CRS (with a background of urosepsis and herpetic stomatitis) and declined further intensive management for CRS, resulting in fatal outcome.

Figure 6. CRS by cycle and grade.*



Hutchings M et al. ASH 2023; Abstract 4460.

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Glofitamab + Co-Stim (CD19 x 4-1BBL) Dosing Schedule

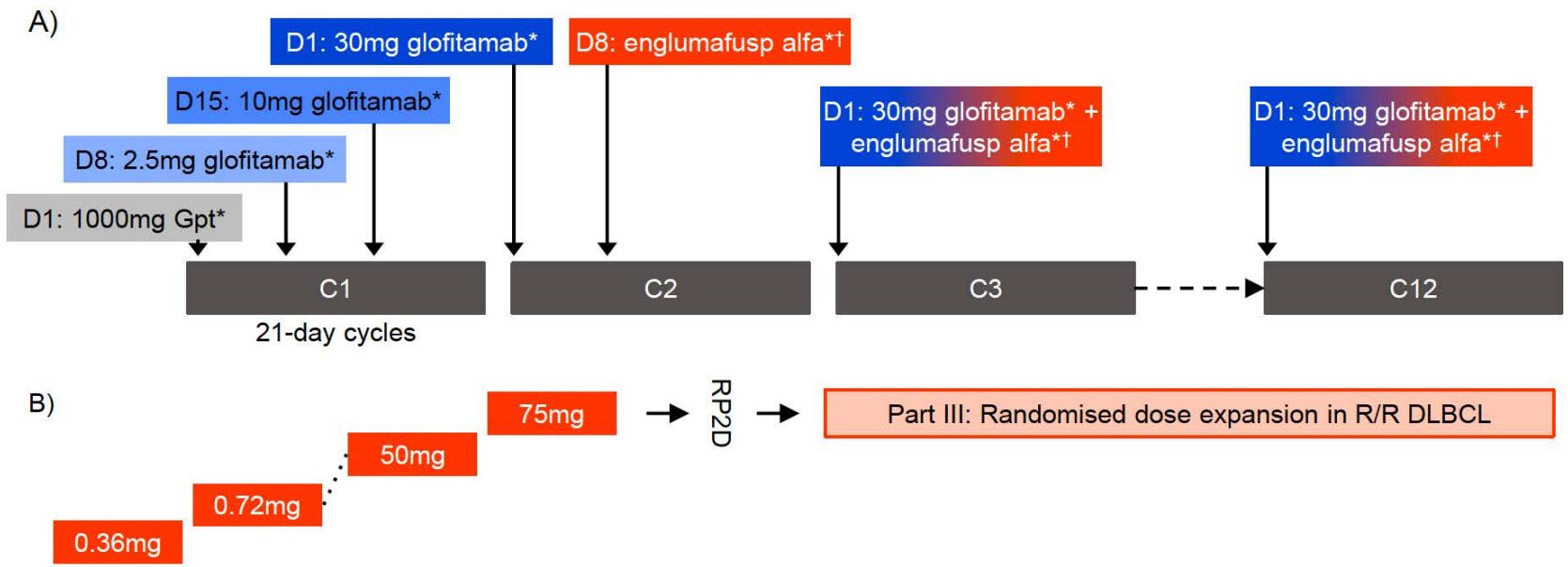
Patients

- Age ≥18 years
- R/R B-cell NHL
- ≥1 measurable lesion
- ≥2 prior therapies
- Adequate haematologic and liver function
- ECOG PS ≤1

Primary objectives

- Safety
- Tolerability
- PK
- RP2D

Treatment schedule (A) and dose escalation (B)



Englumafusp alfa is initiated after glofitamab step dosing on C2D8 and is co-administered with glofitamab on the same day from C3 onwards

*IV administration; †escalating dose levels; C, Cycle; D, Day; DLBCL, diffuse large B-cell lymphoma; Gpt, obinutuzumab pre-treatment
IV, intravenous; NHL, non-Hodgkin lymphoma; PK, pharmacokinetics; PS, performance status; RP2D, recommended Phase 2 dose; R/R, relapsed/refractory

Dickinson M et al. Presented at ICML 2023.

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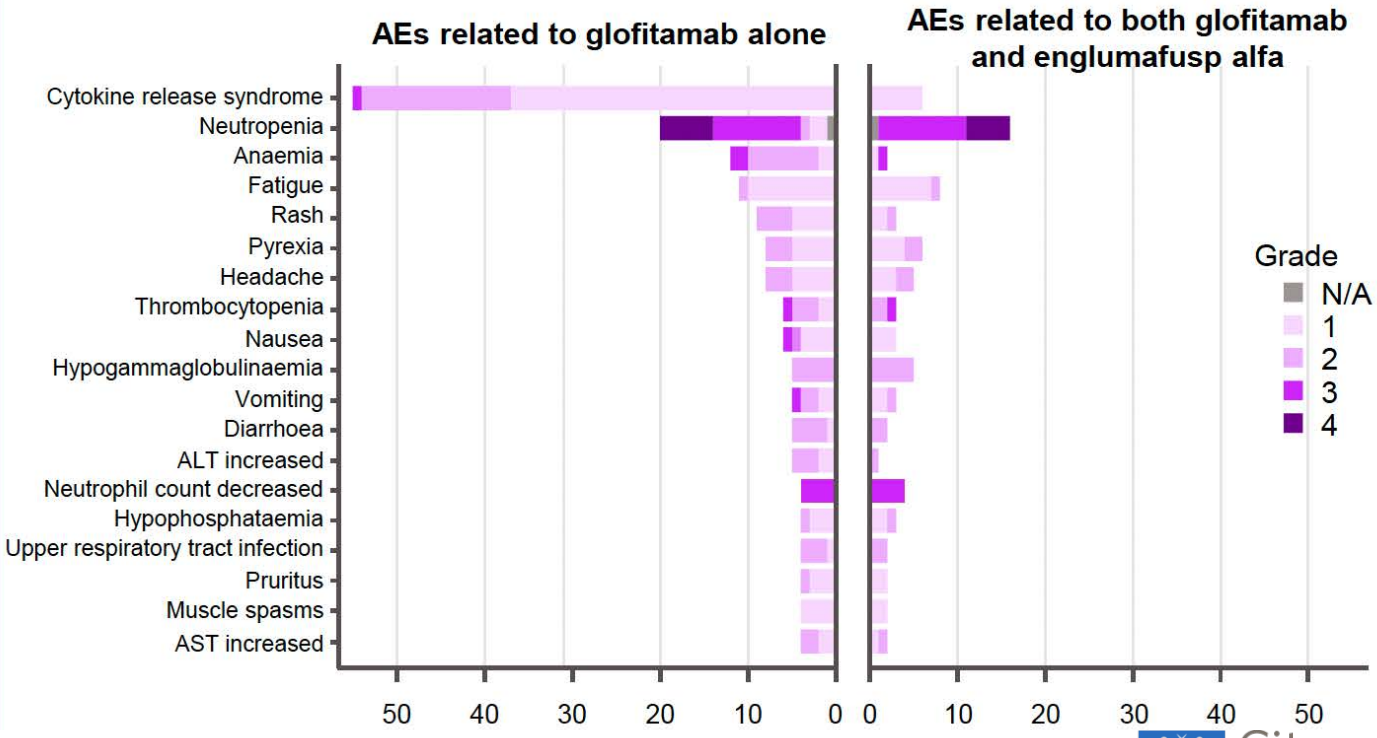
Safety

glofitamab monotherapy

N (%)	N=113
Any AE*	106 (93.8%)
CRS	58 (51.3%)
COVID-19	29 (25.7%)
Neutropenia	28 (24.8%)
Anaemia	24 (21.2%)
Diarrhoea	23 (20.4%)
Any SAE†	72 (63.7%)
CRS	27 (23.9%)
COVID-19	10 (8.8%)
COVID-19 pneumonia	6 (5.3%)
Pyrexia	6 (5.3%)
Any TRAE	95 (84.1%)
Related to glofitamab only	76 (67.3%)
Related to glofitamab and englumafusp alfa	55 (48.7%)

TRAEs in ≥4 patients related to glofitamab or englumafusp alfa plus glofitamab



Dickinson M et al. Presented at ICML 2023.

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Efficacy

Englumafusp alfa plus glofitamab shows promising activity in patients with R/R NHL

Response rates across dosing cohorts in evaluable patients with R/R aNHL or R/R iNHL

	N response evaluable	CRR	BORR
aNHL			
≥1 dose of any study treatment	86	37 (43.0%)	54 (62.8%)
≥1 dose of englumafusp alfa	78	37 (47.4%)	53 (67.9%)
iNHL			
≥1 dose of any study treatment	26	17 (65.4%)	23 (88.5%)
≥1 dose of englumafusp alfa	25	17 (68.0%)	23 (92.0%)

- Median number of cycles received: 7 aNHL; 12 iNHL

Data cut-off date: 28 April 2023; aNHL, aggressive NHL; BORR, best overall response rate; CRR, complete response rate; iNHL, indolent NHL and unknown; NHL, non-Hodgkin lymphoma; R/R, relapsed/refractory

Response rates in evaluable patients with R/R aNHL or iNHL and prior CAR T-cell therapy

	N response evaluable	CRR	BORR
aNHL			
≥1 dose of any study treatment	33	13 (39.4%)	21 (63.6%)
≥1 dose of englumafusp alfa	30	13 (43.3%)	20 (66.7%)
iNHL			
≥1 dose of any study treatment	1	1	1
≥1 dose of englumafusp alfa	1	1	1

Dickinson M et al. Presented at ICML 2023.

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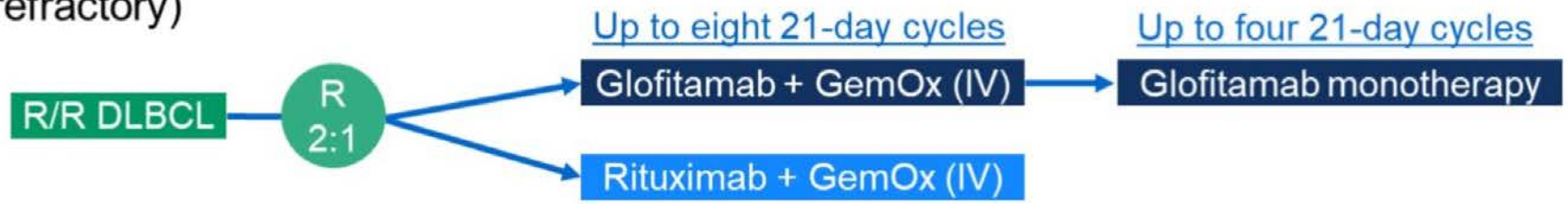
STARGLO Study of Glofitamab + GemOx Met Primary Endpoint of OS

GO41944 (NCT04408638) is a Phase III, open-label, randomized trial designed to evaluate the safety and efficacy of glofit-GemOx vs R-GemOx in patients with R/R DLBCL

- Randomization is stratified by number of prior lines of therapy (1 vs ≥2) and outcome of last systemic therapy (relapsed vs refractory)



- Press release: Sunday, Apr 14, 2024
- The Phase III STARGLO study met its primary endpoint of overall survival. The study demonstrated that people with R/R DLBCL, who have received at least one prior line of therapy and are not candidates for autologous stem cell transplant, lived longer when treated with glofitamab in combination with gemcitabine and oxaliplatin (GemOx) versus rituximab in combination with GemOx. Safety of the combination appeared consistent with the known safety profiles of the individual medicines.

Hertzberg M et al. ASCO 2021;Abstract TPS7575. https://www.gene.com/media/press-releases/15021/2024-04-14/genentechs-columvi-meets-primary-endpoin

Bispecifics

- Epcoritamab approved for DLBCL and FL in US.
  - Data for DLBCL is maturing.
    - How does long term follow up compare to Glofitamab and 3L CAR-T?
      - With Caveat: no CAR-T exposed in any previous CAR-T study.
- Multiple combination regimens in process with both glofitamab and epcoritamab. Goal is to improve CMR which should enhance durability of responses…and lead to potential cure.

Agenda

Introduction: CD3 Bispecific Antibodies in the Community Oncology Setting

Module 1: ASCO and EHA 2024

Module 2: Integration of Bispecific Antibody Therapy into the Management of Diffuse Large B-Cell Lymphoma — Dr Phillips

Module 3: Current and Future Role of Bispecific Antibodies in Follicular Lymphoma and Other B-Cell Lymphomas — Dr Flinn

Module 4: Tolerability and Other Practical Considerations with the Use of Bispecific Antibody Therapy — Dr Brody

Cases from General Medical Oncologists: Potential Role of Bispecific Antibodies in the Management of R/R FL

- **67-year-old woman, relapsed disease s/p R-CHOP and R^2 therapies, receiving mosunetuzumab at tertiary referral center**
- **70-year-old woman, R-CHOP induction and subsequently received CAR T-cell therapy, has experienced prolonged cytopenia**
- **54-year-old man, FL transformed to Hodgkin lymphoma s/p BR, now receiving nivolumab-AVD with pancytopenia**
- **70-year-old man, PD on R monotherapy, R-mini-CHOP and R^2, receiving mosunetuzumab, Grade 2 CRS**

Survey of US-based general medical oncologists, May 2024.

Questions from General Medical Oncologists

- **If a patient progressed on R^2, what treatment would investigators recommend next? Zanubrutinib with obinutuzumab? Mosunetuzumab?**
- **How do you sequence bispecifics and tazemetostat? What if the patient's disease was EZH2 wild type?**

Survey of US-based general medical oncologists, May 2024.

OneOncology

Bi-Specific Antibodies in Follicular Lymphoma

Ian W. Flinn, MD, PhD
Chief Scientific Officer
OneOncology
Nashville, TN

Mosun Pivotal Trial:

Baseline patient characteristics

n, unless stated	N=90
Median age, years (range)	60 (29–90)
Male	55 (61%)
ECOG PS 0 1	 53 (59%) 37 (41%)
Ann Arbor stage I/II III/IV	 21 (23%) 69 (77%)
Median lines of prior therapy, (range)	3 (2–10)
Prior autologous stem cell transplant	28 (31%)*
Refractory to last prior therapy	62 (69%)
Refractory to any prior anti-CD20 therapy	71 (79%)
POD24	47 (52%)
Double refractory to prior anti-CD20 and alkylator therapy	48 (53%)

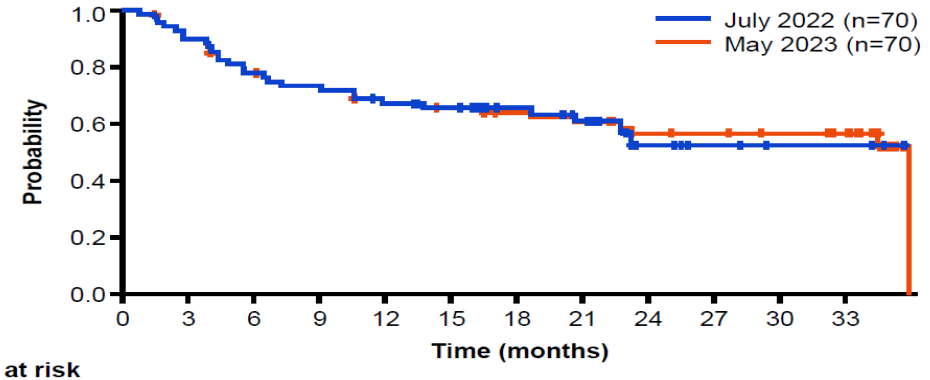
*Data updated based on subsequent snapshot.

Schuster ASH 2023

Mosun Pivotal Trial:

- Efficacy[1–3]
  - **CR rate: 60%** (95% CI: 49–70) by both IRC and INV
  - **ORR: 80%** (95% CI: 70–88) by IRC and 78% (95% CI: 68–86) by INV
  - Consistent benefit in patients with double-refractory disease and POD24

DOR (July 2022 vs May 2023 data cut-off)

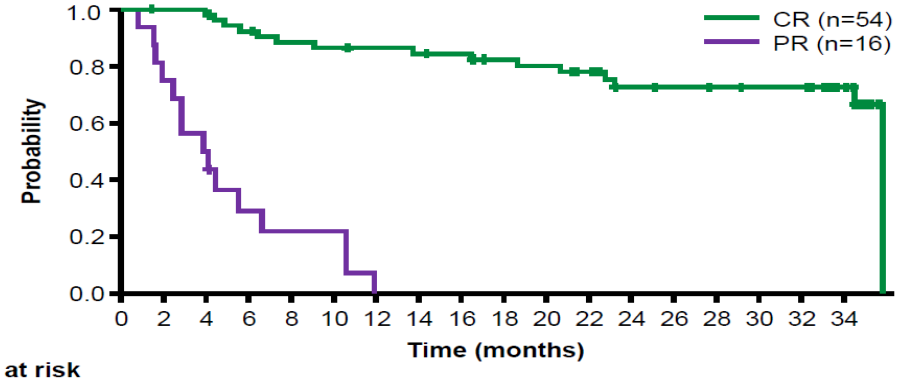


Patients at risk

July 2022	70	62	52	48	42	38	30	25	9	5	3	3
May 2023	70	62	52	48	43	41	38	36	26	25	23	21

	n=70
Median DOR, months (95% CI)*	35.9 (20.7–NE)
30-month DOR rate, % (95% CI)†	56.6% (44.2–68.9)

DOR for CR vs PR (May 2023 data cut-off)



Patients at risk

CR	54	53	52	48	45	44	43	42	41	38	37	34	26	25	24	23	23	15
PR	16	12	8	4	3	3	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE

Median DOR in patients with CR, months (95% CI); n=54*	35.9 (NE–NE)
Median DOR in patients with PR, months (95% CI); n=16*	4.0 (2.5–6.7)

72.7% (95% CI: 60.8–86.8) of patients with a CR are estimated to remain alive and progression-free 30 months after their first response

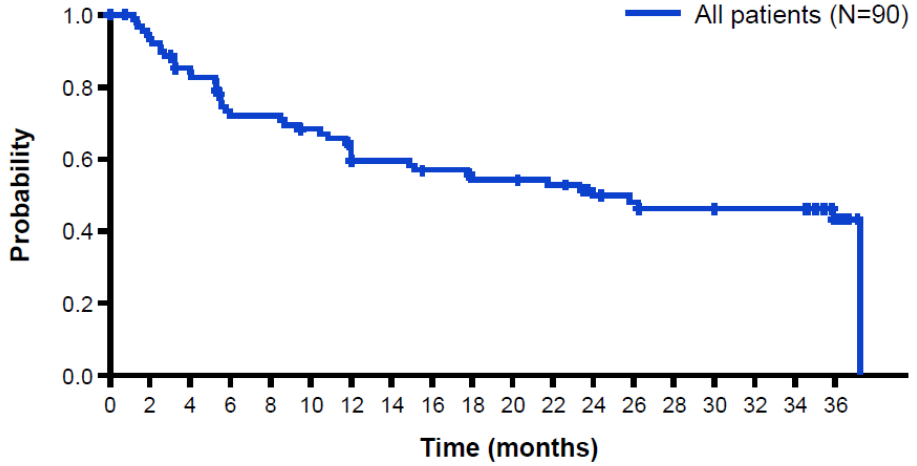
*Responders per INV assessment. †36-month DOR data are not available as this analysis was conducted from the first response assessment, therefore the landmark analysis is shorter for the duration outputs.

Schuster ASH 2023

Mosun Pivotal Trial:

PFS and OS; median follow-up >36 months

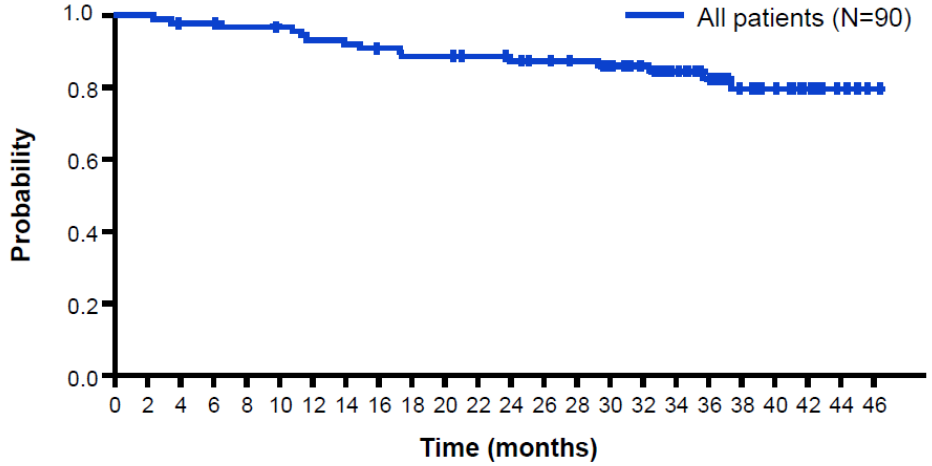
PFS



Patients at risk 90 81 72 60 59 55 47 46 43 40 40 38 30 27 25 25 24 24 13

	N=90
Median PFS, months (95% CI)	**24.0** (12.0–NE)
36-month PFS, months (95% CI)	**43.2%** (31.3–55.2)

OS



Patients at risk 90 89 87 86 85 84 81 80 78 76 76 74 72 70 68 62 56 51 39 26 21 14 8 1

	N=90
Median OS, months (95% CI)	**NR** (NE–NE)
36-month OS, months (95% CI)	**82.4%** (73.8–91.0)

Robust and stable progression-free and overall survival rates at 3 years

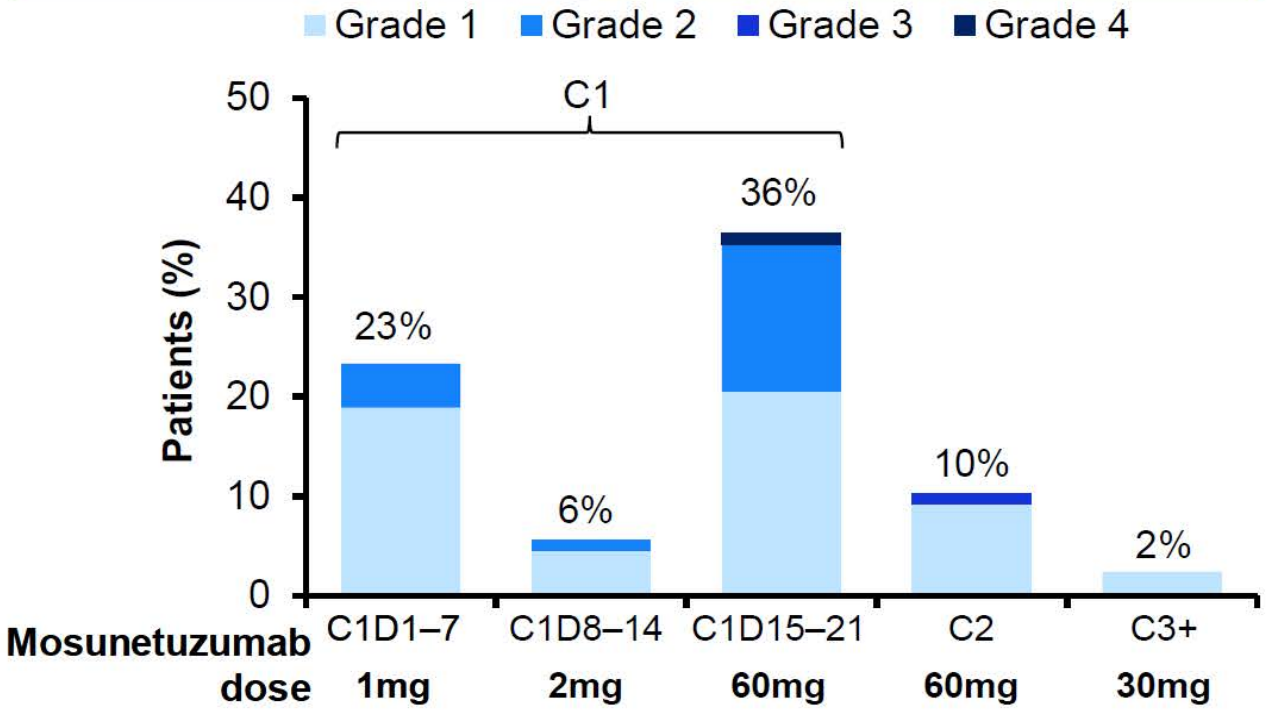
OS, overall survival; PFS, progression-free survival.

Schuster ASH 2023

Mosun: CRS Summary

CRS by ASTCT criteria[1]	N=90
CRS (any grade), n	40 (44%)
Grade 1	23 (26%)
Grade 2	15 (17%)
Grade 3	1 (1%)
Grade 4	1 (1%)
Median time to CRS onset, hours (range)	
C1D1	5 (1–24)
C1D15	27 (0–391)
Median CRS duration, days (range)	3 (1–29)
Corticosteroids for CRS management, n	10 (11%)*
Tocilizumab for CRS management, n	7 (8%)*
Events resolved	100%

CRS by cycle and grade



CRS was predominantly low-grade and occurred during C1
All CRS events resolved; no new events have been reported in this extended follow-up

Data cut-off: August 27, 2021, as no new CRS events occurred subsequently.*Four patients received both corticosteroids and tocilizumab for CRS management. ASTCT, American Society for Transplantation and Cellular Therapy.

1. Lee DW, et al. Biol Blood Marrow Transplant 2019;25:625–38.

First-line Mosunetuzumab for FL: Response Rates

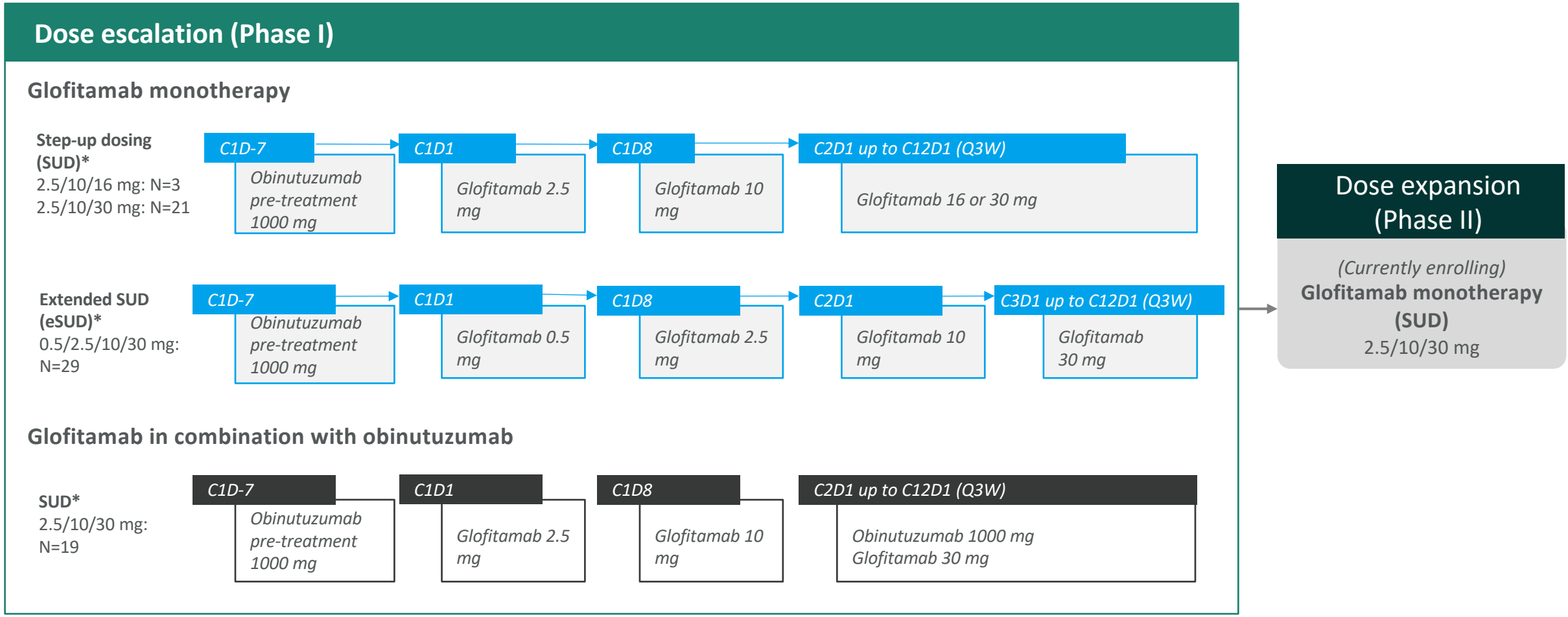
Response, %	Patients (N = 45)
Overall response	96
▪ Complete response	76
▪ Partial response	20
Stable disease	2
Progressive disease	2

Response Across Risk Groups, %	Complete Response	Partial Response
All patients (N = 45)	76	20
Grade		
▪ 1-2 (n = 34)	76	21
▪ 3A (n = 11)	73	18
Bulky disease (>7 cm)		
▪ No (n = 31)	74	19
▪ Yes (n = 14)	79	21
SUV_{max}		
▪ <13 (n = 33)	79	18
▪ ≥13 (n = 12)	67	25

Median follow-up: 5.8 mo.

Falchi. ASH 2023. Abstr 604.

Glofitamab regimens investigated in R/R FL



Population characteristics: R/R FL Gr 1–3A; ≥1 prior systemic therapy; age ≥18 years; ECOG PS ≤1

Clinical cut-off date: May 18, 2021. *Glofitamab IV. Gr=Grade; ECOG PS=Eastern Cooperative Oncology Group Performance Status; IV=intravenous; Q3W=every three weeks.

Morschhauser, Franck. ASH 2021

Baseline characteristics

N (%) of patients unless stated		Glofitamab monotherapy cohorts (N=53)	Glofitamab + obinutuzumab cohort (N=19)
Median age, years (range)		64 (33–83)	61 (41–78)
Male		29 (54.7)	11 (57.9)
FLIPI 1 score 3–5		28 (52.8)	11 (57.9)
Median number of prior lines, n (range)		3 (1–12)	2 (1–5)
Prior systemic therapy	Chemotherapy Anti-CD20 monoclonal antibody Autologous stem-cell transplant PI3K inhibitor CAR-T	51 (96.2) 52 (98.1) 7 (13.2) 9 (17.0) 1 (1.9)	19 (100) 19 (100) 3 (15.8) 3 (15.8) 0
Refractory status	Refractory to any prior therapy Refractory to most recent therapy line Refractory to any prior anti-CD20	36 (67.9) 28 (52.8) 31 (58.5)	13 (68.4) 8 (42.1) 10 (52.6)
High-risk subgroups	Double-refractory* POD24 PI3K inhibitor-refractory Bulky disease >6 cm	16 (30.2) 19 (35.8) 7 (13.2) 10 (18.9)	7 (36.8) 10 (52.6) 2 (10.5) 5 (26.3)

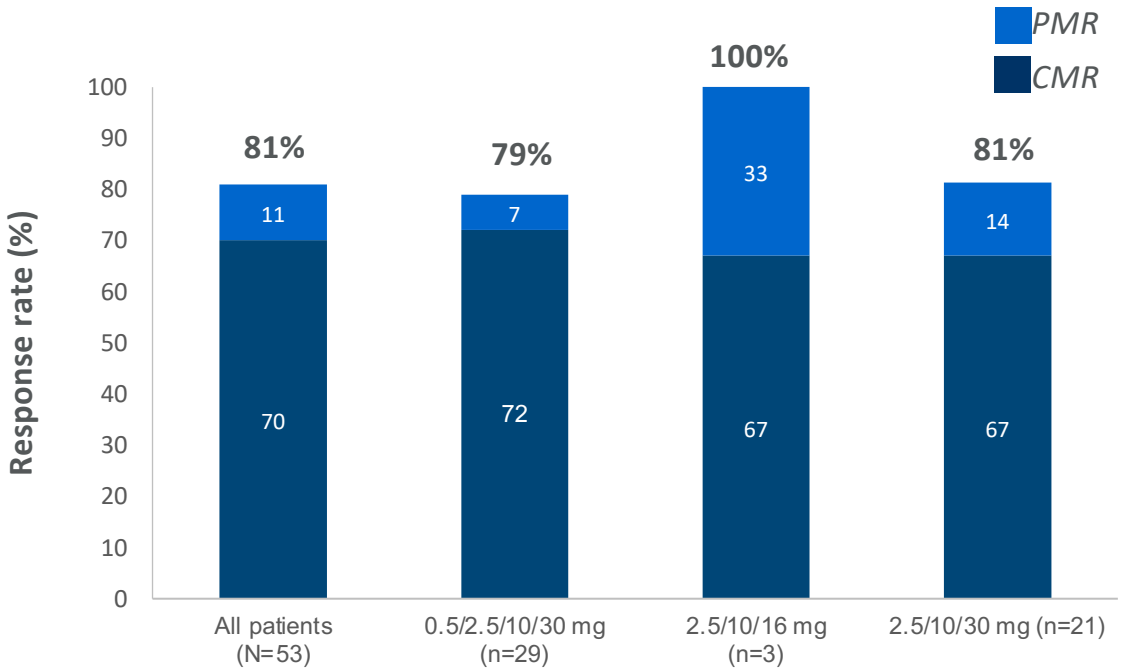
Most patients had heavily pretreated R/R FL and/or characteristics commonly associated with a poor prognosis

*Refractory to prior anti-CD20 antibodies and alkylating agents. CAR-T=chimeric antigen receptor T cell; FLIPI=Follicular Lymphoma International Prognostic Index; Mono=monotherapy; PI3K=phosphoinositide 3-kinase; POD24=progression of disease within 24 months of frontline treatment.

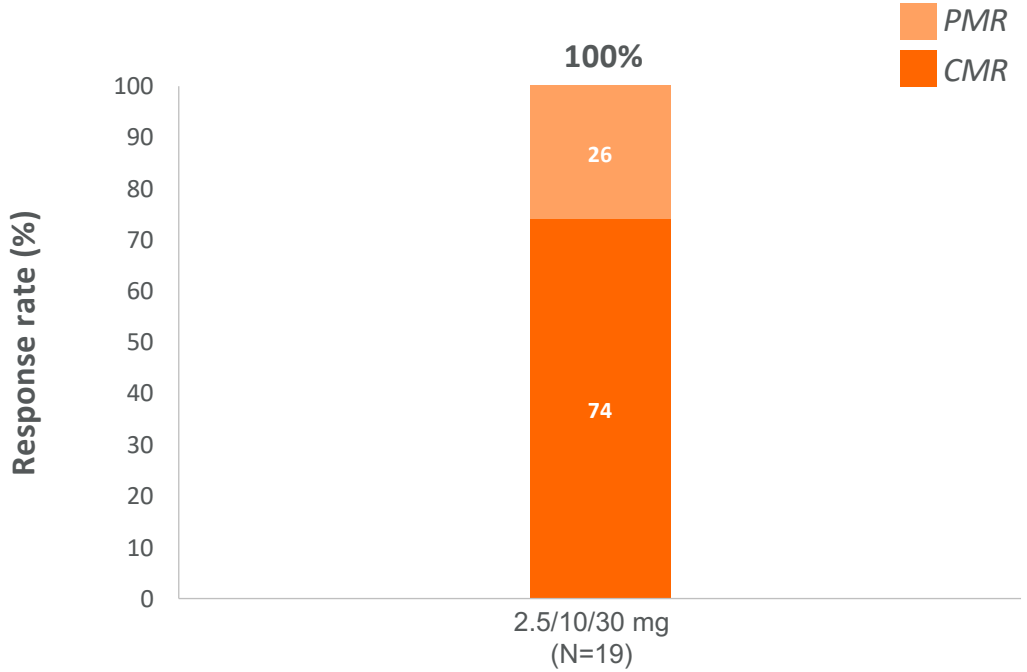
Morschhauser, Franck. ASH 2021

Response rates in R/R FL

Glofitamab monotherapy*



Glofitamab in combination with obinutuzumab



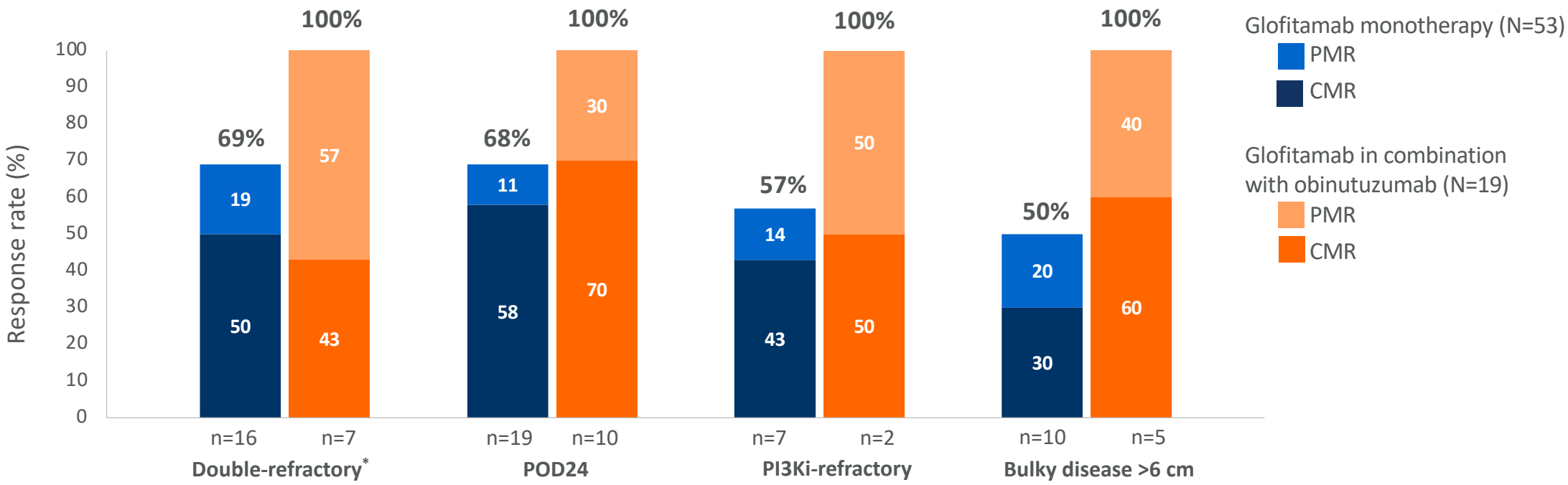
Glofitamab as monotherapy and in combination with obinutuzumab resulted in high response rates

*Data cut-off: May 18, 2021. Best overall response. Secondary efficacy population includes all patients who had a response assessment performed (investigator assessed), or who were still on treatment at the time of their first scheduled response assessment (Lugano 2014 criteria[1]). CMR=complete metabolic response; PMR=partial metabolic response.

1. Cheson BD, et al. J Clin Oncol 2014;32(27):3059–3067.

Response rates in high-risk subgroups

Glofitamab as monotherapy or in combination with obinutuzumab



High and consistent response rates in high-risk patient population

*Patients refractory to anti-CD20 antibodies and alkylating agents.

Cytokine release syndrome

N (%) of patients with ≥1 AE unless stated	Glofitamab monotherapy cohorts		Glofitamab + obinutuzumab cohort (N=19)
	Glofitamab SUD cohorts, 2.5/10/16 mg and 2.5/10/30 mg (N=24)‡	Glofitamab extended SUD cohort, 0.5/2.5/10/30 mg (N=29)	
Any CRS	19 (79.2)	16 (55.2)	15 (78.9)
Grade 1	15 (62.5)	10 (34.5)	10 (52.6)
Grade 2	3 (12.5)	6 (20.7)	5 (26.3)
Grade 3	1 (4.2)†	0	0
Grade ≥4	0	0	0
Serious AE of CRS (any grade)	12 (50)	9 (31.0)	5 (26.3)
Tocilizumab use in patients with CRS	2 (8.3)	6 (20.7)	5 (26.3)

Most CRS events were low grade and no meaningful difference in CRS was observed across glofitamab dosing regimens

*By ASTCT criteria[1]; †One patient in the 2.5/10/16 mg cohort had a Grade 3 CRS event; ‡One pt had not received glofitamab 2.5 mg at CCOD. SUD=step-up dosing.

1. Lee DW, et al. Biol Blood Marrow Transplant 2019;25(4):625–638.

Questions?

RTP
RESEARCH
TO PRACTICE

ELM-2: Baseline Characteristics

Characteristic	Odronextamab (N = 131)
Median age, yr (range)	61 (22-84)
▪ ≥65 yr, %	38.9
Male, %	53.4
ECOG PS 0/1/2, %	51.1/48.1/ 0.8
Ann Arbor stage I-II/III-IV, %	15.3/84.7
FLIPI risk score 0-1/2/3-5, %	14.5/26.7/58.8
Bulky disease per investigator, %	13.7

Characteristic	Odronextamab (N = 131)
Median prior lines of therapy, n (range)	3.0 (2-13)
▪ Prior ASCT, %	30.5
▪ Prior PI3K inhibitor, %	13.7
▪ Prior lenalidomide + rituximab, %	13.7
Refractory to, %	
▪ Last line of therapy	71.0
▪ Anti-CD20 antibody	74.8
▪ Both alkylator and anti-CD20 antibody	43.5
POD24, %	48.1

Kim. ASH 2022. Abstr 949.

ELM-2 Update: Odronextamab Efficacy With Extended Follow-up (ASH 2023)

Best Overall Response	ICR (n = 128 efficacy evaluable)
ORR, %	80
▪ CR	72
Median PFS, mo (95% CI)	20.7 (16.7-26.5)
Median OS, mo	NR
▪ 3-yr OS, %	63

Median follow-up: 26.6 mo.

Villasboas. ASH 2023. Abstr 3041.

ELM-2: Cytokine-Release Syndrome

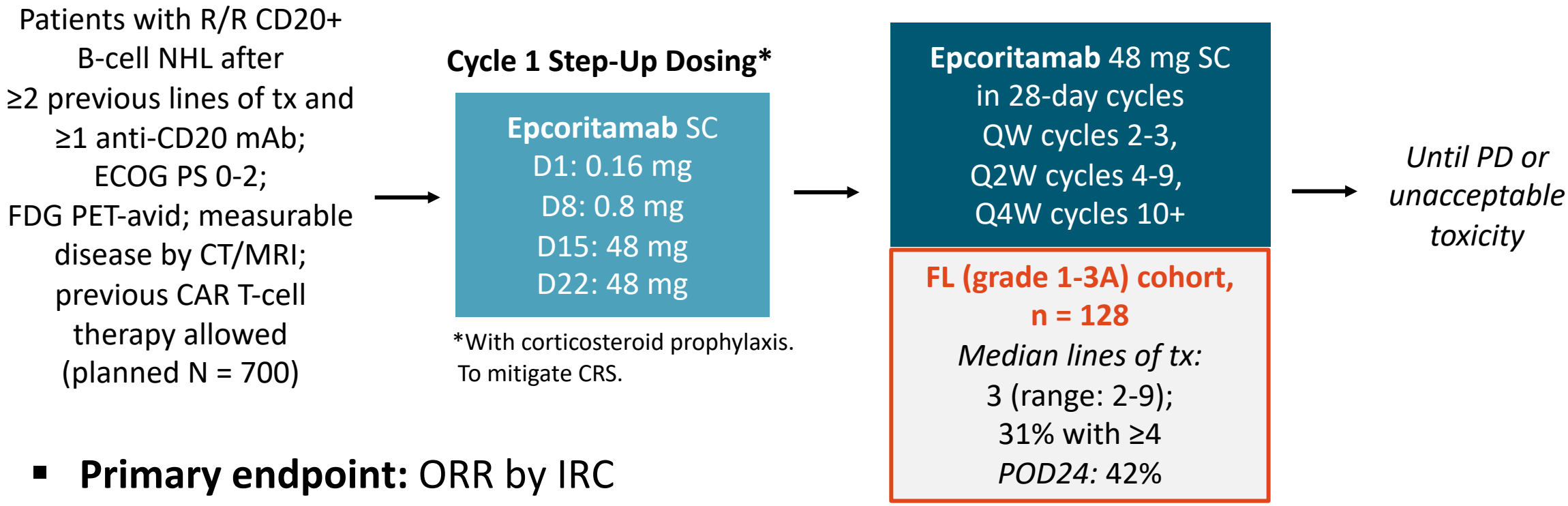
CRS Parameter, n (%)	1/20-mg Step-Up Regimen (n = 68)	0.7/4/20-mg Step-Up Regimen (n = 63)
Any-grade CRS	38 (55.9)	36 (57.1)
▪ Grade 1	22 (32.4)	28 (44.4)
▪ Grade 2	12 (17.6)	7 (11.1)
▪ Grade 3	4 (5.9)	1 (1.6)
▪ Grade 4	0	0
▪ Grade 5	0	0
CRS management		
▪ Corticosteroids	11 (16.2)	17 (27.0)
▪ Tocilizumab	9 (13.2)	12 (19.0)
▪ Vasopressors	4 (5.9)	1 (1.6)

- CRS in ~50% of patients
  - Mostly grade 1, no grade ≥4
- Incidence of grade 2/3 CRS reduced with 0.7/4/20-mg step-up regimen
  - Only 1 case of grade 3 CRS
- All CRS events resolved
  - Median time to resolution: 2 days (range: 1-51)
  - No patients needed mechanical ventilation or ICU admission

Kim. ASH 2022. Abstr 949.

EPCORE NHL-1: Epcoritamab in R/R B-Cell NHL

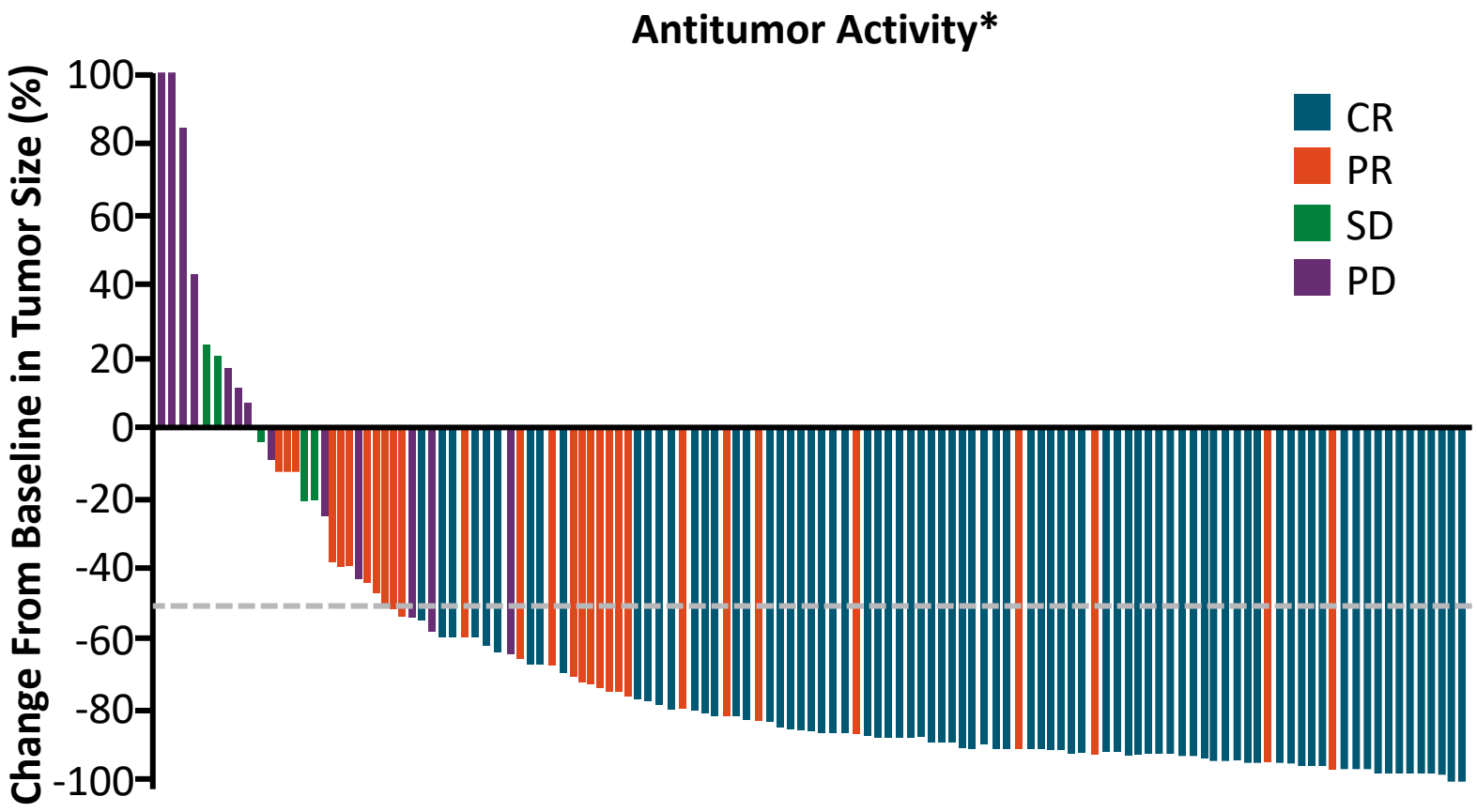
- Phase I/II open-label, dose escalation/expansion study



- **Primary endpoint:** ORR by IRC
- **Secondary endpoints:** DoR, TTR, PFS, OS, CR rate, safety

Linton. ASH 2023. Abstr 1655. NCT03625037.

EPCORE NHL-1: Outcomes With Epcoritamab in R/R FL



*n = 2 > 100% change from BL. n = 7 not evaluable.

- ORR: 82%; CR: 63%
- Median PFS: 15.4 mo
- Median OS: NR
- CRS
  - Any grade: 66%
  - Grade 1: 40%
  - Grade 2: 25%
  - Grade 3: 2%
- ICANS in 8 patients

Median follow-up: 17.4 mo.

Linton. ASH 2023. Abstr 1655.

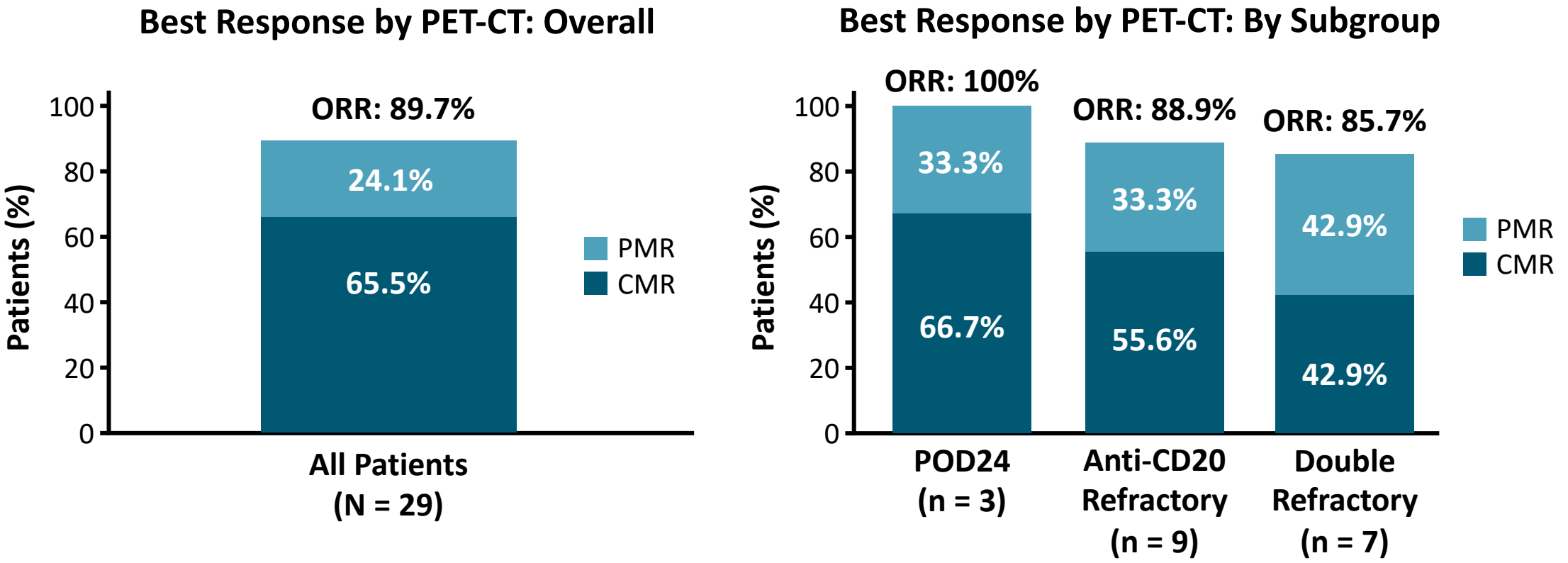
Epcoritamab + R^2 in 1L FL

- Arm 6: ORR 95%, CR 85%

Arm 6 (Epcoritamab + R^2 in 1L FL) N=41	At 18 mo, %[a]
Responders remaining in response	86
Pts with CR remaining in CR	93
Pts remaining progression free	89
Pts remaining alive	90

Leslie, Lori: J Clin Oncol 42, 2024 (suppl 16; abstr 7014). Leslie Lori: ASCO 2024; Abstract 7014.

Phase Ib/II Study: Response With Mosunetuzumab + Lenalidomide in R/R FL



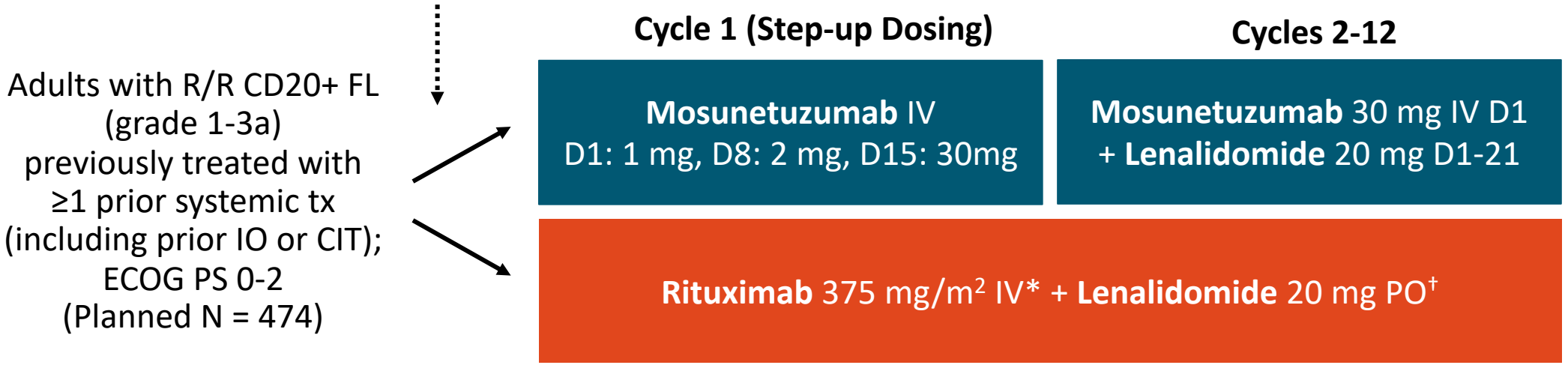
- Median time to first/best response: 2.5 mo (range: 1.4-5.3)/2.5 mo (range: 1.4-10.7)
- High ORR and CMR rate in overall population, including those with high-risk disease

Morschhauser. ASH 2021. Abstr 129. (Update: Morschhauser. ASH 2023. Abstr 605.)

CELESTIMO: Mosunetuzumab + Lenalidomide vs R^2 in R/R FL

- Multicenter, open-label, randomized phase III trial

Stratified by POD24 (yes v no), prior tx lines (1 v ≥2), refractory to anti-CD20 (yes v no)



28-day cycles. *D1, D8, D15, D22 in cycle 1. D1 in cycles 3, 5, 7, 9, 11. †Day 1-21 in cycles 1-12.

- **Primary endpoint:** PFS by IRC
- **Secondary endpoints:** PFS by inv, ORR, CR, DoR, OS, safety, PRO

Nastoupil. ASCO 2022. Abstr TPS7588. NCT04712097.

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Tolerability and Other Practical Considerations with the Use of Bispecific Antibody Therapy

Joshua Brody, MD

Director, Lymphoma Immunotherapy Program

Icahn School of Medicine at Mount Sinai

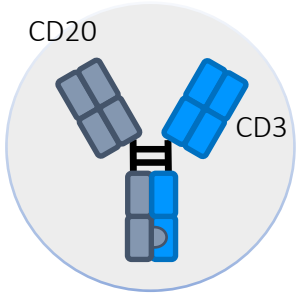
Hess Center for Science and Medicine

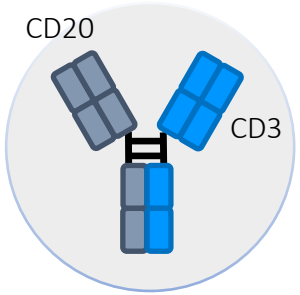
New York, NY

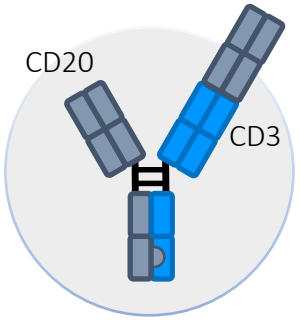
Comparison of CD20 × CD3 Bispecifics in Lymphoma

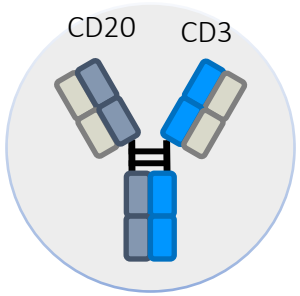
Bispecific Ab:

- CD20
- CD3









mAb	Mosunetuzumab	Epcoritamab	Glofitamab	Odronextamab
Status (as of Mar 2024):	Approved for FL (third line)	Approved for DLBCL* (third line)	Approved for DLBCL* (third line)	Investigational
Format:	IgG1	IgG1	IgG1	IgG4
Technology:	Knobs-into-holes (different Fabs)	Controlled Fab-arm exchange	Head-to-tail fusion	Heavy chains with different affinity
CD20:CD3 ratio:	1:1	1:1	2:1	1:1

- Fab, fragment antigen binding; IgG, immunoglobulin G.
- Falchi L, et al. Blood. 2023;141:467-480; NCCN guidelines. Classic follicular lymphoma v1.2024; Accessed March 2024. *Also includes transformed low-grade lymphoma and high-grade B-cell lymphoma.

Bispecific Antibodies: Key Differences from CAR T-Cell

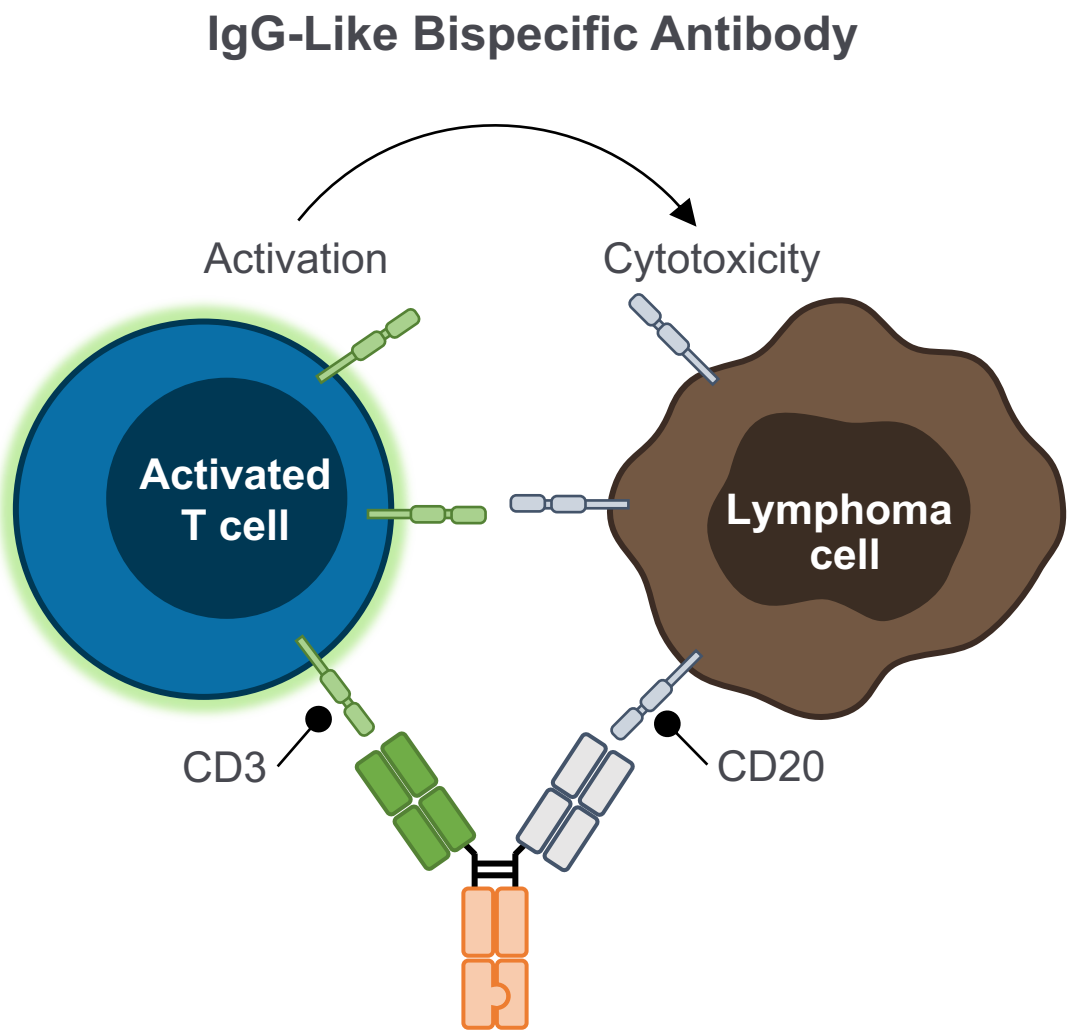
Bispecific Antibody

- No bridging therapy needed
- Short interval between decision and treatment “Brain to Vein”
- Off-the-shelf therapy
- Evolving to be either primarily or totally outpatient
- Prepare patient to possibly spend the night close to the clinic after early doses

CAR T-Cell

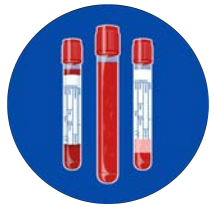
- Bridging therapy usually needed
- 1 to 3 months preparation time
  - Many delays possible
- Hospitalization needed
  - Need advance planning

More Readily Available Than CAR T-Cell Therapy, Bispecific Antibodies Can Help Improve Access to Care



- Bivalent IgG-like, full-length Ab co-targeting CD20 (B-cells) and CD3 (pan-T-cell marker)
- Off-the-shelf availability
- Target different epitopes on CD20 (potential for co-administration with anti-CD20 antibodies)
- Fc mutations to avoid killing of anti-tumor T-cells
- Preserved binding for prolonged half-life
- Share pharmacokinetic properties with mAbs

Bispecific Antibodies: Pretreatment Preparation



Recommended Baseline Labs: CBC, CMP, LDH

Unclear Value: Inflammation markers (cytokine level, ferritin, C-reactive protein)

Baseline cardiac ultrasound or MUGA is not required

Only if clinically indicated. May affect decisions on treatment location.

Premedications

- Follow manufacturer labeling
- Dexamethasone is preferred
  - Potential lower incidence of CRS
- Before and after administration can be stopped after cycle 2 is complete if no CRS occurred

Outpatient Considerations:

- Identify closest intensive care unit
- At least 2 doses of tocilizumab available at all times

Bispecific Antibodies in Lymphoma: Dosing Details

	Mosunetuzumab	Epcoritamab	Glofitamab
Route	**IV**	**SC**	**IV**
Hospitalization	**Optional**	**C1D15: 24-h admission**	**C1D8: 24-h admission (after infusion complete)**
Dosing schedule	**C1: days 1, 8, 15; C2+: day 1, every 21 d, for up to 8 cycles in CR or up to 17 cycles for PR or SD**	**C1-3: days 1, 8 ,15, and 22; C4-9: days 1 and 15; C10+: day 1, every 28 d until progression**	**C1: obin, day 1; glofit, days 8 and 15; C2-12: day 1, every 21 d**
Step-up Dosing	**C1D1: 1 mg C1D8: 2 mg C1D15: 60 mg C2D1: 60 mg C3+D1: 30 mg**	**C1D1: 0.16 mg C1D8: 0.8 mg C1D15: 48 mg C1D22: 48 mg C2D1+: 48mg**	**C1D1: obin 1000 mg C1D8: 2.5 mg C1D15: 10 mg C2D1+: 30 mg**
Median Duration of CRS	**3 d (1-29 d)**	**2 d (1-27 d)**	**30.5 h (0.5-317 h)**

- Jennifer L. Crombie, et al. *Blood* 2024; 143 (16): 1565–1575

Bispecific Antibodies: Inpatient vs Outpatient Dosing Details

	Initial Dosing	Chronic Dosing
Mosunetuzumab[a]	**Cycle 1** Day 1: 1 mg IV over 4 h Day 8: 2 mg IV over 4 h Day 15: 60 mg IV over 4 h	**Cycle 2** Day 1: 60 mg IV over 2 h (if infusion from cycle 1 well tolerated) **Cycles 3 and beyond, up to 17 cycles** Day 1: **30** mg IV over 2 h (if infusion from cycle 1 well tolerated)
Epcoritamab[b] (investigational in FL)	**Cycle 1** Day 1: 0.16 mg SC Day 8: 0.8 mg SC **Day 15: 48 mg SC- 24 h admit** Day 22: 48 mg SC **Cycles 2 and 3** Days 1, 8, 15, 22: 48 mg SC	**Cycles 4 to 9** Day 1: 48 mg SC Day 15: 48 mg SC **Cycle 10 and beyond, until progression or intolerance** Day 1: 48 mg SC every 28 days
Glofitamab[c] Infusion time may be extended depending on tolerance of previous dose (investigational in FL)	**Cycle 1** Day 1: Obinutuzumab 1 gm IV **Day 8: 2.5 mg IV over 4 h, 24 admit** Day 15: 10 mg IV over 4 h	**Cycles 2 and beyond, up to 12 cycles** Cycle 2: **30** mg IV over 4 h (may be extended up to 8 hours) Cycles 3 to 12: 30 mg over 2 h

a. Mosunetuzumab [PI]. Approved 2022. Revised December 2022; b. Epcoritamab [PI]. Approved 2023. Revised May 2023; c. Glofitamab [PI]. Approved 2023. Revised June 2023.

Bispecific Antibodies: Side-Effect Management

Online References and Resources

Developing class of medications

Guidance is variable on AE management

Individual agent manufacturer labeling; Clinical trial data

Consensus recommendations on management of toxicities associated with bispecifics[a]

Published April 2024

Association for Community Cancer Centers "Bispecific Antibodies Checklist for Community Providers"[b]

NCCN: Overview of Lymphocyte Engager-Related Toxicities[c]

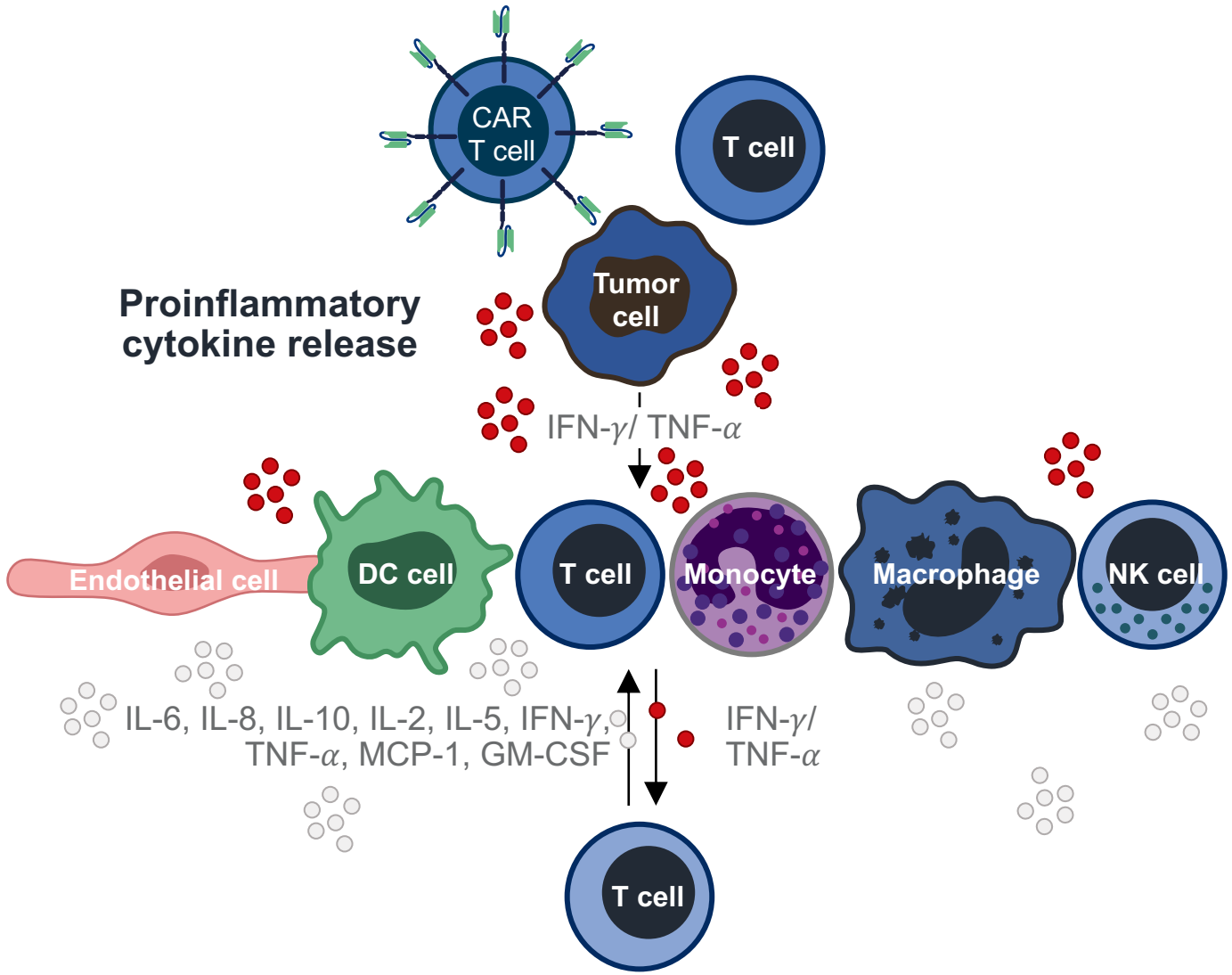
American Society for Transplantation and Cellular Therapy (ASTCT)[d]

Consensus grading for CRS and neurologic toxicity associated with immune effector cells

a. Crombie JL, et al. Blood. 2024;143:1565-1575; b. Association of Cancer Care Centers. 2022. Accessed May 2024. https://www.accc-cancer.org/docs/projects/bispecific-antibodies/checklist-for-bispecific-antibodies-jan-2022.pdf; c. NCCN. Management of immunotherapy-related toxicities. v1.2024. Accessed May 2024. https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf; d. Lee DW,et al. Biol Blood Marrow Transplant. 2019;25:625-638.

Cytokine Release Syndrome

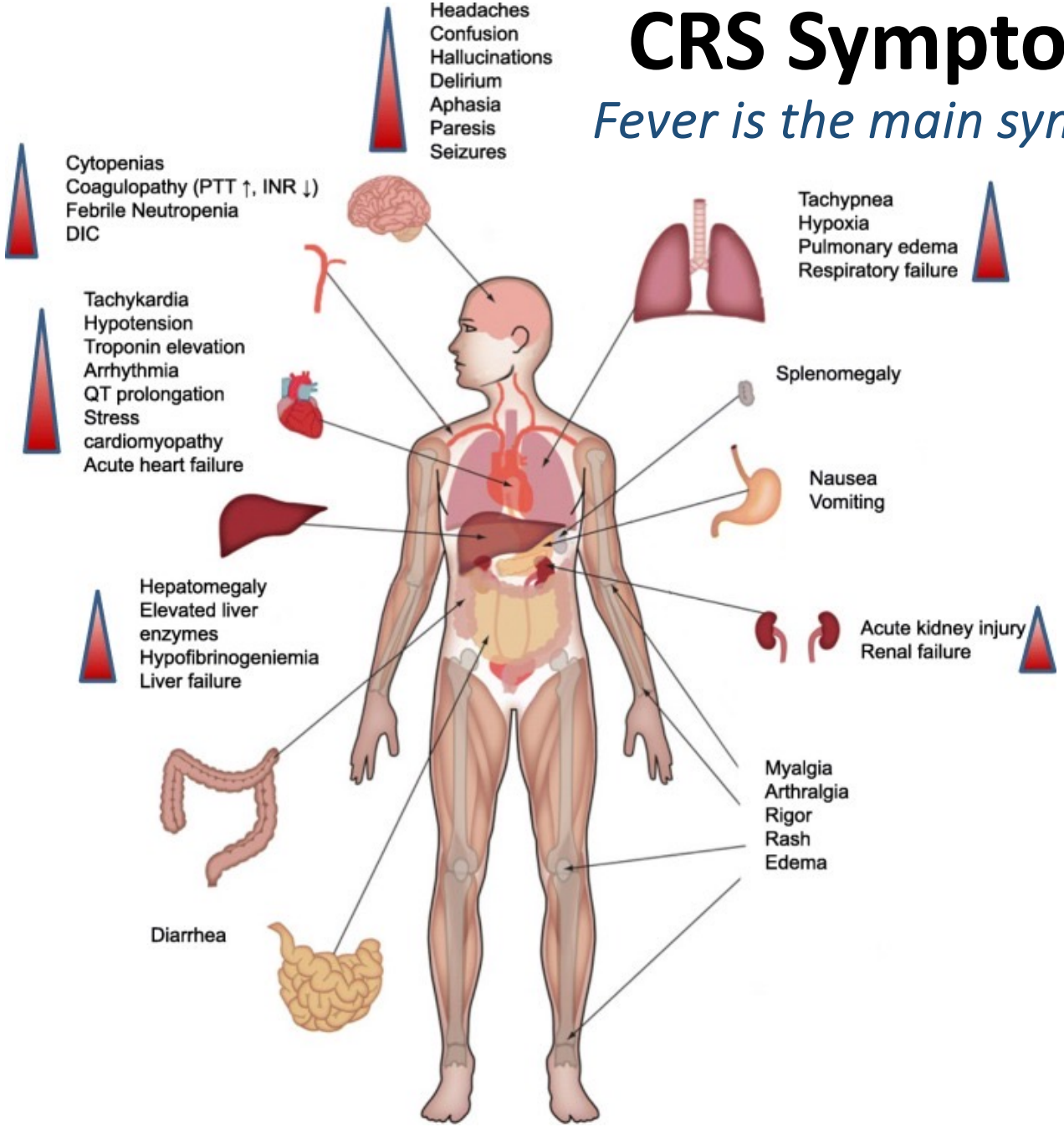
- Higher disease burden is associated with more severe CRS
- Variable onset: can occur within hours of the infusion or up to 2 weeks later
- Subsequent episodes may occur; subsequent episodes after full dose is achieved is typically less severe, but patients and caregivers should be instructed to report symptoms



1. Cosenza M, et al. Int J Mol Sci. 2021;22:7652.

CRS Symptoms

Fever is the main symptom



Level of Severity

Less severe

More severe

Nonspecific Symptoms:

- **Fever**
- Fatigue
- Anorexia

Shimabukuro-Vornhagen A, et al. J Immunother Cancer. 2018;6:56.

CRS: ASTCT Grading System and Presentation

CRS typically manifests with constitutional symptoms (fever, flulike symptoms) and can progress to hypotension, hypoxia, multiorgan failure, and HLH/MAS

ASTCT Parameter for CRS	Grade 1	Grade 2	Grade 3	Grade 4
Fever	Temp ≥ 38 °C (100.4 °F)	Temp ≥ 38 °C (100.4 °F)	Temp ≥ 38 °C (100.4 °F)	Temp ≥ 38 °C (100.4 °F)
with				
Hypotension	None	Not requiring vasopressors	Requiring a vasopressor with or without vasopressin	Requiring multiple vasopressors (excluding vasopressin)
and/or				
Hypoxia	None	Requiring low-flow nasal cannula or blow-by	Requiring high-flow nasal cannula, facemask, nonrebreather mask, or Venturi mask	Requiring positive pressure (eg CPAP, BiPAP, intubation, and mechanical ventilation)

Lee D, et al. Biol Blood Marrow Transplant. 2019;25:625-638.

CRS Management

Grade	Management	Notes
Grade 1	Fluid hydration 1-3L IV or PO as feasible and anti-pyretics (ibuprofen 800 mg or APAP 1000 mg)	▪ Patients with early fever (within 72 h) or significant comorbidities can consider early tocilizumab
Grade 2	Tocilizumab 8 mg/kg (Consider alternative agents after 2 doses) *No more than 3 doses in a 24-h period or 4 doses in total	▪ For patients with early fevers or significant comorbidities, consider early dexamethasone (10 mg x 1) ▪ Patients not responding to tocilizumab should consider initiation of dexamethasone (10 mg every 12-24 h)
Grade 3	Tocilizumab 8 mg/kg (Consider alternative agents after 2 doses) *No more than 3 doses in a 24-h period or 4 doses in total	▪ Dexamethasone (10 mg every 12-24 h) with initial tocilizumab ▪ For patients with disease refractory to dexamethasone, can increase to 20 mg every 6-12 h
Grade 4	Tocilizumab 8 mg/kg (Consider alternative agents after 2 doses) *No more than 3 doses in a 24-h period or 4 doses in total	▪ In dexamethasone-refractory patients, consider high-dose methylprednisolone 2 mg/kg x 12 h ▪ For patients with refractory disease, consider alternative therapies

Always look for infections and treat infectious complications, especially in patients with neutropenia

Lee D, et al. Biol Blood Marrow Transplant. 2019;25:625-638.

Similar CRS Rates With Bispecific Antibodies

Mosunetuzumab[a]

▪ Grade 1: 26% ▪ Grade 2: 17%	▪ Grade 3/4: 2%

Epcoritamab[b]

▪ Grade 1: 34% ▪ Grade 2: 15%	▪ Grade 3: 2.5% (no grade 4)

Glofitamab[c]

▪ Grade 1: 47% ▪ Grade 2: 12%	▪ Grade 3/4: 4%

Odronextamab[d]

▪ Grade 1: 35% to 39% ▪ Grade 2: 13% (DLBCL)	▪ Grade 3/4: 0%

In general, CRS with bispecific antibodies is **less frequent** and **less severe** than observed with CAR T-cell therapy

a. Budde LE, et al. Lancet Oncol. 2022;23:1055-1065; b. Thieblemont C, et al. J Clin Oncol. 2023;41:2238-2247; c. Dickinson MJ, et al. N Engl J Med. 2022;387:2220-2231; d. Crombie JL, et al. Blood. 2024;143(16):1565-1575.

Questions?

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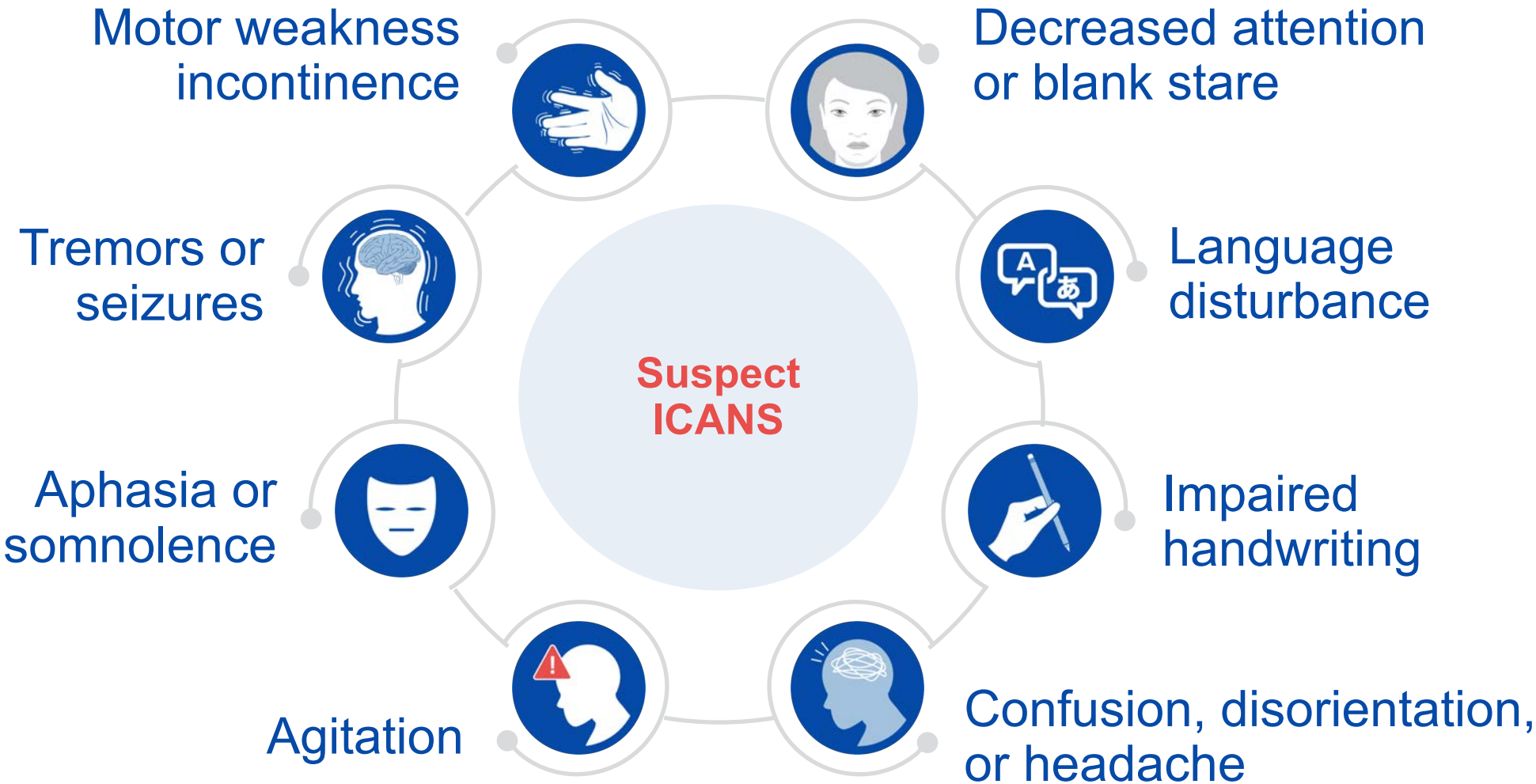
Incidence of Neurotoxicity With Bispecific Antibodies

Bispecific	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Mosunetuzumab	3%		0	0	0
Epcoritamab	4.5%	1.3%	0	0	0.6
Glofitamab	5%		3%		0
Odronextamab	4% (DLBCL)		0	0	0

Crombie JL, et al. Blood. 2024;143 1565-1575.

Bispecific Antibodies: ICANS Symptoms



Lee D, et al. Biol Blood Marrow Transplant. 2019;25:625-638.

ICANS: ASTCT Guidelines for Grading

Neurotoxicity Domain	Grade 1	Grade 2	Grade 3	Grade 4
ICE score*	7 to 9	3 to 6	0 to 2	0 (patient is unarousable)
Depressed level of consciousness	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse; stupor or coma
Seizure	N/A	N/A	Any clinical seizure focal or generalized that resolves rapidly or nonconvulsive seizures on EEG that resolve with intervention	Life-threatening prolonged seizure (>5 min) or repetitive clinical or electrical seizures without return to baseline in between
Motor findings	N/A	N/A	N/A	Deep focal motor weakness such as hemiparesis or paraparesis
Elevated intracranial pressure or cerebral edema	N/A	N/A	Focal or local edema on neuroimaging	Diffuse cerebral edema on neuroimaging; decerebrate or decorticate posturing; or cranial nerve VI palsy; or papilledema; or Cushing's triad

Lee D, et al. Biol Blood Marrow Transplant. 2019;25:625-638.

ICANS: Grading and Management Potential Treatment Parameters

Neurotoxicity Grade	Tocilizumab	Steroids
Grade 1: ICE score 7 to 9, mild drowsiness, confusion, limiting ADLs, dysphagia	Concurrent CRS: Manage by grade No CRS: Do not give tocilizumab	Dexamethasone 10 mg once daily
Grade 2: ICE score 3 to 6, moderate drowsiness, confusion, disorientation, limiting ADLs, dysphagia limiting communication	Concurrent CRS: Manage by grade No CRS: Do not give tocilizumab	Dexamethasone 10 mg × 4/d
Grade 3: ICE score 0 to 2, awakens to tactile stimuli only, focal/rapid seizure	Concurrent CRS: Manage by grade No CRS: Do not give tocilizumab	Methylprednisolone 1 g IV daily
Grade 4: ICE score 0, requires vigorous stimuli to arouse, coma, prolonged seizure >5 min	Concurrent CRS: Manage by grade No CRS: Do not give tocilizumab	Methylprednisolone 1 g IV × 4/d

Lee D, et al. Biol Blood Marrow Transplant. 2019;25:625-638.

Lymphoma bispecifics vs Myeloma bispecifics Adverse events

Lymphoma bispecifics are different from myeloma bispecifics

Agent	Grade ≥3 infections	Grade 5 infections	Grade ≥3 CRS	Grade ≥3 neutropenia
BCMA target[a]				
Linvoseltamab	29%	4%	1%	23%
Elranatamab	32%	5%	0%	48%
Teclistamab	45%	12%	1%	64%
Non-BCMA target[a] (talquetamab)	18%	0%	3%	37%
Combination BCMA + GPRC5D[a] (teclistamab + talquetamab)	49%	--	3%	76%
Mosunetuzumab[b]	14%	--	1%	27%
Epcoritamab[c]	14%	--	4%	23%

- a. Gemma Reynolds, et al. Blood Adv. 2023;7:5898-5903; b. Budde LE, et al. Lancet Oncol. 2022;23:1055-1065; c. Thieblemont, et al. J Clin Oncol. 2023 20;41:2238-2247.

Investigator Perspectives on Available Research and Challenging Questions in Melanoma and Nonmelanoma Skin Cancers: A Post-ASCO 2024 Annual Review

Tuesday, June 11, 2024
5:00 PM – 6:00 PM ET

Faculty

Nikhil I Khushalani, MD
Jason J Luke, MD

Moderator

Neil Love, MD

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