

19th International Ultmann Chicago Lymphoma Symposium

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SCIENCES

Bispecific Antibodies

Rajat Bannerji MD PhD

Professor of Medicine

Rutgers Cancer Institute of New Jersey

Rutgers Robert Wood Johnson Medical School



Disclosures

- Research Funding: AbbVie, Roche, Genentech, Regeneron, Merck & Co., Pharmacyclics (an AbbVie Company)
- Other: Spouse is an employee of Sanofi-Pasteur
- The data described in this presentation will report on the investigational use of a number of agents, including those which have not been approved by any health authority

Bispecific Antibodies in Development for B-NHL

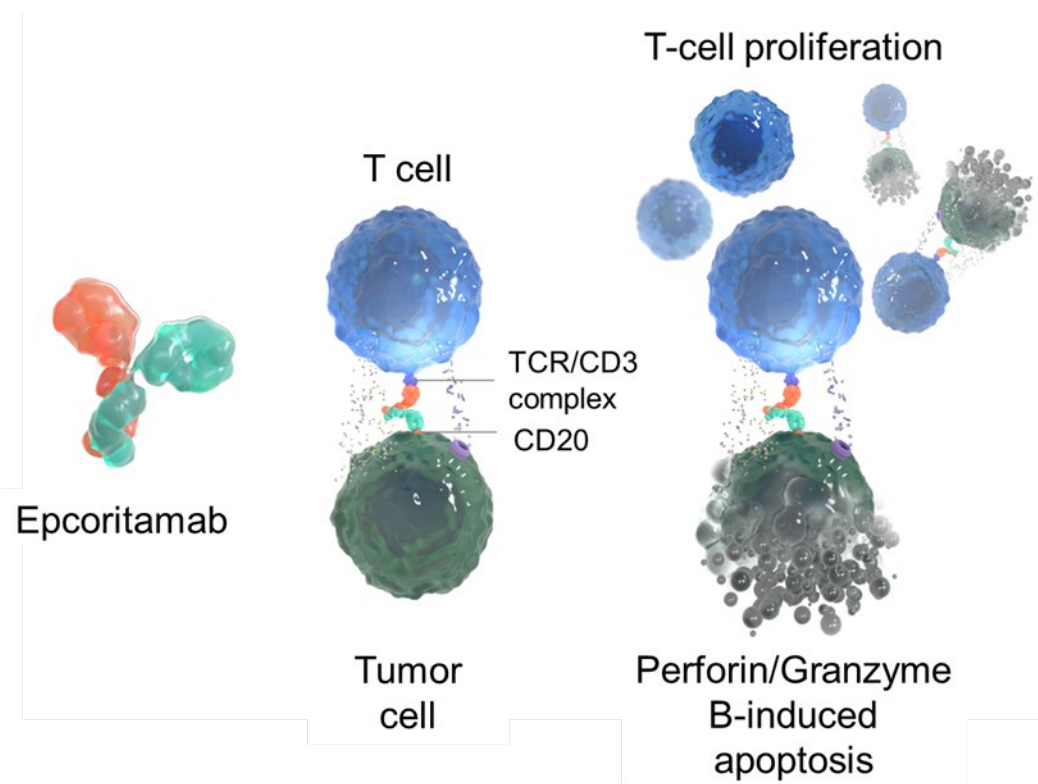
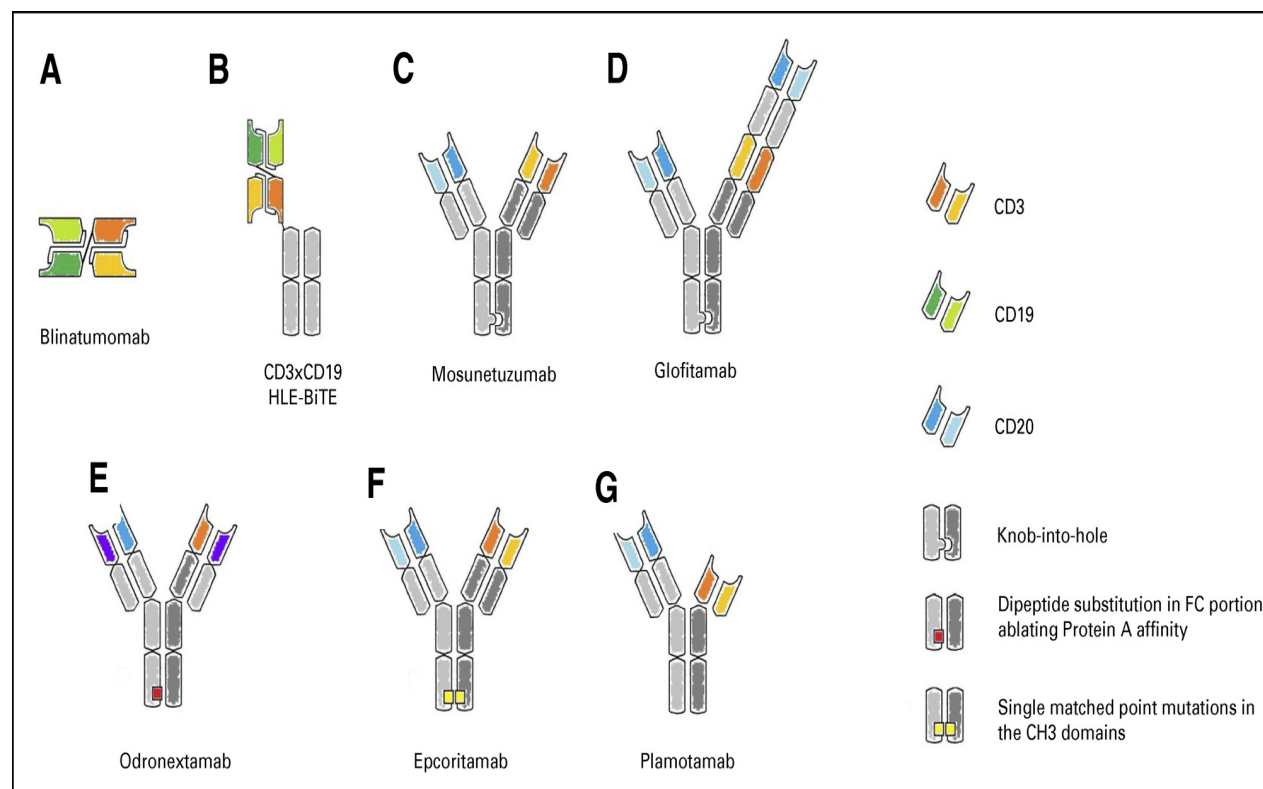


FIG 1. Main T cell–redirecting bispecific antibodies in clinical development. (A) Blinatumomab, the first bispecific T-cell engager (BiTE), is a tandem single-chain variable fragment (scFv). (B) To increase the half-life, the CD3xCD20 BiTE it is linked to a silent fragment crystallizable region (constant; FC) portion to form the half-life extended (HLE)-BiTE. (C, D) The knob-into-hole technology facilitates the correct pairing of FC portion of mosunetuzumab and glofitamab; this latter is characterized also by an asymmetric 2:1 format that incorporates bivalent binding to CD20 and monovalent binding to CD3 (CrossMAb). (E) Design of odronextamab exploits differences in the affinities of the immunoglobulin isotypes for Protein A coupled with the use of common light chain, allowing efficient large-scale purification. (F) In the Duo-Body, each parental antibody contains single matched point mutations in the constant region of the heavy chain 3 (CH3) domains, which allows the correct reassembly after in vitro separation (controlled fragment antigen-binding [Fab]-arm exchange). (G) Plamotamab uses FC domain variants that spontaneously form stable, heterodimeric bispecific antibodies allowing the use of standard antibody production methods. Different from the other molecules, the FC domain is functional.

Federico Lussana; Giuseppe Gritti; Alessandro Rambaldi; *Journal of Clinical Oncology* 2021 39:444-455.DOI: 10.1200/JCO.20.01564

Epcoritamab cartoon: Kater et al, *Blood* (2021) 138 (Supplement 1): 2627.

The Difference A Year Makes!

rapid communication Glofitamab, a Novel, Bivalent CD20-Targeting T-Cell–Engaging Bispecific Antibody, Induces Durable Complete Remissions in Relapsed or Refractory B-Cell Lymphoma: A Phase I Trial

Martin Hutchings, PhD¹; F
Anna Sureda, MD, PhD²; C
Peter N. Morcos, PharmD
Natalie Dimier, PhD¹⁴; D
Tom Moore, MD¹²; Martin

Dose escalation of subcutaneous epcoritamab in patients with relapsed or refractory B-cell non-Hodgkin lymphoma: an open-label, phase 1/2 study

Martin Hutchings, R
Anna Sureda Balari,
Tahamtan Ahmadi,

original reports Single-Agent Mosunetuzumab Shows Durable Complete Responses in Patients With Relapsed or Refractory B-Cell Lymphomas: Phase I Dose-Escalation Study

Lihua E. Budde, MD¹; Sarit
Dok Hyun Yoon, MD, PhD⁶; M
Ian W. Flinn, MD, PhD¹¹; Ma
Antonia Kwan, MBBS, PhD¹⁴
Nancy L. Bartlett, MD¹⁶

Odronextamab, a human CD20×CD3 bispecific antibody in patients with CD20-positive B-cell malignancies (ELM-1): results from the relapsed or refractory non-Hodgkin lymphoma cohort in a single-arm, multicentre, phase 1 trial

Schedule and RP2D

	Glofitamab	Epcoritamab	Mosunetuzumab	Odronextamab
Treatment schedule	IV dosing 21-day cycles Gazyva pretreatment day -7 Day 1 & 8 (C 1) Day 1 (C 2-12)	SC dosing 28-day cycles Day 1,8,15,22 (cycles 1-2) Day 1,15 (C 3-6) Day 1 from C7 onwards	IV dosing 21-day cycles Day 1, 8 & 15 (C1) Day 1 (C2-17)	IV dosing 21-day cycles Day 1,2,8,9,15,16 (C1) Day 1,8 & 15 (C2-4) Day 1 q 2 weeks maintenance
Duration of treatment	12 cycles	Until disease progression or unacceptable toxicity	8 cycles (CR) 17 cycles (PR/SD)	Until disease progression or unacceptable toxicity
Step up dosing and RP2D	2.5/10/30 mg	0.16/0.8/48 mg	1/2/60 mg C1 60 mg C2 30 mg C3-C17	0.7/4/20/80 or 160 80 mg FL 160 mg DLBCL

Adverse Events of Interest – CRS and Neurotoxicity

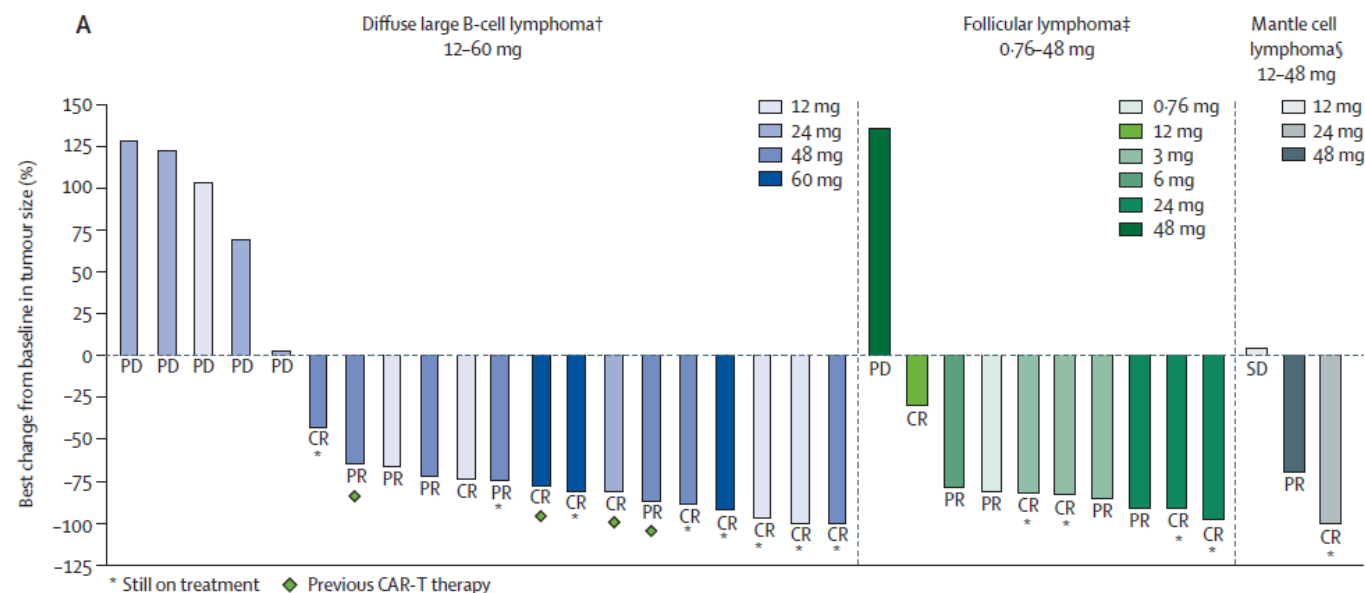
	Glofitamab	Epcoritamab	Mosunetuzumab	Odronextamab
CRS	71.4% any grade 6% \geq grade 3 at RPTD	59% grade 1-2 No grade 3-4	27.4% any grade 1% grade ≥ 3	54% any grade 7% \geq grade 3
CRS mitigation	Gpt SUD 4-hour infusion anti-histamines, acetaminophen methylprednisolone (80 mg).	Subcutaneous SUD Prednisolone 100mg Benadryl 50mg Tylenol 650- 1000mg	SUD Iv dexamethasone 20 mg or methylprednisolone 80 mg)	SUD 4-hour infusion Steroids Tylenol Benadryl
CNS toxicity	Neurologic 31.4% ICANS-like 5.7%	3% grade 1 3% grade 3	Headache 17.8% Insomnia 11.2% Dizziness 10.2% 4.1% grade 3	12% any grade 3% grade 3

Epcoritamab safety and activity

	Grade 1-2	Grade 3	Grade 4
Pyrexia*	43 (63%)	4 (6%)	0
Cytokine release syndrome	40 (59%)	0	0
Injection site reaction	32 (47%)	0	0
Fatigue	26 (38%)	4 (6%)	0
Diarrhoea	18 (26%)	0	0
Hypotension*	17 (25%)	4 (6%)	0
Dyspnoea	16 (24%)	0	1 (1%)
Tachycardia*	14 (21%)	0	0
Anaemia	7 (10%)	9 (13%)	0

*Most pyrexia, hypotension, and tachycardia events were associated with cytokine release syndrome.

Table 2: Treatment-emergent adverse events that occurred in at least 20% of the full analysis population (n=68)

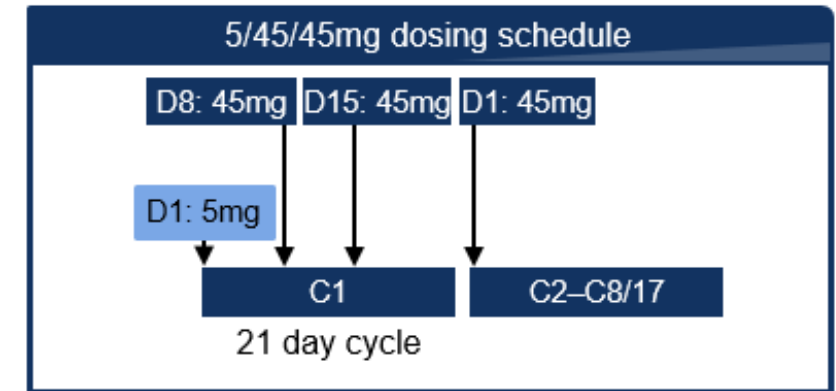
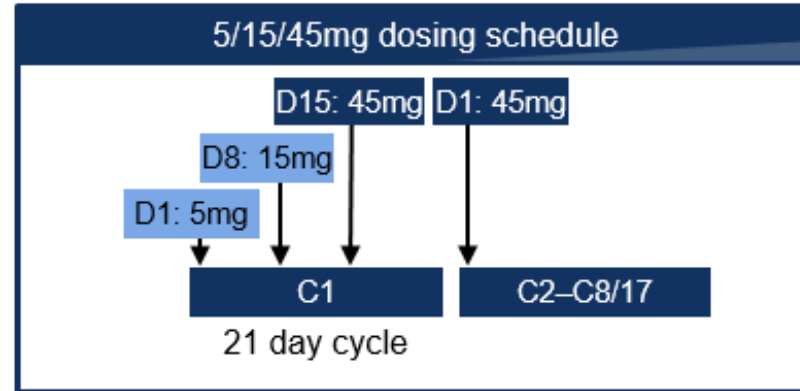


Hutchings et al, Lancet 2021; 398: 1157-69.

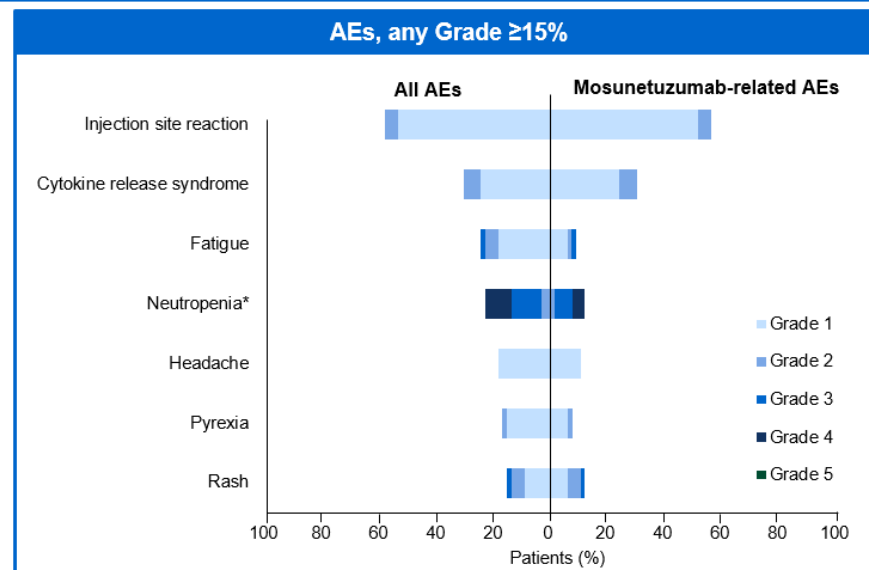
Subcutaneous Administration of Mosunetuzumab with Cycle 1 Step-Up Dosing is Tolerable and Active in Patients with Relapsed/Refractory B-Cell Non-Hodgkin Lymphoma: Initial Results from a Phase I/II Study

Mosunetuzumab administration

- Q3W SC injections for 8 cycles if in CR or 17 cycles if in PR/SD
- CRS mitigation
 - C1 step-up dosing
 - C1–2 corticosteroid pre-medication
- No mandatory hospitalization during dose expansion

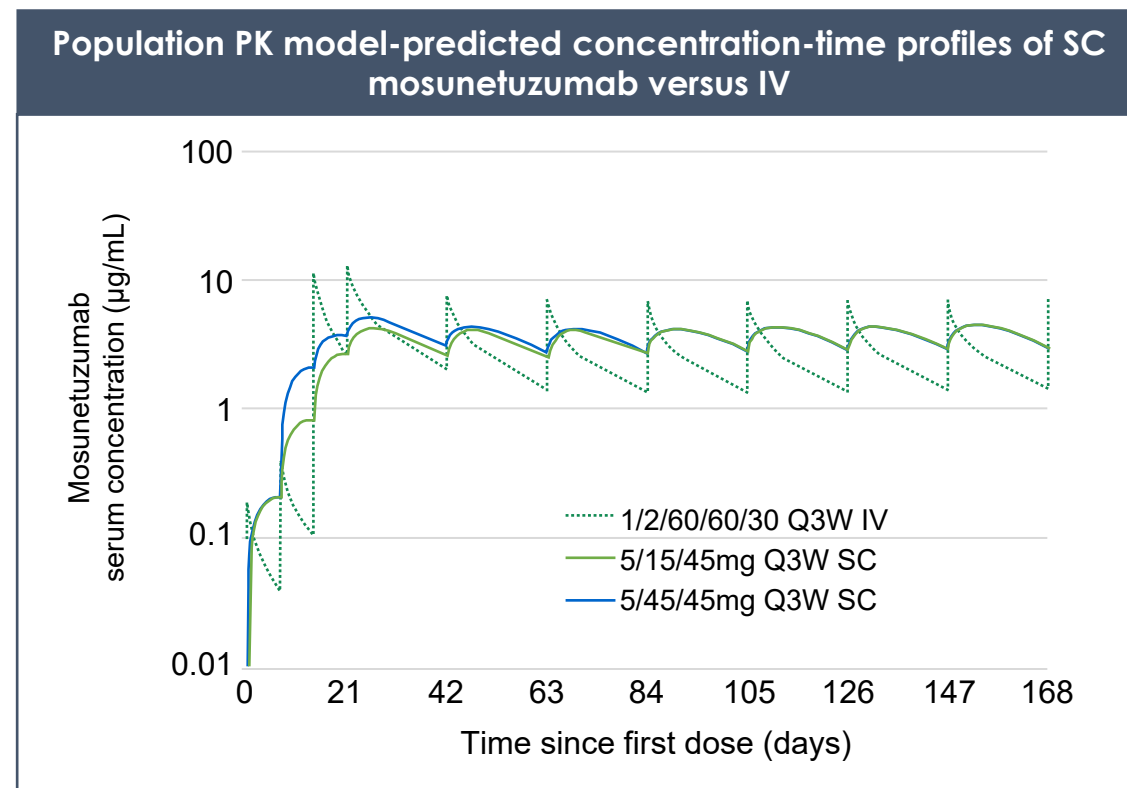
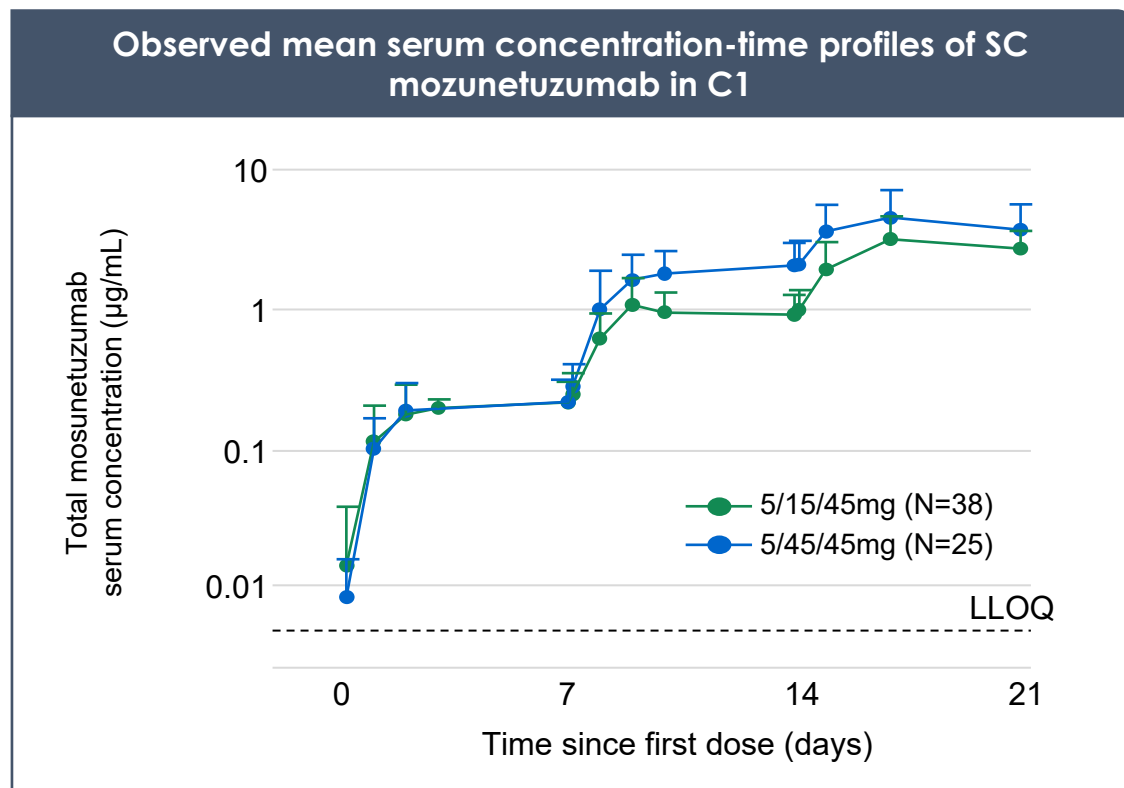


N (%) of patients with ≥1 AE	N=66
AE	64 (97.0)
Mosunetuzumab related	55 (83.3)
Gr 3–4 AE	34 (51.5)
Mosunetuzumab related	16 (24.2)
Serious AE	25 (37.9)
Mosunetuzumab related	15 (22.7)
Gr 5 (fatal) AE (excluding 3 Gr 5 events of PD)	2 (3.0) [‡]
Mosunetuzumab related	0
AE leading to mosunetuzumab discontinuation	1 (1.5) [§]
Mosunetuzumab related	0



Pharmacokinetics

- SC mosunetuzumab showed high bioavailability (>80%) and offered a favorable PK profile relative to IV with comparable exposure, reduced C_{\max} and higher C_{trough}



LLOQ, lower limit of quantification

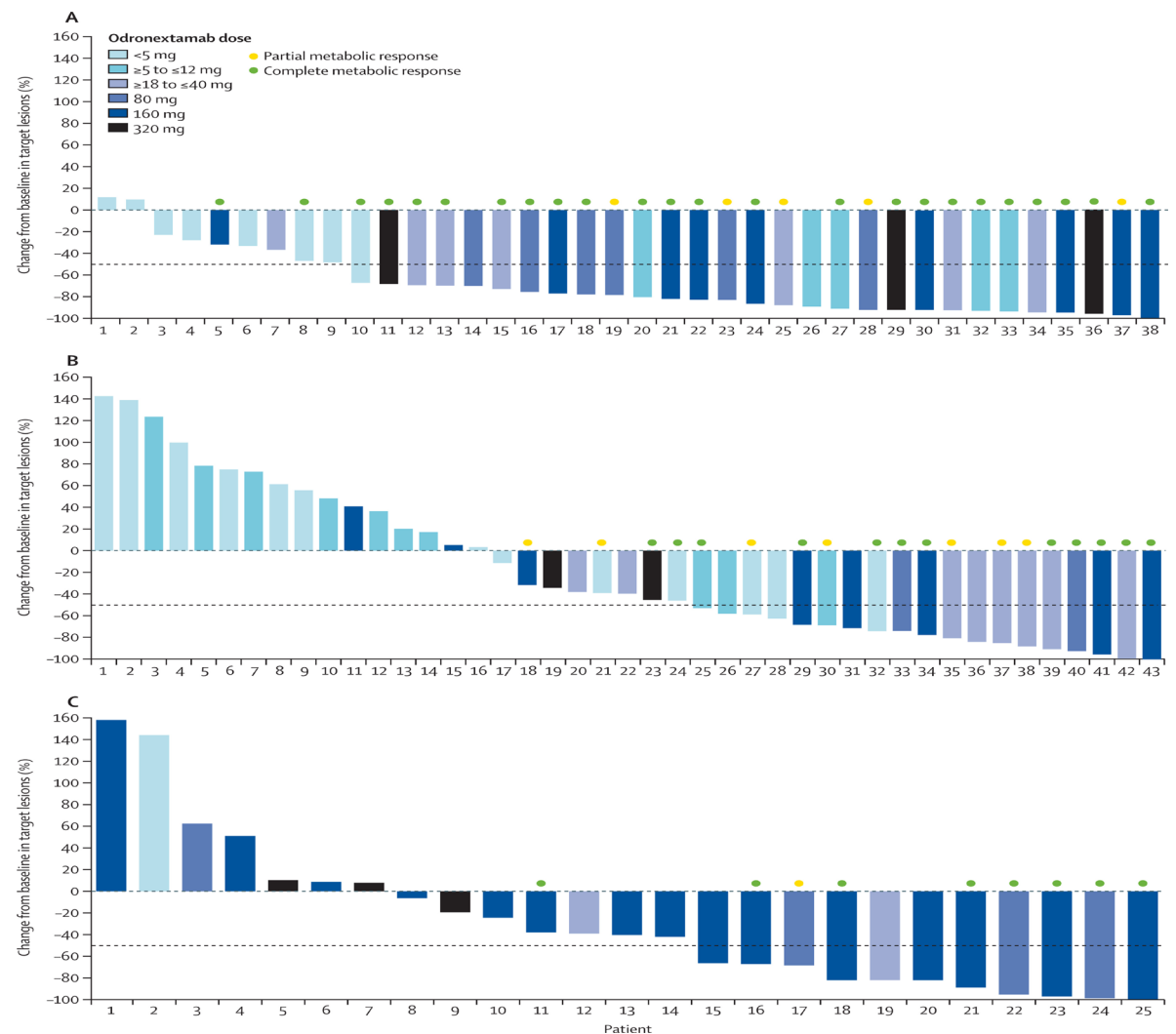
Odronextamab activity

	Relapsed or refractory follicular lymphoma grade 1-3a (n=40)	Relapsed or refractory diffuse large B-cell lymphoma without previous CART T-cell therapy (n=49)	Relapsed or refractory diffuse large B-cell lymphoma with previous CART T-cell therapy (n=33)	Mantle cell lymphoma (n=12)	Marginal zone lymphoma (n=6)	Other B-cell non-Hodgkin lymphoma (n=2)
Objective response (complete or partial)	31 (78%; 61.5-89.2)	19 (39%; 25.2-53.8)	11 (33%; 18.0-51.8)	6 (50%; 21.1-78.9)	4 (67%; 22.3-95.7)	1 (50%; 1.3-98.7)
Best overall complete tumour response	25 (63%; 45.8-77.3)	12 (24%; 13.3-38.9)	8 (24%; 11.1-42.3)	4 (33%; 9.9-65.1)	2 (33%; 4.3-77.7)	1 (50%; 1.3-98.7)
Best overall partial tumour response	6 (15%; 5.7-29.8)	7 (14%; 5.9-27.2)	3 (9%; 1.9-24.3)	2 (17%; 2.1-48.4)	2 (33%; 4.3-77.7)	0 (0.0-84.2)
Time to first response, months	1.2 (1.0-2.5)	1.4 (1.0-2.6)	1.1 (0.8-2.5)	1.0 (0.7-2.0)	1.2 (1.0-1.3)	1.8 (1.0-2.6)
Estimated duration of response, months	12.7 (95% CI 6.1-NE)	4.4 (95% CI 2.9-NE)	NR (95% CI 1.6-NE)	10.9 (95% CI 1.4-NE)	18.1 (95% CI 1.5-NE)	13.2 (95% CI NE-NE)
Observed duration of response, months	10.4 (4.4-19.9)*	4.4 (2.8-21.0)†	6.7 (1.6-12.8)‡	7.6 (1.4-24.9)	9.8 (0.8-25.4)	13.2 (13.2-13.2)
Time to first complete response, months	2.6 (2.5-2.9)	2.3 (1.0-2.8)	1.5 (0.8-2.6)	1.3 (0.7-2.7)	2.5 (1.3-2.7)	1.8 (1.0-2.6)
Estimated duration of complete response, months	14.5 (95% CI 8.8-NE)	NR (95% CI 4.0-NE)	NR (95% CI NE-NE)	NR (95% CI 4.3-NE)	NR (95% CI 16.6-NE)	13.2 (95% CI NE-NE)
Observed duration of complete response, months	9.9 (3.9-19.9)	10.3 (4.2-21.4)	7.4 (2.6-15.8)	13.7 (2.2-30.1)	23.8 (16.6-31.1)	13.2 (13.2-13.2)

Data are n (%; 95% CI), median (IQR), or median (95% CI). CAR=chimeric antigen receptor. NE=not estimable. NR=not reached. *Range 1.2-53.0+. †Range 1.5-41.4+. ‡Range 0.0+-20.5+ (plus sign denotes an ongoing response).

Table 3: Investigator-assessed response in the overall population

Odronextamab activity



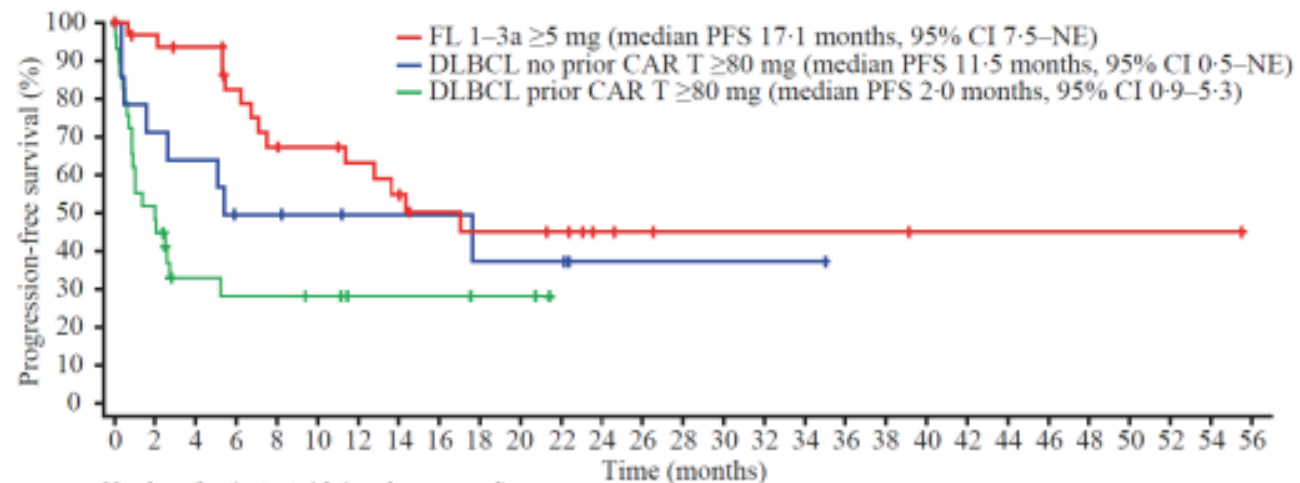
Follicular lymphoma

DLBCL w/o prior CAR-T

DLBCL with prior CAR-T

Odronextamab PFS in FL and DLBCL

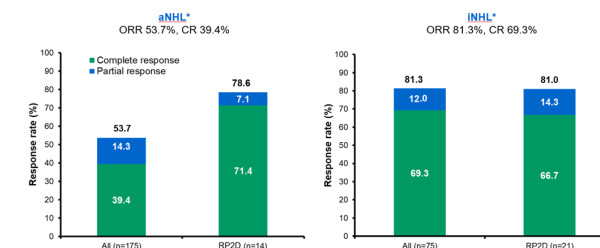
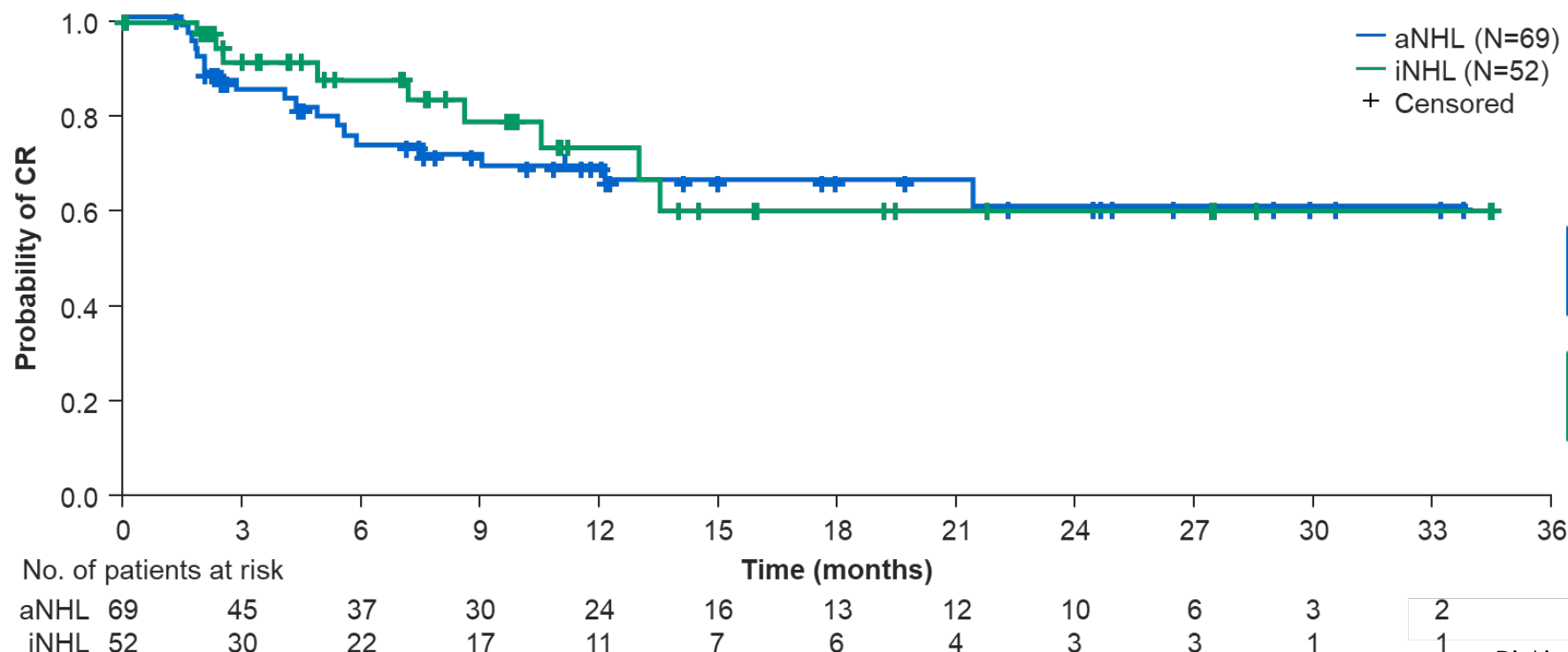
Supplementary figure 5: Progression-free survival in efficacy-evaluable patients with R/R FL grade 1–3a (odronextamab ≥ 5 mg), DLBCL without prior CAR T (≥ 80 mg), and DLBCL with prior CAR T (≥ 80 mg)



Bannerji et al, Lancet Haematol 2022; doi: 10.1016/S2352-3026(22)00072-2.

Glofitamab Monotherapy Provides Durable Responses After Fixed-Length Dosing in R/R non-Hodgkin Lymphoma Patients

- Median follow-up of patients who achieved CR exceeded 12 months for patients with aNHL and median follow-up of CR was 5.3 months for iNHL
- Responses were durable beyond the end of treatment (approximately month 9):
 - **aNHL:** after a median CR follow-up of 12 months, 50/69 (72.5%) patients had an ongoing CR
 - **iNHL:** after a median CR follow-up of 5.3 months, 43/52 (82.7%) patients had an ongoing CR



Median CR follow-up (aNHL):
12.0 months (range: 0–34 months)

Median CR follow-up (iNHL):
5.3 months (range: 0–34 months)

Mosunetuzumab activity in FL

Mosunetuzumab Monotherapy is an Effective and Well-Tolerated Treatment Option for Patients with Relapsed/Refractory (R/R) Follicular Lymphoma (FL) who have Received ≥ 2 Prior Lines of Therapy: Pivotal Results from a Phase I/II Study

L Elizabeth Budde,¹ Laurie H Sehn,² Matthew Matasar,³ Stephen J Schuster,⁴ Sarit Assouline,⁵ Pratyush Giri,⁶ John Kuruvilla,⁷ Miguel Canales,⁸ Sascha Dietrich,⁹ Keith Fay,¹⁰ Matthew Ku,¹¹ Loretta Nastoupil,¹² Michael C Wei,¹³ Shen Yin,¹³ Michelle Y Doral,¹³ Chi-Chung Li,¹³ Huang Huang,¹⁴ Raluca Negricea,¹⁵ Elicia Penuel,¹³ Carol O'Hear,¹³ Nancy L Bartlett¹⁶

N= 90 FL subjects

Poor risk population with 53% double refractory, 52% POD24 and median 3 (2-10) prior lines of treatment.

- ORR 80%
- CR 60%

Budde et al, Blood (2021) 138 (Supplement 1): 127.

19th International Ultmann Chicago Lymphoma Symposium

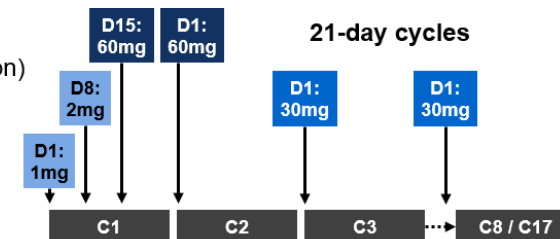
- Single-arm, pivotal Phase II expansion in patients with R/R FL and ≥ 2 prior therapies

Key inclusion criteria

- FL (Grade 1–3a)
- ECOG PS 0–1
- ≥ 2 prior regimens, including
 - ≥ 1 anti-CD20 Ab
 - ≥ 1 alkylating agent

Mosunetuzumab administration

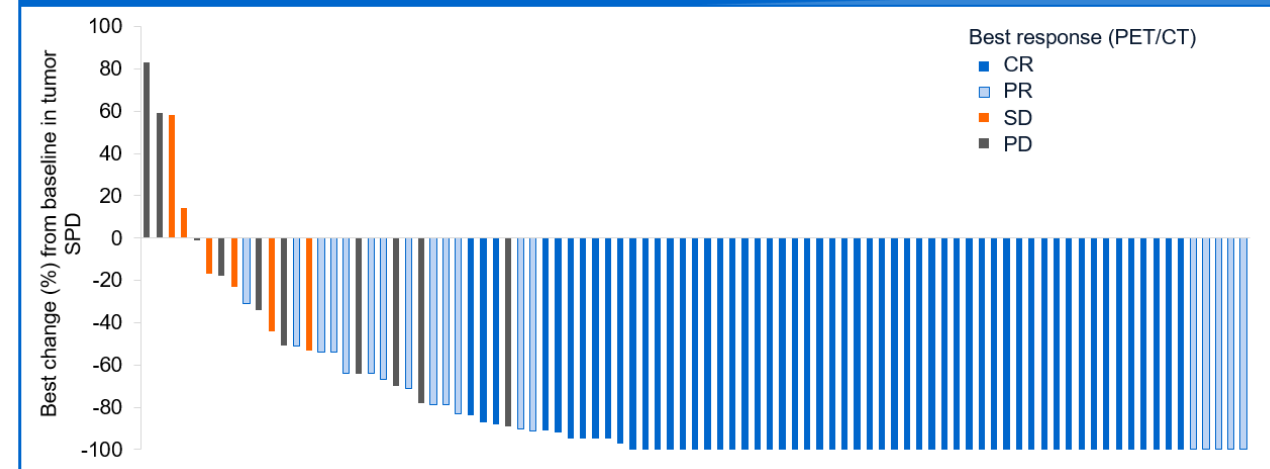
- Q3W intravenous administration
- C1 step-up dosing (CRS mitigation)
 - 8 cycles if CR after C8
 - 17 cycles if PR/SD after C8
- **Fixed-duration treatment**
- **No mandatory hospitalization**



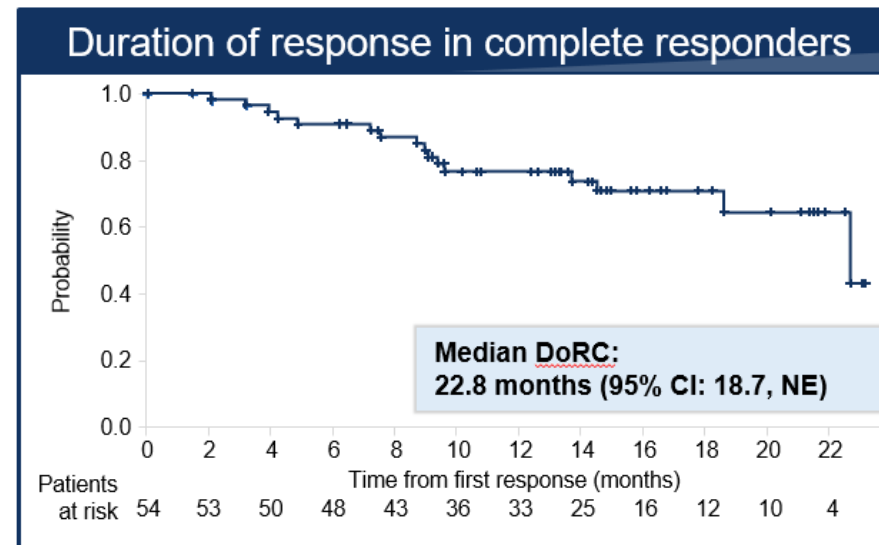
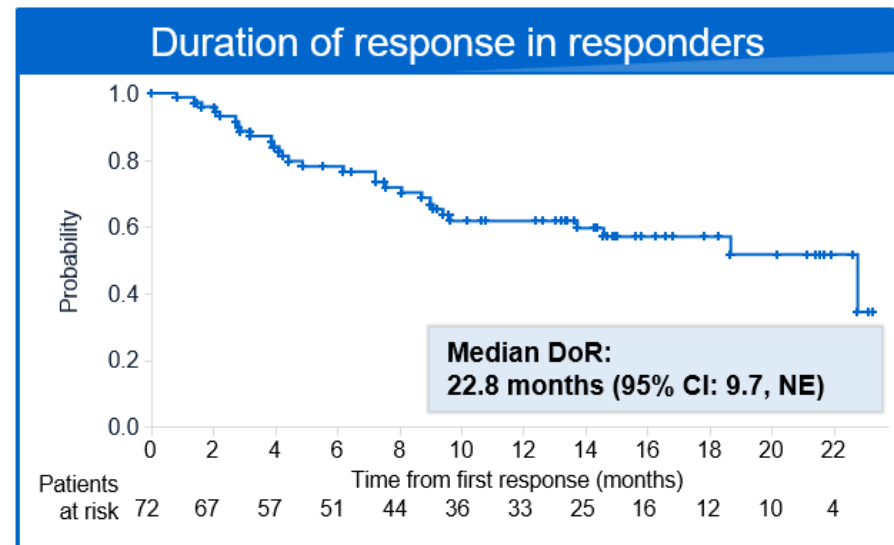
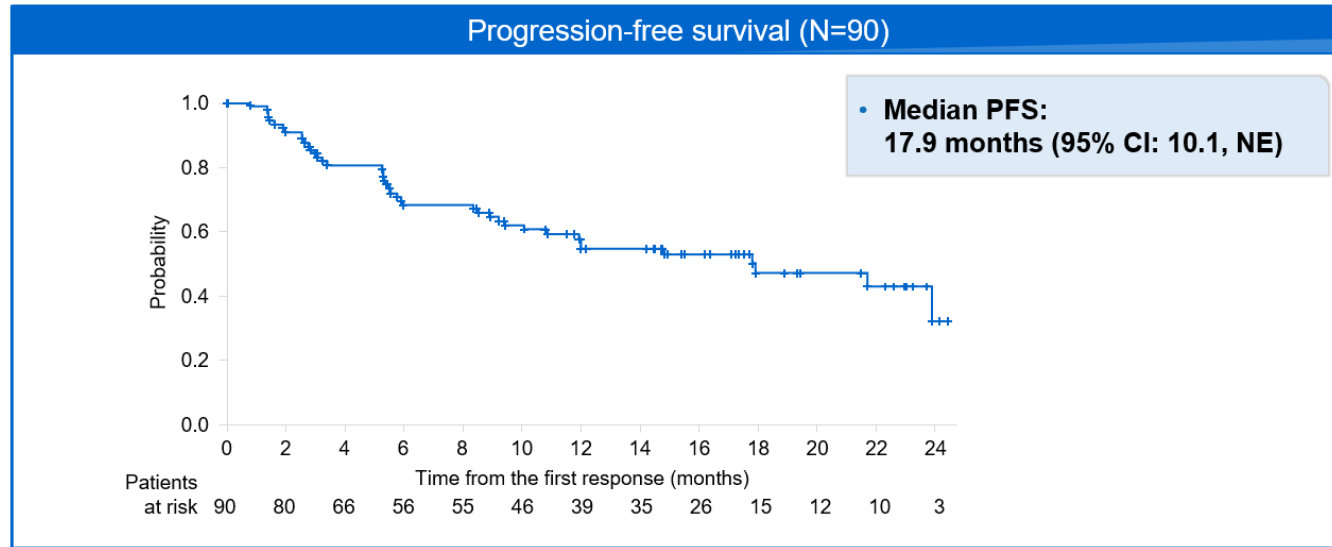
Endpoints

- Primary: CR (best response) rate by IRF* – assessed vs 14% historical control CR rate¹
- Secondary: ORR, DoR, PFS, safety and tolerability

Best percentage change from baseline in tumor SPD*



Duration of Response and Progression-free survival



Budde et al, Blood (2021) 138 (Supplement 1): 127.

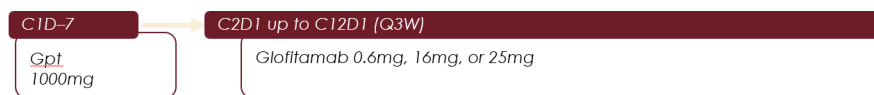
Glofitamab regimens investigated in R/R MCL

Dose escalation (Phase I)

Glofitamab fixed dosing

Gpt 1000mg

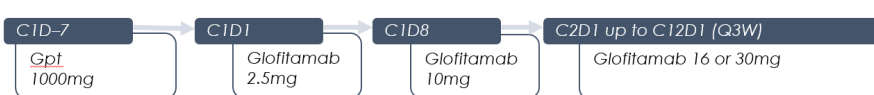
Glofitamab
0.6, 16 or 25mg*:
n=3



Glofitamab SUD

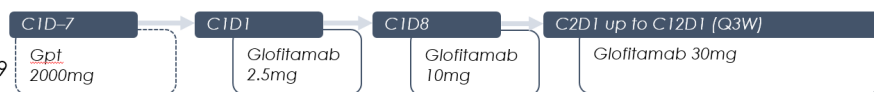
Gpt 1000mg

Glofitamab
2.5/10/16mg or
2.5/10/30mg†:
n=7



Gpt 2000mg

Glofitamab
2.5/10/30mg: n=19

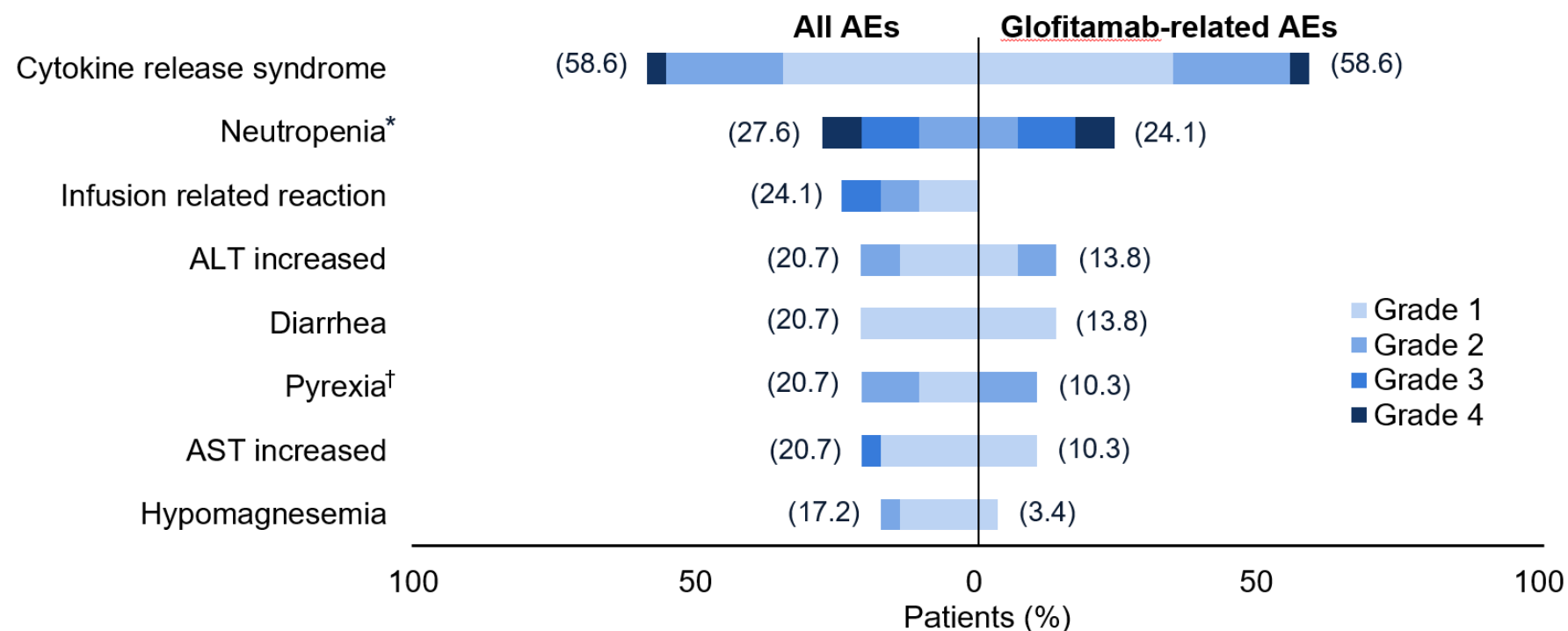


n (%) of patients unless stated	Glofitamab fixed dosing + 1000mg Gpt (n=3)	Glofitamab SUD + 1000mg Gpt (n=7)	Glofitamab SUD + 2000mg Gpt (n=19)	All patients (N=29*)	
Median age, years (range)	81.0 (66–84)	69.0 (64–75)	66.0 (41–84)	69.0 (41–84)	
Male	2 (66.7)	6 (85.7)	12 (63.2)	20 (69.0)	
Ann Arbor stage III–IV at study entry	2 (66.7)	6 (85.7)	16 (84.2)	24 (82.8)	
MCL IPI score ≥6 at study entry	3 (100)	3 (42.9)	12 (63.2)	18 (62.1)	
Median time since last therapy, months (range)	1.1 (1.0–8.5)	3.4 (1.2–53.2)	1.6 (0.1–107.5)	1.7 (0.1–107.5)	
Prior lines of therapy, median (range)	3 (2–5)	4 (3–5)	3 (1–6)	3 (1–6)	
Prior therapy	BTKi	3 (100)	11 (57.9)	20 (69.0)	
	Lenalidomide	0	3 (15.8)	4 (13.8)	
	Chemotherapy	3 (100)	7 (100)	18 (94.7)	28 (96.6)
	Alkylator	0	6 (85.7)	7 (36.8)	13 (44.8)
	Anti-CD20 monoclonal antibody	3 (100)	6 (85.7)	14 (73.7)	23 (79.3)
	Refractory to any prior therapy	3 (100)	7 (100)	16 (84.2)	26 (89.7)
Refractory status	Refractory to prior anti-CD20 therapy	2 (66.7)	3 (42.9)	10 (52.6)	15 (51.7)
	Refractory to first-line therapy	2 (66.7)	2 (28.6)	11 (57.9)	15 (51.7)
	Refractory to last prior therapy	2 (66.7)	5 (71.4)	13 (68.4)	20 (69.0)

Most patients had received prior BTKi therapy

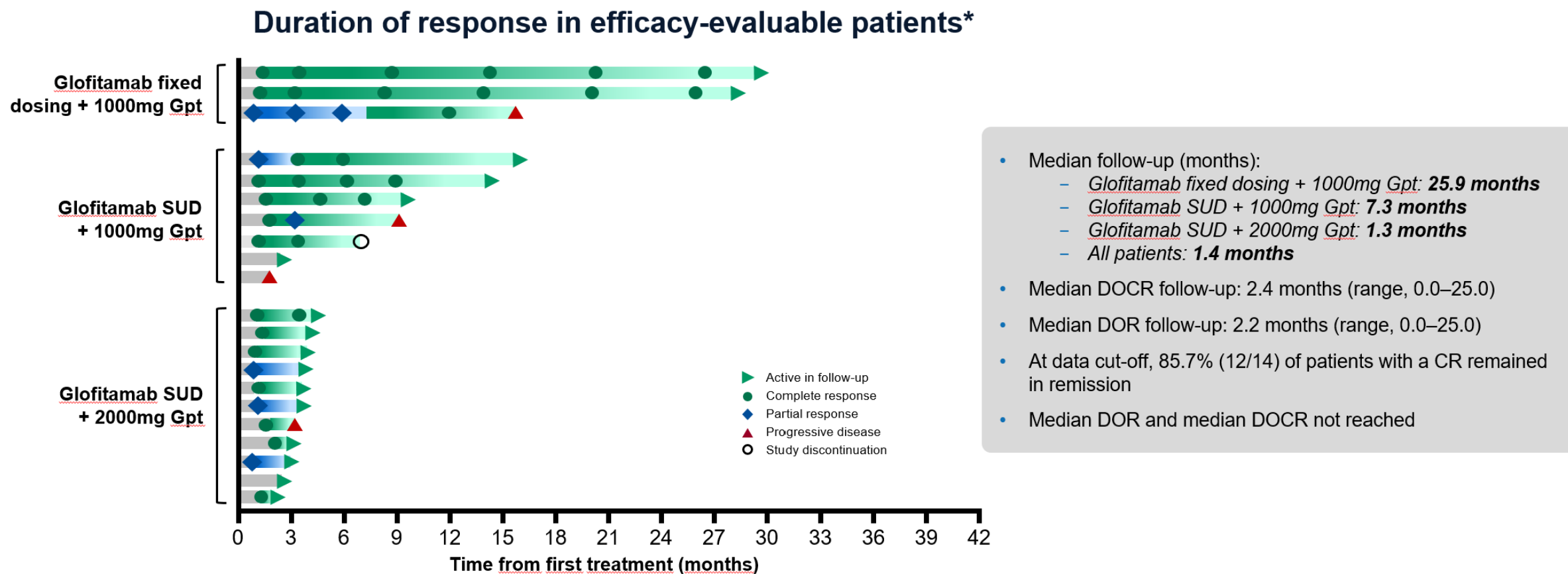
Common adverse events of Glofitamab in R/R MCL

AEs with an incidence of $\geq 15\%$ in all patients (N=29)



The most common AE (all grades) was CRS

Glofitamab time on treatment and response in R/R MCL



Most patients had ongoing responses at the time of the data cut-off

Study Design: EPCORE CLL-1 (NCT04623541)

Open-label, multicenter, phase 1b/2 trial of single-agent epcoritamab in adults with R/R CLL

Key inclusion criteria

- Diagnosis of CLL with evidence of CD20⁺
- Previously treated with ≥2 prior lines of systemic therapy, including treatment with (or intolerance to) a BTK inhibitor
- Measurable disease with ≥5×10⁹/L B lymphocytes *or* measurable lymphadenopathy, *and/or* organomegaly
- ECOG PS 0–2
- Acceptable laboratory parameters

Epcoritamab^a in 4-wk (28-d) cycles

QW C1–3, Q2W C4–9, Q4W C10+ until progression or unacceptable toxicity

Phase 1b: Dose escalation

- 2 full-dose levels
24 mg → 48 mg

Primary objectives:
DLT/Safety and tolerability

Key secondary objective:
Antitumor activity^b

Phase 2: Expansion

- 2 arms at RP2D (48 mg)
– Cohort 1: R/R CLL

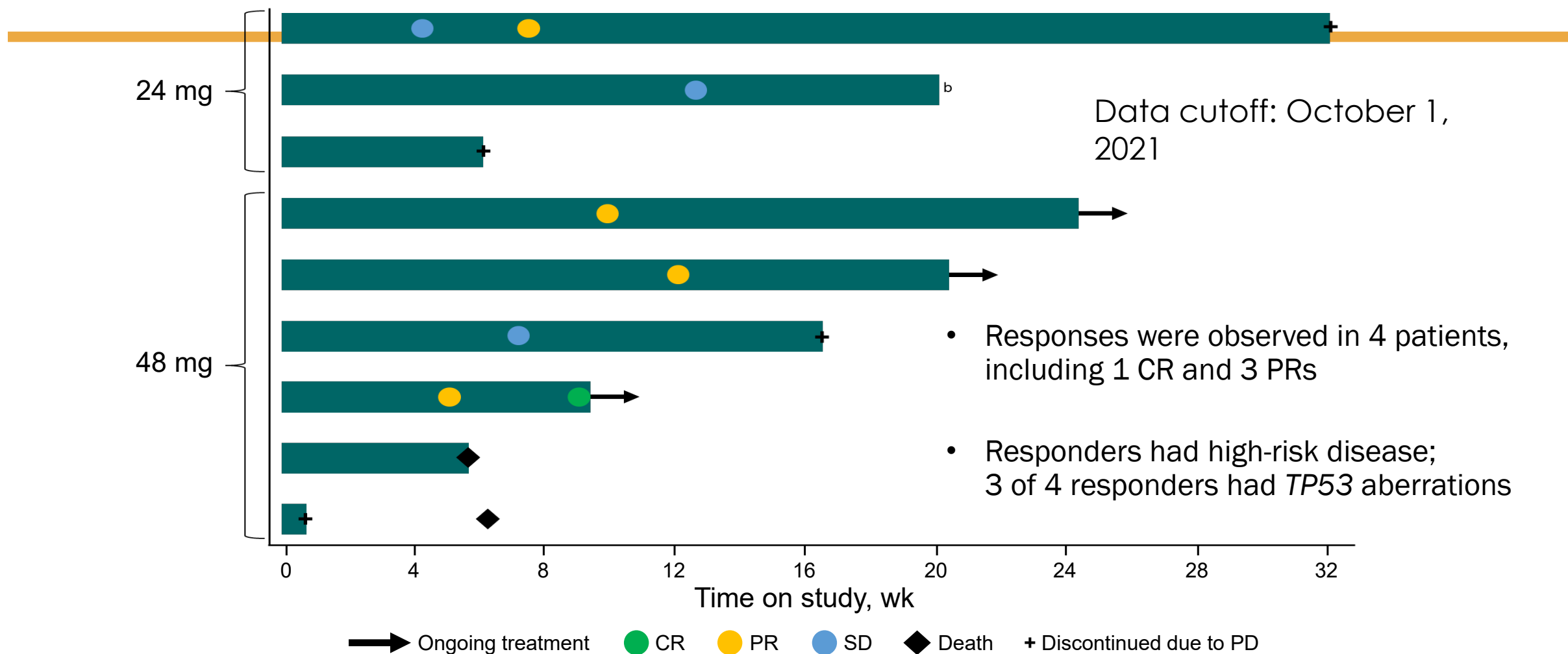
Primary objective:
Antitumor activity^b

Data cutoff: October 1, 2021

^aPatients received SC epcoritamab with step-up dosing (ie, priming and intermediate doses before first full dose) and corticosteroid prophylaxis to mitigate CRS.

^bTumor response was evaluated by CT/MRI every 8 wk up to wk 24, and then every 24 wk until PD, start of new anticancer therapy, consent withdrawal, or death.

Response-Evaluable Population^a (n=9)



- Responses were observed in 4 patients, including 1 CR and 3 PRs

- Responders had high-risk disease; 3 of 4 responders had *TP53* aberrations

^aThe response-evaluable population includes patients who had evaluable disease at baseline and ≥ 1 postbaseline response evaluation or died within 60 d of first dose.

^bPatient discontinued due to physician decision.

Kater et al, Blood (2021) 138 (Supplement 1): 2627.

Glofit + R-CHOP demonstrates manageable safety in patients with R/R NHL and 1L DLBCL

TEAE, n (%)	R/R NHL Dose-escalation phase (N=31)	1L DLBCL Safety run-in phase (N=26)
TEAE	31 (100)	20 (76.9)
Related to Glofit	26 (83.9)	12 (46.1)
Grade ≥3 AE	28 (90.3)	15 (57.7)
Related to Glofit	20 (64.5)	4 (15.4)
Grade 5 (fatal) AE	1 (3.2) ^a	1 (3.8) ^b
Related to Glofit	0	0
AE leading to Glofit dose modification/interruption	9 (29.0)	2 (7.7)
AE leading to Glofit discontinuation	3 (9.7) ^c	0
ICANS^d	1 (3.2)	0
Neutropenia	24 (77.4)	12 (46.1)
Grade ≥3	24 (77.4)	11 (42.3)
Febrile neutropenia	6 (19.4)	2 (7.7)
Infections	20 (64.5)	2 (7.7)
Grade ≥3	6 (19.4)	1 (3.8)
Tumor flare	0	0

^aGrade 5 COVID-19 pneumonia not related to study treatment in the R/R NHL cohort. ^bGrade 5 infusion-related reactions related to rituximab in one patient on C1D1 in the 1L DLBCL cohort.

^cAEs leading to Glofit discontinuation in the R/R NHL cohort included: Grade 4 CRS, Grade 4 ileus paralytic and Grade 3 pneumonia in one patient with R/R MCL, Grade 3 epilepsy in one patient during the maintenance period and Grade 1 influenza-like illness in one patient during the maintenance period. ^dGlofit-related neurologic AEs potentially consistent with ICANS occurred in one patient (treated with Glofit 2.5/10/10mg) who experienced Grade 1 neurotoxicity (non-serious) and Grade 3 epilepsy (serious) which resolved at the clinical cut-off date. 1L, first-line; AE, adverse event; C, cycle; CRS, cytokine release syndrome; D, day; DLBCL, diffuse large B-cell lymphoma; ICANS, immune effector cell-associated neurotoxicity syndrome; NHL, non-Hodgkin lymphoma; PTs, preferred terms; SOC, System Organ Class.

Conclusions

- Both limited duration and indefinite therapy lead to durable responses
- Subcutaneous dosing avoids high grade CRS and remains active
- Activity is seen across a number of B-cell NHL including FL, DLBCL, MCL and CLL/SLL
- Combination with chemotherapy is safe
- Awaiting the 1st regulatory approval in this class
- My ideal: Outpatient subcutaneous administration of limited duration in chemotherapy free regimens