

# 3<sup>rd</sup> MEETING ON T-CELL AND NK-CELL BASED IMMUNOTHERAPIES FOR LYMPHOID MALIGNANCIES

Carmelo Carlo-Stella, M.D.

## **Bispecific Antibodies in Aggressive NHL**



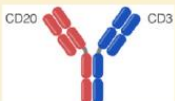
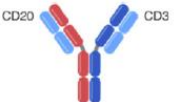

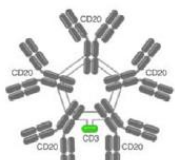
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# Disclosures of C. Carlo-Stella

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Sanofi	X		X			X	
ADC Therapeutics	X		X			X	Honorarium
Karyopharm Tx						X	
Celgene/BMS						X	Honorarium
Incyte							Honorarium
Hoffmann-La Roche Ltd	X					X	Honorarium
Janssen Oncology							Honorarium
Takeda							Honorarium
Merck Sharp & Dohme						X	Honorarium
AstraZeneca							Honorarium
Gilead							Honorarium
Scenic Biotech						X	
SOBI						X	
AbbVie						X	
Genmab						X	

# Comparative characteristics of CD20XCD3 BsAb currently in development

Product name	Schematic depiction	Format	Technology	CD20:CD3 ratio	CD3 clone	CD20 clone	Fc silencing mutations*
Mosunetuzumab <sup>18</sup>		IgG1	Knobs-into-holes (different Fabs)	1:1	UCHT1v9 (CD3δε)	2H7 (type 1 epitope, identical to rituximab)	N297G (no FcγR binding)
Glofitamab <sup>15</sup>		IgG1	Head-to-tail fusion	2:1	SP34-der.(CD3ε)	By-L1 (type 2 epitope, identical to obinutuzumab)	IgG1-P329G-LALA (no FcγR binding)
Epcoritamab <sup>16</sup>		IgG1	Controlled Fab-arm exchange	1:1	huCACAO (SP34-der.)(CD3ε)	7D8 (type 1 epitope, shared by ofatumomab)	L234F,L235E,D265A (no FcγR,C1q binding)
Odronexamab <sup>17</sup>		IgG4	Heavy chains with different affinity	1:1	REG1250 (CD3δε)	3B9-10 (type 1 epitope, shared by ofatumomab)	Modified IgG4 (no FcγRIII binding)
Plamotamab <sup>90</sup>		IgG1	Fab-Fc x scFv-Fc	1:1	α-CD3_H1.30 (SP34-der.)(CD3ε)	C2B8_H1_L1 (type 1 epitope, shared by rituximab)	G236R, L328R (no FcγR binding)
IgM 2323 <sup>19</sup>		IgM	IgM + modified J chain	10:1	Not reported	Not reported	No

\*These Fc-silencing mutations do not abolish the binding of BsAb to neonatal FcR.

# Clinical Characteristics – Pivotal data in 3L+ DLBCL

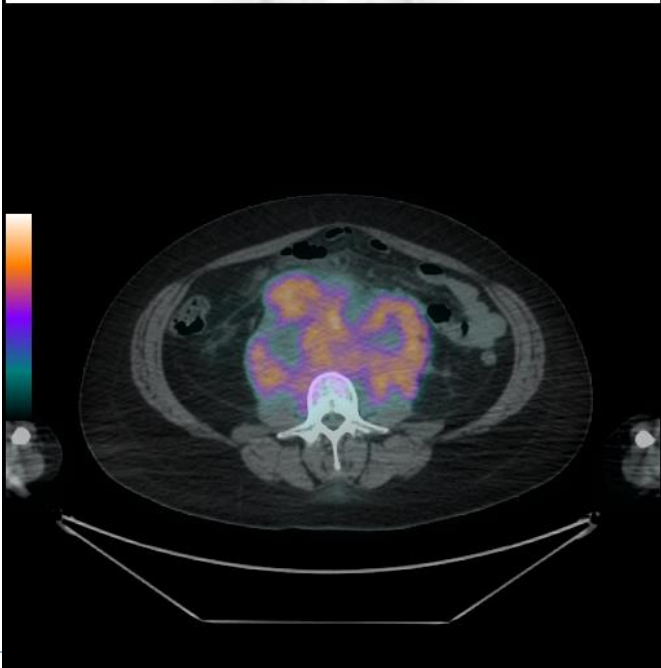
Characteristics	Glofitamab (n=155)*	Epcoritamab (n=157)**	Odronextamab*** (n=141)
Age (median, range)	66 (21-90)	64 (20-83)	66 (24-88)
Prior lines of therapy (median, range)	3 (2-7)	3 (2-11)	2 (2-8)
Primary refractory	58%	61%	57%
Refractory to last therapy	86%	83%	86%
HGBCL	7%	6%	18%
Transformed lymphoma	17%	25%	17%
PMBCL	4%	3%	0%
Prior CAR-T	33%	39%	0%
Prior ASCT	18%	20%	17%

\*Dickinson M, NEJM 387:2220-2231, 2022; \*\*Thieblemont C, JCO, 41:2238-2247, 2023; \*\*\*Ayyappan S, Blood 142: 436-38, 2023

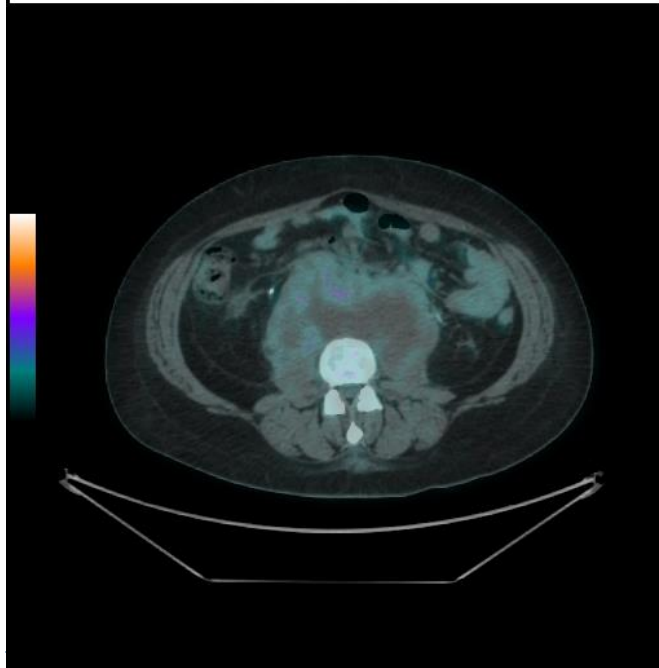
# Response rates at RP2D – Pivotal data in 3L+ DLBCL

Characteristics	Glofitamab (n=155)*	Epcoritamab (n=157)**	Odronextamab*** (n=141)
CRR	61 (39.5%) [95% CI: 31.6%, 47.5%]	61 (39%) [95% CI: 31–47]	39 (31%)
ORR	80 (51.6) [95% CI: 43.5%, 59.7%]	99 (63) [95% CI: 55–71]	66 (52%)

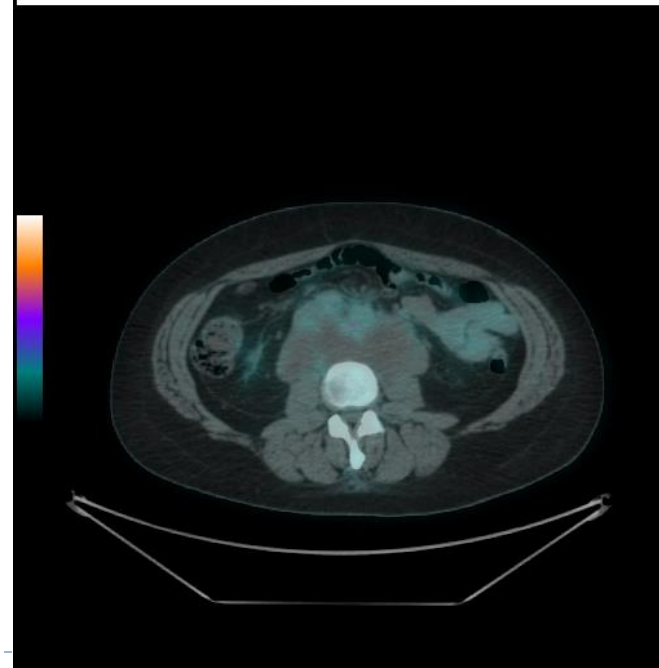
\*Dickinson M, NEJM 387:2220-2231, 2022; \*\*Thieblemont C, JCO, 41:2238-2247, 2023; \*\*\*Ayyappan S, Blood 142: 436-38, 2023



06/09/2020 (BL)



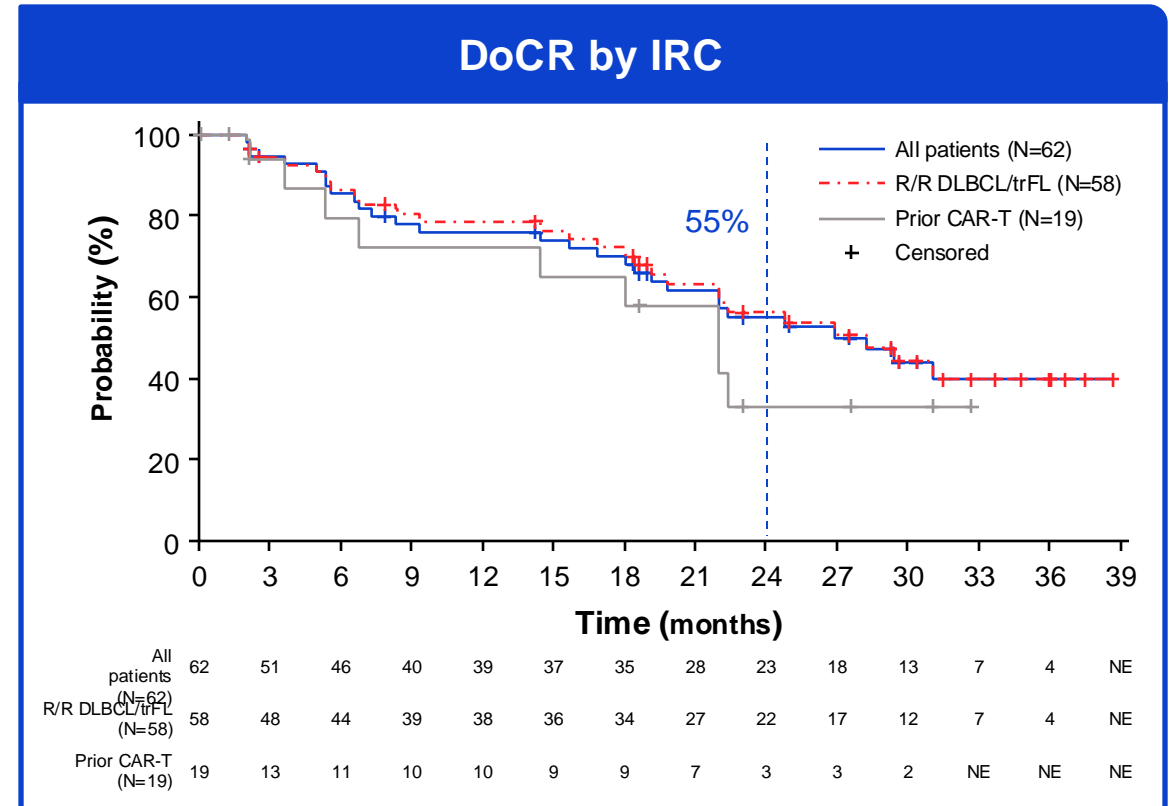
30/11/2020 1° assessment



14/01/2021 2° assessment

# Glofitamab CR Remained Durable

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

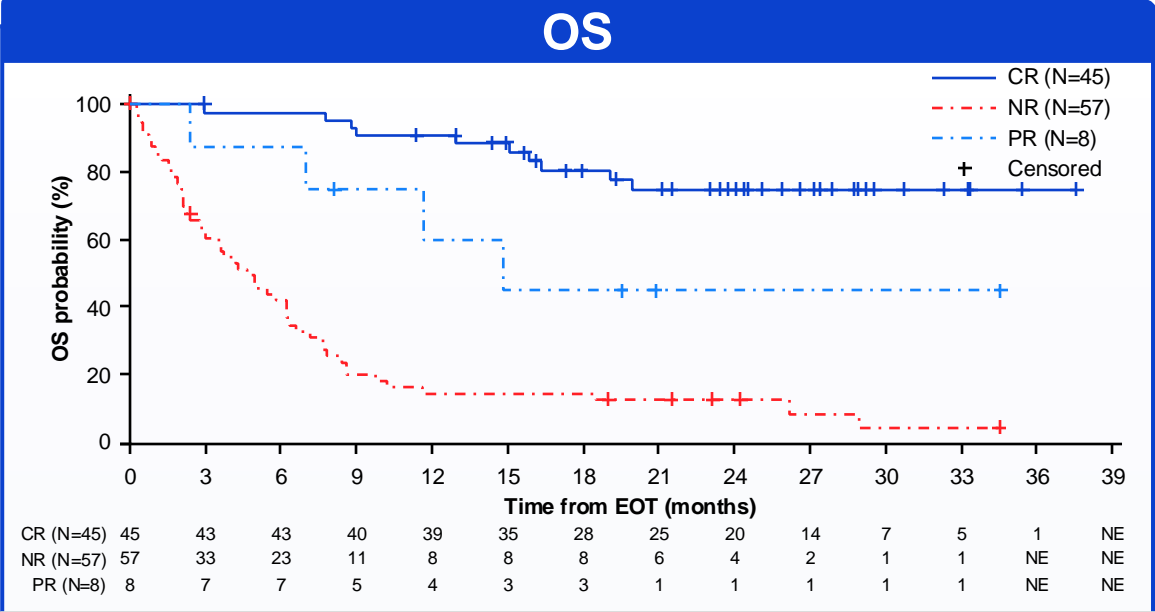
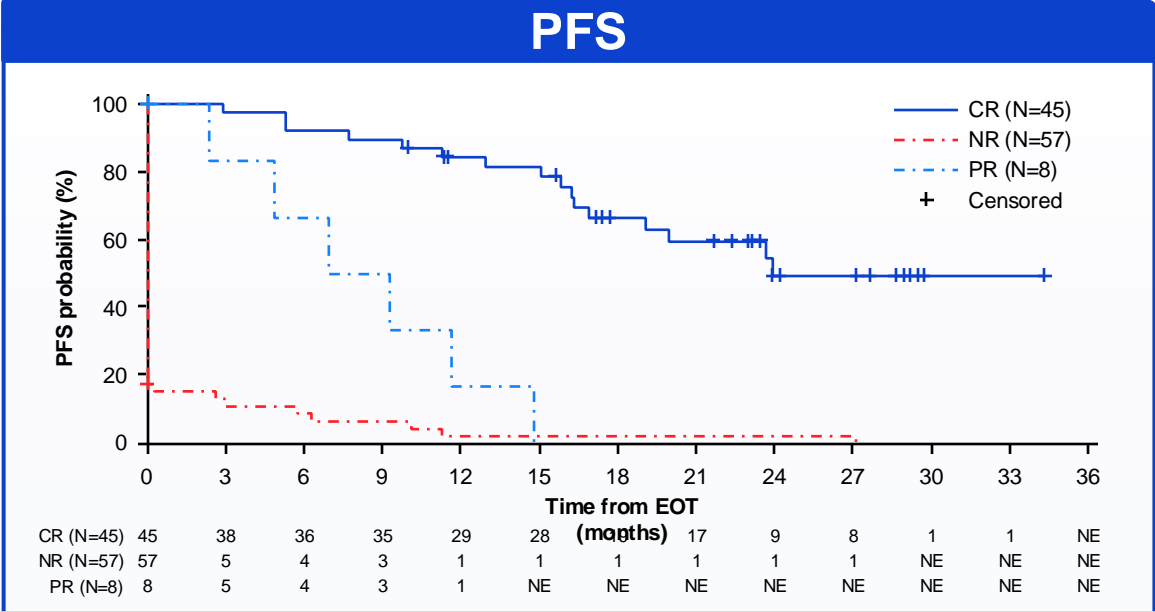


- Median time on study: 32.1 months (range: 0–43)

**With 32 months median follow-up, glofitamab showed high response rates and durable remissions across subgroups**

\*Intent-to-treat population (DLBCL, trFL, HGBCL, and PMBCL); <sup>†</sup>Patients in this subgroup had similar baseline characteristics to the overall population; <sup>††</sup>Primary efficacy population reported in the glofitamab USPI, all patients received at least one dose of glofitamab. CI, confidence interval; NE, not estimable; NR, not reached; USPI, United States prescribing information.

# Landmark analysis by response at EOT



**Landmark PFS from EOT in patients with CR at EOT\* N=45**

Median PFS, months (95% CI)	24.0 (19.1–NE)
18-month PFS rate, % (95% CI)	66.6 (51.0–82.2)

**Landmark OS from EOT in patients with CR at EOT\* N=45**

Median OS, months (95% CI)	NE (NE)
18-month OS rate, % (95% CI)	80.7 (68.6–92.8)

**Majority of patients with a CR at EOT remained progression-free and alive at 18 months after EOT**

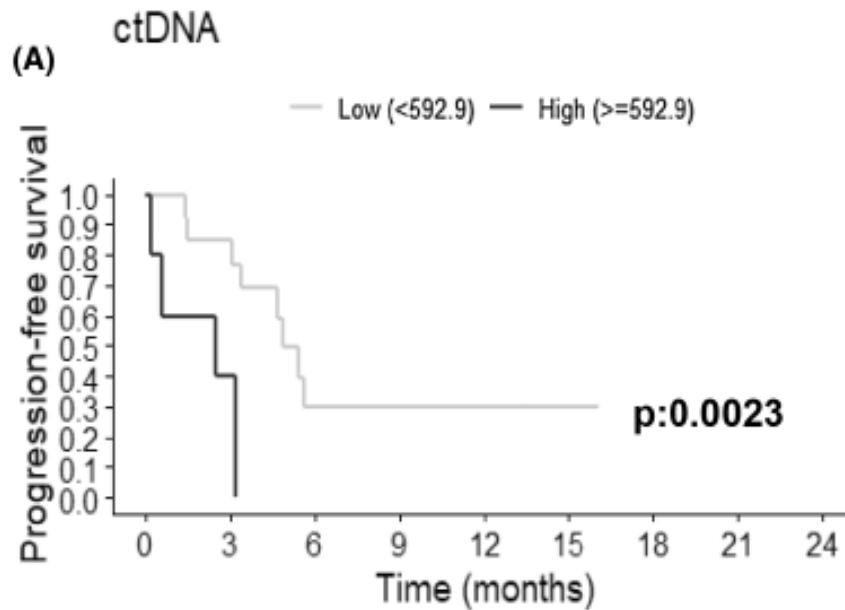
\*KM estimates.  
EOT, end-of-treatment.



# Outcome after chimeric antigen receptor (CAR) T-cell therapy failure in large B-cell lymphomas

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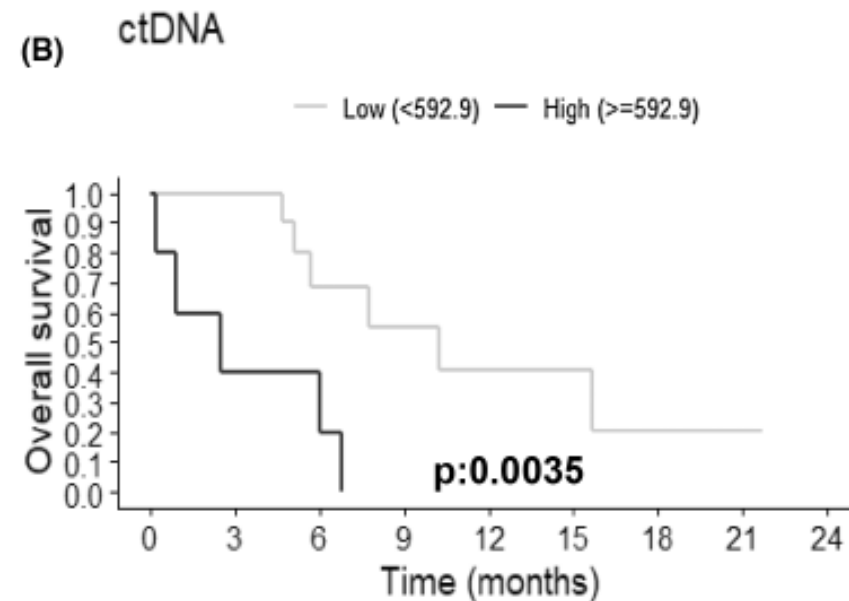
Br. J. Haematol, 2023



ctDNA

—	13 (0)	11 (0)	3 (2)	2 (3)	2 (3)	1 (4)	1 (4)	1 (4)	0 (5)
—	5 (0)	2 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

**6-month PFS: 0% vs. 30%**



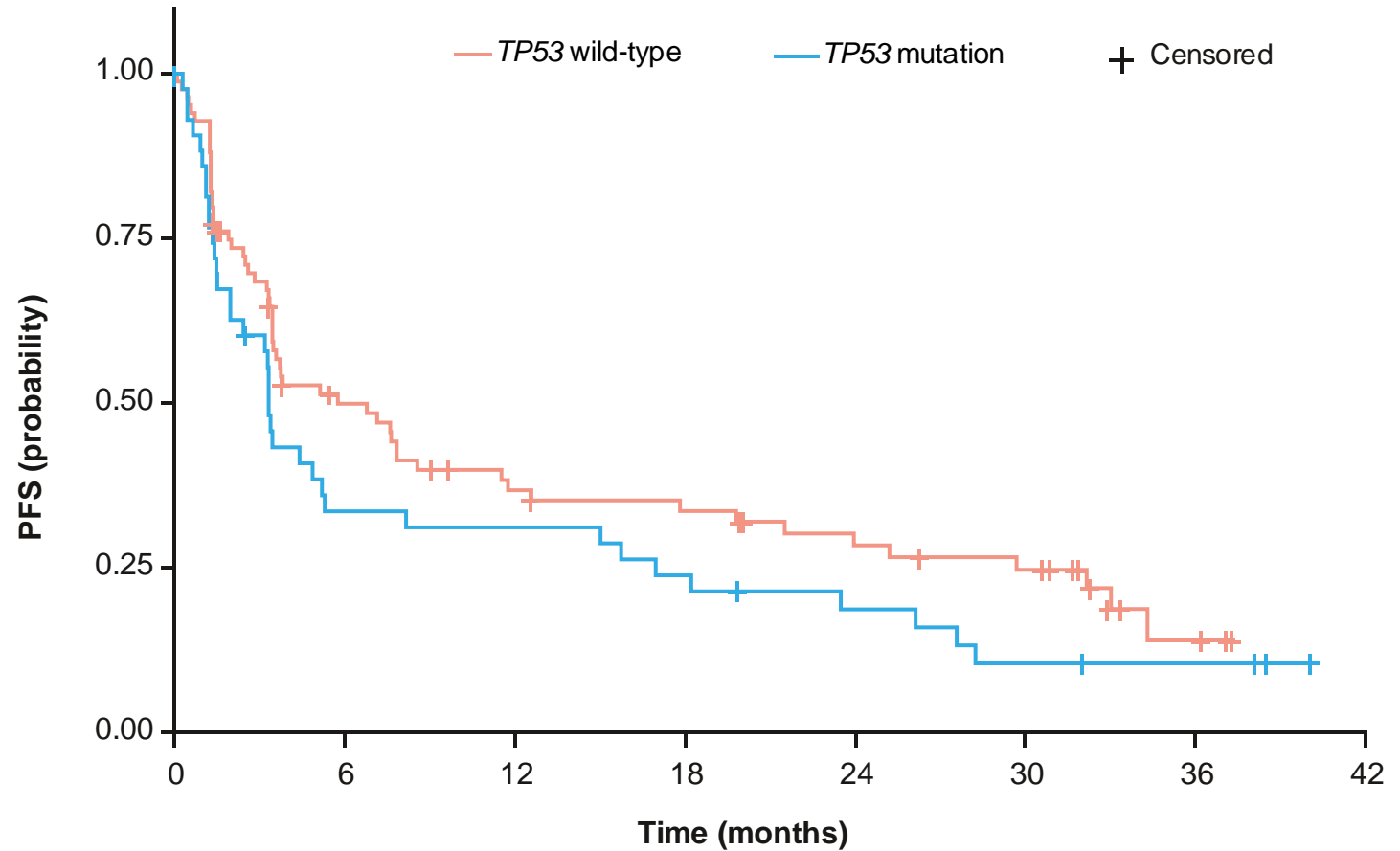
ctDNA

—	13 (0)	13 (0)	6 (4)	4 (5)	3 (5)	2 (6)	1 (6)	1 (6)	0 (7)
—	5 (0)	2 (0)	1 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

**6-month OS: 20% vs. 68%**

# Progression-Free Survival by TP53 Status

- At Baseline, TP53 mutations were detected in 33% (44/132) of patients
- CR rate for TP53 mutation was 25% (11/44) vs 43% (38/88) for TP53 wild-type patients
- Patients with TP53 mutation had a PFS comparable to TP53 wild-type patients (HR 1.34, 95% CI: 0.89–2.02)

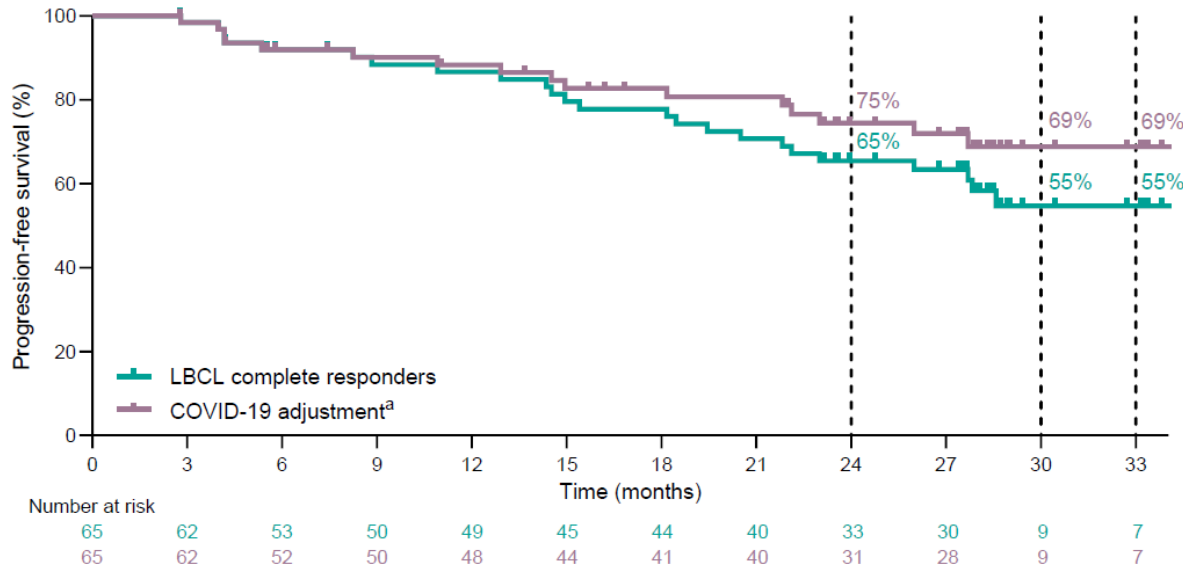


Number at risk

—	88	35	24	21	16	13	3	0
—	44	14	13	10	7	4	3	0

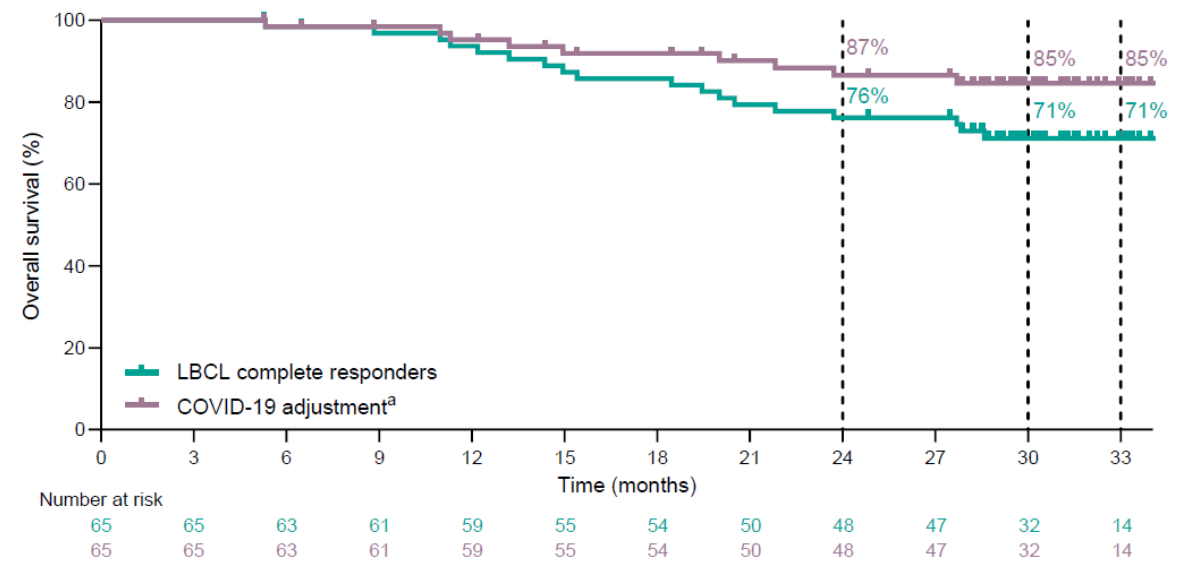
# Epocoritamab CR Remained Durable

PFS



Kaplan-Meier estimates are shown. <sup>a</sup>Based on COVID-19-adjusted sensitivity analyses, which censored deaths due to COVID-19.

OS



Kaplan-Meier estimates are shown. <sup>a</sup>Based on COVID-19-adjusted sensitivity analyses, which censored deaths due to COVID-19.

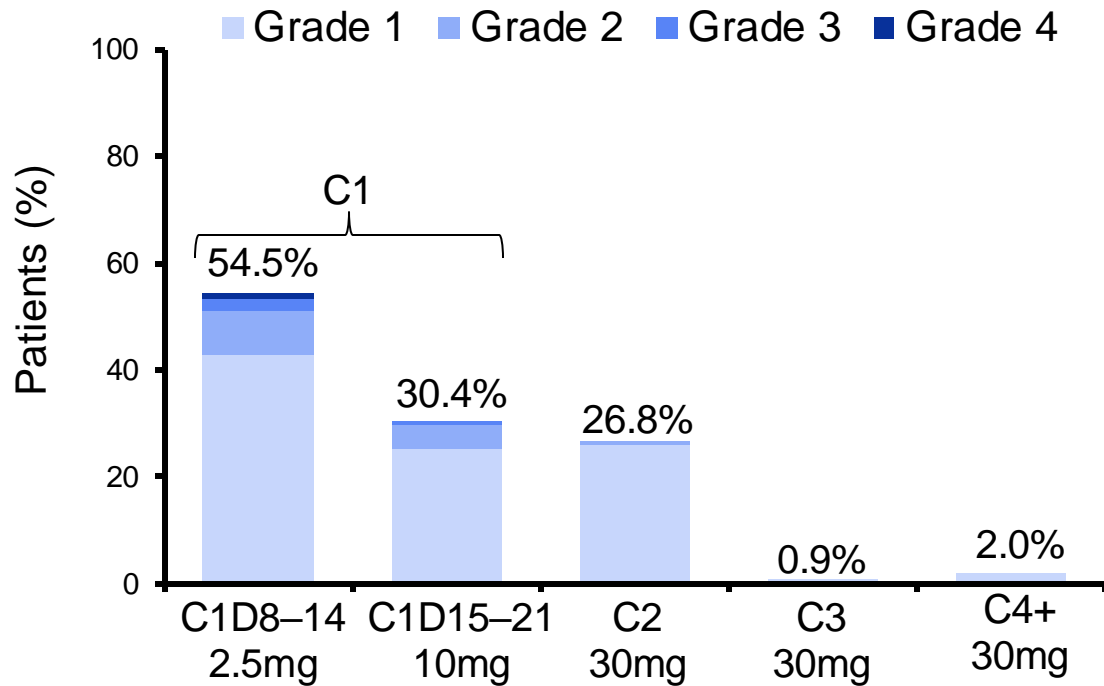
# Odronextamab - ELM-2 DLBCL Cohort

Response by ICR	All DLBCL (N = 127)
<b>ORR, % (primary endpoint)</b>	<b>52.0</b>
▪ CR	31.5
DoR	(n = 66)
▪ Median, mo (95% CI)	10.2 (5.0-17.9)
▪ 24-mo, % (95% CI)	36.9 (24.2-49.6)
<b>DoCR</b>	(n = 40)
▪ Median, mo (95% CI)	<b>17.9 (10.2-NE)</b>
▪ 24-mo, % (95% CI)	<b>47.2 (29.7-62.9)</b>

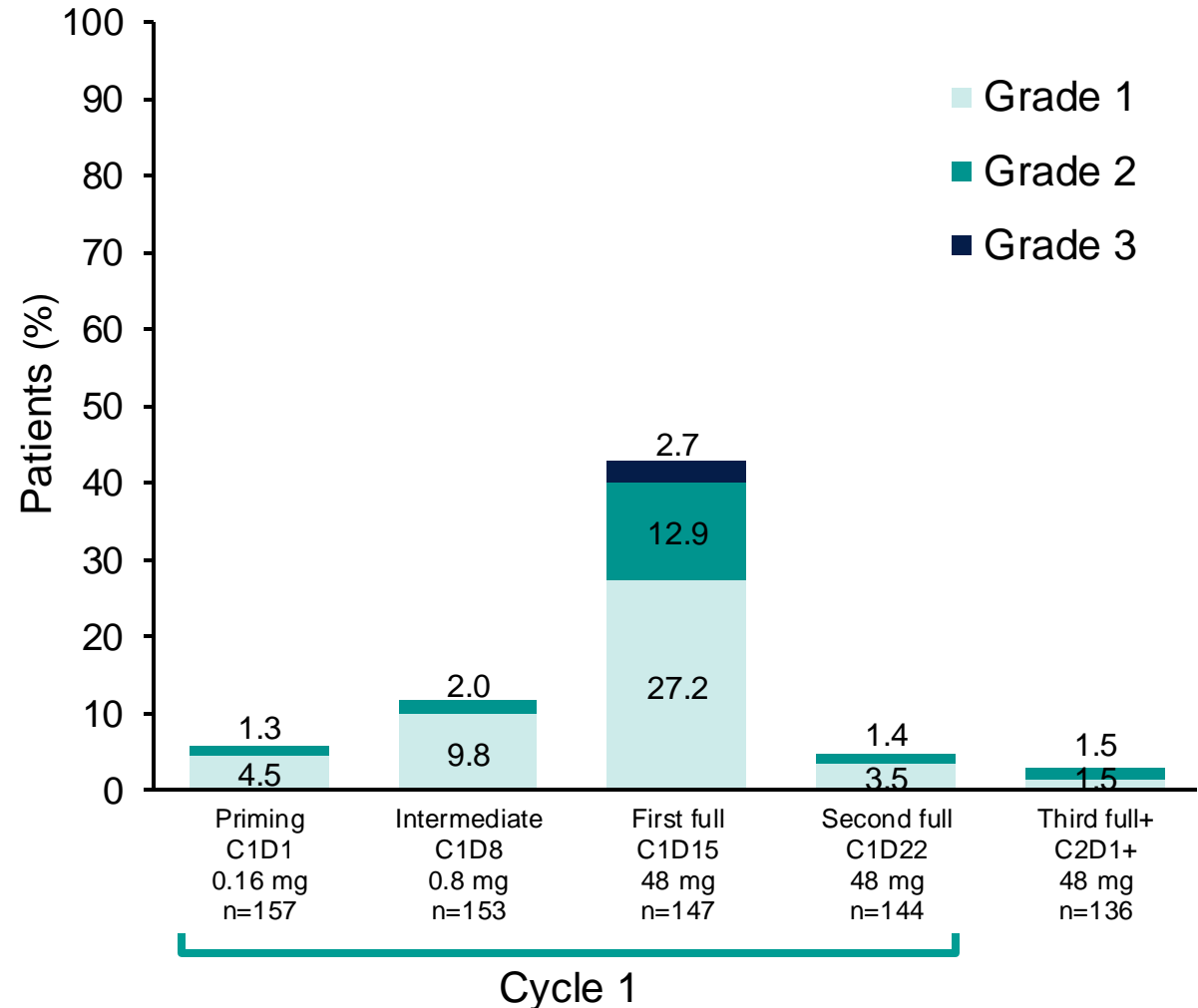
Parameter by Best Objective Response	CR (n = 40)
<b>PFS by best response</b>	
▪ Median, mo (95% CI)	<b>20.4 (12.7-NE)</b>
▪ 24 mo, % (95% CI)	<b>47.5 (29.9-63.1)</b>
<b>OS by best response</b>	
▪ Median, mo (95% CI)	<b>NR (17.2-NE)</b>
▪ 24 mo, % (95% CI)	<b>59.6 (41.7-73.7)</b>

- Median duration f/u for efficacy: 29.9 mo (95% CI: 20.4-32.6)

# CRS Rates and Grades – Glofit vs Epco



**CRS was mostly low grade, time of onset was predictable, and most events occurred during C1**



# Odronextamab - ELM-2 DLBCL Cohort - AEs

CRS	Cycle 1 0.7/4/20 mg Step-up Dosing (n = 60)
CRS, n (%)	32 (53.3)
▪ Grade 1	24 (40.0)
▪ Grade 2	7 (11.7)
▪ Grade 3	1 (1.7)*
▪ Grade ≥4	0
Median time to onset CRS, hr (range)	18.00 (-3.4 to 221.0)
Median CRS duration, days (range)	2.00 (1.0-7.0)
Systemic steroid for CRS management, n (%)	13 (21.7)
Tocilizumab for CRS management, n (%)	15 (25.0)

\*At Wk 6 in patient with pancreatitis.

Infections, n (%)	All DLBCL (N = 127)	
	Any TEAE	COVID-19
Any grade	82 (64.6)	23 (18.1)
Grade 1	4 (3.1)	2 (1.6)
Grade 2	29 (22.8)	5 (3.9)
Grade 3	33 (26.0)	11 (8.7)
Grade 4	1 (0.8)	0
Grade 5	15 (11.8)	5 (3.9)

- Most common infections: COVID-19 (16.5%), pneumonia (14.2%), URTI (8.7%), UTI (8.7%), *Pneumocystis jirovecii* pneumonia (6.3%)
- Treatment-related infections in 4.7% of patients required d/c of odronextamab

## CD20:CD3 bi-specific antibody therapy – *other toxicities*

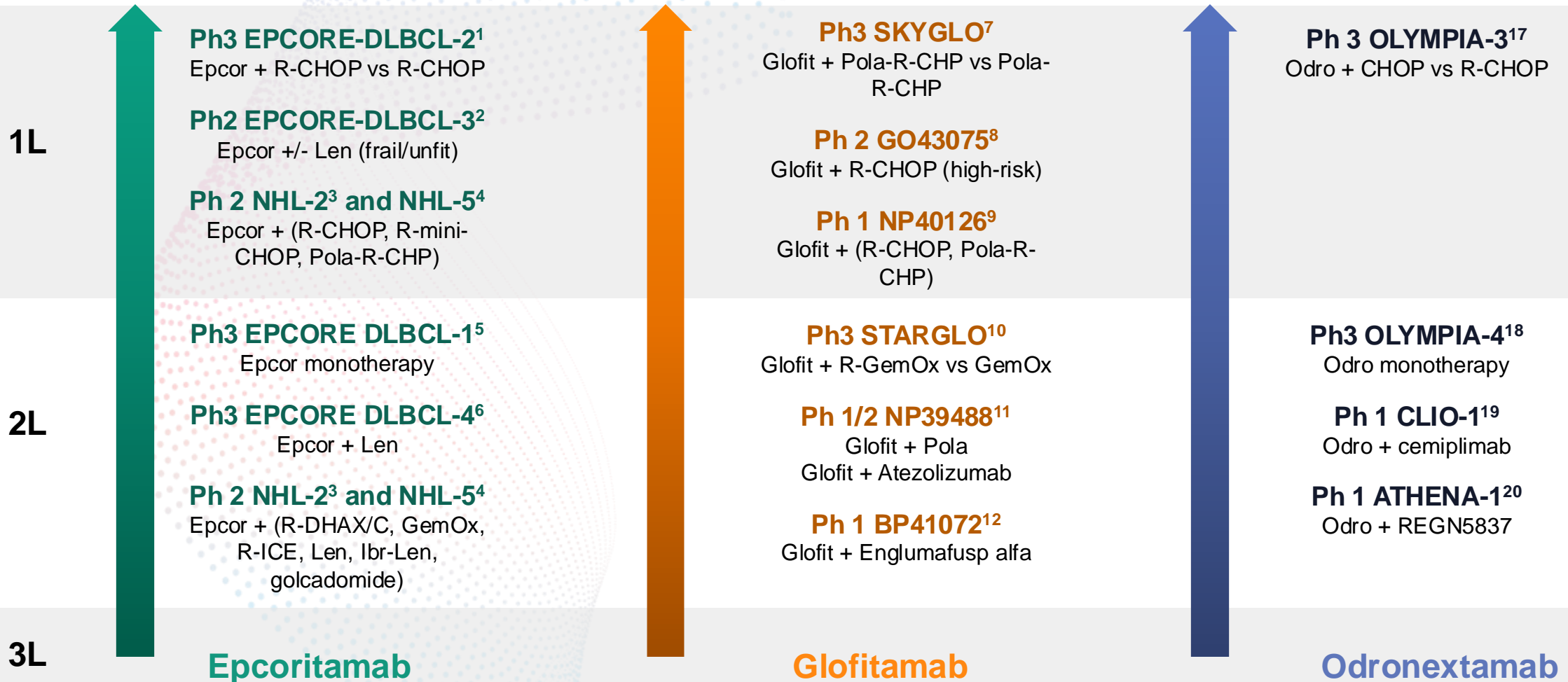
- **Neurological toxicity**
  - Difficult to interpret significance/relatedness in some datasets
  - CTCAE-defined neurologic AEs consistent with ICANS are uncommon and mostly mild e.g. Gd $\geq$ 3 in 3% of patients with Glofitamab
- **Cytopenias and infections**
  - Neutropenia common but febrile neutropenia rare; typically G-CSF responsive
  - No good data on hypogammaglobulinaemia, but this is observed very frequently
  - COVID-19 deaths reported in pivotal studies
- **Tumour flare**
  - Rare but warrants consideration in bulky sites with compartmental risk

# Characteristics of Bispecific Abs

- Off-the-shelf treatment – eventually administered at fixed duration, reducing overall treatment burden
- Premedication but no lymphodepletion or bridging therapy
- Monotherapy induces high CR rates, even in high-risk pts (CAR-T exposed, P53mut)
- Durable CR in DLBCL with a high proportion of pts in CR beyond two years
- Predictable and manageable safety profile supports long-term disease control
- Limited CNS toxicity compared to other therapies
- MoA makes the bispecifics ideal for combination strategies
- Potential to enhance effectiveness and use in earlier lines of therapy



# Bispecific Development in DLBCL



DLBCL, diffuse large B-cell lymphoma; Epcor, epcoritamab; GemOx, gemcitabine+oxaliplatin; Glofit, glofitamab; Ibr, ibrutinib; Len, lenalidomide; Mosun, mosunetuzumab; Odro, odronextamab; Pola, polatuzumab; R, rituximab; SC, subcutaneous.

1. NCT05578976 2. NCT05660967. 3. NCT04663347. 4. NCT05283720. 5. NCT04628494. 6. epcore-trials.com/dlbcl-4/. 7. NCT06047080. 8. NCT04980222. 9. NCT03467373. 10. NCT04408638. 11. NCT03533283. 12. NCT04077723. 13. NCT03677154. 14. NCT05171647. 15. NCT05207670. 16. NCT03671018. 17. NCT06091865. 18. NCT06230224. 19. NCT02651662. 20. NCT05685173.

# Glofitamab Monotherapy in Patients with Heavily Pretreated Relapsed/Refractory (R/R) Mantle Cell Lymphoma (MCL): Updated Analysis from a Phase I/II Study

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# NP30179 Phase I/II study design

## Study design<sup>1</sup>

- Multicenter, open-label, dose-escalation and dose-expansion study of glofitamab with Gpt

## Glofitamab IV administration

- Fixed-duration treatment: maximum 12 cycles

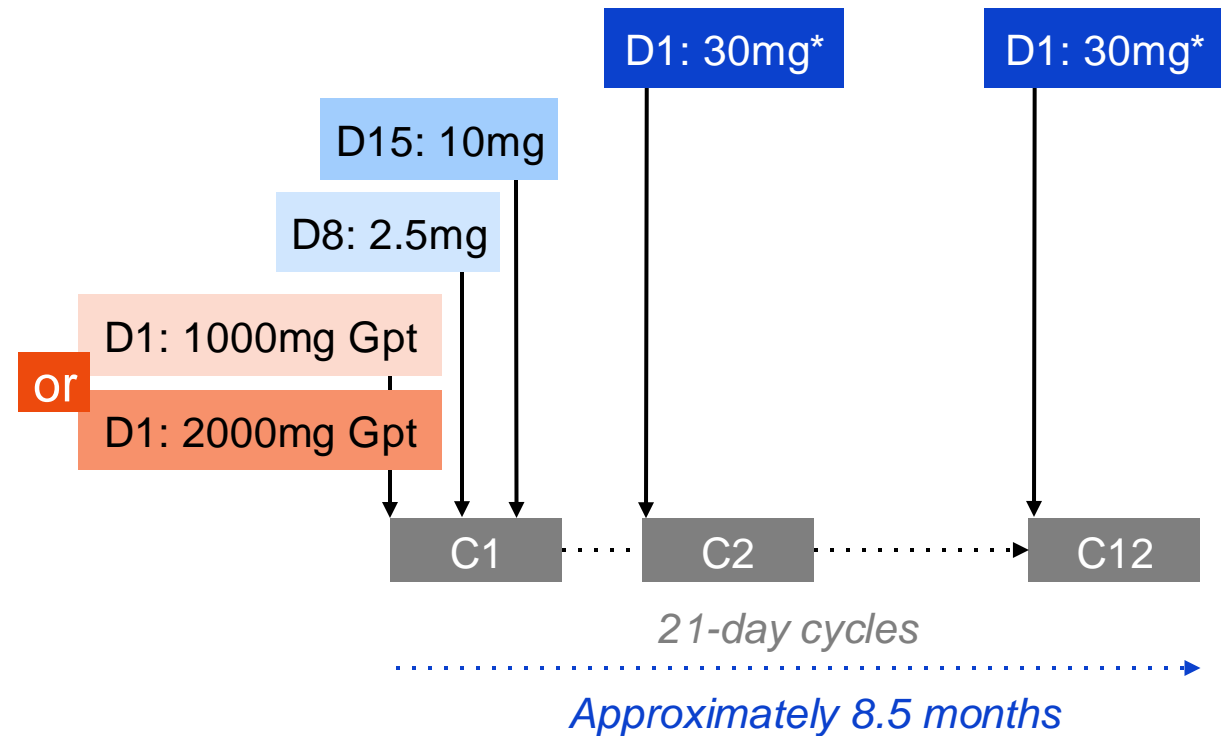
## Population characteristics

- Age  $\geq 18$  years
- $\geq 1$  prior systemic therapy
- ECOG PS 0 or 1

## CRS mitigation

- Obinutuzumab pretreatment (1000mg or 2000mg)
- C1 step-up dosing
- Monitoring after first dose (2.5mg)

## Dosing schedule



Clinical cut-off date: September 04, 2023.

\*In the 1000mg Gpt cohort, two patients had 16mg glofitamab as their target dose in the dose escalation phase.

C, cycle; CRS, cytokine release syndrome; D, day; ECOG PS, Eastern Cooperative Oncology Group performance status; Gpt, obinutuzumab pretreatment; IV, intravenous.

# Baseline characteristics

n (%) of patients unless stated	Prior BTKi (n=31)*	BTKi naïve (n=29)*	All patients (N=60)*
Median age, years (range)	70.0 (41–84)	72.0 (52–86)	72.0 (41–86)
Male	23 (74.2)	21 (72.4)	44 (73.3)
Ann Arbor stage III/IV	28 (90.3)	24 (82.8)	52 (86.7)
MIPI score ≥6	7 (22.6)	8 (27.5)	15 (25.0)
Median no. of prior lines (range)	3.0 (1–5)	2.0 (1–4)	2.0 (1–5)
Median time since last prior therapy to first study treatment, months (range)	1.3 (0.1–53.2)	7.4 (1.1–132.5)	2.4 (0.1–132.5)
Median time since last anti-CD20 therapy to first study treatment, months (range)	15.1 (0.7–159.0)	25.1 (1.4–132.5)	16.3 (0.7–159.0)
Refractory status	Refractory to any prior therapy	30 (96.8)	50 (83.3)
	Refractory to 1L therapy	17 (54.8)	31 (51.7)
	Refractory to last prior therapy	27 (87.1)	17 (58.6)

Patients with R/R MCL were heavily pretreated and highly refractory to their last prior therapy  
 A higher proportion of patients with prior BTKi therapy were refractory to their last prior therapy compared with BTKi-naïve patients

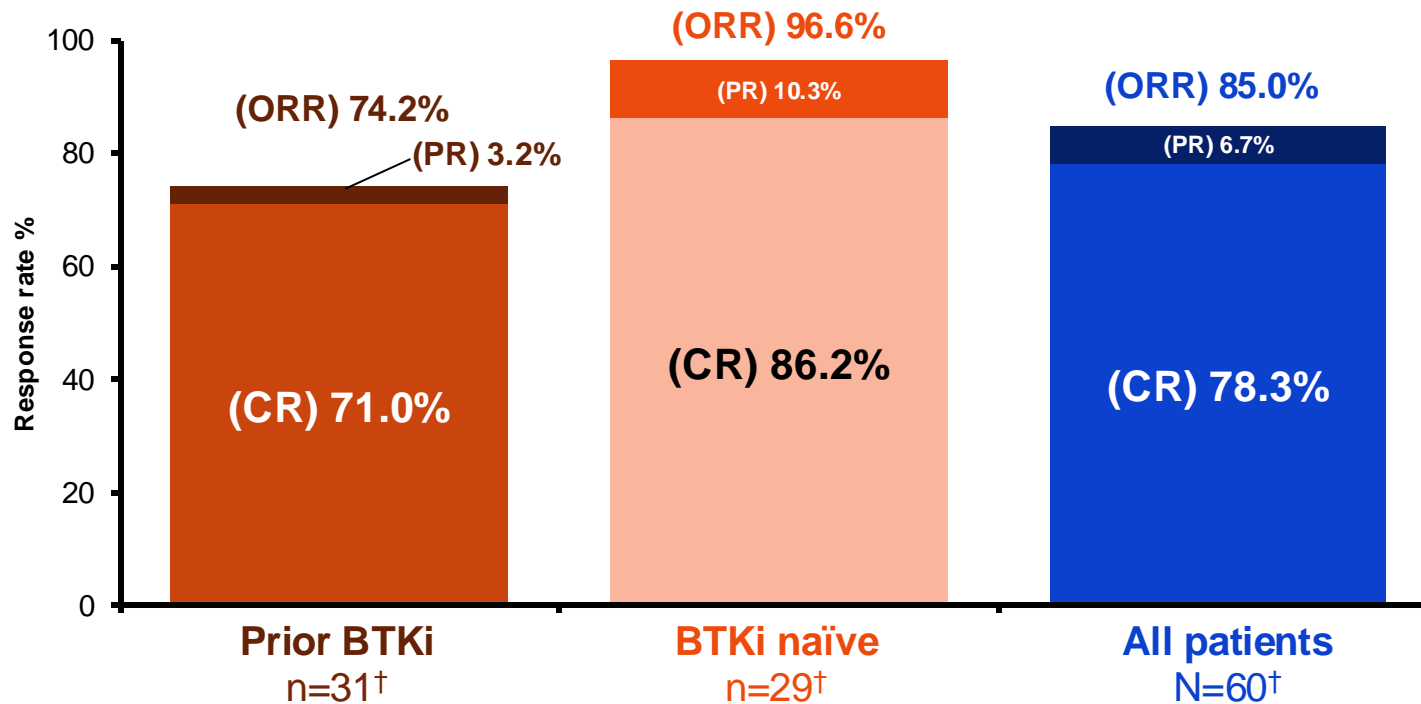
Clinical cut-off date: September 04, 2023.

\*Efficacy evaluable population.

MIPI, mantle cell lymphoma international prognostic index.

# Response rates

## Response rates\* in patients with R/R MCL



- Median time to first response among responders (n=51): **42 days** (95% CI: 42.0–45.0)

**High CR and OR rates were observed in the overall population and in both BTKi-naïve patients and those with prior BTKi therapy**

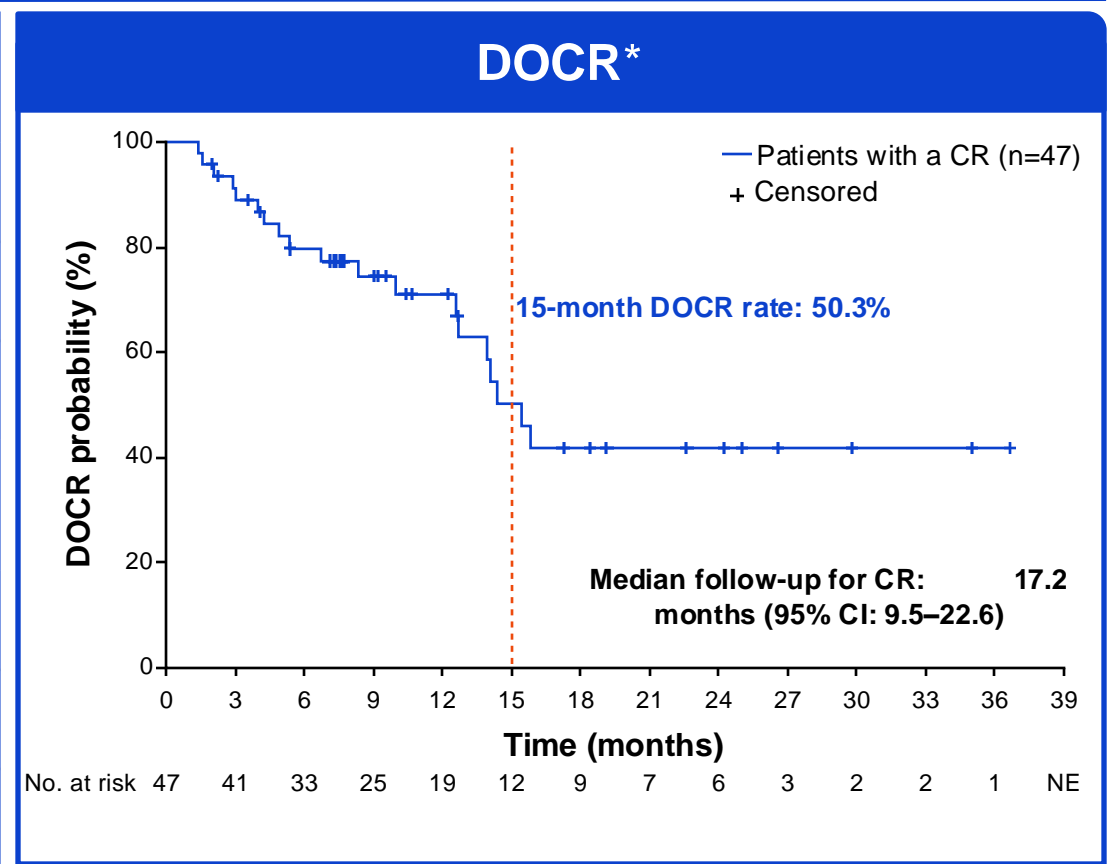
Clinical cut-off date: September 04, 2023.

\*Investigator-assessed. †Efficacy evaluable population.

CI, confidence interval; ORR, overall response rate; PR partial response.

# Duration of response

DOCR*	Prior BTKi n=22	All patients n=47
<b>Median DOCR, months (95% CI)</b>	12.6 (5.4–NE)	<b>15.4 (12.7–NE)</b>
<b>15-month DOCR rate, % (95% CI)</b>	33.5 (10.6–56.4)	50.3 (32.0–68.6)
Ongoing CR, n (%)	10 (45.5)	28 (59.6)
DOR*	n=23	n=51
<b>Median DOR, months (95% CI)</b>	12.6 (7.4–NE)	16.2 (12.6–NE)
<b>15-month DOR rate, % (95% CI)</b>	NA	59.7 (44.1–75.3)
Ongoing response, n (%)	10 (43.5)	28 (54.9)



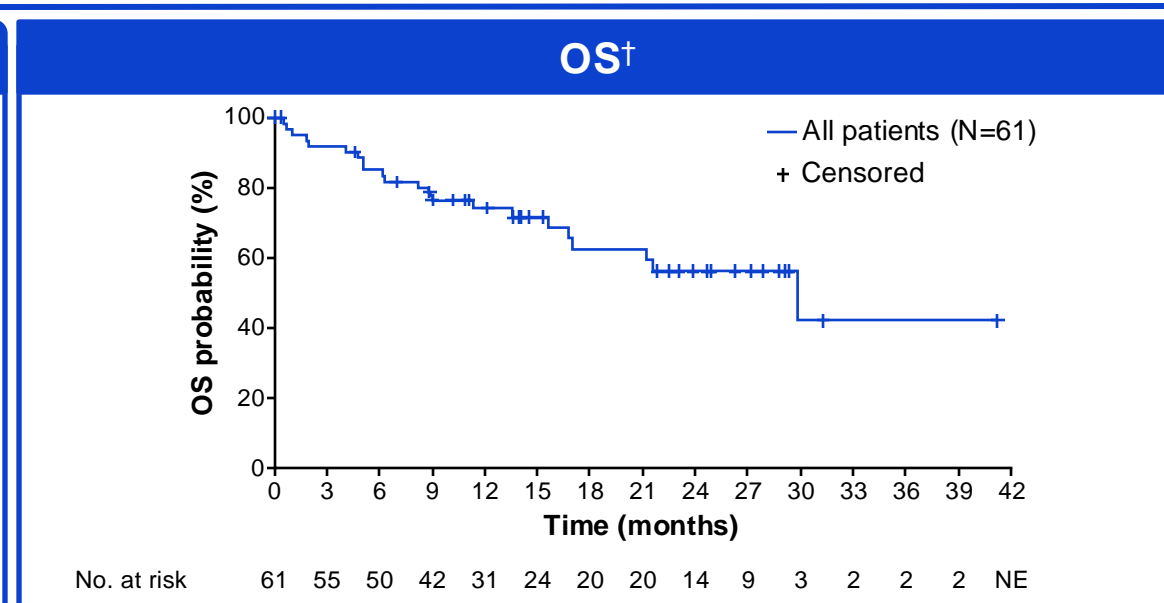
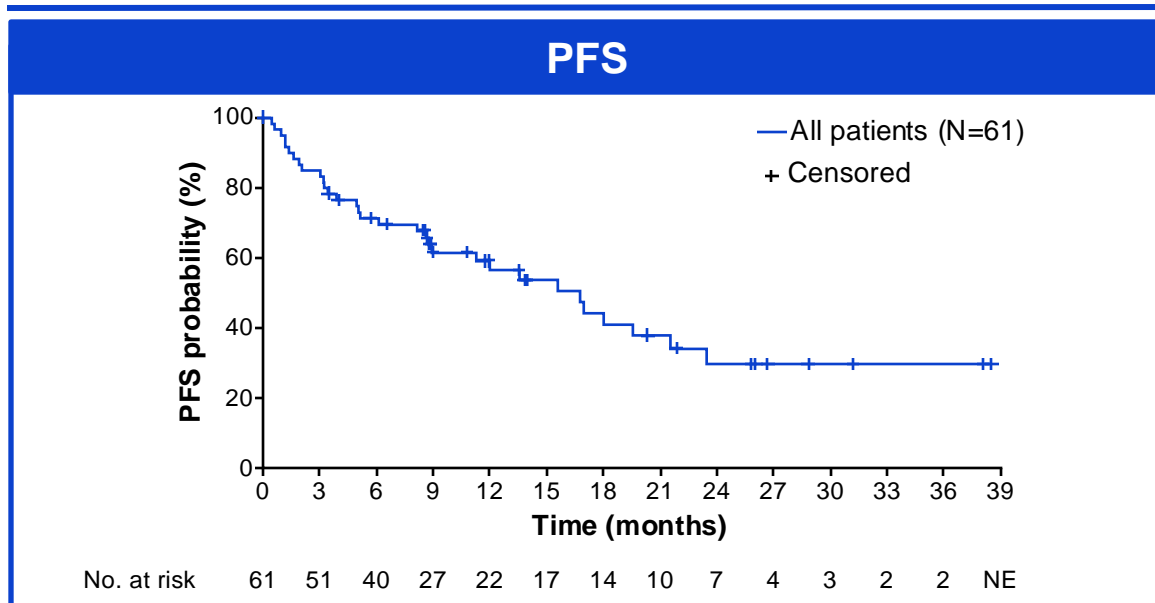
With 17 months' median follow-up, fixed-duration glofitamab monotherapy achieved durable CRs with the majority of CRs (59.6%) still ongoing at data cut-off

Clinical cut-off date: September 04, 2023.

\*Investigator-assessed.

DOR, duration of response; DOCR, duration of complete response; NA, not available; NE, not estimable.

# Time-to-event endpoints



	Prior BTKi n=32*	All patients N=61*
<b>Median PFS follow-up, months (95% CI)</b>	26.1 (13.5–31.2)	19.6 (11.9–26.1)
<b>Median PFS, months (95% CI)</b>	8.6 (3.4–15.6)	16.8 (8.9–21.6)
<b>15-month PFS rate, % (95% CI)</b>	33.0 (14.8–51.1)	54.0 (40.1–67.8)

	Prior BTKi n=32*	All patients N=61*
<b>Median OS follow-up, months (95% CI)</b>	24.7 (13.6–28.8)	21.8 (14.0–24.9)
<b>Median OS, months (95% CI)</b>	21.2 (9.0–NE)	29.9 (17.0–NE)
<b>15-month OS rate, % (95% CI)</b>	55.0 (36.5–73.6)	71.4 (59.3–83.5)

Clinically significant PFS and OS at 15 months were achieved with fixed-duration glofitamab

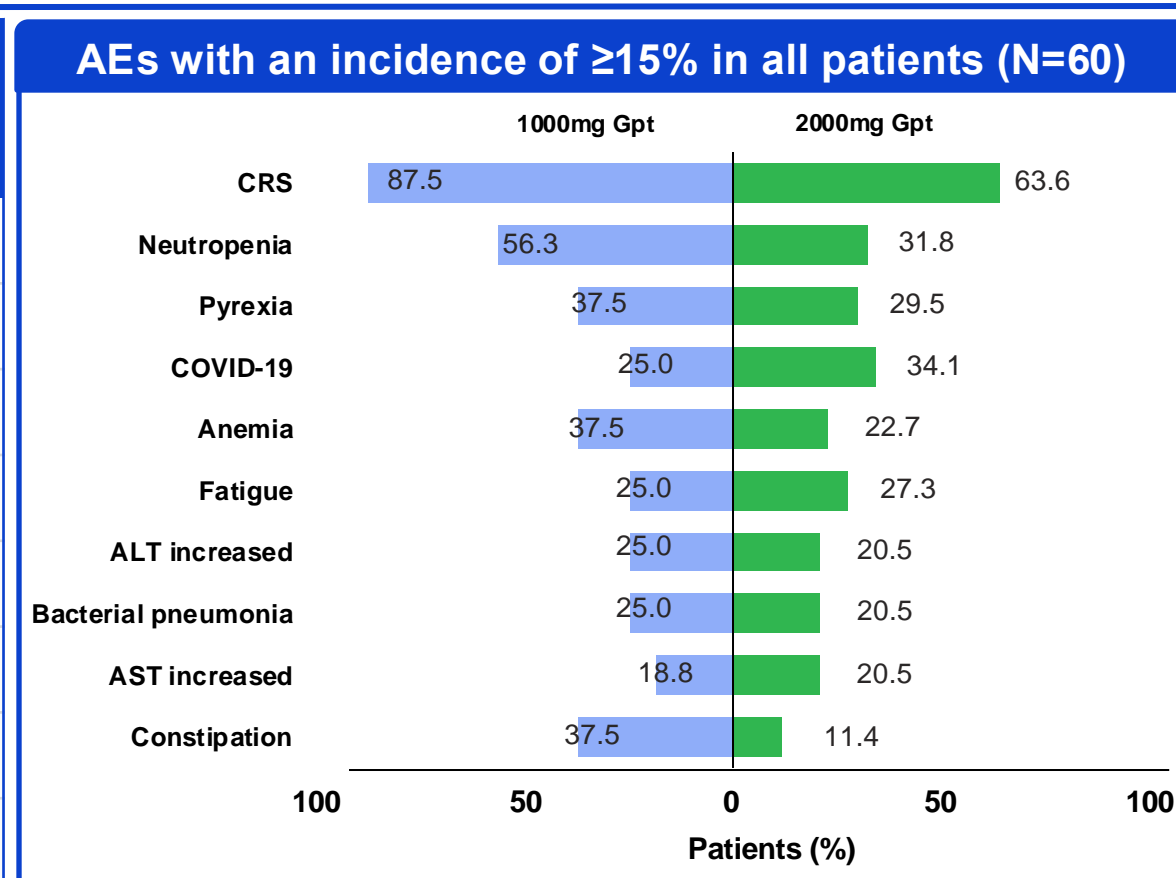
Clinical cut-off date: September 04, 2023.

\*ITT population. †At the time of analysis, 22 patients had died, the majority due to PD (n=7) or COVID-19 (n=7); other causes of death were pneumonia (n=1), septic shock (n=1), cardiac arrest (n=1), and unknown/other (n=5). All patients who died due to COVID-19 had achieved a CR.

OS, overall survival; PD, progressive disease; PFS, progression-free survival.

# Safety summary

AEs, n (%)	1000mg Gpt cohort (n=16)	2000mg Gpt cohort (n=44)	All patients (N=60)
<b>Any grade AE</b>	16 (100)	44 (100)	60 (100)
Glofitamab related	16 (100)	39 (88.6)	55 (91.7)
<b>Serious AE</b>	15 (93.8)	32 (72.7)	47 (78.3)
Glofitamab related	12 (75.0)	24 (54.5)	36 (60.0)
<b>Grade 3/4 AE</b>	13 (81.3)	26 (59.1)	39 (65.0)
Glofitamab related	13 (81.3)	22 (50.0)	35 (58.3)
<b>Grade 5 AE</b>	2 (12.5)	7 (15.9)	9 (15.0)
Glofitamab related	0	0	0



The incidence and severity of AEs were consistent with the known safety profile of glofitamab<sup>1</sup>



# CRS summary

n (%)	1000mg Gpt cohort (n=16)	2000mg Gpt cohort (n=44)	All patients (N=60)	n (%)	1000mg Gpt cohort (n=16)	2000mg Gpt cohort (n=44)	All patients (N=60)
<b>Any grade CRS*</b>	14 (87.5)	28 (63.6)	42 (70.0)	<b>CRS management</b>			
Grade 1	4 (25.0)	18 (40.9)	22 (36.7)	Tocilizumab	11 (68.8)	11 (25.0)	22 (36.7)
Grade 2	6 (37.5)	7 (15.9)	13 (21.7)	Corticosteroid	8 (50.0)	10 (22.7)	18 (30.0)
Grade 3	2 (12.5)	3 (6.8)	5 (8.3)	Tocilizumab and corticosteroids	6 (37.5)	7 (15.9)	13 (21.7)
Grade 4	2 (12.5)	0	2 (3.3)	ICU admission	5 (31.3)	4 (9.1)	9 (15.0)
<b>Serious AE of CRS†</b>	11 (68.8)	12 (27.3)	23 (38.3)				

The majority of CRS events were Grade 1/2, and a lower incidence of CRS was observed in the 2000mg versus 1000mg cohort

Clinical cut-off date: September 04, 2023.

\*CRS by ASTCT consensus grading criteria.<sup>1</sup> †Serious AE of CRS is defined as per International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use.

ASTCT, American Society for Transplantation and Cellular Therapy; ICU, intensive care unit.

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

# Conclusions

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- Fixed duration glofitamab monotherapy induced high response rates and durable responses in heavily pretreated patients with R/R MCL, including in patients with prior BTKi therapy
  - Durable responses were maintained beyond EOT
- The majority of patients with a CR at EOT remained progression-free and were alive 15 months post-EOT
- The observed safety profile was manageable and consistent with the known safety profile of glofitamab
  - CRS events were predominantly Grade 1/2 and most occurred during Cycle 1
  - A lower incidence of CRS was observed following glofitamab treatment in the higher Gpt dose cohort (2000mg vs 1000mg), this regimen is being used in the ongoing Phase III GLOBRYTE study<sup>1</sup>
  - Strategies to minimize COVID-19 related events will be implemented going forward
- Glofitamab monotherapy is a promising treatment option for patients with R/R MCL