LA RIVOLUZIONE NEL MONDO DEL
LINFOMA MANTELLARE!

Milano, Hilton Milan Hotel
27 gennaio 2025

Responsabili Scientifici
Paolo Corradini, Pier Luigi Zinzani

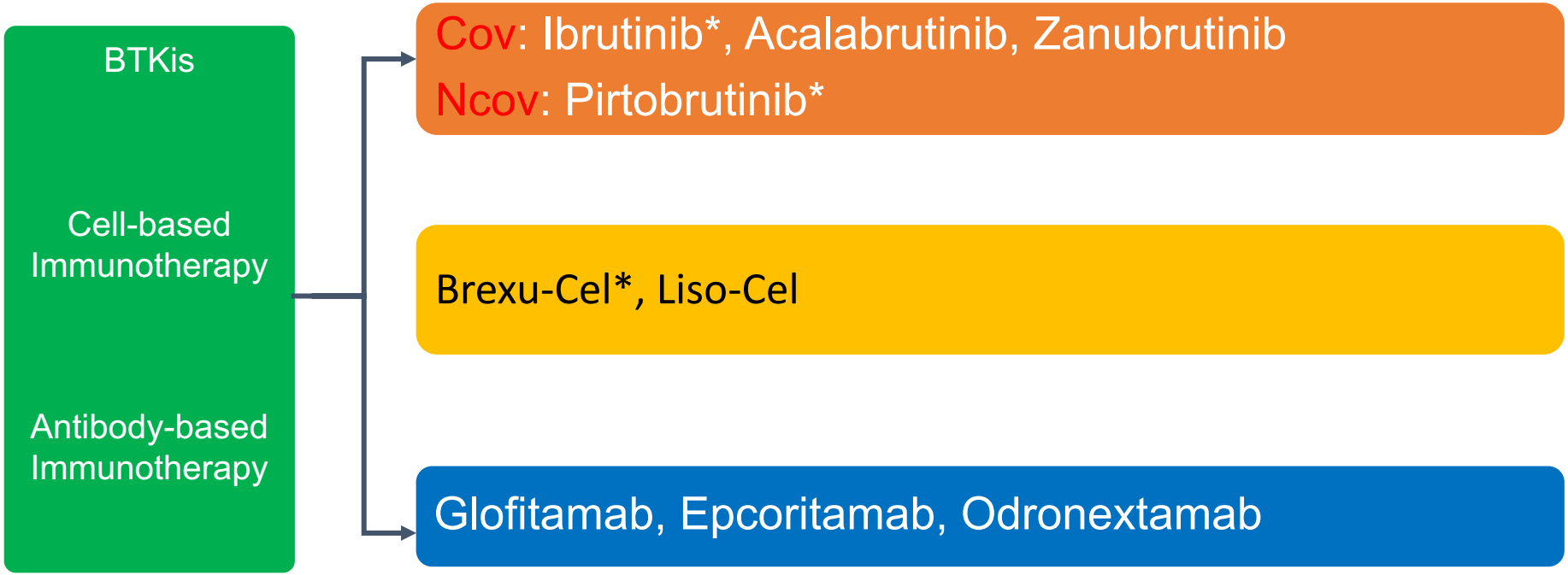
I Bispecifici anche Qui!

Carmelo Carlo-Stella

Disclosures of Carmelo Carlo-Stella

Company name	Research support	Consultant	Stockholder	Advisory board	Other
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
SOBI				X	Honorarium
AbbVie				X	
Genmab				X	

The Pillars of Revolution



*EMA/AIFA approved

The Pillars of Revolution

Cov: Ibrutinib*, Acalabrutinib, Zanubrutinib

> CR 23%, PFS 25- 33 mos

Ncov: Pirtobrutinib*

> CR 24%, PFS 6 mos

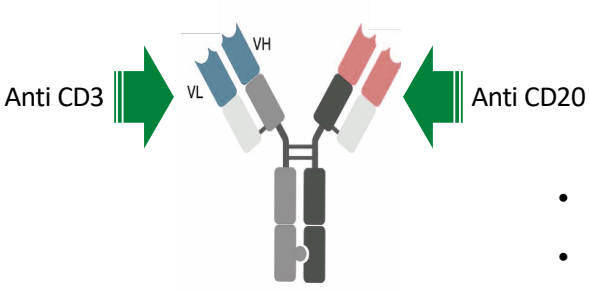
Brexu-Cel* > CR 68%, PFS 26 mos G≥3 CRS & NE (15%-30%)

Liso-Cel > CR 72%, PFS 15 mos Lower TOX but response duration requires longer FU

Structural Features of the CD20x3 Bispecific Antibodies

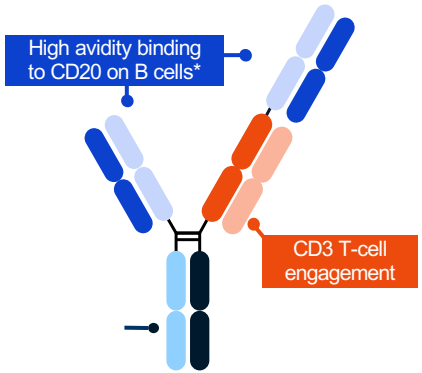
T-cell, binding, activation, expansion, T-cell mediated target cell death at low receptor occupancy

•*Monovalent binding (1:1 format)*
[epcoritamab, odronextmab] reduces avidity and results in lower antitumour activity in preclinical models



- CD3 on T-cells
- CD20 on B-cells (normal and malignant)
- Full length antibody
- Fc modifications and silencing
- Long half-life and reduced toxicity

•*Bivalent binding (2:1 format)*
[glofitamab] increases avidity binding and results in higher antitumour activity in preclinical models



Glofitamab in Relapsed/Refractory Mantle Cell Lymphoma: Results From a Phase I/II Study

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JCO, 2024

Aim: To report updated efficacy and safety data for patients with R/R MCL treated with glofitamab monotherapy, after a median follow-up of 19.6 months

NP30179 Phase I/II study design

Study design[1]

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

Glofitamab IV administration

- Fixed-duration treatment: maximum 12 cycles

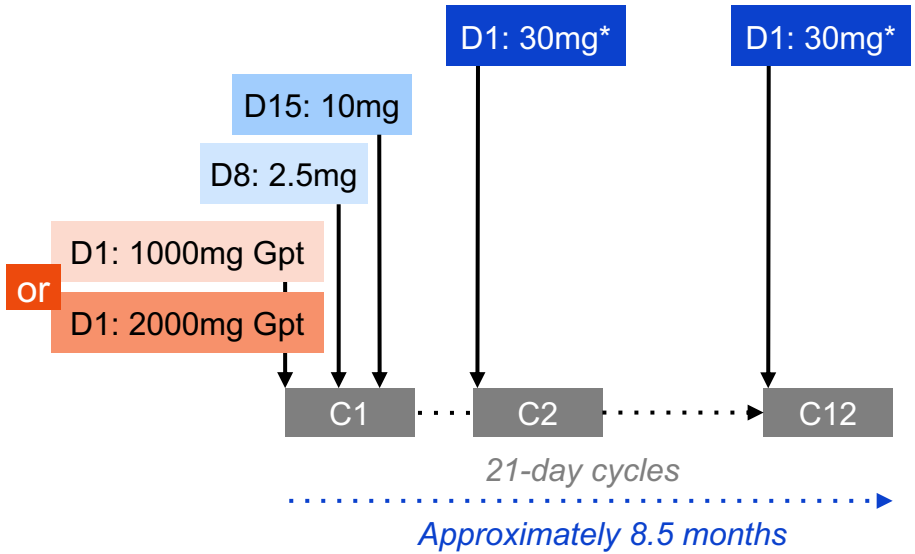
Population characteristics

- Age ≥18 years
- ≥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.

1. NCT03075696. Available at: https:www.clinicaltrials.gov.

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)	20 (69.0)	50 (83.3)
	Refractory to 1L therapy	17 (54.8)	14 (48.3)	31 (51.7)
	Refractory to last prior therapy	27 (87.1)	17 (58.6)	44 (73.3)

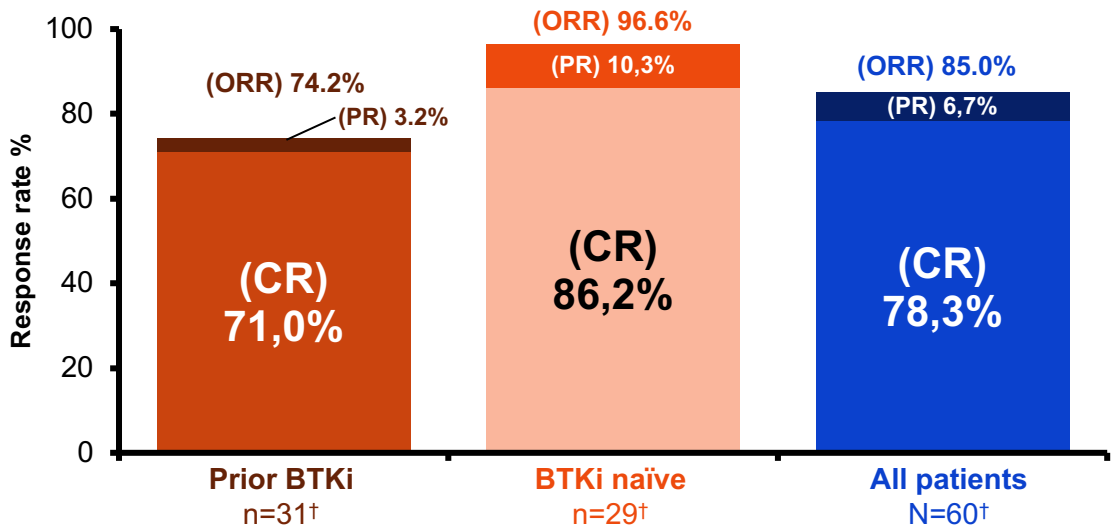
Patients with R/R MCL were heavily pretreated and highly refractory to their last prior therapy

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)

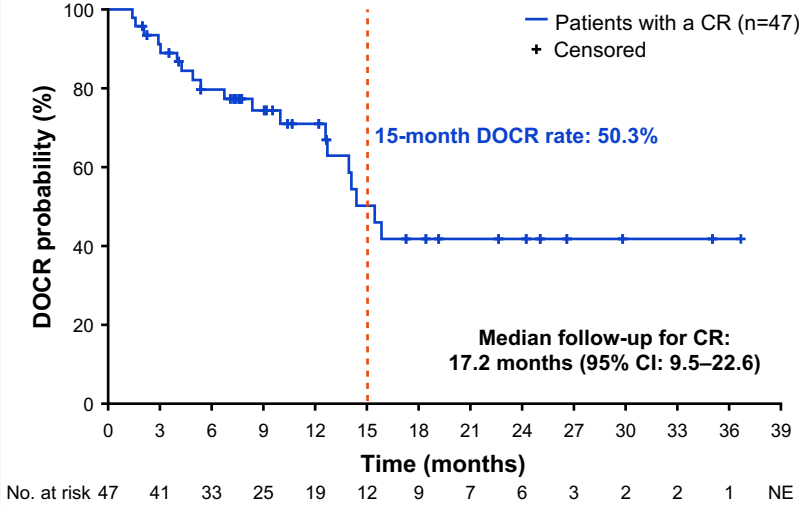
High CR and OR rates were observed in the overall population and in both BTKi-naïve patients and those with prior BKTi therapy

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
Median DOCR, months (95% CI)	12.6 (5.4–NE)	15.4 (12.7–NE)
15-month DOCR rate, % (95% CI)	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**
Median DOR, months (95% CI)	12.6 (7.4–NE)	16.2 (12.6–NE)
15-month DOR rate, % (95% CI)	NA	59.7 (44.1–75.3)
Ongoing response, n (%)	10 (43.5)	28 (54.9)

DOCR*

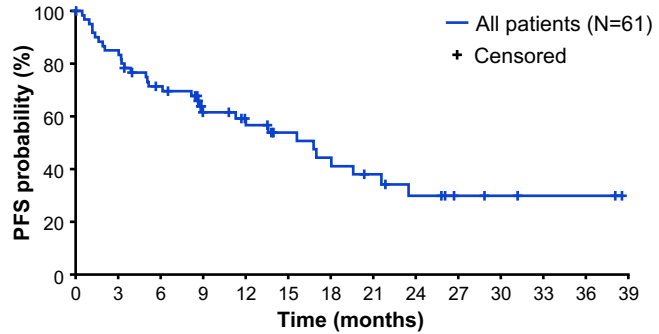


With 17 months' median follow-up, fixed-duration glofitamab monotherapy achieved **durable CRs** with the **majority of CRs (59.6%) still ongoing at data cut-off**

Clinical cut-off date: September 04, 2023.
*Investigator-assessed.
DOR, duration of response; DOCR, duration of complete response; NA, not available; NE, not estimable.

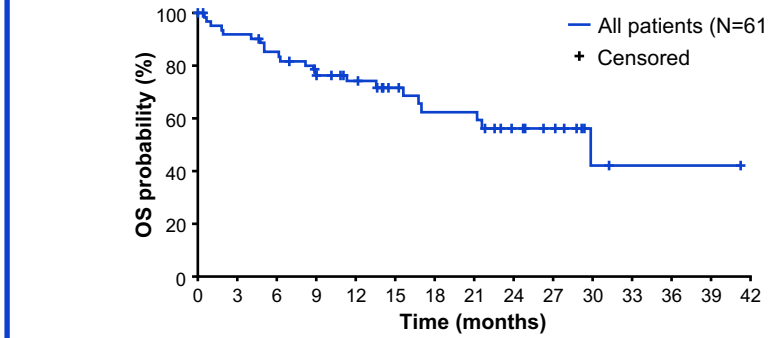
Time-to-event endpoints

PFS



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

OS†



	Prior BTKi n=32*	All patients N=61*
Median OS follow-up, months (95% CI)	24.7 (13.6–28.8)	21.8 (14.0–24.9)
Median OS, months (95% CI)	21.2 (9.0–NE)	29.9 (17.0–NE)
15-month OS rate, % (95% CI)	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

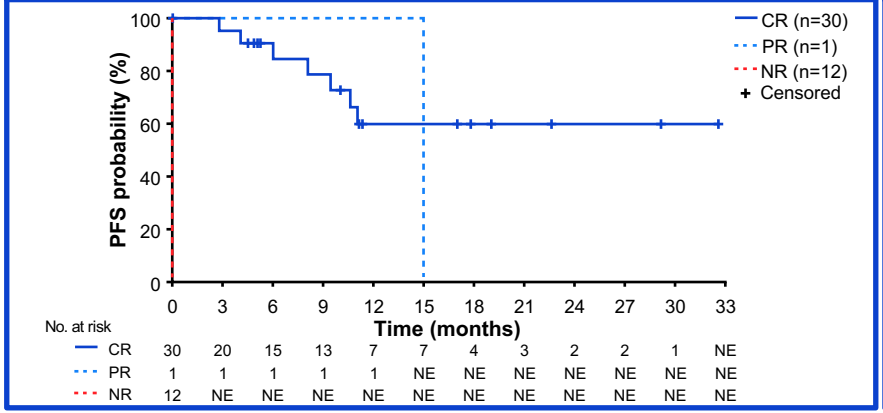
Clinical cut-off date: September 04, 2023.

*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.

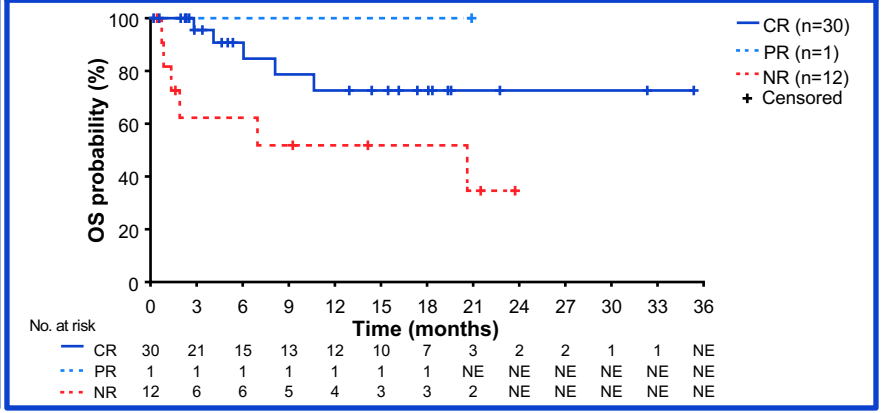
Landmark analyses by response at EOT

PFS



Landmark PFS from EOT in patients with CR at EOT	n=30
Median PFS, months (95% CI)	NE (10.6–NE)
15-month PFS rate, % (95% CI)	59.2 (35.5–83.0)

OS



Landmark OS from EOT in patients with CR at EOT	n=30
Median OS, months (95% CI)	NE (NE)
15-month OS rate, % (95% CI)	72.7 (51.9–93.5)

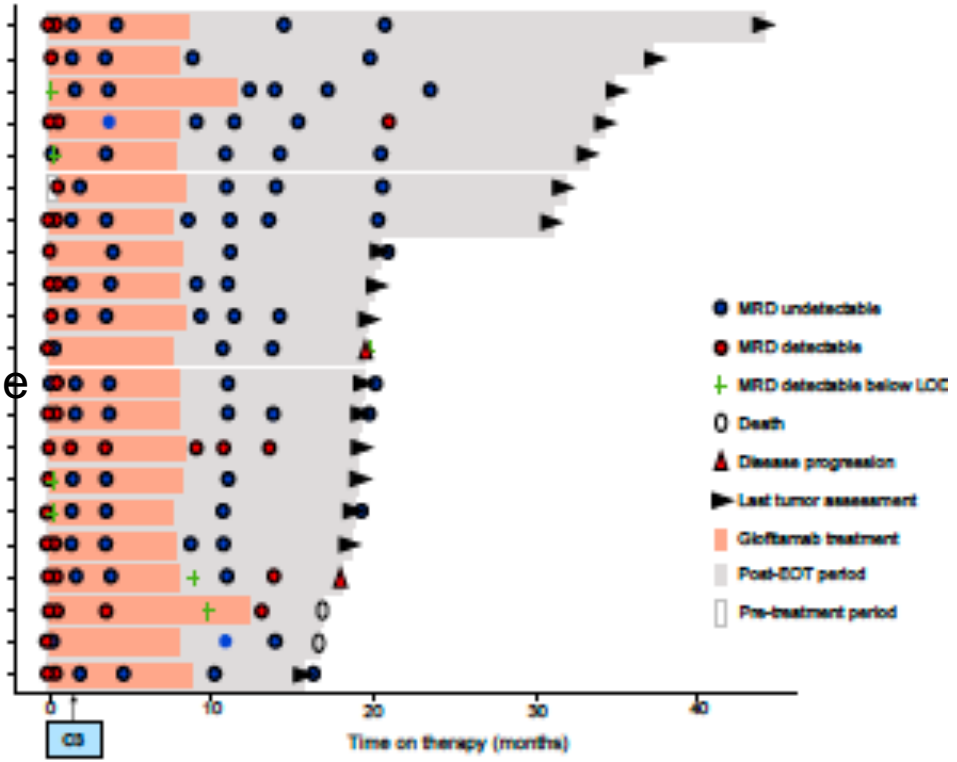
The majority of patients with a CR at EOT **remained progression-free and were alive** at 15 months post-EOT

Clinical cut-off date: September 04, 2023.
EOT, end of treatment; NR, no response.

MRD

14/15 (93.3%) patients with evaluable samples had **undetectable MRD at C3**

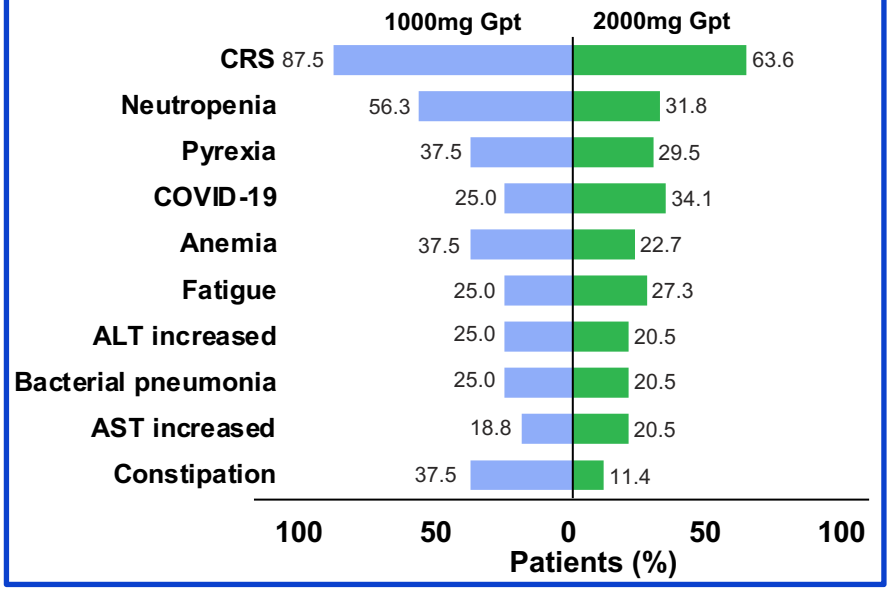
Most patients who achieved undetectable MRD maintained molecular remissions after EOT



Safety summary

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

AEs with an incidence of ≥15% in all patients (N=60)



The incidence and severity of AEs were consistent with the known safety profile of glofitamab[1]

Clinical cut-off date: September 04, 2023.
AE, adverse event; ALT, alanine aminotransferase; AST, aspartate transaminase.

1. Dickinson MJ, et al. N Engl J Med 2022;387:2220–31.

CRS summary

n (%)	1000mg Gpt cohort (n=16)	2000mg Gpt cohort (n=44)	All patients (N=60)
Any grade CRS*	14 (87.5)	28 (63.6)	42 (70.0)
Grade 1	4 (25.0)	18 (40.9)	22 (36.7)
Grade 2	6 (37.5)	7 (15.9)	13 (21.7)
Grade 3	2 (12.5)	3 (6.8)	5 (8.3)
Grade 4	2 (12.5)	0	2 (3.3)
Serious AE of CRS†	11 (68.8)	12 (27.3)	23 (38.3)

n (%)	1000mg Gpt cohort (n=16)	2000mg Gpt cohort (n=44)	All patients (N=60)
CRS management			
Tocilizumab	11 (68.8)	11 (25.0)	22 (36.7)
Corticosteroid	8 (50.0)	10 (22.7)	18 (30.0)
Tocilizumab and corticosteroids	6 (37.5)	7 (15.9)	13 (21.7)
ICU admission	5 (31.3)	4 (9.1)	9 (15.0)

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.[1] †Serious AE of CRS is defined as per International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use.

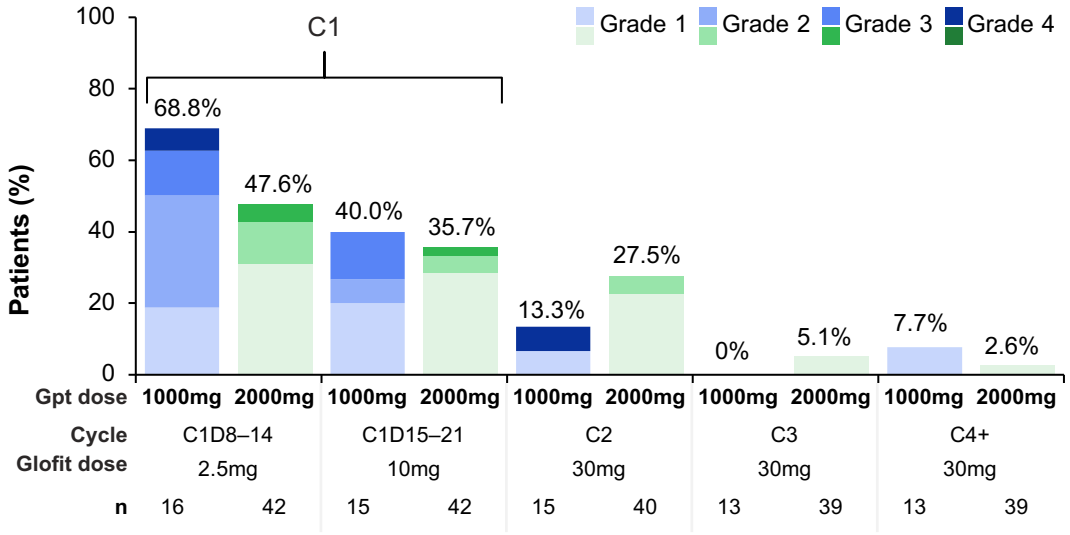
ASTCT, American Society for Transplantation and Cellular Therapy; ICU, intensive care unit.

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

CRS by cycle and grade

	1000mg Gpt cohort (n=16)	2000mg Gpt cohort (n=44)	All patients (N=60)
2.5mg glofitamab			
Median time to CRS* onset, hours (range)	6.1 (3.4–13.0)	17.5 (4.0–46.3)	9.7 (3.4–46.3)
Median CRS duration, hours, (range)	53.3 (9.0–171.2)	21.0 (2.0–692.7)	49.0 (2.0–692.7)
10mg glofitamab			
Median time to CRS onset, hours (range)	17.5 (8.5–34.3)	20.6 (6.7–32.6)	20.6 (6.7–34.3)
Median CRS duration, hours (range)	44.9 (1.0–625.5)	19.5 (1.5–83.0)	24.6 (1.0–625.5)

CRS events by cycle, grade* and Gpt dose



Most CRS events were predominantly in Cycle 1, and the median duration of CRS was shorter in patients in the 2000mg versus 1000mg cohort

Clinical cut-off date: September 04, 2023.
*CRS by ASTCT consensus grading criteria.[1]
Glofit, glofitamab.

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

Other adverse events of interest

n (%)	1000mg Gpt cohort (n=16)	2000mg Gpt cohort (n=44)	All patients (N=60)
Infections			
Any grade	12 (75.0)	32 (72.7)	44 (73.3)
Grade 3/4	4 (25.0)	9 (20.5)	13 (21.7)
Grade 5	2 (12.5)	6 (13.6)	8 (13.3)
ICANS (derived) related to glofitamab			
Any grade	2 (12.5)	1 (2.3)	3 (5.0)
Grade 1	1 (6.3)*	1 (2.3)‡	2 (3.3)
Grade 2	1 (6.3)†	0	1 (1.7)

n (%)	1000mg Gpt cohort (n=16)	2000mg Gpt cohort (n=44)	All patients (N=60)
COVID-19/COVID-19 pneumonia			
Any grade	4 (25.0)	15 (34.1)	19 (31.7)
Grade 3/4	1 (6.3)	4 (9.1)	5 (8.3)
Grade 5	0	5 (11.4)	5 (8.3)

- One additional patient died due to post-acute COVID-19 syndrome and one further patient died due to COVID-19/COVID-19 pneumonia outside of the AE reporting window
- All patients who died due to COVID-19 had achieved a CR, and six remained in remission at the time of death

COVID-19-related events, including deaths, were observed during the pandemic

All ICANS events were resolved and considered non-serious

Clinical cut-off date: September 04, 2023.

*Confusional state. †Disorientation. ‡Mental state changes.

ICANS, immune effector cell-associated neurotoxicity syndrome.

Conclusions

- 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[1]
  - 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

1. NCT06084936. Available at: https:www.clinicaltrials.gov.