9th POSTGRADUATE
Lymphoma
Conference

Bispecifics in MCL: Last Molecule Standing

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City of Hope National Medical Center

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Hotel Brunelleschi

President:
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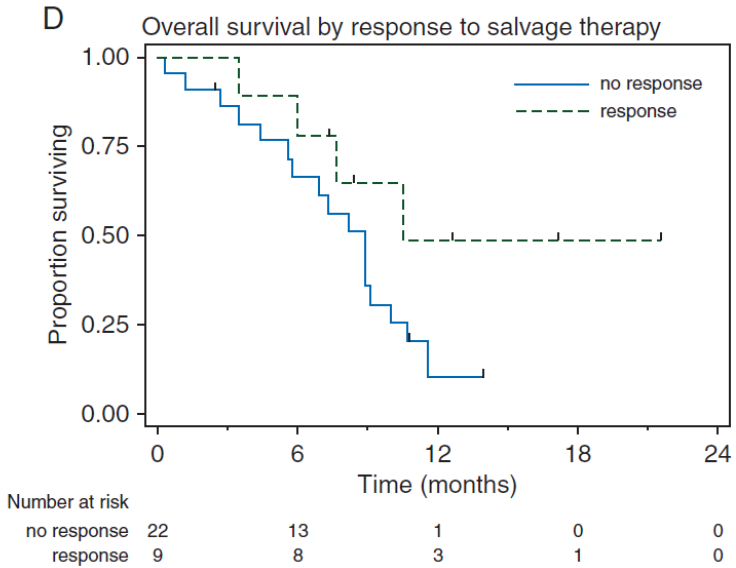
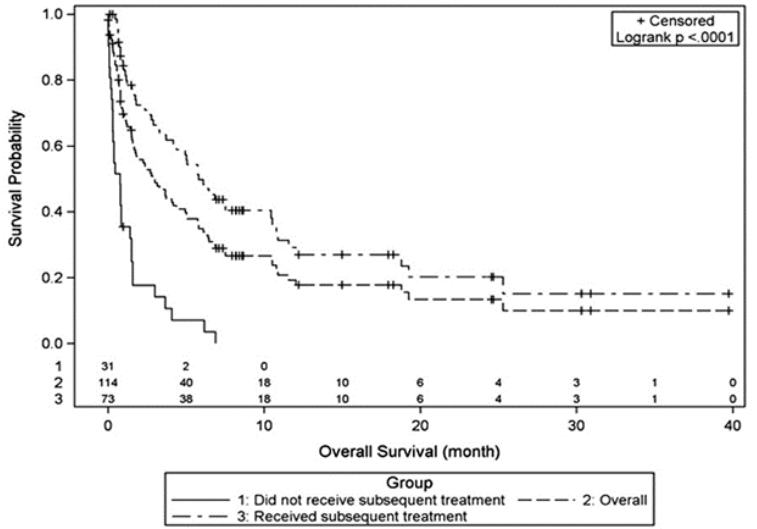
Disclosures

Disclosures of Tycel Phillips

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Abbvie, ADC Therapeutics, AstraZeneca, Bayer, Beigene, BMS, Genmab, Genentech, Gilead, Eli Lily, Epizyme, Incyte, Pharmacyclics, TG Therapeutics, Seattle Genetics			x				
Abbvie, Bayer, BMS, Genentech	x						
Epizyme, Genmab							x
Genentech, Merck, Genmab						x	

Post BTKi Outcomes





Martin et al. Blood 2016;127:1559-1563, Cheah et al. Annals of Oncology Volume 26 | No. 6 | June 2015

What's the best option for this patient?

Options within the United States

- FDA approved options
  - Currently pirtobrutinib and CAR-T
    - Brexu-cel
    - Lis-ocel
- Per NCCN
  - Adds Glofitamab as a 2B recommendation

Glofitamab

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

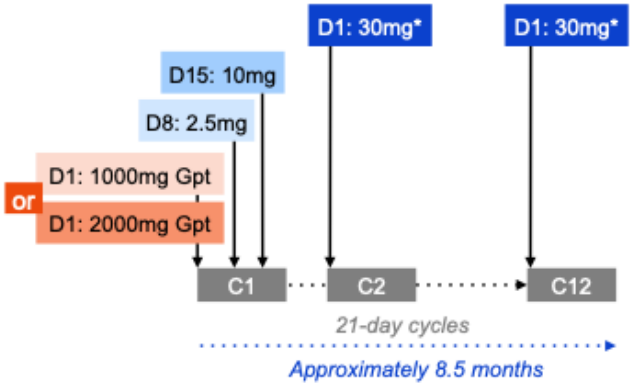
Population characteristics

- 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

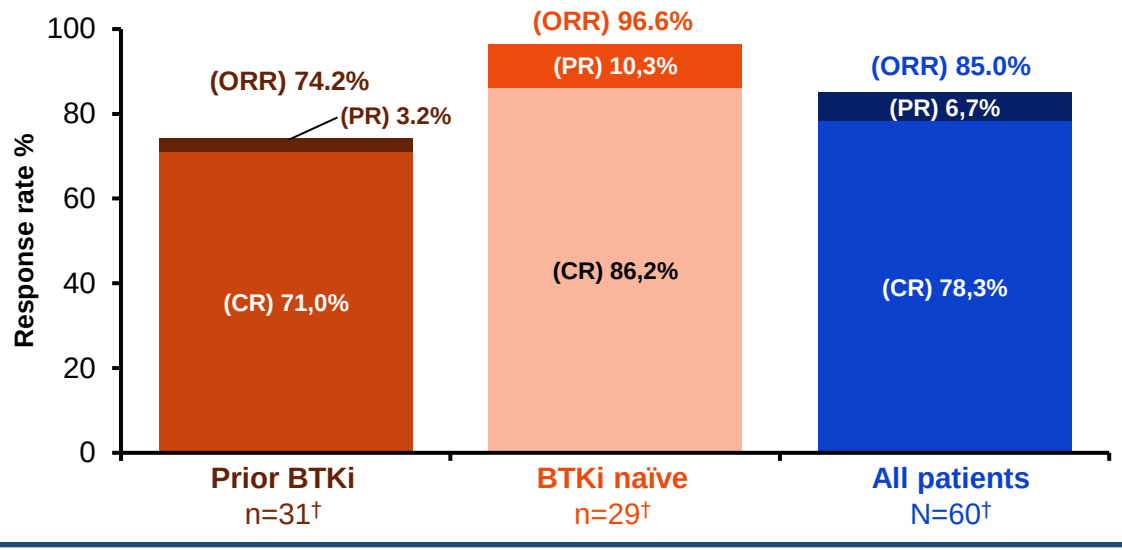


Clinical cut-off date: September 04, 2023.
*In the 1000mg Gpt cohort, two patients had 16mg glofitamab as their target dose in the dose escalation phase.
C, cycle; CRS, cytokine release syndrome; D, day; ECOG PS, Eastern Cooperative Oncology Group performance status; Gpt, obinutuzumab pretreatment; IV, intravenous.

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

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

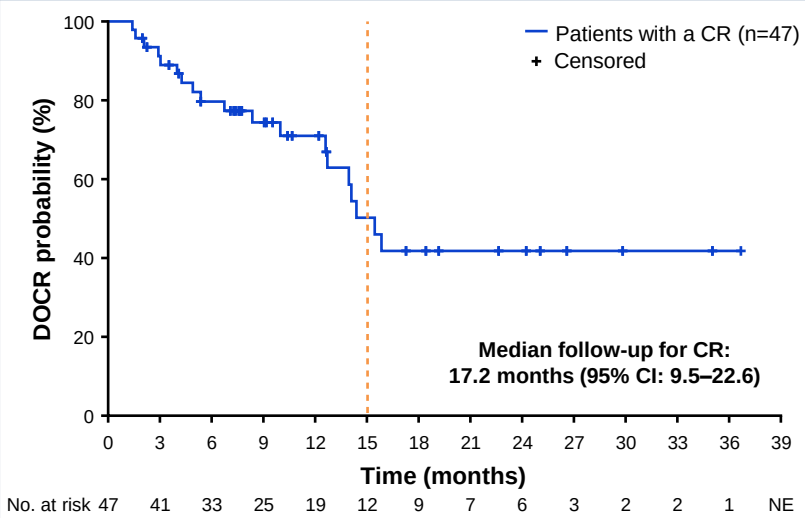
- Clinical cut-off date: September 04, 2023.

*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)	38.0 (15.5–60.6)	59.7 (44.1–75.3)
Ongoing response, n (%)	10 (43.5)	28 (54.9)

DOCR*

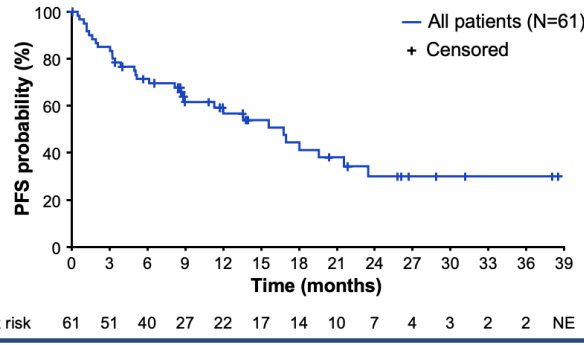


With 17 months' median follow-up, fixed-duration glofitamab monotherapy achieved **durable CRs** with the **majority of CRs (59.6%) still ongoing at data cut-off**

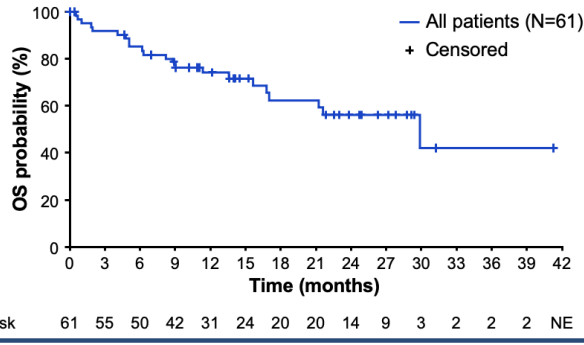
- Clinical cut-off date: September 04, 2023.
- *Investigator-assessed.
- DOR, duration of response; DOCR, duration of complete response; NE, not estimable.

Time-to-event endpoints

PFS



OS†



	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)

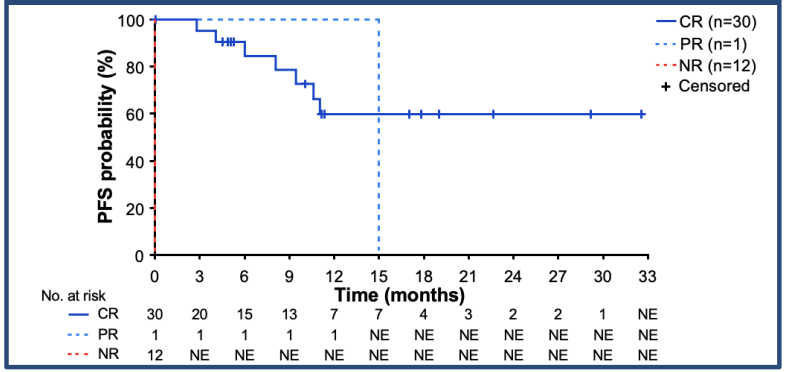
	Prior BTKi n=32*	All patients N=61*
Median OS follow-up, months (95% CI)	24.7 (13.6–28.8)	21.8 (14.0–24.9)
Median OS, months (95% CI)	21.2 (9.0–NE)	29.9 (17.0–NE)
15-month OS rate, % (95% CI)	55.0 (36.5–73.6)	71.4 (59.3–83.5)

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

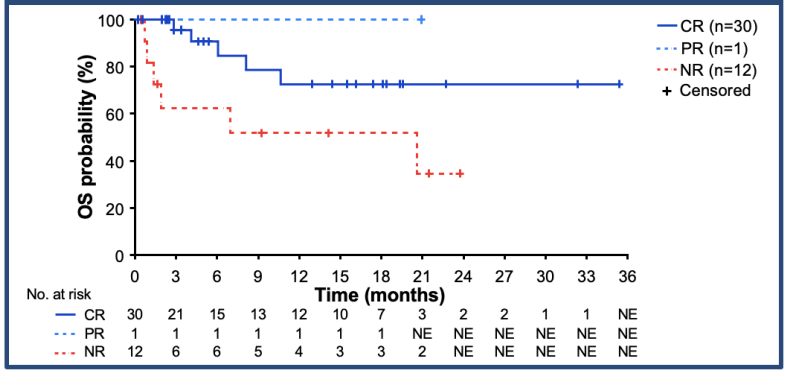
Clinical cut-off date: September 04, 2023. *ITT population. †At the time of analysis, 22 patients had died, the majority due to PD (n=7) or COVID-19 (n=7); other causes of death were pneumonia (n=1), septic shock (n=1), cardiac arrest (n=1), and unknown/other (n=5). All patients who died due to COVID-19 had achieved a CR.
ITT, intention to treat; OS, overall survival; PD, progressive disease; PFS, progression-free survival.

Landmark analyses by response at EOT

PFS



OS



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)

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)

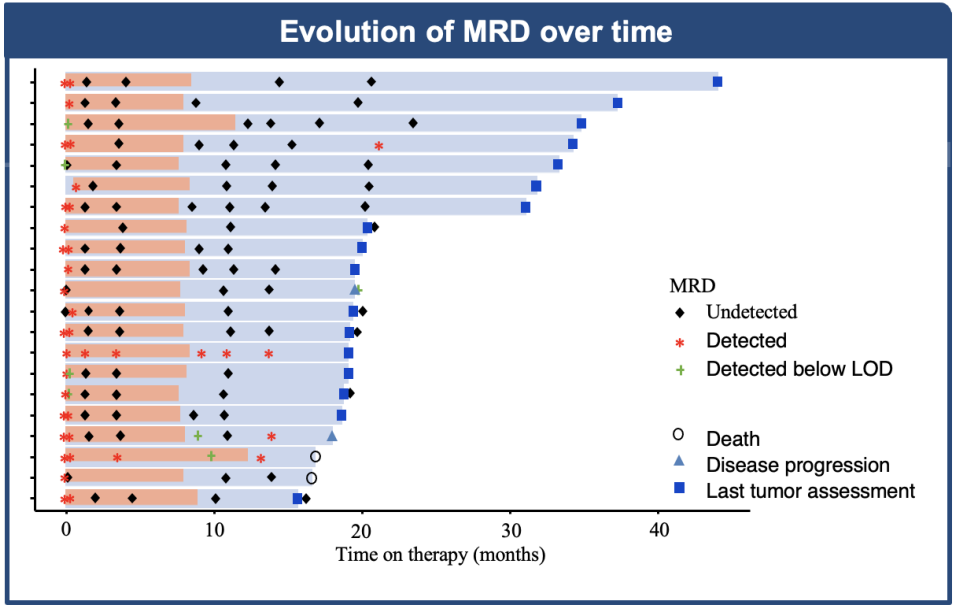
The majority of patients with a CR at EOT **remained progression-free and were alive** at 15 months post-EOT

Clinical cut-off date: September 04, 2023.

EOT, end of treatment; NR, no response.

MRD kinetics are consistent with observed durable responses

- A trackable MRD clone was identified in 21/31 (67.7%) patients in CR at EOT
- Among those patients:
  - 14/15 (93.3%) with evaluable samples had undetectable MRD at C3
  - Most patients with evaluable samples had undetectable MRD at EOT
  - Most patients with evaluable samples who achieved undetectable MRD at C3 had enduring molecular remissions after EOT
- 9/12 (75%) patients with a study visit between 12–18 months had a B-cell count evaluation; of these, 4/9 (44%) showed
  B-cell recovery, defined as ≥70 cell/µL while still in remission



LOD, limit of detection

High response rates were observed in clinically and/or histologically defined high-risk subgroups

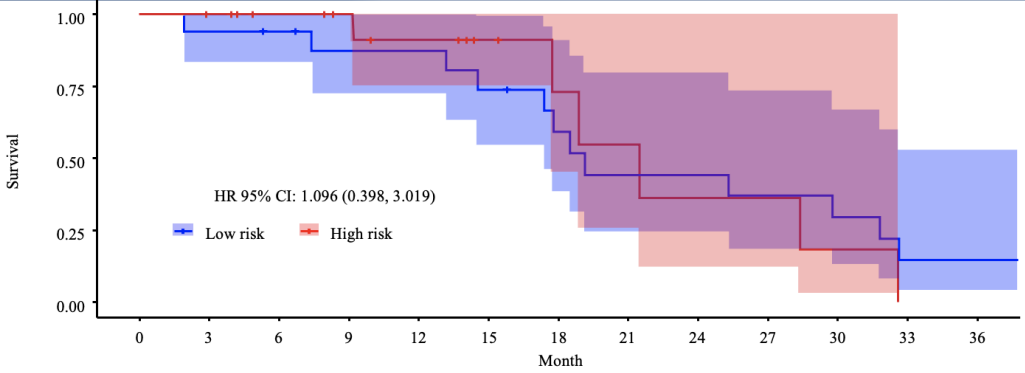
CR, %	N=60 unless stated
Age (years)	
<70 (n=25)	76
≥70 (n=36)	78
Prior lines of therapy	
1 (n=15)	80
2 (n=18)	78
≥3 (n=28)	75
Prior BTKi exposure	
Yes (n=34)	71
No (n=27)	85
Refractory to last prior therapy	
Yes (n=45)	76
No (n=16)	81

CR, %	N=60 unless stated
≥1 high-risk features	N=46
Yes (n=25)	68
No (n=21)	81
Blastoid morphology	N=42
Yes (n=5)	60
No (n=37)	73
Ki-67 expression >50%	N=46
Yes (n=19)	68
No (n=27)	78
p53 expression >50%	N=46
Yes (n=9)	67
No (n=37)	76

Durable remissions were also observed in clinically and/or histologically defined high-risk subgroups

- Median DOCRs in patients with (n=17/21) and without (n=17/25) ≥1 high-risk features were 21.5 months (95% CI: 17.7, NE) and 19.2 months (95% CI: 17.4, 42.8), respectively

DOCR in those with (red) and without (blue) high-risk features



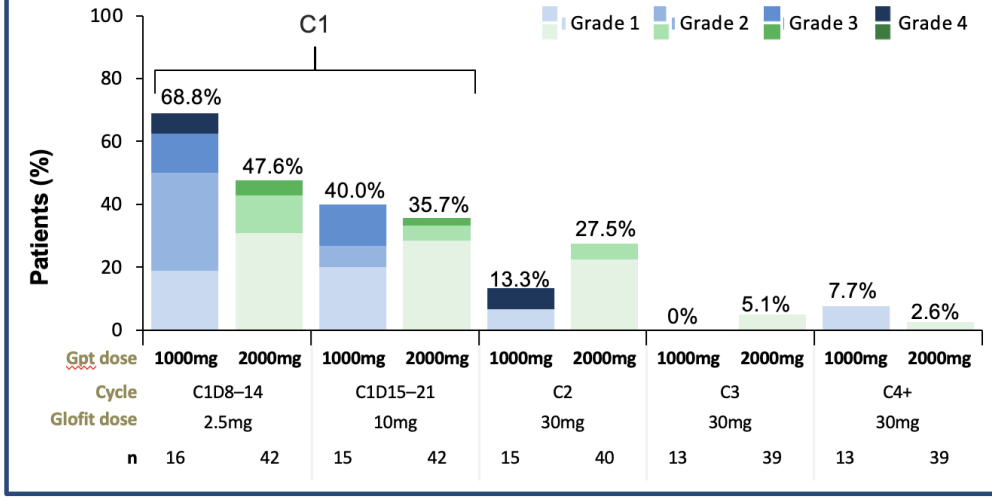
Landmark analysis indicated that most patients who were in CR at EOT were progression-free and alive at 18 months post-EOT

CI, confidence interval; HR, hazard ratio

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



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.

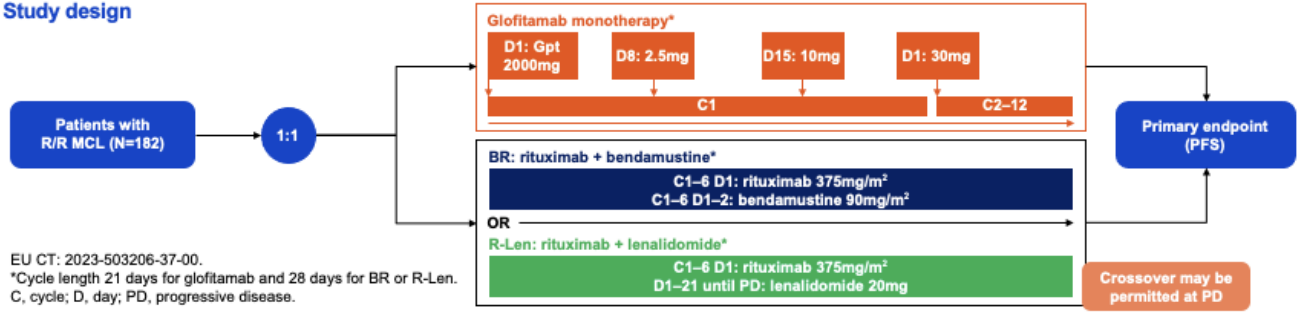
ICANS, immune effector cell-associated neurotoxicity syndrome.

Concern w/ Glofitamab

- Still w/ limited follow up compared w/ data from brexu-cel.
  - More mature data is needed.
    - How durable are the majority of the CRs
    - What is driving relapse
      - CD20 expression
  - Safety
    - CRS is concerning related to our lymphoma subtypes
      - Zero to 100
        - Limited time to monitor
        - Earlier use of toci likely best in most patients

GLOBRYTE (NCT06084936) is a Phase III, open-label, multicenter, randomized, controlled trial in R/R MCL

Study design



EU CT: 2023-503206-37-00.
*Cycle length 21 days for glofitamab and 28 days for BR or R-Len.
C, cycle; D, day; PD, progressive disease.

Key eligibility criteria

Inclusion criteria	Exclusion criteria
• Aged ≥18 years • Histologically confirmed MCL with documentation of either overexpression of cyclin D1 or the presence of t(11:14) • R/R MCL; measurable disease • ECOG performance status 0–2 • ≥1 prior line of systemic therapy including BTKi and another option (e.g. anti-CD20 monoclonal antibody, chemotherapy, or targeted agent such as bortezomib) • Life expectancy ≥12 weeks • Confirmed availability of tumor biopsy tissue (pre-treatment or recent archival specimen)	• Leukemic, non-nodal MCL • Prior CAR T-cell therapy or treatment with glofitamab or other CD20xCD3 bispecific antibodies • Primary/secondary CNS lymphoma, or history of CNS lymphoma or other malignancies* • Current or prior CNS disease (including epilepsy or CNS vasculitis; stroke or transient ischemic attack within the past 2 years) • Significant CV disease (New York Heart Association Class III or IV cardiac disease/Objective Assessment Class C or D), MI within the last 6 months, unstable arrhythmias, or unstable angina • Known active infection at time of enrollment

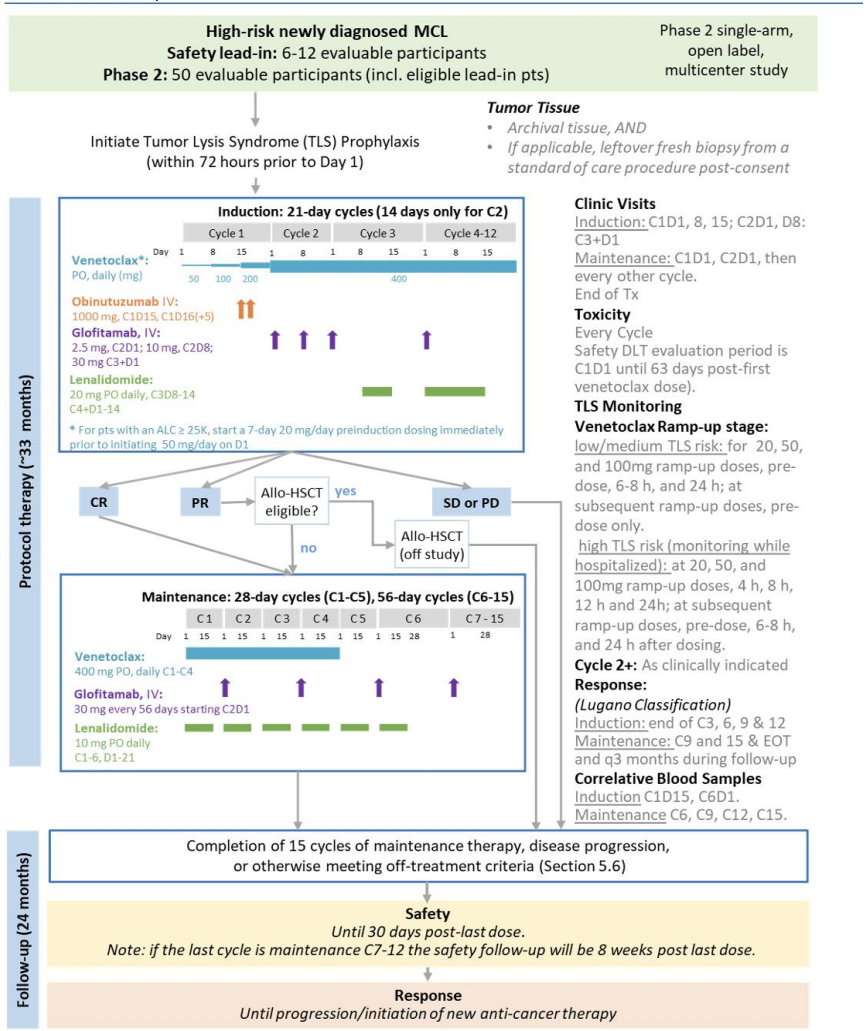
*Except for curatively-treated basal or squamous cell skin cancer, *in-situ* cervical cancer, low-grade early prostate cancer, or any other malignancy treated with curative intent and in remission for ≥2 years. CNS, central nervous system; CV, cardiovascular; ECOG, Eastern Cooperative Oncology Group; MI, myocardial infarction.

Upcoming clinical trials....

NCT	Title	1L or 2L+	Phase	Multisite	Location	Open
NCT05833763	A Phase 2 Trial of Glofitamab and Pirtobrutinib in Mantle Cell Lymphoma Pts w/ Prior BTK Inhibitor Exposure. **(GOIDiLOX)**	2L+	2	Y	AUS	Y
NCT06054776	Acalabrutinib, Obinutuzumab, and Glofitamab for the Treatment of Relapsed or Refractory Mantle Cell Lymphoma.	2L+	½	N	US	Y
NCT06192888	A Study of Glofitamab and Lenalidomide in People with Mantle Cell Lymphoma	2L+	2	Y	US	Y
NCT05861050	Glofitamab With Obinutuzumab, Venetoclax, and Lenalidomide for the Treatment of Patients With Newly Diagnosed High Risk Mantle Cell Lymphoma. **(GLOVe)**	1L	1/2	Y	US	Y
NCT06656221	A Prospective, Single-Center Study Evaluating the Efficacy and Safety of Glofitamab Combined With Orelabrutinib and Bortezomib in Patients With High-Risk Mantle Cell Lymphoma	N/A	N/A	N/A	China	N
NCT06558604	A Phase II Study Evaluating Glofitamab in Combination With Venetoclax Plus Zanubrutinib or Venetoclax Alone in Subjects With Untreated or Relapsed/Refractory High-risk Mantle-cell Lymphoma	1L	2	Y	France	Y
NCT06357676	Glofitamab Plus Ibrutinib With Obinutuzumab for the Treatment of Patients With Mantle Cell Lymphoma	1L	2	Y	US	N

GLOVe in 1L high-risk MCL

- **Inclusion**
  - High risk features as classified by Jain et al. JCO 2020
    - Blastoid/Pleomorphic variants
    - Ki67≥50%
    - Presence of a TP53 mutation defined by either molecular testing or IHC
    - del (17p) by FISH
    - complex karyotype
      - 3 or more cytogenetic abnormalities in addition to t(11:14)
    - High-risk MIPI score (≥6.2)
    - Bulky disease
- **Exclusion**
  - Prior systemic therapy excluding corticosteroids.



Enrollment

Patient Characteristics																
Age Group			Gender		Race					Ethnicity*		P53 status		Blastoid Morph		Enrolled/ Evaluable
Pediatric[1]	Adult[2]	65+	Male	Female	AI	A/PI	B	W	O	H	NH	wt	mut	Y	N	
0	17	13	8	9		1	1	15		3	14	9	8	2	15	17/14

[1]Age 16 and under; [2]Age 17 to 64; [3]Age 65 and up

AI – American Indian; A/PI – Asian/Pacific Islander; B-Black; W- White; O-Other; NA-Unknown H-Hispanic; NH-Non-Hispanic or Latino

wt – wild type; mut – mutation; morph - morphology

Mosunetuzumab

- Published data from Mosunetuzumab Budde et al.
  - 13 enrolled patients
    - ORR 30.8% (CR 23.1%)

Study design: Phase II dose expansion (MCL)

Study design: Phase II dose expansion

Key inclusion criteria

- R/R MCL
- ECOG PS 0–2
- ≥2 prior therapies (including an anti-CD20 antibody, anthracycline or bendamustine therapy, and BTKi)

Objectives

- Primary: efficacy of mosun-pola (best ORR[1] by IRC)
- Secondary: efficacy by INV, durability of response, and safety

Mosun-pola fixed duration administration (NCT03671018)

Mosun

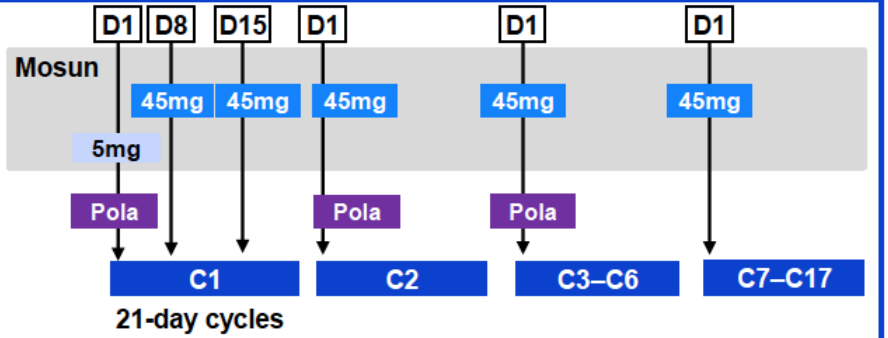
- SC administered in 21-day cycles with step-up dosing in Cycle (C) 1; total of 17 cycles

Pola

- 1.8mg/kg IV on Day [D],1 of C1–6

No mandatory hospitalization

All patients received corticosteroid premedication prior to each dose in C1*



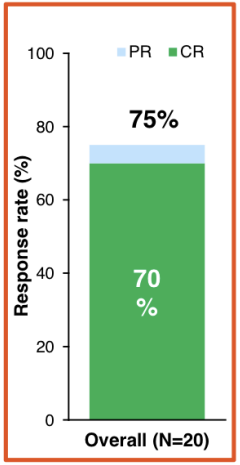
*From C2 and beyond, premedication was optional for patients who did not experience CRS in the previous cycle; corticosteroid premedication consisted of 20mg of dexamethasone or 80mg of methylprednisolone, either IV or orally.

1. Cheson BD, et al. J Clin Oncol 2014;32:3059–68.

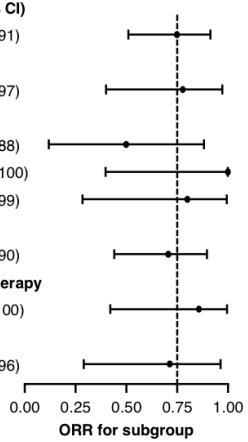
*From C2 and beyond, premedication was optional for patients who did not experience CRS in the previous cycle; corticosteroid premedication consisted of 20mg of dexamethasone or 80mg of methylprednisolone, either IV or orally.

INV-assessed best ORR

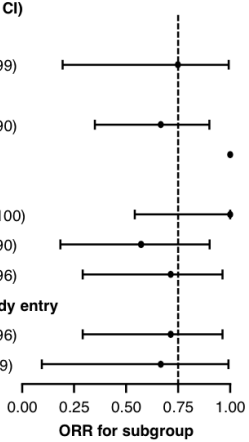
ORR and CR rates in the overall population were 75% and 70%, respectively



Subgroups	No. Patients	ORR (95% CI)
Overall	20 (100%)	75% (51–91)
Age group, in years		
≥70	9 (45%)	78% (40–97)
No. of prior lines of therapy		
3	6 (30%)	50% (12–88)
4	4 (20%)	100% (40–100)
≥5	5 (25%)	80% (28–99)
R/R to last prior therapy		
Refractory	17 (85%)	71% (44–90)
Relapse within 12 months of first prior therapy		
Yes	7 (35%)	86% (42–100)
Received prior CAR-T therapy		
Yes	7 (35%)	71% (29–96)



Subgroups	No. Patients	ORR (95% CI)
R/R to any prior CAR-T therapy		
Refractory	4 (57%)	75% (19–99)
Ki-67		
≥50%	12 (60%)	67% (35–90)
≥30% but <50%	1 (5%)	100%
TP53 aberration at study entry		
Mutation/deletion	6 (30%)	100% (54–100)
Wildtype	7 (35%)	57% (18–90)
Unknown/not done	7 (35%)	71% (29–96)
Morphologic characteristics of MCL at study entry		
Blastoid MCL	7 (35%)	71% (29–96)
Pleomorphic MCL	3 (15%)	67% (9–99)



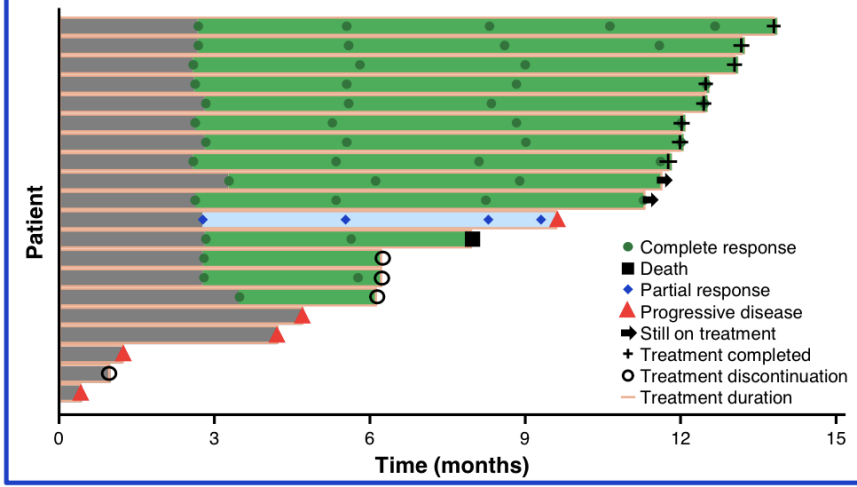
Best ORR rates were generally consistent across high-risk MCL subgroups

Clinical cut-off date: July 6, 2023.

*From C2 and beyond, premedication was optional for patients who did not experience CRS in the previous cycle; corticosteroid premedication consisted of 20mg of dexamethasone or 80mg of methylprednisolone, either IV or orally.

Durability of response

Swimlane plot



- Median follow-up: 15.8 months (range: 0–25)
- Median time to first response: 2.8 months (range: 2.6–3.4)
- Of 14 patients with CR, 11 remain in remission*

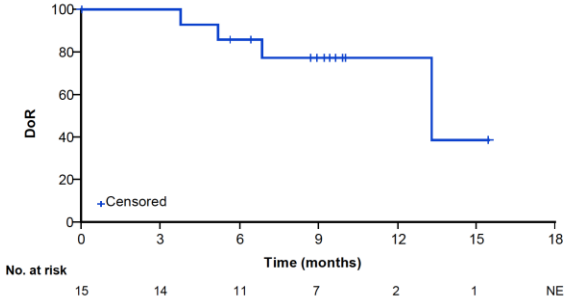
Complete remission was achieved early and remained durable

Clinical cut-off date: July 6, 2023. *Out of the three patients who were not in remission, 1 patient had progressive disease, and two died from non-lymphoma causes.

K/M Curves

Duration of response (DoR)

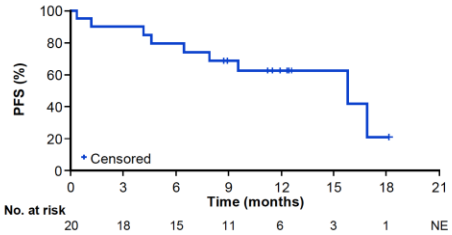
Median DoR: 13.3 months (95% CI: 13.3–NE)



PFS and OS

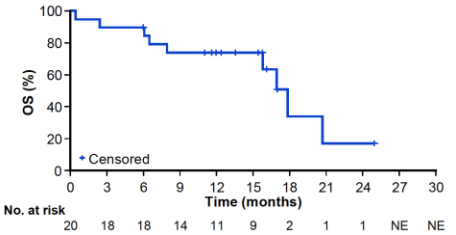
Median follow-up: 15.8 months (95% CI: 12.4–NE)

PFS



	N=20
Median PFS, months (95% CI)	15.8 (8.0–NE)
9-month event-free rate, % (95% CI)	68.8% (48.1–89.6)

OS

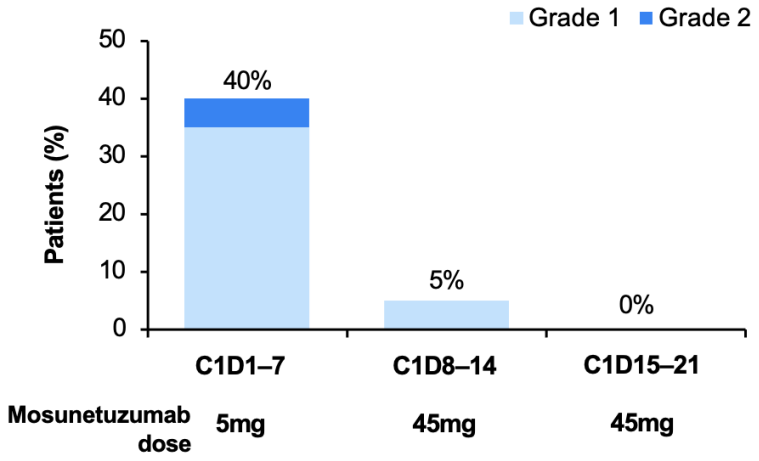


	N=20
Median OS, months (95% CI)	17.9 (15.8–20.7)
9-month event-free rate, % (95% CI)	74.1% (54.5–93.7)

CRS summary

CRS by ASTCT criteria[1]	N=20
Any grade, n (%)	9 (45)
Grade 1	8 (40)
Grade 2*	1 (5)
Grade 3+	0
Median time to first CRS onset relative to last dose, days (range)	1 (0–2)
Median CRS duration, days (range)	3 (1–9)
CRS management, n (%)	
Corticosteroids	1 (5)
Tocilizumab	1 (5)
Low-flow oxygen	1 (5)

CRS by cycle and grade



All CRS events were low grade and resolved within C1

Clinical cut-off date: July 6, 2023. *This patient experienced Grade 2 fever, confusion, and hypoxia on D3; management included tocilizumab, low-flow oxygen, acetaminophen, and broad-spectrum antibiotics.
ASTCT, American Society for Transplantation and Cellular Therapy

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

Other adverse events of interest

AE summary, n (%)	N=20
ICANS*	
Any grade	4 (20)
Grade 3–4	0
Peripheral neuropathy	
Any grade	2 (10.0)
Grade 3–4	0
Tumor flare	
Any grade	2 (10.0)
Grade 3–4	0

AE summary, n (%)	N=20
Serious infections	
Any grade	8 (40.0)
Grade 3–4	3 (15.0)
Grade 5†	3 (15.0)
Neutropenia	
Any grade	4 (20.0)
Grade 3–4	3 (15.0)
Febrile Neutropenia	1 (5.0)

Mosun-pola demonstrated a manageable safety profile consistent with that of the individual agents in patients with R/R MCL, including those with high-risk features

Clinical cut-off date: July 6, 2023. *Treatment-related neurologic AEs potentially consistent with ICANS; patient cases included two cases of memory impairment (Grade 1 and Grade 2), amnesia (Grade 2), agitation (Grade 1), confusional state (Grade 1).
†Grade 5 infections included 2 cases of COVID-19 pneumonia and 1 case of COVID-19.

Concern w/ Mosun/Pola

- Small numbers in original study
  - Study was expanded pending update
- Very w/ limited follow up compared w/ data with other treatments.
  - No updated data after 1 year
    - Mosun as single agent w/ limited impact
      - concern about durability?

Thank you