Bispecifics in Mantle Cell Lymphoma: Path Forward

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Associate Professor

City of Hope

Disclosures

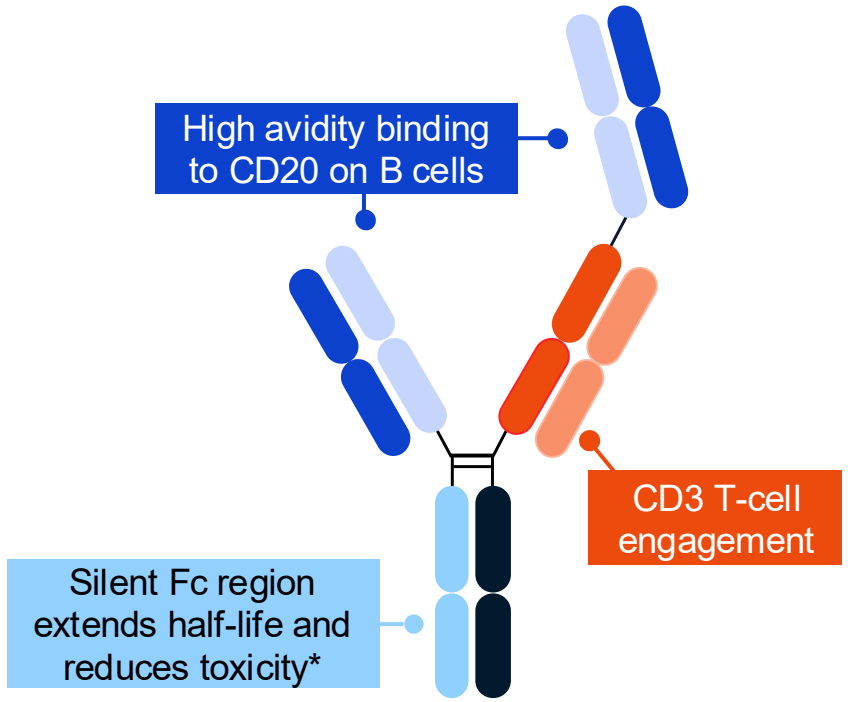
- Advisory Board: Abbvie, Celgene/BMS, Eli Lily, BeOne, ADCT, Seattle Genetics/Pfizer, Merck, Genmab, Genentech, Pharmacyclics,
- Research Funding: Celgene/BMS (sponsoring clinical trial in MCL), Genentech (sponsoring clinical trial in MCL), Sobi (sponsoring clinical trial in MCL), Abbvie (sponsoring clinical trial in MCL)
- Consultancy: Abbvie, Astra Zeneca, Xencor, Caribou , Genentech, Incyte, Gilead/KITE, Janssen, Pfizer, Ipsen, BMS, Johnson and Johnson, Legend Biotech.

Outline

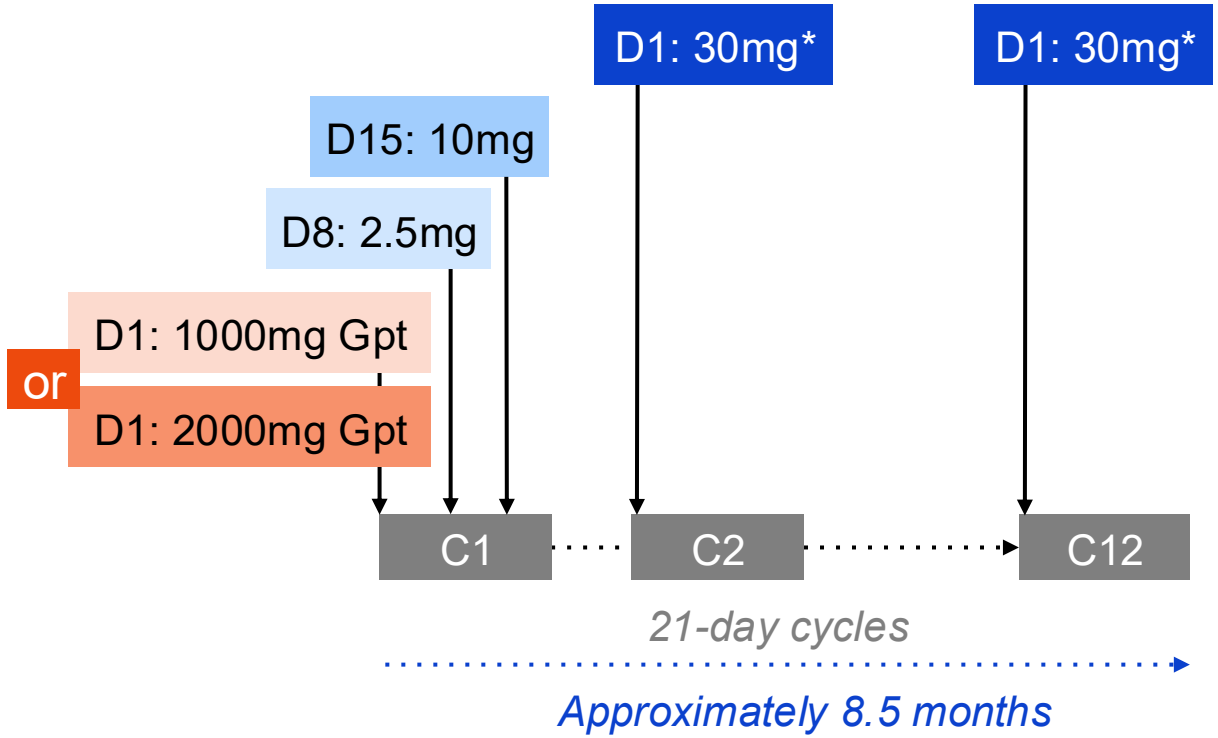
- Monotherapy
  - Glofitamab
  - Mosunetuzumab
- Combinations
  - R/R
    - Mosun/Pola
    - Pending data
    - Upcoming studies
  - 1L
    - Glofit
    - Mosun

NP30179 Phase I/II study design (MCL)

Glofitamab: *CD20xCD3 bispecific antibody with 2:1 format for increased potency versus 1:1 format*[9]



Dosing schedule



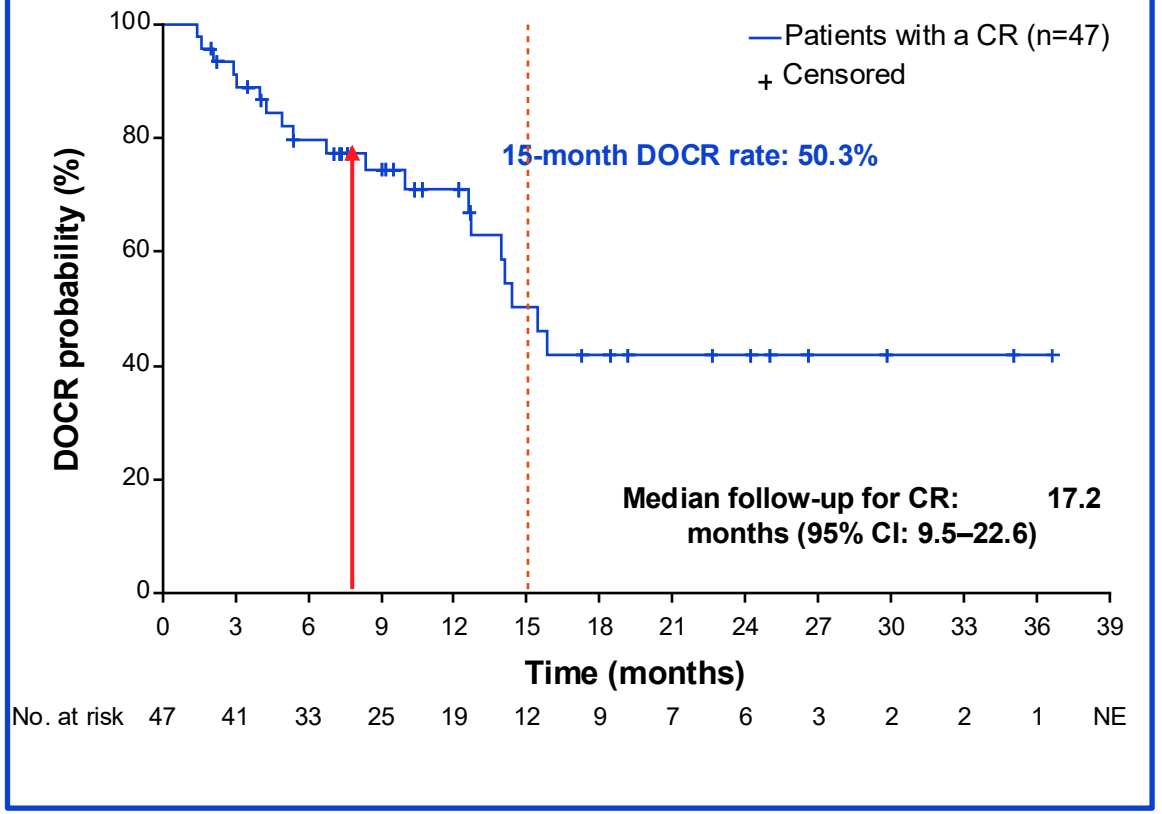
Clinical cut-off date: September 04, 2023.
*In the 1000mg Gpt cohort, two patients had 16mg glofitamab as their target dose in the dose escalation phase.
C, cycle; CRS, cytokine release syndrome; D, day; ECOG PS, Eastern Cooperative Oncology Group performance status; Gpt, obinutuzumab pretreatment; IV,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

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

Duration of response

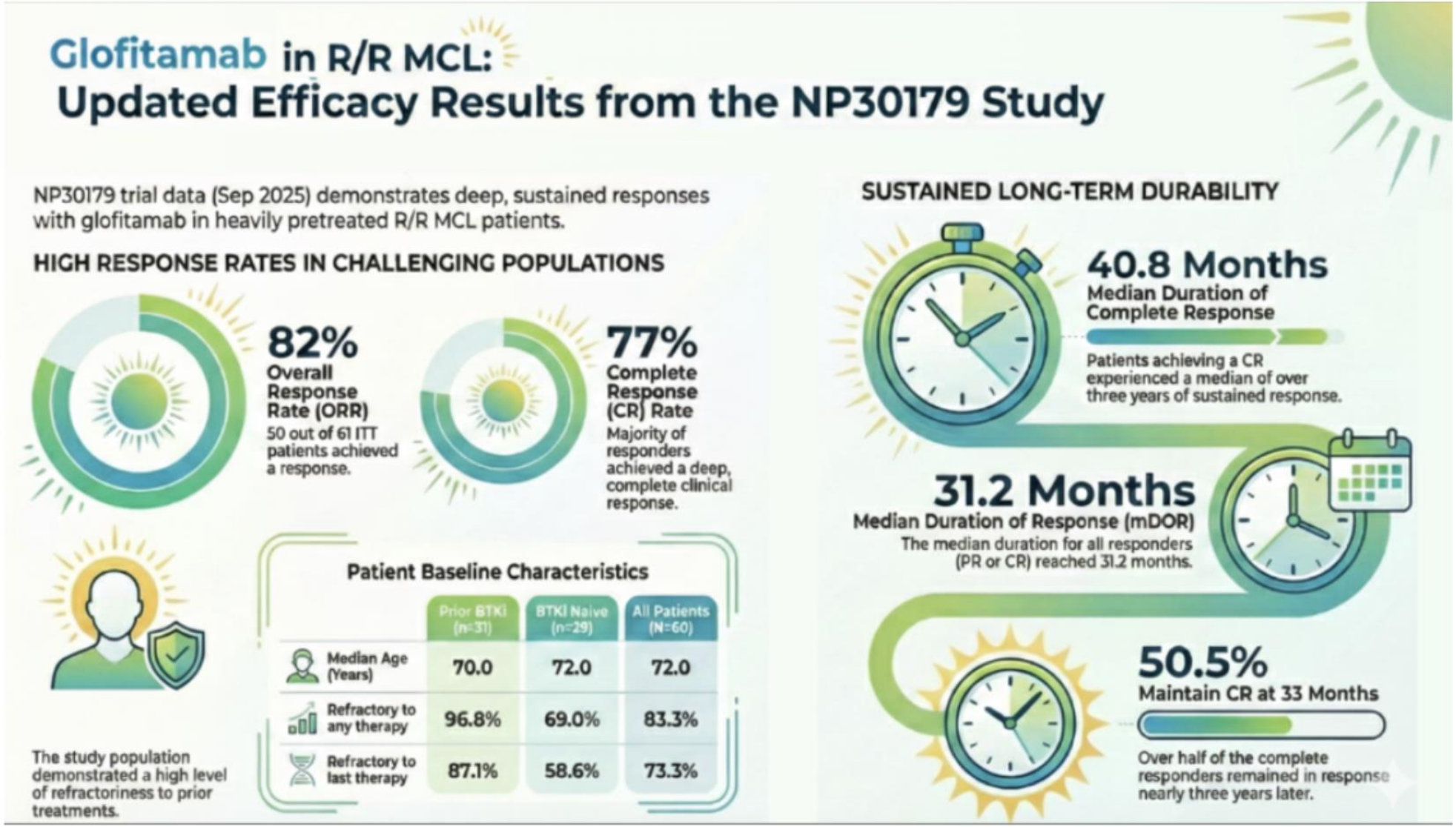
DOCR*	Prior BTKi n=22	All patients n=47
Median DOCR, months (95% CI)	12.6 (5.4–NE)	15.4 (12.7–NE)
15-month DOCR rate, % (95% CI)	33.5 (10.6–56.4)	50.3 (32.0–68.6)
Ongoing CR, n (%)	10 (45.5)	28 (59.6)
DOR*	**n=23**	**n=51**
Median DOR, months (95% CI)	12.6 (7.4–NE)	16.2 (12.6–NE)
15-month DOR rate, % (95% CI)	38.0 (15.5–60.6)	59.7 (44.1–75.3)
Ongoing response, n (%)	10 (43.5)	28 (54.9)

DOCR*



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

Updated Response Data



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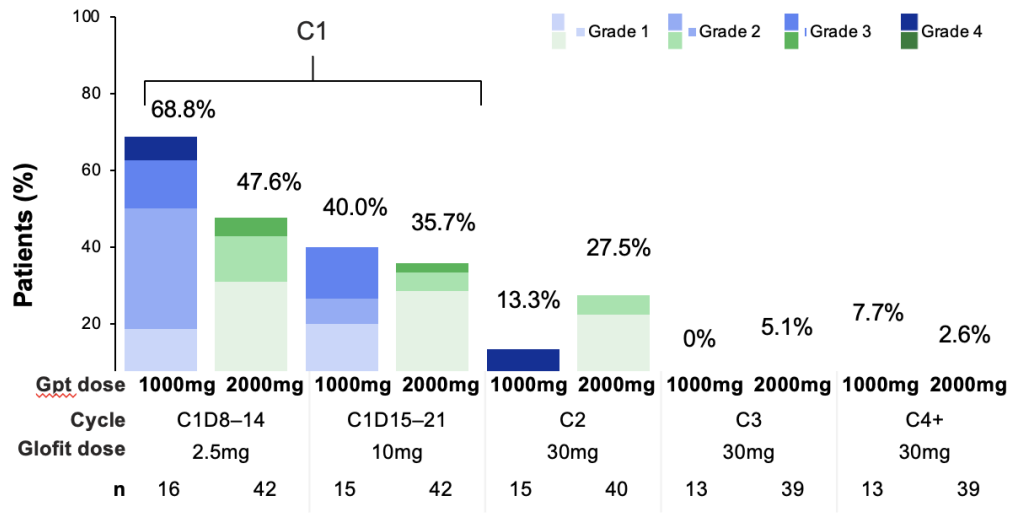
CRS by cycle and grade

n (%)	1000mg Gpt cohort (n=16)	2000mg Gpt cohort (n=44)
Any grade CRS*	14 (87.5)	28 (63.6)
Grade 1	4 (25.0)	18 (40.9)
Grade 2	6 (37.5)	7 (15.9)
Grade 3	2 (12.5)	3 (6.8)
Grade 4	2 (12.5)	0
Serious AE of CRS†	11 (68.8)	12 (27.3)

	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.

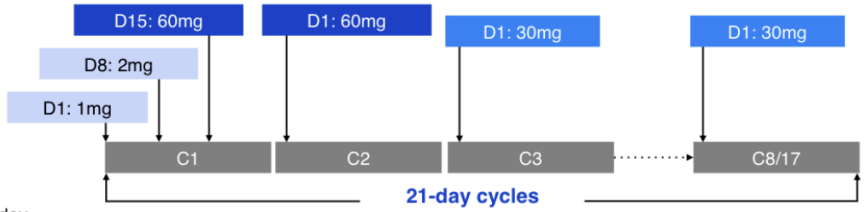
1. Lee DW, et al. Biol Blood Marrow Transplant 2019;25:625–38

Glofitamab Summary

- Maturing data indicates ongoing responses in those w/ a CMR on the 179 study
  - Official update in ASCO/EH
- Safety remains biggest issue
  - New mitigation strategy implemented during SUD
- Ongoing phase 3 study

Mosunetuzumab

Figure 1. Mosunetuzumab dosing schedule.



C, cycle; D, day.

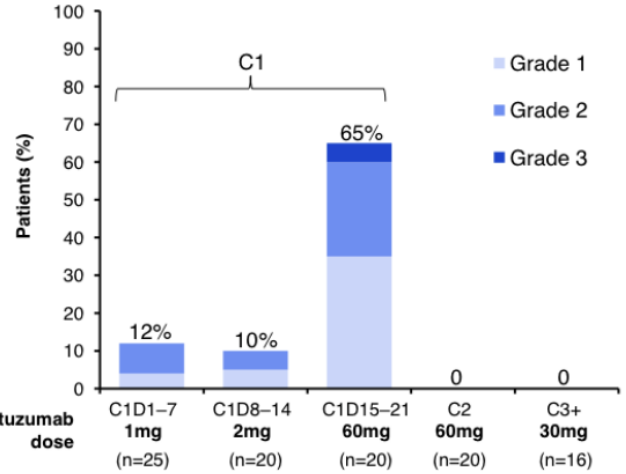
Table 1. Summary of patient demographic and baseline characteristics.

n (%) unless stated otherwise	All patients (N=25)
Median age, years (range)	70 (50–89)
Male	20 (80.0)
ECOG PS 0 / 1	9 (36.0) / 16 (64.0)
Ann Arbor stage III/IV	23 (92.0)
Ki-67 status <30% / ≥30–<50% / ≥50% / unknown	1 (4.0) / 2 (8.0) / 11 (44.0) / 11 (44.0)
MIPI score <6 / ≥6	4 (16.0) / 21 (84.0)
Bulky disease >6cm / >7cm / >10cm	10 (40.0) / 5 (20.0) / 3 (12.0)
Morphology at baseline Blastoid MCL / classic MCL not known / other	7 (28.0) / 10 (40.0) 7 (28.0) / 1 (4.0)
Bone marrow involvement	13 (52.0)
Prior autologous stem cell transplant	8 (32.0)
Median lines of prior therapy, n (range)	3 (2–6)
Number of prior lines of therapy 2 / ≥3	5 (20.0) / 20 (80.0)
Refractory to Last prior therapy / prior BTKi / prior anti-CD20 therapy	23 (92.0) / 24 (96.0) / 18 (72.0)
Failed to respond to prior BTKi	16 (64.0)

Table 5. Summary of CRS events.

n (%), unless stated otherwise	All patients (N=25)
CRS (any grade)	13 (52.0)
Grade 1	6 (24.0)
Grade 2	6 (24.0)
Grade 3	1 (4.0)
Patients with events resolved (n=13)	13 (100.0)
Median CRS duration, days (range)	3 (1–7)
Corticosteroids for CRS management*	2 (8.0)
Tocilizumab for CRS management	4 (16.0)

Figure 4. CRS events by cycle and grade.



There were no Grade 4 or 5 CRS events. *All patients received mandatory corticosteroid premedication; patients who received corticosteroids for CRS management are defined as those who received it concurrently, not as prophylaxis, and indicated for CRS.

- Suspected immune effector cell-associated neurotoxicity syndrome events occurred in three patients (Grade 1 confusional state [n=2]; Grade 2 delirium [n=1]); two events occurred concurrently with CRS.

Mosunetuzumab Efficacy

Table 2. Efficacy summary.

Months (95% CI) unless stated otherwise	All patients (N=25)
ORR, n (%) [95% CI]	11 (44.0) [24.4–65.1]
CR	6 (24.0) [9.4–45.1]
PR	5 (20.0) [6.8–40.7]
Median DoR	10.3 (2.3–19.5)
Median DoCR	18.0 (10.3–22.3)
Median PFS	3.7 (1.4–5.8)
Median OS	7.3 (3.6–25.9)

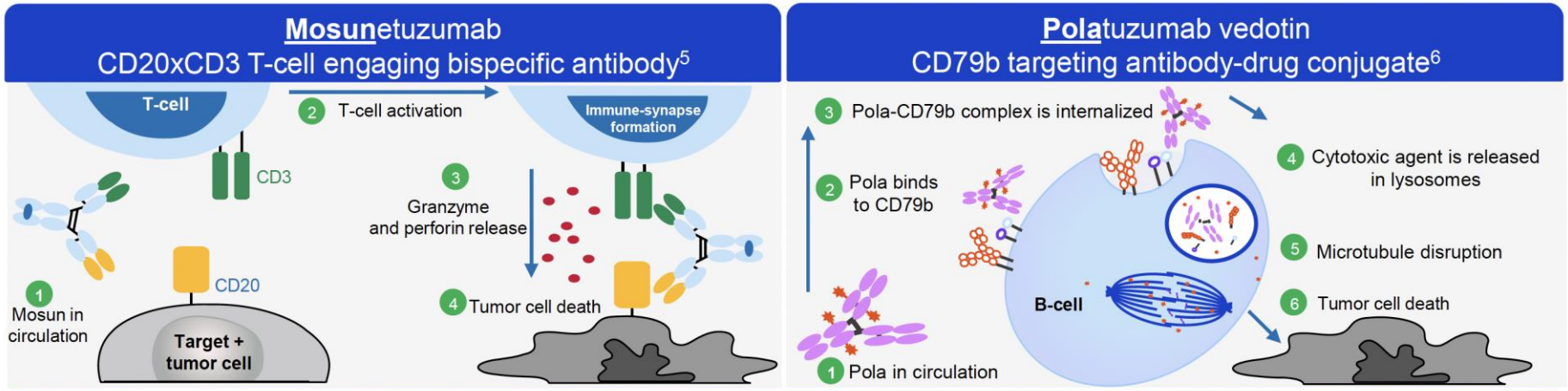
CI, confidence interval.

Table 3. Efficacy summary in high-risk subgroups.

	Patients with Ki-67 status ≥30% (n=13)	Patients with Ki-67 status ≥50% (n=11)	Patients with blastoid MCL (n=7)	Patients with MIPI ≥6 (n=21)
ORR, n (%) [95% CI]	6 (46.2) [19.2–74.9]	6 (54.5) [23.4–83.3]	2 (28.6) [3.7–71.0]	9 (42.9) [21.8–66.0]
CR, n (%)	4 (30.8)	4 (36.4)	2 (28.6)	5 (23.8)
PR, n (%)	2 (15.4)	2 (18.2)	0	4 (19.0)

Combinations

Mosun/Pola



We report updated data from the Phase II expansion cohort (NCT03671018) in patients with R/R MCL who had received prior BTKi therapy

Mosun-Pola fixed duration administration (NCT03671018)

Mosun

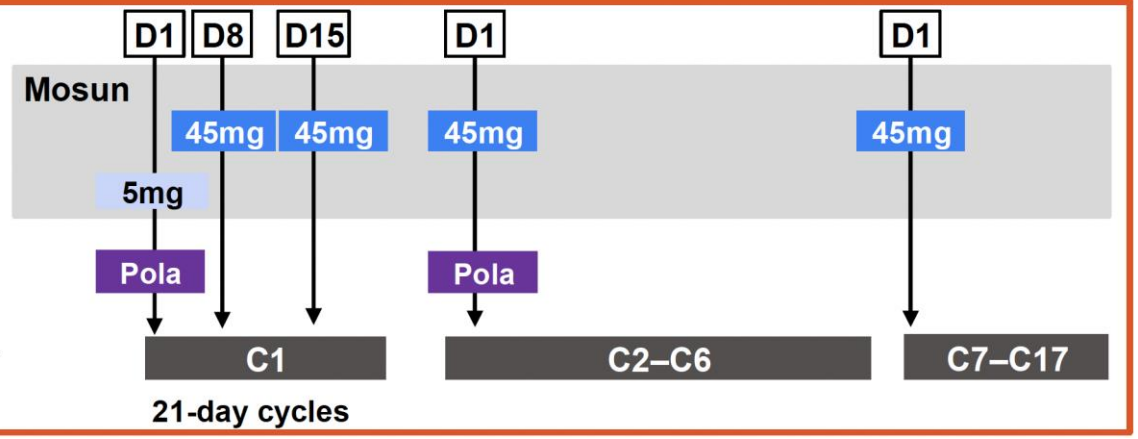
- SC administered in 21-day cycles with step-up dosing in C1; total of 17 cycles

Pola

- 1.8mg/kg IV on D1 of C1–6

No mandatory hospitalization

Corticosteroid premedication was given prior to each dose in C1*



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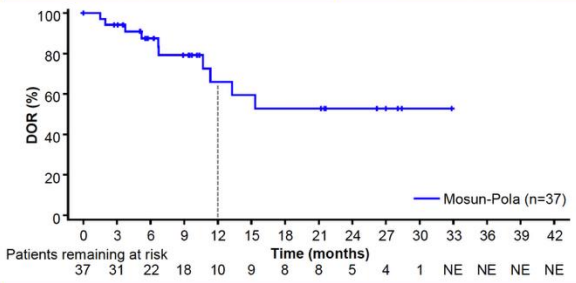
Mosun/Pola

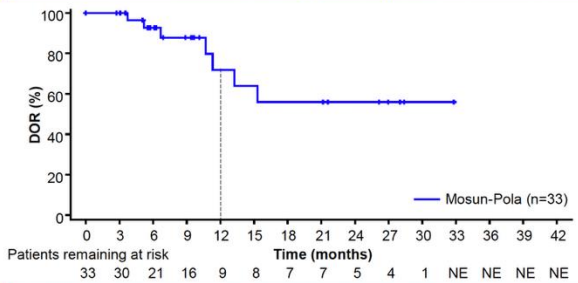
DOR and DOCR

Median follow-up: 15.9 months (95% CI: 13.6–29.0)

Duration of response*



Duration of complete response*



Patients with response	n=37
Median time to first response, months (range)	2.7 (1–7)
Median DOR, months (95% CI)	NR (11.4–NE)
12-month rate, % (95% CI)	66.0 (45.0–86.9)

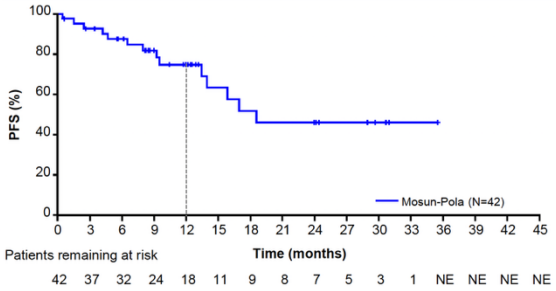
Patients with complete response	n=33
Median time to first CR, months (range)	2.8 (2–18)
Median DOCR, months (95% CI)	NR (11.4–NE)
12-month rate, % (95% CI)	71.9 (49.2–94.6)

Mosun-Pola demonstrated early and durable responses

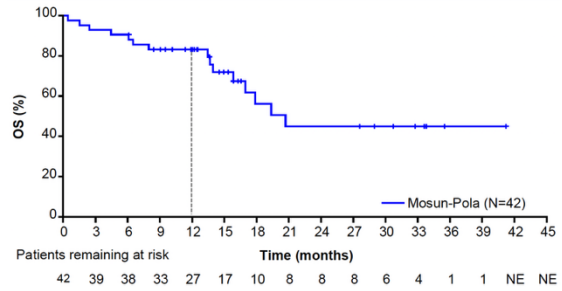
CCOD: November 8, 2024. *IRC-assessed. CI, confidence interval; NE, not evaluable; NR, not reached.

PFS and OS

Progression-free survival*



Overall survival



Patient population	n=42
Median PFS, months (95% CI)	18.6 (13.9–NE)
12-month rate, % (95% CI)	74.8 (60.2–89.4)

Patient population	n=42
Median OS, months (95% CI)	20.7 (17.0–NE)
12-month rate, % (95% CI)	83.1 (71.7–94.5)

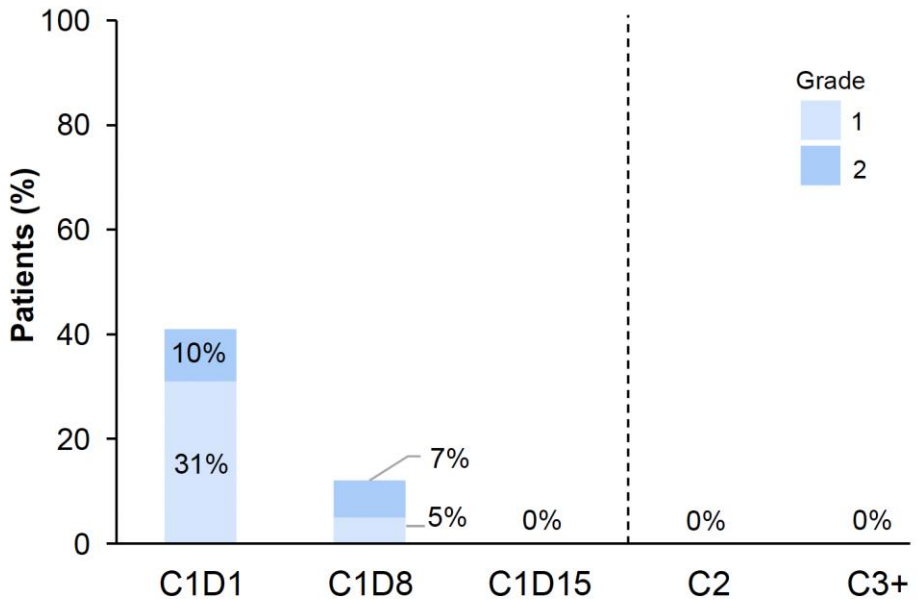
Mosun-Pola demonstrated promising PFS and OS

Mosun/Pola

CRS summary

CRS by ASTCT criteria[1]	N=42
Any grade, n (%)	18 (43)
Grade 1	12 (29)
Grade 2	6 (14)
Grade ≥3	0
Median time to first CRS onset relative to last dose, days (range)	2 (1–5)
Median CRS duration, days (range)	3 (1–9)
CRS management, n (%)	
Corticosteroids	6 (14)
Tocilizumab	6 (14)
Low-flow oxygen	4 (10)
Fluids	3 (7)
ICU	1 (2)

CRS by cycle and grade



All CRS events were low grade and resolved within C1

CCOD: November 8, 2024.
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.

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Mosun/Pola Summary

- Excellent ORR in high-risk patient population
- Safety shines
  - Low CRS rates (mostly all grade 1)
    - Better situated to integrate into US community space
- Early DOR and PFS encouraging
  - Look forward to updated data…

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Current/Upcoming Combination Studies 2L+

- Glofitamab and pirtobrutinib
  - Australia and US
- GLOASIS
  - Glofitamab With venetoclax +/- zanubrutinib in High-risk Mantle-cell Lymphoma
    - France/Belgium
- Glofitamab + lenalidomide
  - US
- Glofitamab and Polatuzumab
  - R/R
    - US – Lycon group
- Glofitamab and Loncastuximab
  - R/R
    - US - COH

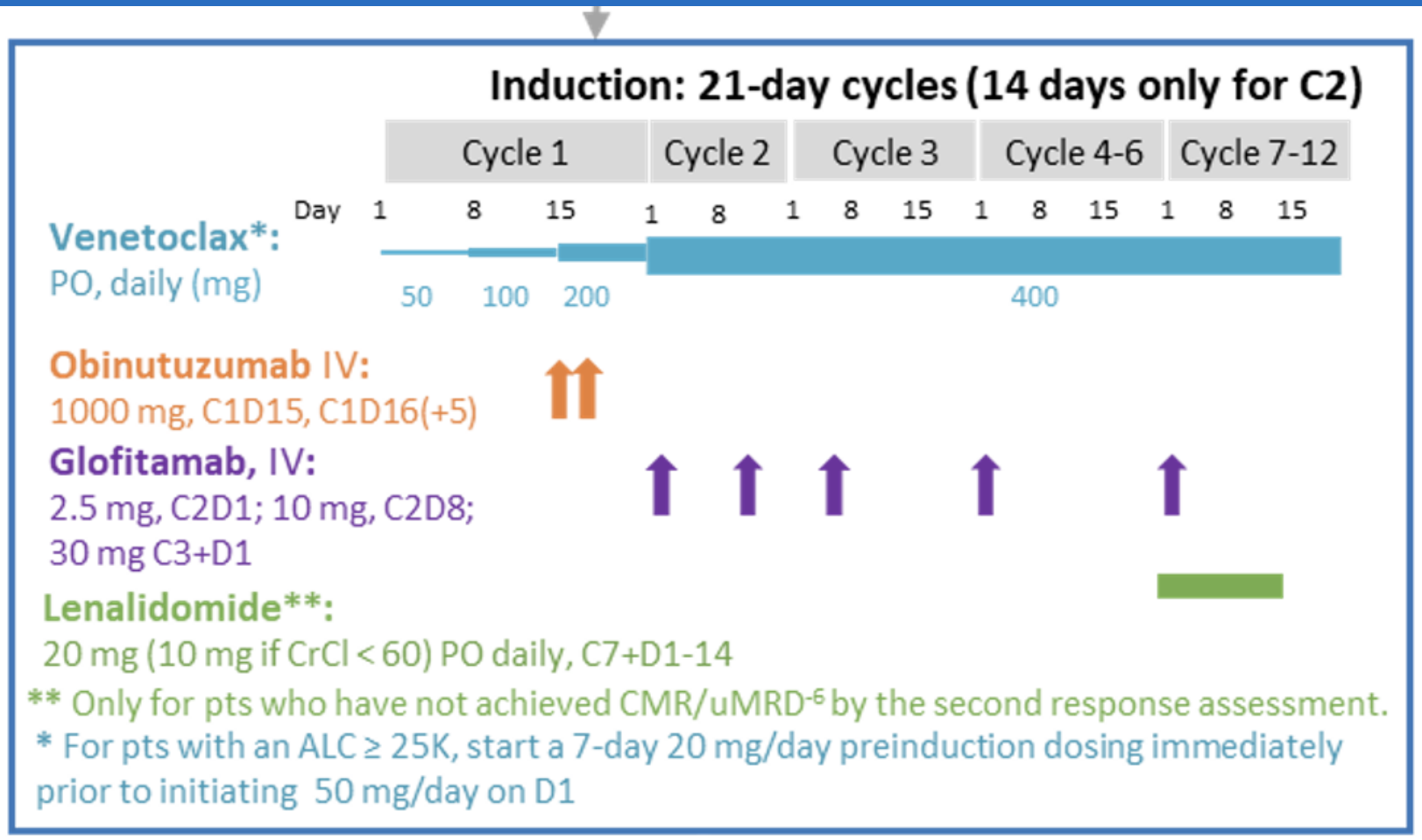
GLOVe: Phase 2 study of Glofitamab LenalidOmide and Venetoclax in 1L patients w/ High Risk Mantle Cell Lymphoma

Tycel Phillips, MD[1], Allison Bock, MD[2], Alex Herrera, MD[1], Geoff Shouse MD[1], Daniel Ermann, MD[2], Reem Karmali, MD[3], Adam Kittai, MD[4], Victor Orellana-Noia, MD[1], Avy Kallam, MD[1], Narendranath Epperla, MD[2] Diane Smith[1], Lu Chen, PhD[1], Tiffanie Barnhizer[1], Stacy Pak Pharm D[1], Taylor Orndorf[1], Brian Sworder, MD[1], James Godfrey, MD[1], John Baird, MD[1], Swetha Thiruvengadam, MD[1], Christina Poh, MD[1], Matt Mei, MD[1], Manali Kamdar, MD[5], Elizabeth Budde, MD[1], Alexey Danilov MD[1]

1. City of Hope National Medical Center, Duarte, CA, 2. University of Utah Huntsman Cancer Institute, Salt Lake City, UT, United States, 3. Northwestern University, Chicago, United States, 4. Icahn School of Medicine at Mount Sinai Hospital, New York, NY, United States, 5 University of Colorado Denver, CO, United States

- Inclusion criteria on Jain et al. JCO 2020. This includes
  - 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-b score (≥6.2)
  - Bulky disease

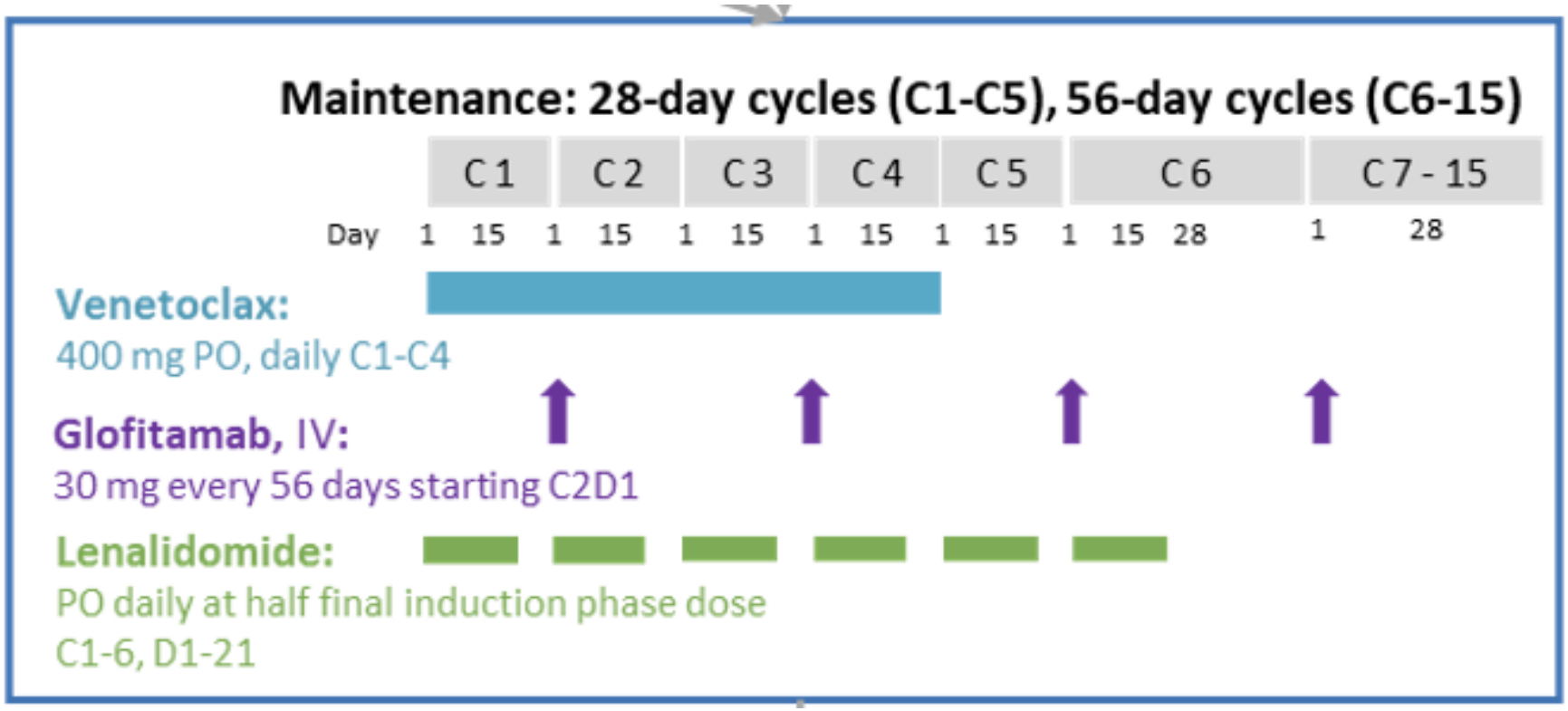
GLOVe (Induction)



- Patients start w/ a lead in of venetoclax starting at 50 mg which is increased weekly until a dose of 400 mg was reached.
- Once a dose of 200 mg is reached (C1D15), patients start the obinutuzumab pretreatment.
- Glofitamab is started C2D1 w/ standard weekly step-up dosing to goal of 30 mg.
- Patients start one week of lenalidomide once the 30 mg dose of Glofit is reached (C3D8). Thereafter dosed two weeks on and one-week C3-12.

Patients start one week of lenalidomide once the 30 mg dose of Glofit is reached (C3D8). Thereafter dosed two weeks on and one-week C3-12.

GLOVe (Maintenance)



- With maintenance Glofitamab is given once every 8 weeks for 2 years.
- Lenalidomide is given at half of the dose given at completion of induction three weeks on and one week off for 6 months
- Venetoclax is given for 4 months

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Baseline Patient Characteristics

Baseline	N=28
Age (median/range)	65 (53-79)
Male	16 (57%)
Race	
White	31 (88%)
Black	1 (4%)
Asian	2 (6%)
Unknown	1 (4%)
Ethnicity/Hispanic	4 (14%)
Stage	
II	2 (7%)
III	1 (4%)
IV	32 (91%)
BM involved	32 (91%)
GI involved	
Yes	20 (57%)
No	11 (31%)
N/A	4 (14%)
Leukemic only	3 (9%)
ALC > ULN	12/28 (43%)
Ki67>=50%:	**17/30 (57%)**
P53 mutation	**16 (47%)**
Del_17p	
Yes	**15 (47%)**
No	**17 (53%)**
N/A	**1 (4%)**

Morphology	
Classical	24 (71%)
Blastoid	**8 (24%)**
Leukemic non-nodal	2 (6%)
CK	
Yes	**26 (75%)**
No	**4 (14%)**
N/A	**5 (14%)**
MIPI-c	
Low (0)	1 (4%)
Low-intermediate (1)	5 (18%)
High-intermediate (2)	14 (47%)
High (3)	**10 (33%)**
Unknown	5 (14%)
Missing Ki-67	3 (9%)
Pending K-67	2(6%)

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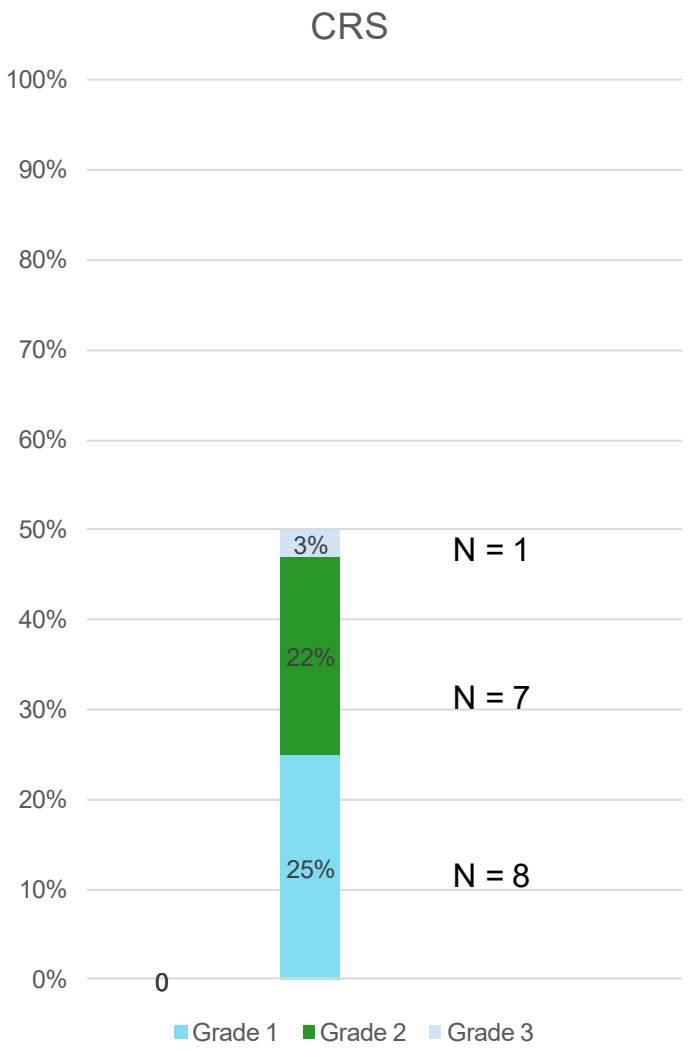
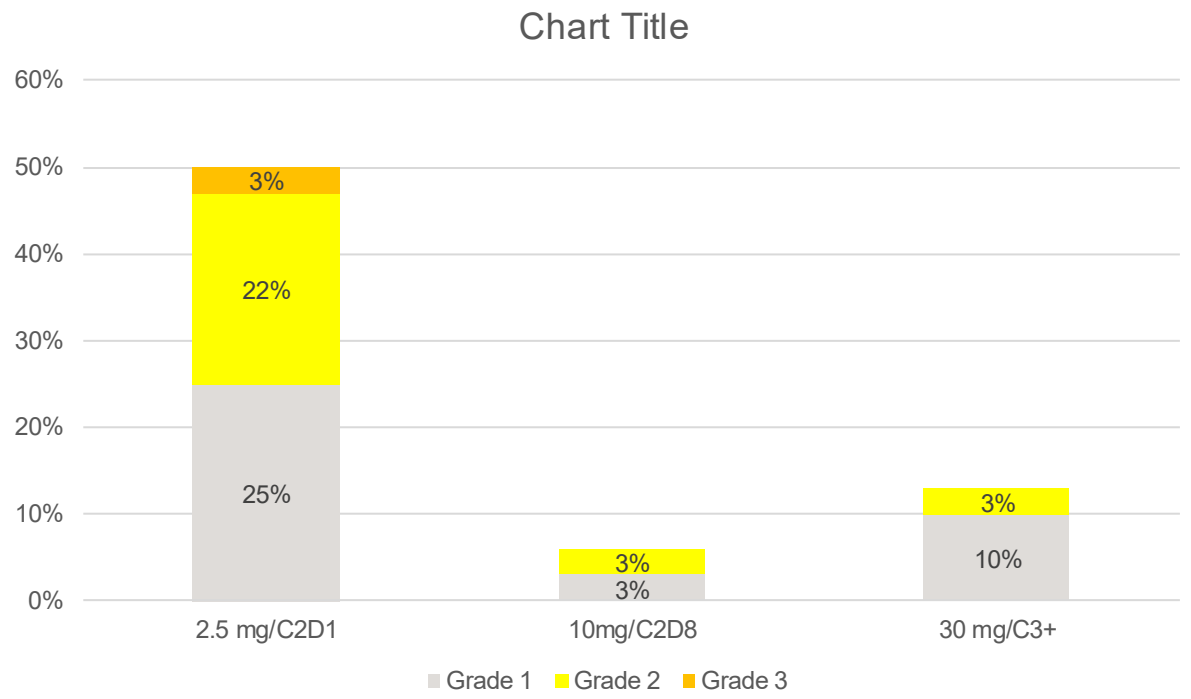
CRS rates and timing





	C2D1	C2D8	C3+
	2.5 mg	10 mg	30 mg
Grade 1	8	1	3
Grade 2	7	1	1
Grade 3	1	0	0

Tocilizumab	
Patients	14
Doses	16

- Two patients received a dose of toci w/ subsequent CRS

CRS	
Median Duration	1 (0-6)
Time to Resolution	1 (0-3)

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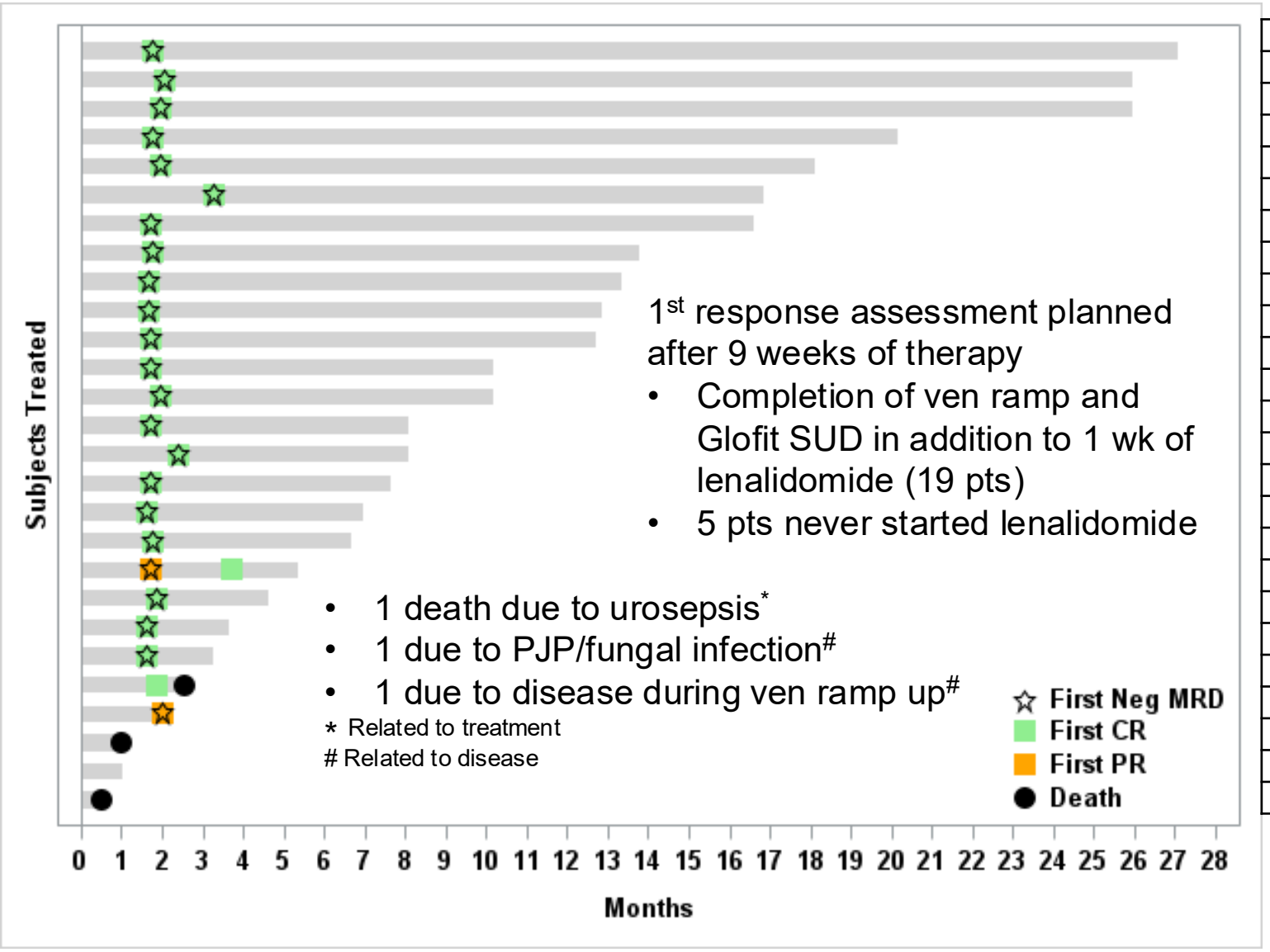
Response



Treatment data	N = 35
Off-Treatment	N = 7
Completed treatment	N = 3
Deaths on treatment	N = 4
Related to treatment (#4)	N = 1
Other (PJP, Disease, Beta Amyloid Plaques)	
Still on treatment	N = 28
Follow up among survivors	10 (1 – 27)
CR	N = 31
PR (#31)	N = 1
Death without response assessed	N = 2
Pending (#34, 35)	N = 2
MRD status (10^{-6})	
Negative	N = 28
Positive (#4, #27, #31, #32)	N = 4
Death w/o response assessed (#13, #25)	N = 2
Pending (#34, 35)	N = 2
MRD negative CR	
Yes	N = 30
No (#4, #27)	N = 2
Death w/o response assessed (#13, #25)	N = 2
Pending (#34, 35)	N = 2

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Ongoing/Pending Combination Studies in 1L

- Glofitamab and ibrutinib
  - US
- GLOASIS
  - Glofitamab With venetoclax +/- zanubrutinib in High-risk Mantle-cell Lymphoma
    - France/Belgium
- Several recently approved Mosun/Pola + BTKi concepts
  - US

Conclusions

- Bispecifics offer great potential in MCL
  - Single agent data with some concerns
    - Glofit – CRS
    - Mosun – efficacy/CRS
  - Future of agents likely will be in combinations similar to other lymphoma subtypes
    - Mosun/Pola
    - Pending Glofit combinations.

Thank you