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Bispecific Antibodies in Mantle Cell Lymphoma

Disclosures

- Research Support
  - Abbvie, Bayer, BMS, Genentech, Incyte
- Advisory Board
  - Abbvie, ADC Therapeutics, AstraZeneca, Bayer, Beigene, BMS, Genmab, Genentech, Gilead, Eli Lily, Epizyme, Incyte, Pharmacyclics, TG Therapeutics, Seattle Genetics
- Strategic Counsel
  - Epizyme
- Scientific Board
  - Genentech

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Agenda

- Where we are in MCL
  - Glofitamab
  - Mosunetuzumab
    - Single Agent
    - Combination
  - Everyone else
    - Issues!!!!
- Why and what's next

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Landscape

- MCL remains a difficult disease to treat mainly due to the variability in patient presentations/outcomes with current therapy
  - BTKi continue to move into the 1L setting
    - How does this (1L BTKi) either continuous or intermittent impact 2L space as this isn't going to cure patients
    - Potentially moves up other agents and accentuates the need for novel treatments in MCL

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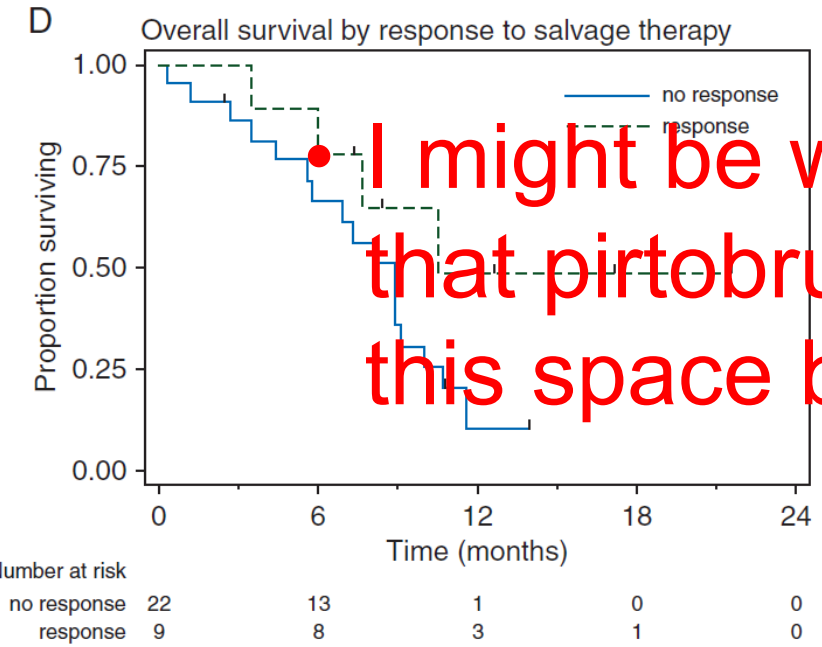
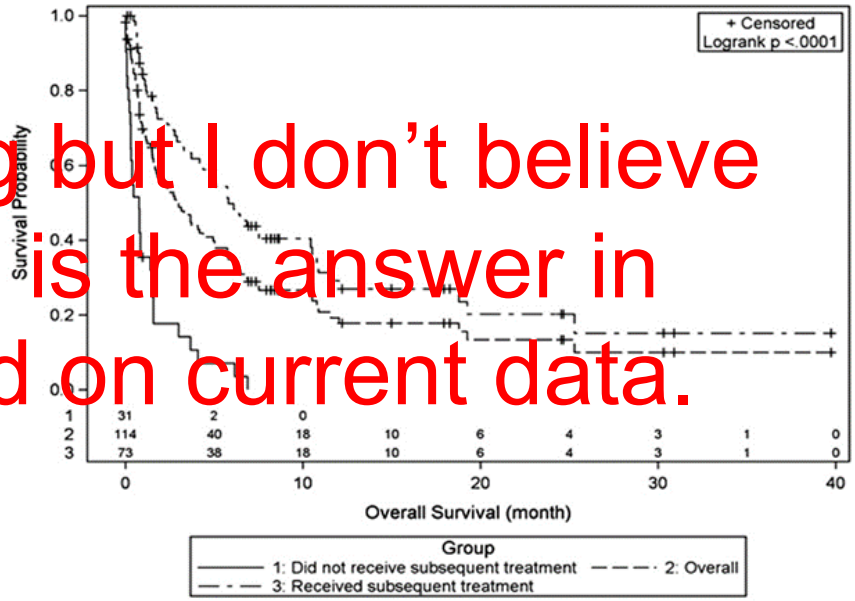
Post BTKi Outcomes



I might be wrong but I don't believe that pirtobrutinib is the answer in this space based on current data.



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

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T cell directed therapy

- Historical data has supported the benefit of allo-transplant in patients with MCL.
  - Including those with p53 mutations
  - Utilization hindered by age and potential complications
- Car-T data further lends credence to the benefits of using the immune system in MCL
  - Still limited by accessibility and concern with toxicity (Neuro-tox)
- Bispecifics with approval in DLBCL and FL
  - Limited data in MCL

Goebeler et al. JCO 2016
Dufner et al. Blood Adv. 2019

Bispecifics MCL

- We will discuss the Genentech products
- What about the others

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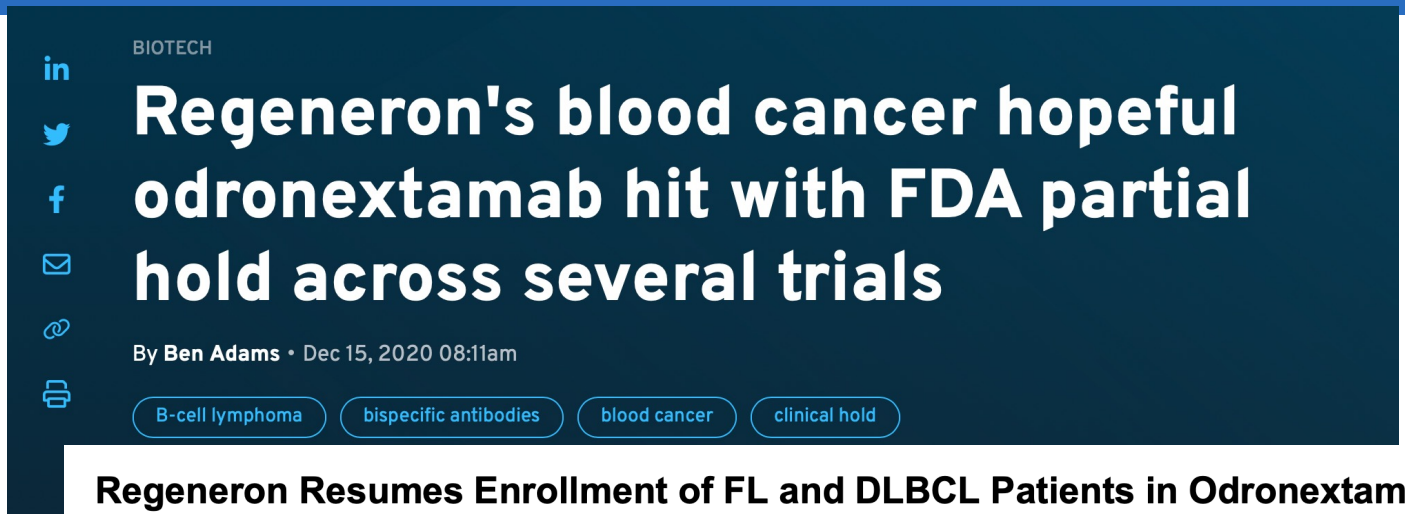

BIOTECH

Regeneron's blood cancer hopeful odronextamab hit with FDA partial hold across several trials

By **Ben Adams** • Dec 15, 2020 08:11am

B-cell lymphoma | bispecific antibodies | blood cancer | clinical hold

Regeneron Resumes Enrollment of FL and DLBCL Patients in Odronextamab Trials

Regeneron is resuming enrollment of patients with follicular lymphoma (FL) and diffuse large B-cell lymphoma (DLBCL) in its monotherapy trials of odronextamab, a CD20xCD3 bispecific antibody, following agreement with the U.S. Food and Drug Administration to lift the partial clinical trial hold for those patient cohorts. Trial protocols have been amended to further reduce the incidence of ≥Grade 3 cytokine release syndrome during step-up dosing. Regeneron will recommence enrollment in these patient cohorts effective immediately (trials NCT02290951 and NCT03888105).

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So what’s the problem

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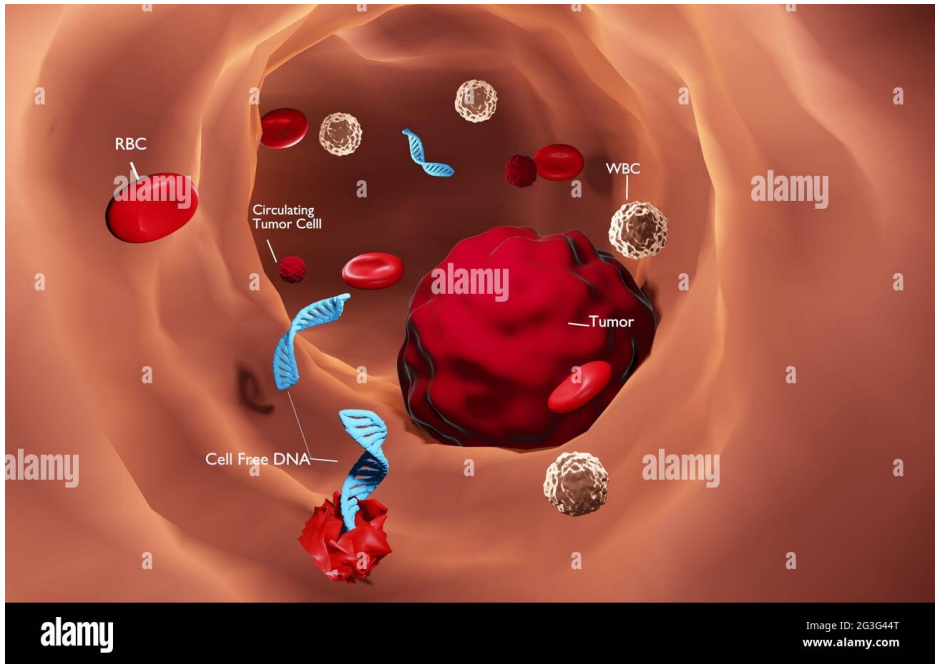
Theories…

- Due to aggressive nature of most patients with R/R disease there is a higher tumor burden then most of subtypes of NHL
  - Tends to be even more aggressive after a BTKi
- Thus far limited data with another common B-cell malignancy….CLL
  - But what we have seen indicates higher rates of CRS as compared to other subtypes
  - So, what's the common theme?



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How common is peripheral blood involvement in Mantle Cell??

- Several studies have looked at this in small patient populations
  - Results ranged from 20-92%
    - Higher frequency with studies that utilized flow cytometry in addition to morphology review.
  - Study by Ferrer et al. noted high % even after sub-classifying patients with blastoid features.
- Overall likely more common than we suspect thus allowing for significant and rapid contact between antigen (MCL) and antibody

Cohen et al. 1998 British Journal of Haematology 1998
Ferrer et al. Cancer. 2007 Jun 15;109(12):2473-80.
Argatoff et al. 1997 Mantle cell lymphoma: a clinicopathologic study of 80 cases. *Blood*, **89,** 2067 207

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The Greeting

Result

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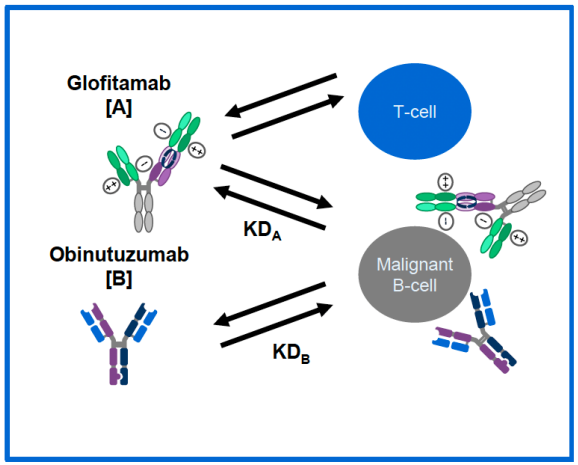
So what can be done to improve tolerance?

Glofitamab dosing in R/R MCL



CD20 – receptor occupancy (RO; tumor cell)

- Glofitamab and obinutuzumab compete for binding to the same epitope on CD20 receptors
- Gpt reduces glofitamab RO, which aims to mitigate CRS incidence and severity, by competitive binding

Patients with MCL have:

- Higher clearance of obinutuzumab (2-fold) compared with other NHL histologies[1]
- Lower obinutuzumab concentration which leads directly to higher glofitamab RO[2]

CRS

- Direct relationship between glofitamab RO and CRS at the first dose in NHL
- A higher Gpt dose prior to glofitamab SUD may further reduce risk of CRS in MCL

Response

- Direct relationship between glofitamab RO and CR rate at Cycle 3 in aNHL

aNHL, aggressive non-Hodgkin lymphoma; CR, complete response.

1. Gibiansky, E et al. CPT Pharmacometrics Syst Pharmacol 2014;
2. Djebli, N et al. Blood 2020

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MCL

Glofitamab dosing schedules

Phase I dose escalation in R/R MCL

Glofitamab IV administration

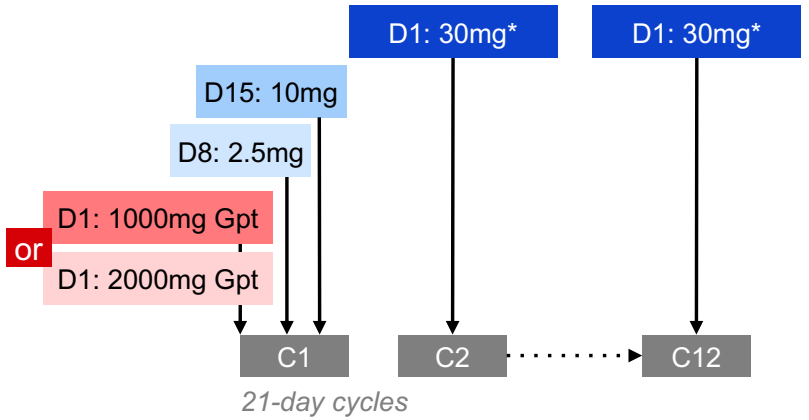
- Fixed-duration treatment: maximum 12 cycles

CRS mitigation

- Obinutuzumab pretreatment (1 x 1000mg or 1 x 2000mg)
- C1 step-up dosing
- Monitoring after first dose (2.5mg)

Population characteristics:

- Age ≥18 years
- ≥1 prior systemic therapy
- ECOG PS ≤1



Clinical cut-off date: March 14, 2022; *In the glofitamab SUD + 1000mg Gpt cohort, two patients had 16mg glofitamab as their target dose.

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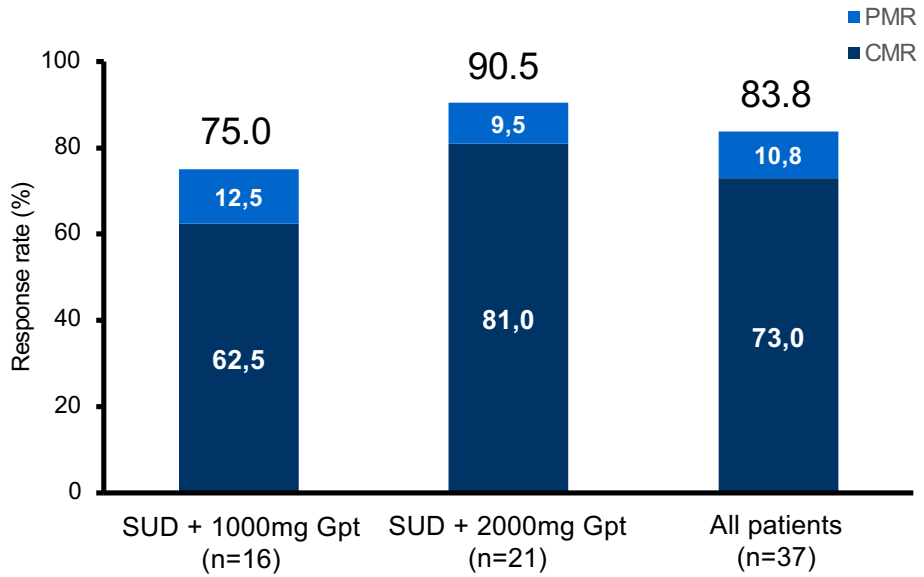
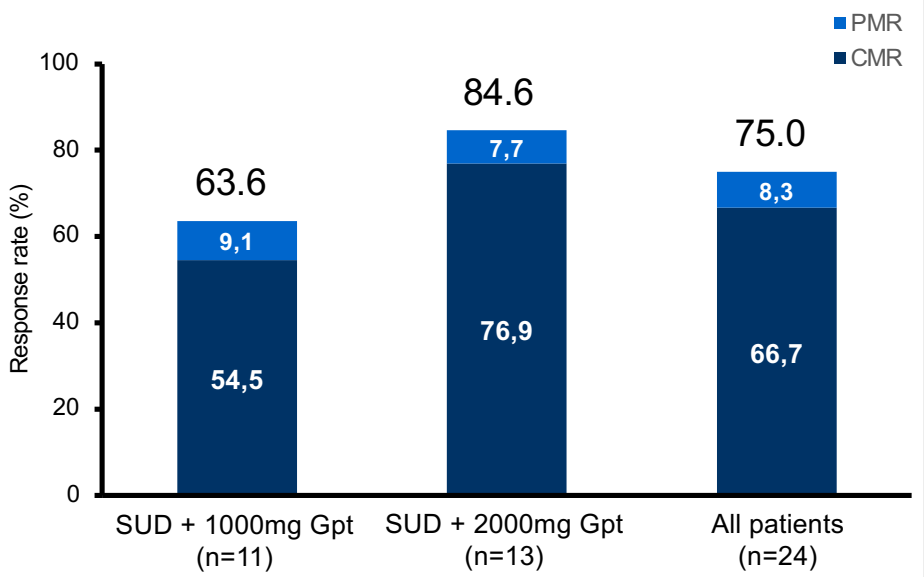
Response rates by glofitamab regimen

All patients*



Patients with prior BTKi



High response rates with glofitamab monotherapy in patients with R/R MCL

*Efficacy results are reported for the secondary efficacy population (includes all patients who had a response assessment performed, withdrew early from treatment or study, or are on still on treatment at the time of their first scheduled response assessment). Prior lines of therapy ranged from 1–5 in both the responder and non-responder groups. CMR, complete metabolic response; PMR, partial metabolic response.

Cheson et al. J Clin Oncol 2014.

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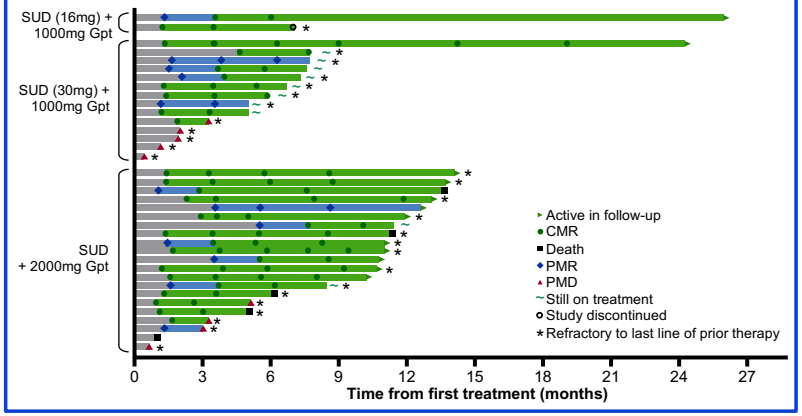
Response Cont.

Time on treatment and response

Durability of response in efficacy-evaluable patients

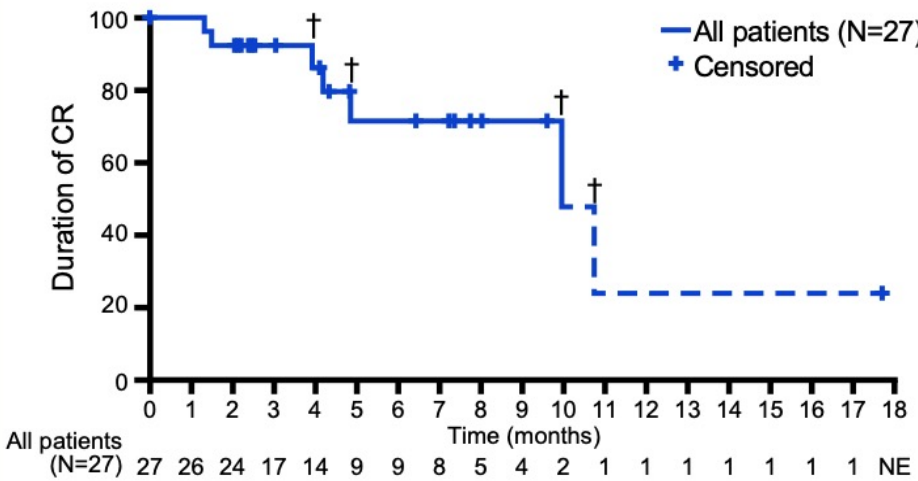


- **Median follow-up (months):**
  - 8.0 months
- **Median time to first response:**
  - **51 days** (range, 29–234)
- **Response at first assessment:**
  - CRR: 48.6%, ORR: 73.0%
- **No PD was reported beyond EO**
  in patients with response at EO

Most responses were achieved early and were durable

EOT, end of treatment; CRR, complete response rate; ORR, overall response rate.

Duration of CR*

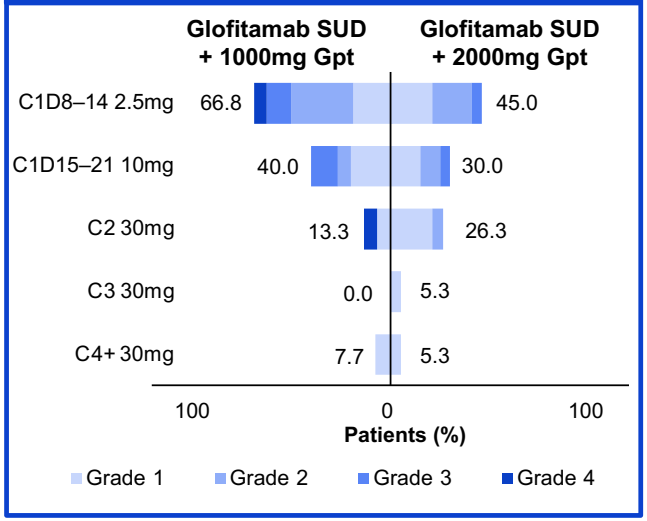


CRS

Cytokine release syndrome*

n (%) of patients with ≥1 AE unless stated	Glofitamab SUD + 1000mg Gpt (n=16)	Glofitamab SUD + 2000mg Gpt (n=21)	All patients (N=37)
Any CRS	14 (87.5)	14 (66.7)	28 (75.7)
Grade 1	4 (25.0)	7 (33.0)	11 (29.7)
Grade 2	6 (37.5)	5 (23.8)	11 (29.7)
Grade 3	2 (12.5)	2 (9.5)	4 (10.8)
Grade 4	2 (12.5)	0 (0.0)	2 (5.4)
Serious AE of CRS (any grade)	10 (62.5)	5 (23.8)	15 (40.5)
Median time to CRS onset, hours (range)	7.55 (4.4–14.0)	9.77 (5.0–20.8)	9.31 (4.4–20.8)
Tocilizumab for CRS management	11 (68.8)	6 (28.6)	17 (45.9)
Corticosteroid for CRS management	8 (50.0)	6 (28.6)	14 (37.8)

CRS by cycle, grade and regimen



Higher Gpt (2000mg) was associated with a lower rate of CRS, with no Grade 4 events reported in this group

*By American Society for Transplantation and Cellular Therapy (ASTCT) criteria.[1]

1. Lee et al. Biol Blood Marrow Transplant 2019.

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ICANS

Other adverse events of interest

AE, n (%)	All grades (N=37)	Grade ≥3 (N=37)
Infections and infestations	24 (64.9)	12 (32.4)*
Neutropenia	17 (45.9)	10 (27.0)
Febrile neutropenia	1 (2.7)	1 (2.7)
Tumor flare	5 (13.5)	0 (0.0)
Neurologic AEs	18 (48.6)	1 (2.7)
ICANS (derived)†	5 (13.5)‡	0 (0.0)‡
AEs leading to treatment discontinuation	0 (0.0)	0 (0.0)

- No Grade ≥3 ICANS AEs or tumor flare events
- Only one Grade 1 ICANS event was reported in the higher Gpt (2000mg) cohort, which resolved

*Includes one Grade 4 event (endocarditis) and three Grade 5 events (COVID-19, n=2; COVID-19 pneumonia, n=1); †Glofitamab-related neurologic AEs potentially consistent with ICANS; mental status changes (n=1), disorientation (n=1), confusional state, agitation and memory impairment (n=1), cognitive disorder and agitation (n=1), memory impairment and agitation (n=1, ongoing at CCOD); ‡CTCAE. ; ICANS, immune effector cell-associated neurotoxicity syndrome; CTCAE, common terminology criteria for adverse events.

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Mosunetuzumab

- All original bispecific studies enrolled MCL patients
  - Thus far only two products have published results
    - We have already discussed Glofitamab
  - Published data from Mosunetuzumab Budde et al.
    - 13 enrolled patients
      - ORR 30.8% (CR 23.1%)

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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

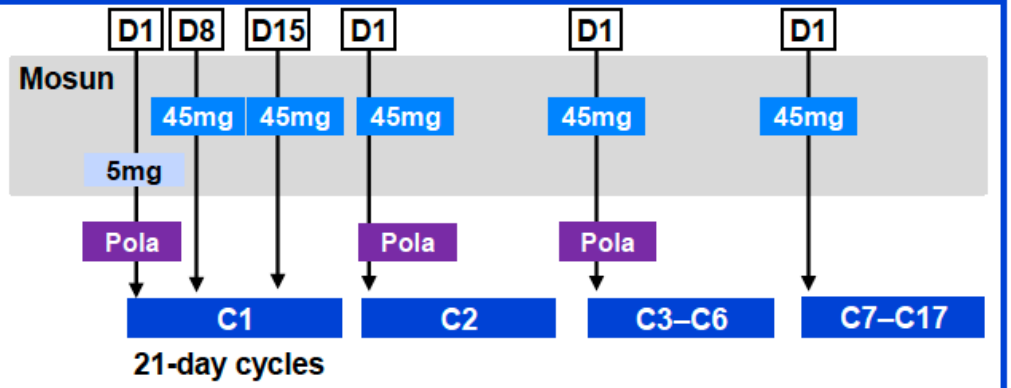
- SC administered in 21-day cycles with step-up dosing in Cycle (C) 1; total of 17 cycles

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 C
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.

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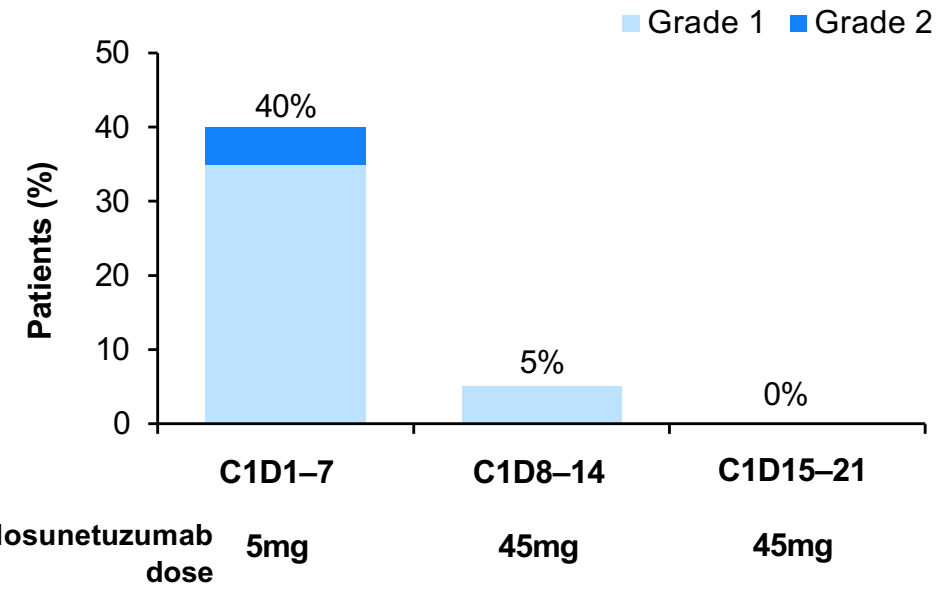
CRS summary

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.

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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.

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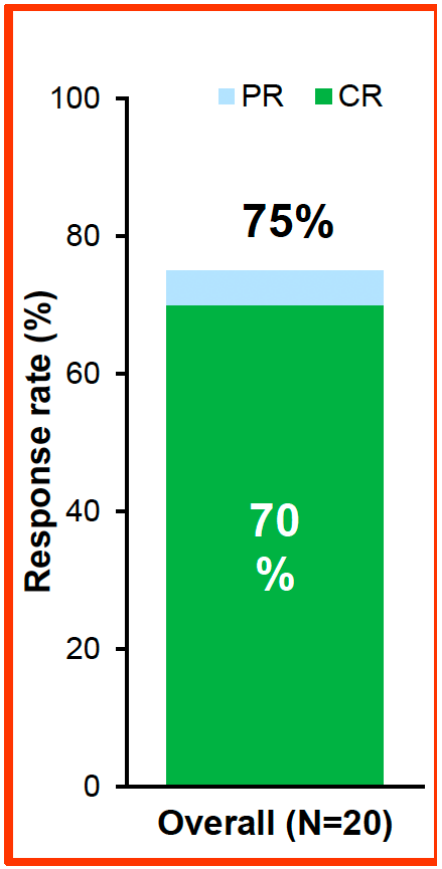
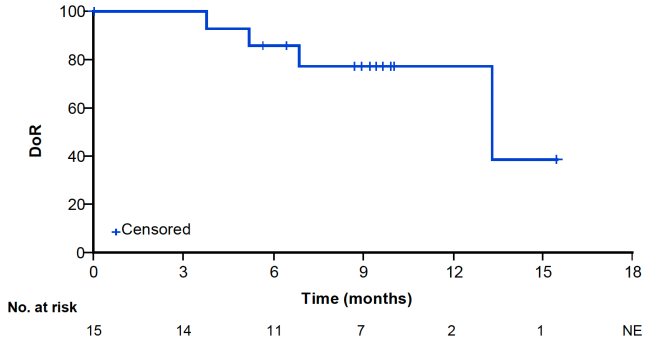


Duration of response (DoR)

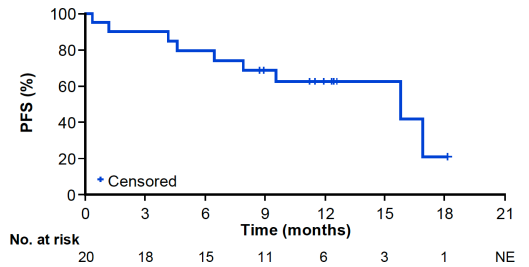
Median DoR: 13.3 months (95% CI: 13.3–NE)



PFS and OS

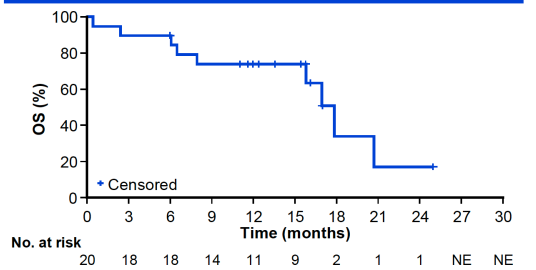
Median follow-up: 15.8 months (95% CI: 12.4–NE)

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)

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Lingering questions

- Do bispecifics cross the BBB??
  - If not, then limits patient population for which agents can/will be effective
- CRS for bispecifics is different than CAR-T but still more likely to happen in MCL vs. what we see in other B-NHL patients
- So, is outpatient administration as a single agent really an option for these patients during SUD??
    - We now have some published guidelines, but this is based on DLBCL and FL.
  - Does this require more interaction between community and academic docs?

- Improvement of CRS
  - Can combinations assist with reduction in bulk, clearance of circulating disease, and improve responses?
    - Mosun/Pola appears to have less Grade 2 + CRS as compared to Glofit
      - No clarity on CRS for single agent Mosun in MCL patients
  - Inclusion of steroids
    - Already a part of Glofitamab and Epcoritamab SUD
    - Would higher doses have better efficacy??
- Extend SUD
  - Being explored with epcoritamab (data pending)

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Upcoming clinical trials….

- Several clinical trials ongoing with glofitamab

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	N
NCT06054776	Acalabrutinib, Obinutuzumab, and Glofitamab for the Treatment of Relapsed or Refractory Mantle Cell Lymphoma	2L+	1/2	Y	US	N
NCT06192888	A Study of Glofitamab and Lenalidomide in People With Mantle Cell Lymphoma	2L+	2	Y	France	Y
NCT06084936	A Phase III, Open-label, Multicenter, Randomized Trial Evaluating Glofitamab Monotherapy in Patients with Relapsed or Refractory Mantle Cell Lymphoma	2L+	3	Y	Global	Y
NCT05861050	Glofitamab With Obinutuzumab, Venetoclax, and Lenalidomide for the Treatment of Patients With Newly Diagnosed High Risk Mantle Cell Lymphoma	1L	1/2	Y	US	Y
NCT06252675	Glofitamab With Pirtobrutinib for Relapsed or Refractory Mantle Cell Lymphoma	2L+	2	Y	US	N

Conclusions

- While bispecific antibodies with impressive clinical data in FL and DLBCL
  - Currently one with FDA approval (mosunetuzumab)
  - Two agents in DLBCL approved
- MCL more difficult space
  - Multitude of reasons
  - Currently one single agent (glofitamab) and one combination (mosunetuzumab/polatuzumab) with substantial data
  - Planned phase 3 study and several IITs in progress

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