20TH INTERNATIONAL ULTMANN CHICAGO LYMPHOMA SYMPOSIUM

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Incorporation of Bispecific Antibodies into Lymphoma Therapy

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20TH ULTMANN
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MEDICINE & BIOLOGICAL SCIENCES

Disclosures

- **Research Funding**: ADC Therapeutics, Autolus, Bristol-Meyers Squibb, Celgene, Forty Seven, Gilead, Janssen, Kite Pharma, Merck, Millennium, Pharmacyclics, **Roche/Genentech**, SeaGen

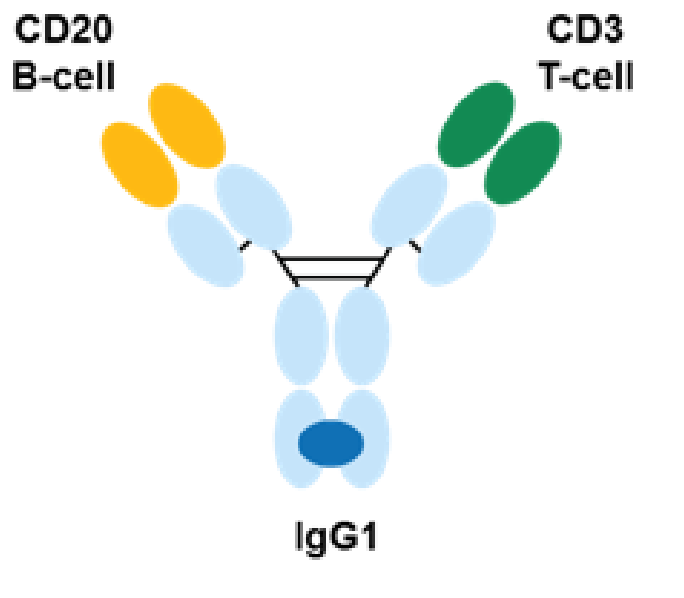
- **Advisory Boards**: ADC Therapeutics, **Roche/Genentech**, SeaGen

Background

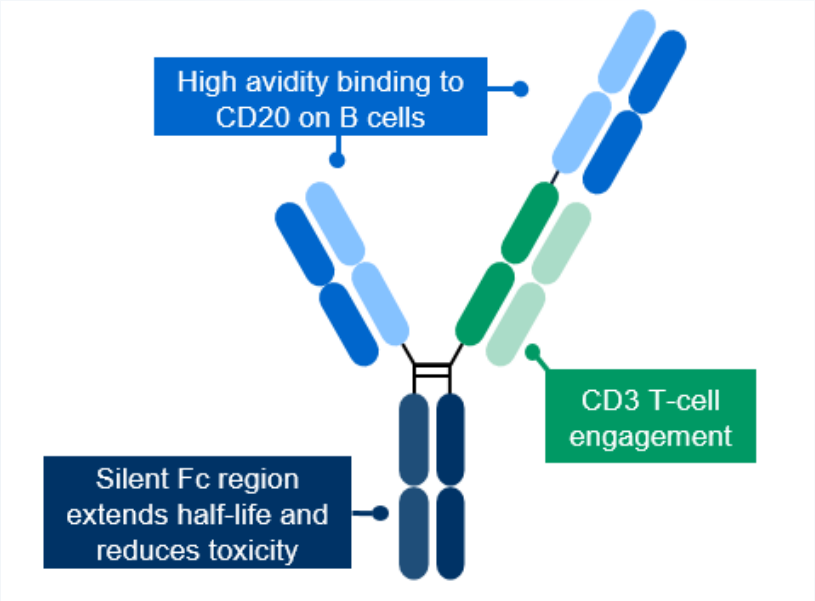
CD20xCD3 Bispecific Antibodies for Lymphoma

Structure of T-cell engaging bispecific antibodies

1:1 configuration



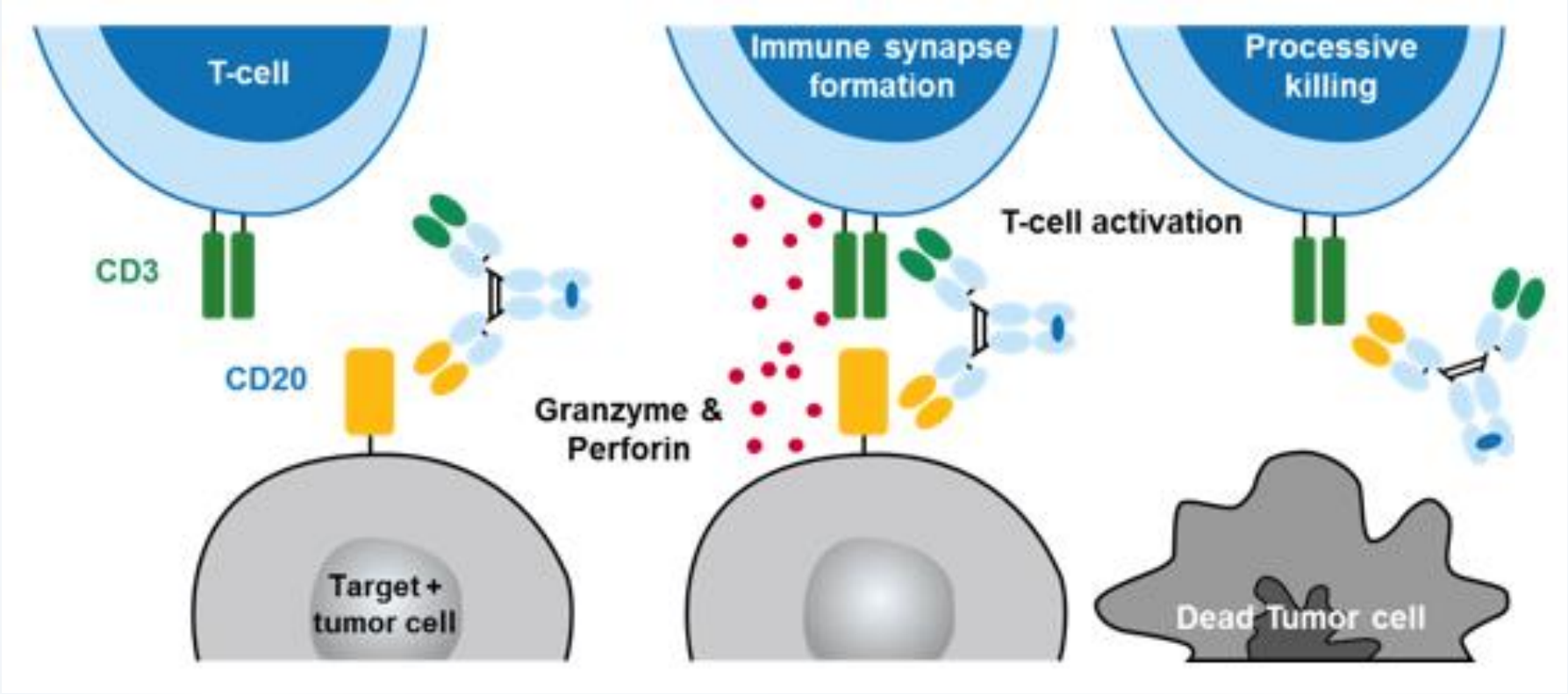
Glofitamab: 2:1 configuration (2 CD20 sites)



- All target CD3 as T-cell engager
- Other T-cell targets ”less robust”, more CRS
- Different epitopes on CD3 may preferentially enhance T-cell activation

Sun et al. Sci Transl Med 2015;7:287ra70

Mechanism of action of T-cell engaging bispecific antibodies

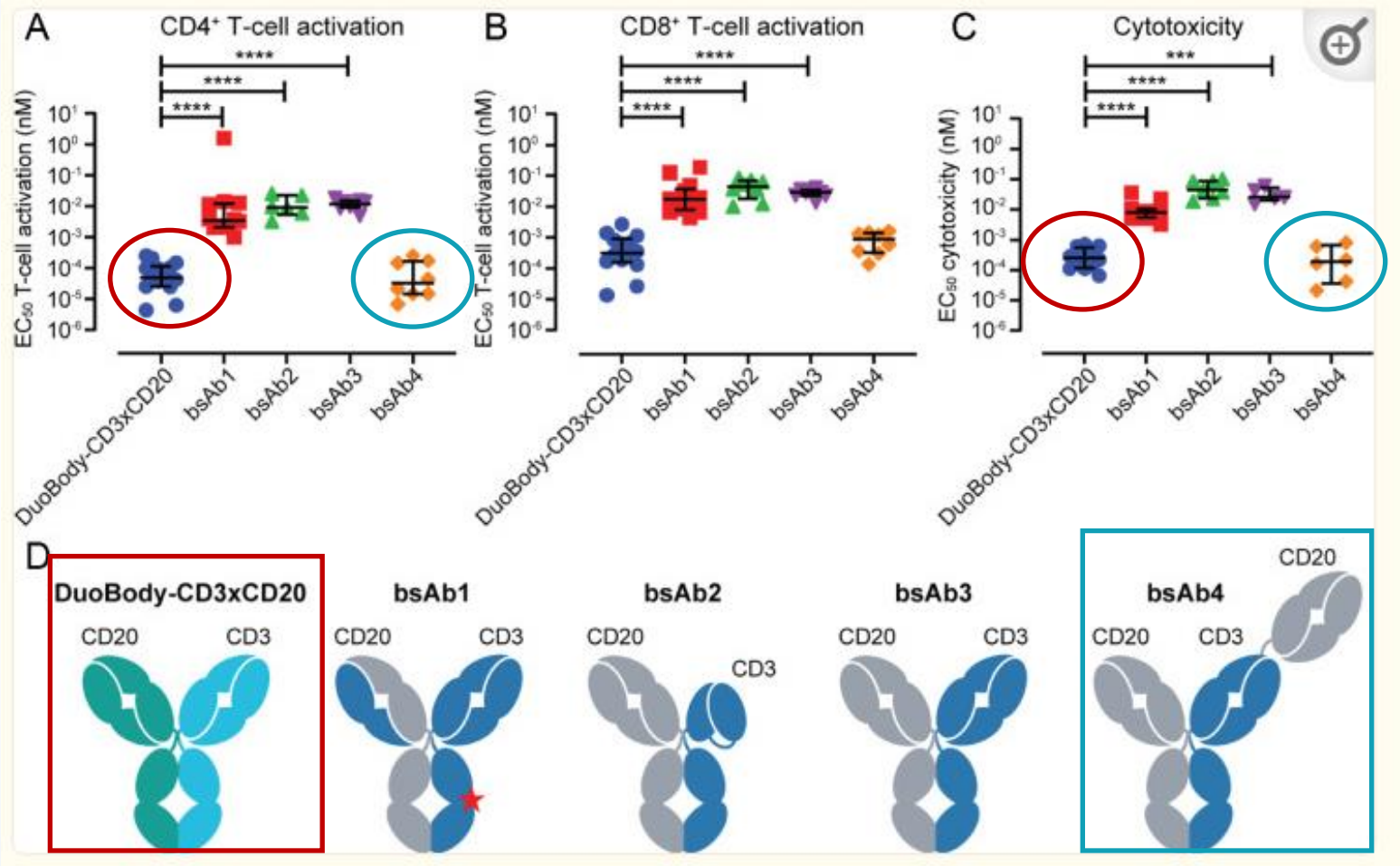


- **Simultaneous** binding of a tumor associated antigen and endogenous T cells triggers T-cell activation and release of granzyme B and perforin

Sun et al. Sci Transl Med 2015;7:287ra70

In vitro comparison of CD20xCD3 cytotoxicity (Daudi cells)

Epcoritamab



Glofitamab

Engelberts PJ et al. EBioMedicine 2020:52:102625

CD20xCD3 Bs Abs in late stage development

Agent	Mode of admin.	Schedule	Duration
Glofitamab	IV	Weekly C1, Q 3wks	12 cycles
Mosunetuzumab	IV (SC in dev)	Weekly C1, Q 3wks	8 cycles if CR 17 cycles if PR
Odronextamab	IV (SC in dev)	Twice weekly C1, weekly C2-4, Q 2wks C≥5	Until PD
Epcoritamab	SC	Wkly C1-3, Q 2wks C4-9 Q 4wks C≥10	Until PD

Schedules/doses may vary by histology

Regulatory Approval Status for CD20xCD3 Bispecific Abs

- **Mosunetuzumab**
  - EMA approval for R/R follicular lymphoma, ≥ 3rd line, **04/25/2022**
  - FDA approval for R/R follicular lymphoma, ≥ 3rd line, **12/22/2022**
- **Epcoritamab**
  - Submitted to EMA/FDA Oct 2022 for R/R DLBCL
  - FDA decision expected **05/21/2023**
- **Glofitamab**
  - Submitted to EMA/FDA Dec 2022 for R/R DLBCL
  - FDA decision expected **07/01/2023**
- **Odronextamab**
  - Granted fast track designation in FL and DLBCL, May 2022
  - Potential submission for R/R FL and DLBCL 2023

Toxicity of Bispecific Antibodies

Cytokine Release Syndrome with Bispecifics

Incidence and risk factors

- All grades (24%-59%)
  - Fever most common symptom
- Grade ≥ 3 (0-7%)
  - Product dependent
- Most common on C1D1
- Uncommon after C2D1
- ↑ risk with higher disease burden, PB involvement

Mitigation strategies

- Step up dosing C1
- Corticosteroid premed
- Subcutaneous administration
- Prephase anti-CD20mAb admin
  - Deplete non-malignant B-cells
  - Decrease initial occupancy of BsAb on non-malignant and malignant B-cells

Consider 24-48 hr hospitalization for C1D1 and possibly C1D15 (first full dose) in high risk patients, especially with Glofit (? label)

Other Toxicities with Bispecifics

- Gr ≥3 neurological toxicity rare 0-4%
- Gr ≥3 neutropenia 20-30%
  – febrile neutropenia rare 0-6%
- Gr ≥3 thrombocytopenia 2-14%
- Gr ≥3 hypophosphatemia 20-25%
- Gr ≥3 infection <10%
- tumor flare <5%

Budde et al JCO 2022:40:481; Hutchings et al JCO 2021: 39:1959; Bannerji et al Lancet Haem 2022:9, e327; Hutchings et al Lancet 2021:398:1157

Follicular Lymphoma

Incorporation of Bispecifics Antibodies

Efficacy of CD20xCD3 Bispecifics for r/r FL Gr 1-3a

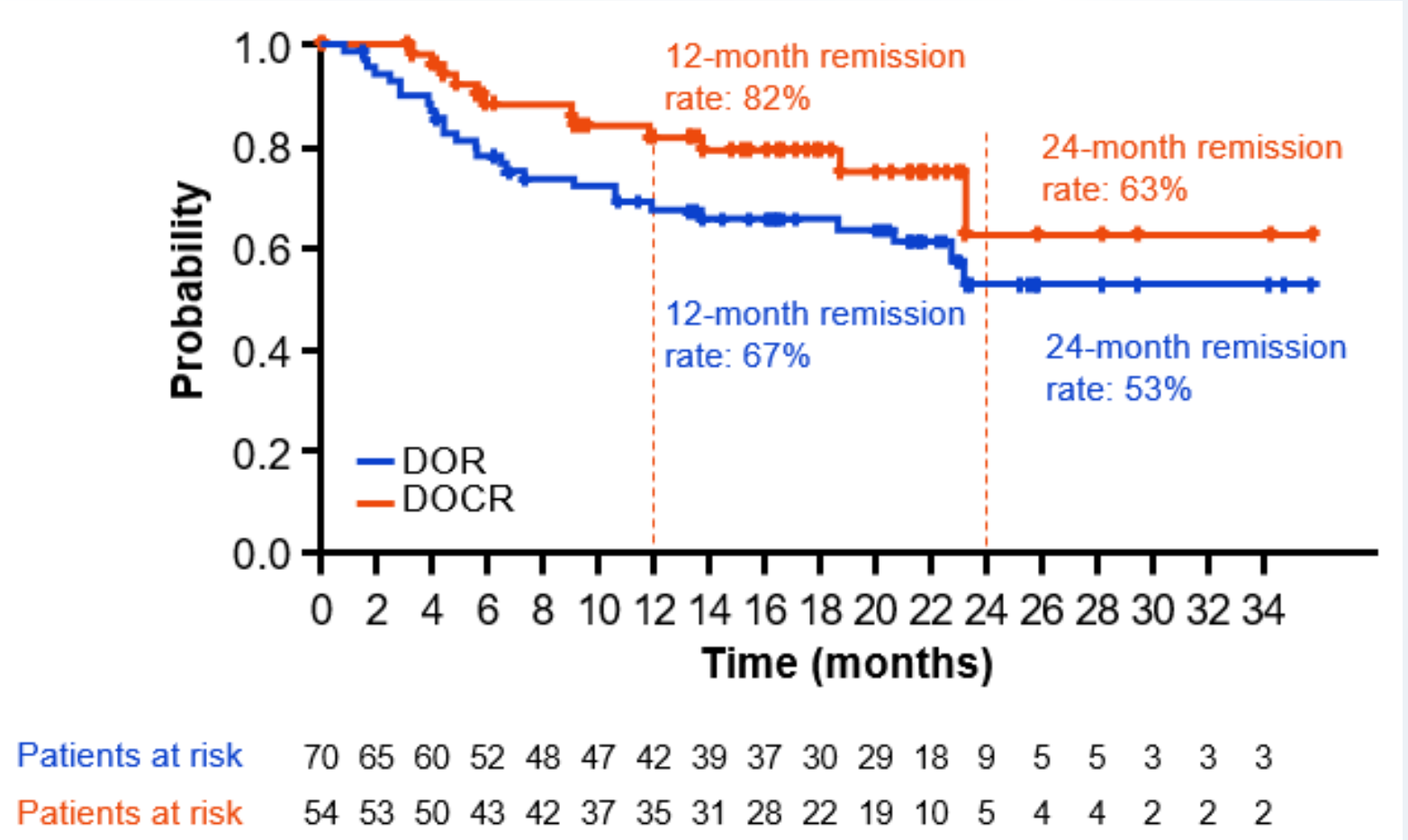
Agent	No. of pts	ORR %	CR %	Med DOCR mo	PFS mo	Ref
Glofitamab	44	71	48	NR	11.8	1, 2
Mosunetuzumab	90	79	60	NR	24	3, 4
Odronextamab	85	81	75	18.2	20.2	5, 6
Epcoritamab	10	90	50	NA	NR	7

- Response rates held up across clinical prognostic groups including POD24, double-refractory
- At least one study showed lower ORR in pts with bulky disease
- **Responses including CRs occur early (median time ≤ 3 mo)**

1. Hutchings 2021: JCO 39:1959-1970; 2. Morschhauser et al, ASH 2021, 3. Budde Lancet Oncol 2022; 4. Bartlett ASH 2022; 5. Bannerji Lancet Haem 2022: 9: e327–39;23: 1055–65; 6. Kim ASH 2022; 140: 2 280–2282; 7. Hutchings Lancet 2021; 398: 1157–69

Duration of complete remission, Mosun r/r FL

- Encouraging
- Plateau?
- Cure?



Bartlett et al, ASH 2022, Blood, 140, Supplement 1

Toxicity of CD20xCD3 Bispecifics for r/r FL Gr 1-3a

Agent	No. of pts	Phase 2 Step-up dosing	CRS Gr 2	CRS Gr≥3	Toci	Neuro Gr≥3	Ref
Glofitamab	44/53	Obin, 2.5, 10, 30	17%	2%	15%	0	1, 2
Mosunetuzumab	90	1, 2, 60, 60, 30	17%	2%	8%	1%	3, 4
Odronextamab	85	0.2/0.5, 2/2, 10/10, 80	0	0	1%	0	5, 6
Epcoritamab	10	0.16, 0.8, 48	NA	0	NA	0	7

1. Hutchings 2021: JCO 39:1959-1970; 2. Morschhauser et al, ASH 2021, 3. Budde Lancet Oncol 2022; 4. Bartlett ASH 2022; 5. Bannerji Lancet Haem 2022: 9: e327–39;23: 1055–65; 6. Kim ASH 2022; 140: 2 280–2282; 7. Hutchings Lancet 2021; 398: 1157–69

Selected bispecific trials in 1st or 2nd line therapy for FL

- First line
  - Mosun-single agent
  - Mosun-pola
  - Mosun-tazemetostat
  - Epcor-R-Len Phase 1/2 (Falchi ASH 2022), ORR 90%, CR 69%
  - Mosun vs Rituximab (proposed NCTN trial in low tumor burden FL)

- Second line (or later)
  - Epcor-R-Len Phase 1/2 (Falchi ASH 2022), ORR 95%, CR 73%
  - Epcorit-R-len vs R-len (international Phase 3)
  - Mosun-len vs R-len (international Phase 3)

Current recommendations for incorporating Mosun into FL therapy

- Mosun first choice as third line therapy
  - Safe for outpatient administration with close f/u post-each step up dose.
  - Anxiously awaiting label for SC admin (less CRS!)
  - Only scenario where CAR-T *might* precede BsAb in FL is HIGH suspicion of tFL
  - If second bispecific approved in this setting, need to compare efficacy/tox/schedule

- If available, participation in bispecific trials in first/second line therapy
  - Appealing to avoid bone marrow damaging agents in early lines of therapy in FL.

Diffuse B-cell Lymphoma

Incorporation of Bispecific Antibodies

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Efficacy of CD20xCD3 Bispecifics for r/r DLBCL

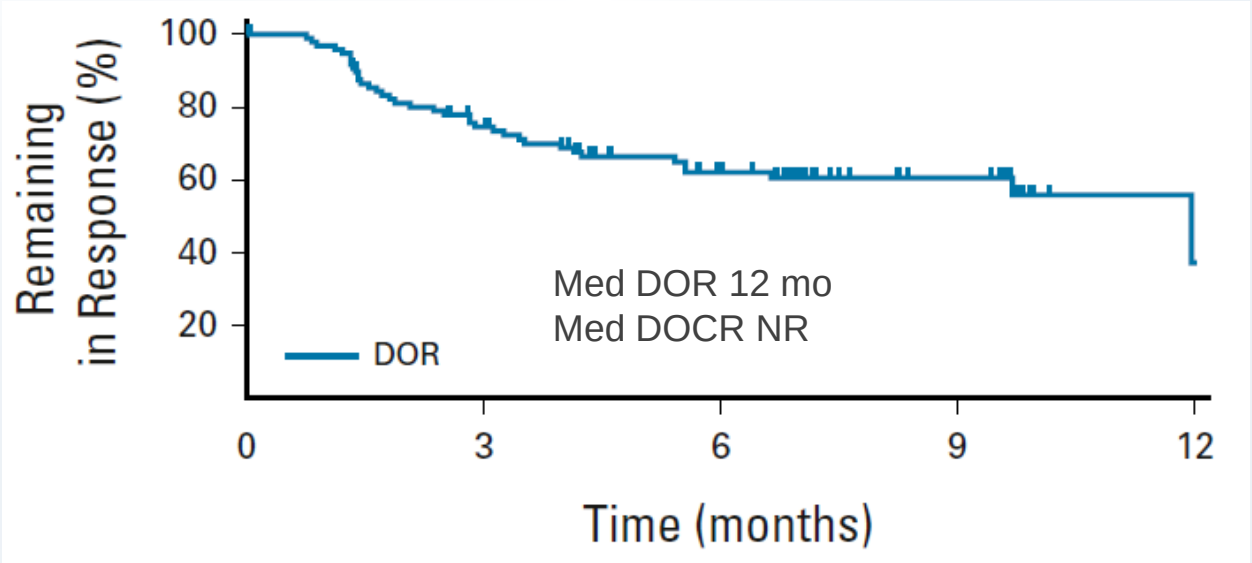
Agent	No. of patients	ORR%	CR %	Med DOCR	Ref
Glofitamab	155	52	**39**	NR	1
Mosunetuzumab	88	42	**24**	NR	2
Odronextamab	90	53	**37**	NR	3, 4
Epcoritamab	157	63	**39**	NR	5

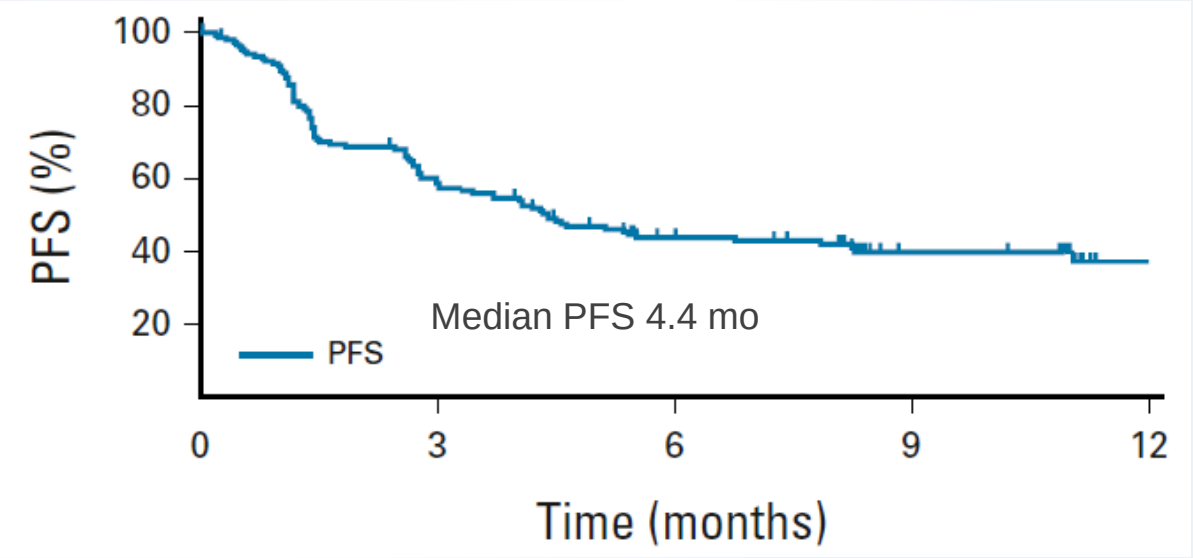
- Median time to CR ≤ 3 mo (small number of PRs convert to CR 6-12 mo)
- CR rates “similar” in pre- and post-CART setting
  - Glofit: 42% (pre) vs 35% (post), Epcorit 42% (pre) vs 34% (post), Mosun 29% (pre) vs 12% (post)

1. Dickinson NEJM 2022; 387:2220-2231, 2Bartlett et al Blood Adv 2023; https://doi.org/10.1182/bloodadvances.2022009260;. 3. Bannerji Lancet Haem 2022;9: e327–39, 4. Kim Blood 2022; 140: 1070–1071,
2. 5. Thieblemont JCO DOI: 10.1200/JCO.22.01725

Epcoritamab for r/r DLBCL, ≥ 2 prior lines of therapy

- Phase 1/2, **N=157**
- Schedule (SC admin)
  - Weekly x 12 weeks (step-up wk 1-3)
  - Q 2wk x 20 weeks
  - **Monthly until PD** or unacceptable tox
- ORR 63%, CR 39%
- CRS G1-2 47%, Gr≥3 **2.5%**
- Gr 3 ICANS n=1
- Gr 5 ICANS n=1

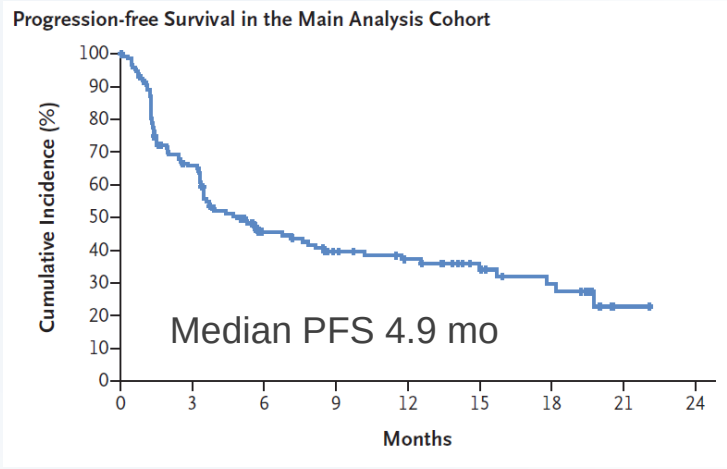


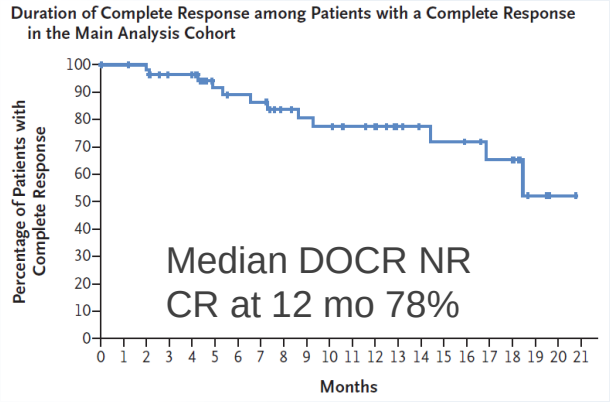


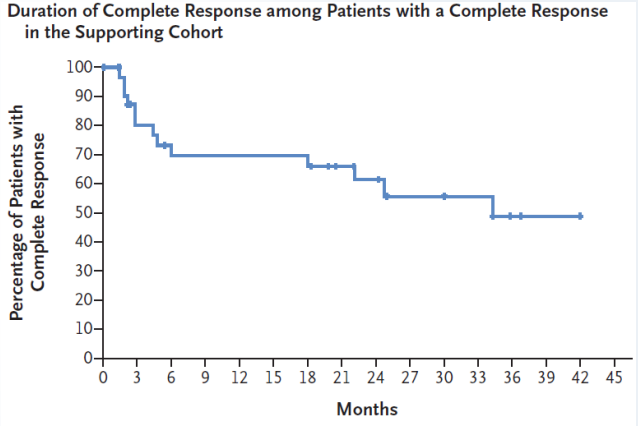
Thieblemont JCO DOI: 10.1200/JCO.22.01725

Glofit for r/r DLBCL, ≥ 2 prior lines of therapy

- Phase 2, **N=155**
- Schedule (IV admin), **Fixed duration**
  - **Obinu D-7**
  - C1: Step up dosing Q wk x 3
  - C2-12: Q 3 wk
- ORR 52%, CR 39%
- Subgroup CR rates (small #)
  - HGBCL 0%
  - DH/DE 25% / 20%
  - Bulky 33%
  - Rel/ref 70% / 34%
- CRS G1-2 59%, Gr≥3 **4%**
- ICANS Gr≥3 **3%**
- **Gr 5 events 5%** (n=8, COVID 5, sepsis 1, delirium 1)







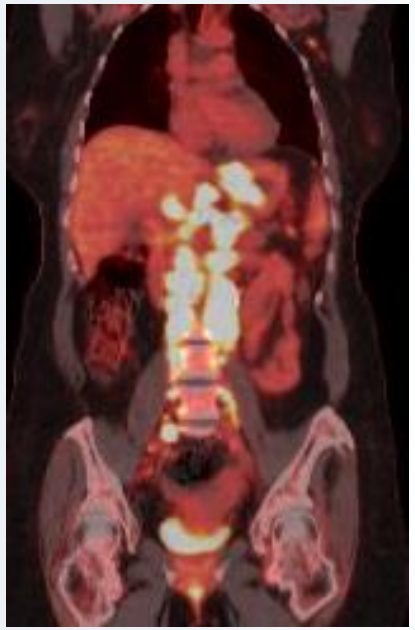
Dickinson NEJM 2022; 387:2220-2231

Case presentation

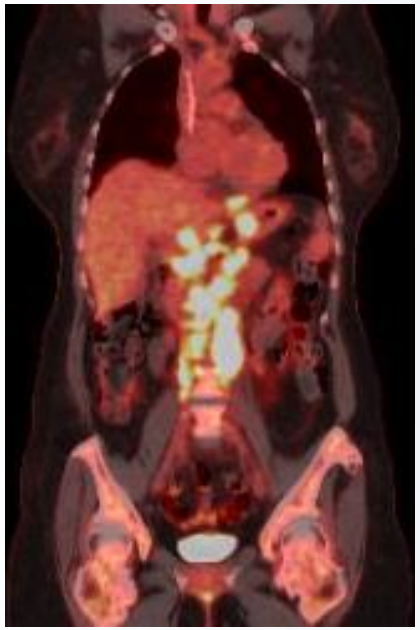
- 43 yo woman with stage IVA MZL, dx 2016 (tonsils, BM, PB)
- **Observation** x 4 years
- Presented with wt loss/epigastric pain, 2020
- EGD revealed large ulcerated mass, Bx → **Transformed DLBCL** arising from gastric MALT, FISH negative, Stage IVA, IPI 2
- **R-CHOP x 6** → CR by PET/EGD
- Progressive disease, 10/2022 (2.5 yrs post R-CHOP), Stage IVA
- EGD → Gastric biopsy consistent with MYC-positive DLBCL
- **R-ICE x 2** with no response (plans for ASCT scrapped)
- CAR-T cell therapy approval pending when pt developed recurrent significant abdominal pain/bloating, constipation
- Enrolled on clinical trial of **glofitamab, obinutuzumab, and RO7227166 (bispecific targeting CD19 and 4-1BB)**

PET response

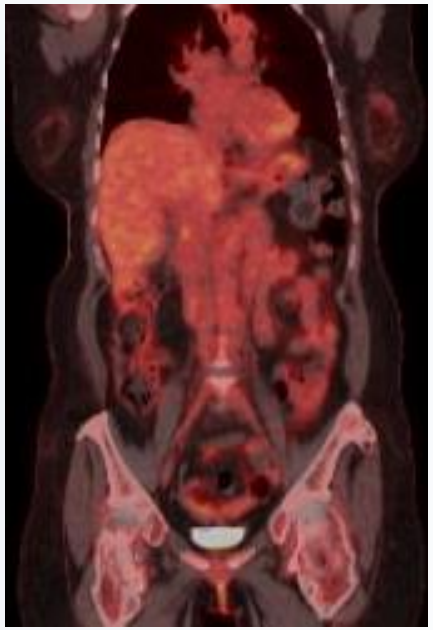
Pre-ICE

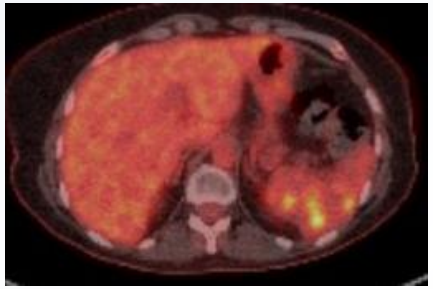


Post-ICE x 2/Pre-Glofit

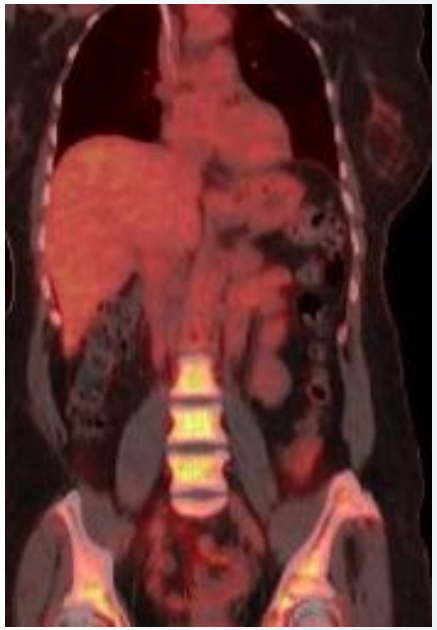


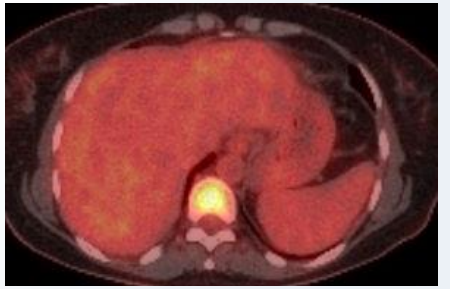
Post-C2 Glofit (5PS 4 vs 5)





Post-C5 Glofit (PS 1)





Bispecific Ab vs CAR T cell in r/r DLBCL

Characteristic	Bispecific	CAR-T
Availability	**Off-the shelf**	Prolonged insurance approval Slot availability Production (3-6 wks)
Pre-treatment	Not applicable	Lymphodepleting chemo FluCy or Benda
ORR	52-63%	52%-83%
CR	**39%**	**40-53%**
Duration of treatment	Fixed course (12 cycles) OR until PD	One time treatment
Duration of CR	**12 mo 78-88%**	**12 mo 66-86%**
Hospitalization	Required x 24-48 hrs for Glofit D1.	Usually required
Gr≥3 CRS	0-7%	1-28%
Gr≥3 neurotoxicity	0-4%	1-27%
Gr 3-4 cytopenias	27%	70%

Selected bispecific trials in 1st or 2nd line therapy for DLBCL

- First line
  - R-CHOP ± Epcoritamab (Phase 3)
  - Glofit + pola-RCHP or RCHOP (Phase 1-2)
  - R-CHOP + Glofit (C3+) if <2 log ↓ ctDNA post-C1.

- Second line (or later)
  - Glofit-GemOx vs R-GemOx (Phase 3)
  - Epcoritamab vs R-GemOx or R-Benda (Phase 3, investigator choice)
  - Mosun-pola vs R-Gem-Ox (Phase 3)

Current recommendations for incorporating bispecifics into r/r DLBCL therapy

- Epcoritamab or Glofit (not yet approved but close) ≥ 3rd line if
  - Failed CAR-T as 2nd or 3rd line
  - Ineligible for CAR-T (e.g. comorbidities / logistical challenges / highly symptomatic)
- If bispecific given prior to CAR-T and pt becomes CAR-T eligible →
  - If interim CR, consider waiting until relapse and retreating with BsAb as lead-in/bridge
  - If interim PR, “bad PR” → CAR-T, VGPR → consider continuing BsAb with repeat PET
- PR post-CAR-T
  - S2114, D+30 PR randomize Mosun vs. Pola vs. Mosun + Pola vs. Obs
- If available, participation in bispecific trials in first/second line therapy

Mantle Cell Lymphoma

Incorporation of Bispecific Antibodies

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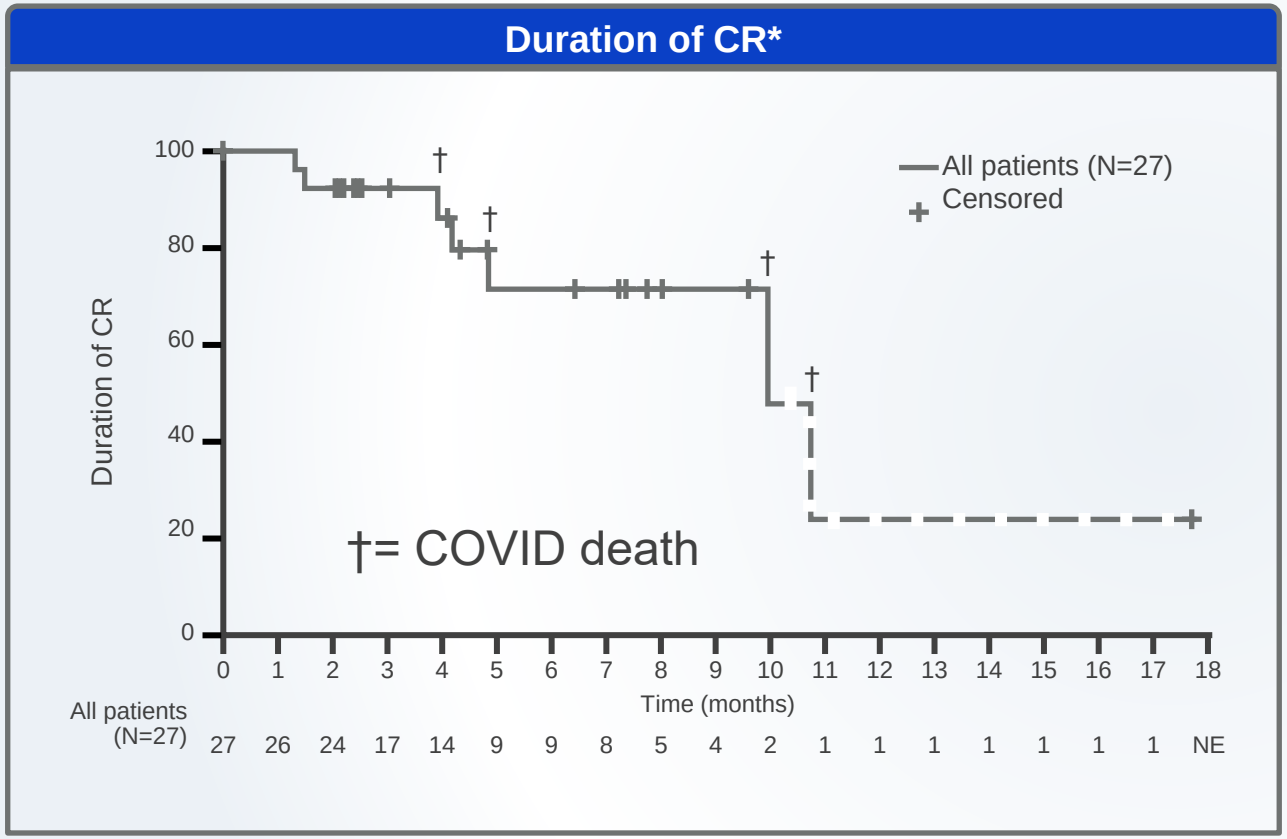
CD20xCD3 Bispecifics for r/r Mantle Cell ≥2 lines of therapy

Agent	No. of pts	ORR%	CR %	Ref
Glofitamab	37	**84**	**73**	1
Mosunetuzumab	13	31	23	2
Odronextamab	12	50	33	3
Epcoritamab	5	60	20	4

1. Philips 2022 Blood: 140 (Sup 1): 178–180;. Budde JCO 2022; 40: 481-91; 1055–65, 3. Bannerji Lancet Haem 2022: 9: e327–39; 2. 4. Hutchings et al Lancet 2021; 398: 1157–69;1.

Glofit: Duration of CR in MCL



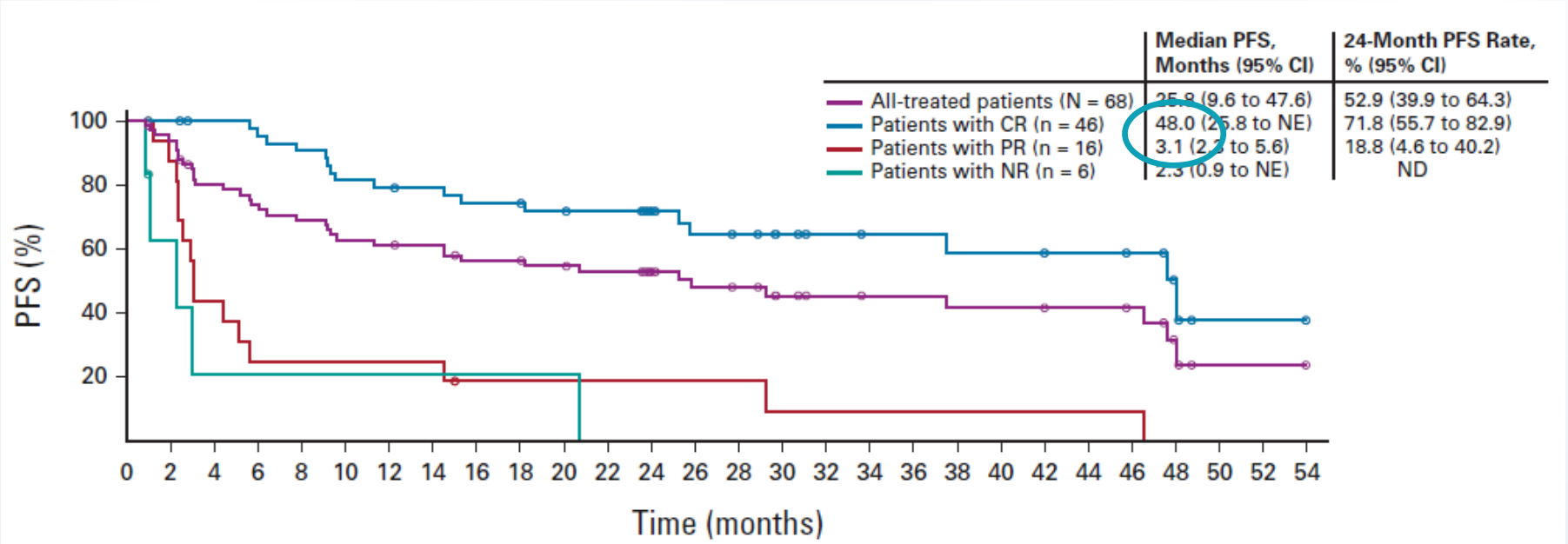
- Phase 2, N=37, median f/u 5 mo
- ORR 83%, CR 73%
- Median DOCR: 10.0 months (95% CI: 4.9–NE)
- At data cut-off, **74.1%** (20/27) of pts CR remained in remission
- **Four deaths due to COVID-19 (11% of pts)**
  - when excluded, median not reached and
  - 87% (20/23) CRs were ongoing
- **CRS Gr 3-4 16.8% (no Gr 3/4 ICANS)**
  - Toci 46%, steroids 38%
  - *Lower incidence if 2000 vs 1000 mg Obinu*

Need to explore COVID deaths on bispecific trials in more detail. Publications often indicate “not related” to treatment

Philips 2022 Blood: 140 (Sup 1): 178–180

CAR-T (Brexucabtagene autoleucel) in MCL

- Phase 2, N=74, 68 treated
- IIT ORR 84%, CR 62% (treated pts 91%/ 68%)
- CRS Gr 1-2 76%, Gr≥3 **15%** (59% tocilizumab, 22% steroids, 16% vasopressors)
- Neurological Gr 1-2 32%, **Gr ≥3 neurological 31%**
- **Grade 5 AEs, 3%** (n=2), organizing pneumonia, staph sepsis



Wang et al N Engl J Med 2020;382:1331-42.; Wang et al J Clin Oncol 2023;41:555-567.

Recommendations for incorporating bispecifics into r/r MCL therapy

- Not yet approved for this indication (Glofit most likely candidate)
- Glofit and CAR-T have **nearly identical ORR/CR** rates in r/r MCL
- CRS similar, but neurotox much less with Glofit
- Durability unknown for Glofit but encouraging at 12 months
- If bispecifics approved, suspect “off-the shelf” and less neuro tox will result in choosing **bispecific before CAR-T** (likely 3rd line)
- No data presented for bispecific activity in TP53 mutated MCL

Conclusions

Incorporation of CD20xCD3 bispecifics in lymphoma therapy

- Bispecifics provide a promising option for
  - 3rd line r/r FL (Mosun) and DLBCL (Glofit, Epcoritamab)…maybe MCL
  - Need longer f/u to assess for potential cure but seems possible
- User friendly, off-the-shelf product
  - SC formulations especially appealing
- Toxicity manageable and usually limited to C1
  - CRS usually low grade, SC < IV
  - Glofit highest rate of side effects – may require 1-2 day hospitalization for C1D1
  - Neuro tox, prolonged cytopenias, serious infections uncommon (? COVID worse)
  - No reports of serious late effects
- Use in earlier lines of therapy under investigation