BISPECIFIC ANTIBODIES FOR FOLLICULAR LYMPHOMA

David Russler-Germain, MD/PhD
Instructor, Division of Oncology

SITEMAN CANCER CENTER

Washington University in St. Louis School of Medicine | BJC HealthCare

SITEMAN Kids AT ST. LOUIS Children's HOSPITAL Washington University Physicians

NCCN National Comprehensive Cancer Network®

NCI Comprehensive Cancer Center
A Cancer Center Designated by the National Cancer Institute

Disclosures

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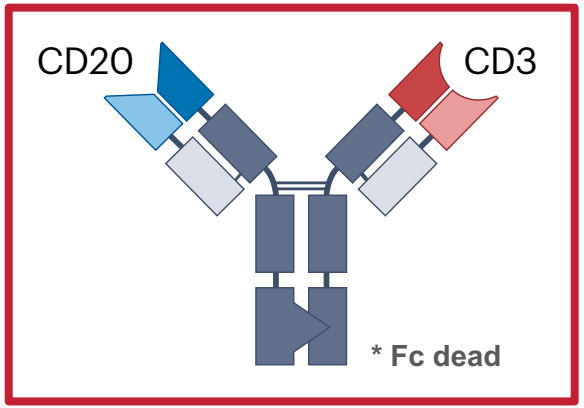
Advisory board: AstraZeneca

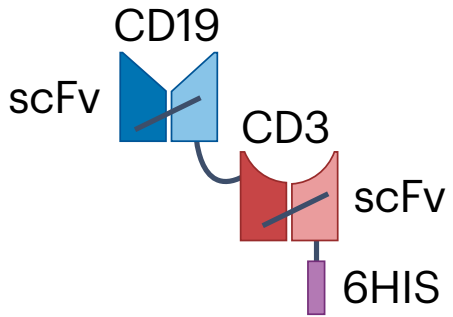
FL Bispecifics: Mechanism and Design

- Typically IgG antibody format
- Bispecific binding to surface antigens
  - Tumor-associated (**target**) = CD20
  - Pan-T cell (**effector**) = CD3



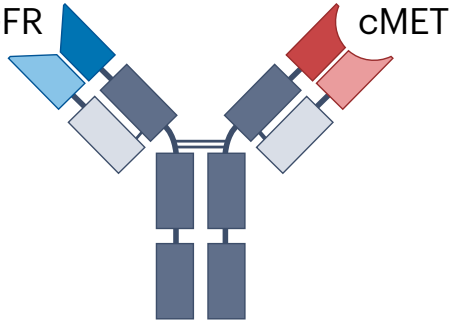
Mosunetuzumab

vs.



Blinatumomab

vs.



Amivantamab

Klein, C, et al. *Nat Rev Drug Disc* 2024.

FL Bispecifics: Mechanism and Design

Agent	Structure	Anti-CD3 Clone	Anti-CD20 Clone	Status (as of 3/2024)
Mosunetuzumab	IgG1	UCHT1 (CD3ε)	2H7 *Epitope shared w/ rituximab*	**FDA accelerated approval 12/2022**
Epcoritamab	IgG1	SP34-der (CD3ε)	7D8 *Epitope shared w/ ofatumumab*	FDA priority review 2/2024
Odronextamab	IgG4	REG1250 (CD3δε)	3B9-10 *Epitope shared w/ ofatumumab*	FDA priority review 9/2023

Russler-German, DA, et al. *Frontiers Oncol* 2023.

FL Bispecifics: Administration

Agent	Route of Admin		Treatment Duration	CRS Mitigation		
	IV	SC	Time Limited	Step-up Dosing	Mandated Steroids	Minimum Required Pred Equiv.
Mosunetuzumab	Y	Y	Y	C1 D1/8/15 C2-8 D1 (C9-17 D1 if PR)	Dex 20 mg for all C1-2 doses	533 mg
Epcoritamab	N	Y	N	C1-3 D1/8/15/22 C4-9 D1/15 C10+ D1	Pred 100 mg daily x4 for all C1 doses	1600 mg
Odronextamab	Y	Y	N	C1 D1/2/8/9/15/16 C2-4 D1/8/15 C5+ Q2W vs Q4W	Dex 20 mg on the day before, of, and after all C1 plus C2 D1 doses	2000 mg

FL Bispecifics: Efficacy

Impressive outcomes in phase 2 studies in rel/ref FL after 2+ prior lines of therapy

Agent	N	Overall Response Rate	Complete Response Rate	Median Follow-up (months)	Median PFS (months)	Median DoCR (months)
Mosunetuzumab[1]	90	78%	60%	37.4	24.0	Not reached
Epcoritamab[2]	128	82%	63%	17.4	15.4	Not reached
Odronextamab[3]	128	81%	73%	17.7	20.7	Not reached

[1]Schuster, SJ, et al. *ASH* 2023 (NCT02500407). [2]Linton, KM, et al. *ASH* 2023 (NCT03625037). [3]Villasboas, JC, et al. *ASH* 2023 (NCT03888105).

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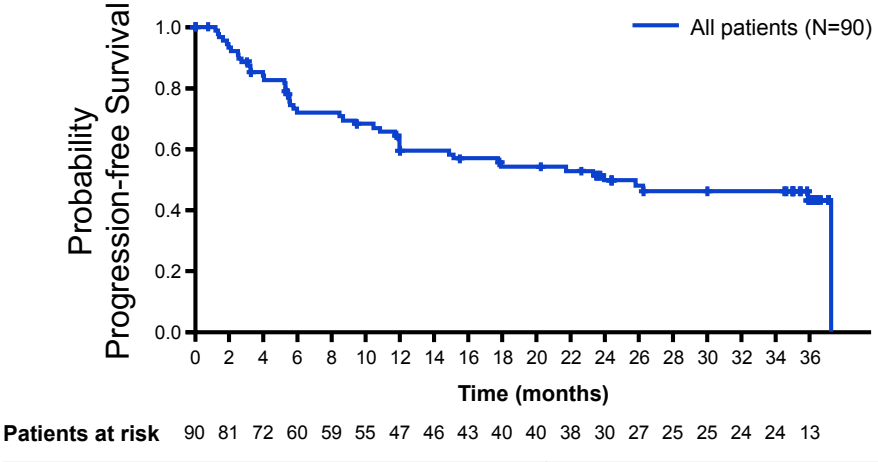
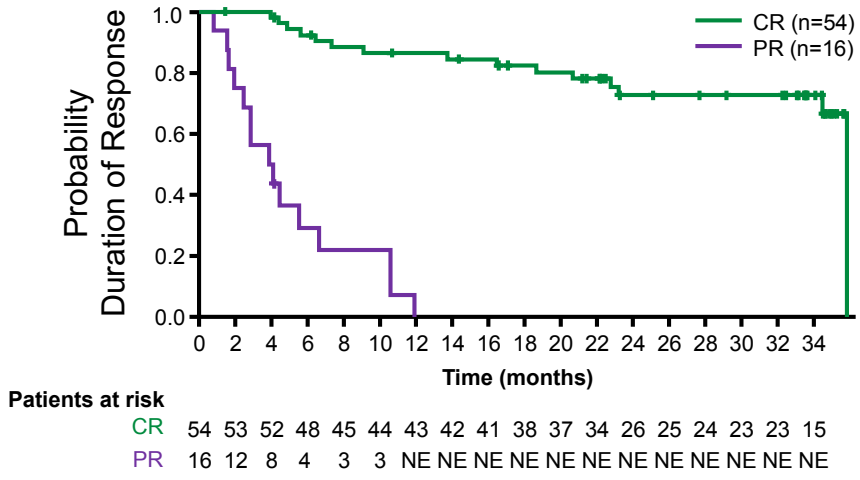
FL Bispecifics: Efficacy

Impressive outcomes in phase 2 studies in rel/ref FL after 2+ prior lines of therapy

- **Mosunetuzumab**
  - Median time to first response: 1.4 months (1.0–11)
  - Median time to first CR: 3.0 months (1.0–19)





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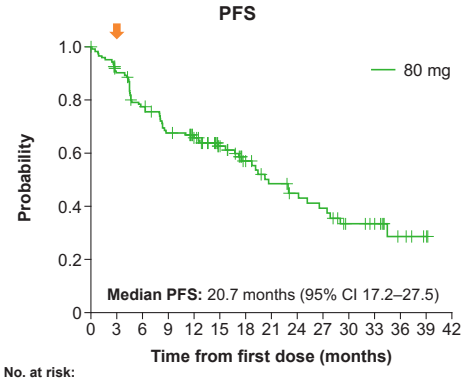
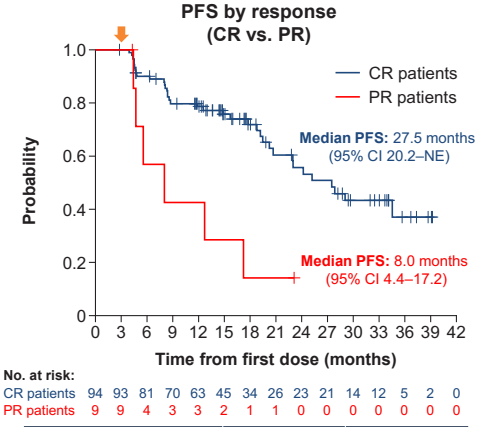
FL Bispecifics: Efficacy

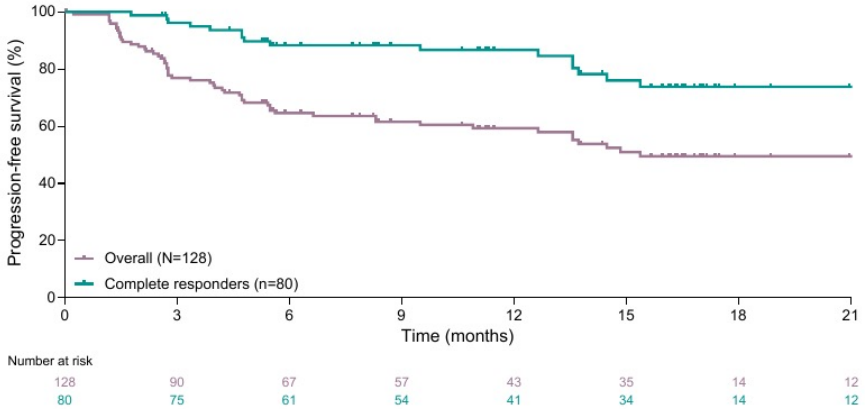
Impressive outcomes in phase 2 studies in rel/ref FL after 2+ prior lines of therapy

Odronextamab





Epcoritamab



Villasboas, JC, et al. *ASH* 2023 (NCT03888105). Linton, KM, et al. *ASH* 2023 (NCT03625037).

FL Bispecifics: Safety

Predictable toxicity profile

- CRS, fatigue, headache, neutropenia, hypophosphatemia, rash, nausea/diarrhea/constipation

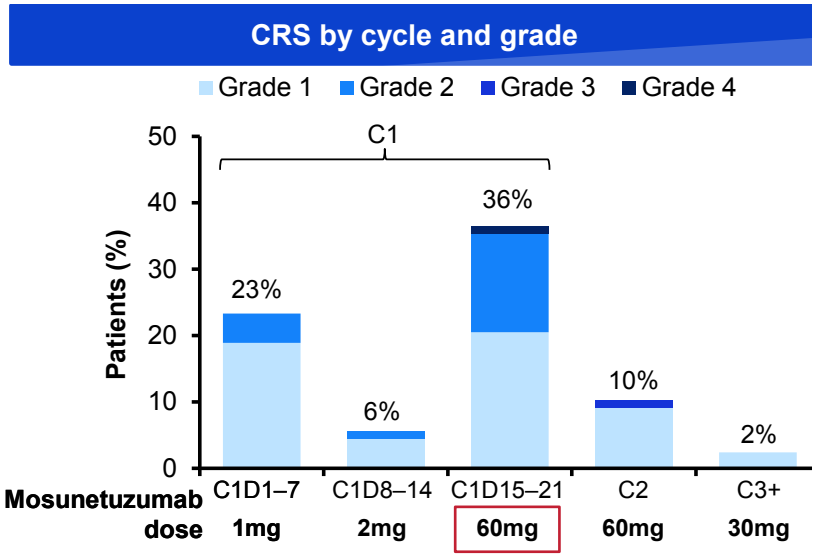
Agent	N	Related AE Leading to Discont.	Cytokine Release Syndrome				Neurologic AEs
			Any Grade	Gr 1	Gr 2	Gr 3+	
Mosunetuzumab[1]	90	2%	44%	26%	17%	2%	<5% *Any ICANS?*
Epcoritamab[2]	128	19% *~½ COVID-19*	67%	65%	2%	0%	<5% *Any ICANS?*
Odronextamab[3]	128	8%	57%	45%	10%	2%	<5% *Any ICANS?*

[1]Schuster, SJ, et al. *ASH* 2023 (NCT02500407). [2]Linton, KM, et al. *ASH* 2023 (NCT03625037). [3]Villasboas, JC, et al. *ASH* 2023 (NCT03888105).

FL Bispecifics: Safety

No required hospitalization

- Median time to CRS onset (C1 D1): 5 hours (1–24)
- Median time to CRS onset (C1 D15): 27 hours (0–391)



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FL Bispecifics: Logistics

Community vs. specialty center

- **Mosunetuzumab**
  - Required steroids: 11%
  - Required tocilizumab: 8%
- Unaddressed issues at non-specialty centers
  - Familiarity with recognizing CRS (vs. typical infectious etiologies for fevers)
  - Bandwidth for managing CRS (e.g., after-hours exchange, “urgent care” in-person evaluations, access to tocilizumab)
- Potential solutions
  - ‘Pill in pocket’ PRN steroids for in-home CRS care
  - Shared management (e.g., C1-3 at specialty center, C4+ at community center)

FL Bispecifics: Line of Therapy and Combinations

Current approval and pivotal phase 2 studies: **monotherapy in 3L+**

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Current approval and pivotal phase 2 studies: **monotherapy in 3L+**

- **Mosunetuzumab** clinical trials
  - Frontline setting
    - Mosunetuzumab monotherapy (phase 2)
    - Mosunetuzumab + response-adapted obinutuzumab/polatuzumab vedotin (phase 2)
    - Mosunetuzumab + lenalidomide (phase 2)
    - Mosunetuzumab + polatuzumab vedotin (phase 2)
    - Mosunetuzumab + tazemetostat (phase 2)
    - Mosunetuzumab vs. SOC rituximab (phase 3; *planned*)
    - Mosunetuzumab + lenalidomide vs. SOC rituximab + chemotherapy (phase 3; *planned*)
  - Relapsed/refractory setting
    - Mosunetuzumab + lenalidomide vs. SOC rituximab + lenalidomide (phase 3)

FL Bispecifics: Line of Therapy and Combinations

Current approval and pivotal phase 2 studies: **monotherapy in 3L+**

- **Epcoritamab** clinical trials
  - Frontline setting
    - Epcoritamab + rituximab + lenalidomide (phase 2)
    - Epcoritamab + lenalidomide (phase 2)
    - Epcoritamab + rituximab (phase 2)
    - Epcoritamab + rituximab + lenalidomide vs. SOC anti-CD20 + chemo or lenalidomide (phase 3)
  - Relapsed/refractory setting
    - Epcoritamab + rituximab + lenalidomide vs. SOC rituximab + lenalidomide (phase 3)
    - Epcoritamab vs. SOC anti-CD20 + chemo or lenalidomide (phase 2)

FL Bispecifics: Line of Therapy and Combinations

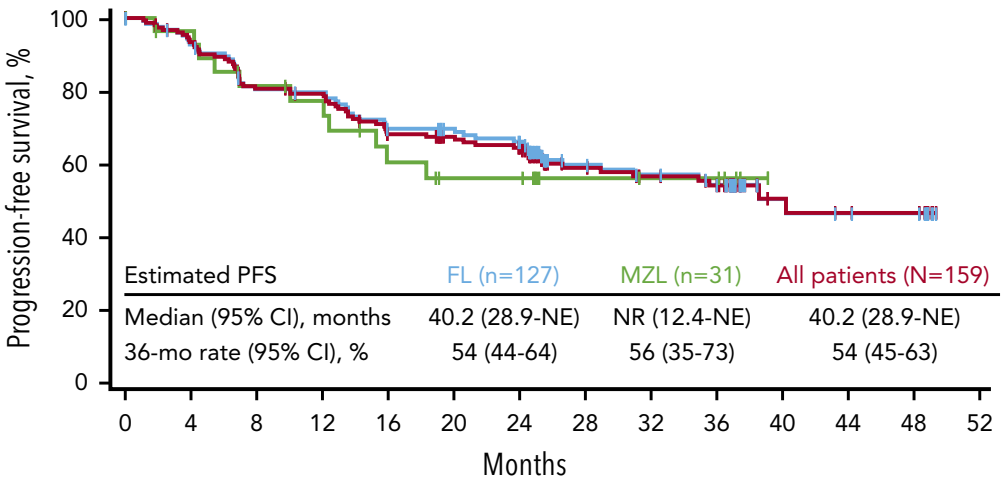
Current approval and pivotal phase 2 studies: **monotherapy in 3L+**

- **Odronextamab** clinical trials
  - Frontline setting
    - Odronextamab vs. SOC rituximab + CHOP/CVP/bendamustine (phase 2/3)
    - Odronextamab + CHOP/CVP vs. SOC rituximab + CHOP/CVP (phase 2/3)
  - Relapsed/refractory setting
    - Odronextamab + lenalidomide vs. SOC rituximab + lenalidomide (phase 2/3)

FL Bispecifics: Sequencing with Other Therapies

Axi-cel CAR T cells (ZUMA-5) — is all that glitters really gold?

	FL (n = 127)
ORR, n (%)	119 (94)
CR	100 (79)
PR	19 (15)
SD, n (%)	2 (2)
PD, n (%)	2 (2)
Not done, n (%)	4 (3)
DOR, median (95% CI), mo	38.6 (29.0-NE)
Estimate at 36 mo (95% CI), %	57 (47-66)
Duration of CR, median (95% CI), mo	NR (35.4-NE)
Estimate at 36 mo (95% CI), %	62 (48-72)
Duration of PR, median (95% CI), mo	4.9 (2.2-8.2)
Estimate at 36 mo (95% CI), %	NR (NE-NE)



Neelapu, SS, et al. *Blood* 2024.

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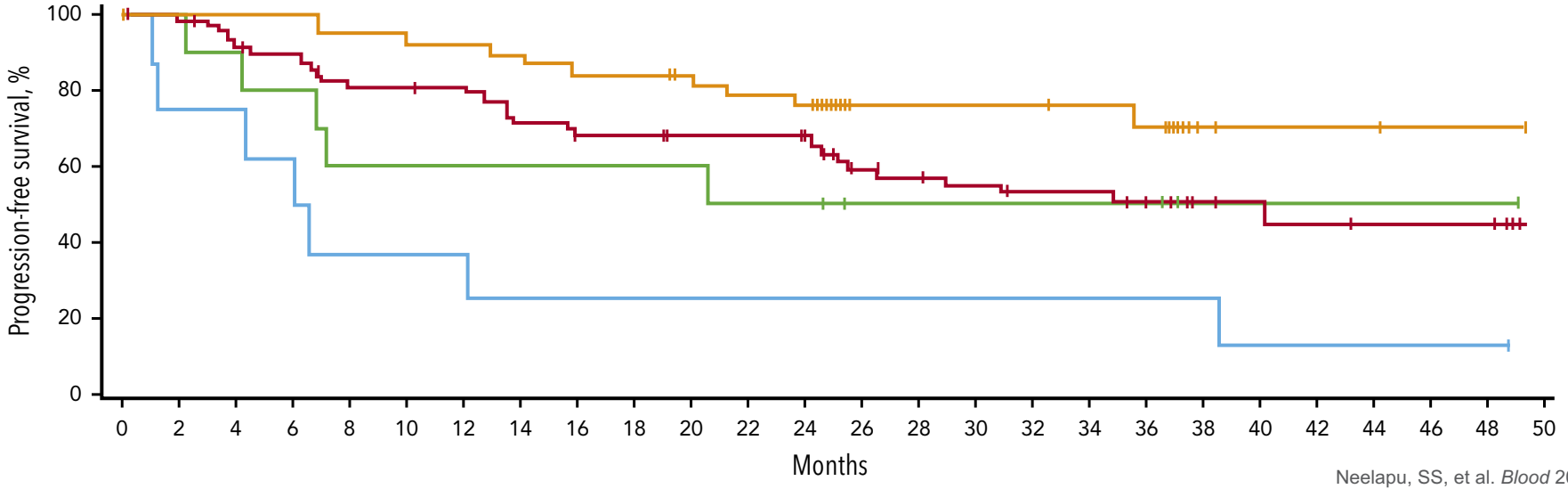
Axi-cel CAR T cells (ZUMA-5) — is all that glitters really gold?

Bendamustine prior to leukapheresis

Estimated PFS	≤6 months (n=8)	6-12 months (n=10)	>12 months (n=70)	None (n=39)
Median (95% CI), months	6.4 (1.1-38.6)	NR (2.3-NE)	40.2 (24.6-NE)	NR (35.5-NE)
36-month rate (95% CI), %	25 (4-56)	50 (18-75)	50 (37-63)	70 (50-83)

Neurologic AEs
- Gr 1–2: 41%
- Gr 3–4: 19%



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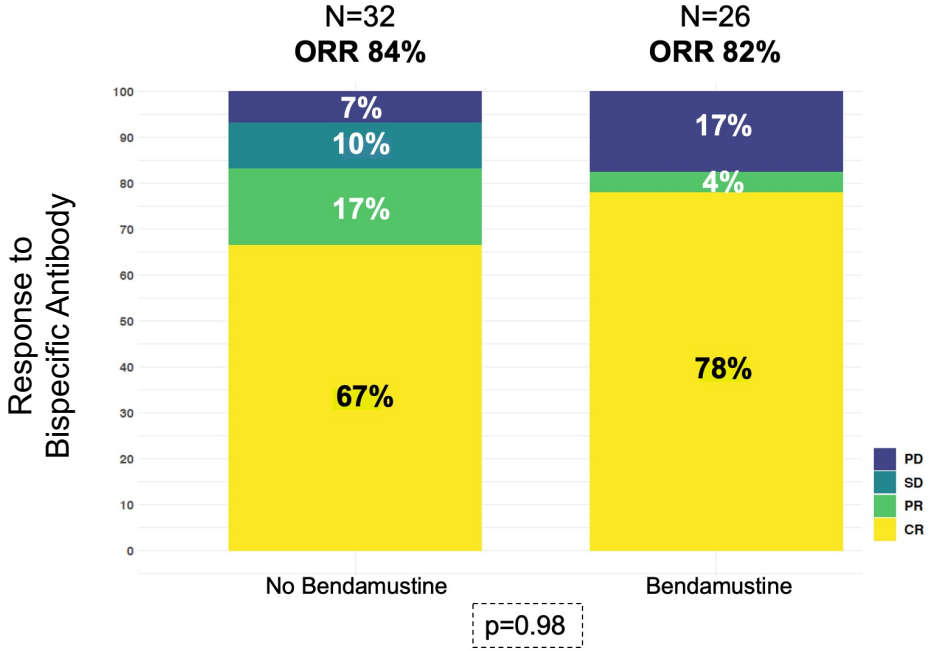
FL Bispecifics: Sequencing with Other Therapies

Could prior bendamustine be less deleterious for bispecifics than CAR T cells?

- Spanish study in FL suggests possibly; larger cohort study planned



Iacoboni, G, et al. *ASH* 2023.

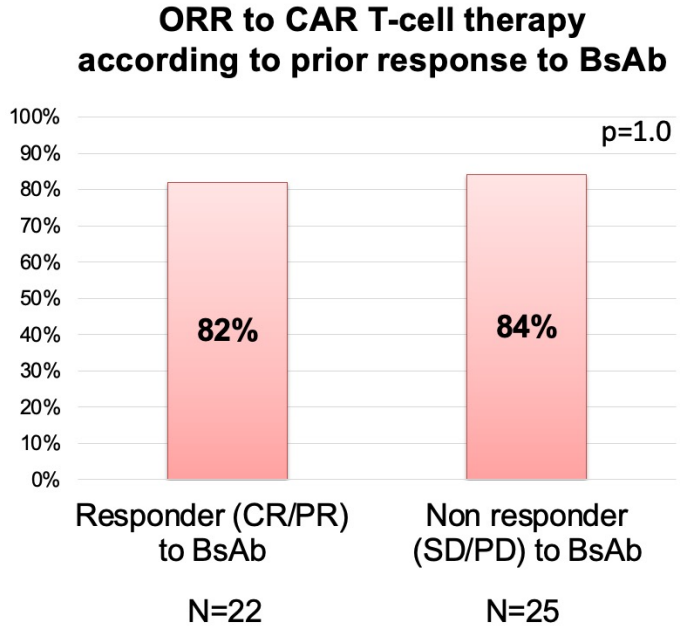
FL Bispecifics: Sequencing with Other Therapies

Could a bispecific reasonably precede CAR T cells?

- Spanish study in DLBCL suggests possibly; larger cohort study planned

Median follow-up of 10.5 months

Efficacy	N=47
Best ORR (CR), %	85 (43)
PFS, median mo (95% CI)	6.6 (2.6-NR)
OS, median mo (95% CI)	NR (9.0-NR)
DoR, median mo (95% CI)	8.8 (2.3-NR)



Iacoboni, G, et al. *ASH* 2023.

Conclusions

Mosunetuzumab is the current standard-of-care third-line treatment for follicular lymphoma

Soon, the decision will (likely) be mosunetuzumab vs. epcoritamab vs. odronextamab

Later, the decision will (likely) be which bispecific antibody, to combine or not to combine, and what line of therapy makes the most sense for my patient to receive a bispecific?

Future questions include:

- What is the optimal bispecific antibody treatment duration?
- Will CAR T cells become as ‘easy’ (AEs, $$$, logistics) as bispecifics?