Pro bispecific antibodies

Debate: CARTs vs. bispecifics in follicular lymphoma

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Disclosures

- **Advisory boards/consultancy:**
  - AbbVie, AstraZeneca, Genmab, Johnson&Johnson, Merck, Roche, Takeda
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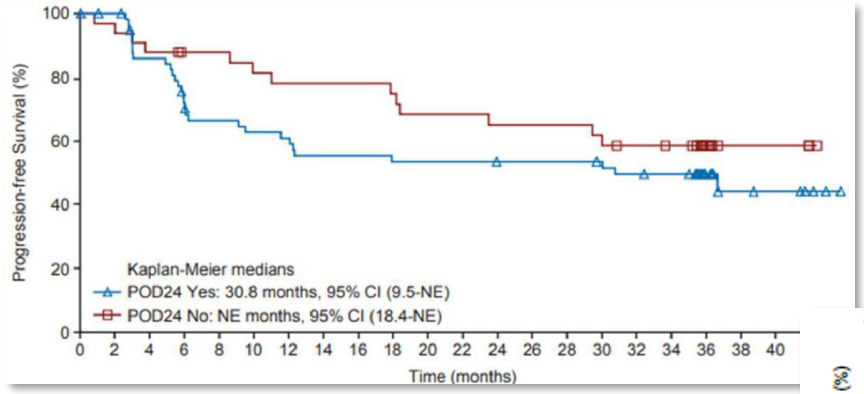
Phase 2 studies of CARTs in r/r FL

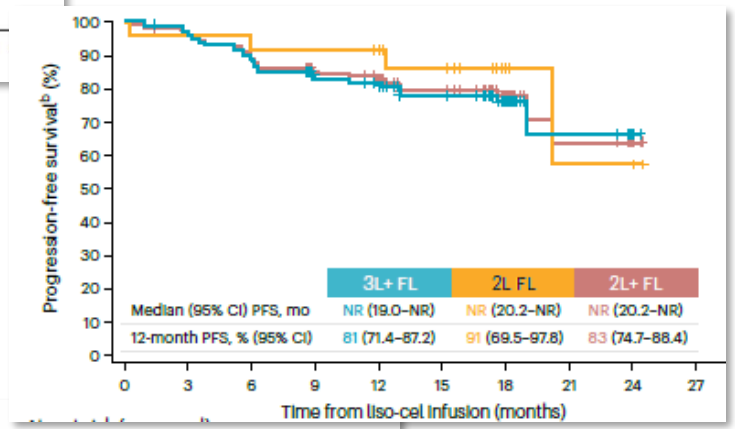
ELARA[1] – Tisagenlecleucel:

- ORR 86%
- CRR 68% (59% for POD24)
- PFS: 57% at 24 months



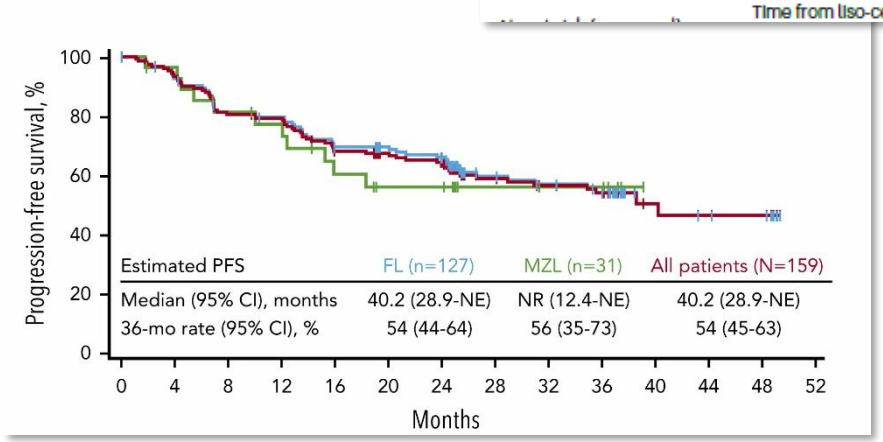
TRANSCEND FL[2] – Lisocabtagene maraleucel

- ORR 93% (ITT)
- CRR 90% (ITT)
- PFS: 72% at 24 months[3] (PP)



ZUMA 5[4] – Axicabtagene ciloleucel:

- ORR 94%
- CRR 79%
- PFS: 54% at 36 months



1. Dreyling M, et al. Blood 2024; 143 (17): 1713–1725.
2. Morschhauser F, et al. Nature Med 2024; 30(8): 2199-2207.
3. Nastoupil L, et al. ASH 2024, abstract #4387 (poster).
4. Neelapu SS, et al. Blood 2024; 143(6): 496-506.

Phase 2 studies of CARTs in r/r FL versus old and cheap treatment

ELARA[1] – Tisagenlecleucel:

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- CRR 68% (59% for POD24)
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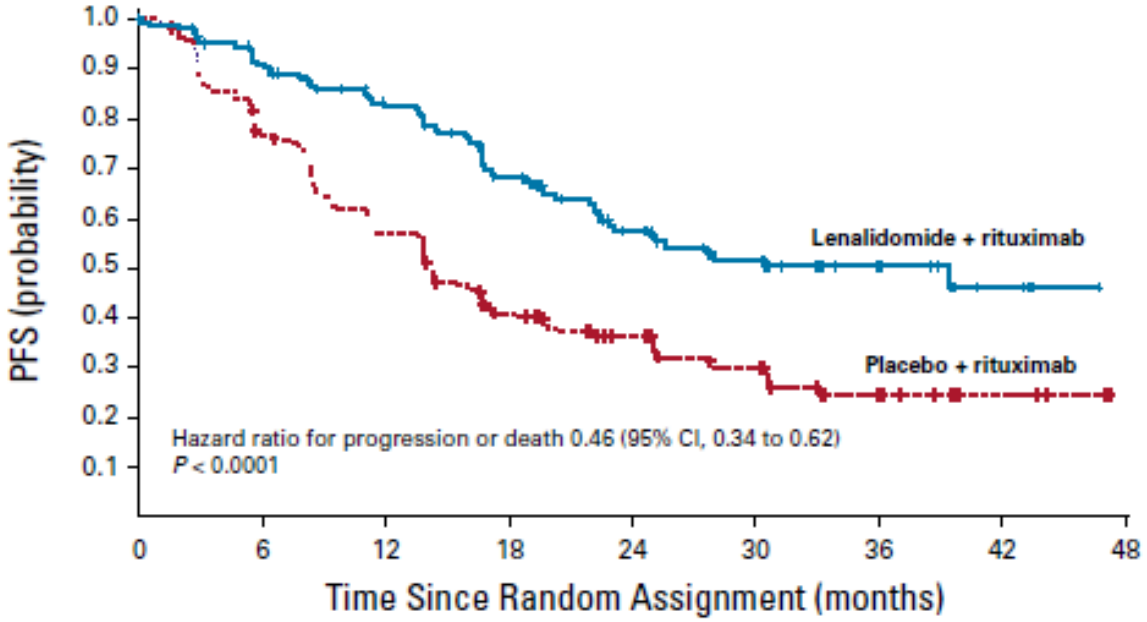
ZUMA 5[4] – Axicabtagene ciloleucel:

- ORR 94%
- CRR 79%
- PFS: 54% at 36 months

AUGMENT[4] – Rituximab + lenalidomide:

- ORR 78%
- CRR 34% (by CT scan)
- PFS: ~82% at 12 months and 58% at 24 months



1. Dreyling M, et al. Blood 2024; 143 (17): 1713–1725.
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3. Nastoupil L, et al. ASH 2024, abstract #4387 (poster).
4. Neelapu SS, et al. Blood 2024; 143(6): 496-506.
5. Leonard JP, et al. J Clin Oncol 2019; 37: 1188-1199.

Single-agent phase 1 studies of bispecific CD3/CD20 antibodies in B-NHL - across various dose levels and histologies

Bispecific antibody	Aggressive B-NHL			Indolent B-NHL			CRS / > gr 2
	No	ORR	CRR	No	ORR	CRR	
Mosunetuzumab	124	35%	19%	68	**66%**	**49%**	27% / 1%
Odronextamab	45	40%	36%	32	**91%**	**72%**	91% / 7%
Glofitamab	69	61%	49%	29	**69%**	**59%**	50% / 3.5%
Epcoritamab	22	68%	45%	10	**90%**	**50%**	59% / 0%

1. Budde E, et al. J Clin Oncol 2022;40(5):481-491.
2. Bannerji R, et al. Lancet Haematol 2022;9(5):e327-e339.
3. Hutchings M, et al. Clin Oncol. 2021;39(18):1959-1970.
4. Hutchings M, et al. Lancet 2021;398(10306):1157-1169.

Recent data from phase 1b-2 studies of mosunetuzumab, odronextamab, epcoritamab, and glofitamab in r/r FL

Pivotal phase 2 study of mosunetuzumab in r/r FL

- **ORR 78%**
- **CRR 60%**

Pivotal, single-arm, Phase II expansion study in patients with R/R FL and ≥2 prior therapies (NCT02500407)

Key inclusion criteria

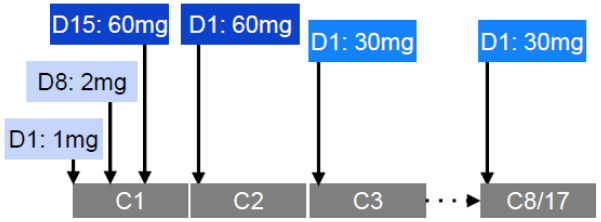
- FL Grade 1–3a
- ECOG PS 0–1
- ≥2 prior therapies including an anti-CD20 antibody and an alkylator

Data analysis

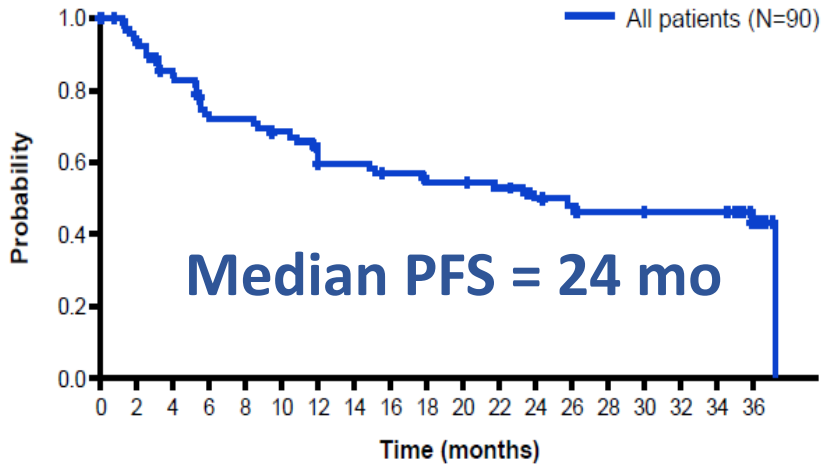
- Study met its primary endpoint: 60% CR rate versus 14% historic control ($p<0.0001$)[1,2]
- Updated efficacy and safety analysis with a median follow-up of 37.4 months

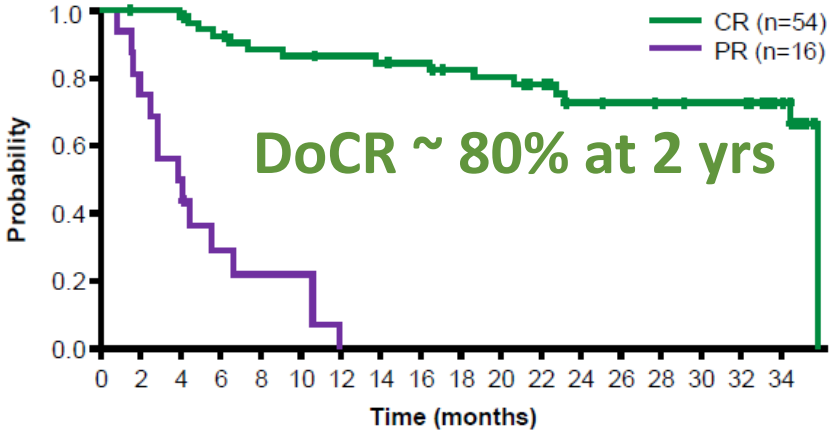
Mosunetuzumab administration

- IV mosunetuzumab administered in 21-day cycles with step-up dosing in C1
- Fixed-duration treatment: 8 cycles if CR after C8; 17 cycles if PR/SD after C8
- Retreatment with mosunetuzumab permitted at relapse for patients who achieved CR
- No mandatory hospitalization



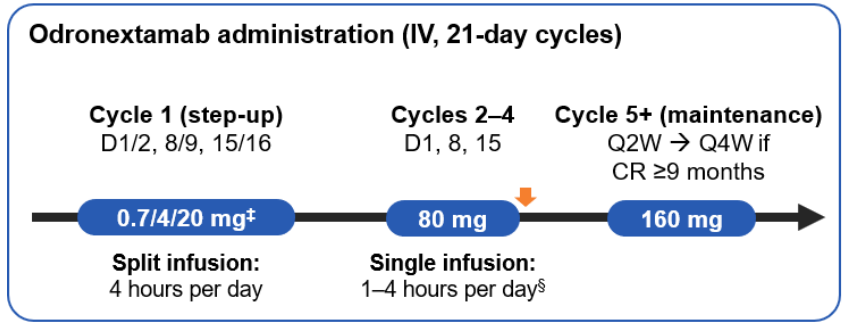
Refractory to last prior therapy	62 (69%)
Refractory to any prior anti-CD20 therapy	71 (79%)
POD24	47 (52%)
Double refractory to prior anti-CD20 and alkylator therapy	48 (53%)





Budde LE, et al. Lancet Oncol 2022;23:1055-65.
Sehn L, et al. Blood 2025, 145(7): 708–719.

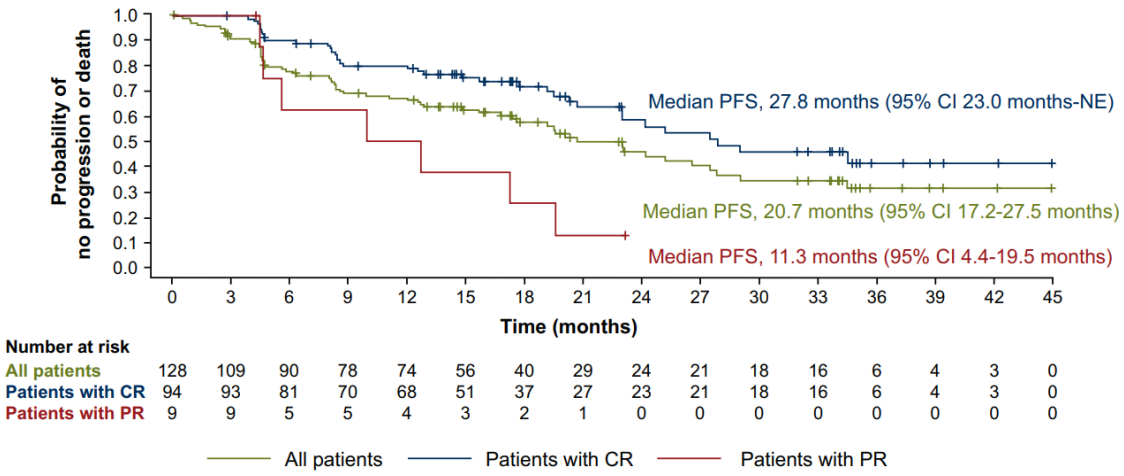
Phase 2 study of odronextamab in r/r FL (ELM-2)

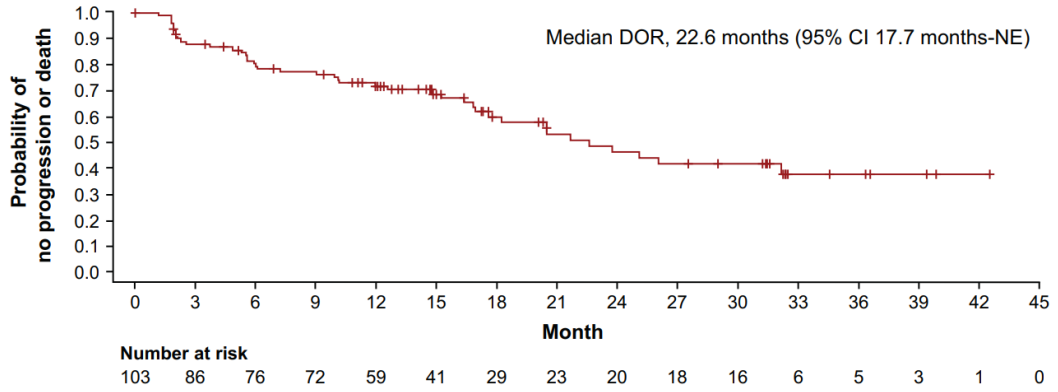


Refractory to last line of therapy, %	**72**
Refractory to anti-CD20 antibody, %	74
Double refractory to alkylator and anti-CD20 antibody, %	41
POD24, %	49

In 128 FL patients, median FU 20 months:

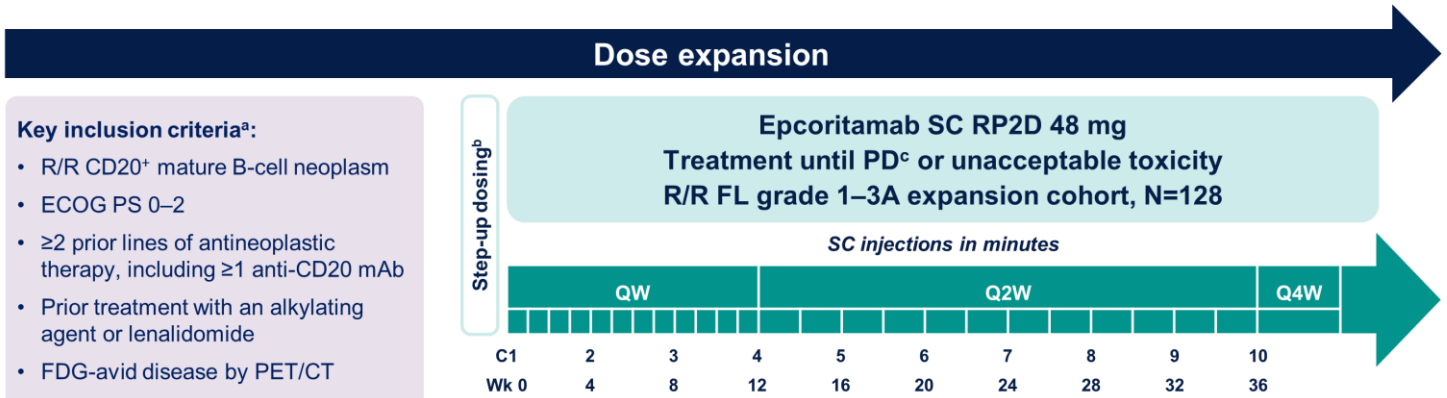
- ORR 80%
- CRR 73%
- Median PFS 21 months
- 2-year PFS rate 46%
- No impact of POD24 on response





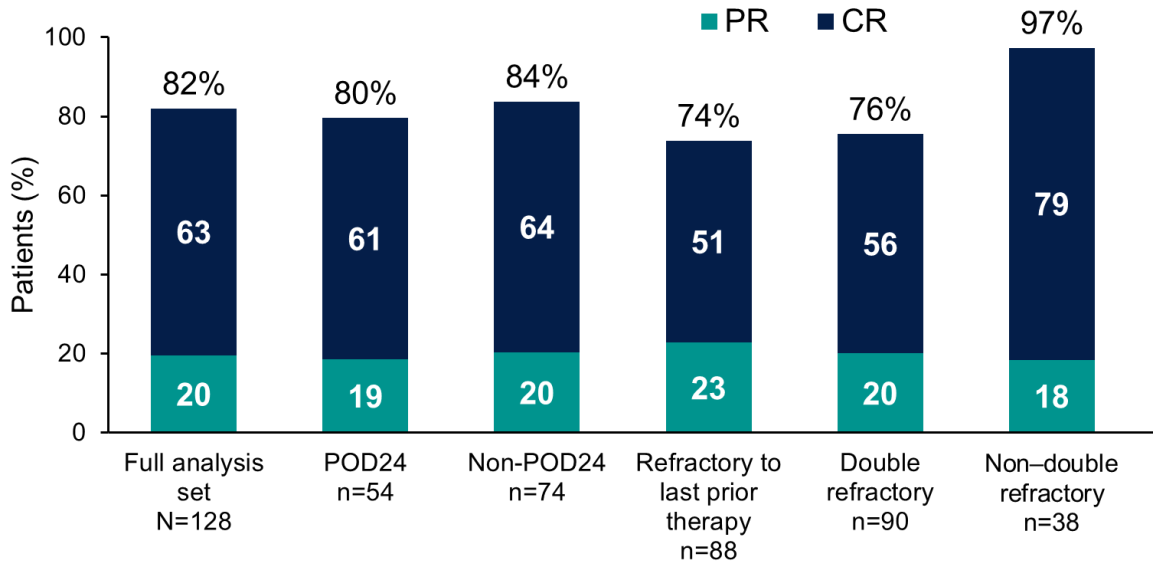
Chong G, et al. AACR 2024, abstract CT243.
Kim TM, et al. Ann Oncol 2024; 35(11): 1039-1047.

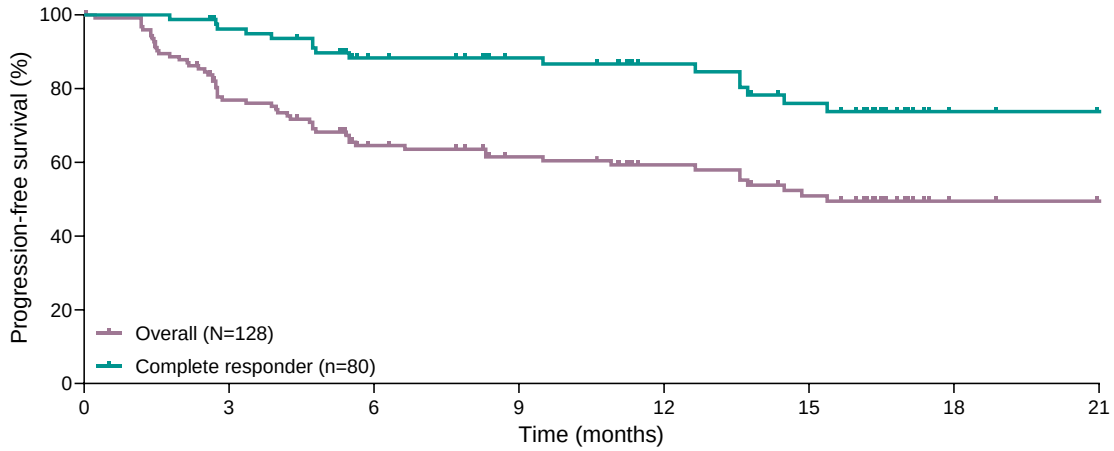
FL expansion cohort from the phase I-II study of epcoritamab in B-NHL (EPCORE NHL-1)



≥4 prior lines, n (%)	40 (31)
POD24,[a] n (%)	54 (42)
Double refractory,[b,c] n (%)	90 (70)
Primary refractory,[b] n (%)	69 (54)
Refractory[b] to last prior systemic therapy, n (%)	88 (69)

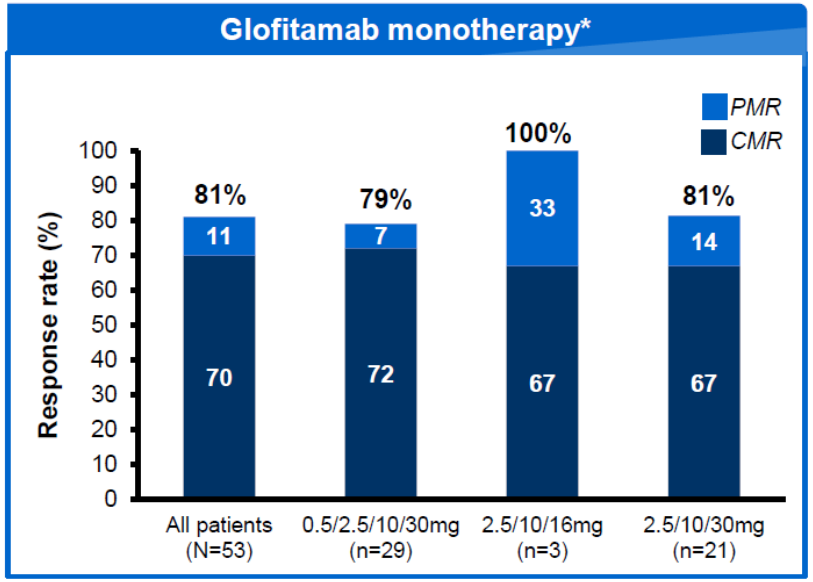
ORR: 82%
CRR: 63%
Median time to CR: 6 weeks

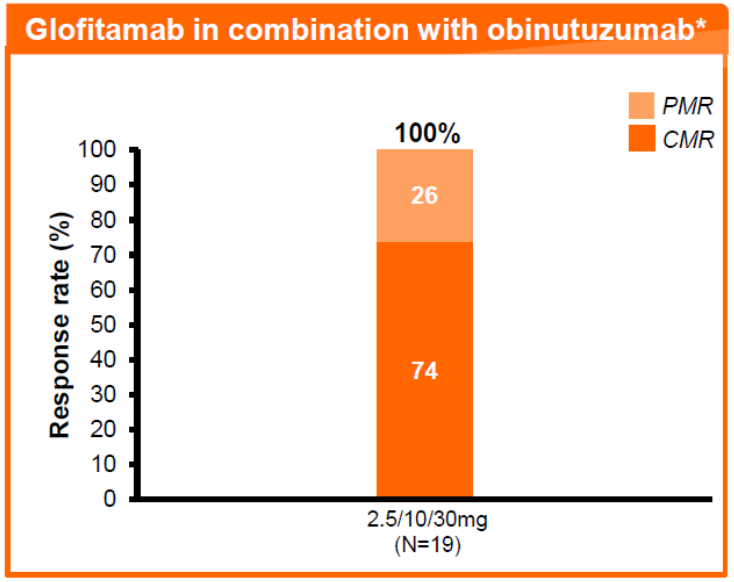


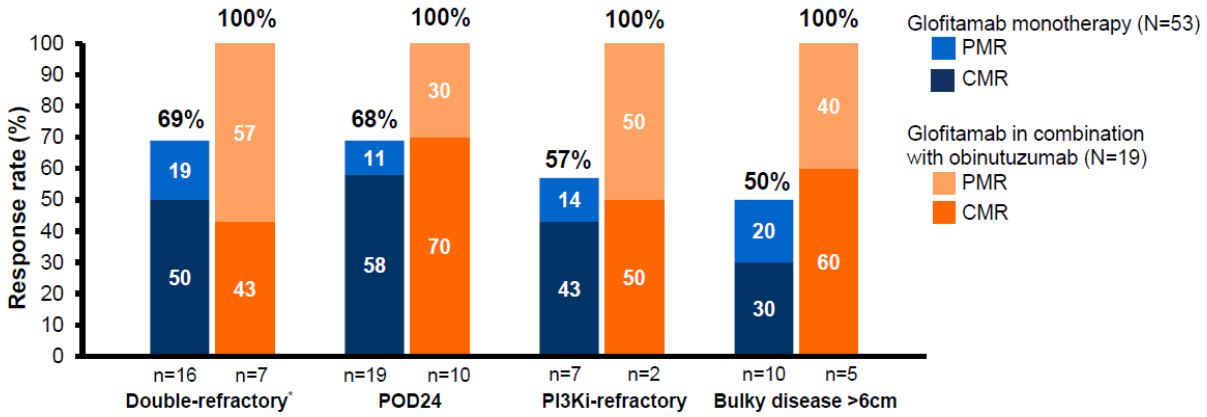


Linton K, et al. Ann Oncol 2024; 11(8): e593-e605.

Glofitamab alone and in combination with obinutuzumab in r/r FL







N (%) of patients unless stated	Glofitamab + obinutuzumab cohort (N=19)
Refractory to any prior therapy	13 (68.4)
Refractory to most recent therapy line	8 (42.1)
Refractory to any prior anti-CD20	10 (52.6)
Double-refractory*	7 (36.8)
POD24	10 (52.6)
PI3K inhibitor-refractory	2 (10.5)
Bulky disease >6cm	5 (26.3)

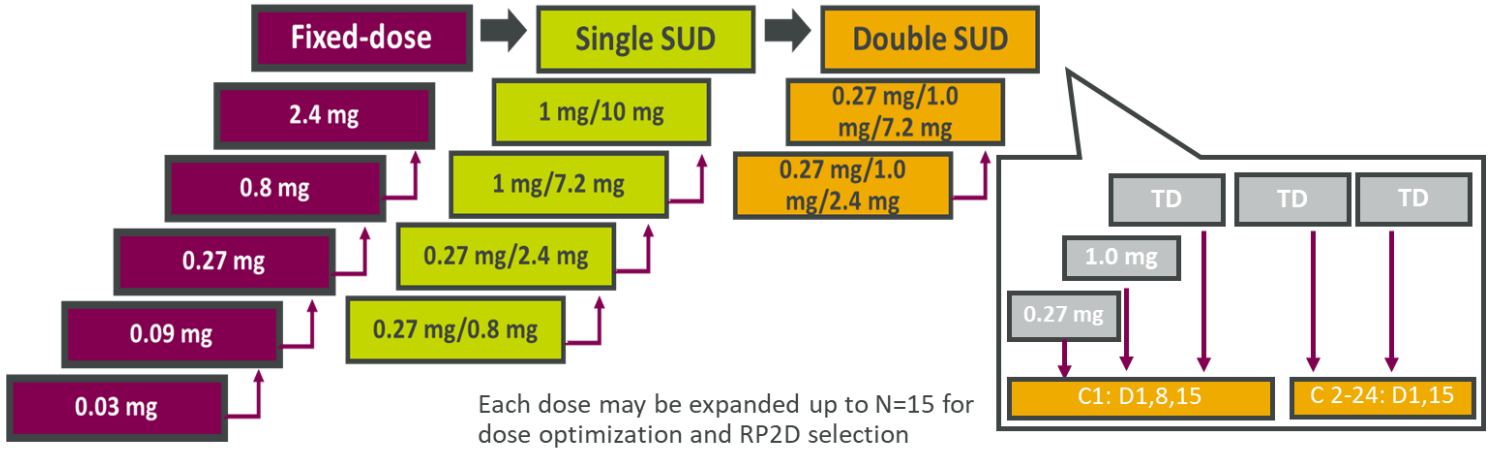
Morschhauser F, et al. ASH 2021, abstract #128.

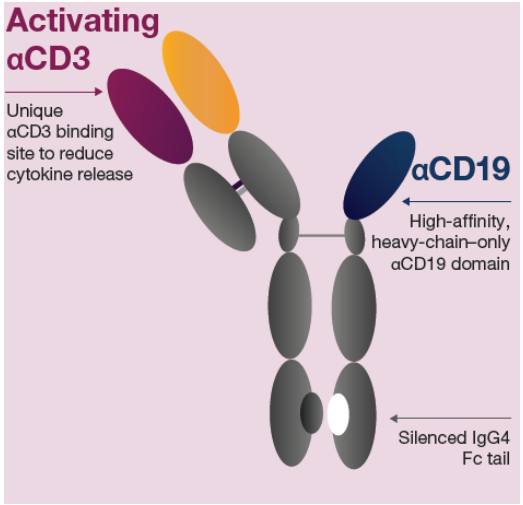
Phase 1 study of AZD0486 (CD19xCD3 bispecific) in r/r B-NHL

Key Eligibility

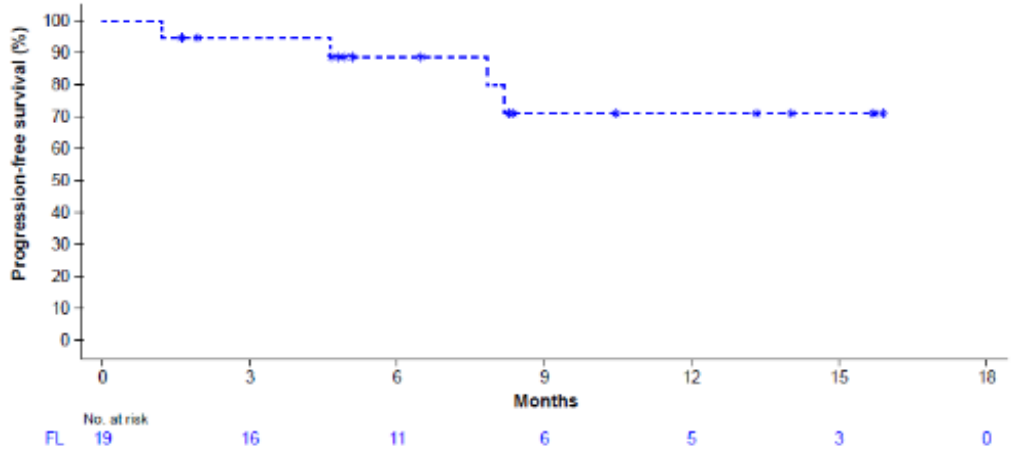
- Age ≥18 years
- CD19+ R/R B-NHL
- ≥ 2 prior lines of therapy (anti-CD19 directed regimens and prior TCEs allowed)
- ECOG PS ≤ 2
- ≥ 1 measurable lesion
- No active CNS disease

Study Design





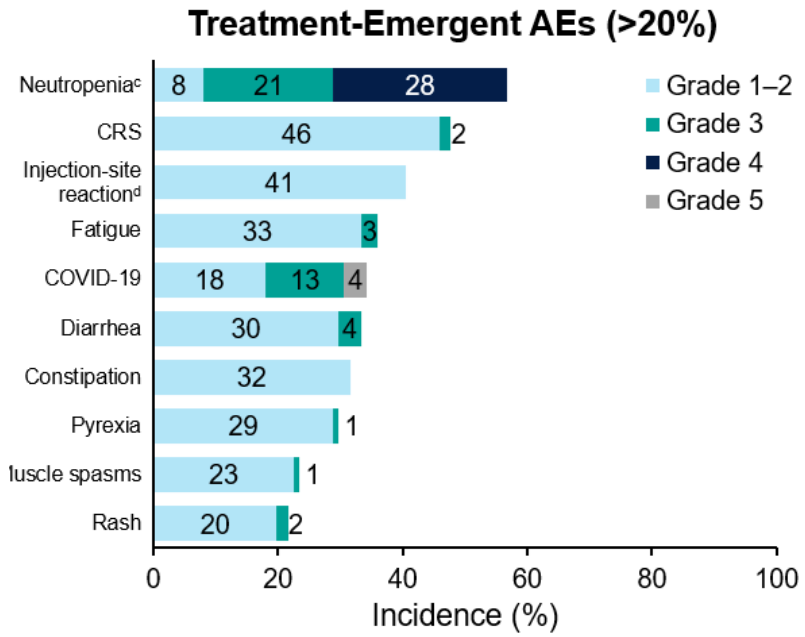
- So far 56 FL patients treated in this phase 1 study
- For the 41 patients treated at doses ≥2.4 mg:
  - ORR 95%, CRR 85%
  - CR in 6 out of 7 patients with CD20-negative disease
  - CR in both patients with prior CD20xCD3 therapy
  - No impact of POD24 on response (14 patients, CR 100%)

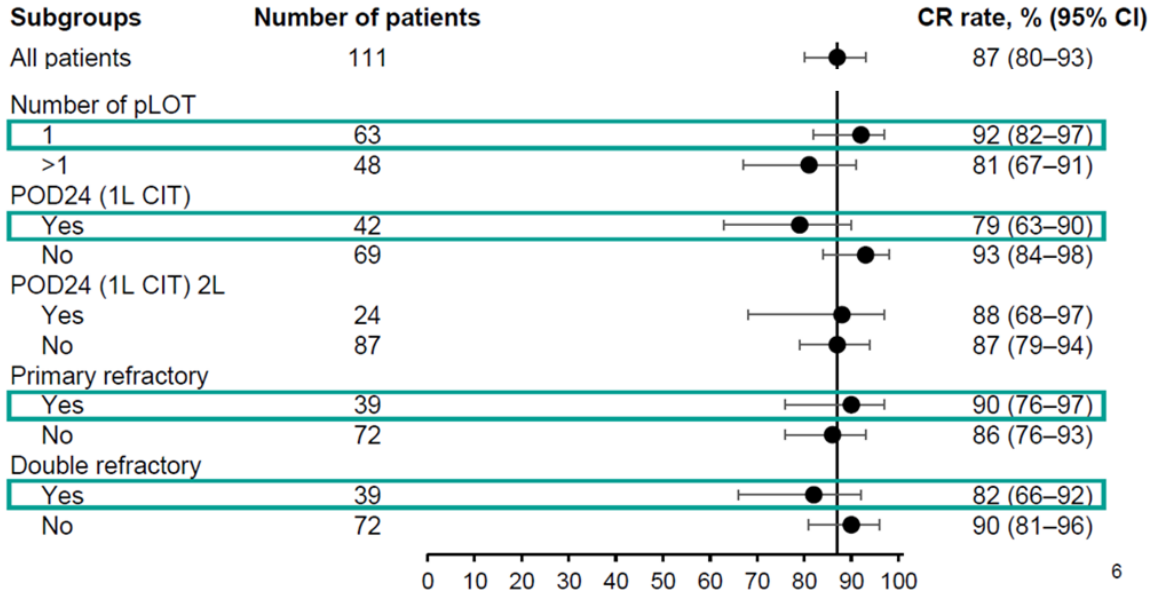


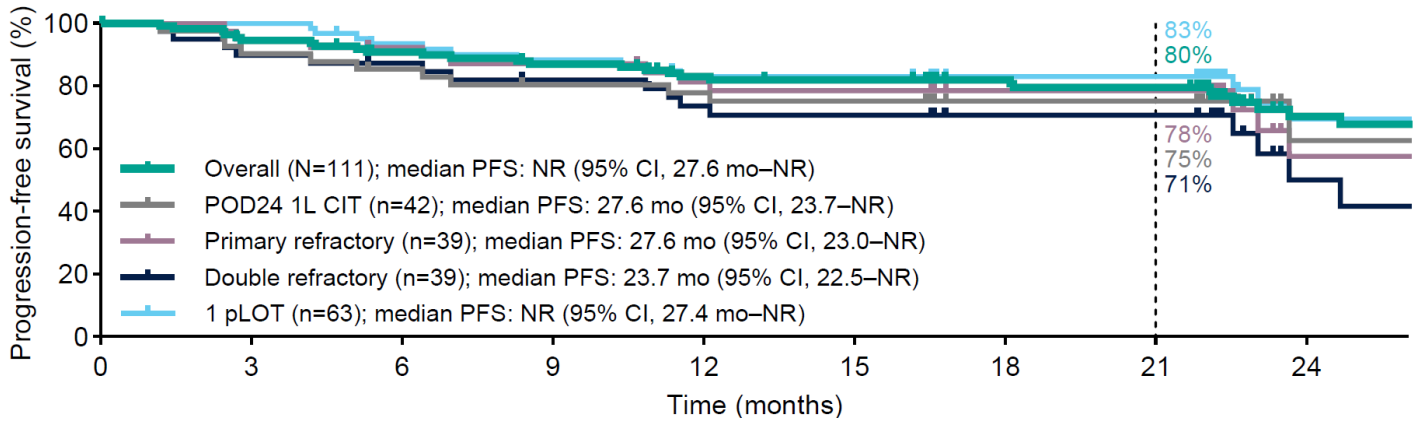
Hou J-Z, et al. ASH 2024, abstract #341 (oral).

Phase Ib/II study of fixed-duration epcoritamab + R^2 in patients with R/R FL

Best Response, n (%)[a]	N=111
Overall response	107 (96)
Complete response	97 (87)
Partial response	10 (9)
Progressive disease	2 (2)







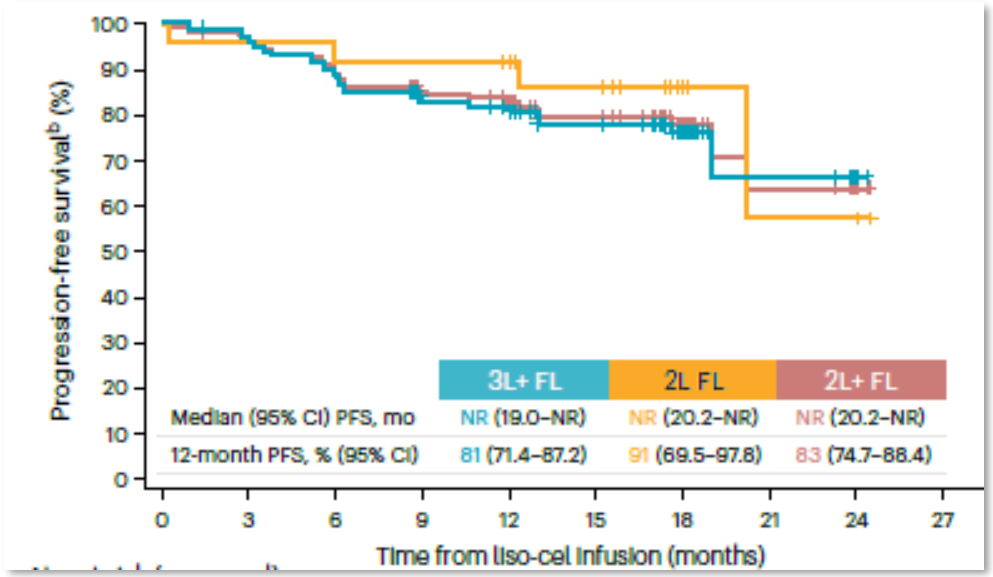
Falchi L, et al. ASH 2024, abstract #342 (oral).

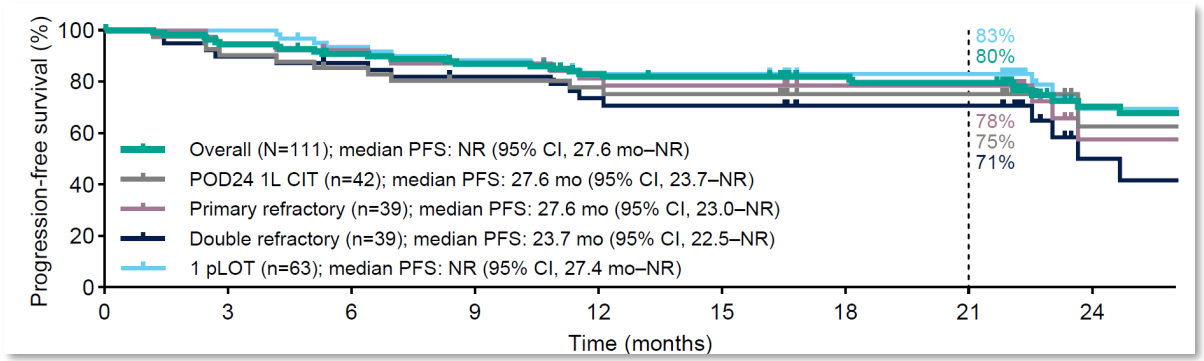
TRANSCEND FL (Liso-cel)

- ITT = 139 patients
- CRS: 59%, mainly grade 1-2
- ICANS: **15%**
- MAS/HLH in one patient
- Second primary malignancies in 4 patients
- ORR 93%
- CRR 90%
- PFS: 72% at 24 months (PP)

EPCORE NHL-2 arm 2 (Epco + R^2)

- ITT = 111 patients
- CRS: 48%, mainly grade 1-2
- ICANS: **2%**
- MAS/HLH not observed
- Second primary malignancies not observed
- ORR 96%
- CRR 87%
- PFS: 80% at 21 months





Morschhauser F, et al. Nature Med 2024; 30(8): 2199-2207.
Nastoupil L, et al. ASH 2024, abstract #4387 (poster).
Falchi L, et al. ASH 2024, abstract #342 (oral).

Summary

- CARTs are highly active in r/r FL
  - ORR 86-94% and CRR 68-90%
  - PFS 57-72% at 24 months and no plateau
- Mosunetuzumab is FDA and EMA approved for treatment of r/r FL with ≥ prior treatment lines, based phase 2 data
  - ORR 80% and CRR 60%
  - Median PFS 24 months
- Phase 2 data are similar for single-agent glofitamab, epcoritamab, and odronextamab
  - Glofitamab: ORR 81%, CRR 70%
  - Epcoritamab ORR 82%, CRR 63%
  - Odronextamab ORR 80%, CRR 73%
- The toxicity profile is favourable:
  - Very little CRS > grade 2
  - Very little treatment-related CNS toxicity

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The advantages of the bispecific antibodies:

- The safety:
  - Less CRS, less ICANS
- The simplicity
  - Off-the-shelf and easy to deliver
- The price:
  - Not as expensive as CARTs
  - You can stop treatment if no CR, as only complete responses are durable
- The combinability
  - Epco + R^2: ORR 96%, CRR 87%, 21-m PFS 80%
  - Glofit + Obinutuzumab: ORR 100%, CRR 74%
  - Glofit + Englumafusp alfa: ORR 91%, CRR 74%*

*Hutchings M, et al. ASH 2022, abstract #4259 (poster).

Look out for the following studies

- OLYMPIA-5:
  - Phase 3 trial of odronextamab plus lenalidomide vs rituximab plus lenalidomide in relapsed/refractory follicular lymphoma and marginal zone lymphoma
- EPCORE FL-1:
  - Phase 3 trial of subcutaneous epcoritamab with rituximab and lenalidomide (R2) Vs R2 alone in patients with relapsed or refractory follicular lymphoma
- CELESTIMO:
  - Phase III trial of mosunetuzumab plus lenalidomide versus rituximab plus lenalidomide in patients with relapsed or refractory follicular lymphoma who have received ≥ 1 line of systemic therapy