

SESSION V: CONTROVERSIES IN R/R FL

CAR-T cell before new drugs: No

Massimo Gentile

UOC Ematologia AO Cosenza/UNICAL

COACHES

**Current
Opinions,
Advances,
Controversies in
HEmatology in
Salerno**

Updates in **Chronic Lymphocytic Leukemia** and **Lymphomas**



Salerno | 14 aprile 2025 | Grand Hotel Salerno

Disclosures of Name Surname

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
ABBVIE					X	X	
JANSSEN					X	X	
ASTRAZENECA					X	X	
MENARINI					X	X	
OTSUKA					X	X	
BEIGENE					X	X	
SOBI					X	X	
GSK					X	X	
SANOFI					X	X	



FIRST-LINE THERAPY

Preferred regimens, high tumor burden (in alphabetical order)

- Bendamustine^d + obinutuzumab^e or rituximab
- CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) + obinutuzumab^e or rituximab

FIRST-LINE EXTENDED THERAPY (optional)

Preferred regimens following chemoimmunotherapy

- Rituximab maintenance 375 mg/m² one dose every 8–12 weeks for 2 years for patients initially presenting with high tumor burden (category 1)^g
- Obinutuzumab maintenance (1 g every 8 weeks for 12 doses)

SECOND-LINE THERAPY^h

Preferred regimens (in alphabetical order)

- Bendamustine^{d,i} + obinutuzumab^j or rituximab (not recommended if treated with prior bendamustine)
- CHOP + obinutuzumab^j or rituximab
- CVP + obinutuzumab^j or rituximab
- Lenalidomide + rituximab
- Tafasitamab-cxix^k + lenalidomide + rituximab (≥ 1 prior systemic therapy including an anti-CD20 mAb)

SECOND-LINE CONSOLIDATION THERAPY (optional)

- High-dose therapy with autologous stem cell rescue (HDT/ASCR)

THIRD-LINE AND SUBSEQUENT THERAPY

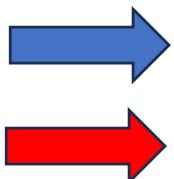
Subsequent systemic therapy options include second-line therapy regimens ([FOLL-B 2 of 6](#)) that were not previously given.

Preferred regimens (in alphabetical order)

- T-cell engager therapy
 - ▶ Bispecific antibody therapy^{l,m}
 - ◊ Epcoritamab-bySp
 - ◊ Mosunetuzumab-axgb
 - ▶ Chimeric antigen receptor (CAR) T-cell therapyⁿ
 - ◊ Axicabtagene ciloleucel (CD19-directed)
 - ◊ Lisocabtagene maraleucel (CD19-directed)
 - ◊ Tisagenlecleucel (CD19-directed)

Other recommended regimens

- EZH2 inhibitor
 - ▶ Tazemetostat^l (irrespective of EZH2 mutation status)
- BTK inhibitor (BTKi)
 - ▶ Zanubrutinib^l + obinutuzumab
- Loncastuximab tesirine-lpyl + rituximab (category 2B)^k



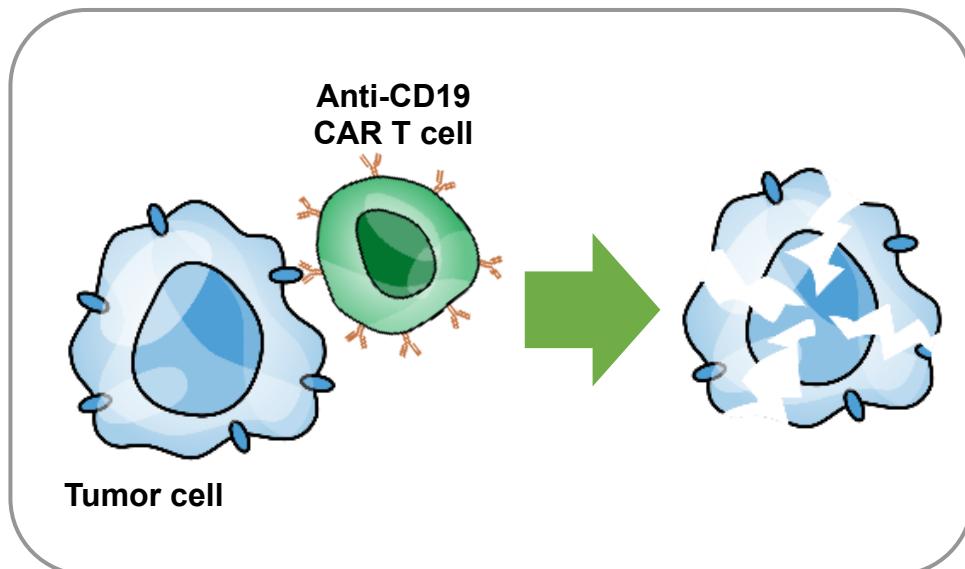
THIRD-LINE CONSOLIDATION THERAPY

Useful in Certain Circumstances

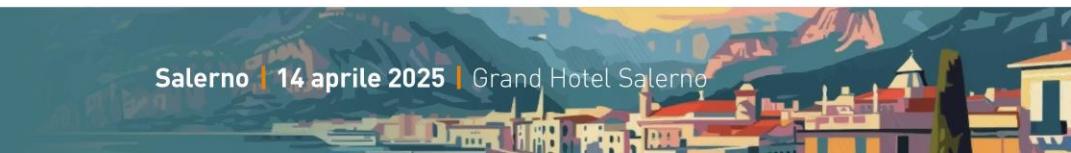
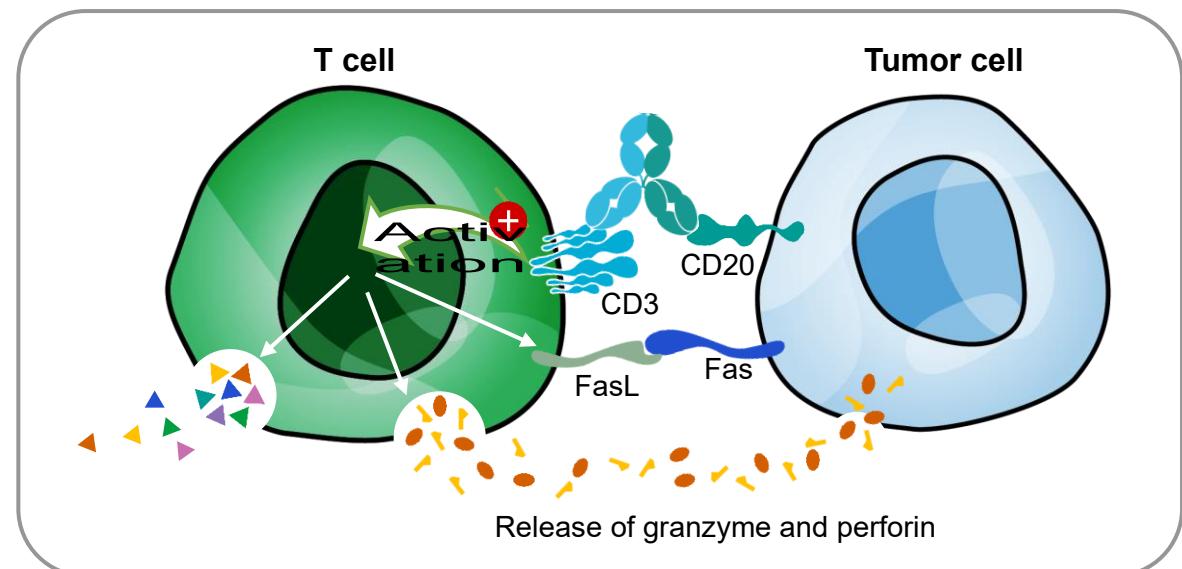
- Allogeneic hematopoietic cell transplantation (HCT) in selected cases^o

Introduction to Current T-Cell Engagers

CAR T cells recognize and kill CD19-expressing cancer cells¹



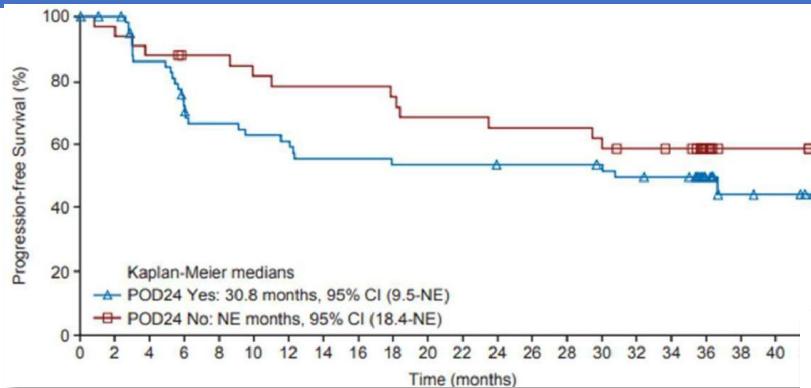
CD3×CD20 bsAbs simultaneously engage T cells and CD20+ tumor cells to induce T cell-mediated killing of the tumor cell²



Phase 2 studies of CARTs in r/r FL

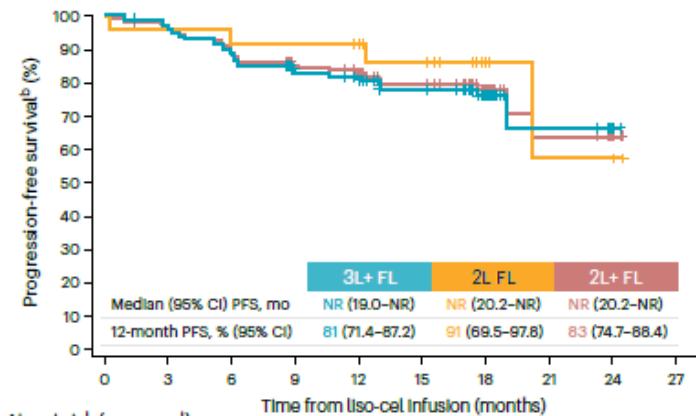
ELARA¹ – Tisagenlecleucel:

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



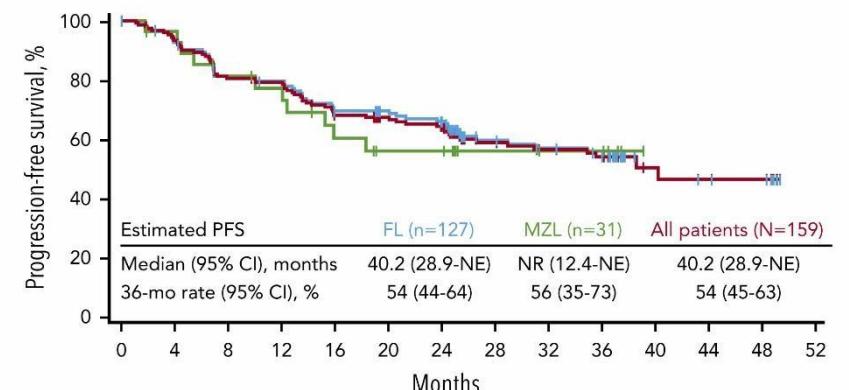
TRANSCEND FL² – Lisocabtagene maraleucel

- ORR 93% (ITT)
- CRR 90% (ITT)
- PFS: 72% at 24 months³ (PP)



ZUMA 5⁴ – 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

ELARA¹ – Tisagenlecleucel:

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

AUGMENT⁵ – Rituximab + lenalidomide:

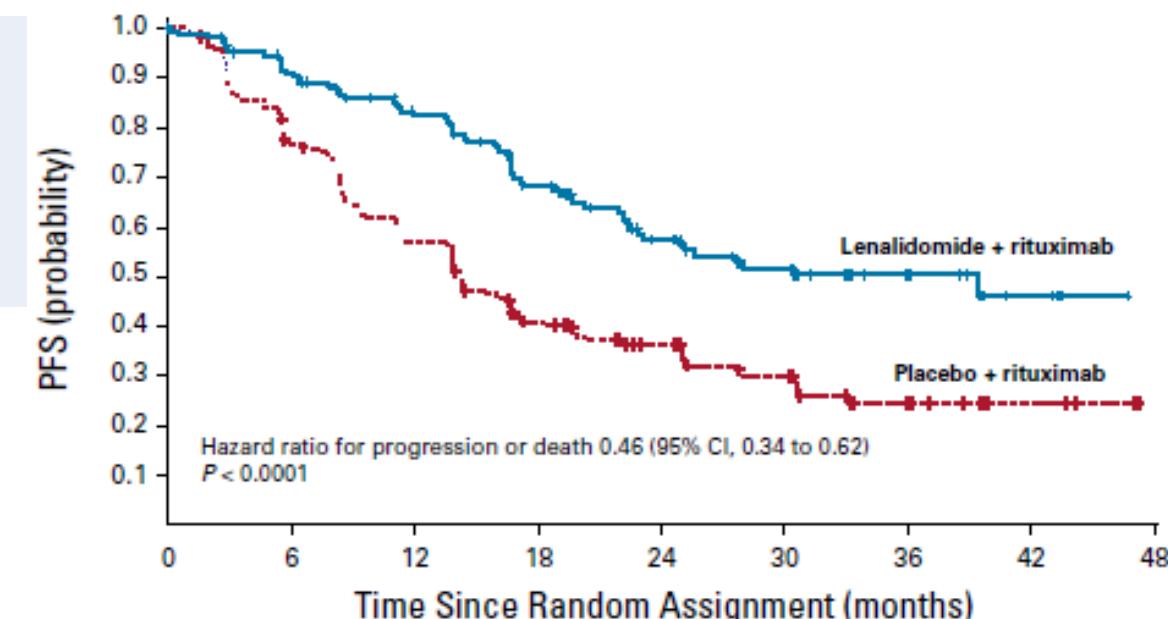
- ORR 78%
- CRR 34% (by CT scan)
- PFS: ~82% at 12 months and 58% at 24 months

TRANSCEND FL² – Lisocabtagene maraleucel

- ORR 93% (ITT)
- CRR 90% (ITT)
- PFS: 72% at 24 months³

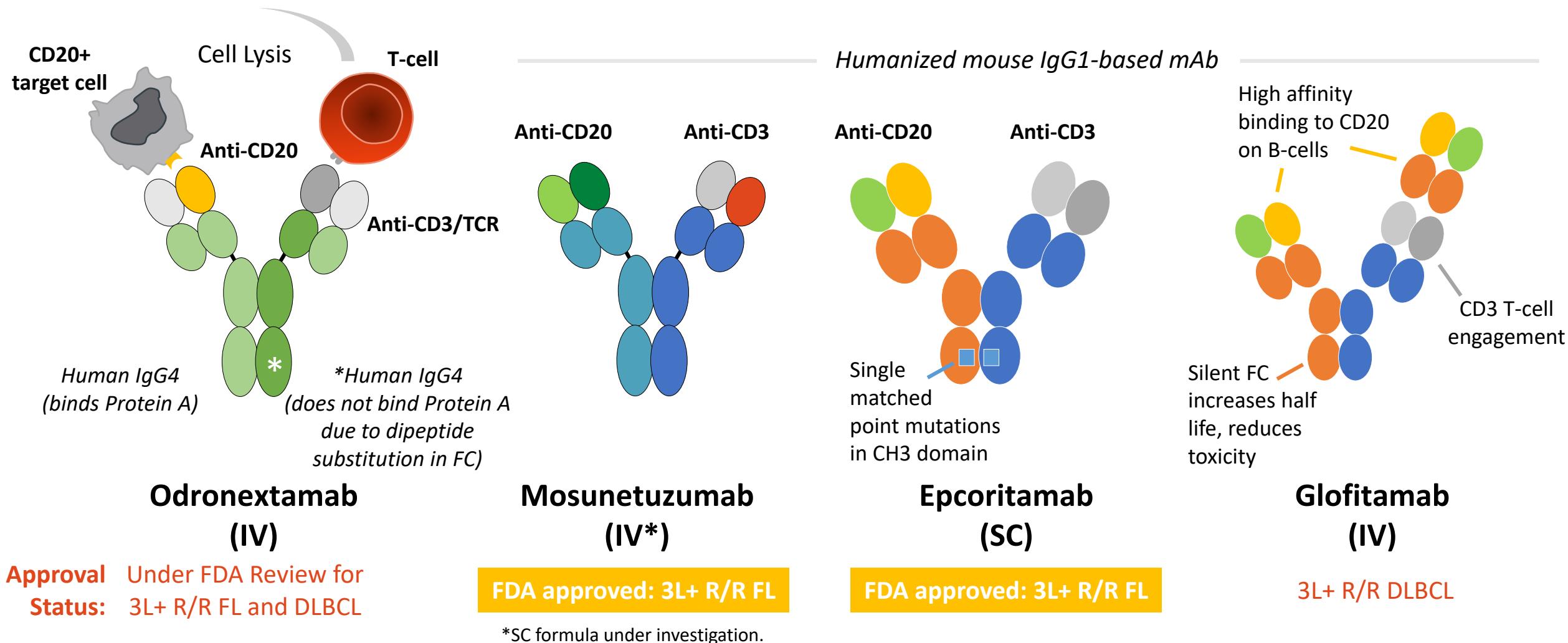
ZUMA 5⁴ – Axicabtagene ciloleucel:

- 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.
5. Leonard JP, et al. J Clin Oncol 2019; 37: 1188-1199.

CD20/CD3 Bispecific Antibodies in B-Cell Lymphomas



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



Phase II Study of Mosunetuzumab Monotherapy in R/R FL

- Single-arm, pivotal phase II expansion study^{1,2}
 - Primary endpoint met: 60% CR vs 14% historical control ($P < .0001$) at 10-mo follow-up²

Adults with R/R FL
(grades 1-3a)
after ≥2 prior systemic tx
including ≥1 anti-CD20 mAb
and ≥1 alkylating agent;
ECOG PS ≤1
(N = 90)

Cycle 1*: Step-up Dosing^{†‡}

Mosunetuzumab IV
D1: 1 mg > D8: 2 mg >
D15: 60 mg

Cycle 2**

Mosunetuzumab IV
D1: 60 mg

Cycles 3-8*‡

Mosunetuzumab IV
D1: 30 mg

*Discontinue if
CR by cycle 8§;
if PR or SD, continue
at 30 mg for
17 cycles
(unless PD or
unacceptable
toxicity)*

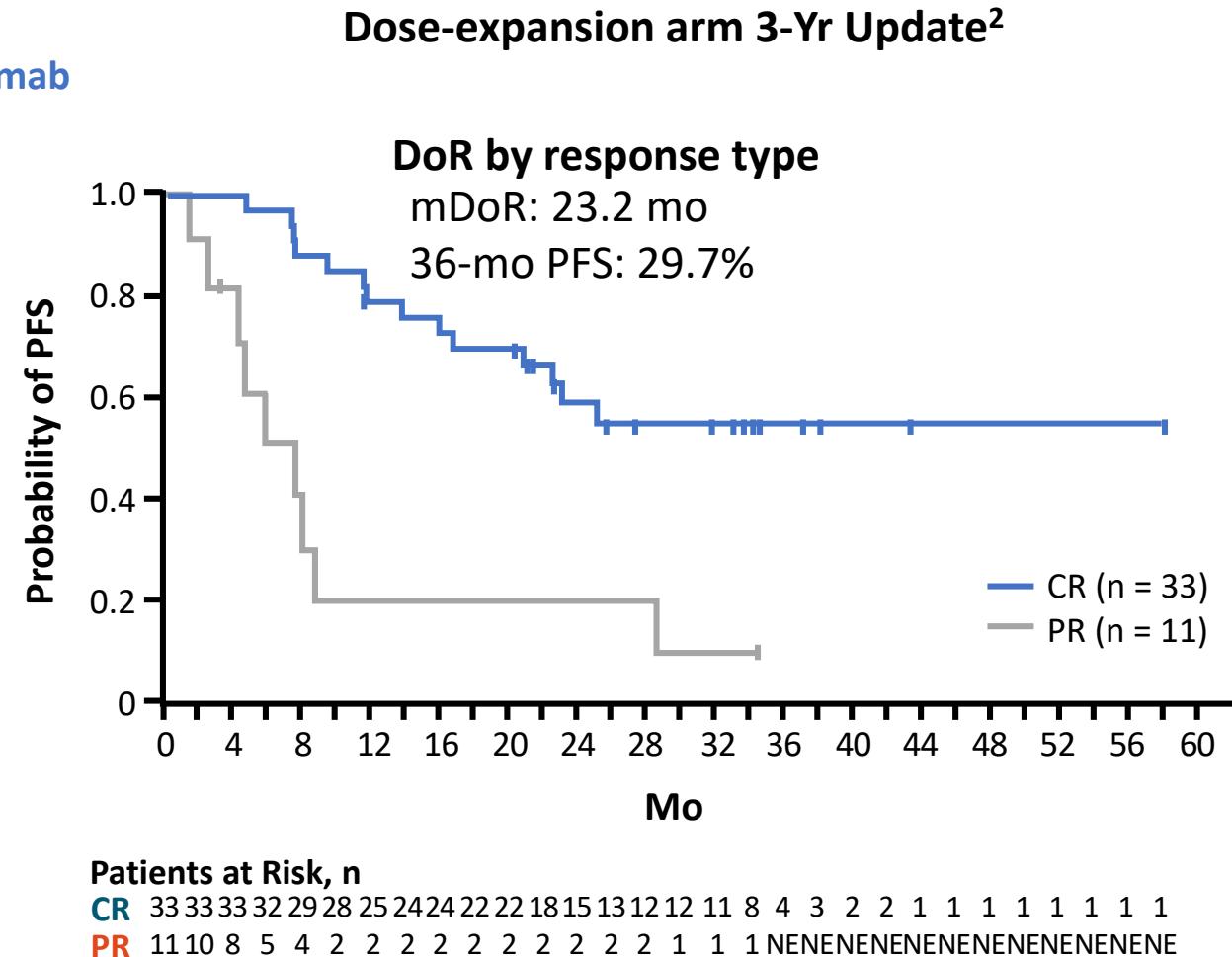
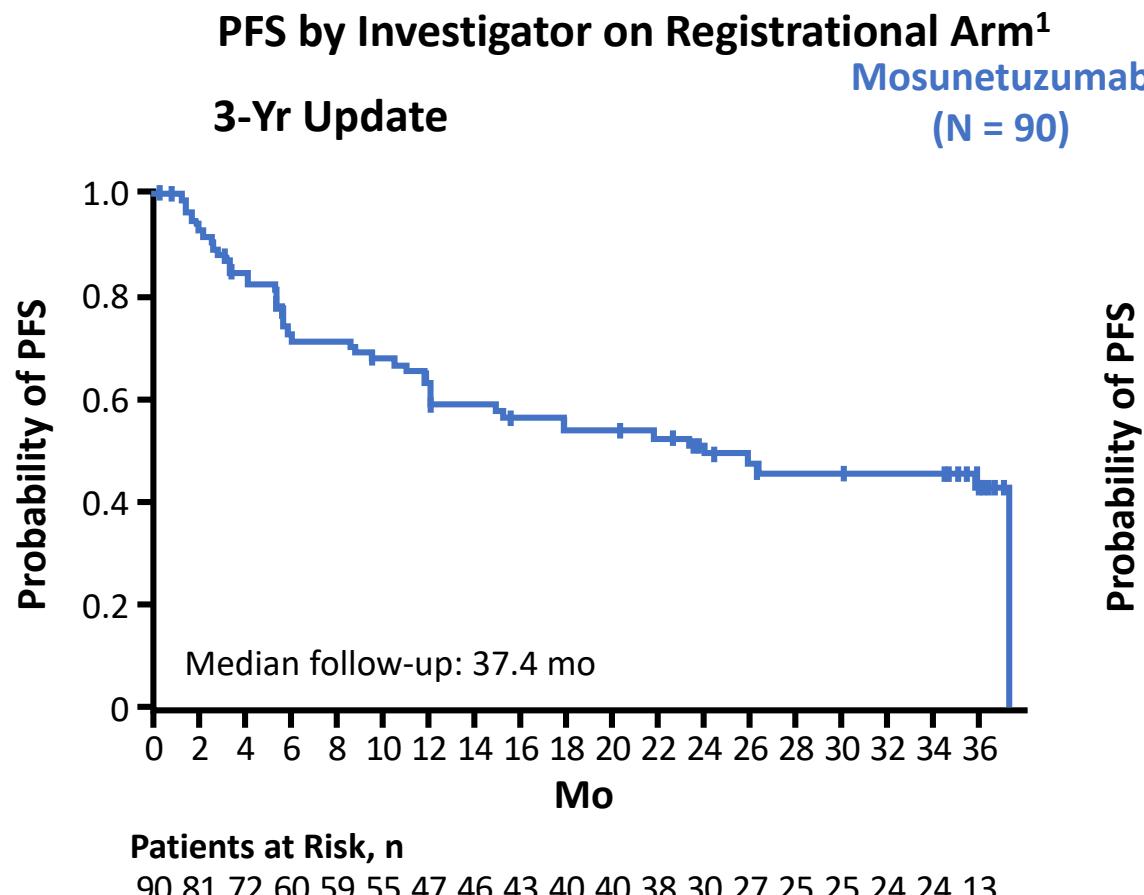
*21-day cycles. †Cycle 1 step-up dosing for CRS mitigation. ‡Premedication before each mosunetuzumab dose in cycles 1 and 2, optional from cycle 3+: IV corticosteroid given 1 hr before, IV antihistamine and oral antipyretic given 30 min before. §Retreatment allowed at relapse for those achieving CR.

No mandatory hospitalization for treatment administration.

- Primary endpoint:** CR (best response) rate by IRF, assessed vs 14% historical control CR rate
- Secondary endpoints:** ORR, DoR, PFS, safety, and tolerability

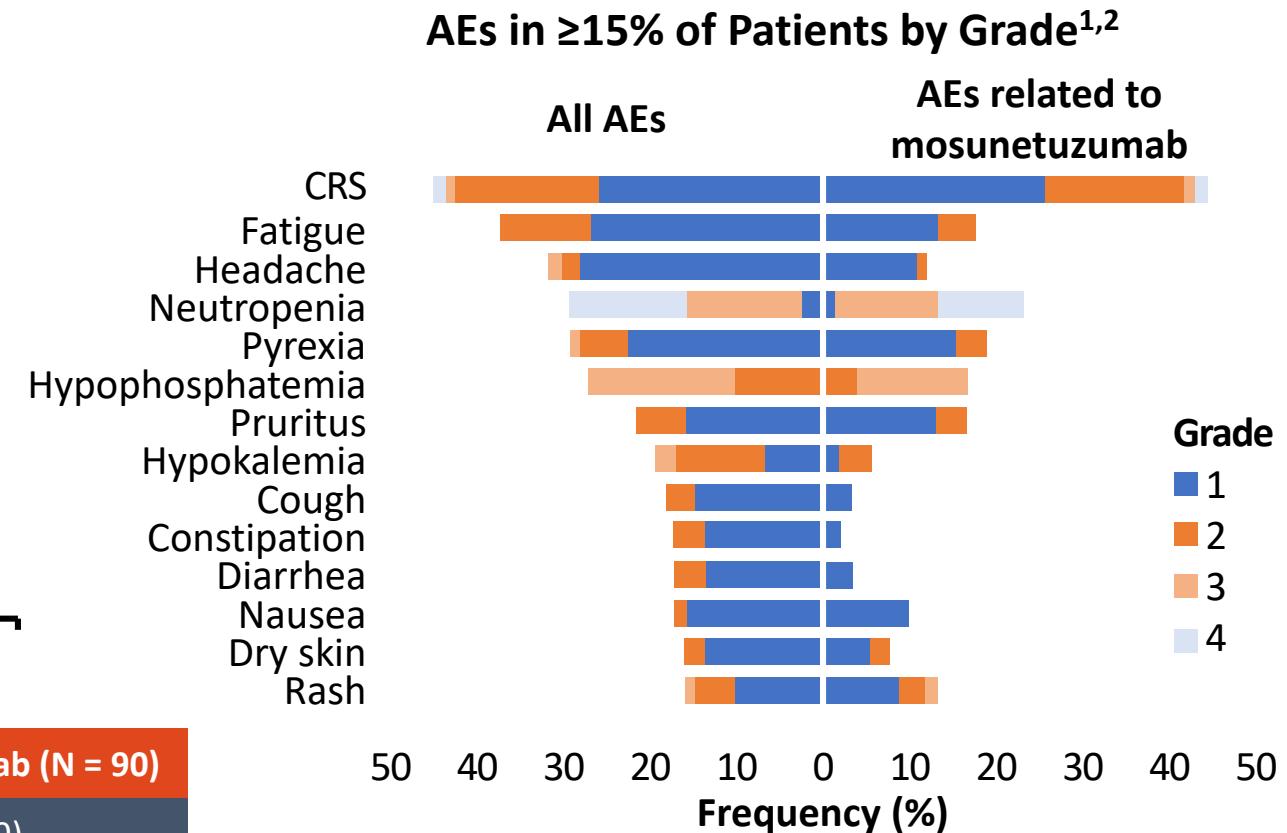
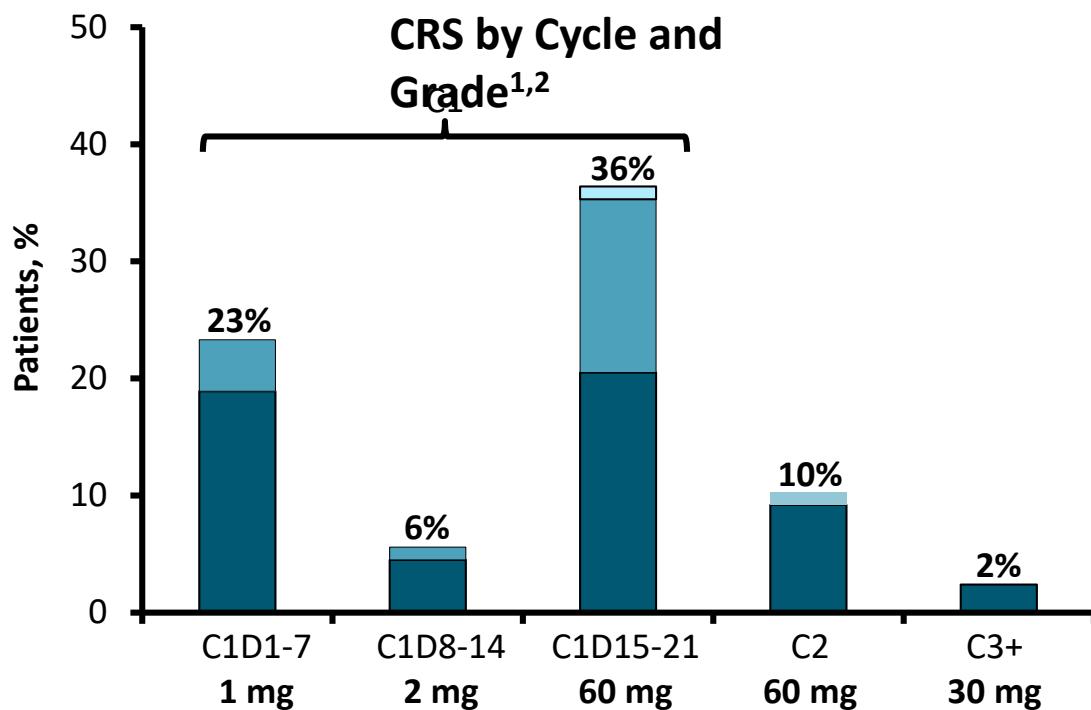
1. Bartlett. ASH 2022. Abstr 610. 2. Budde. Lancet Oncol. 2022;23:1055. NCT02500407.

Mosunetuzumab Phase II Study (Updates): Efficacy



1. Schuster. ASH 2023. Abstr 603. 2. Budde. JCO. 2024;42:2250.

Mosunetuzumab Phase II Study: Safety



CRS per ASTCT Criteria	Mosunetuzumab (N = 90)
Median duration, days (range) ^{1,2}	3 (1-29)
Patients who received tx for CRS (n = 40), n (%) ²	
▪ Corticosteroids only	6 (15)
▪ Tocilizumab only	3 (8)
▪ Both	4 (10)

1. Bartlett. ASH 2022. Abstr 610. 2. Budde. Lancet Oncol. 2022;23:1055.

2 ICANS

*Fatal AEs: malignant neoplasm progression (n = 1) and unexplained (n = 1). [†]D/c: mosunetuzumab related, CRS (n = 2); unrelated to mosunetuzumab, EBV viremia (n = 1), Hodgkin disease (n = 1).

EPCORE NHL-1: Epcoritamab in R/R B-Cell NHL

- Phase I/II open-label, dose escalation/expansion study

Patients with R/R CD20+
B-cell NHL after
 ≥ 2 previous lines of tx and
 ≥ 1 anti-CD20 mAb;
ECOG PS 0-2;
FDG PET avid; measurable
disease by CT/MRI;
previous CAR T-cell
therapy allowed
(planned N = 700)

Cycle 1 Step-up Dosing*

Epcoritamab SC
D1: 0.16 mg
D8: 0.8 mg
D15: 48 mg
D22: 48 mg

*With corticosteroid prophylaxis.
To mitigate CRS.

Epcoritamab 48 mg SC
in 28-day cycles
QW cycles 2-3,
Q2W cycles 4-9,
Q4W cycles 10+

FL (grade 1-3A) cohort, $n = 128$

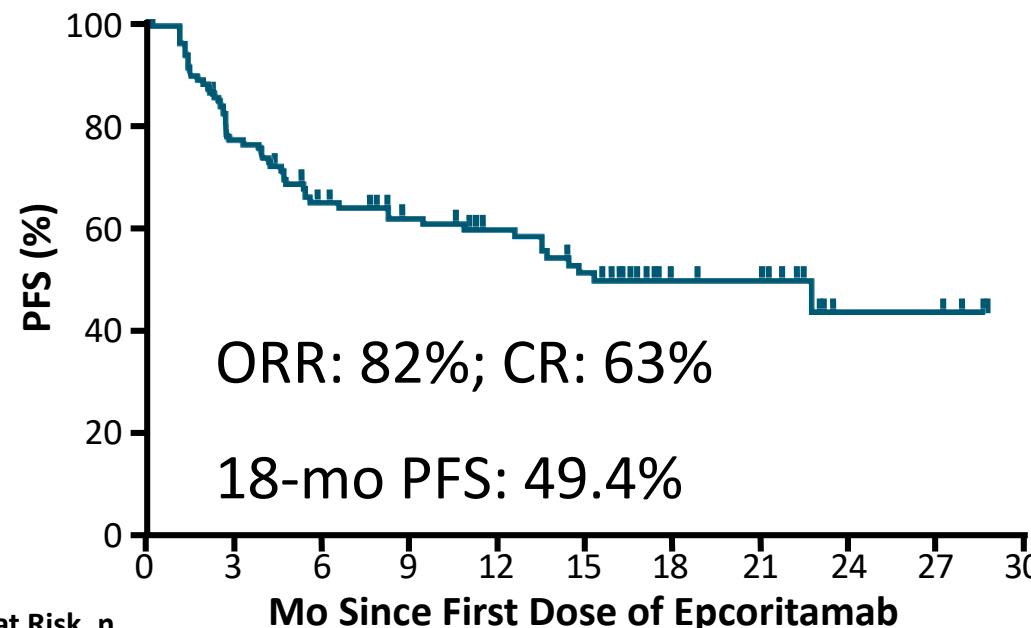
Median lines of tx:
3 (range: 2-9);
31% with ≥ 4
POD24: 42%

→ *Until PD or
unacceptable
toxicity*

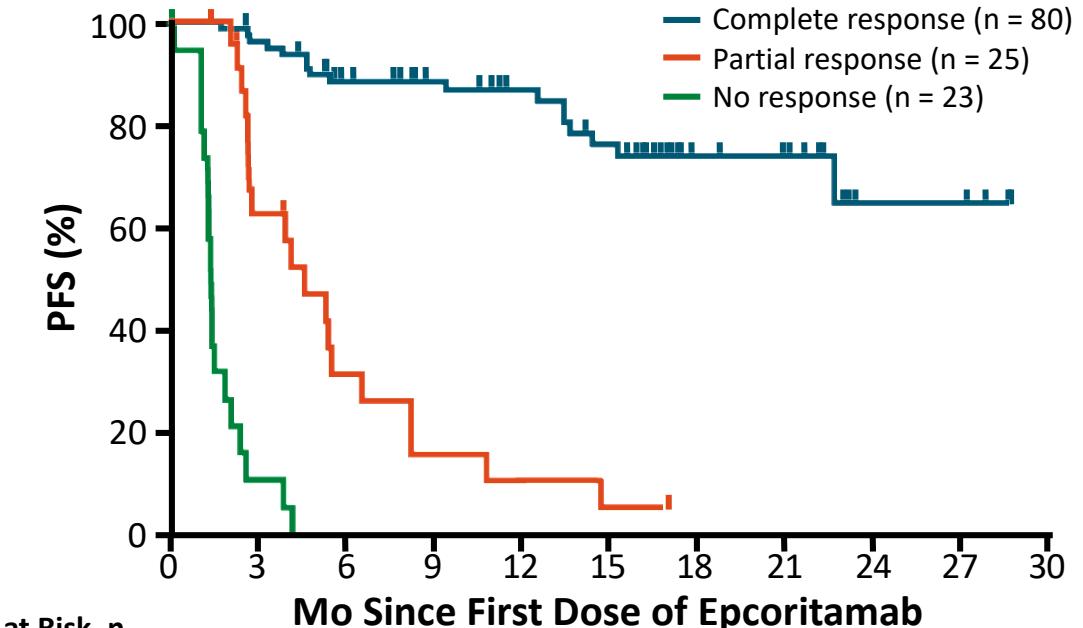
- Primary endpoint:** ORR by IRC
- Secondary endpoints:** DoR, TTR, PFS, OS, CR rate, safety

Linton. ASH 2023. Abstr 1655. NCT03625037.

EPCORE NHL-1: Efficacy of Epcoritamab in FL



Patients at Risk, n (number censored)											
Pivotal cohort											
128	90	67	57	43	35	14	12	4	4	0	
(0)	(10)	(19)	(26)	(38)	(40)	(60)	(62)	(69)	(69)	(73)	
Median FU: 17.4 mo											



Patients at Risk, n (number censored)											
Complete response (n = 80)											
80	75	61	54	41	34	14	12	4	4	0	
(0)	(2)	(10)	(17)	(29)	(31)	(50)	(52)	(59)	(59)	(63)	
Partial response (n = 25)											
25	13	6	3	2	1	0	0	0	0	0	
(0)	(4)	(5)	(5)	(5)	(5)	(6)	(6)	(6)	(6)	(6)	
No response (n = 23)											
23	2	0	0	0	0	0	0	0	0	0	
(0)	(4)	(4)	(4)	(4)	(4)	(4)	(4)	(4)	(4)	(4)	

Linton. Lancet Haematol 2024;11:E593.

EPCORE NHL-1: AEs in Pivotal vs Optimization Cohort

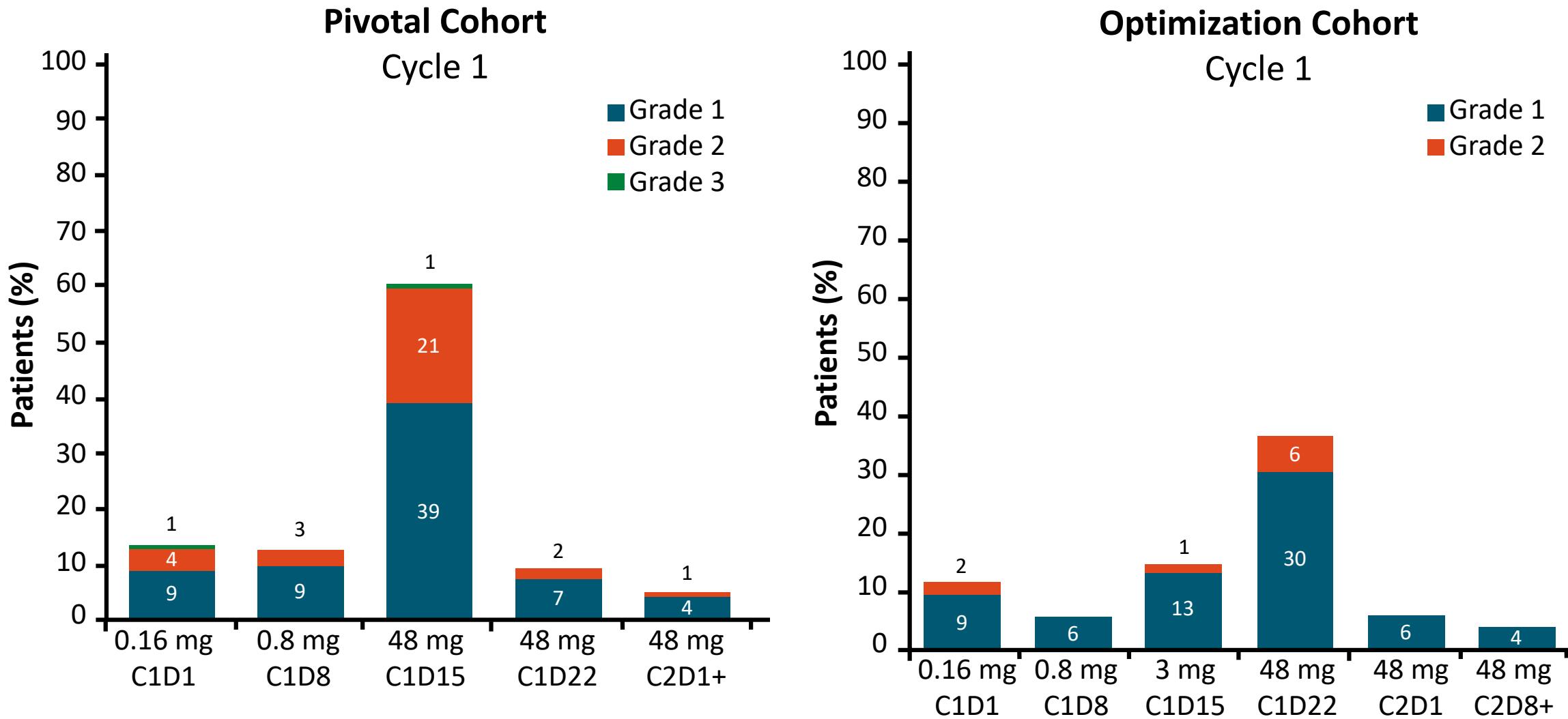
Event, n (%)	Pivotal Cohort (n = 128)				Event n (%)	Cycle 1 Optimization Cohort (n = 86)			
	Gr 1/2	Gr 3	Gr 4	Gr 5		Gr 1/2	Gr 3	Gr 4	Gr 5
CRS	83 (65)	2 (2)	0	0	CRS	42 (49)	0	0	0
Injection-site reaction	73 (57)	0	0	0	Injection-site reaction	28 (33)	0	0	0
COVID-19	27 (21)	18 (14)	0	6 (5)	Constipation	18 (21)	0	0	0
Fatigue	36 (28)	3 (2)	0	0	COVID-19	13 (15)	5 (6)	0	0
Neutropenia	4 (3)	16 (13)	16 (13)	0	Neutropenia	1 (1)	9 (10)	8 (9)	0
Diarrhea	32 (25)	2 (2)	0	0	Fatigue	17 (20)	0	0	0
Pyrexia	29 (23)	3 (2)	0	0	Cough	14 (16)	0	0	0
Headache	25 (20)	0	0	0	Headache	11 (13)	1 (1)	0	0

- In the cycle 1 optimization cohort, a second intermediate dose of 3 mg was administered on Day 15

Linton. Lancet Haematol. 2024;11:E593.



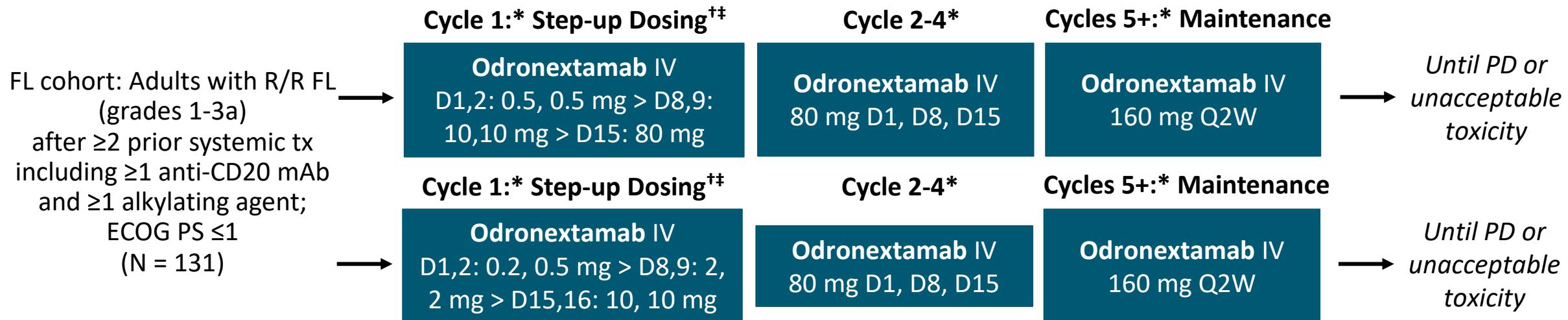
EPCORE NHL-1: CRS



Linton. Lancet Haematol. 2024;11:E593.

ELM-2: Odranextamab Monotherapy in R/R

- Multicohort, open-label phase II study in R/R B-cell NHL (FL, DLBCL, MCL, MZL, others)



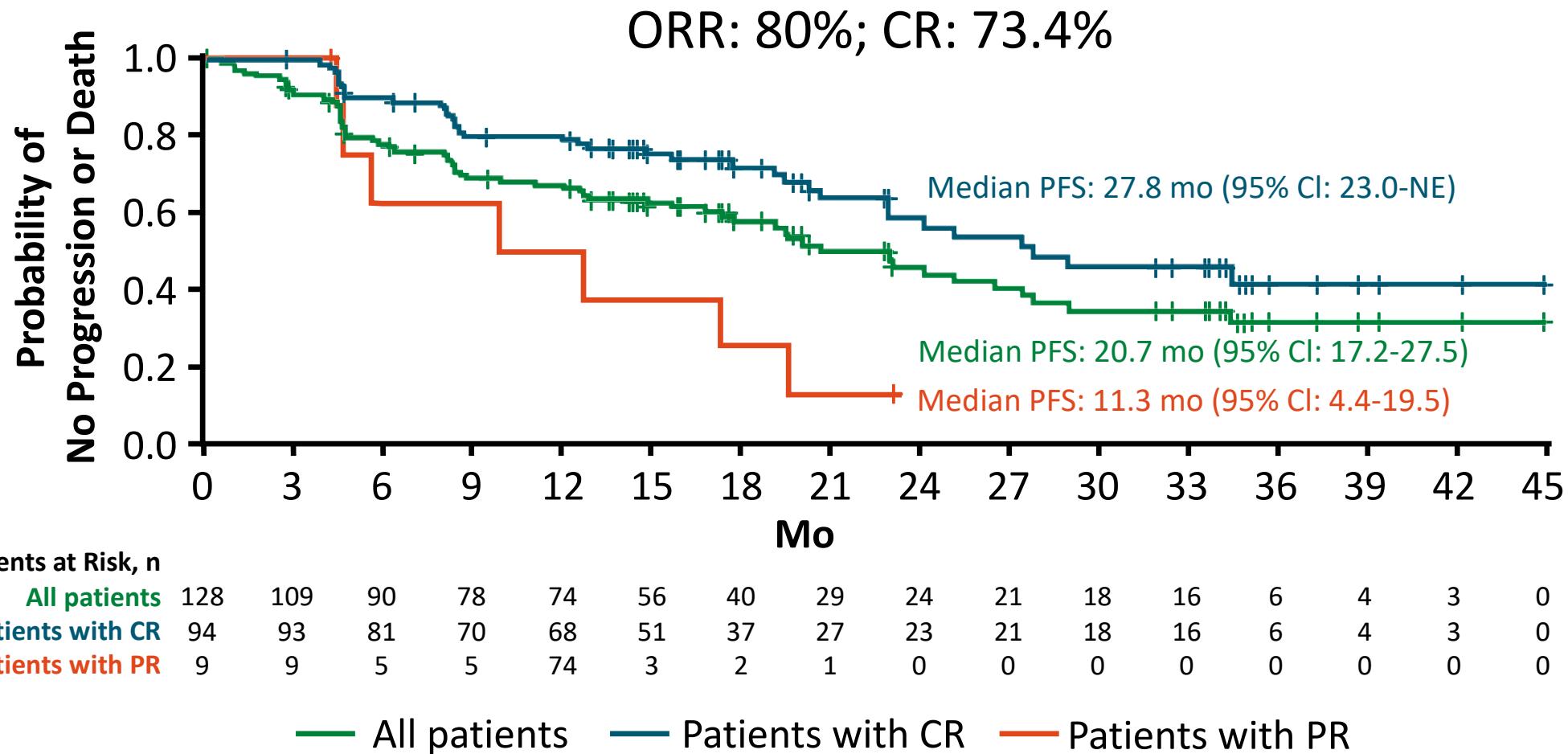
*21-day cycles. [†]Cycle 1 step-up dosing at study initiation was 1/20/80 mg but was modified to further mitigate CRS risk.

[‡]Each step-up dose delivered as split infusions and is accompanied with premedication to further mitigate CRS risk.

- Primary endpoint:** ORR by ICR per Lugano criteria
- Secondary endpoints:** ORR by investigator, CR rate, DoR, PFS, OS, safety/tolerability
- Patients were admitted for inpatient monitoring for 24 h following each infusion up to and including C2D1

Kim. ASH 2022. Abstr 949. NCT03888105.

ELM-2: Survival by Response Type



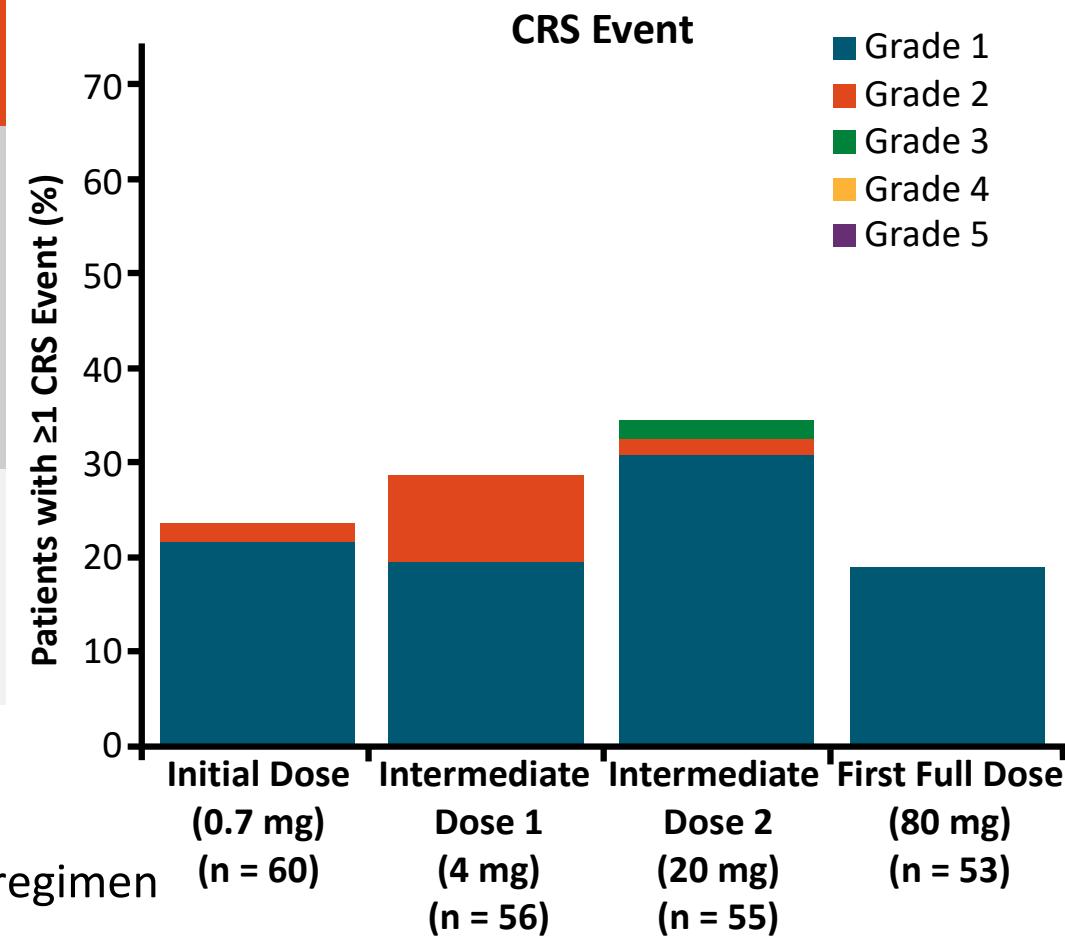
Kim. Ann Oncol. 2024;35:1039.

ELM-2: Cytokine-Release Syndrome

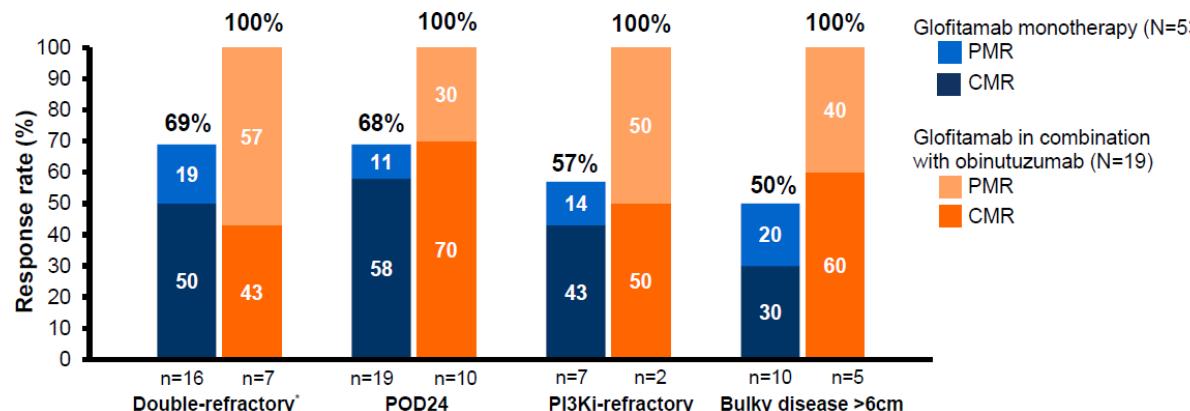
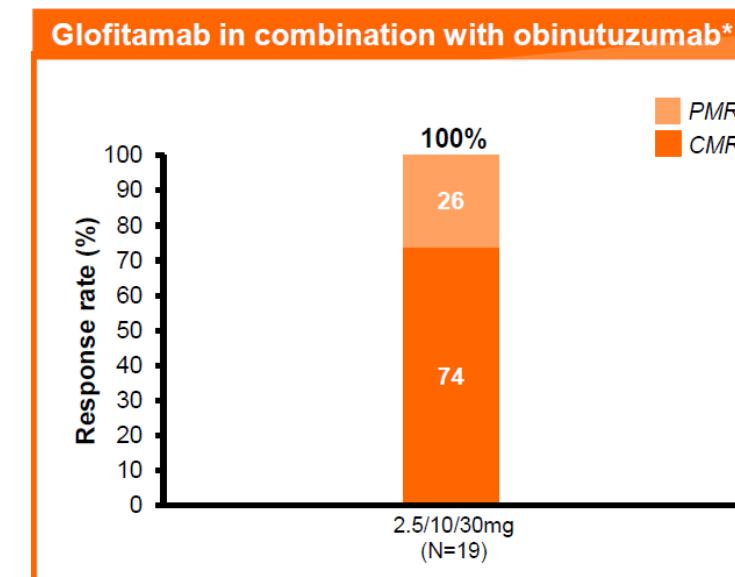
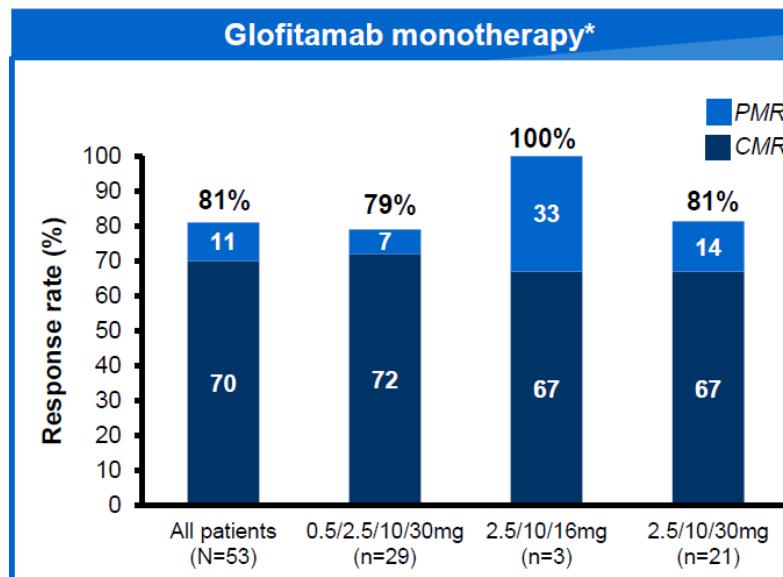
CRS Parameter, n (%)	1/20-mg Step-up Regimen (n = 68)	0.7/4/20-mg Step-up Regimen (n = 63)
Any-grade CRS	38 (55.9)	36 (57.1)
▪ Grade 1	22 (32.4)	28 (44.4)
▪ Grade 2	12 (17.6)	7 (11.1)
▪ Grade 3	4 (5.9)	1 (1.6)
▪ Grade 4	0	0
▪ Grade 5	0	0
CRS management		
▪ Corticosteroids	11 (16.2)	17 (27.0)
▪ Tocilizumab	9 (13.2)	12 (19.0)
▪ Vasopressors	4 (5.9)	1 (1.6)

- CRS in ~50% of patients; mostly grade 1, no grade ≥4
- Incidence of grade 2/3 CRS reduced with 0.7/4/20-mg step-up regimen
- All CRS events resolved; median time to resolution: 2 days (range: 1-51)
- 1 ICANS

Kim. ASH 2022. Abstr 949. Kim. Ann Oncol. 2024;35:1039.



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



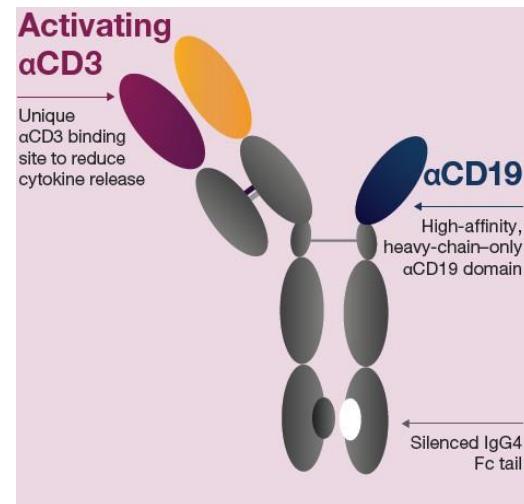
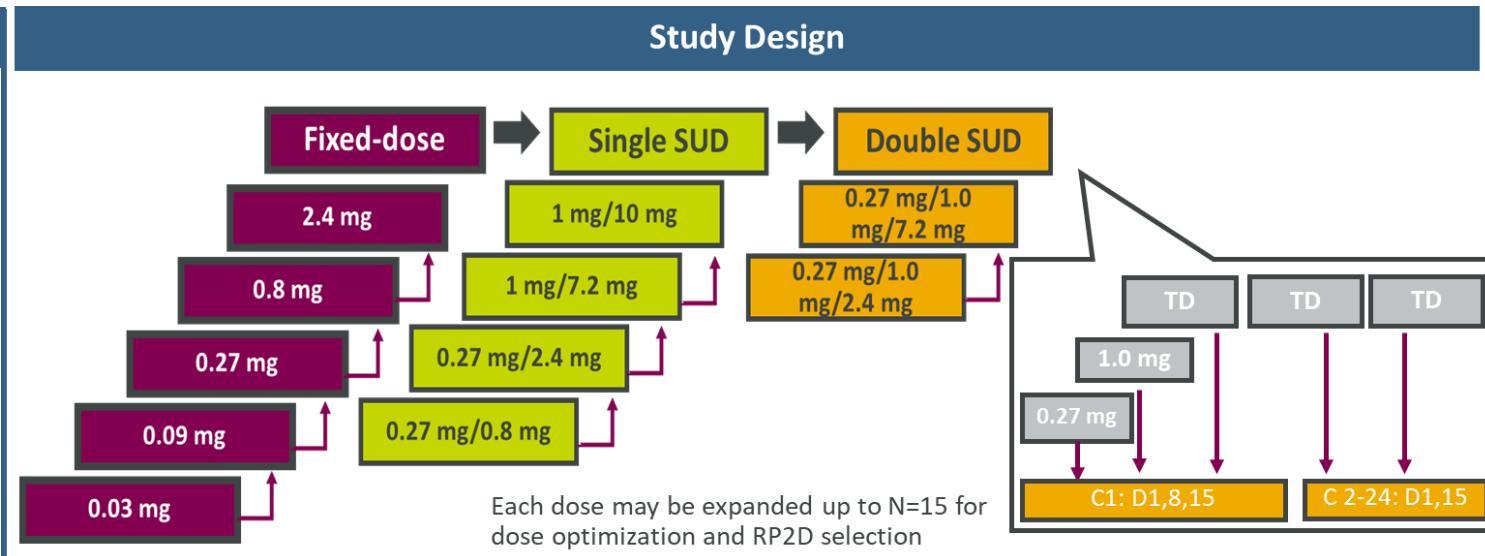
N (%) of patients unless stated	Glofitamab + obinutuzumab cohort (N=19)
Refractory to any prior therapy	13 (68.4)
Refractory to most recent therapy line	8 (42.1)
Refractory to any prior anti-CD20	10 (52.6)
Double-refractory*	7 (36.8)
POD24	10 (52.6)
PI3K inhibitor-refractory	2 (10.5)
Bulky disease >6cm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

CRS: mono 66% (G3=1); combo 52.6% (G3=0), no ICANS

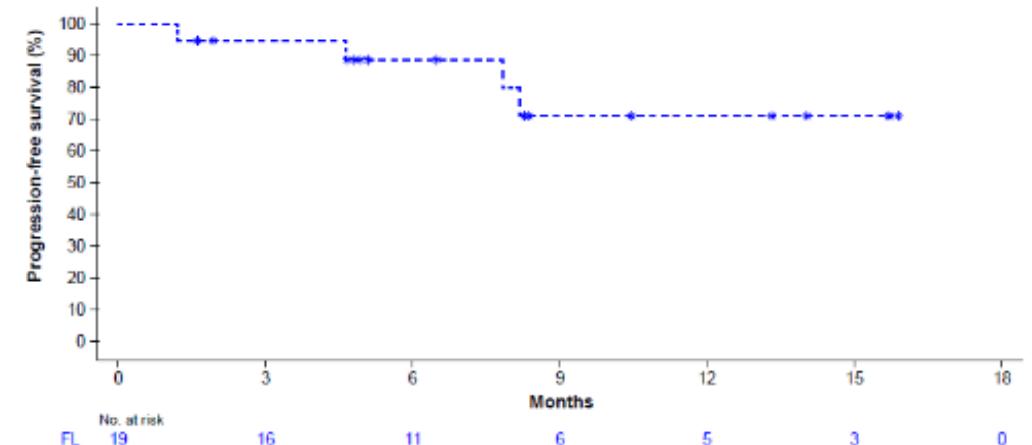
Morschhauser F, et al. ASH 2021, abstract #128.

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

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	



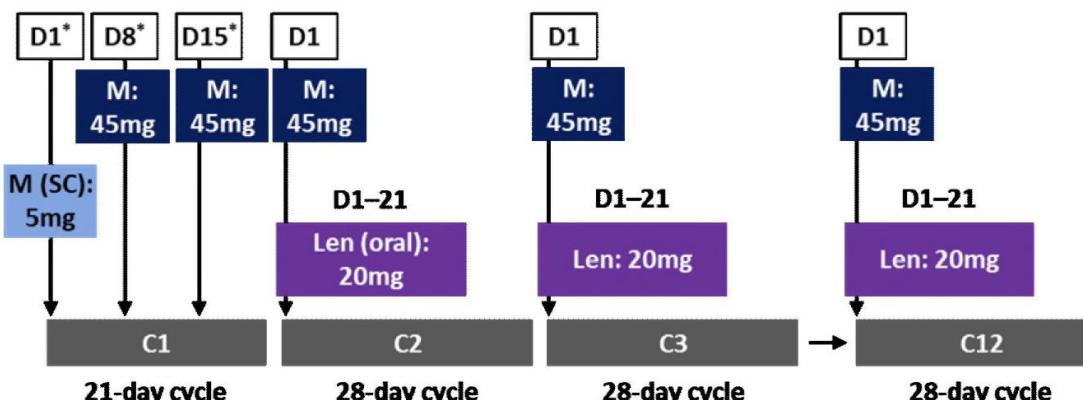
- So far 56 FL patients treated in this phase 1 study
- For the 41 patients treated at doses ≥ 2.4 mg:
 - ORR 95%, CRR 85%
 - CR in 6 out of 7 patients with CD20-negative disease
 - CR in both patients with prior CD20xCD3 therapy
 - No impact of POD24 on response (14 patients, CR 100%)



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

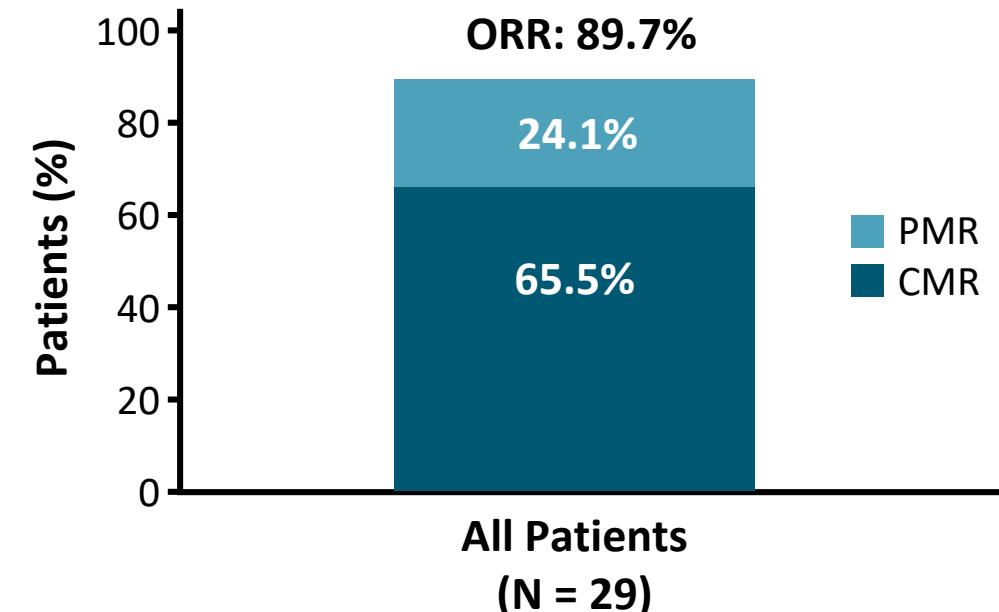
Phase Ib/II Study: Response With Mosu + Lenalidomide in R/R FL

(A)



*A single dose of oral or intravenous dexamethasone or methylprednisolone as premedication was required during C1; it was optional after C1 to mitigate risk of cytokine release syndrome.

Best Response by PET-CT: Overall



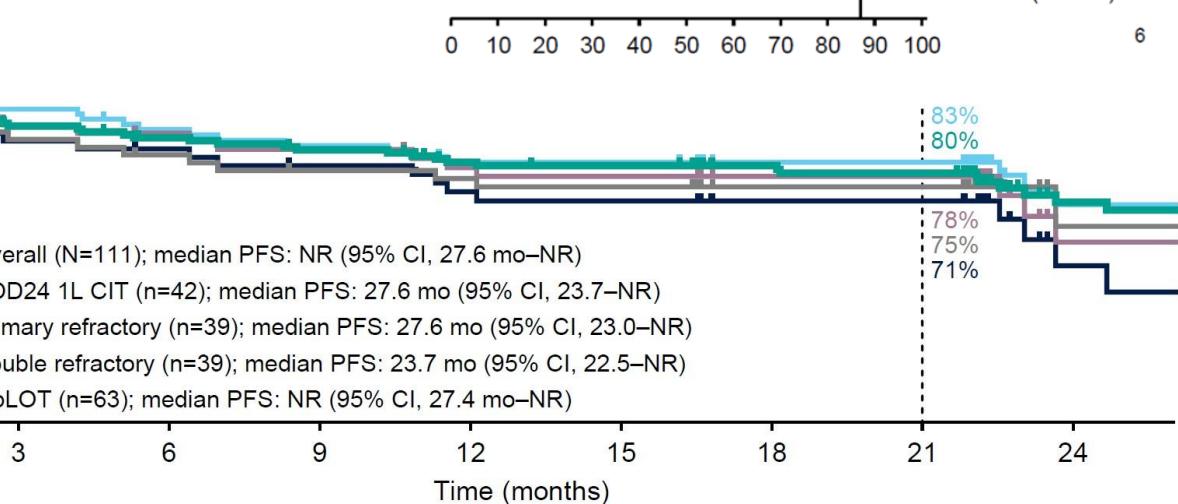
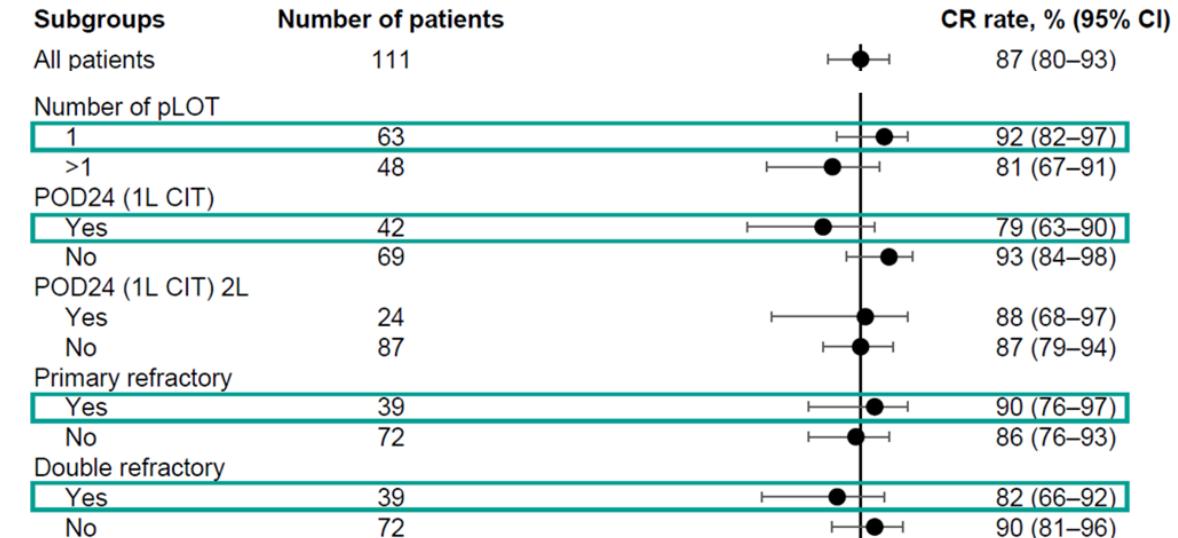
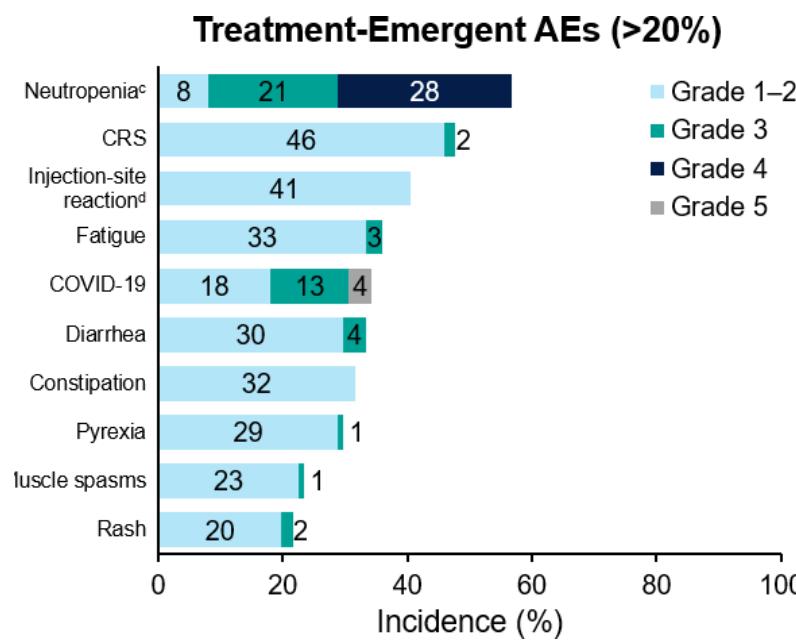
- Median time to first/best response: 2.5 mo (range: 1.4-5.3)/2.5 mo (range: 1.4-10.7)
- High ORR and CMR rate in overall population, including those with high-risk disease

Morschhauser. ASH 2021. Abstr 129. (Update: Morschhauser. ASH 2023. Abstr 605.)

CRS 54.1% (G2=1 pt no ICANS)

Phase Ib/II study of fixed-duration epcoritamab + R2 in patients with R/R

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).

BsAbs and CAR T: Efficacy

Class	Agent	Trial	N	Demographics		Follow-up (months)	ORR (%)	CRR (%)	Survival outcomes	Duration of response
				POD24 (%)	Refractory to prior therapy					
Bispecific antibody	Mosunetuzumab	NCT02500407 (GO29781)	90	52	69	37	78	60	36-mo PFS: 43% DOCR: 72%	30-mo
Bispecific antibody	Epcoritamab	NCT03625037 (EPCORE NHL-1)	128 ^a	42	69	17	82	63	Median PFS: 15.4 mo	18-mo DOCR: 72%
Bispecific antibody	Odronextamab	NCT02290951 (ELM-1)	128 ^b	49	72	27	81	73	24-mo PFS: 45%	24-mo DOCR: 48%
CAR T cell	Axicabtagene-ciloleucel	NCT03105336 (ZUMA-5)	127	55	69	42	94	79	36-mo PFS: 54%	36-mo DOCR: 62%
CAR T cell	Tisagenlecleucel	NCT03568461 (ELARA)	97	63	78	29	86	68	24-mo PFS: 57%	24-mo DOCR: 78%
CAR T cell	Lisocabtagene-maraleucel	NCT04245839 (TRANSCEND FL)	107 ^c	43	38	19	97	94	12-mo PFS: 81%	12-mo DOCR: 82%

Russler-Germain & Bartlett. ASH 2024

BsAbs and CAR T: Toxicity

Agent	CRS rate		Neurotoxicity rate		Treatment discontinuation due to AEs	Grade 3+ infections	Tocilizumab required
	Any grade	Grade 3+	Any grade	Grade 3+			
Mosunetuzumab	44%	2%	5%	2%	4%	13%	8%
Epcoritamab ^a	49%	0%	0%	0%	19%	NR	12%
Odronextamab ^b	57%	1%	1%	0%	16%	41%	17%
Axicabtagene-ciloleucel	78%	6%	56%	15%	NA	15%	50%
Tisagenlecleucel	49%	0%	4%	1%	NA	9%	34%
Lisocabtagene-maraleucel ^c	58%	1%	15%	2%	NA	5%	25%

Russler-Germain & Bartlett. ASH 2024



BsAbs vs CAR T

Bispecific Antibodies

CAR T-Cell Therapy

Bispecific Antibodies

CAR T-Cell Therapy

Administration

Multiple cycles of intravenous administration

Single infusion after T-cell engineering



Response Rate

Generally lower RR

Generally higher RR



Tolerability

Well-tolerated, fewer severe adverse events

Higher rates of severe adverse events



Severe Side Effects

Lower incidence (mild CRS, infections)

Higher incidence (CRS, ICANS, cytopenias)



Dosing Frequency

Requires repeated dosing (weekly or biweekly)

Single administration after preparation



Cost

Typically lower upfront costs

High upfront costs



Accessibility

More widely available, outpatient setting

Limited to specialized centers



Patient Selection

Wide range of patients, also with poorer PS

High-risk patients with good PS



Caregiver Support

Generally minimal to moderate CS needed

Intensive Caregiver Support



Long-Term Outcomes

Still under study

Potential long-term remission



- The combinability

- Epcoritamab + R2: ORR 96%, CRR 87%, 21-m PFS 80%;
Glofitamab + Obinutuzumab: ORR 100%, CRR 74%
- Glofitamab + Englumafusp alfa: ORR 91%, CRR 74%

★ Matasar M et al, Open Arch 2023

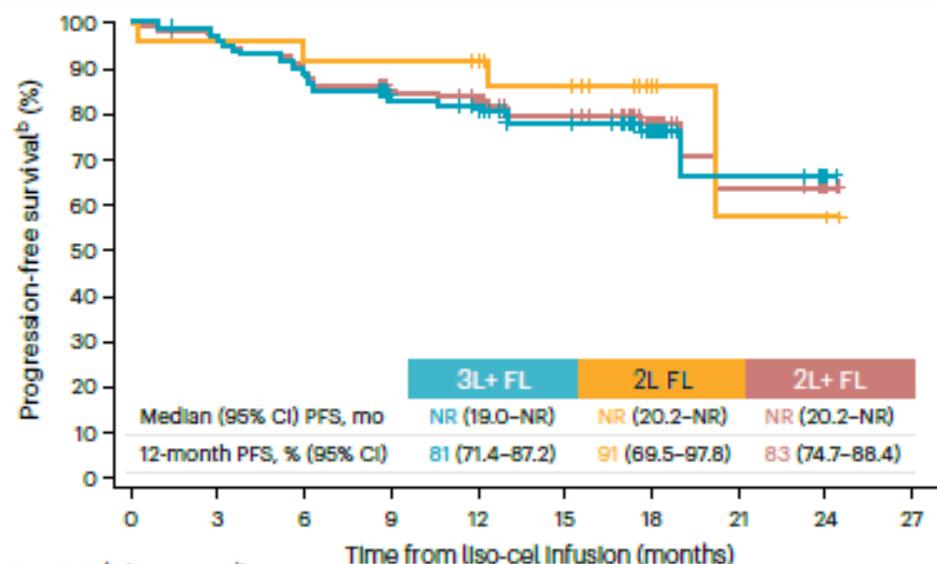
Lin et al, ASH 2023

Oluwole et al, Front Immunol 2024

BsAbs vs CAR T

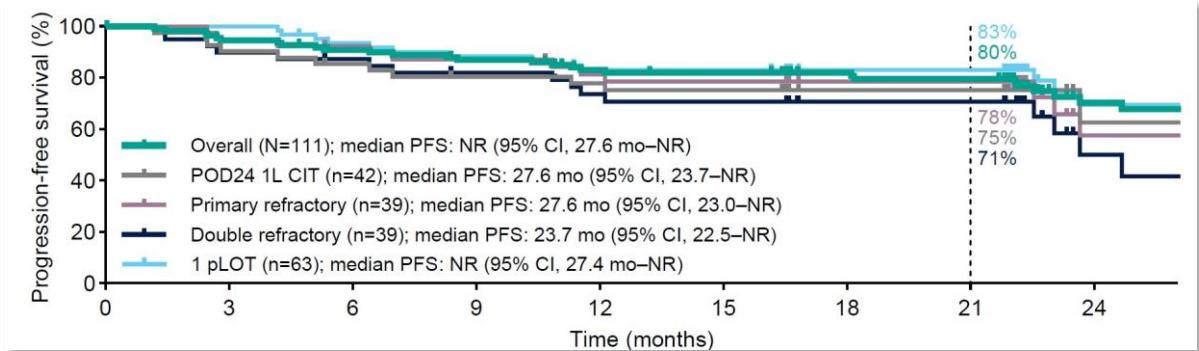
TRANSCEND FL (Liso-cel)

- 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 (Epcot + R²)

- 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).

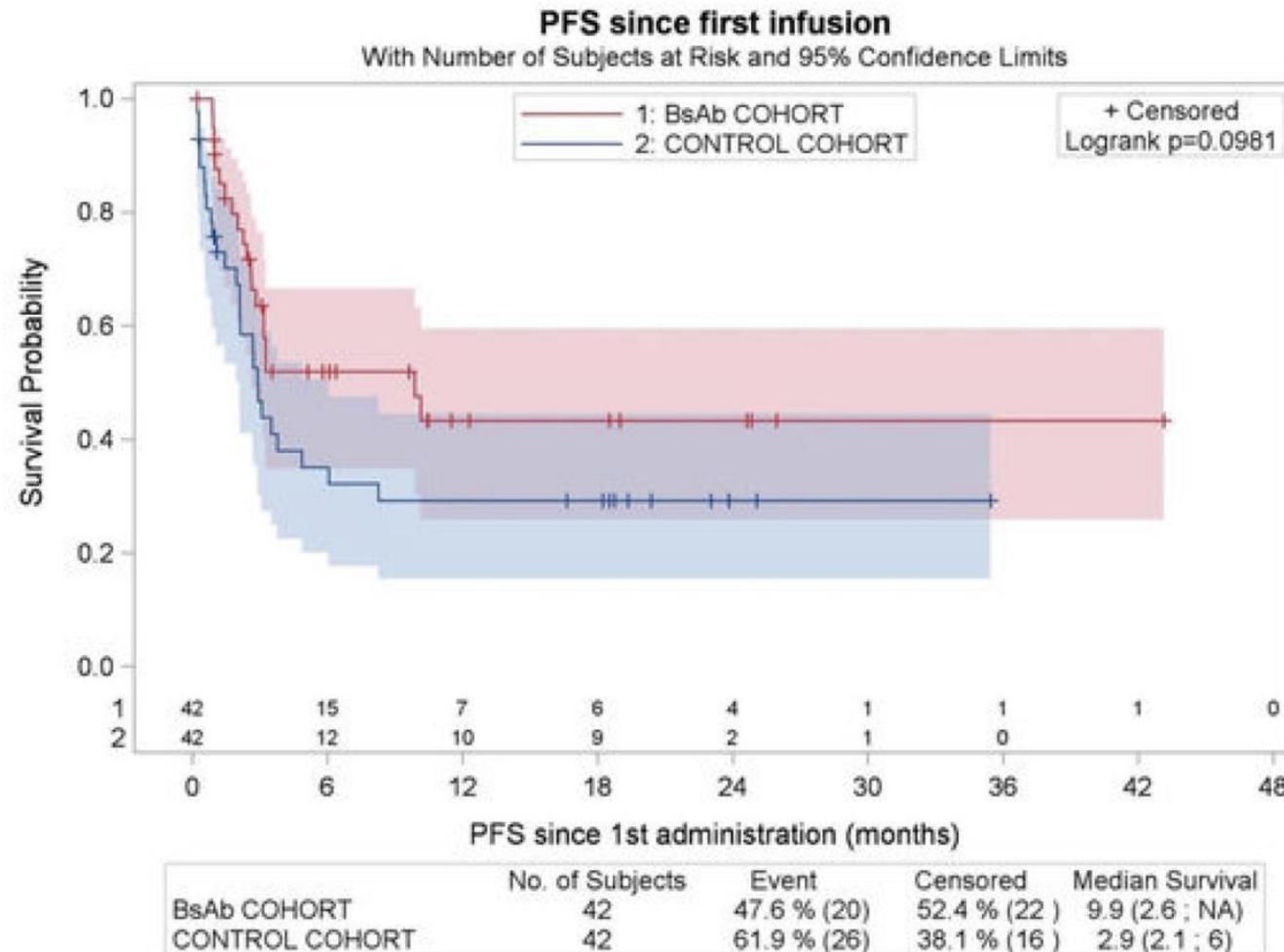
Falchi L, et al. ASH 2024, abstract #342 (oral).

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



Efficacy of CAR T-Cell Therapy Is Not Impaired By Previous BsAb Treatment in Patients with Large B-Cell Lymphoma



Iacoboni et al. ASH 2023

Take Home Messages



Sequencing bispecific antibodies and CAR T cells for FL

Treatment for relapsed/refractory (R/R) follicular lymphoma (FL) has evolved over recent years with the introduction of multiple novel immunotherapies: anti-CD3 × CD20 bispecific antibody (BsAb) T-cell engagers and anti-CD19 chimeric antigen receptor T cells (CAR T). Both drug classes are highly active, and their adverse event profiles overlap considerably, with cytokine release syndrome, cytopenias, and infections being most common. However, key differences include accessibility and logistical considerations as well as distinct neurologic toxicities, which make recommending a BsAb or CAR T a nuanced decision for each patient with R/R FL. Notably, patients could receive both classes of therapies in sequence; however, data guiding this decision are sparse. Considering the 3 most advanced agents in each class, we generally favor BsAbs before CAR T as the standard-of-care third-line treatment for the typical patient with R/R FL without concern for aggressive histologic transformation (HT). This is based on a 3-year follow-up of the mosunetuzumab phase 2 trial in R/R FL highlighting durable complete responses after a time-limited therapy with an acceptable safety profile for patients of all ages and reasonable performance status. We generally prioritize CAR T before BsAbs for patients with proven or suspected HT given the curative-potential of this approach based on trial data from R/R diffuse large B-cell lymphoma; it is unknown whether BsAbs offer the same long-term benefit in transformed FL. Overall, with the ability to personalize the sequencing of BsAbs and CAR T, the recently expanding portfolio of highly effective immunotherapies for R/R FL is poised to offer considerable benefit to this patient population.

Russler-Germain & Bartlett. ASH 2024

CAR might be preferred for **higher-risk disease**, including **POD24** followed by rapid relapse after 2L therapy.
CARs are also attractive for a **young patient** with minimal medical comorbidities who values a “one and done” approach to maximize time off therapy.

Haydu & Abramson. Blood 2024

