Sequencing of Bispecifics with Other Therapies

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Disclosures

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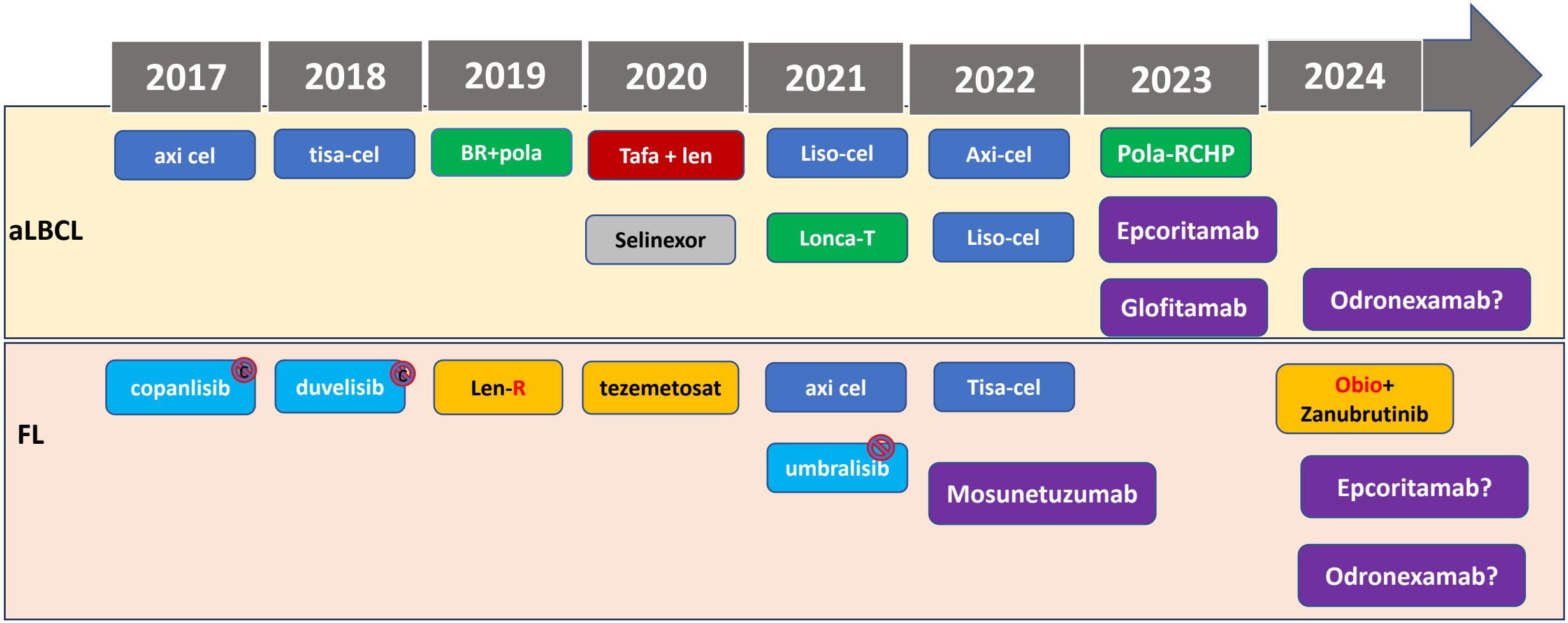
AstraZeneca, Mustang Therapeutics, Merck, Amgen

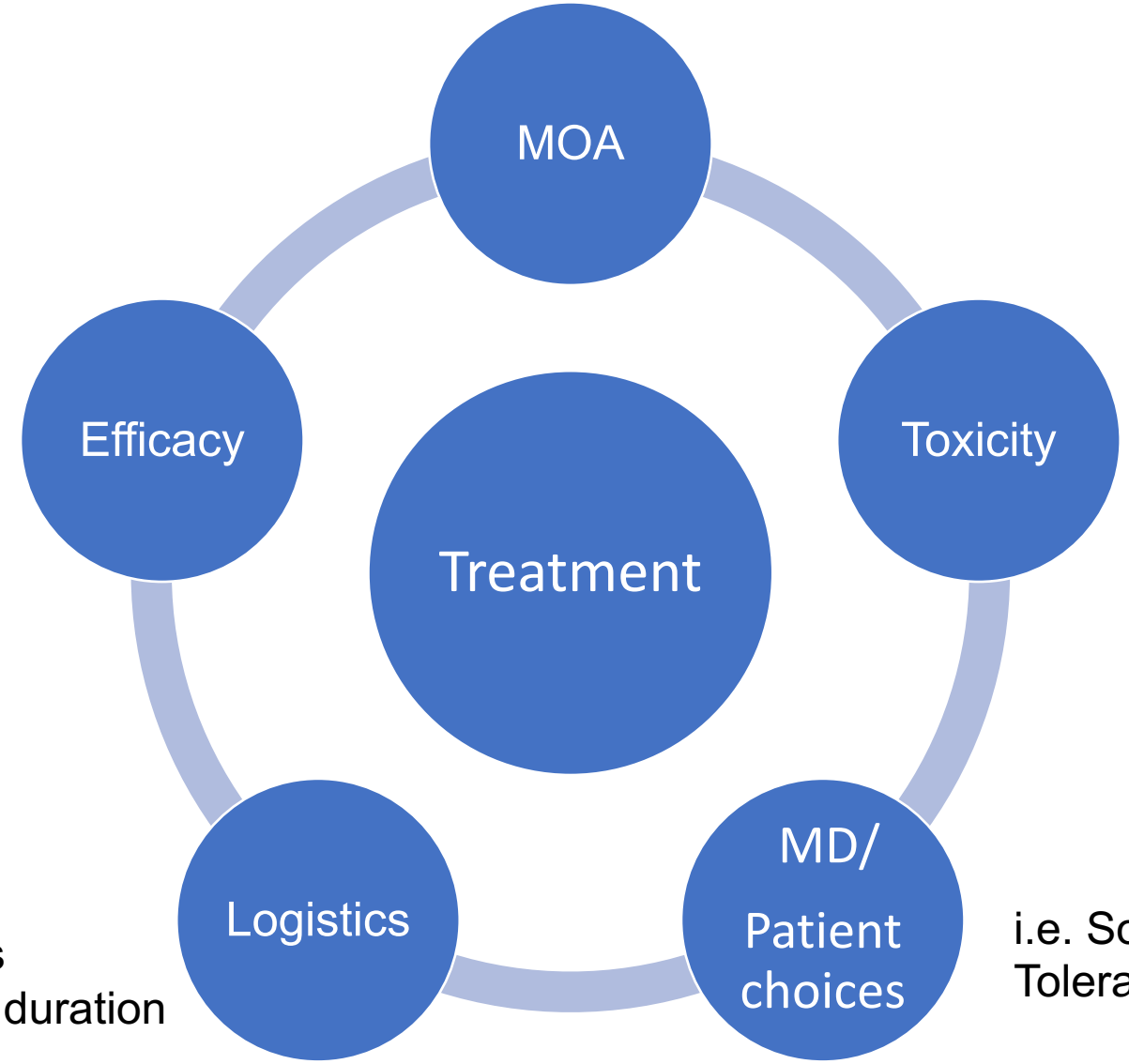
Consultancy:
AbbVie, ADC Therapeutics, BMS, Kite Pharma, Nurix, Genentech, Roche

I will be discussing non-FDA approved indications during my presentation.

Timeline of recent approvals of novel agents



Factors to consider when sequencing treatments



CR,
PFS,
TTNT,
OS

Short-term,
long term.
Financial

IP/OP
Caregivers
Treatment duration

i.e. Social events
Tolerance of toxicites


Who is first? CAR T or BsAb

CAR T therapy in the 2nd line setting: CAR is better than ASCT

CAR T cell therapy in 2nd line setting vs chemo followed by autologous stem cell transplant (ASCT)

- Three phase 3 clinical trials: ZUMA-7, TRANSFORM, BELINDA
- Randomized LBCL pts with no response or relapse within 12 months from the first line treatment) to either CD19CAR T or standard of care chemo followed auto transplant

ZUMA-7

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Axicabtagene Ciloleucel as Second-Line Therapy for Large B-Cell Lymphoma

F.L. Locke, D.B. Miklos, C.A. Jac
O.O. Oluwole, A. Ghobadi, A.P. Rap
U. Farooq, T. van Meerten, P.M. Reaga
K.W. Song, M. Dickinson, M.C. Minne
Y. Yang, S. Filosto, J. Shah, M. Sch
J.R. Westin, for All ZUMA-7 Investig

TRANSFORM

Articles

Lisocabtagene maraleucel versus standard of care with salvage chemotherapy followed by autologous stem cell transplantation as second-line treatment in patients with relapsed or refractory large B-cell lym results from an interim analysis of ar randomised, phase 3 trial

Manali Kamdar, Scott R Solomon, Jon Arnason, Patrick B Johnston, Bertram Glass, Veror
Pim Mutsaers, Francisco Hernandez-Ilizaliturri, Koji Izutsu, Franck Morschhauser, Matth
Sandrine Montheard, Alessandro Previtali, Lara Stepan, Ken Ogasawara, Timothy Mack*

BELINDA

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

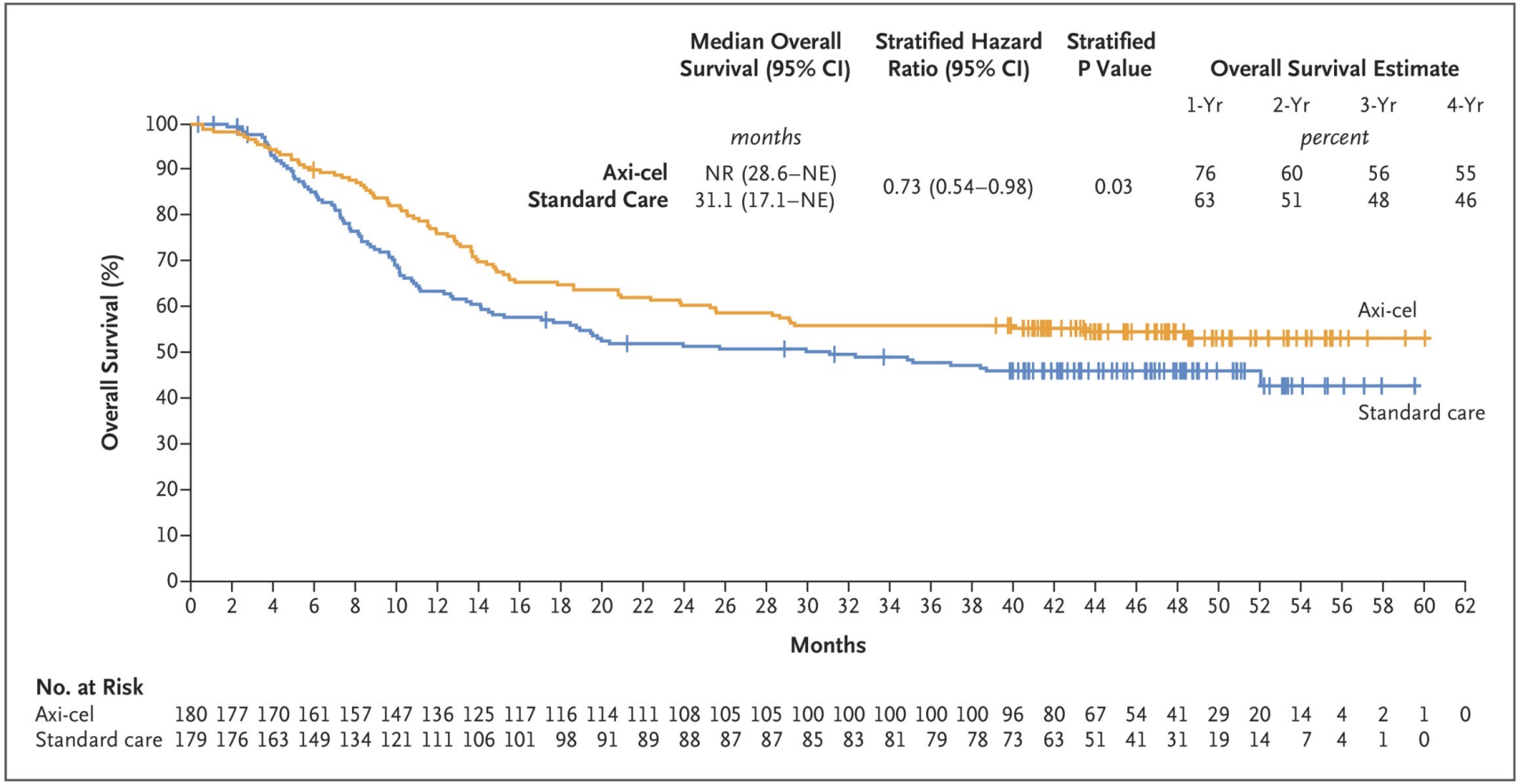
Second-Line Tisagenlecleucel or Standard Care in Aggressive B-Cell Lymphoma

M.R. Bishop, M. Dickinson, D. Purtill, P. Barba, A. Santoro, N. Hamad, K. Kato, A. Sureda, R. Greil, C. Thieblemont, F. Morschhauser, M. Janz, I. Flinn, W. Rabitsch, Y.-L. Kwong, M.J. Kersten, M.C. Minnema, H. Holte, E.H.L. Chan, J. Martinez-Lopez, A.M.S. Müller, R.T. Maziarz, J.P. McGuirk, E. Bachy, S. Le Gouill, M. Dreyling, H. Harigae, D. Bond, C. Andreadis, P. McSweeney, M. Kharfan-Dabaja, S. Newsome, E. Degtyarev, R. Awasthi, C. del Corral, G. Andreola, A. Masood, S.J. Schuster, U. Jäger, P. Borchmann, and J.R. Westin

Locke et al. NEJM 2021; Bishop et al. NEJM 2021; Kamda et. al. Lancet 2021

Overall Survival Benefit with Axi cel

Median follow-up of 47.2 months



Median PFS
14.7 months vs 3.7 months

In the second line setting, CD19CAR T is the choice for transplant eligible, early relapse pts

Westin JR et al. N Engl J Med2023;389:148-157

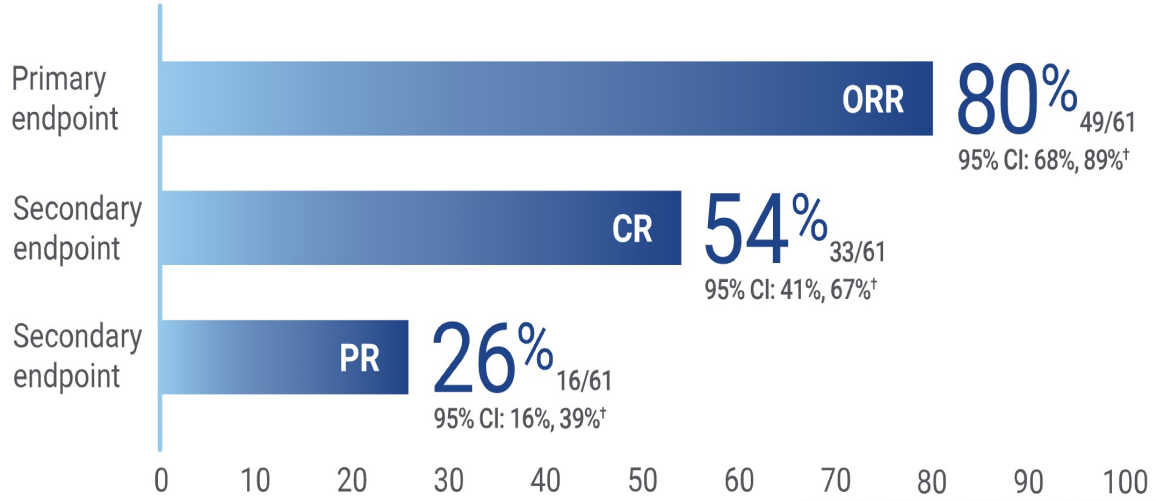
Transplant ineligible patients, 2L?

Scenario: 81 y.o with DLBCL relapse 24 months post CHOP x 6. H/o HTN, A-fib, moderate-severe AS, LVEF 55%, NL organ function, ECOG 2

- Should CAR T be the first consideration?

Scenario: 81 y.o with DLBCL relapse 24 months post CHOP x 6.
H/o HTN, A-fib, moderate-severe AS, LVEF 55%, NL organ function, ECOG 2

Response rates in the PILOT trial (N=61 infused, 74 leukapheresed)*



* Per the Lugano criteria, as assessed by an IRC.

† Two-sided 95% exact Clopper-Pearson confidence intervals.

Sehgal A, Lancet Oncology 2022
Hoda D, et al. ASTCT 2024

≥ 1 of the following criteria:

- age ≥ 70 years; 74 (53-84)
- adjusted DLCO) ≤ 60%;
- LVEF < 50%;
- CrCl< 60mL/min; in 25%
- AST or ALT >2 × ULN, or
- ECOG 2. ECOG 2

- CRS 38% with 1 grade 3
- ICANS: 31%, with 3 grade 3

Median follow-up 23.1 months

PFS: 9.0 (4.2, NR)†
DOR: 23.3 (6.2-NR)
OS: NR (16.3, NR)§

ALCANTE Study: axi-cel in transplant ineligible aBCL patients

Median f/u 12.0 months

	N=67
age	70 (49-81)
ECOG 1	98.4%
HCT-CI	<3 in 67.7%
DLBCL, NOS	84%
HGBCL	10%
Refractory to 1st line	54.8%
Bridging received	84%

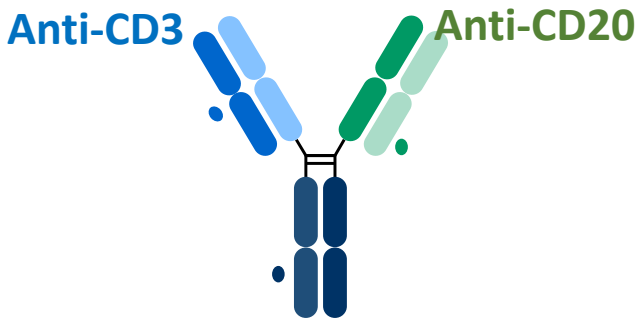
	ALCANTE
CR	**66% at 3 months**
DOR	NR
mPFS	11.8 mo (8.4-NR)
CRS all, >=gr3	93.5%, 8.1%
ICANS	51.6%, 14.5%
ICU transfer	25.8%
Infection	53.8%, 9.7%-gr5

Transplant ineligibility: Based on physician's assessment

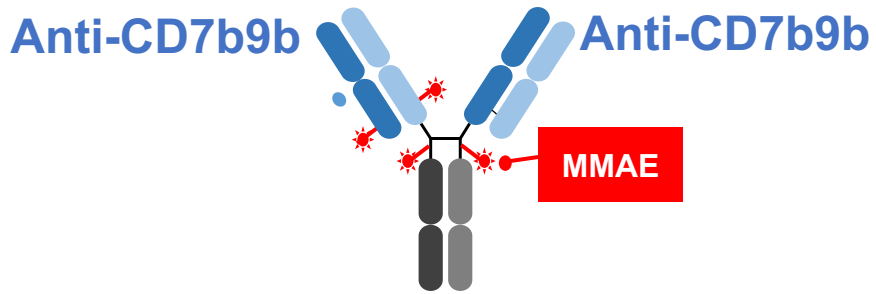
Houot R et al. *Nature Medicine* **volume 29**, pages2593–2601 (2023)

GO40516: Mosunetuzumab + Polatuzumab for aggressive B-NHL

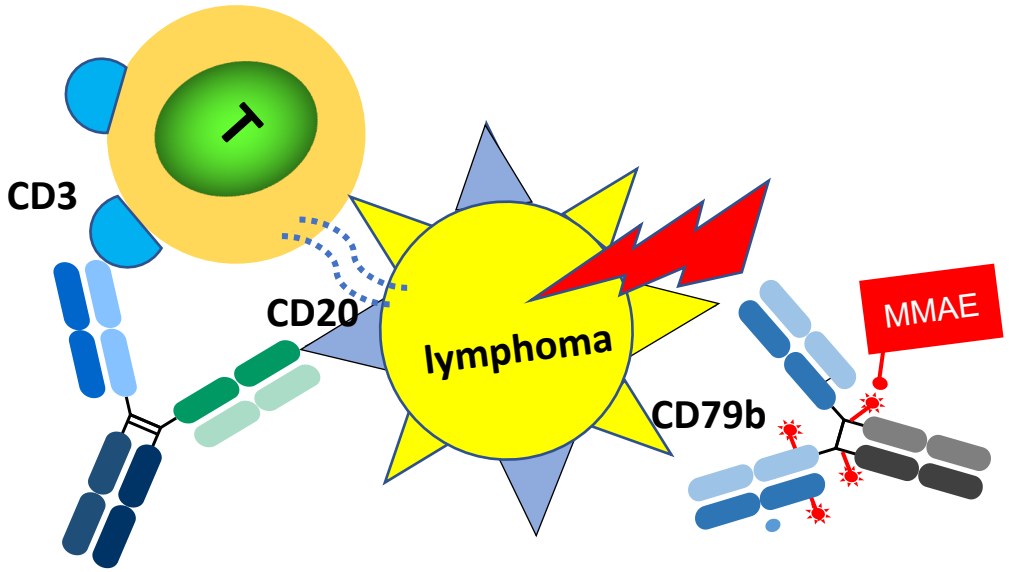
- **Phase Ib/II study (NCT03671018)**[5->] evaluating M-Pola combination in R/R aBNHL



Mosunetuzumab



Polatuzumab vedotin



1. Sun et al. Sci Transl Med 2015;7:287ra70; 2. Budde et al. J Clin Oncol 2021 [in press]
3. Sehn et al. J Clin Oncol 2020;38:155–65; 4. Tilly et al. ASCO 2019
5. NCT03671018. Available at: https://clinicaltrials.gov/; 6. Budde et al. ASH 2021

Study overview (NCT03671018)

Key inclusion criteria

- LBCL (*de novo* DLBCL, HGBCL, trFL, or Grade 3b FL)
- ≥1 prior line of therapy, including an anti-CD20-directed therapy
- Patients who were ineligible for ASCT

Objectives

- Efficacy and safety of mosun-pola
- Primary endpoint: Best ORR[1] by independent review committee (IRC)

Mosun-pola fixed duration administration*

Mosun†

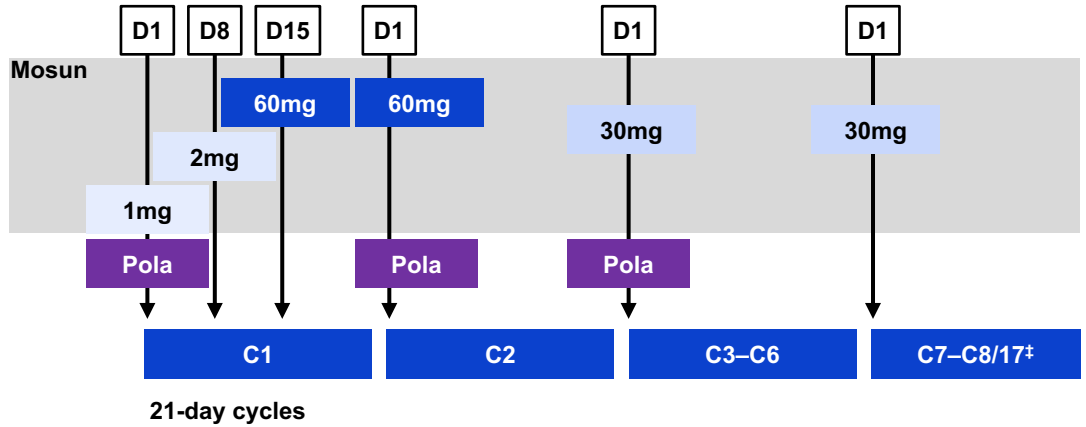
- Cycle (C) 1 step-up dosing for CRS mitigation
- Q3W intravenous infusions at RP2D (C1–8/17)‡

Pola

- Q3W intravenous infusions (1.8mg/kg) (Day [D]1, C1–6)

No mandatory hospitalization

Retreatment with mosun-pola was permitted



*Mosunetuzumab RP2D: C1D15 and C2D1 (1/2/60mg), and 30mg for subsequent cycles.

†**Corticosteroid premedication was required prior to each dose in C1 and C2 and was optional for C3+.**

‡Patients who achieved CR completed mosunetuzumab after C8, while patients who had PR or SD continued mosunetuzumab for a total of 17 cycles, unless progressive disease or unacceptable toxicity occurred.

1. Cheson BD, et al. J Clin Oncol 2014;32:3059–68.

Baseline characteristics

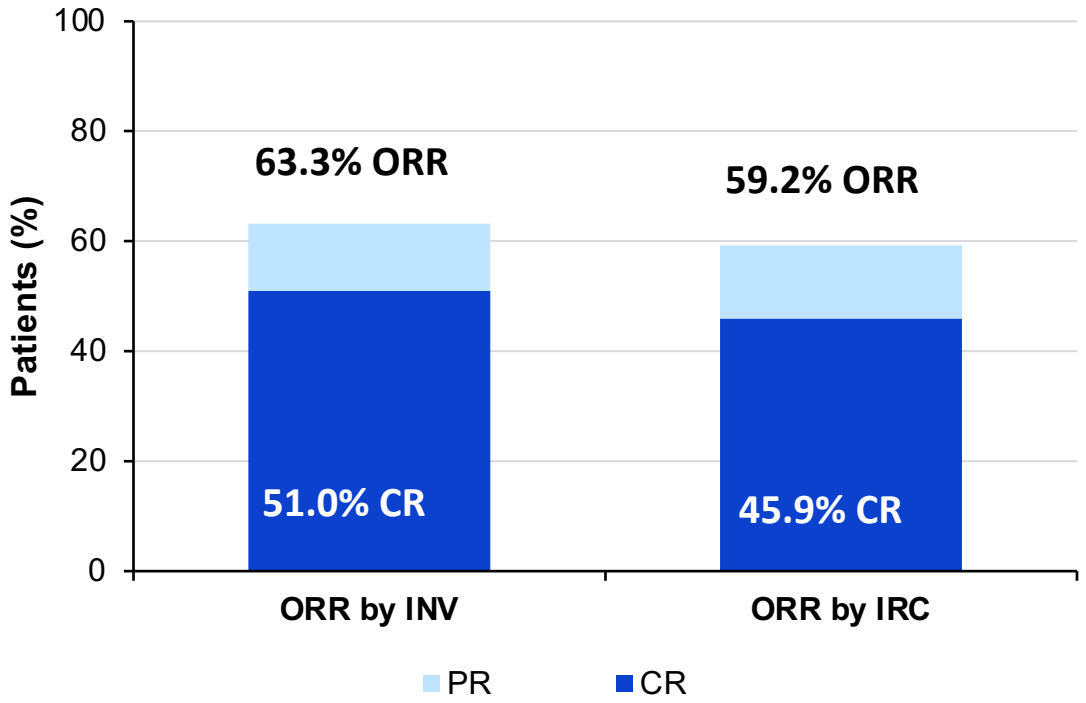
n, unless stated	N=98
Median age, years (range)	**68** (20–88)
Gender, male	70 (71.4%)
ECOG PS score	
0	36 (36.7%)
1	55 (56.1%)
2	7 (7.1%)
NHL histology	
DLBCL	68 (69.4%)
HGBCL	18 (18.4%)
trFL	8 (8.2%)
FL Grade 3b	4 (4.1%)
Cell-of-origin (n=94)*	
GCB	53 (56.4%)
Non-GCB	33 (33.7%)
Unknown	8 (8.5%)

n, unless stated	N=98
Ann Arbor stage III–IV	85 (86.7%)
Bulky disease, ≥6cm	33 (33.7%)
Extranodal involvement	65 (66.3%)
Number of prior lines of therapy	
1	35 (35.7%)
≥2	63 (64.3%)
Median lines of prior therapy, n (range)	2 (1–8)
Prior ASCT	11 (11.2%)
Prior CAR T-cell therapy	35 (35.7%)
Refractory to CAR T-cell therapy	26/35 (74.3%)
Primary refractory	56 (57.1%)
Refractory to†	
Last prior therapy	76 (77.6%)
Any prior CD20 therapy	80 (81.6%)

Enrollment: June 23, 2020 – February 15, 2022

Best response rates

Efficacy endpoint* results



prior CAR T treatment	n=35
Best ORR, n [95% CI]	**20 (57.1%)** [39.4–73.7]
Median **DoR**, months (95% CI)	**NR** (8.8–NE)
CR rate, n [95% CI]	**14 (40.0%)** [23.9–57.9]
Median **DoCR**, months (95% CI)	**NR** (12.5–NE)

Primary efficacy endpoint of best ORR by IRC was met (59.2%; p=0.0003† vs historical control [42%]‡)

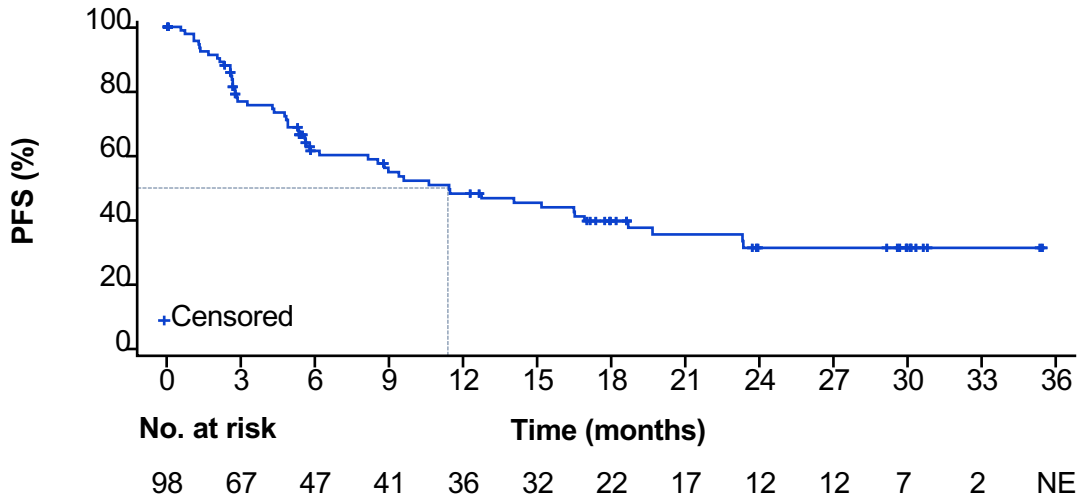
Clinical cut-off date: July 6, 2023.
*As determined by the investigator (INV) or independent review committee (IRC) using Lugano 2014 criteria.[1]
†Exact binomial test with one-sided alpha level of 2.5%. ‡Historical control based off the ROMULUS study.[2]

1. Cheson BD, et al. J Clin Oncol 2014;32:3059–68;
2. Morschhauser F, et al. Lancet Haematol 2019;6:e245–65.

PFS and OS

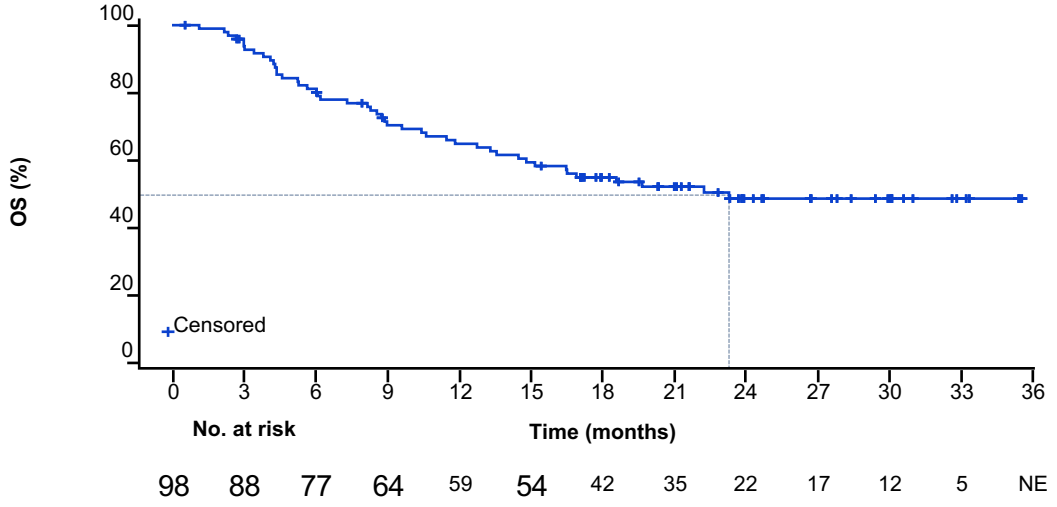
Median follow-up: 23.9 months (95% CI: 21.3–26.8)

PFS



	N=98
Median PFS*, months (95% CI)	**11.4 (6.2–18.7)**
12-month event-free rate, % (95% CI)	48.2 (37.3–59.0)
24-month event-free rate, % (95% CI)	31.3 (20.1–42.6)

OS



	N=98
Median OS, months (95% CI)	23.3 (14.8–NE)
12-month event-free rate, % (95% CI)	64.9 (55.2–74.5)
24-month event-free rate, % (95% CI)	48.6 (37.9–59.3)

Encouraging PFS and OS benefit observed at 2 years

Clinical cut-off date: July 6, 2023.
*IRC assessed.
PFS, progression-free survival; OS, overall survival.

Toxicity summary

CRS by ASTCT criteria[1]	N=98
Any grade, n	**18 (18.4%)**
Grade 1	10 (10.2%)
Grade 2	5 (5.1%)
Grade 3	3 (3.1%)
Median time to first CRS onset relative to last dose, days (range)	1.0 (0–2)
Median CRS duration, days (range)	2 (1–5)
CRS management, n	
Corticosteroids	6 (6.1%)
Tocilizumab	3 (3.1%)
Single vasopressors	2 (2.0%)
Events resolved	100%

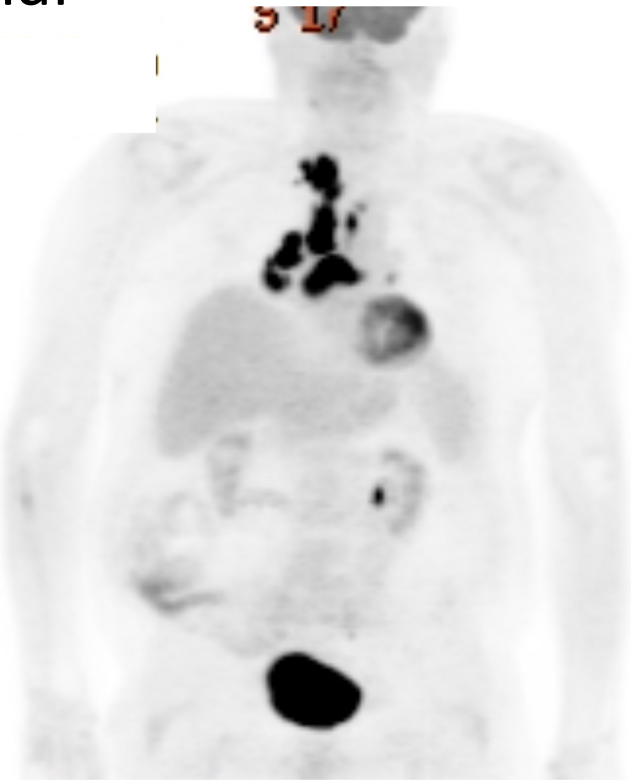
AE summary, n	N=98
ICANS*	
Any grade	5 (5.1%)
Grade 3–4†	2 (2.0%)
Peripheral neuropathy	
Grade 1	16 (16.3%)
Grade 2	12 (12.2%)
Neutropenia	
Any grade	29 (29.6%)
Grade 3–4	20 (20.4%)
Serious infections	
Any grade	**13 (13.3%)**
Grade 3–4	9 (9.1%)
Grade 5‡	3 (3.1%)

Clinical cut-off date: July 6, 2023.
ASTCT, American Society for Transplantation and Cellular Therapy criteria.

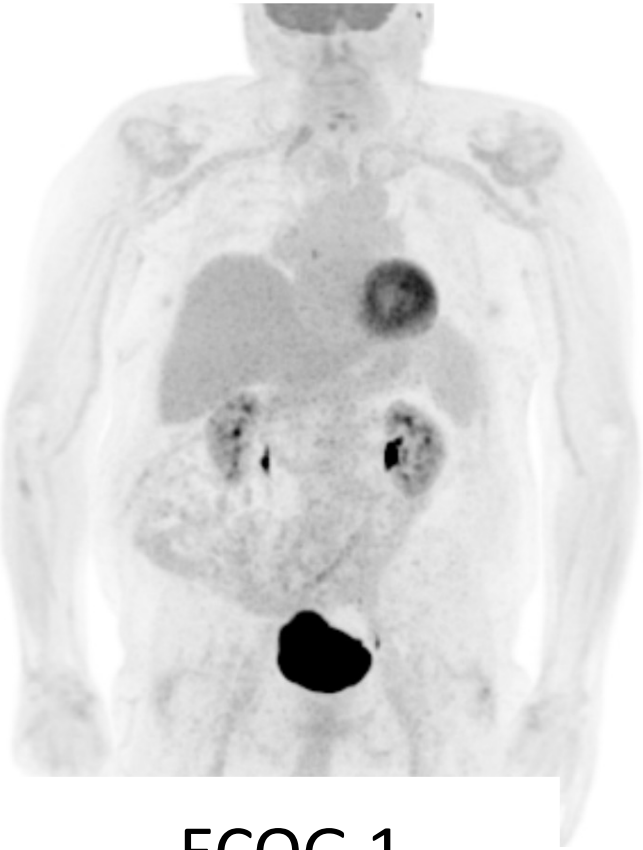
1. Lee DW, et al. Biol Blood Marrow Transplant 2019;25:625–38.

Scenario: 81 y.o with DLBCL relapse 24 months post –CHOP x 6.
H/o HTN, A-fib, moderate-severe AS, LVEF 55%, NL organ function, ECOG 2

Mosun i.v.+pola trial



ECOG 2



ECOG 1

CR ongoing

How does BsAb fit into 3L+ treatment landscape?

3L+ options (R/R aBCL)

- Investigational agent
- Immunochemotherapy
- CART (if not given in 2L)
- Pola-BR
- Selinexor
- Tafasitamab + Len
- Loncastuximab tesirine
- BsAb (Glofitamab, Epcoritamab)
- Best supportive care or XRT

3L+ options (R/R FL)

- Investigational agent
- CD19CAR T
- Immunochemotherapy (BR, RCHOP, …)
- Rituximab + Lenalidomide
- Tezemetostat
- Mosunetuzumab
- Obinotuzumab + zanubrutinib
- Best supportive care or XRT

3rd line + setting

- 68 y.o. man with DLBCL who has relapsed disease
- Prior treatment: RCHOP x 6, Pola-BR x 2(bridging), CD19AR T

Can CD20/CD3 BsAb monotherapy work well in CAR experienced patients?

Bispecific TCEs: Aggressive Large B Cell Lymphoma

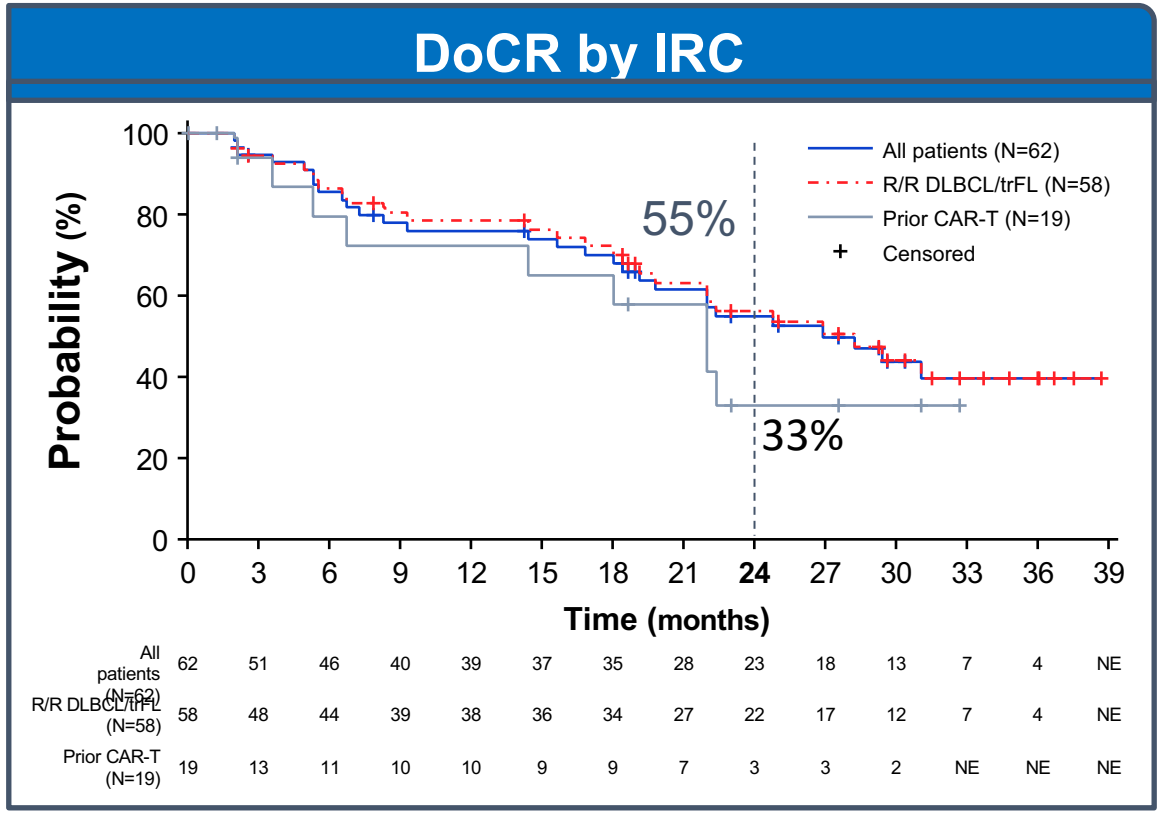
	Glofitamab	Epcoritamab	Odronexamab
Trial name	NP30179	EPCOR ENHL-1 LBCL	ELM-2
Trial phase	Phase2	Phase 2	Phase 2
N	155	157	127
Median lines of prior therapies	3 (2-7)	3 (2-11)	2 (2-8)
ORR	53%	63%	53%
CR	39%	39%	31.5%
Post-CAR /CR%	61/35%	52/35%	n/a
Median PFS	4.9 mo	4.4 mo	4.4 mo
CRS any/≥ Gr 3, %	63%/4%	50%/3%	53.3%/1.7%
ICANS any/≥ Gr 3, %	15%/3%	6%/1%	4%/0

Bartlett et al. Blood Advances 2023; Dickinson et al. NEJM 2022,387:2220-2231; Thieblemont C et al. J Clin Oncol. 2022, et al. ASH 2022

Fixed duration treatment with Glofitamab showed high and durable responses across subgroups

- Median time on study: 32.1 months (range: 0–43)

	All (N=155)*	CAR-T (N=52)†
CR rate, n (%) [95% CI]	62 (40) [32.2–48.2]	19 (37) [23.6–51.0]
Median DoCR mo(95% CI)	26.9 (19.8–NR)	22.0 (6.7–NR)
24-mo DoCR,% (95% CI)	55.0 (41.1–68.8)	33.1 (7.2–59.0)
Median CR F/U months (range)	29.6 (0–39)	23.0 (0–33)
Ongoing CRs, n/N (%)	34/62 (55)	10/19 (53)



Fixed duration treatment: 12 cycles

Abstract #433 ASH 2023

EPCORE NHL-1 LBCL cohort

Prior Treatments	DLBCL & HGBCL, n=148	LBCL, N=157
Median time from initial diagnosis to first dose, mo	19	19
Median time from end of last therapy to first dose, mo	2.4	2.4
Median prior lines of therapy (range)	3 (2–11)	3 (2–11)
≥3 Lines of therapy, n (%)	104 (70)	110 (70)
Primary refractory[b] disease, n (%)	88 (59)	95 (61)
Refractory[b] to last systemic therapy, n (%)	122 (82)	130 (83)
Refractory[b] to ≥2 consecutive lines of therapy, n (%)	112 (76)	118 (75)
Prior ASCT, n (%)	27 (18)	31 (20)
Prior CAR T therapy, n (%)	58 (39)	61 (39)
Refractory[b] to CAR T therapy	43/58 (74)	46/61 (75)

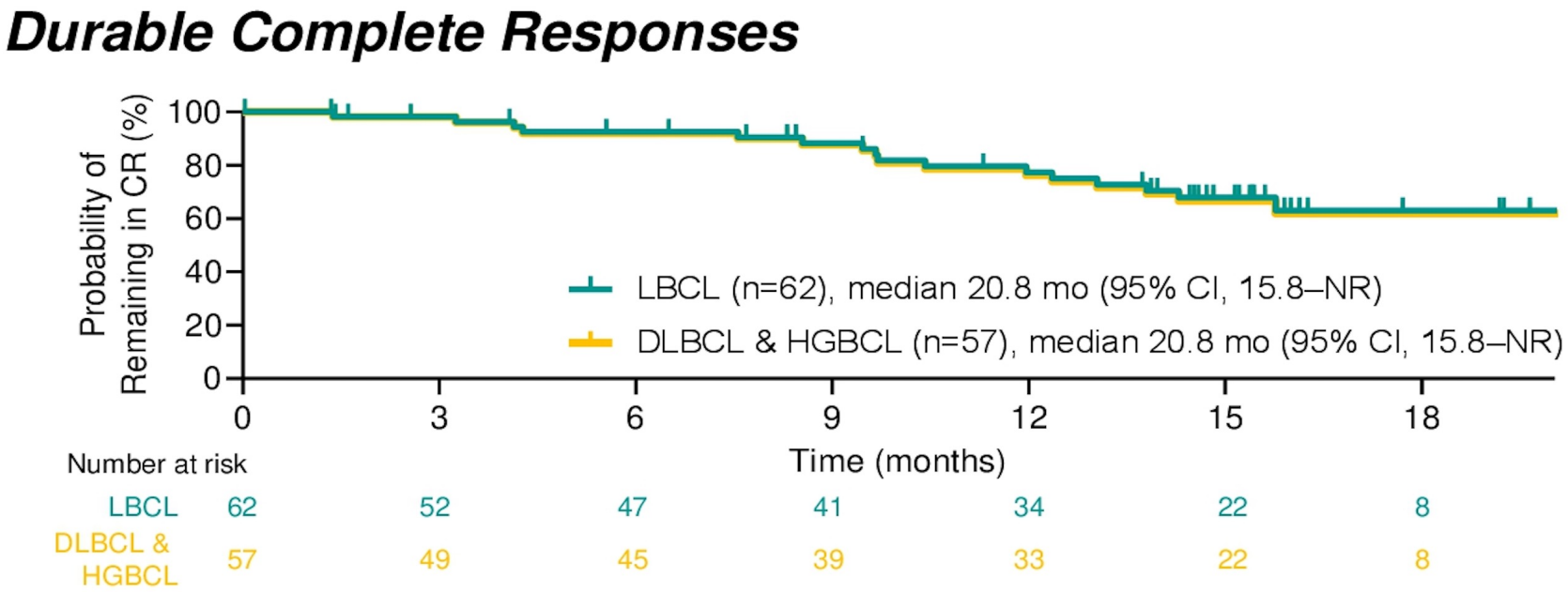
[a]De novo versus transformed status of 2 patients with DLBCL was unknown. [b]Refractory disease is defined as disease that either progressed during therapy or progressed within <6 mo of completion of therapy.

Karimi Y et al. ASCO 2023

EPCORE NHL-1 LBCL cohort

a median follow-up of 15.4 mo

- Median DOR was 15.5 mo (95% CI, 9.7-20.8);
- Median DOR, for patients with prior CAR T, was not reached

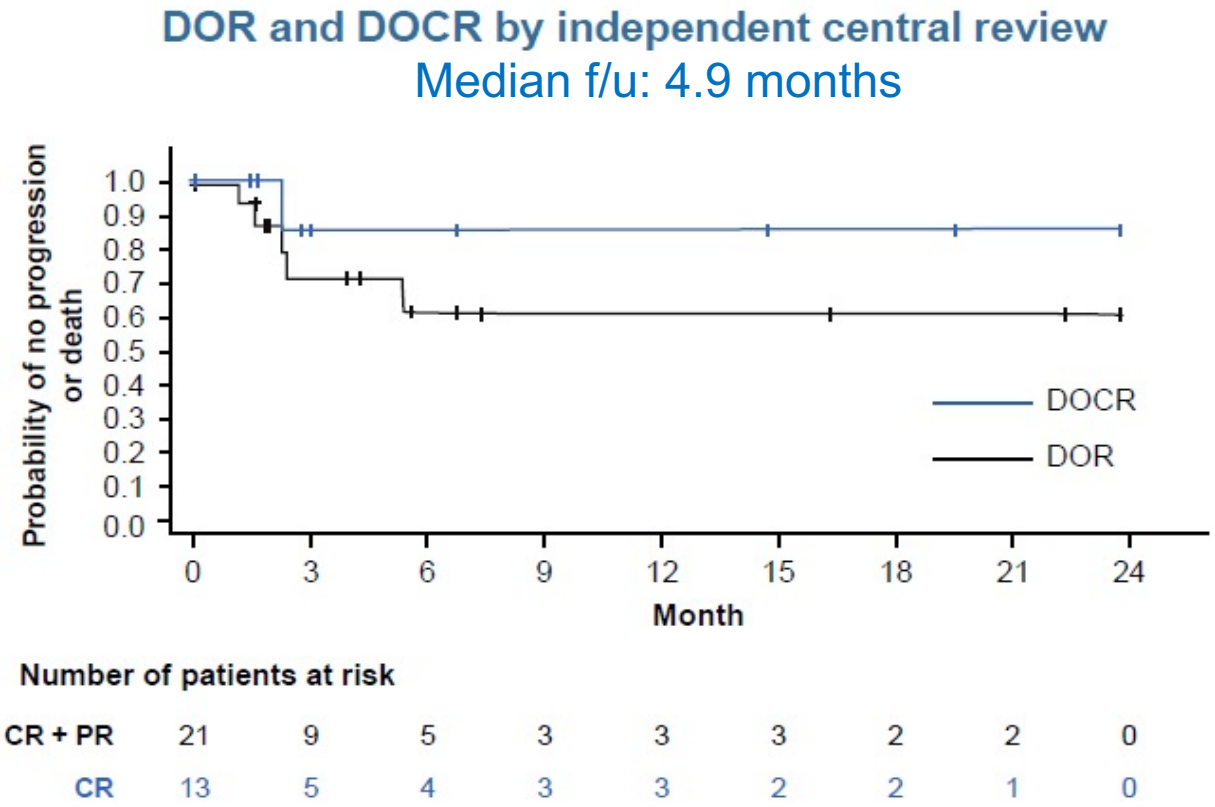


- estimated 85% of patients remained in CR at 12 mo

Karimi Y et al. ASCO 2023

Odronexamab induced durable response in DLBCL- POST CART Cohort (ELM-1)

	All 44 (eval)	Responders 21
Median Age, yrs	63 (27-82)	60 (32-75)
Median LOT	4 (2-9)	3 (2-9)
Median time since CART	7.2 mo	8.0 mo
Refractory to last line	79.5%	76.2%
Refractory to CAR	72.7%	57.1%



- ORR: **48%** (CR: 30%)

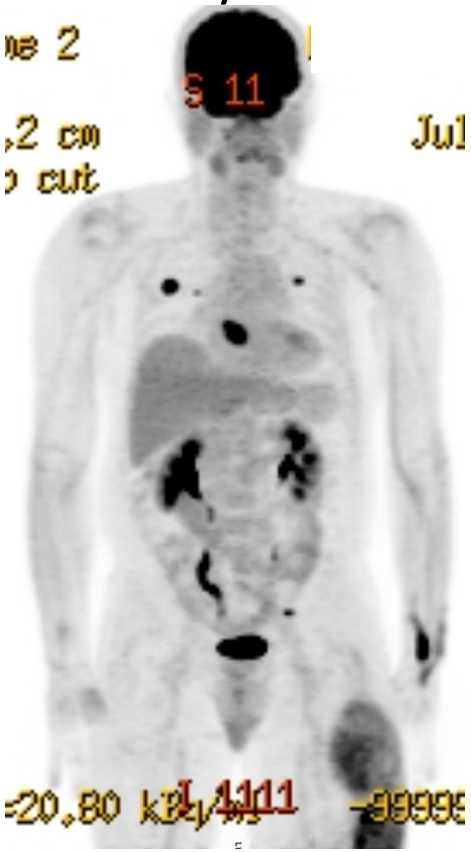
Crombie at al, ASH 2023

CART infusion: 8/10/21

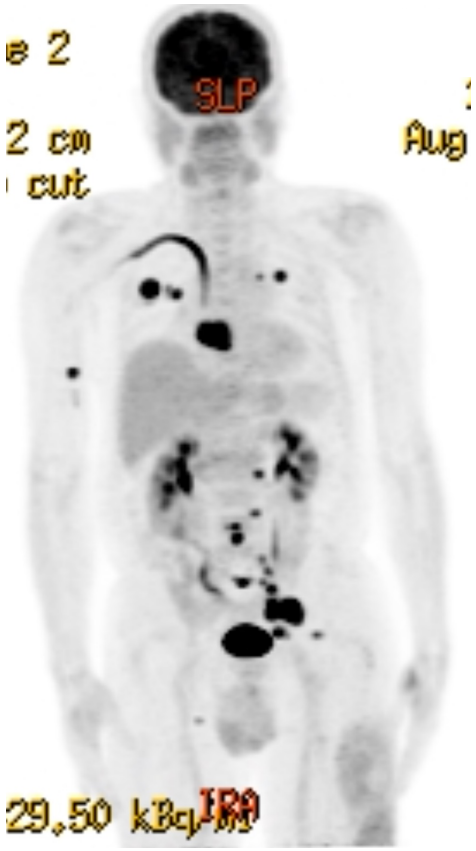
Biopsy
9/21/21

Mosun i.v.+pola trial
C1D1 on D+56 post CAR

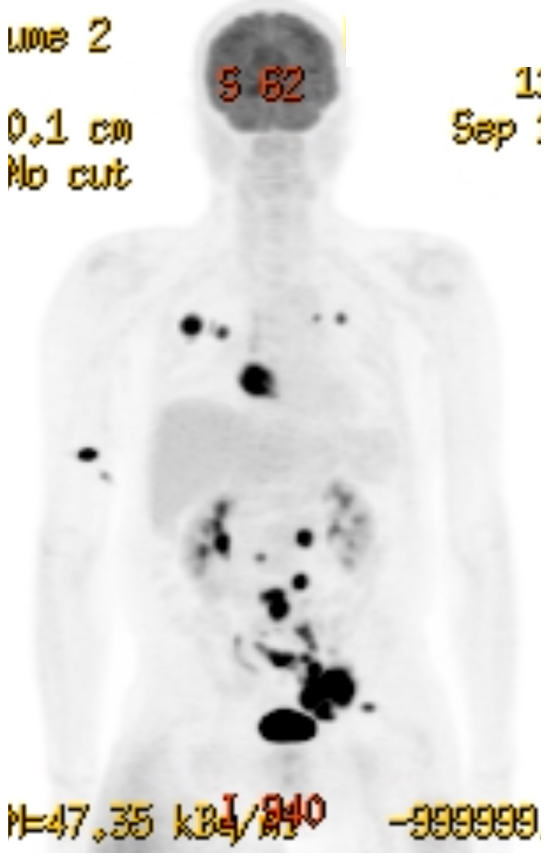
Day -12



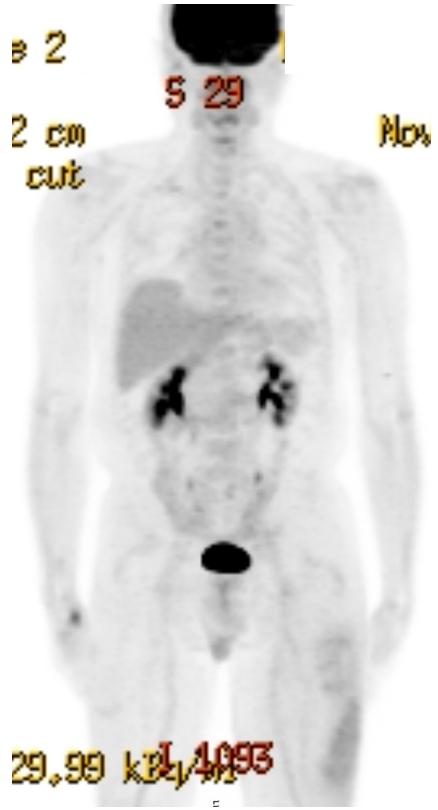
Day + 21



Day + 32



Post C2 (wk 7)



PD

PD

CR

3rd line + R/R DLBCL setting

- 67 y.o. man with DLBCL with relapse after RCHOP, and RICE.
- ECOG 1; organ function wnl

Giving BsAb before CAR T, would it negatively impact CAR T product function?

Impact of BsAb exposure on response to subsequent CAR T treatment

Variables	BsAb cohort n=42	Control cohort n=42	SMD
Patient and lymphoma characteristics			
Male gender, n (%)	29 (69)	31 (74)	-0.085
Age, median years (range)	63 (31-82)	67 (21-78)	0.061
Histology, n (%)			
- DLBCL/HGBL	35 (83)	31 (74)	0.196
- PMBL/Transformed	7 (17)	11 (26)	
> 2 prior lines, n (%)	36 (86)	36 (86)	0
Previous SCT, n (%)	8 (19)	7 (17)	-0.05
Bulky disease, n (%)	15 (36)	19 (45)	0.16
CRP > 3mg/dL, n (%)	16 (38)	12 (29)	-0.164
LDH > 2xULN, n (%)***	12 (29)	16 (38)	0.168
ECOG >1, n (%)***	4 (10)	3 (7)	-0.069
CAR-T related characteristics			
Axi-cel, n (%)	22 (52)	20 (48)	-0.078
Months between last prior treatment and CAR-T infusion, median (IQR)	2.7 (2.3-3.8)	2.5 (2.0-3.5)	0.201

CD20/3 90%
CD22/3 8%

Monotherapy 87%

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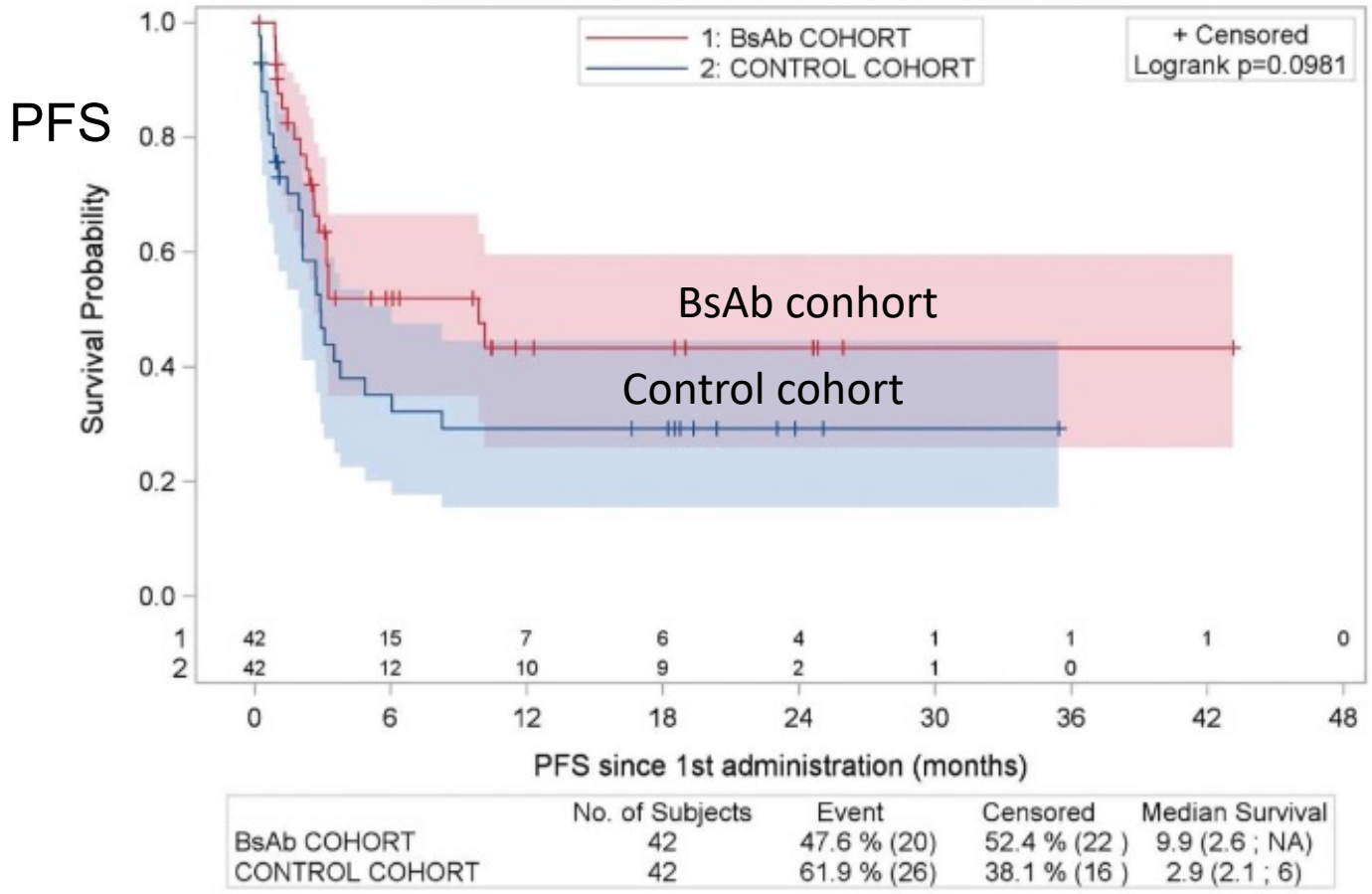
BsAbs before CAR T?

mF/u 11.5M (BsAb); 18.8M (control)

More data from each BsAb study
- timing of bsAb exposure to leukapheresis
- T cell fitness
- T cell expansion and persistence of various CAR products



No impact on efficacy or toxicities

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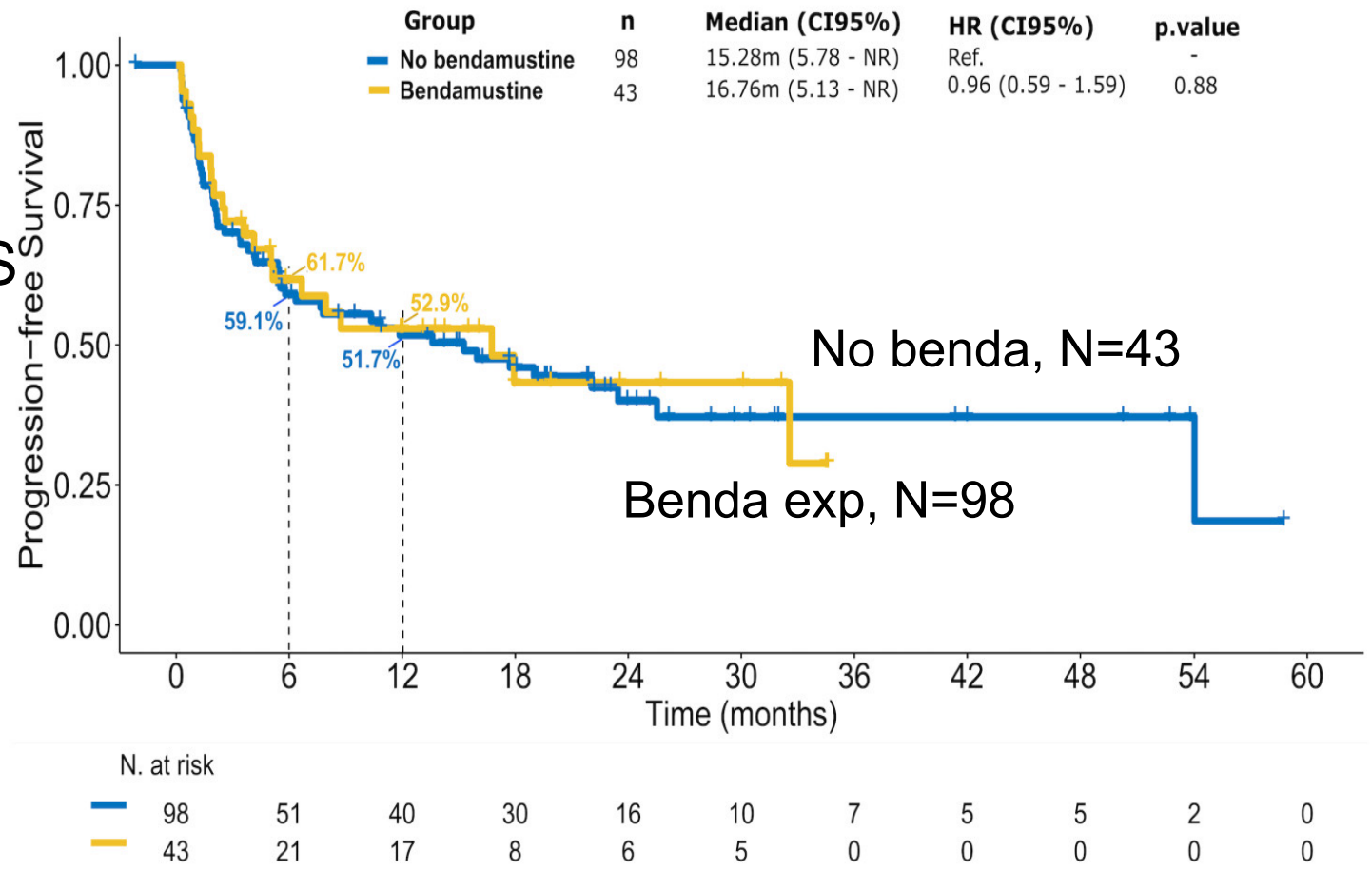
Impact of Prior Bendamustine Exposure on antiCD20/3 Bispecific Antibody Treatment Outcomes for Patients with B-Cell Lymphoma

PFS



Median F/U: 21.8 Months

Benda+ group,
More FL (44%), tFL (47%)
>2 L lines (53%)

Less
Primary refractory
CD3 median counts

Median Benda Exp: 653 days

? Duration of benda exposure
? Time from benda to BsAb
? Difference between diseases, or BsAbs

Iacoboni,G et al, Blood, 2023,

Integration of BsAb to 3L+ treatment landscape

Many factors to consider: clinical data + patient situation

(R/R aLBCL)

- Clinical trials using Investigational agents/combinations
- Before or after CART (if not given in 2L)
- Use BsAb before
  - Loncastuximab tesirine, Pola-BR, Tafasitamab + Len
  - Best supportive care
- Use before chemotherapy

Integration of BsAb to 3L+ treatment landscape

Many factors to consider: clinical data + patient situation

R/R FL

- Clinical trials using Investigational agents/combinations
- Before or after CD19CAR T
- Before Rituximab + Lenalidomide, Obinotuzumab + zanubrutinib
- Before Tezemetostat
- Before Immunochemotherapy (BR, RCHOP, …)
- Best supportive care or XRT

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