BISPECIFIC ANTIBODIES IN RELAPSED B-CELL NHL

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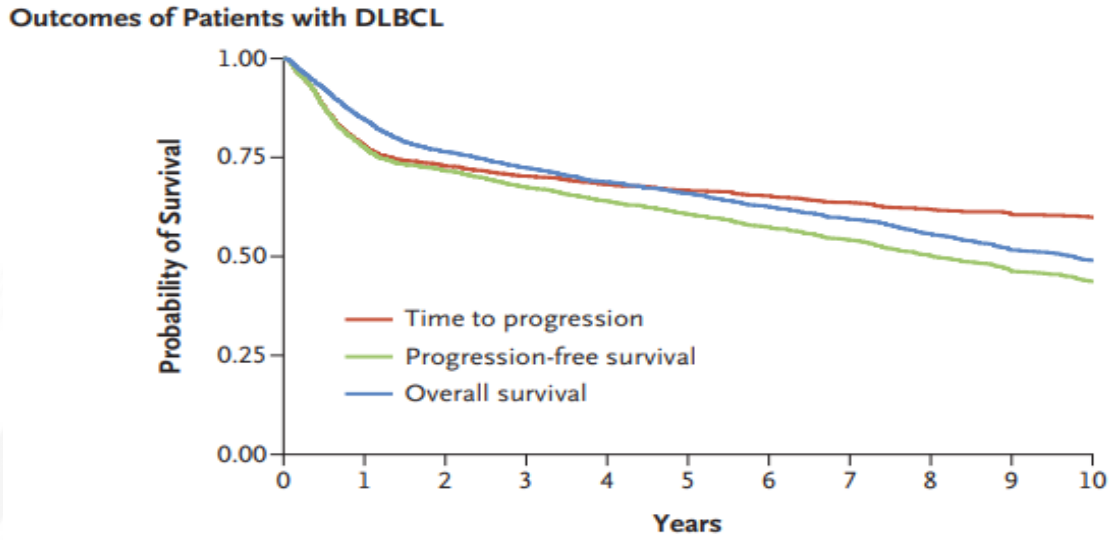
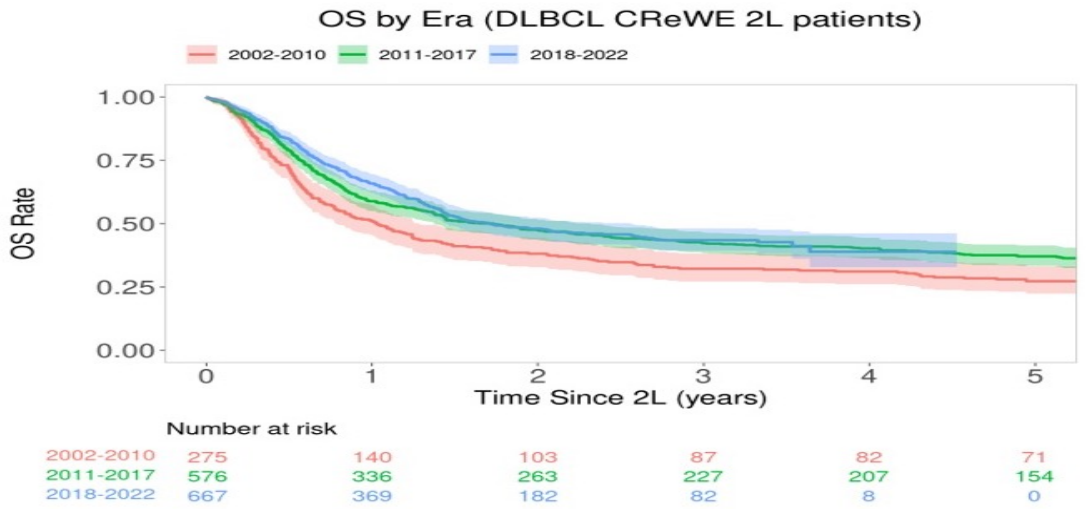
DLBCL BACKGROUND

- DLBCL is the most common subtype of lymphoma, ~25,000 cases/yr in US
- Many patients will be cured with with 1st line chemoimmunotherapy
- Prognosis remains poor for those who relapse, although survival increasing in in more recent treatment eras

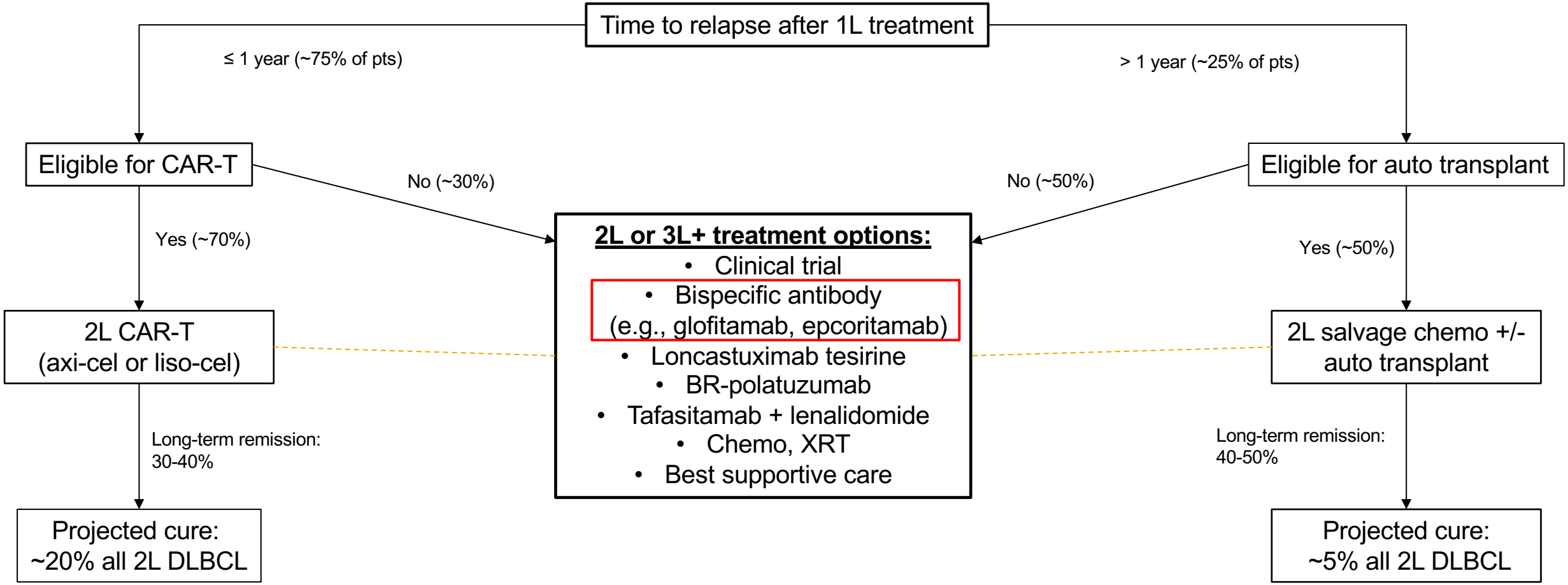


Sehn LH, Salles G. *N Engl J Med*. 2021;384(9):842-858.



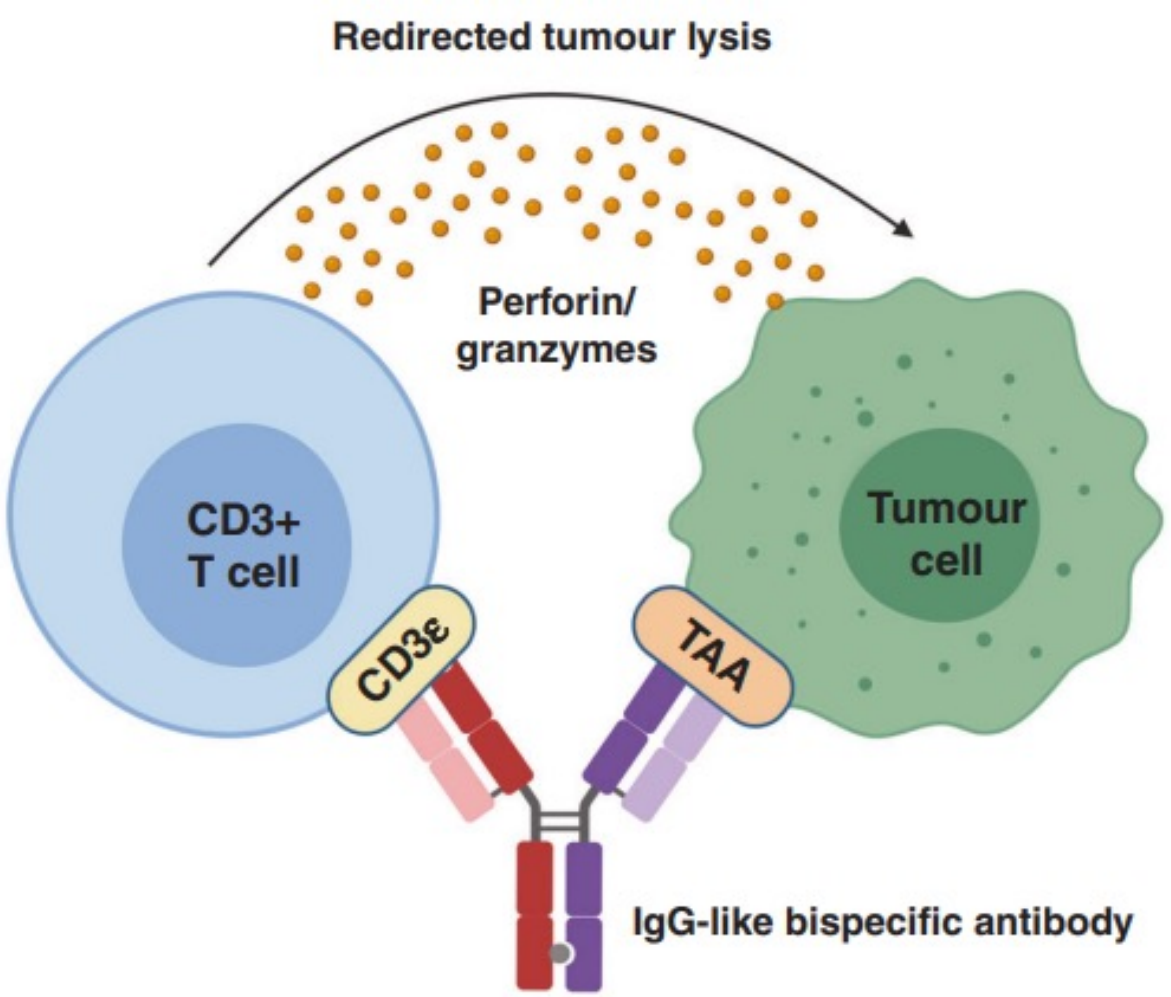
Koff JL, et al. *Blood* 2023; 142 (Supplement 1): 307

TREATMENT ALGORITHM FOR RELAPSED DLBCL



Adapted from: Jason Westin, Laurie H. Sehn; CAR T cells as a second-line therapy for large B-cell lymphoma: a paradigm shift?. *Blood* 2022; 139 (18): 2737–2746

BISPECIFIC ANTIBODIES FOR LYMPHOMA

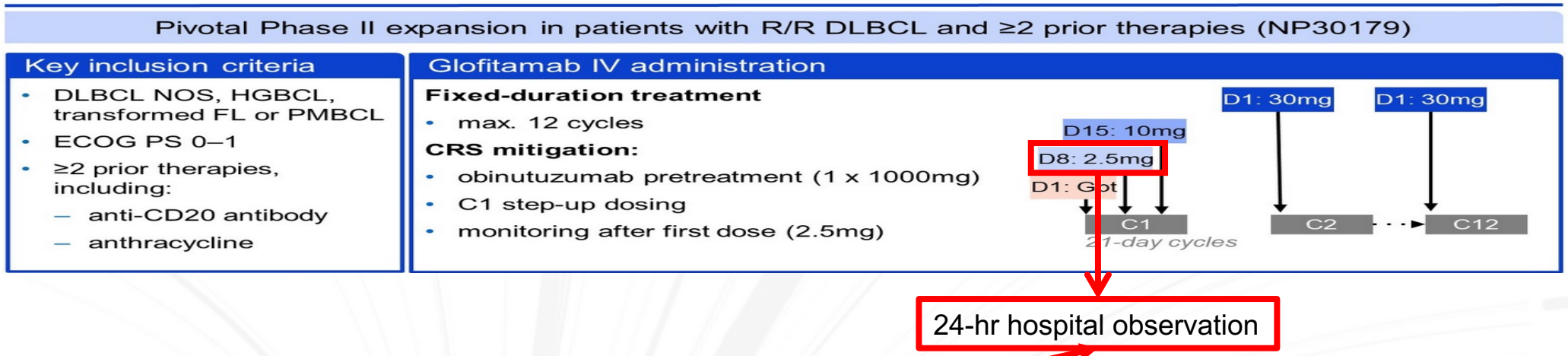


- Bispecific abs bind and redirect cytotoxic activity of T-cells to malignant cells
- "Off-the-shelf", immediately available for use
- Currently approved for R/R DLBCL and FL
  - Encouraging activity in other lymphoma subtypes
- Major adverse effects:
  - Cytokine release syndrome
  - Neurologic toxicity
  - Hypogammaglobulinemia
  - Infection

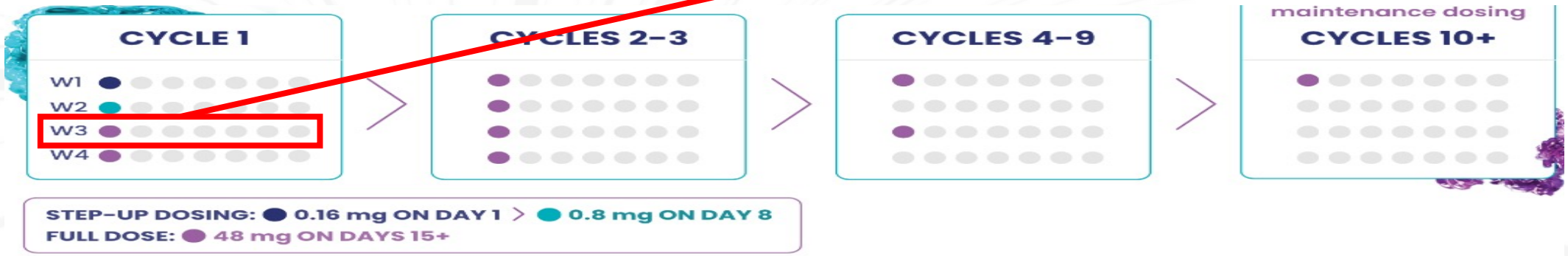
Figure from: Singh A, Dees S, Grewal IS. *Br J Cancer*. 2021;124(6):1037-1048.

DLBCL BISPECIFIC DOSING AND ADMINISTRATION

Glofitamab – IV infusion, fixed duration therapy



Epcoritamab – Subcutaneous injection, indefinite therapy



OTHER CONSIDERATIONS FOR DRUG ADMINISTRATION

Potential Benefits:

- Feasible for administration at community sites
- No REMS or FACT required
- No apheresis, cell processing required
- Opportunities for academic and community onc partnership

Considerations for use in community settings:

- Tocilizumab availability
- Healthcare provider training (nursing, hospitalist, ED)
- In-hospital monitoring logistics
- Afterhours plan, avoiding unnecessary ED visits

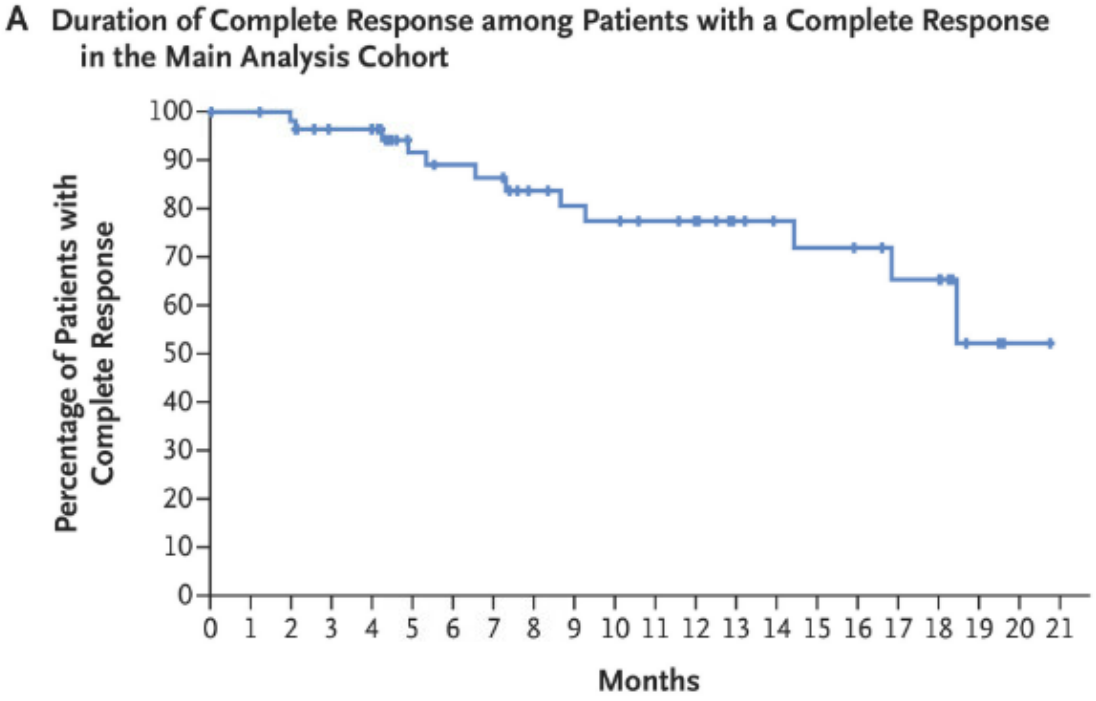
BISPECIFIC MONOTHERAPY EFFICACY IN R/R DLBCL

	Glofitamab	Epcoritamab	Odronextamab
Median Age, yr (range)	66 (21-90)	64 (20-83)	66 (24-88)
# Prior therapies	3 (2-7)	3 (2-11)	2 (2-8)
Prior CAR-T	33%	39%	29%
ORR (CR)	52% (39%)	63% (39%)	49% (31%)
Median PFS	4.9 mo	4.4 mo	4.4 mo
Median OS	11.5 mo	18.5 mo	-

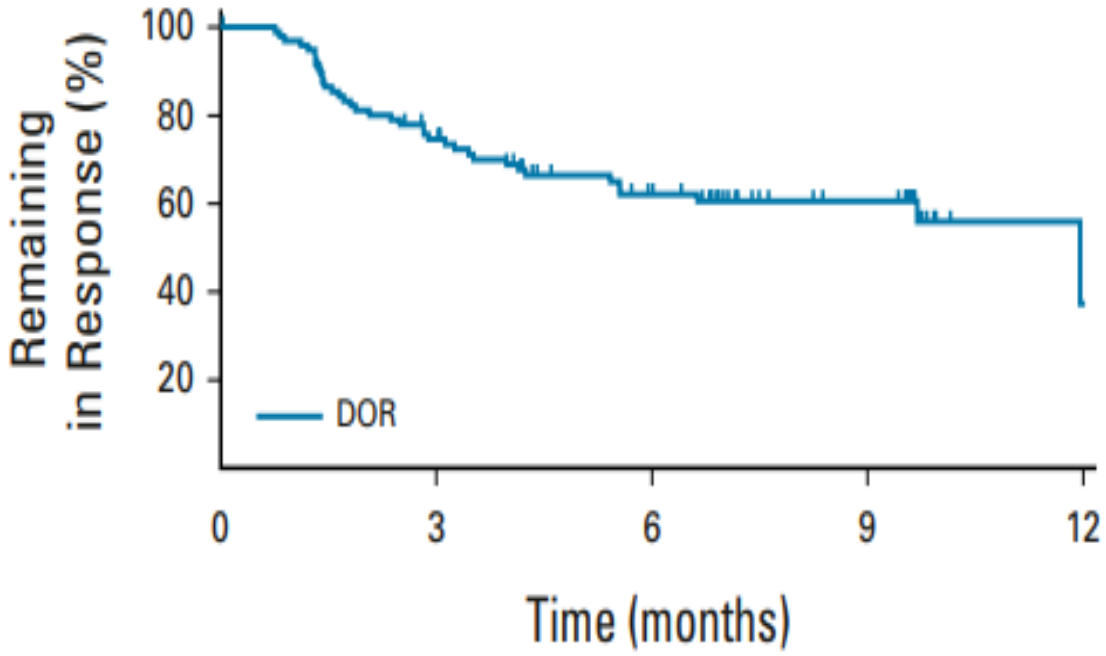
Dickinson MJ, et al. *N Engl J Med*. 2022;387(24):2220-2231.
Thieblemont C, et al. *J Clin Oncol*. 2023;41(12):2238-2247.
Bannerji R, et al. *Lancet Haematol*. 2022;9(5):e327-e339.

BISPECIFIC MONOTHERAPY DURATION OF RESPONSE IN R/R DLBCL

Glofitamab



Epcoritamab



Those who achieve CR may have long-term remission, those who don't do poorly

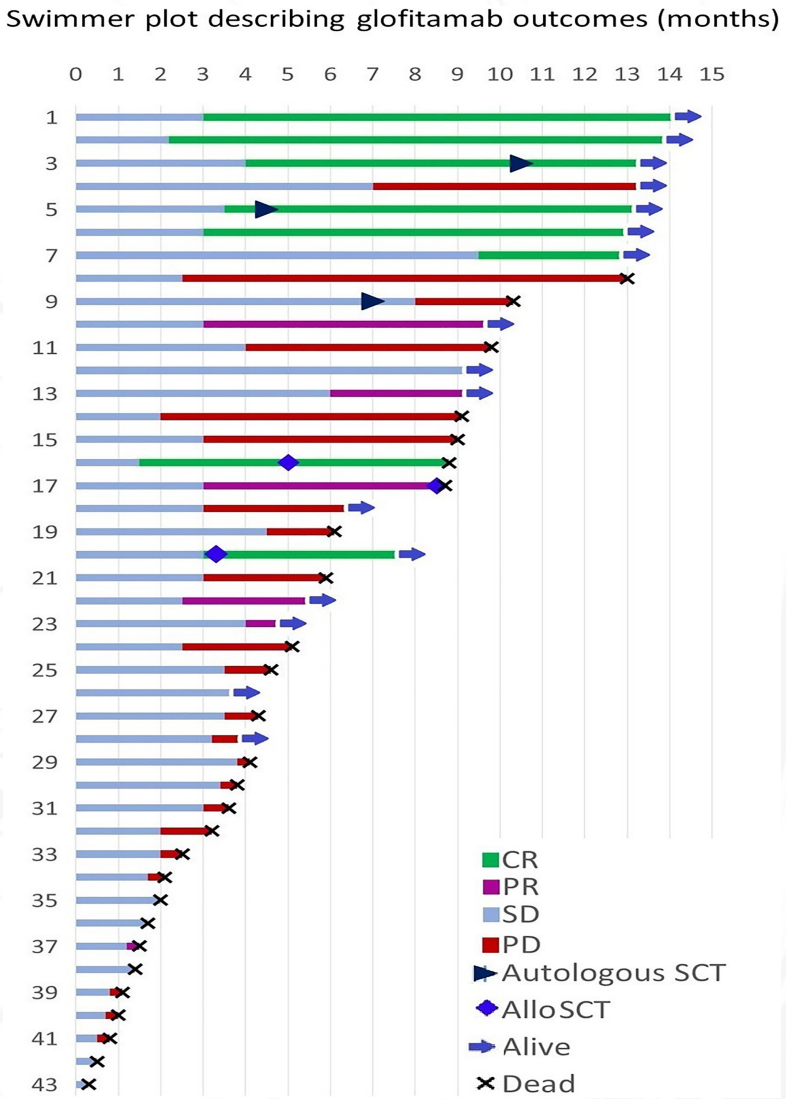
Dickinson MJ, NEJM 2022; 387:2220-2231
Thieblemont C, J Clin Oncol 2023; 41(12):2238-2247

SAFETY OF BISPECIFICS IN DLBCL

	Glofitamab	Epcoritamab	Odronextamab
CRS (All), %	63	50	53
CRS (≥ Grade 3), %	4	3	1
ICANS (All), %	8	6	3
ICANS (≥ Grade 3), %	3	1	1
Infection* (≥ Grade 3), %	15	15	23

*Opportunistic infections including PJP pneumonia and CMV reactiviation

EMERGING REAL-WORLD EFFICACY DATA



43 patients from 20 centers in Turkey

- ORR 37% (CR 21%)
- Median PFS 3.3 mo, OS 8.8 months
- Median DoR 6 months

Limited series so far, but in general, real-world outcomes inferior to what is reported in trials

Real-world data from US consortia coming soon

Birtas Atesoglu E, et al. Glofitamab in relapsed/refractory diffuse large B-cell lymphoma: Real-world data. *Hematol Oncol*. 2023;41(4):663-673.

WHAT'S NEXT FOR BISPECIFIC ANTIBODIES IN DLBCL?

- MANY ongoing studies in a variety of clinical scenarios

- 1st line therapy
  - Phase 3 studies of bispecifics in combination with CHOP-based regimens
  - Bispecific therapy for older/unfit adults (anthracycline inegligible)
  - Bispecific + DA-EPOCH for HGBCL and Burkitt

- R/R DLBCL
  - Bispecific + salvage chemo in transplant eligible patients
  - Bispecific ab in the peri-CAR-T setting
  - Bispecific-containing combinations for multiply relapsed disease

SELECTED BISPECIFIC TRIALS IN R/R DLBCL

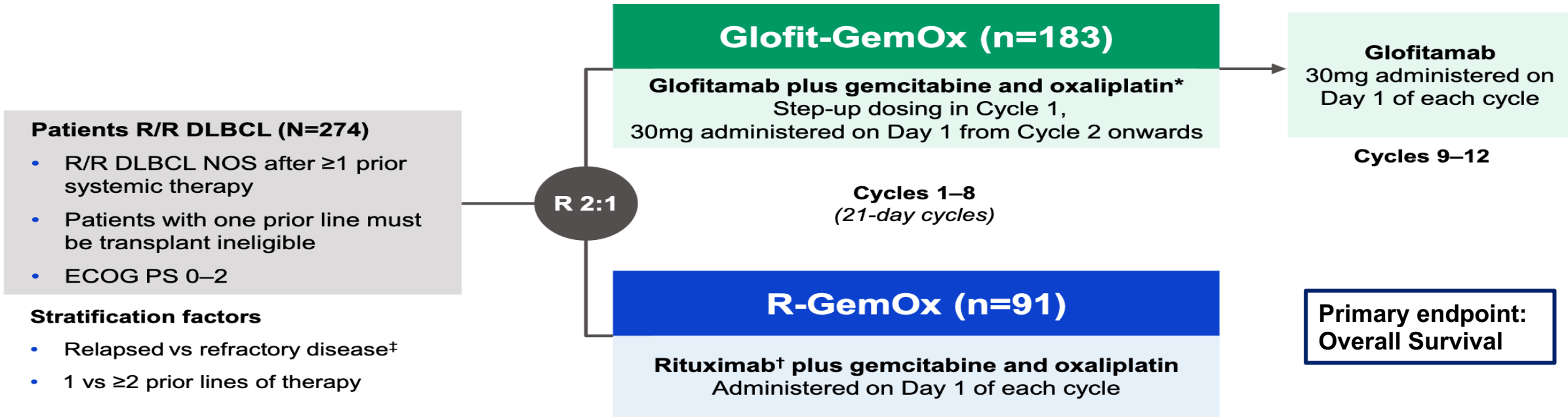
Phase I/II studies with bispecific antibodies in first-line tx for DLBCL

Drugs	NCT	N	Median age, y	ORR (CR), %
Mosun-CHOP	NCT03677141	40	65 (39-79)	82 (79)
Glofit-R-CHOP	NCT03467373	26	68 (26-84)	100 (89)
Epcor-R-CHOP	NCT04663347	24	65 (30-82)	100 (73)

Phase I/II study of epcoritamab combinations in R/R DLBCL (NCT04663347)

Drugs	N	Median age, y	Median prior tx	Median f/u, mo	ORR (CR), %
Epcor-R-DHAX	29	58 (28-75)	1 (1-3)	5.8 (1.5-11.4)	100 (86)
Epcor-GemOx	26	71 (47-87)	2 (1-13)	9 (1-15)	92 (60)

PHASE 3 DATA BEGIN TO EMERGE - STARGLO STUDY

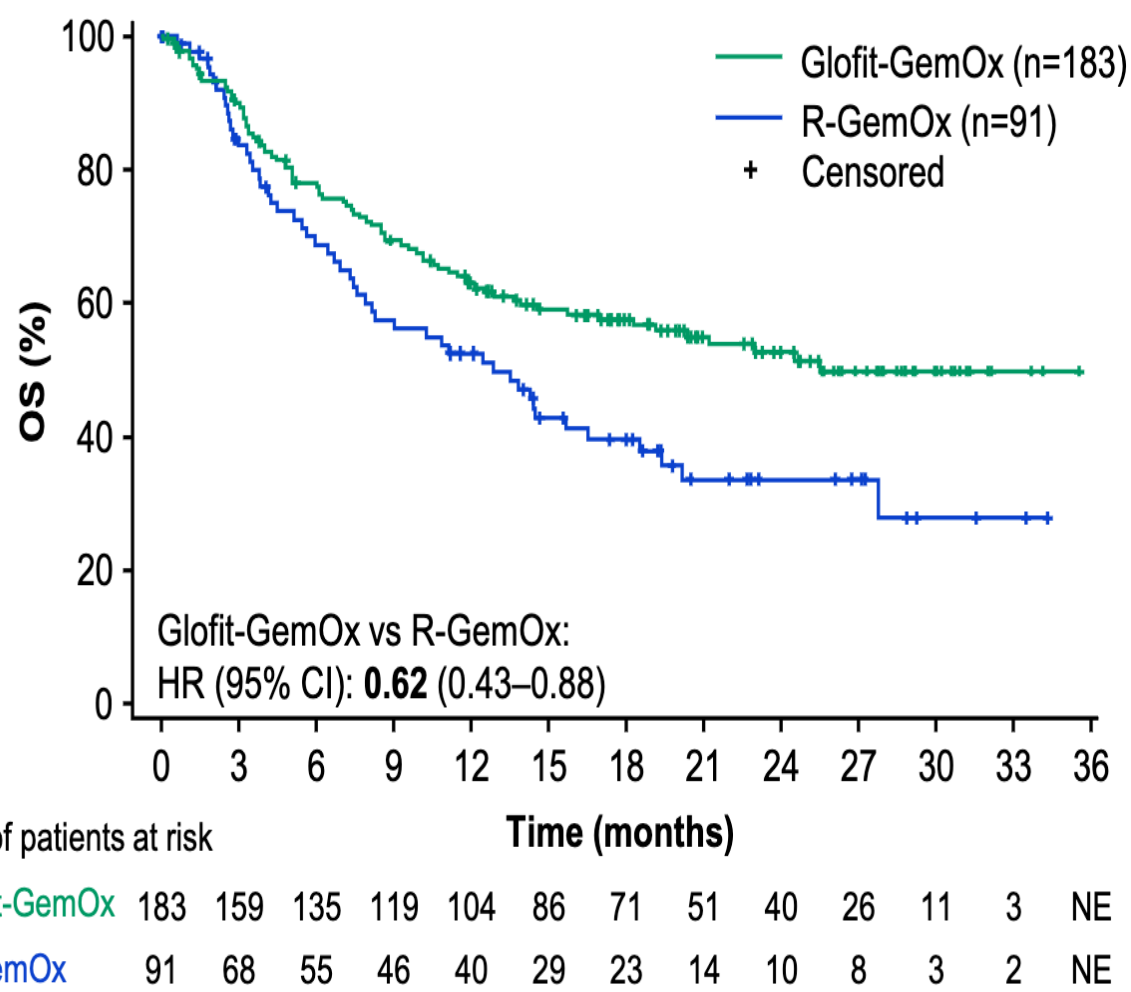


Enrolled mostly transplant ineligible patients
62% treated in 2nd line setting
10% ECOG PS of 2
~50% had primary refractory disease
8% had prior CAR-T therapy

Abramson JS, et al.2024 European Hematology Association Congress; June 13-16, 2024; Madrid, Spain. Abstract LB3438.

STARGLOW STUDY – PHASE 3 GLOFITAMAB-GEMOX VS. R-GEMOX

- Primary endpoint met – OS improved
  - 24-mo OS: 53% vs. 33%
- Secondary endpoints favor Glofit-GemOx:
  - CR rate: 58% vs. 25%
  - 12-mo PFS: 51% vs. 25%
- First Phase 3 study to demonstrate OS advantage with bispecific ab
- Implications for treatment sequencing?
  - For comparison, ZUMA-7 study 12-mo PFS 52% for patients who received 2L CAR-T



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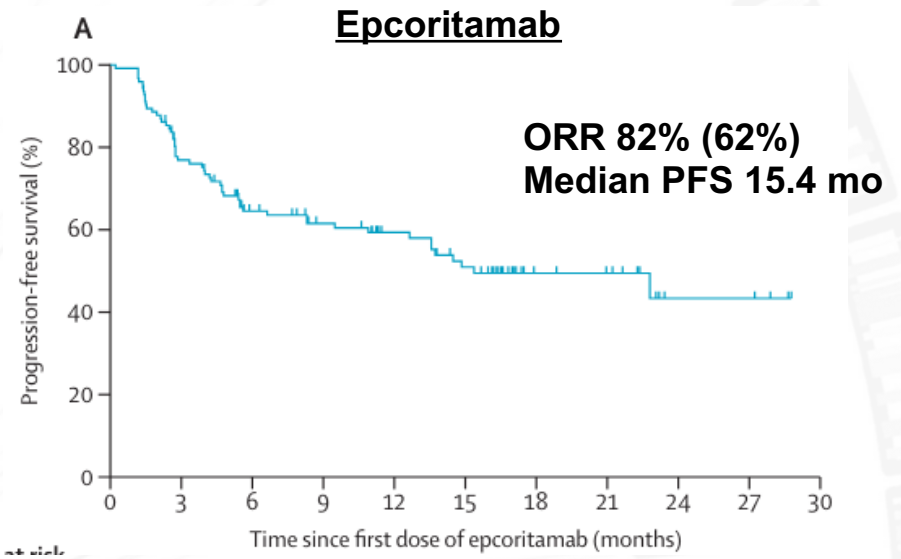
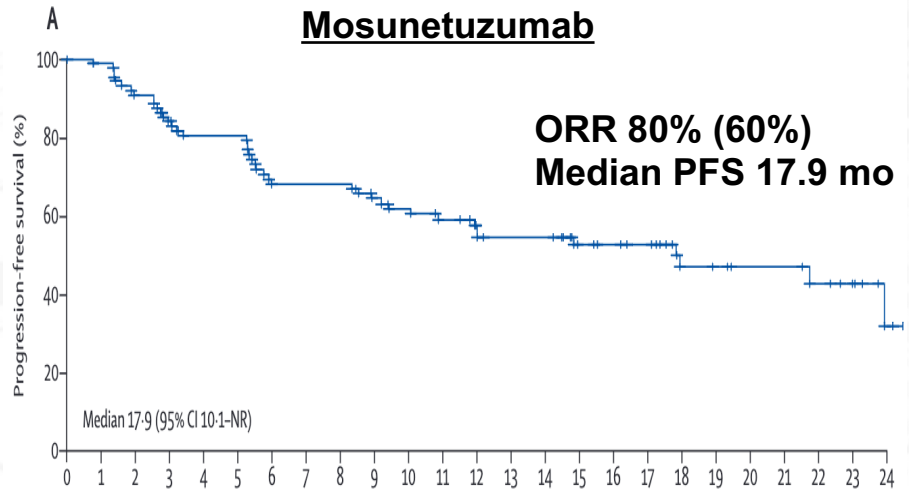
Ongoing studies of bispecific combinations in R/R DLBCL

Salvage therapy	NCT05852717	Epcoritamab + R-GDP → AutoHSCT or CAR-T
Peri-CAR T	NCT05633615	SWOG 2114: Mosunetuzumab, polatuzumab, or mosun+pola for patients with PR early after CAR-T
	NCT06071871	Pola + Obinutuzumab + glofitamab as a peri-CAR-T treatment strategy
	NCT06238648	Epcoritamab vs. observation for patients not in CR after CAR-T
	NCT06213311	Axi-cel and glofitamab as second line therapy for R/R DLBCL
Multiply relapsed disease or transplant/CAR-T ineligible	NCT04663347	Epcoritamab containing combinations for relapsed B-cell NHL
	NCT04970901	LOTIS-7: Loncastuximab containing combinations for relapsed DLBCL
	NCT04408638	Glofitamab + GemOx

MOSUNETUZUMAB FOR FOLLICULAR LYMPHOMA

- Mosunetuzumab and epcoritamab are both FDA-approved for FL after ≥ 2 lines of therapy
- Ongoing efforts to combine bispecifics with other agents like lenalidomide
  - CELESTIMO study, NCT04712097
  - EPCORE FL-1, NCT05409066
- Bispecific or CAR-T for 3rd line therapy for FL?

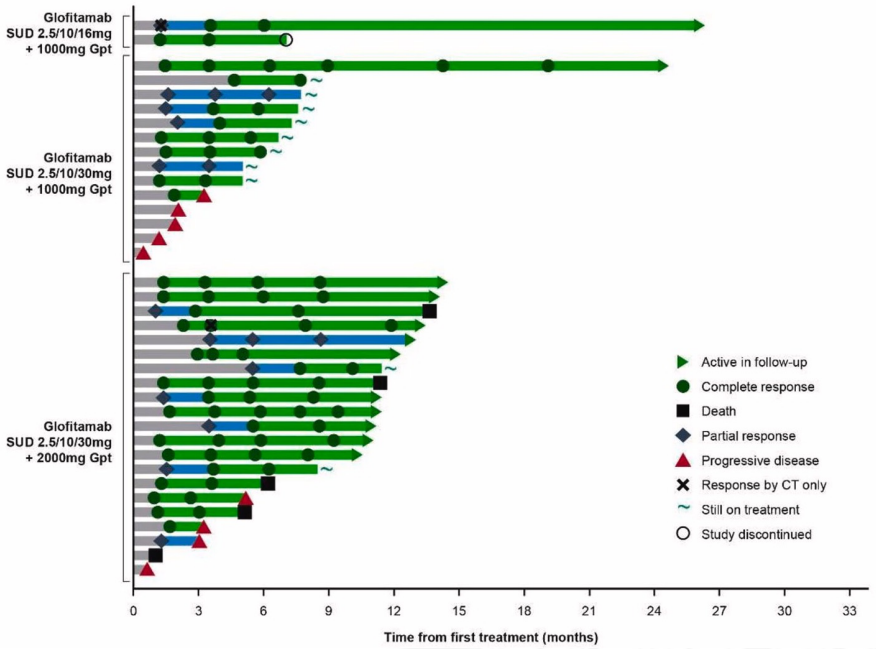




Linton KM, et al. Lancet Haematol. 2024 Jun;13:S2352-3026(24):00166-2.
Budde LE, et al. Lancet Oncol. 2022 Aug;23(8):1055-1065.

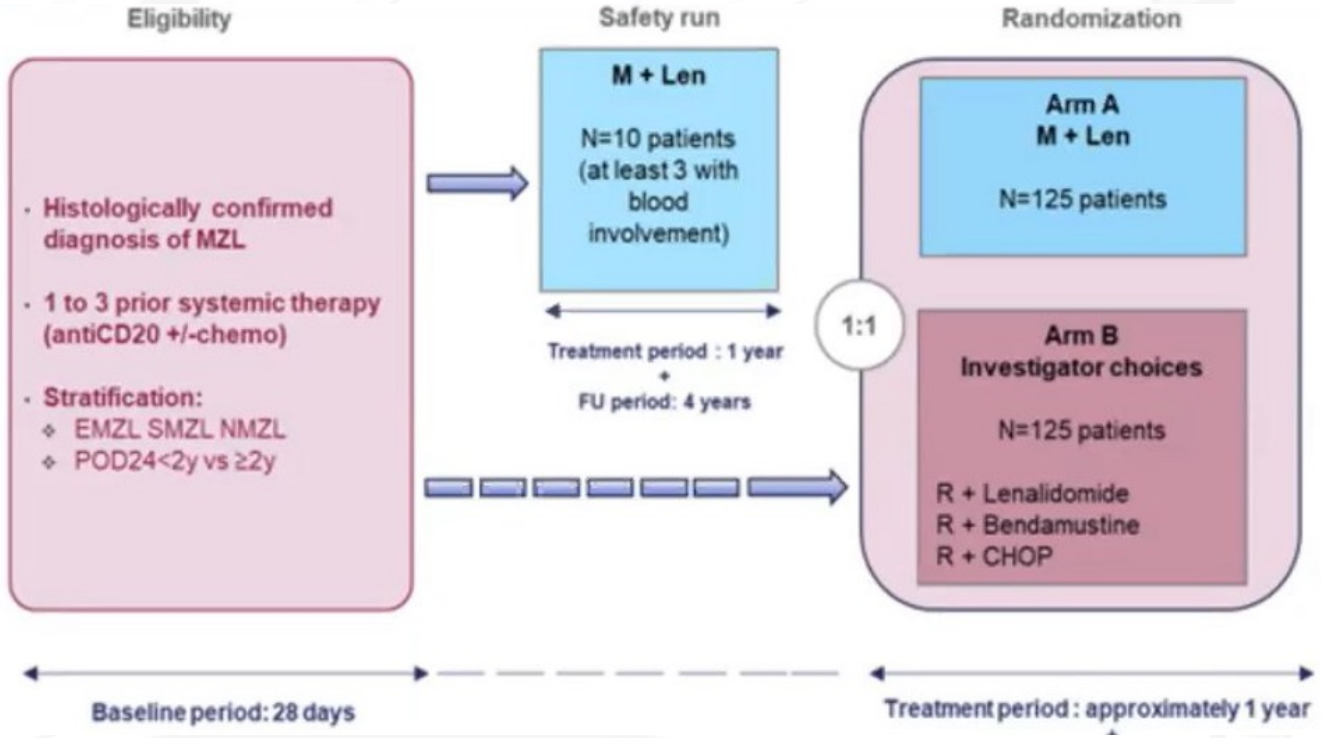
BISPECIFIC ANTIBODIES FOR OTHER B-CELL LYMPHOMA SUBTYPES

Glofitamab in R/R Mantle Cell Lymphoma



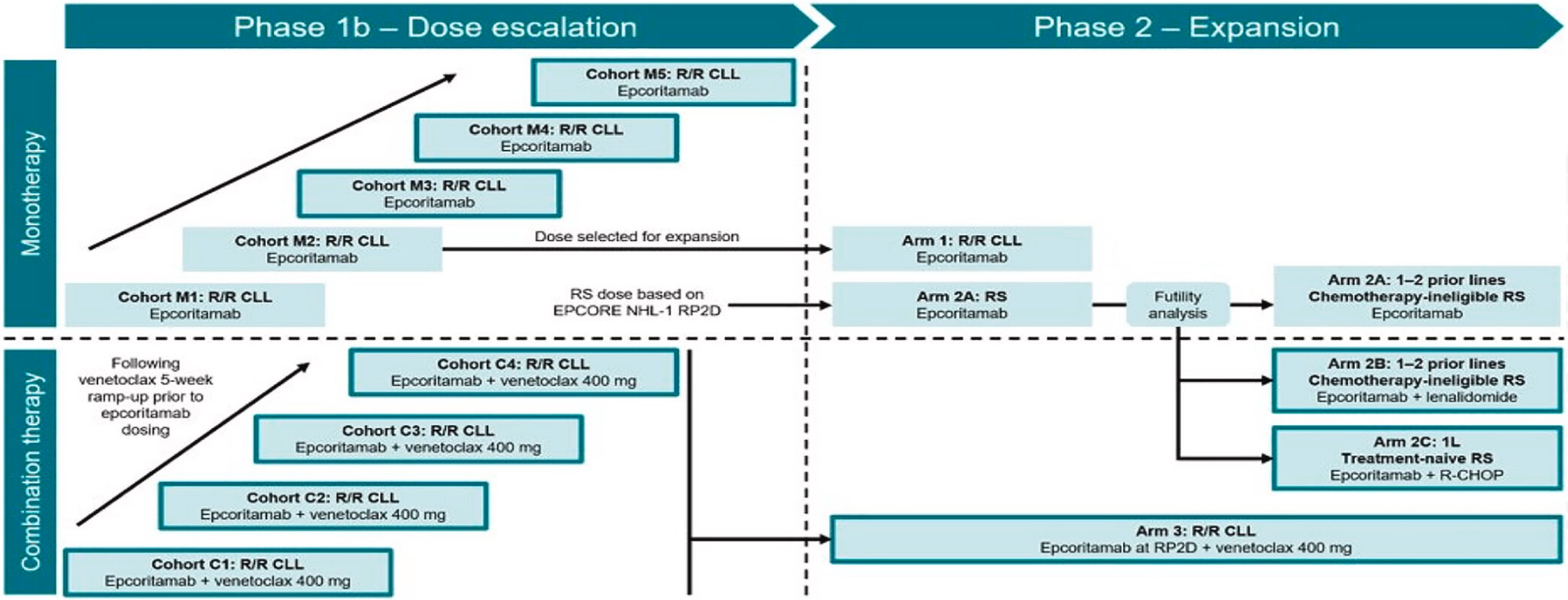
Phillips TJ, et al. Blood (2022) 140 (Supplement 1): 178-180
NCT03075696

Mosunetuzumab + Len vs investigator's choice in R/R MZL



LYSA, FIL, GLA collaboration
NCT06006117

Epcoritamab +/- venetoclax in CLL and Richter's Syndrome



EPCORE-CLL-1 Trial
NCT04623541

TAKE HOME MESSAGE

- Some patients have an excellent response to bispecific monotherapy, but there is much room for improvement
- Ongoing efforts to combine bispecific antibodies with other agents, move to earlier lines of therapy, and study in other lymphoma subtypes
- Bispecific antibodies are generally easier to administer than CAR-T
  - More appealing to administer in community setting
  - Careful consideration of staff training and side effect management is critical

Thank you!