Mass General Brigham
Mass General Cancer Center

CAR T-cells or Bispecifics Debate: *pro CAR T-cells*

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Disclosures for Jeremy Abramson

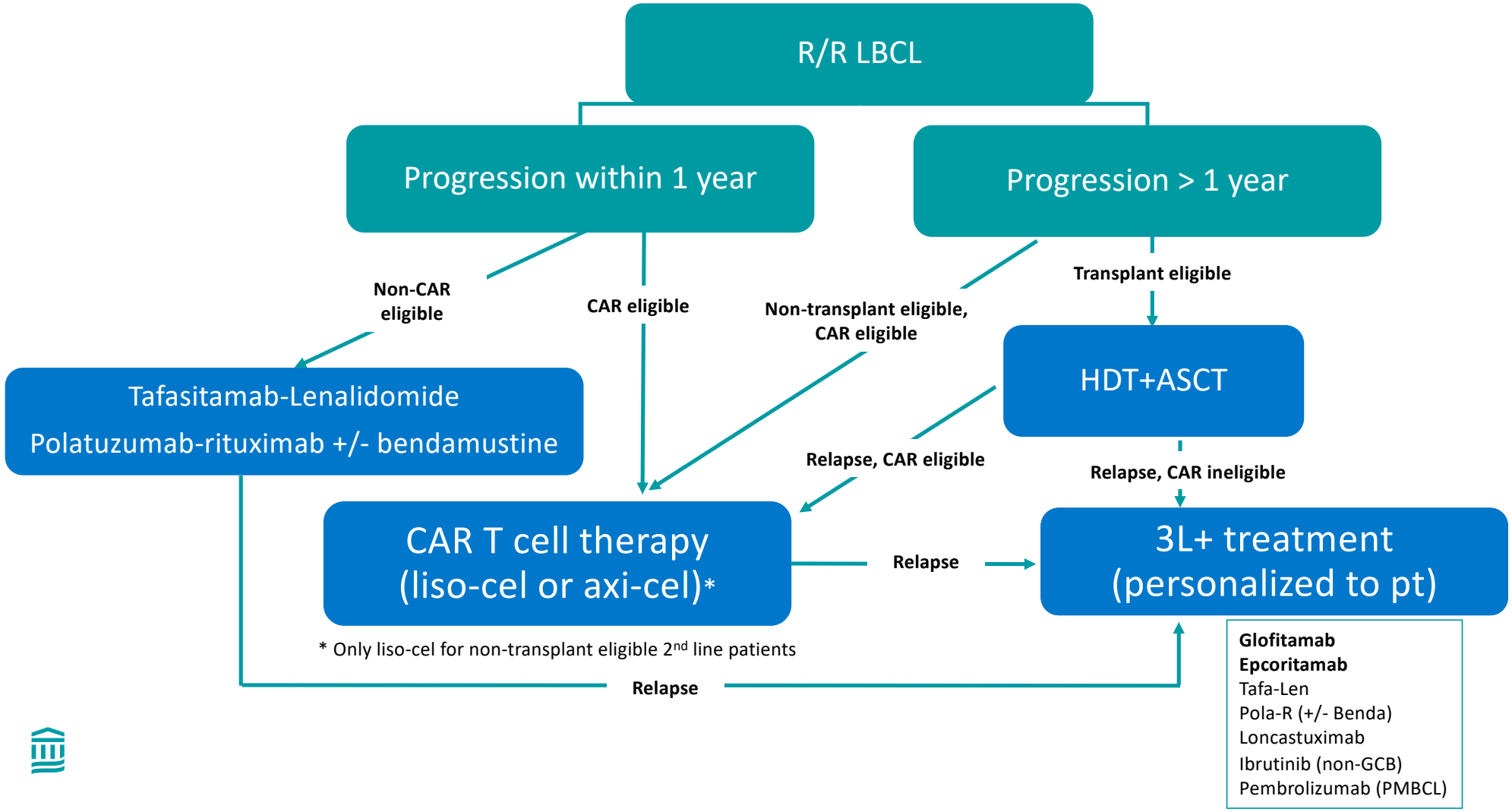
Consulting for AbbVie, Astra-Zeneca, BeiGene, Bristol Myers Squibb, Caribou Biosciences, Cellectar, Genentech, Gilead, Incyte, Interius, Janssen, Lilly, Novartis, Roche, Takeda

A few general observations (caveats)

- CAR T-cells and bispecifics currently “compete” in large B-cell lymphomas and follicular lymphoma, which have distinct considerations
- Deciding to use CAR vs bispecifics is difficult to argue in abstract since numerous patient- and disease-specific variables must be considered in selecting an optimal treatment for a given patient
- A debate is only relevant when patients have uniform access to both drug classes, which is currently not the case in most of the world

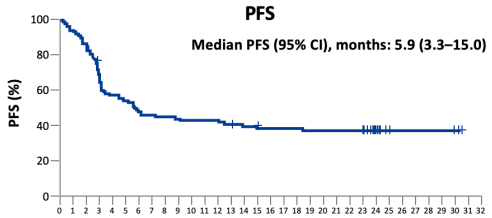
Large B-cell lymphomas

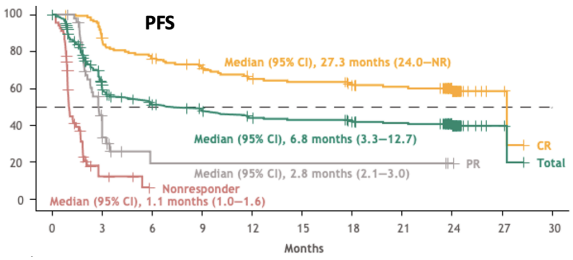
CAR and Bispecifics should not be competing in most patients

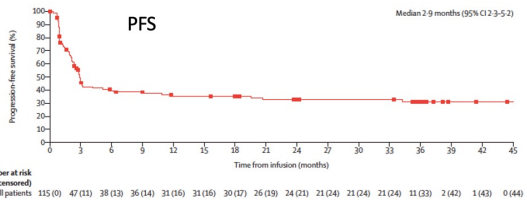


CAR T-cells can CURE chemotherapy-refractory LBCL in the 3rd line+ or later setting

	Axicabtagene Ciloleucel ZUMA-1	Lisocabtagene Maraleucel TRANSCEND	Tisagenlecleucel JULIET
Construct	antiCD19-CD28tm-**CD28**-CD3z	antiCD19-CD28tm-**41BB**-CD3z	antiCD19-CD8αtm-**41BB**-CD3z
Med Age, y (range)	58 (23–76)	63 (18–86)	56 (22–76)
ORR/CRR % (IRC)	74/54	73/53	52/40
Median PFS, mos	5.9	6.8	2.9
PFS (2y) %	42	41	30
Median OS, mos	25.8	27.3	11.1
CRS (Any/severe) %	93/13	42/2	58/22 *different grading scale
NT (Any/severe) %	64/28	30/10	21/12
References	Neelapu, et al. NEJM 2017 Locke, et al. Lancet Onc 2019	Abramson, et al. Lancet 2020 Abramson, et al. Blood 2024	Schuster, et al. NEJM 2019 Schuster, et al. Lancet Onc. 2021





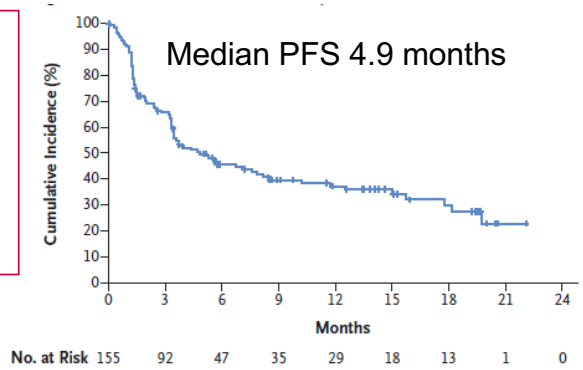


Anti-CD20/CD3 Bispecific antibodies for 3rd line+ LBCL

Glofitamab

Baseline Characteristics	N=154
Median age (range)	66 (21-90)
Median prior tx (range)	3 (2-7)
Prior ASCT	28 (18%)
Prior CAR	51 (33%)
Refractory to last tx	132 (86%)

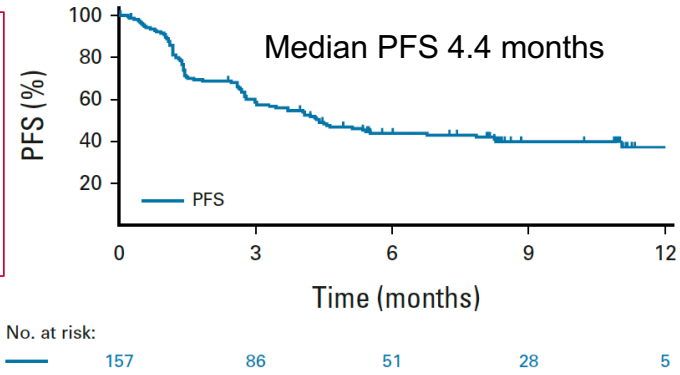
Best response
ORR: 52%
CRR: 39%
Median DoR: 18 mo
Median DoCR: NR



Epcoritamab

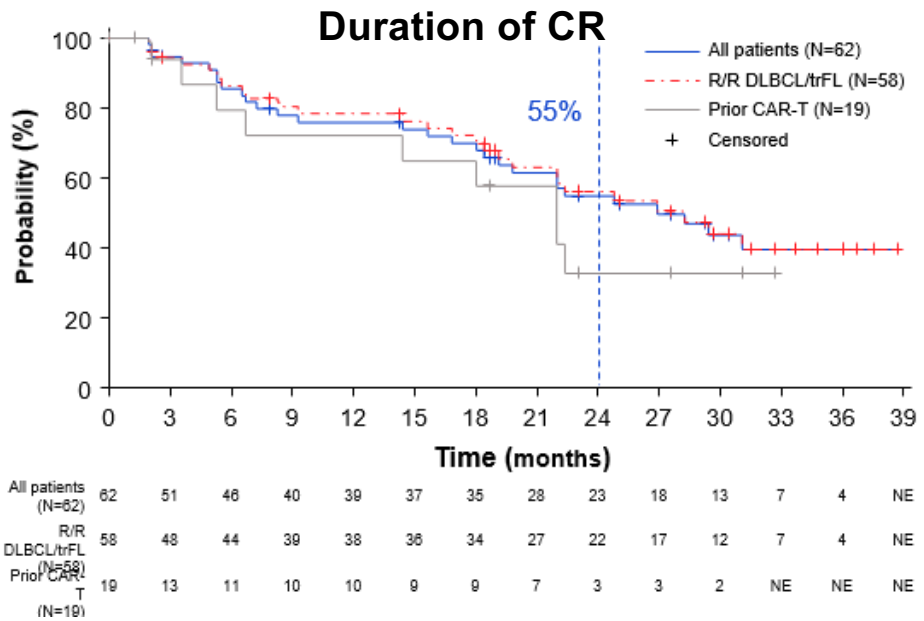
Baseline Characteristics	N=157
Median age (range)	64 (20-83)
Median prior tx (range)	3 (2-11)
Prior ASCT	31 (20%)
Prior CAR	61 (39%)
Refractory to last tx	130 (83%)

Best response
ORR: 63%
CRR: 39%
Median DoR: 12 mo
Median DoCR: NR



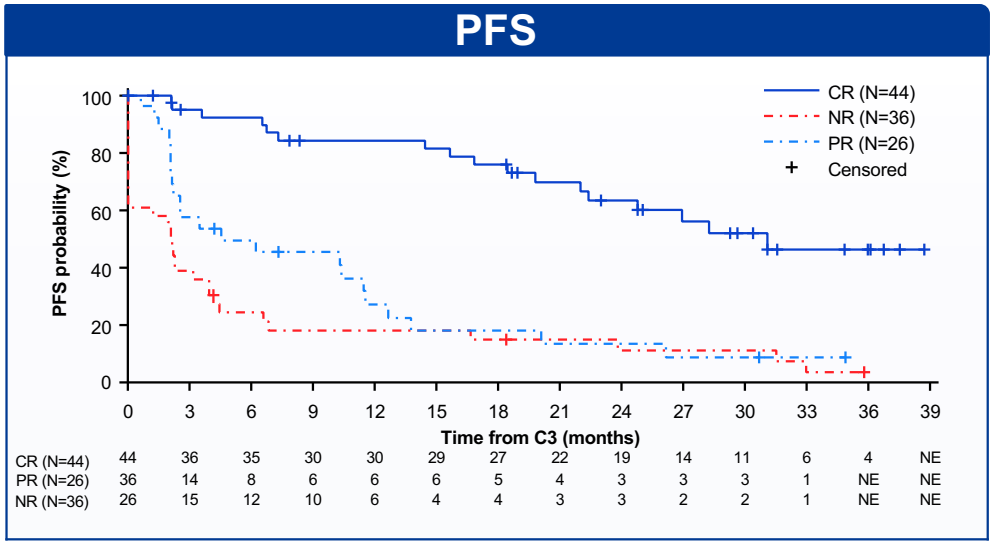
Dickinson, et al. NEJM 2022; Thieblemont, et al. JCO 2022

Glofitamab: No plateau on DOCR or PFS curves



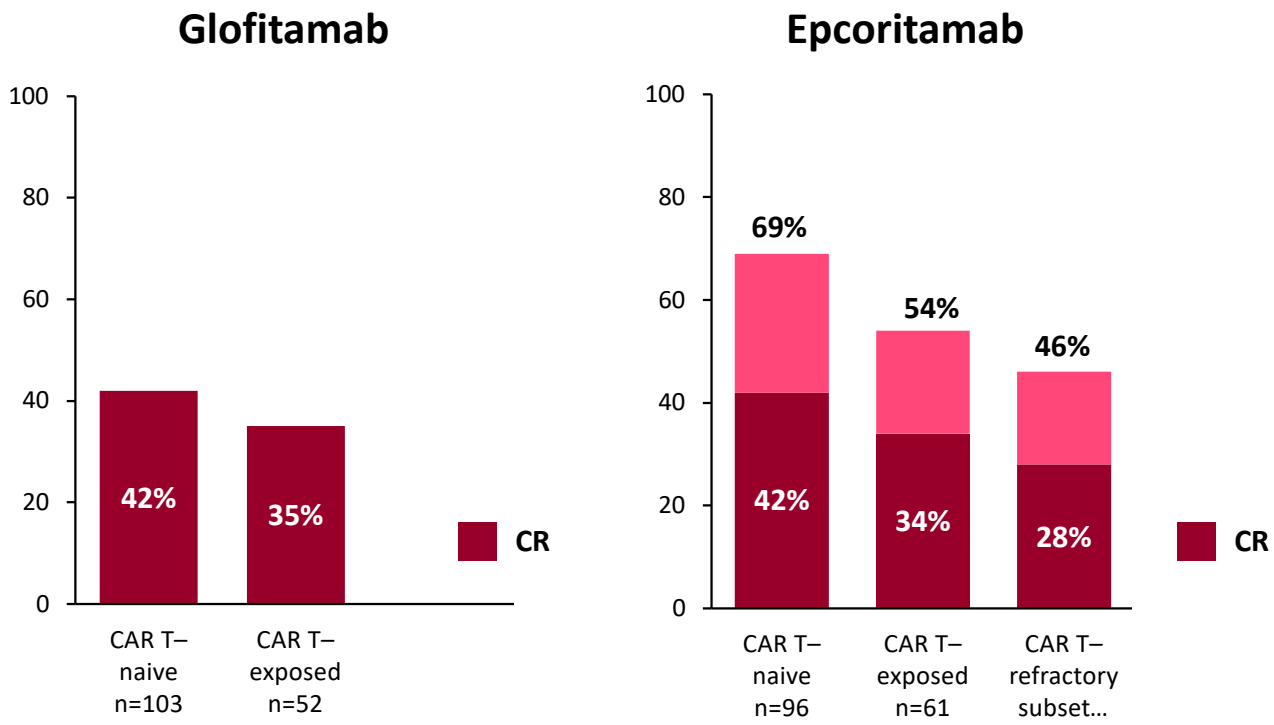
32 months median follow-up

3 month landmark analysis



Hutchings, et al. Proc ASH 2023

Bispecific antibodies remain effective in CAR T exposed patients



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.

Let's summarize the data

	Axi-cel	Liso-cel	Glofitamab	Epcoritamab
N	101	269	154	157
Median prior lines	3	3	3	3
Median follow-up	60 m	24 m	13 m	20 m
Overall response	74%	73%	52%	63%
Complete response	54%	53%	39%	39%
Median PFS	5.9 m	6.8 m	4.9 m	4.4 m
PFS at 2 years	42%	41%	N/A	N/A
Median DOR	11.1 m	23.1 m	12 m	12 m
Median DOCR	62 m	NR	NR	NR
	Locke, et al. Lancet Onc 2019 Neelapu, et al. Blood 2023	Abramson, et al. Proc ASH 2021	Dickinson, et al. NEJM 2022, Hutchings, et al. Proc ASH 2022	Thieblemont, et al. JCO 2023

CR rates and PFS may be better with CAR T-cell therapy, and follow-up with bispecifics is too brief to know if patients are truly cured

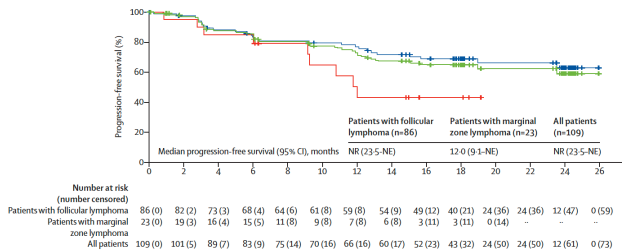
CAR T-cells should be preferred to bispecific antibodies in DLBCL

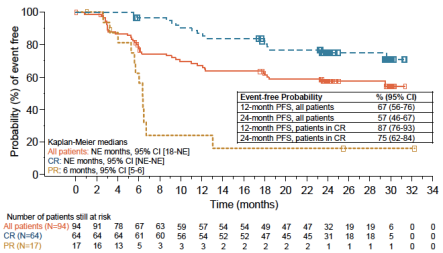
- CAR T-cells are proven to be curative for DLBCL in the 3rd line or later setting with over 5 years of follow-up.
- I am bispecifics may cure some patients, but it is too early to know
- Bispecific antibodies have PROVEN EFFICACY in the post CAR T-cell setting
- CAR T-cells still have limited availability, so bispecifics will certainly be preferred 3rd line therapy if CAR is not accessible
- Ultimately, CAR and bispecifics will not be in direct competition
  - CAR will be optimal 2nd line therapy for most patients with relapsed/refractory DLBCL, for whom bispecifics will be preferred 3rd line treatment if needed
  - I predict bispecifics will leapfrog 2nd line and ultimately be added to frontline therapy

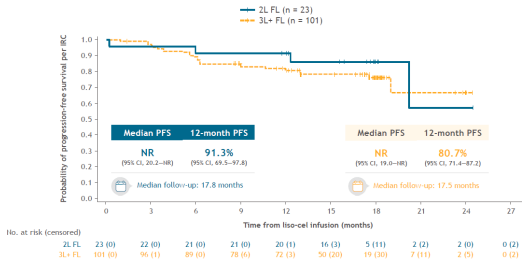
Follicular lymphoma

Three CAR T-cell products for multiple relapsed/ refractory 3rd line + follicular lymphoma

	Axicabtagene Ciloleucel ZUMA-5	Tisagenlecleucel ELARA	Lisocabtagene Maraleucel TRANSCEND-FL
n	124	97	107
Median # prior lines	3	4	3
Chemorefractory	68%	78%	67%
POD24	55%	60%	54%
CR rate	**79%**	**68%**	**94%**
Median PFS, m	NR	NR	NR
PFS	65% at 18m	57% at 24m	91% at 12m
CRS (Any/severe) %	82/7	49/0	58/1
NT (Any/severe) %	59/19	4/1	15/2
References	Jacobson, et al. Lancet Onc 2022	Dreyling, at al. Proc ASH 2022 Fowler, et al. Nat Med 2022.	Morschhauser, et al. Proc ICML 2023 Morschhauser, et al. Proc ASH 2023



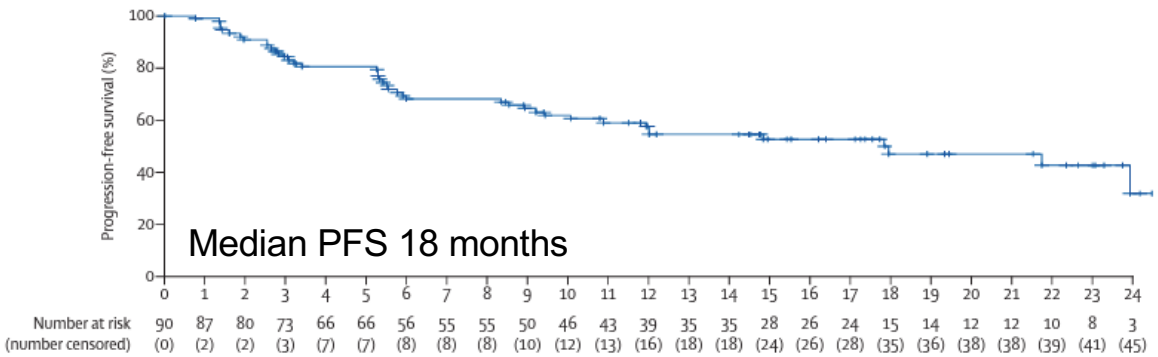




Mosunetuzumab IV in relapsed/refractory follicular lymphoma

Patients in CR at cycle 8 discontinued tx, pts in less than CR completed 9 additional cycles

Characteristic	n=90
Median age (range)	60 (53-67)
Median prior tx (range)	3 (IQR 2-4)
Refractory to last line of tx	69%
POD24	52%
Bulky disease	34%
FLIPI high (≥3)	45%
Double refractory	53%



Best response	
Overall response	**80%**
Complete response	**60%**

AEs of special interest	
CRS, any grade Grade 3-4	44% 2%
Neurotoxicity, any grade Grade 3-4	5.5% 0%

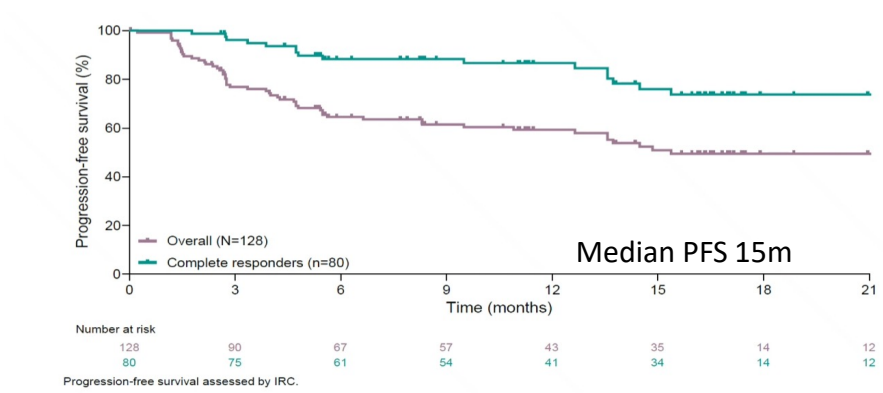
Budde, et al. Lancet Onc 2022

Not yet approved: Epcoritamab and Odronextamab

Epcoritamab

Baseline characteristics	N=128
Median age	65
Median prior lines	3 (2-9)
Double refractory	70%
Refractory to last line	69%
POD24	42%

Best response	N=128
Overall response	**82%**
Complete response	**63%**

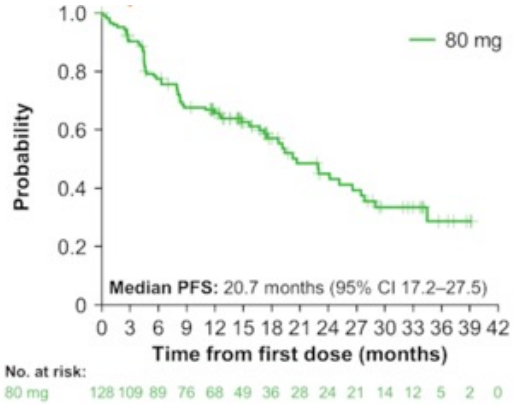


Linton K, et al. Proc ASH 2023

Odronextamab

Baseline characteristics	N=128
Median age	61 (22-84)
Median prior lines	3 (2-13)
FLIPI high risk	58%
Refractory to last line	72%
POD24	49%

Best Response	N=121
Overall response	**81%**
Complete response	**73%**

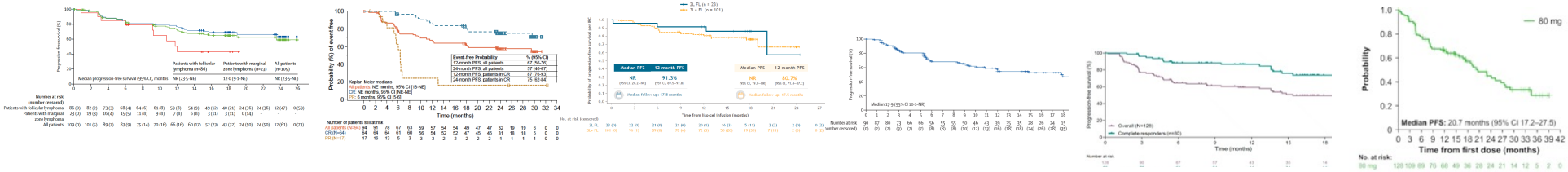


Villasboas, et al. Proc ASH 2023

Let's summarize the data

	Axi-cel	Tisa-cel	Liso-cel	Mosun	Epcor	Odro
n	124	97	107	90	128	128
Median prior lines	3	4	3	3	3	3
Chemorefractory	68%	78%	67%	69%	69%	71%
POD24	55%	60%	54%	52%	42%	48%
CR rate	**79%**	**68%**	**94%**	**60%**	**63%**	**73%**
Median PFS	NR 65% at 18m	NR 57% at 24m	NR 91% at 12m	18m	15m	21m
References	Jacobson, et al. Lancet Onc 2022	Dreyling, at al. Proc ASH 2022 Fowler, et al. Nat Med 2022.	Morschhauser, et al. Proc ICML 2023 Morschhauser, et al. Proc ASH 2023	Budde, et al. Lancet Onc 2022 Sehn, et al. Proc EHA 2023	Linton, et al. Proc ASH 2023	Villasboas, et al. Proc ASH 2023

PFS

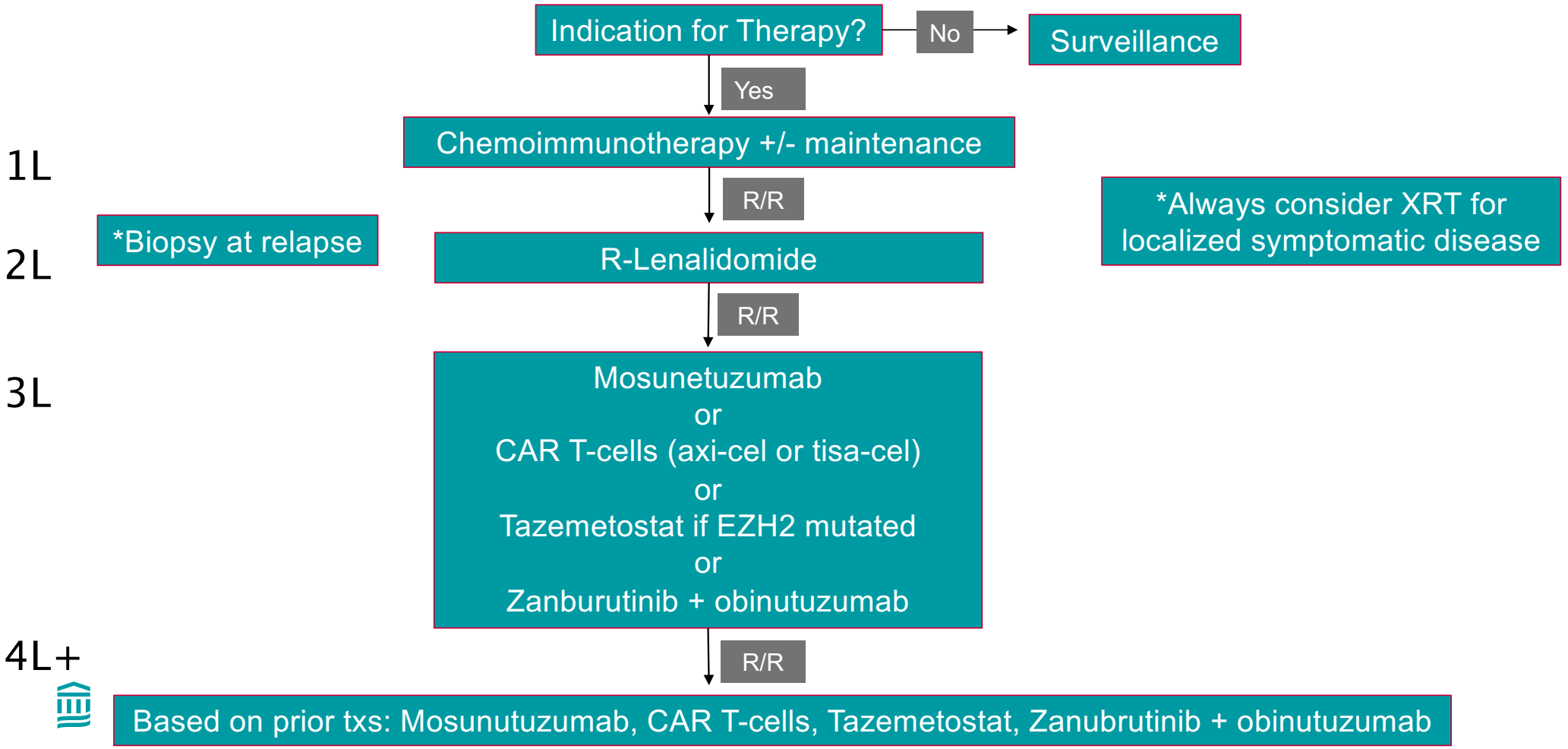


Cure is not definitively being achieved with either class

Considerations in choosing between CAR T-cells and bispecifics in FL

CAR T-cells	Bispecific antibodies
Excellent efficacy, needs longer follow up	Excellent efficacy, needs longer follow up
Requires 3-4 weeks of manufacturing	Off the shelf
Logistically more complex	Logistically less complex
“One and done”	8-17 cycles (mosun) or continuous (epco, odro)
Needs lymphodepleting chemo	No lymphodepleting chemo
Higher risk of CRS and neurotoxicity (tisa-cel and liso-cel better than axi-cel), and cytopenias	Lower risk of CRS, neurotoxicity, and cytopenias
Usually inpatient	Usually outpatient

My usual treatment paradigm for high tumor burden FL (non-localized)



Thank you for your attention!

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