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Current and Potential Role of CAR T-Cell Therapy for Patients with Non-Hodgkin Lymphoma

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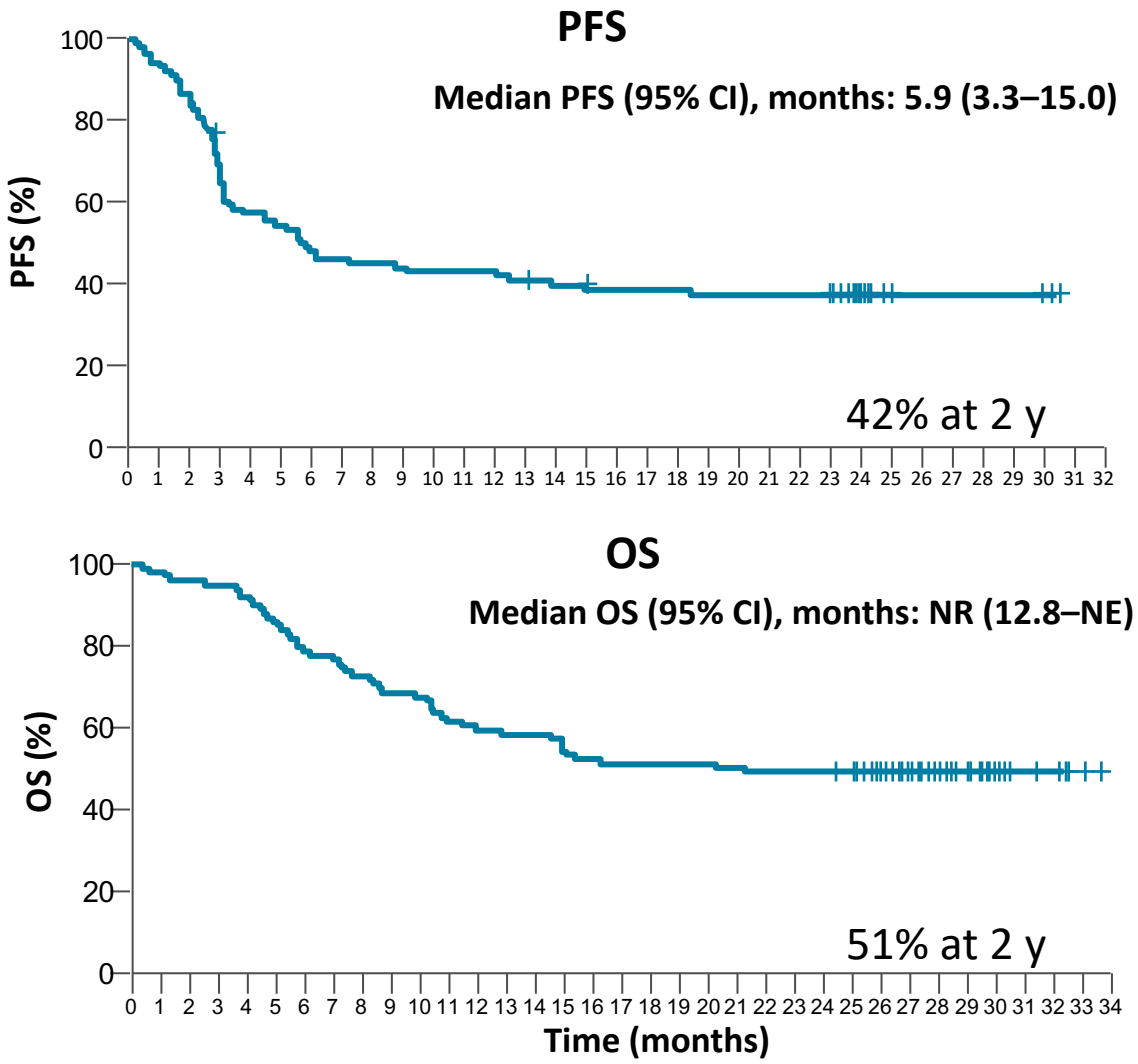
Four Major anti-CD19 CAR T-cell Products for B-cell NHL

	Axicabtagene Ciloleucel	Tisagenlecleucel	Lisocabtagene Maraleucel	Brexucabtagene Autoleucel
Construct	antiCD19-**CD28**-CD3z	antiCD19-**41BB**-CD3z	antiCD19-**41BB**-CD3z	antiCD19-**CD28**-CD3z
Vector	Retrovirus	Lentivirus	Lentivirus	Retrovirus
T-cell manufacturing	Bulk	Bulk	Defined doses CD4, CD8	Bulk
Dose	2×10^6/kg (max 2×10^8)	0.6 to 6.0 $\times 10^8$	1.0 $\times 10^8$	2×10^6/kg (max 2×10^8)
Lymphodepletion	Flu/Cy 500/30 x 3d	Flu/Cy 250/25 x 3d, or Benda 90 x 2d	Flu/Cy 300/30 x 3d	Flu/Cy 500/30 x 3d
Approval status	FDA/EMA approved for DLBCL, high grade B-cell lymphoma, transformed FL, PMBCL	FDA/EMA approved for pediatric B-ALL, DLBCL, high grade B-cell lymphoma, transformed FL	FDA approved for DLBCL, high grade B-cell lymphoma, transformed iNHL, PMBCL, grade 3B FL	FDA/EMA approved for mantle cell lymphoma and B-ALL

ZUMA-1: PFS and OS of patients with R/R DLBCL receiving axicabtagene ciloleucel

Characteristics	Phase 1 and 2 (N = 108)
Median age (range), years	58 (23–76)
Age ≥ 65 years, n (%)	27 (25)
≥ 3 prior therapies, n (%)	76 (70)
Refractory (no response to prior tx or relapse <1y from ASCT)	108 (100%)
Refractory to 2nd- or later-line therapy, n (%)	80 (74)
Best response as PD to last therapy, n (%)	70 (65)
Relapse post ASCT, n (%)	25 (23)

ORR: **83%** [74% by IRC]
CR: **58%** [54% by IRC]



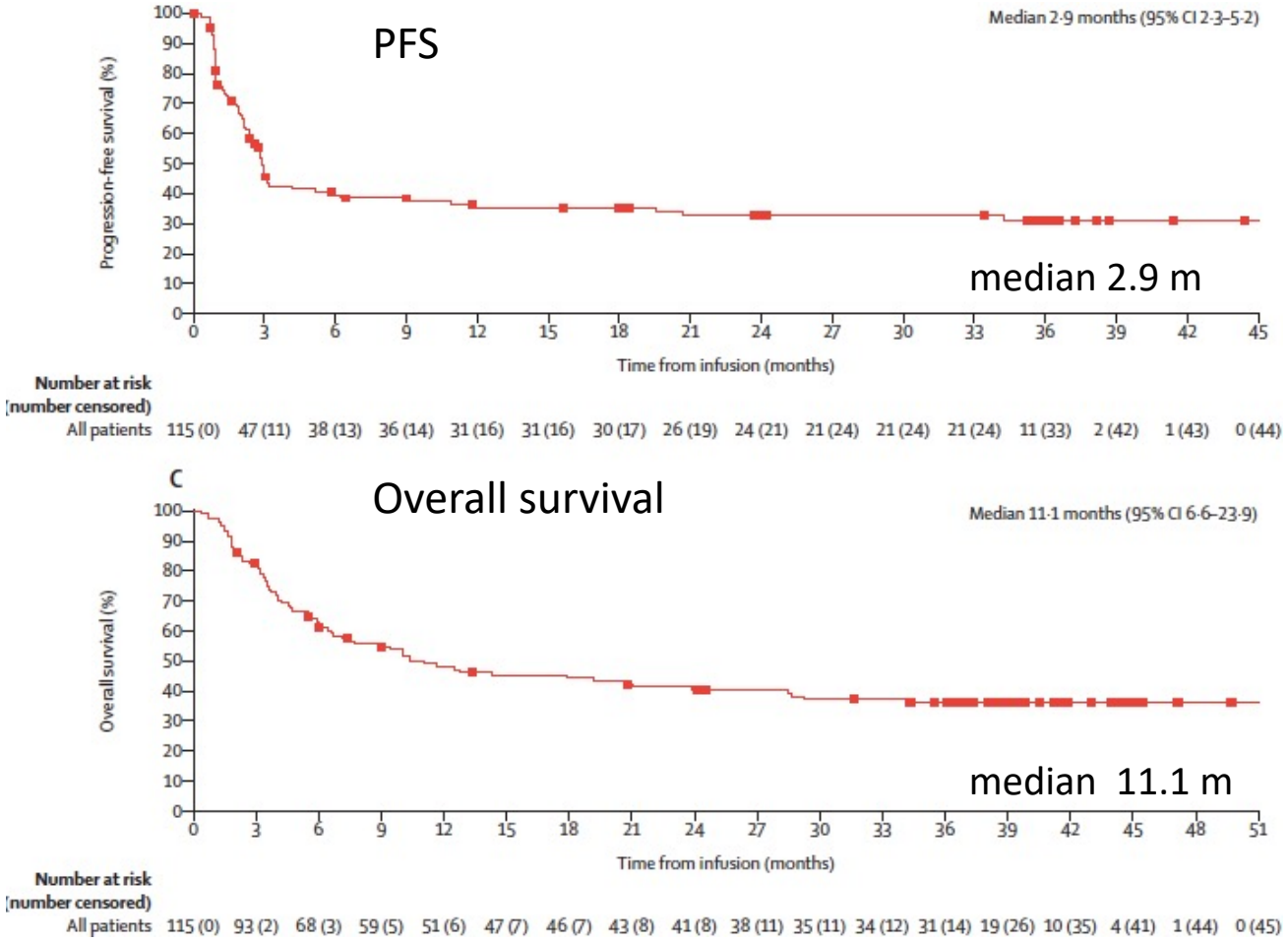
Locke FL, et al. Lancet Oncol. 2019;20:31-42.

JULIET: PFS and OS of patients with R/R DLBCL receiving tisagenlecleucel

Characteristics	Patients (N = 111)
Median age (range), years	56 (22–76)
Double-/triple-hit lymphoma, %	27
Number of prior lines of therapy, %	
2	44
3	31
4–6	21
Refractory to last therapy, %	55
Prior ASCT, %	49

ORR: 52%

CRR: 40%



Schuster SJ, et al. N Engl J Med. 2019;380:45-56.

Schuster, et al. Lancet Onc. 2021

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TRANSCEND-NHL-001 trial: liso-cel in multiply R/R aggressive B-NHL

Characteristic*	Patients (N = 269)
Age, median (range), years	63 (18–86)
Double- / triple-hit lymphoma, n (%)	36 (13)
CNS involvement, n (%)	7 (3)
Median prior lines, n (range)	3 (1–8)
Chemo-refractory, n (range)	181 (67)
Prior HSCT, n (%)	94 (35)

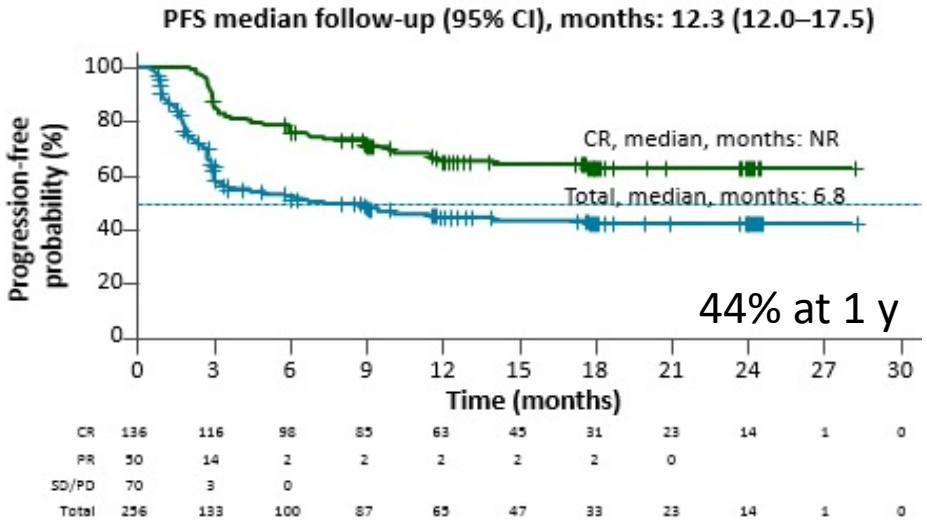
*Only CAR T-cell pivotal trial to include: secondary CNS DLBCL; prior allo SCT; transformed non-follicular iNHL; grade 3B FL; no minimal ALC, ANC, Hgb or platelets; moderate renal or cardiac dysfunction

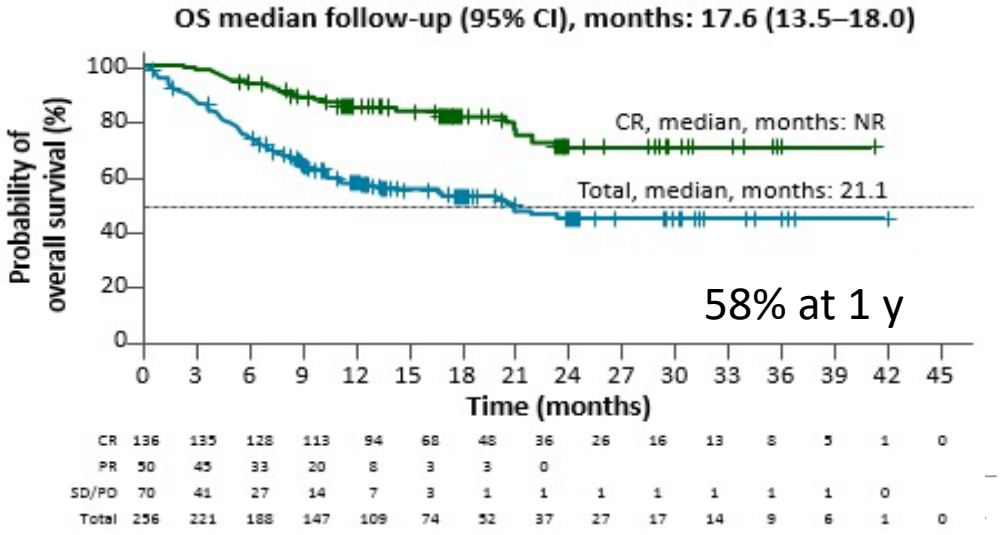
ORR: 73%

CRR: 53%

ASH 2021: 2 year DOR 49.5%, PFS 40.6%, OS 50.5%

Abramson, et al. Abstract 2840





Abramson JS, et al. Lancet 2020

Toxicity of 3 Major CAR T-cell Products for relapsed/refractory DLBCL

	Axicabtagene Ciloleucel	Tisagenlecleucel	Lisocabtagene Maraleucel
Construct	antiCD19-**CD28**-CD3z	antiCD19-**41BB**-CD3z	antiCD19-**41BB**-CD3z
n	101	111	269
Any CRS Median time to onset	93% 2 days	58% 3 days	42% 5 days
≥ Gr 3 CRS†	11%	23%	2%
Any neurotoxicity	64%	21%	30%
≥ Gr 3 neurotoxicity	32%	12%	10%
Tocilizumab	43%	15%	20%
Steroid use	27%	11%	21%
	Locke, et al. Lancet Onc 2018	Schuster, et al. NEJM 2018	Abramson, et al. The Lancet 2020

* Caveats in cross trial comparisons: Different eligibility criteria, phase of study, dose levels

†CRS toxicity grading scales differ across studies. Axi-Cel and Liso-cel used Lee criteria. Tisa-cel used Penn criteria

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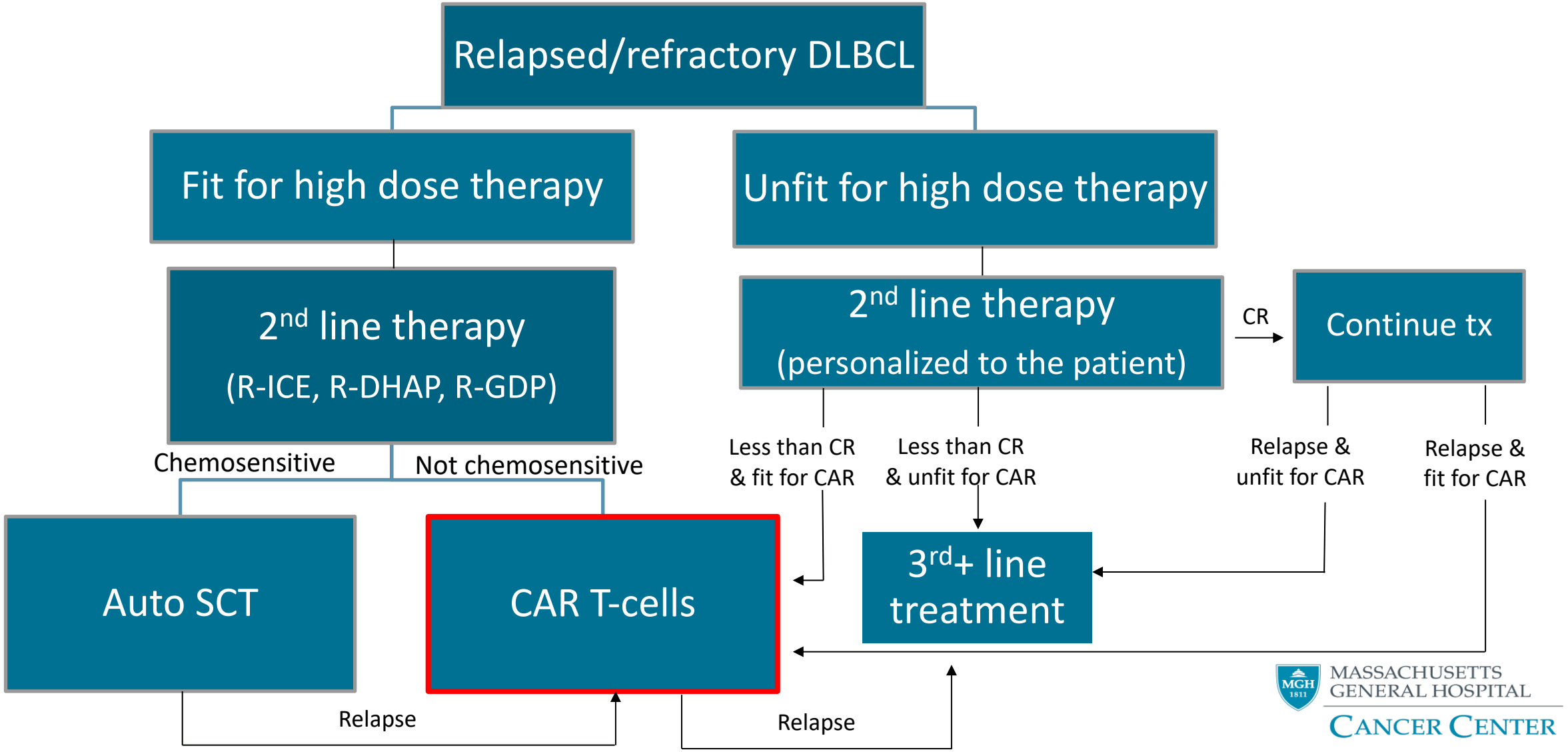
Algorithm for managing relapsed DLBCL



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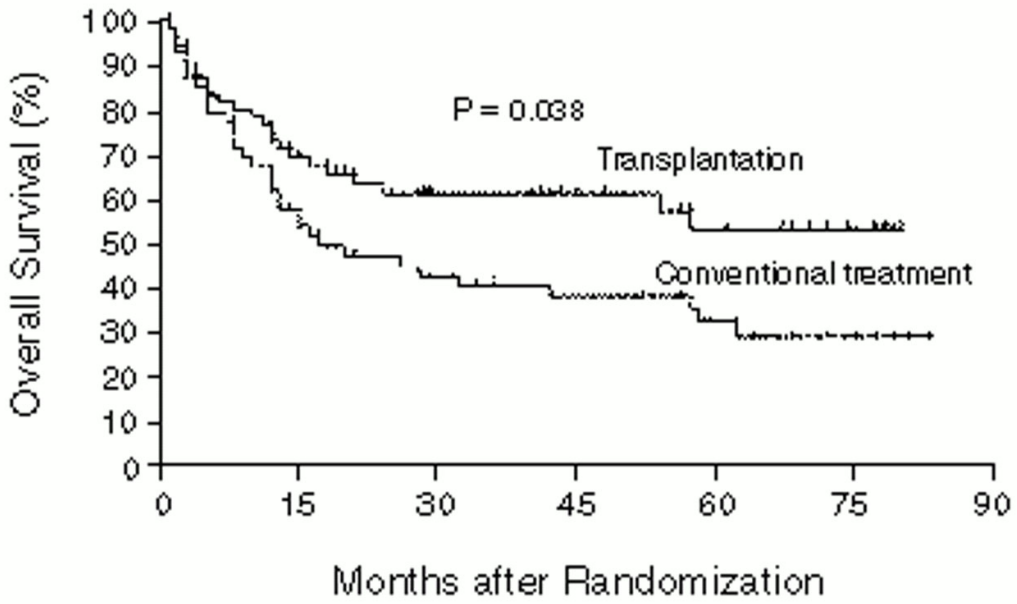
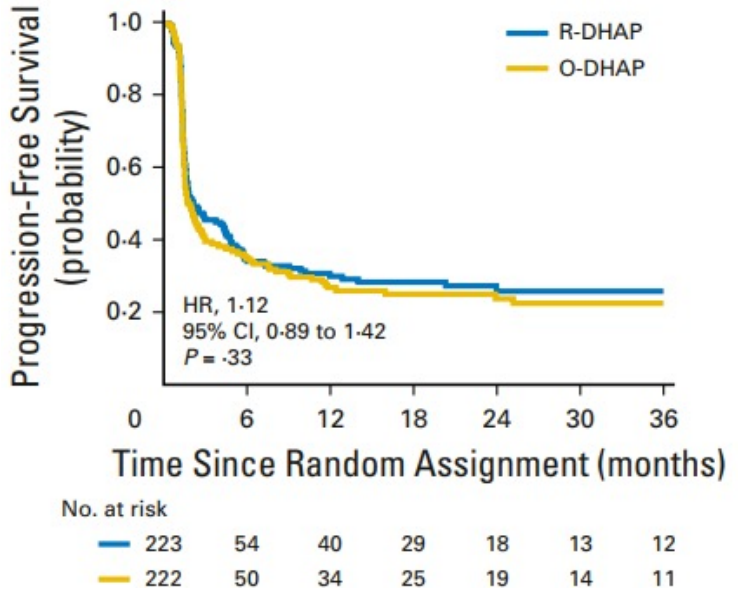
High dose chemotherapy with autologous stem cell transplant

Pre-rituximab era



Philip, et al. NEJM. 1995

Induction response	R-DHAP n=223	O-DHAP n=222
ORR	42%	38%
CRR	22%	15%
Transplanted	37%	33%



van Imhoff, et al. JCO 2017

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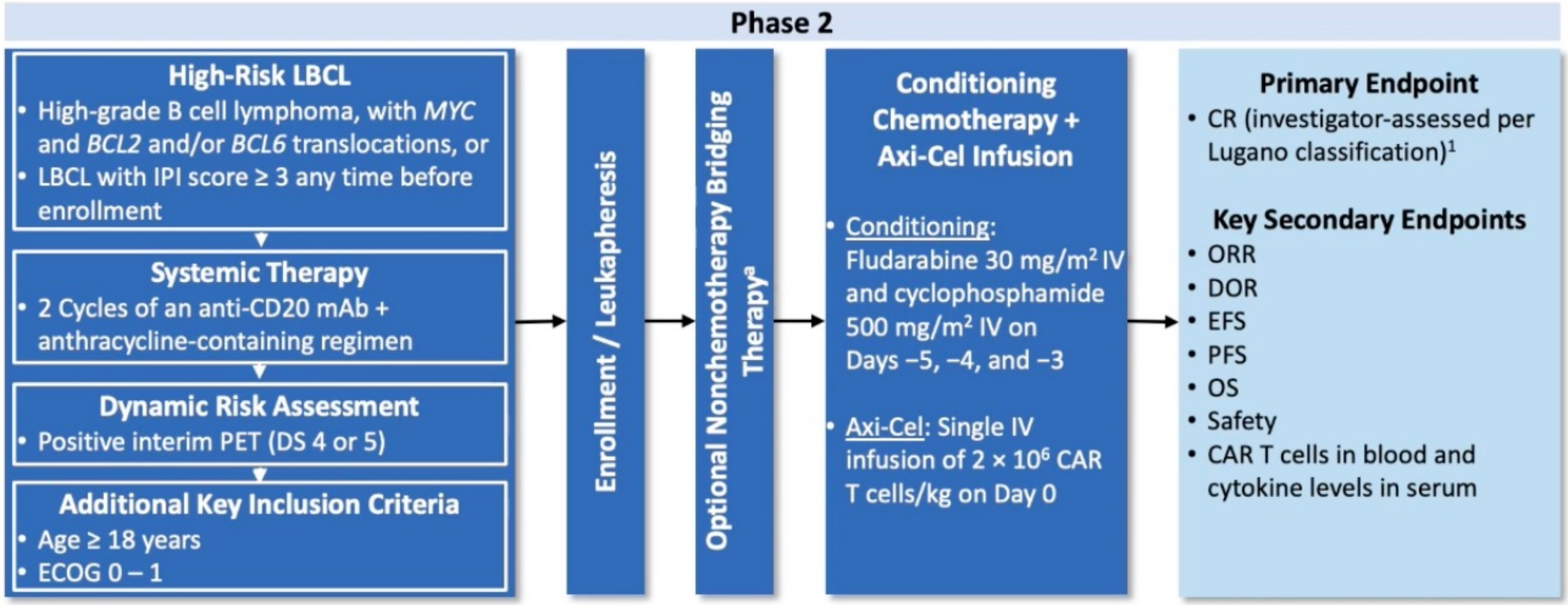
Randomized trials of CAR T-cells vs. SOC in 2nd line transplant-eligible DLBCL with primary refractory disease or relapse within 1 year of 1st line therapy

	ZUMA-7	TRANSFORM	BELINDA
CAR T-cell	Axicabtagene Ciloleucel	Lisocabtagene Maraleucel	Tisagenlecleucel
n	359	184	322
% infused in CAR arm	94%	98%	96%
Median EFS	8.3 mo vs. 2 mo	10.1 mo vs. 2.3 mo	3 mo vs. 3 mo
Hazard ratio	0.398 (*P<0*.0001)	0.349; (*P* < 0.0001)	1.07 (*P*=0.69)
Median follow-up	25 months	6 months	10 months
CR rate	65% vs 32%	66% vs 39%	28% vs 28%
Grade ≥3 CRS/NT	6% / 21%	1% / 4%	5% / 3%
	Locke, et al. Abstract 2	Kamdar, et al. Abstract 91	Bishop, et al. Abstract LBA-6

ZUMA-12 study for early axi-cel in high-risk DLBCL



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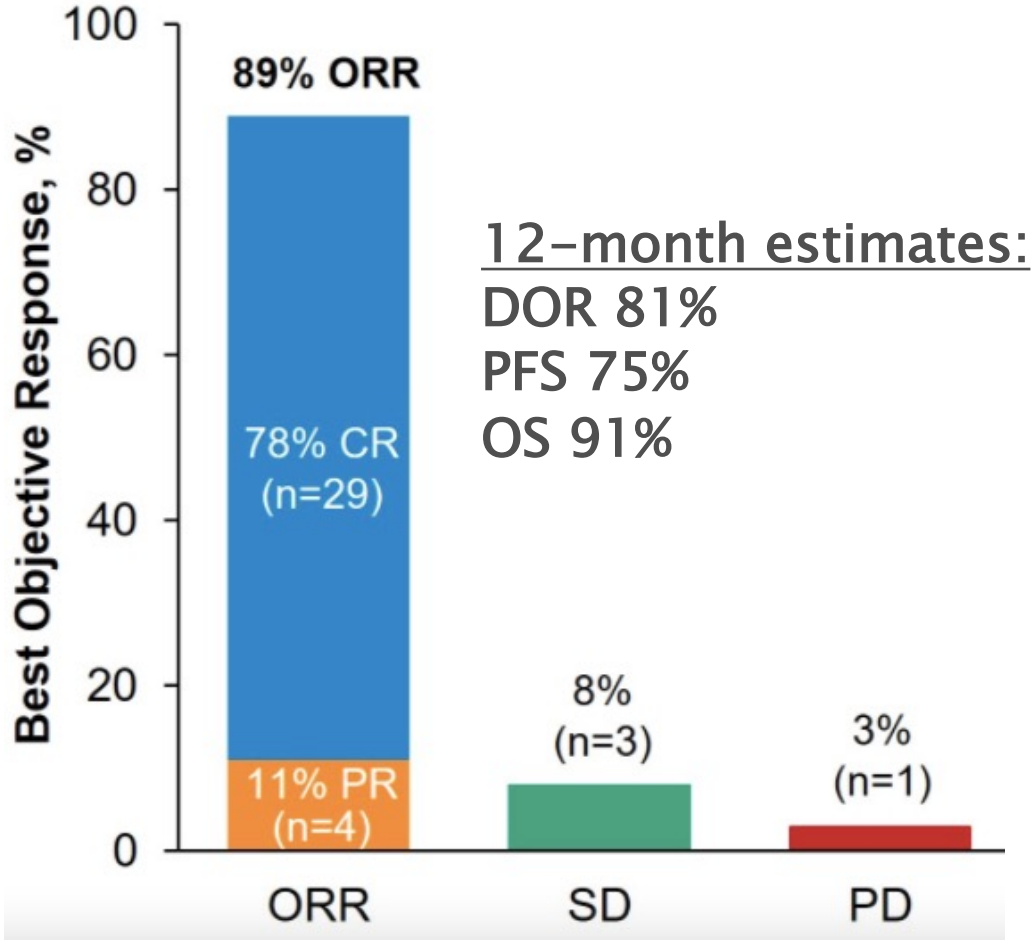
ZUMA-12 study for early axi-cel in high-risk DLBCL (n=40)



12-month estimates:
DOR 81%
PFS 75%
OS 91%

	Response Evaluable (N=37)
Median follow-up (range), months	15.9 (6.0–26.7)
Patients with ≥12-month follow-up, n (%)	23 (62)
Patients with ongoing response as of data cutoff, n (%)	27 (73)
Median time to response (range), months	
Initial objective response	1.0 (0.9–6.8)
CR	1.0 (0.9–6.8)
Patients converted from PR/SD to CR, n (%)	7 (19)
PR to CR	6 (16)
SD to CR	1 (3)

Grade ≥3 CRS in 3 pts (8%), Grade ≥3 NE 9 pts (23%)

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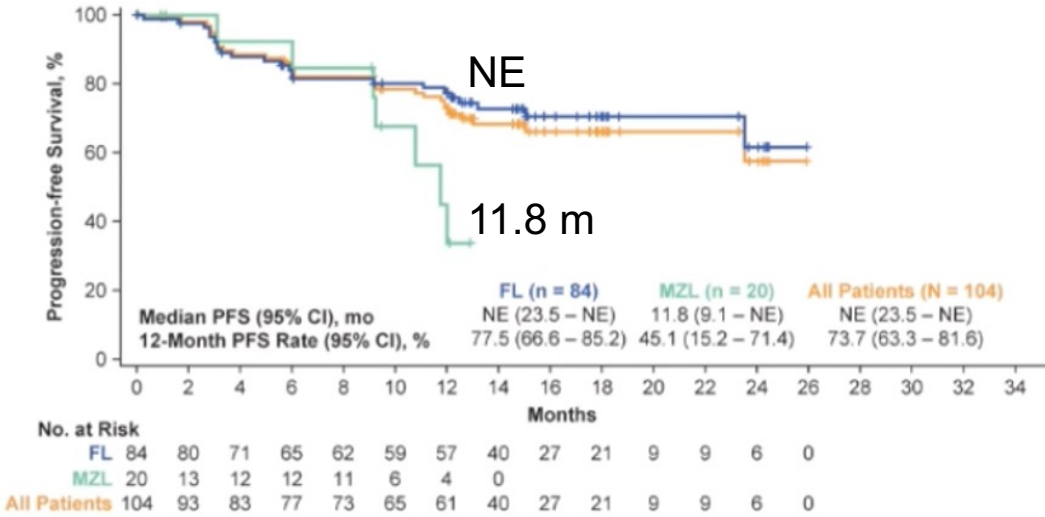
Neelapu, et al. Proc ASH 2021 Abstract 739

ZUMA-5 Study of Axi-cel in relapsed/refractory FL and MZL

Characteristic	FL n=124	MZL N=22	All Patients N=146
Median age (range)	60 (34-79)	66 (48-77)	61 (34-79)
FLIPI 3-5	54 (44%)	14 (64%)	68 (47%)
High tumor burden (GELF)	64 (52%)	8 (36%)	72 (49%)
Median prior tx (range)	3 (1-10)	3 (2-8)	3 (1-10)
Refractory	84 (68%)	16 (73%)	100 (68%)
POD24	68 (55%)	11 (52%)	79 (55%)

Progression-free survival



	All patients (n=104)	FL (n=84)	MZL (n=20)
ORR	92%	94%	85%
CRR	76%	80%	60%
PRR	16%	14%	25%

AEs of Special Interest (n=140)	
Cytokine Release Syndrome	
Any grade	82%
Grade ≧ 3	7%
Neurologic Events	
Any grade	60%
Grade ≧ 3	19%

Jacobson, et al. Proc ASH 2020.

ZUMA-5 ASH 2021 Update

- Follicular lymphoma (n=124)
  - Median follow-up 30.9 months
  - CR rate 79%
  - Estimated median DOR was 38.6 months, PFS 39.6 months, TTNT 39.6 months
- Marginal zone lymphoma (n=25)
  - Median follow-up 23.8 months
  - CR rate 63%
  - Median PFS 17.3 months. Medians for DOR and TTNT not reached

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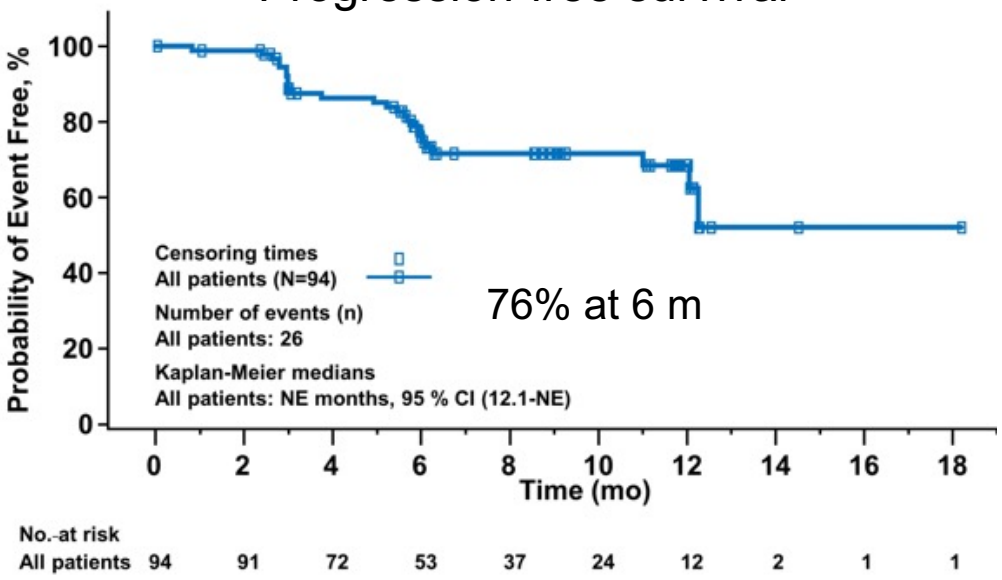
Neelapu, et al. Proc ASH 2021 Abstract 93

ELARA Study of Tisa-cel in relapsed/refractory FL

Characteristic	FL n=97
Median age (range)	57 (29-73)
Median prior tx (range)	4 (2-13)
Refractory	78%
POD24	60%

	All patients n=94
ORR	86%
CRR	66%
PRR	20%

Progression-free survival



AEs of Special Interest (n=97)	
Cytokine Release Syndrome Any grade Grade ≧ 3	 48.5% 0%
Neurologic Events Any grade Grade ≧ 3	 9.3% 1%

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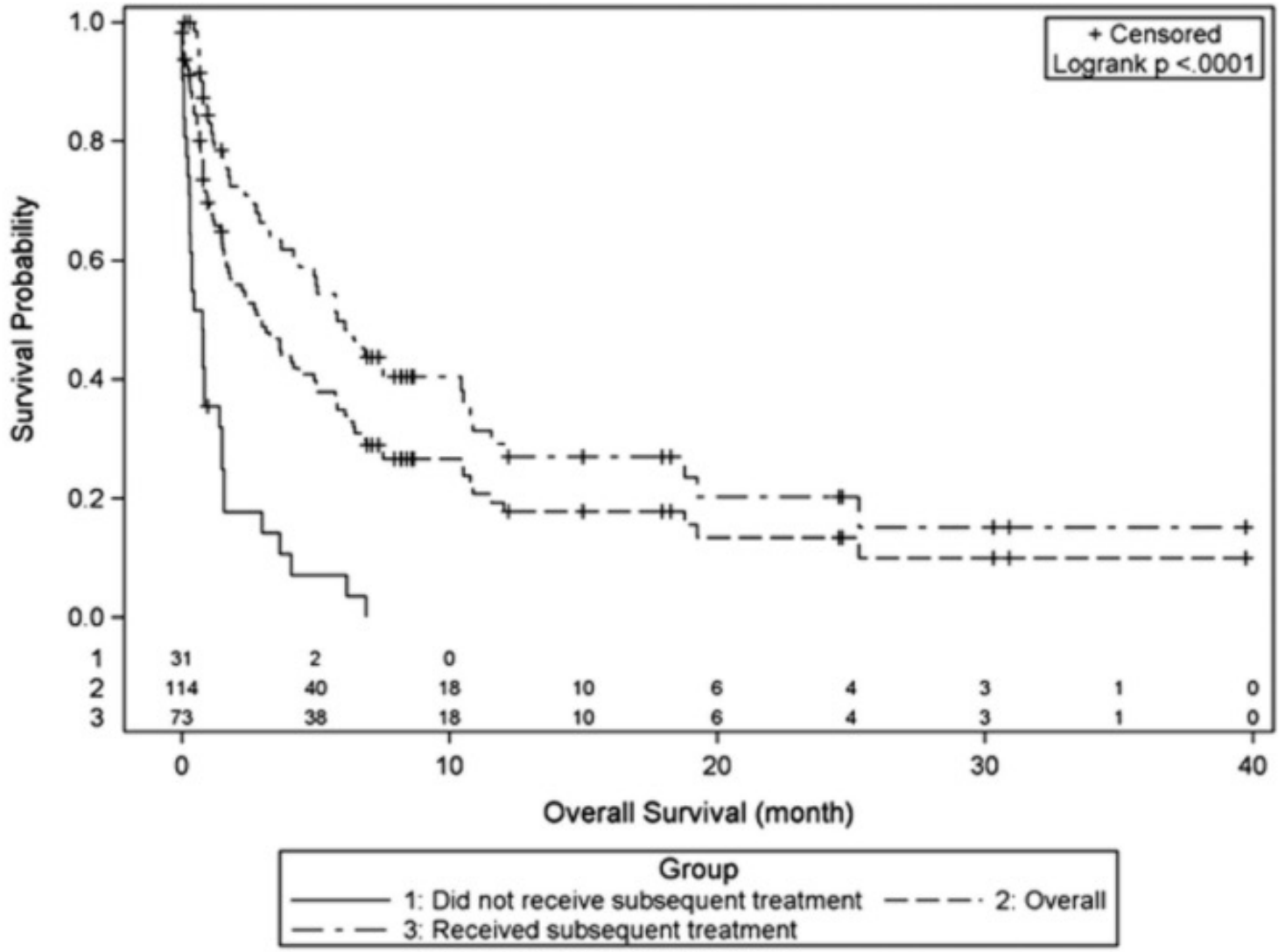
Schuster, et al. Proc ASCO 2021.

Mantle cell lymphoma: Survival after BTK inhibitor failure is poor



Martin, et al. Blood 2016.

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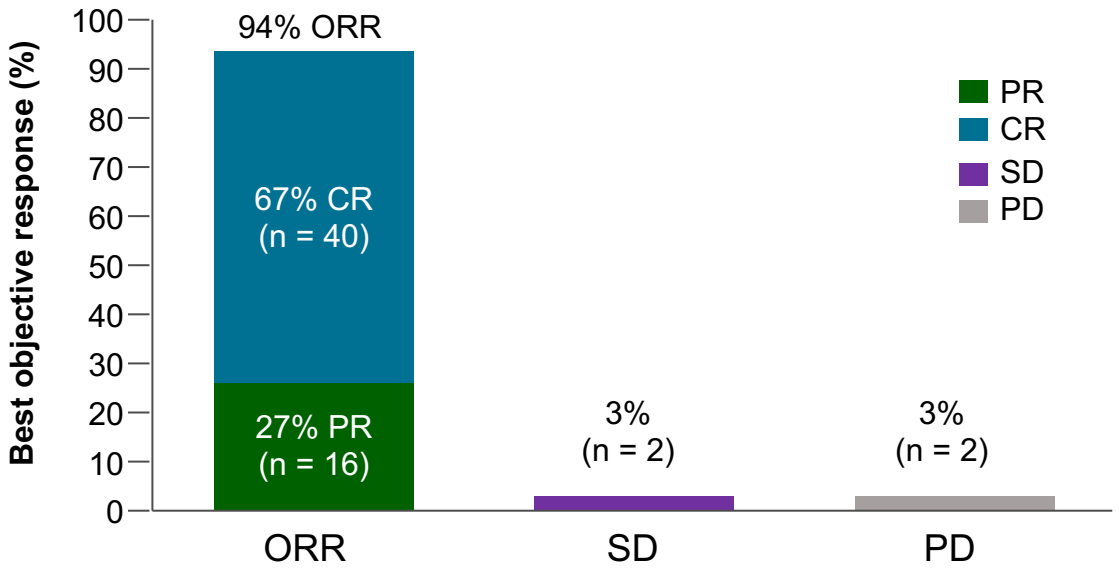
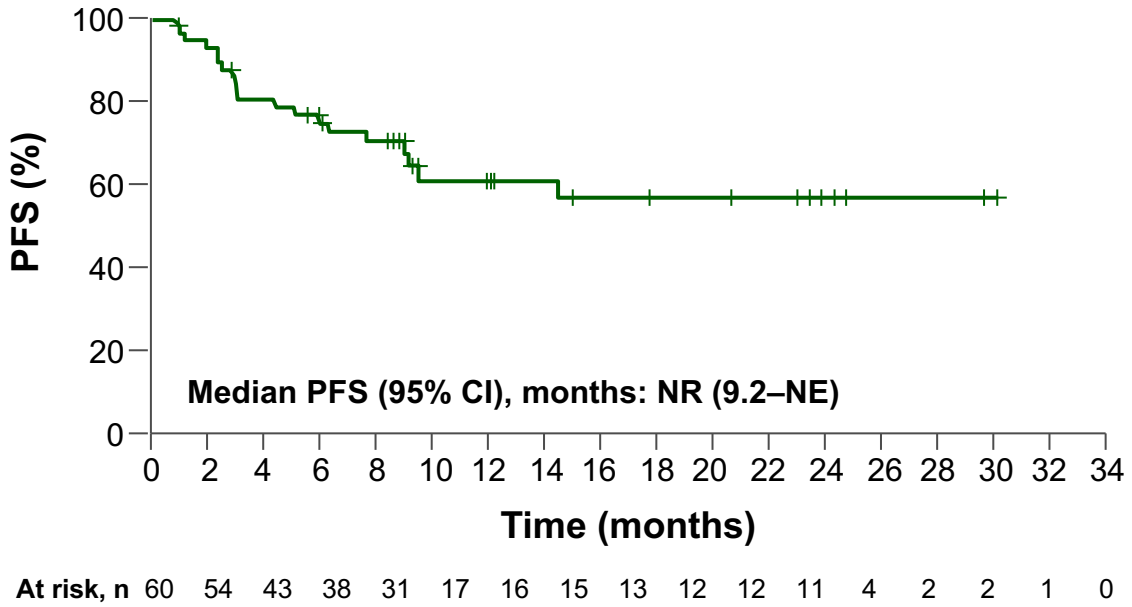
ZUMA-2: Brexucabtagene Autoleucel in Relapsed/Refractory MCL

Characteristics	n = 68
Age, median (range), years	65 (38–79)
Median no. of prior treatments (range)	3 (1–5)
Prior BTKi, n (%)	68 (100)
BTKi refractory, n (%)	42 (62)
Prior ASCT, n (%)	29 (43)



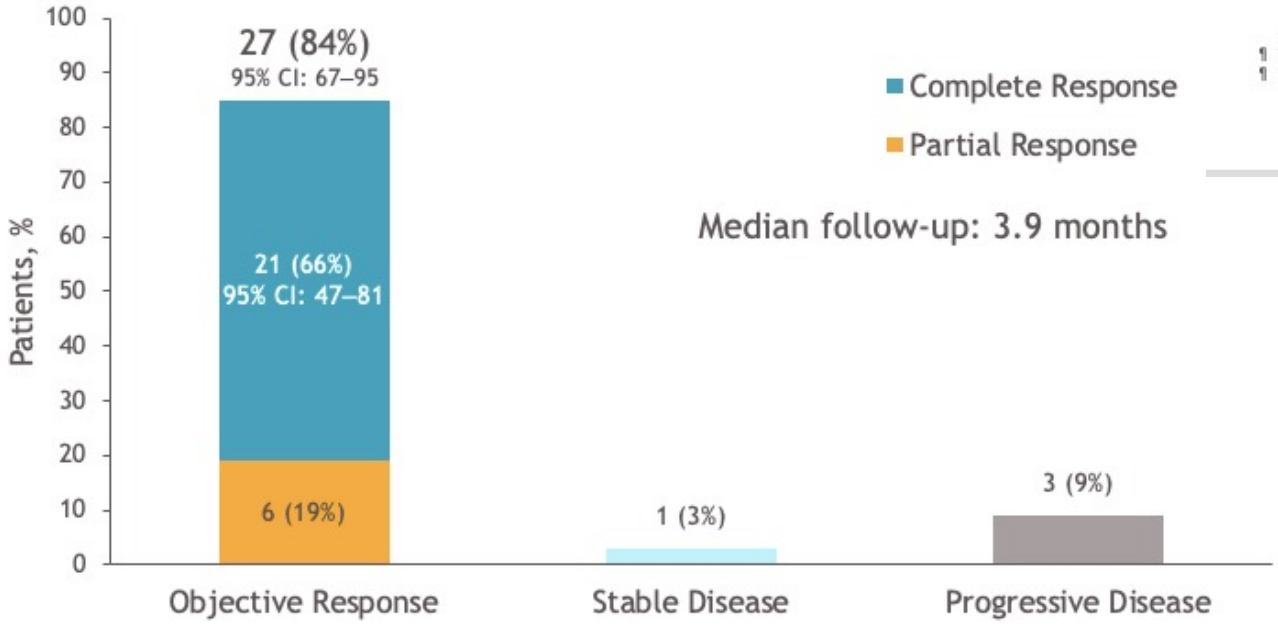


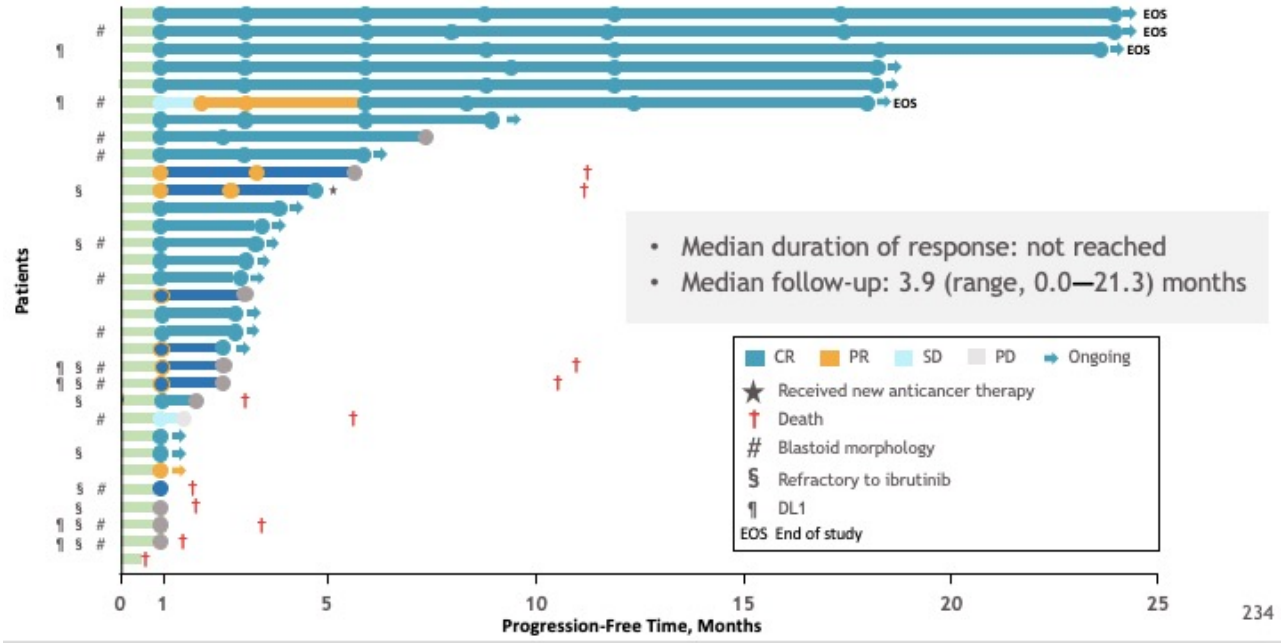
Toxicity	n = 68
Any-grade CRS, n (%)	62 (91)
Grade 3 or 4 CRS, n (%)	10 (15)
Time to onset, median, days (range)	2 (1–13)
Any-grade neurological toxicity, n (%)	43 (63)
Grade 3 or 4 neurological toxicity, n (%)	21 (31)
Time to onset, median, days (range)	7 (1–32)

Wang, at al. NEJM 2020

Lisocabtagene Maraleucel in Relapsed/Refractory MCL

Characteristics	n = 32
Age, median (range), years	67 (36–80)
Median no. of prior treatments (range)	3 (1–7)
Prior BTKi, n (%)	24 (75)
Refractory, n (%)	26 (81)
Prior ASCT, n (%)	11 (34)





Toxicity	n = 32
Any-grade CRS, n (%)	16 (50)
Grade 3 or 4 CRS, n (%)	1 (3)
Time to onset, median, days (range)	6 (2-10)
Any-grade neurological toxicity, n (%)	11 (34)
Grade 3 or 4 neurological toxicity, n (%)	4 (13)
Time to onset, median, days (range)	8 (2–25)

Palomba, at al. Proc ASH 2020

CAR T-cell Updates in Lymphoma

- Liso-cel, axi-cel and tisa-cel induce durable responses in heavily pretreated DLBCL and are approved after at least 2 lines of prior therapy
- Initial randomized data show liso-cel and axi-cel superior to standard 2nd line chemotherapy and transplant in primary refractory and early relapsed patients
- Axi-cel and tisa-cel are effective in heavily pretreated follicular lymphoma and can be considered after at least 2 prior lines of therapy
- Brexu-cel and liso-cel produce high rates of CR in relapsed MCL patients who have failed a prior BTK inhibitor
- Additional indications likely to emerge as data evolve

Thank you for your attention!

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