

Updates in CAR T Cell Therapy

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Outline

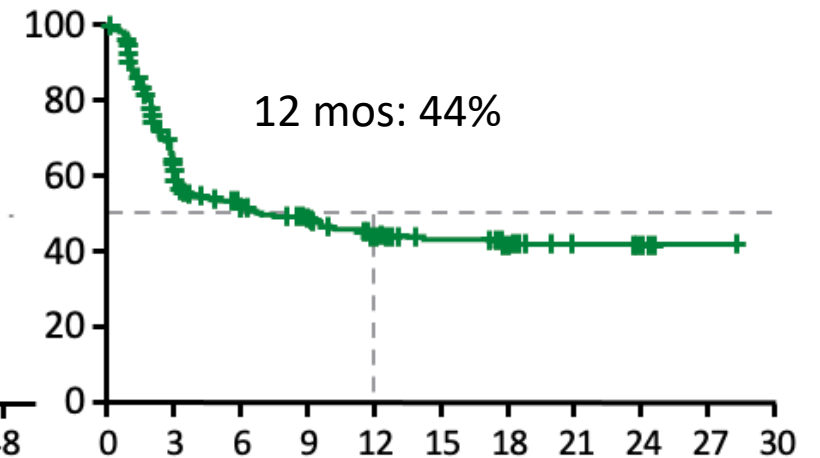
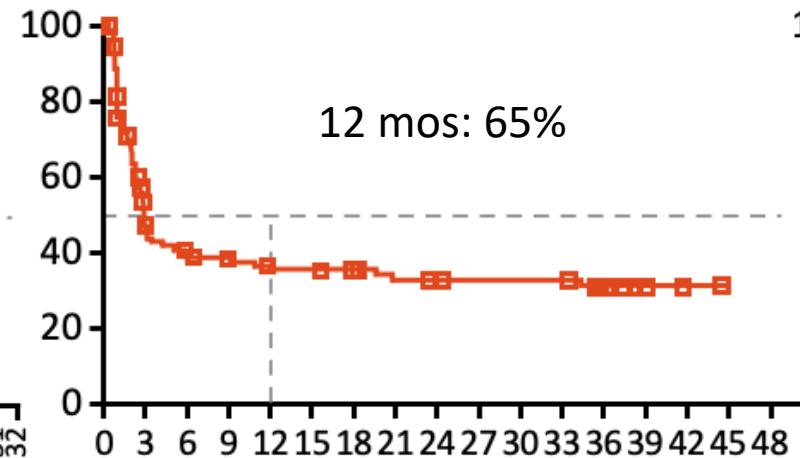
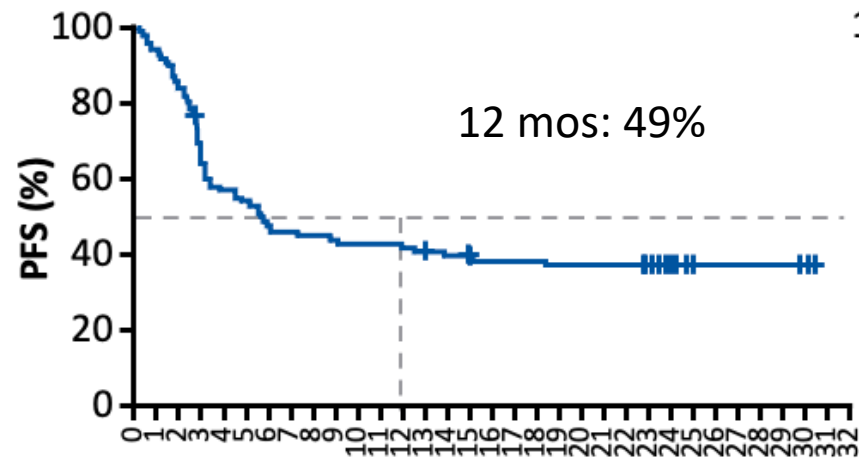
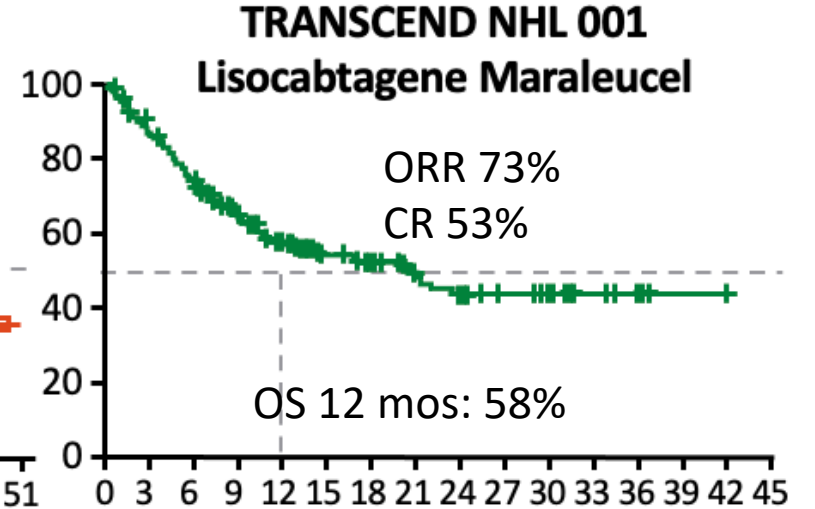
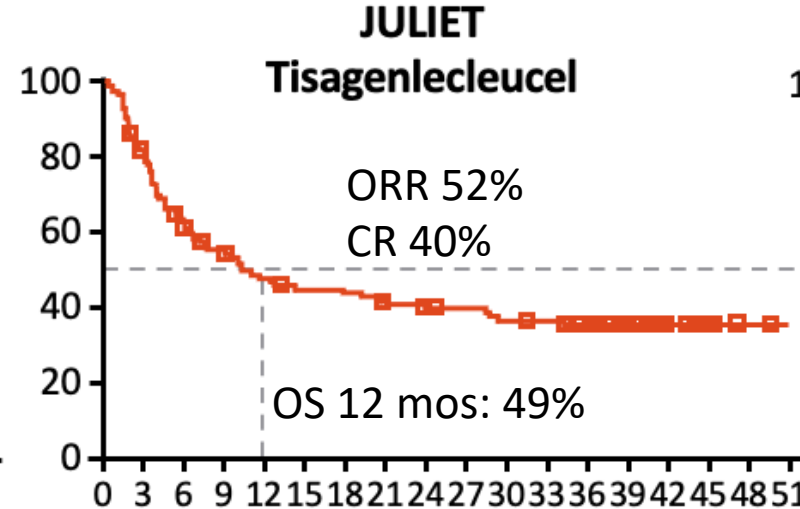
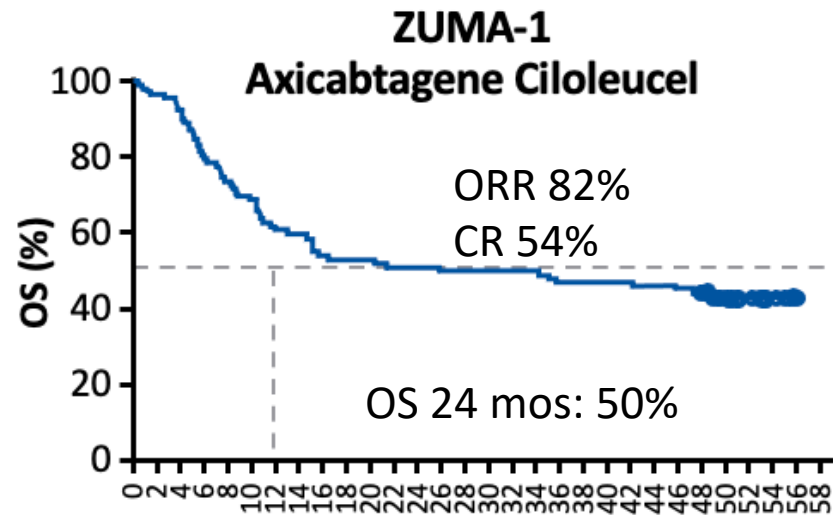
- Current Indications for CAR T Therapy
- Short and Long-Term Toxicity Management
- Treatment Options after CAR T failure
- Ongoing and Upcoming Clinical Trials

Current FDA Approved CAR T Products

Product	Disease State	Target	Indication	Approval Date
Axicabtagene	DLBCL FL	CD19	2 nd line ≥ 2 lines	2017, 2022 2021
Tisagenlecleucel	DLBCL B-ALL (≤ 25)	CD19	≥ 2 lines ≥ 2 lines	2018 2017
Lisocabtagene	DLBCL	CD19	2 nd line	2021, 2022
Brexucabtagene	MCL B-ALL (adults)	CD19	≥ 2 lines	2020 2021
Idecabtagene	Multiple Myeloma	BCMA	≥ 4 lines	2021
Ciltacabtagene	Multiple Myeloma	BCMA	≥ 4 lines	2022

CD19 CAR T therapy in NHL

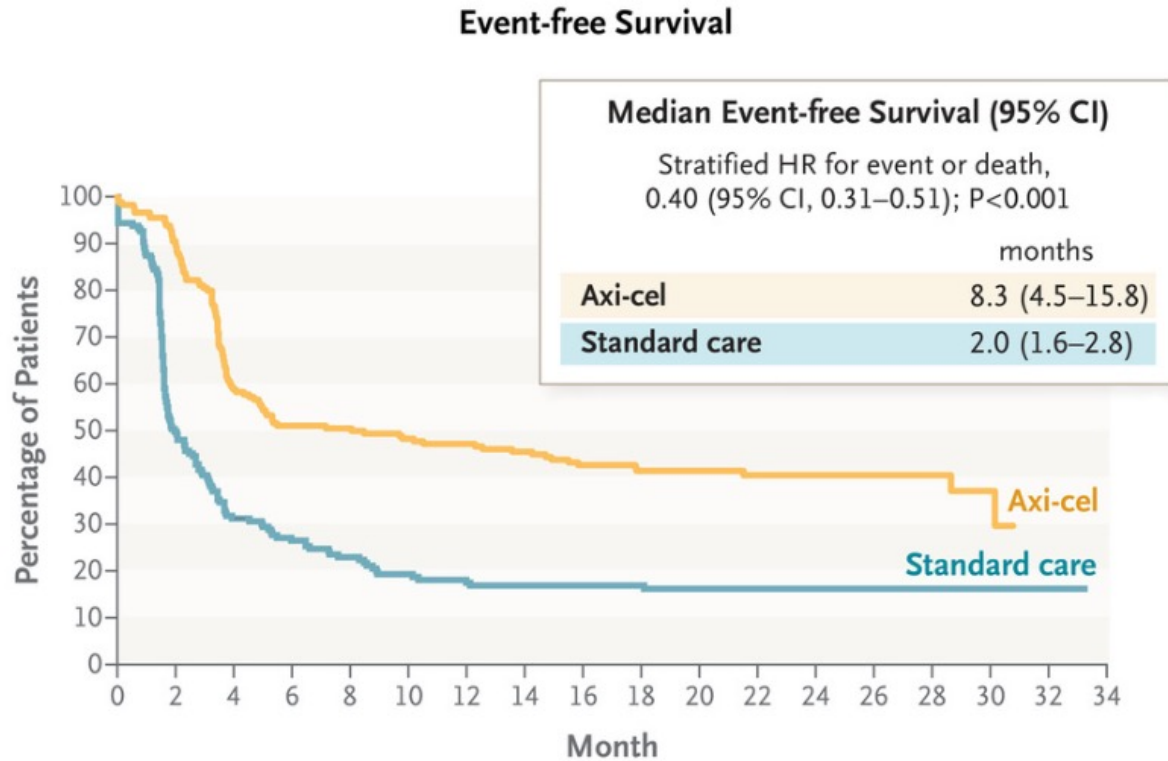
Pivotal Phase I/II CD19 CAR T Trials: NHL



Locke. Lancet Oncol. 2019;20:31. Jacobson. ASH 2020. Abstr 1187. Jaeger. ASH 2020. Abstr 1194. Abramson. Lancet. 2020;396:839.

Slide credit: [ProCE.com](https://proce.com) and clinicaloptions.com

2nd Line CAR T vs Autologous SCT: ZUMA-7

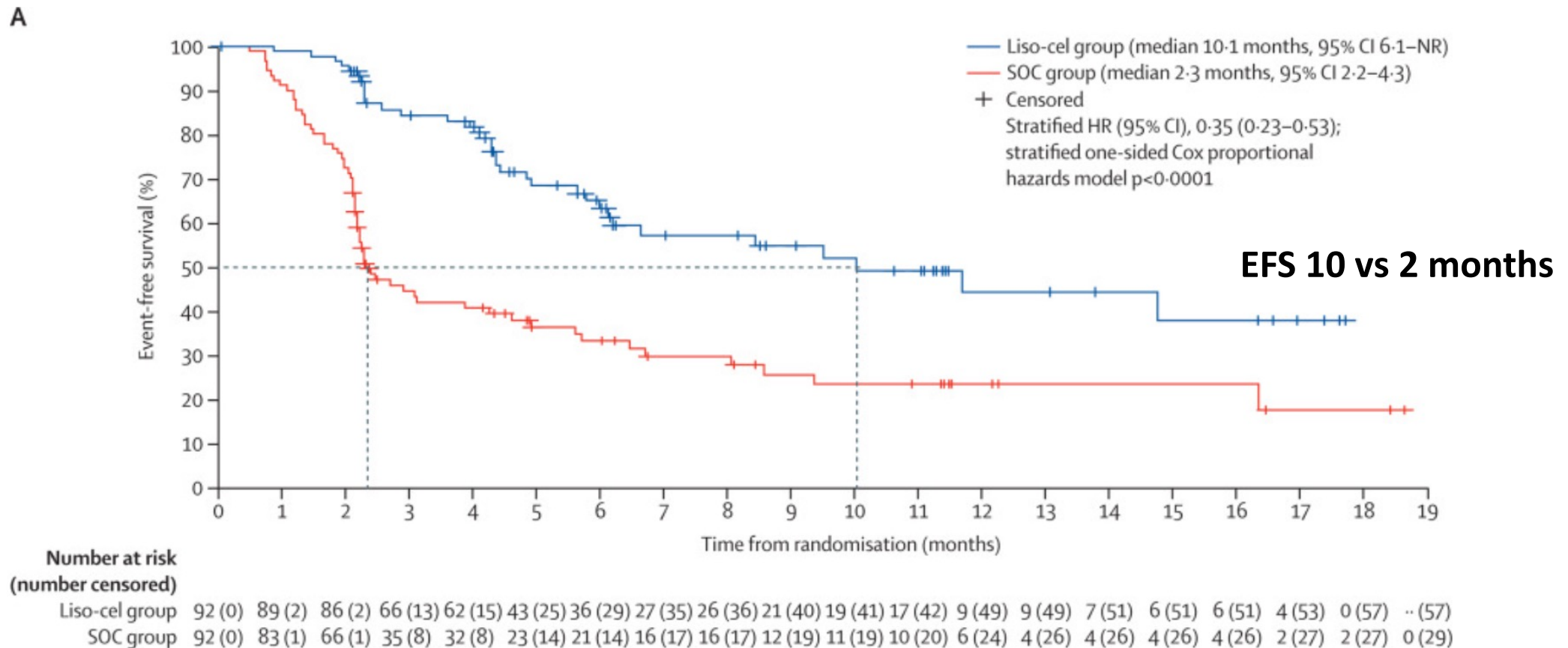


- ~74% Primary Refractory disease
 - Poor prognosis with auto SCT
- No bridging chemo permitted

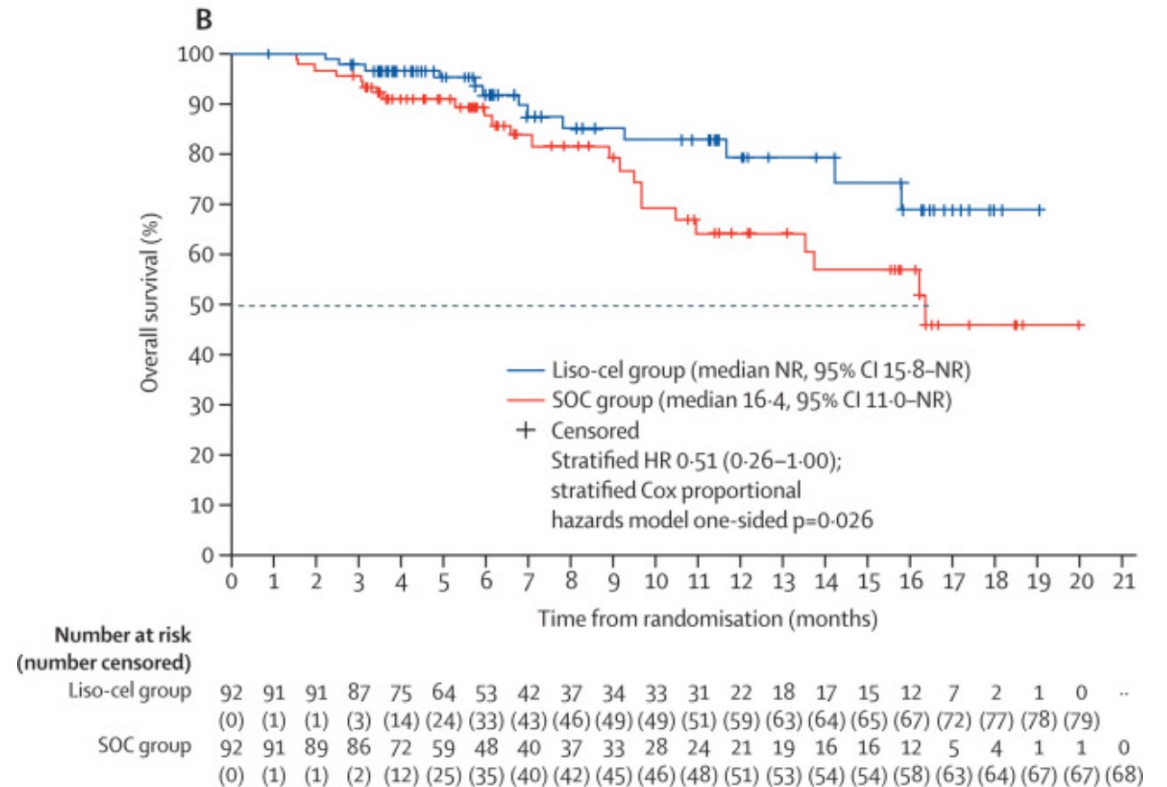
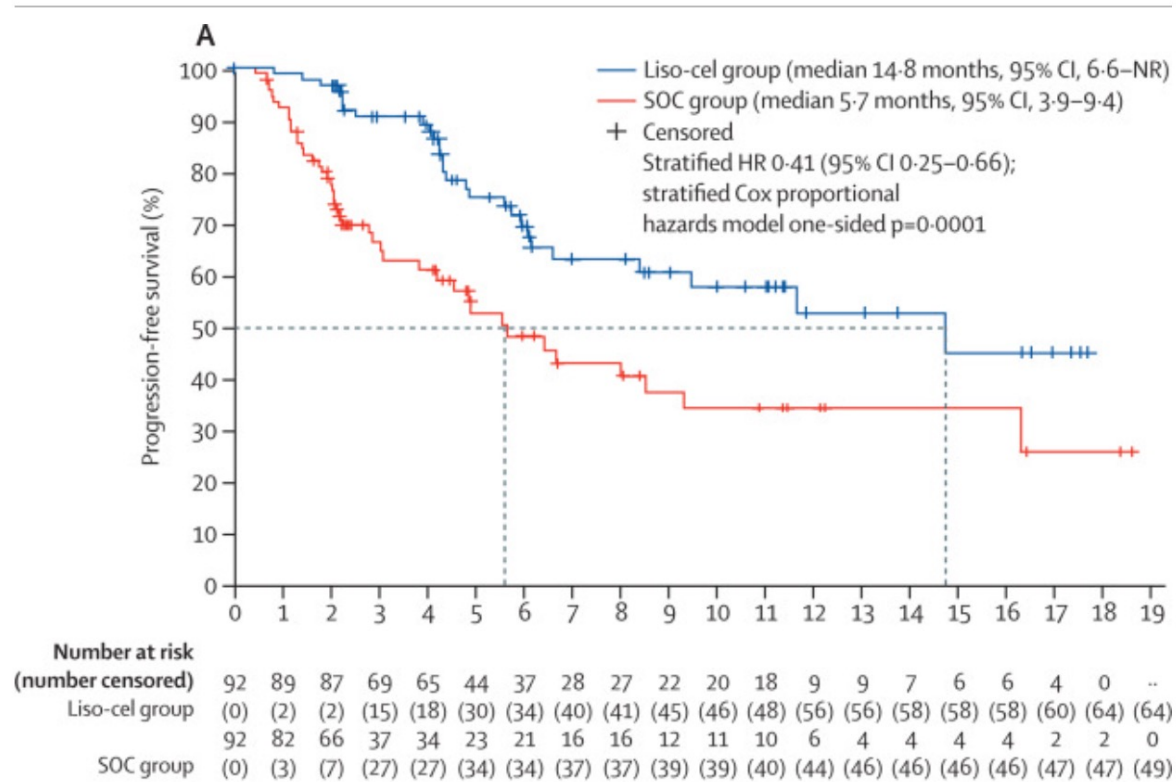
End Point	Axicabtagene
mEFS at 24 mos	41% (vs 16%)
PFS at 24 mos	14.7 mos (vs 3.7)
OS at 24 mos	61% (vs 52%)
ORR	83%
CR	65% (vs 32%)

TRANSFORM: Lisocabtagene 2nd line

- Lisocabtagene vs SOC in early relapsed (≤ 12 mos) or refractory large B-cell lymphoma
 - SOC = 3 cycles platinum-containing salvage $\rightarrow$ HD chemo + auto SCT



TRANSFORM: Lisocabtagene 2nd line

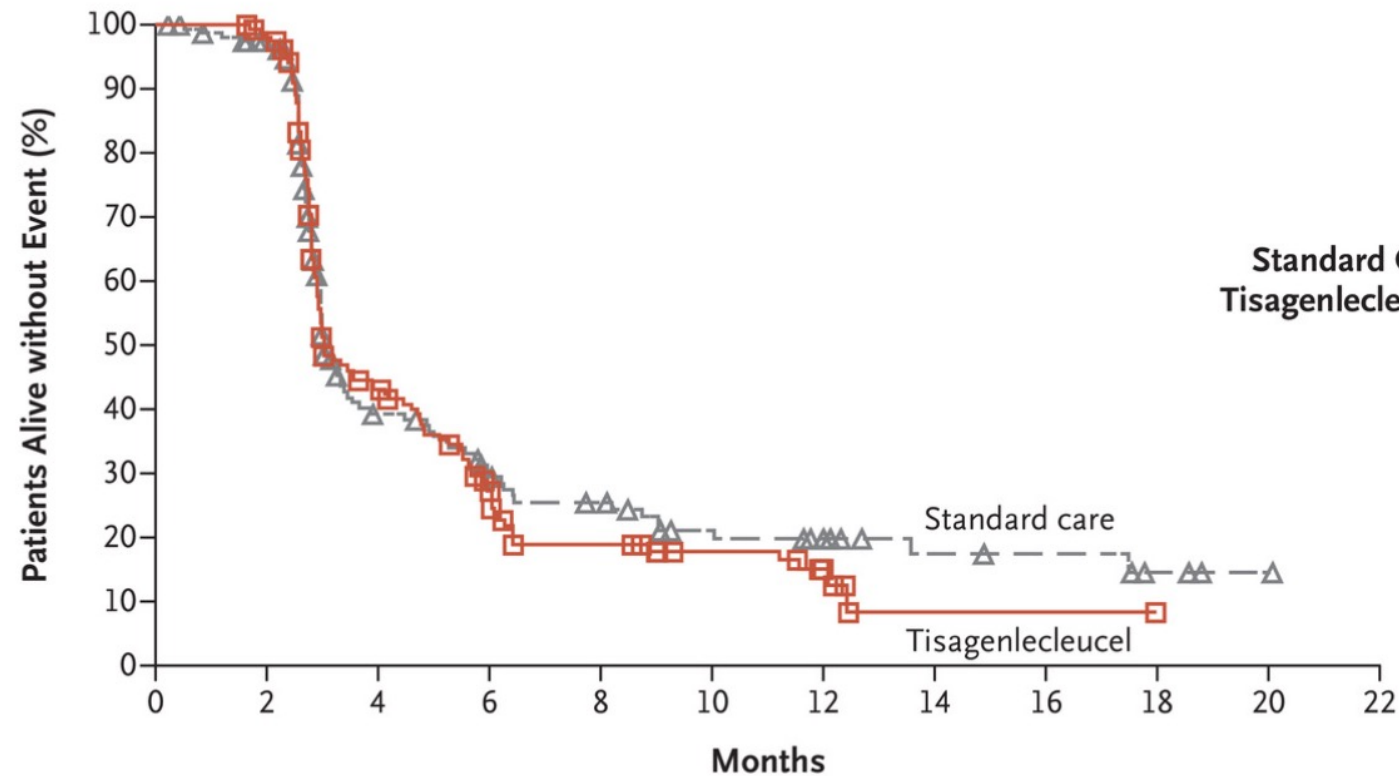


PFS 14.8 v 5.7 months

OS NR v 16 months

BELINDA: Tisagenlecleucel 2nd line

- Optional bridging therapy
- Primary Endpoint: EFS



	No. of Patients	No. of Events	Median Event-free Survival (95% CI) mo
Standard Care	160	104	3.0 (3.0–3.5)
Tisagenlecleucel	162	117	3.0 (2.9–4.2)

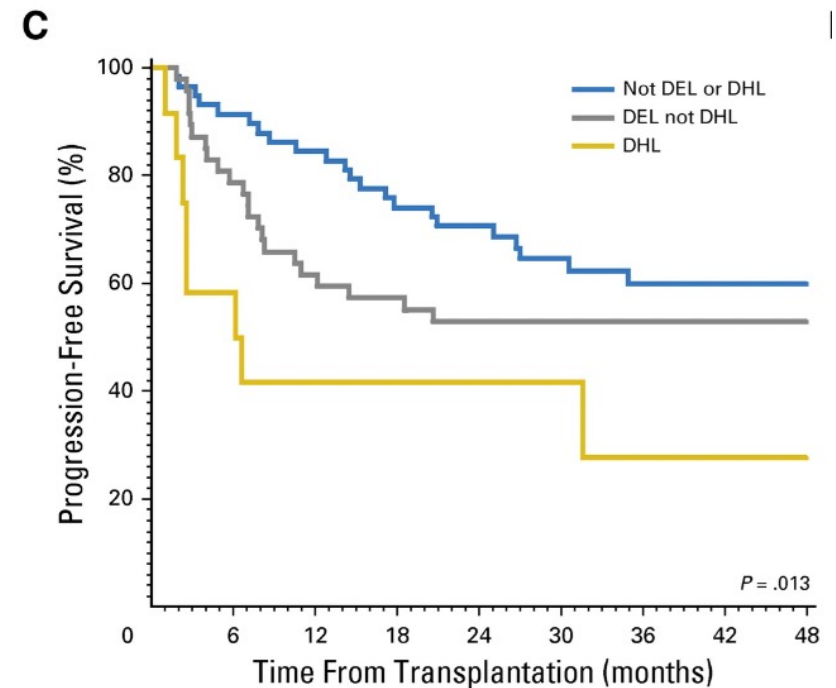
Hazard ratio for event or death (tisagenlecleucel vs. standard care), 1.07 (95% CI, 0.82–1.40)
P=0.61

No. at Risk

Standard care	160	148	45	31	25	17	12	7	6	3	1	0
Tisagenlecleucel	162	156	57	32	19	13	6	1	1	0	0	0

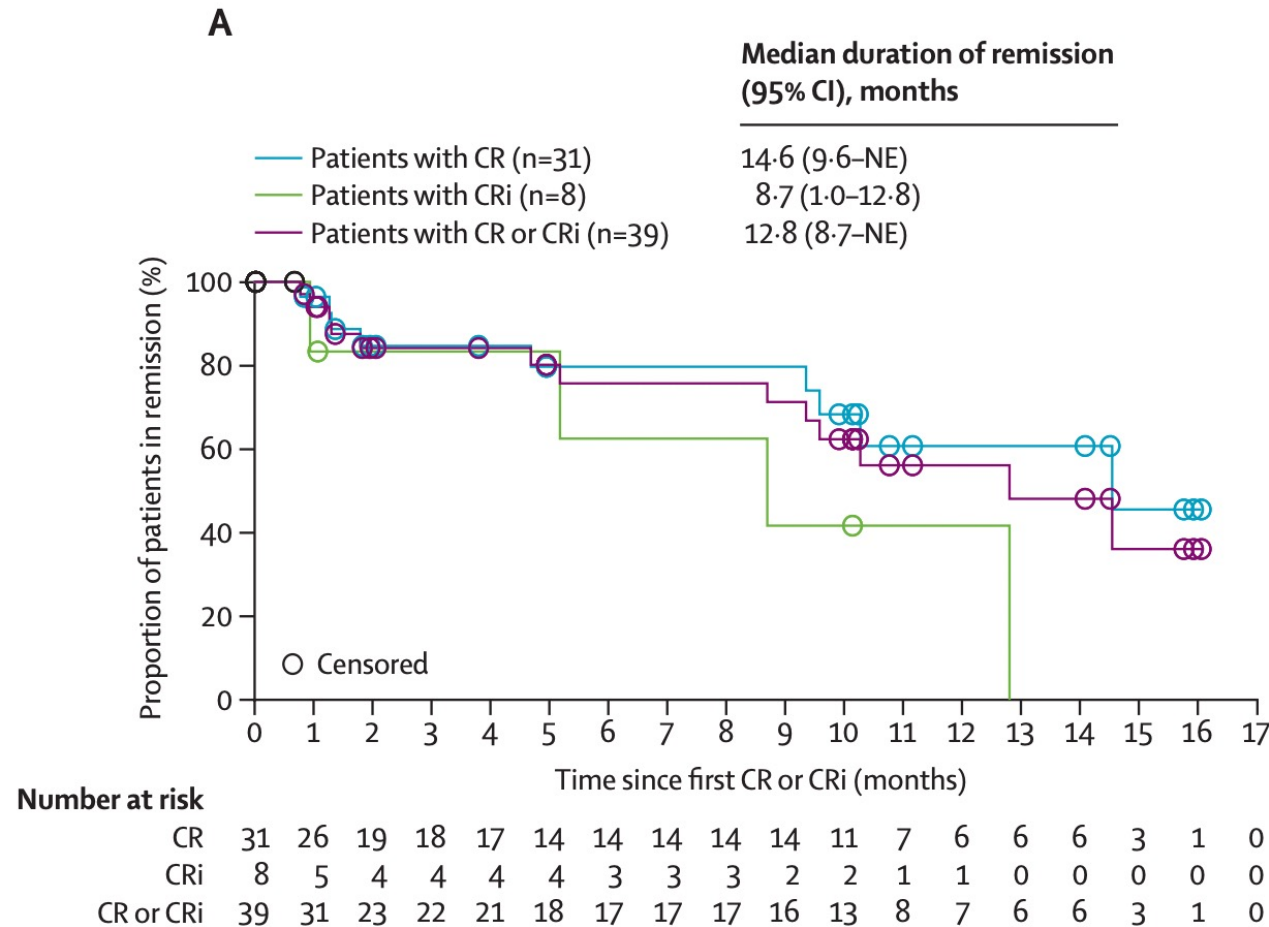
CAR T vs Auto SCT

- R/R DLBCL within 12 months or primary refractory disease → CD19 CAR T
- Relapse after 12 months
 - Auto vs CAR T: response to bridging therapy
 - CAR T after Auto
 - Double Hit/Double Expressor
 - Poor outcomes with auto SCT
 - 4-year PFS DHL 28% vs 57% non-DHL
 - 4-year OS 25% vs 61%



CD19 CAR T in Adults with B-ALL

Brexucabtagene in Adults with R/R B-ALL: ZUMA-3



- ≥ 18 years
- BM blasts $\geq 5\%$
- 71% CR/CRi
- 12-month OS 71%
- Median OS 18 mos
 - NR in responders
 - 76% MRD negative (97% responders)
- Median RFS 11.6 mos

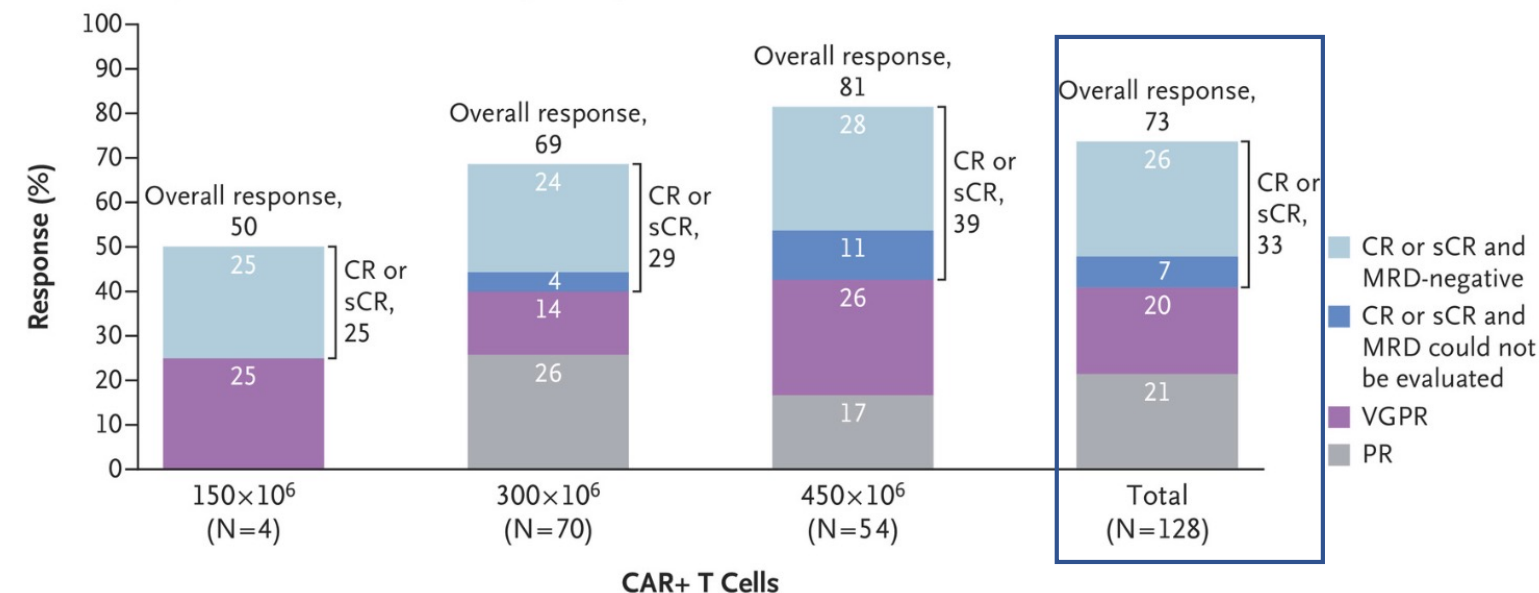
BCMA CAR T Cells for Multiple Myeloma

Idecabtagene Vicleucel: KarMMa Phase 2

- ≥ 4 lines of therapy
- Median 6 prior lines of therapy
 - 94% prior auto SCT

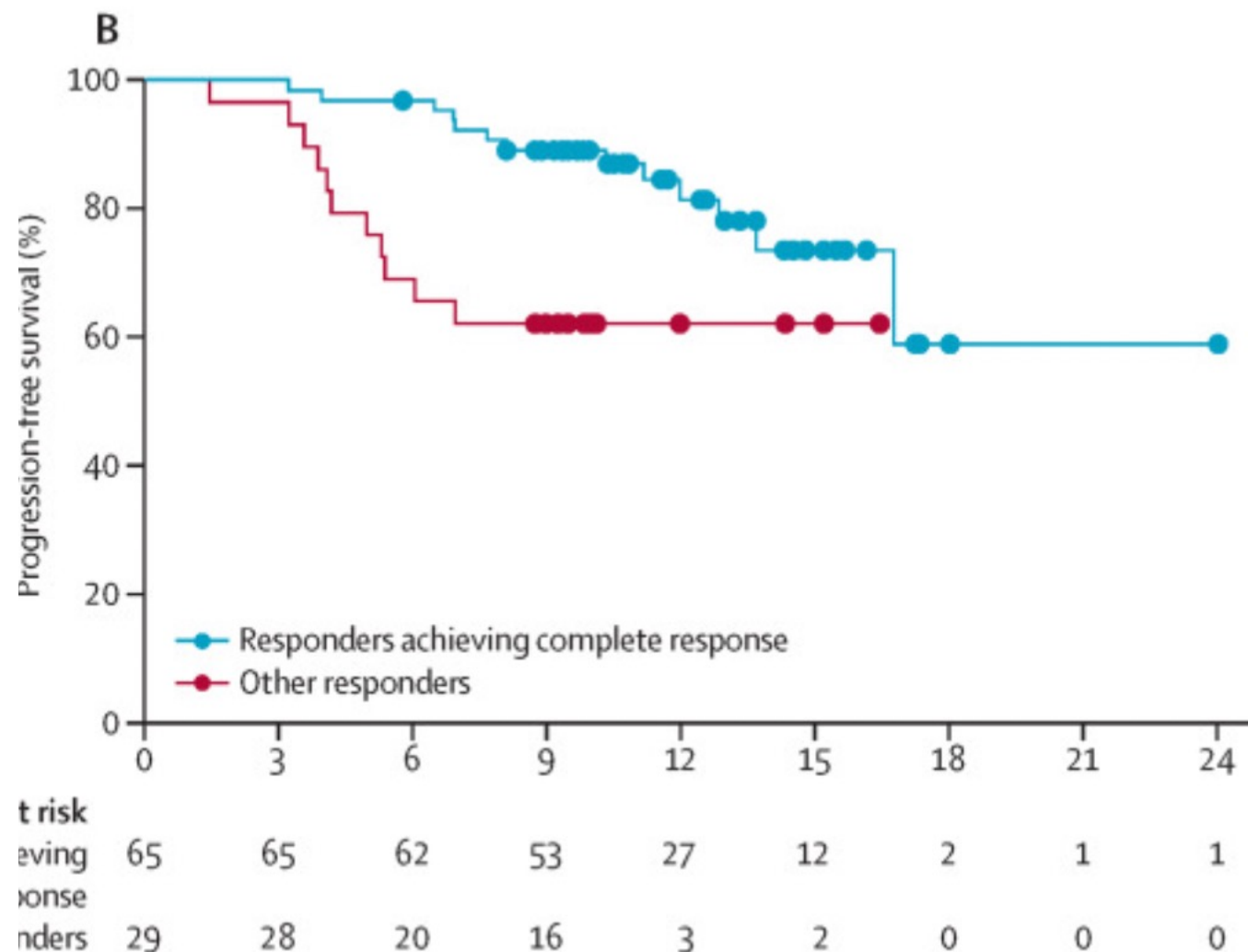
- mDOR 10.7 mos
- mPFS 8.8 mos
- OS 19.7 mos
- MRD-negativity 26%
- CRS 84%
 - 5% $\geq$ G3
- Neurotoxicity 18%
 - 3% $\geq$ G3

Tumor Response, Overall and According to Target Dose



Ciltacabtagene Autoleucel: CARTITUDE Phase 1b/2

- Approved February 2022
 - ≥ 4 lines of therapy
- 6-month PFS 90%
- mDOR not reached
- 12-month PFS 77%, OS 89%
 - PFS 85% if CR or better
- Neurotoxicity 21%
 - 17% ICANS
 - 2% $\geq$ Grade 3 ICANS
- CRS 95% (4% $\geq$ Grade 3)



Management of Toxicities

	Tisagenleucel	Axicabtagene ciloleucel	Brexucabtagene autoleucel	Lisocabtagene maraleucel	Idecabtagene autoleucel
Approval Date	8/30/2017	10/18/2017	6/24/2020	2/5/2021	3/26/2021
Indication(s)	• B-cell precursor acute lymphoblastic leukemia (ALL) • Relapsed/refractory large B-cell lymphoma	• Relapsed/refractory large B-cell lymphoma • Relapsed/refractory follicular lymphoma	• Relapsed/refractory mantle cell lymphoma	• Relapsed/refractory large B-cell lymphoma	• Relapsed/refractory multiple myeloma
Target Antigen	CD-19	CD-19	CD-19	CD-19	BCMA
Incidence of CRS	Any: 74-77% ≥ Grade 3: 23-48%	Any: 84-94% ≥ Grade 3: 8-13%	Any: 91% ≥ Grade 3: 18%	Any: 46% ≥ Grade 3: 4%	Any: 85% ≥ Grade 3: 9%
Incidence of Neurotoxicity	Any: 60-71% ≥ Grade 3: 19-22%	Any: 77-87% ≥ Grade 3: 21-31%	Any: 81% ≥ Grade 3: 37%	Any: 35% ≥ Grade 3: 12%	Any: 28% ≥ Grade 3: 4%

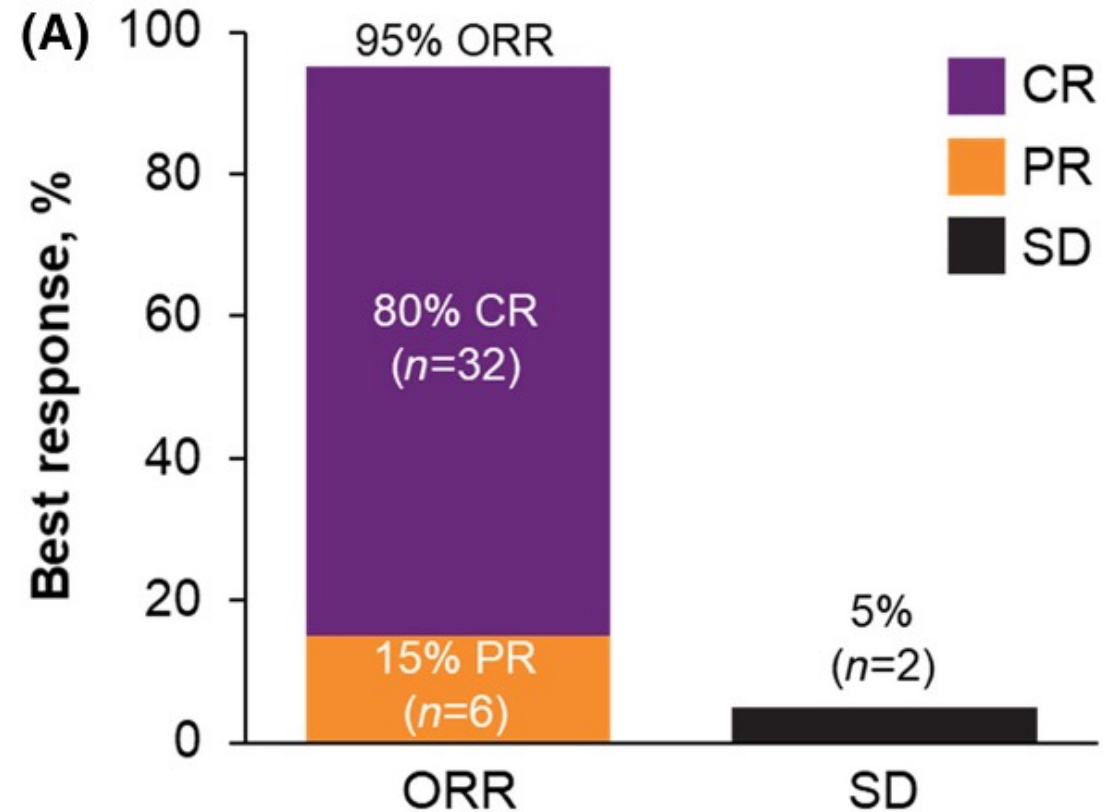
Prophylactic steroid Use: Cohort 6 ZUMA-1

Dexamethasone 10 mg daily Day 0 to Day +2

Original AE Mgmt	CRS	Tocilizumab: No Corticosteroid: No	Tocilizumab: Yes* Corticosteroid: Yes*	Tocilizumab: Yes Corticosteroid: Yes	Tocilizumab: Yes Corticosteroid: Yes
	NE	Tocilizumab: No Corticosteroid: No	Tocilizumab: Yes Corticosteroid: No	Tocilizumab: Yes Corticosteroid: Yes†	Tocilizumab: Yes Corticosteroid: Yes
		↓	↓	↓	↓
		1	2	3	4
		↑	↑	↑	↑
Cohort 6 AE Mgmt	CRS	Tocilizumab: Yes‡ Corticosteroid: Yes§	Tocilizumab: Yes Corticosteroid: Yes	Tocilizumab: Yes Corticosteroid: Yes	Tocilizumab: Yes Corticosteroid: Yes, HD
	NEs	Tocilizumab: No Corticosteroid: Yes	Tocilizumab: Yes Corticosteroid: Yes	Tocilizumab: Yes Corticosteroid: Yes, HD	Tocilizumab: Yes Corticosteroid: Yes, HD

Prophylactic steroid Use: Cohort 6 ZUMA-1

- 80% incidence CRS
 - No Grade 3-4 events
- Neurotoxicity 58%
 - 13% Grade ≥ 3
- Lower cumulative steroid dose to treat CRS and ICANS
- CAR T expansion and efficacy maintained



Long Term Toxicities

Cytopenias

- ~20—40% pts have $\geq$ G3 after Day +30
- More common with increased prior lines of therapy
- Undiagnosed CHIP
- Inflammatory cytokines
- Persistent CARs
- Tx:
 - Growth Factor (> 2 weeks after CAR infusion)
 - Corticosteroids
 - BM biopsy
 - PJP ppx

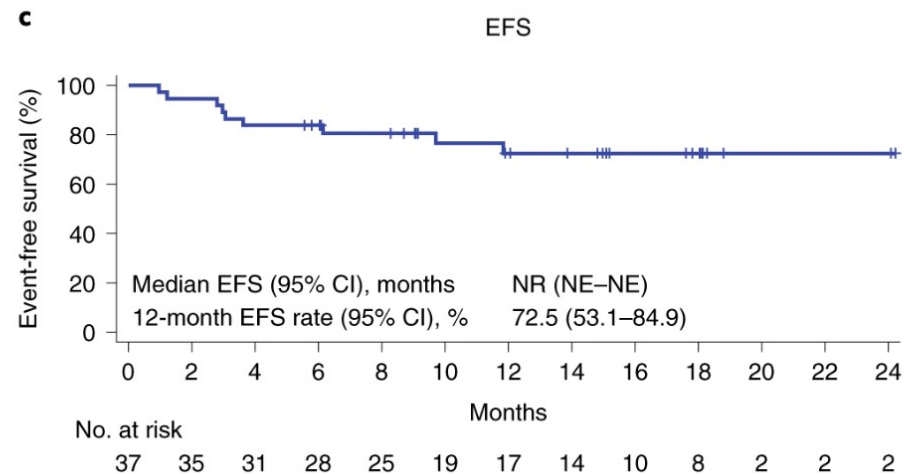
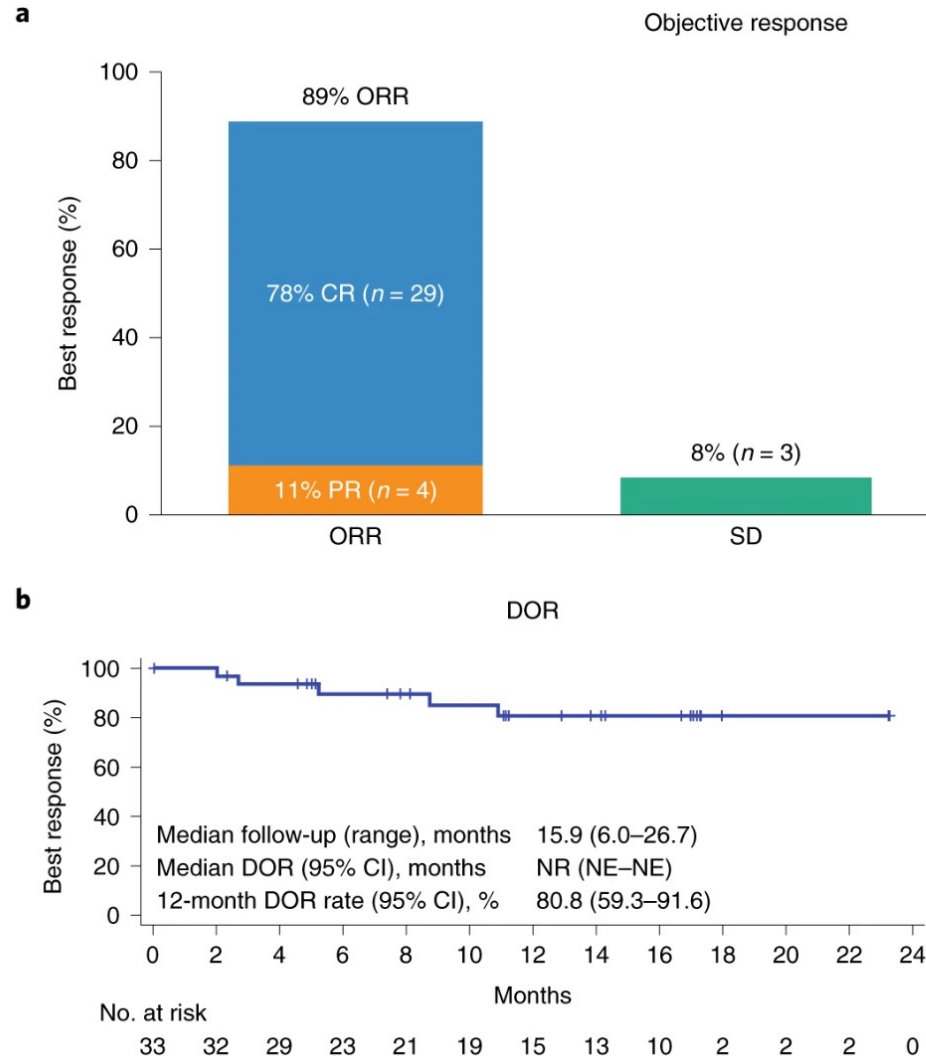
• B-Cell Aplasia

- On-target, off-tumor effect
- Can be prolonged
- Tx
 - Supportive care
 - IVIG
 - PJP PPx
 - COVID, Influenza vaccination

Ongoing and Recently Reported Trials

ZUMA-12

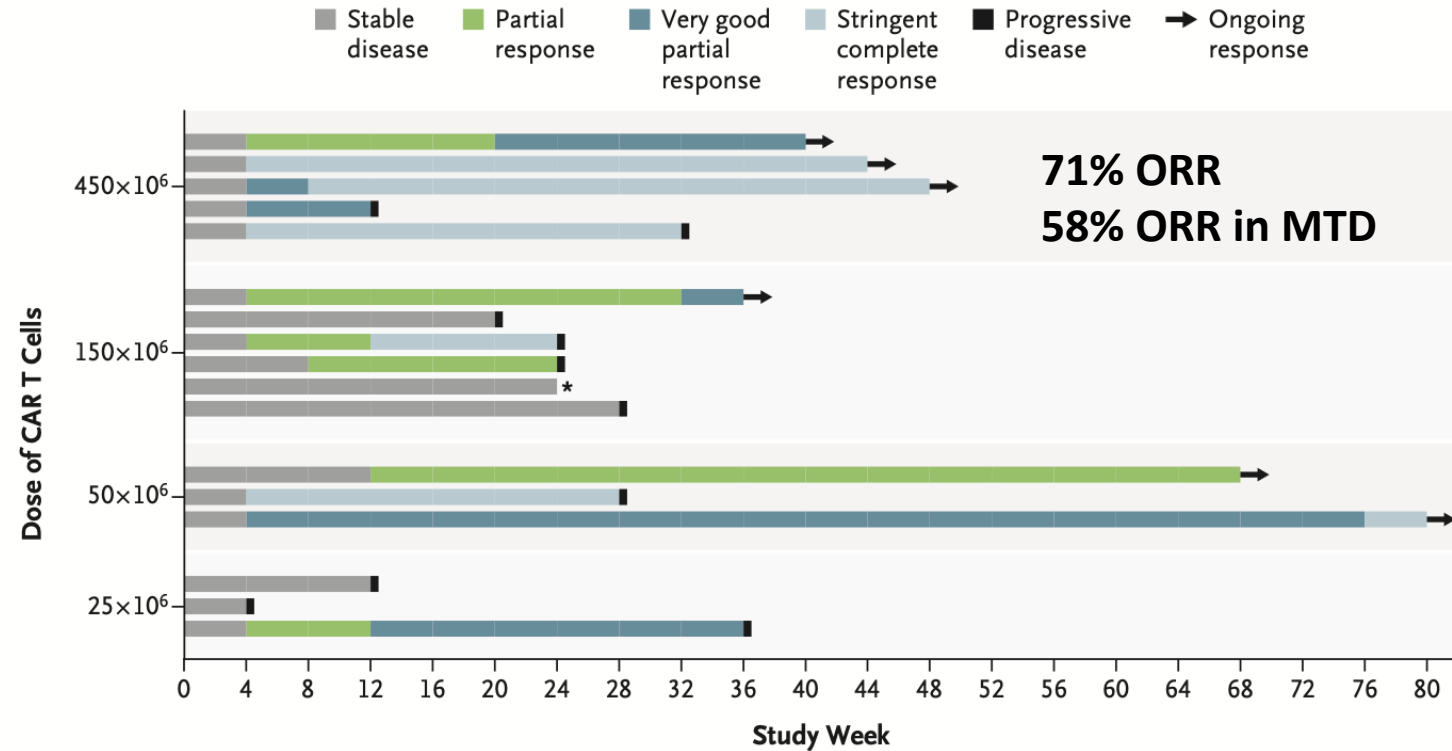
- Phase II, single-arm, high-risk LBCL
 - DHL/THL or IPI ≥ 3
 - PET2-Positive
- 2 cycles SOC chemo $\rightarrow$ Axicel
- Estimated at 12 mos:
 - DOR 81%
 - PFS 75%
 - EFS 73%



GPRC5D-Targeted CAR T cells for MM

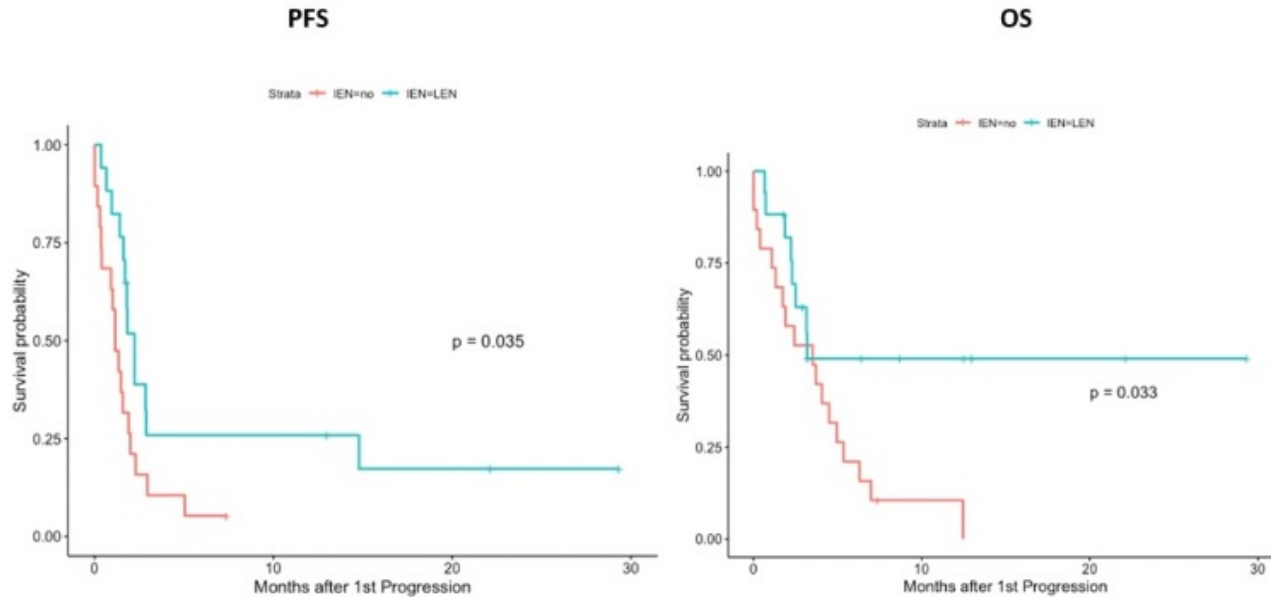
- Phase I dose-escalation study
- R/R MM, including prior BCMA CAR T therapy
- Median 6 lines prior therapy
- 47% prior CAR T

A Clinical Response

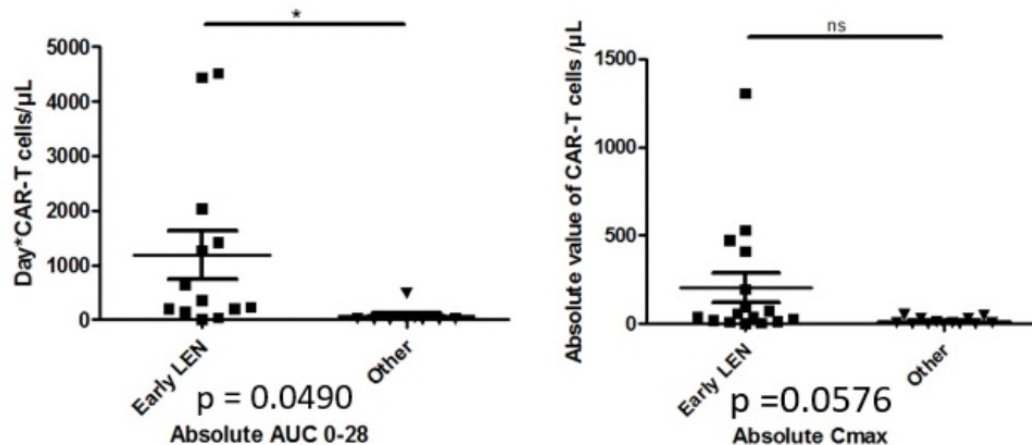


Treatment After CAR T Failure

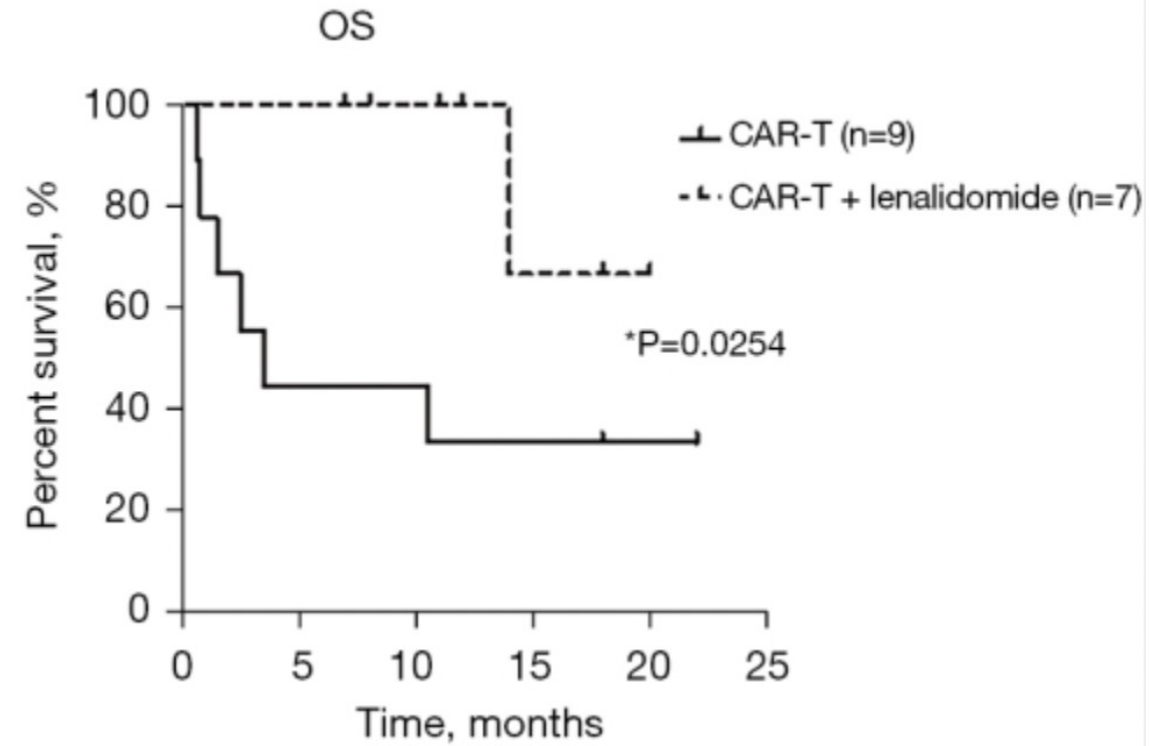
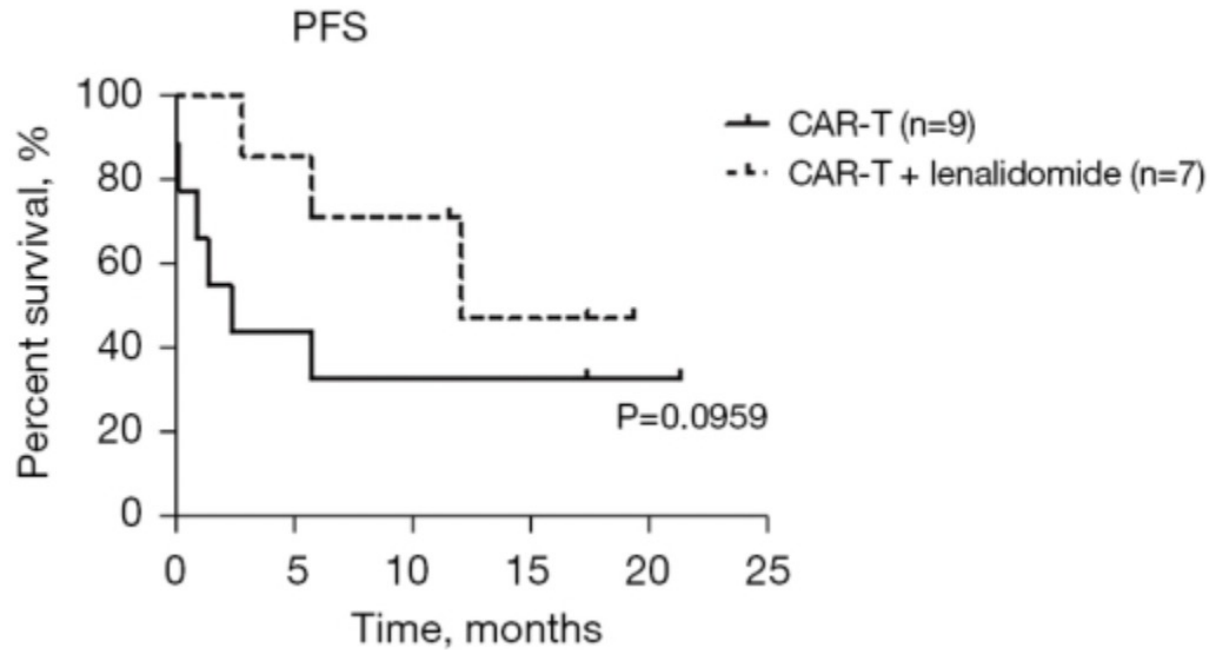
Treatment after CAR T Failure: Lenalidomide



- ~20-40% CAR T failures occur 1st month after infusion
- Lenalidomide
 - Activates CD8 T cells
 - Inhibits Tregs
 - Restores T cell immune synapse
- Len starting D +15 vs No Len after Axicel or Tisacel failure in 1st month
 - ORR 88%
 - PFS 68 vs 35 days
 - CAR T expansion similar to non-relapsed pts



Lenalidomide Maintenance after CAR T



Treatment after CAR T Failure

- Clinical Trials
- Loncastuximab
- Selinexor
- Allogeneic SCT

In the Pipeline

- Allogeneic and NK CARs
- Bivalent, Trivalent CARs
- Upfront CAR T with SOC chemotherapy
- CAR T in CNS Lymphoma

CAR T Clinical Trials at UCD

- UCDC#299: Home-Grown CD19 CAR T cells for R/R DLBCL with escalating doses of lymphodepleting chemotherapy with or w/o rituximab
- AUTO-AL1: R/R B-ALL
- Allogeneic Anti-CD38 Dimeric Antigen Receptor T cells in Multiple Myeloma
- Pemphigus vulgaris: autologous Desmoglein 3 CAART cells
- Auto CD4+ and CD8+ anti-gp120 transduced T cells in HIV-1
- ET140203 T cells in advanced hepatocellular carcinoma