Introduction to cellular therapies: A clinical perspective

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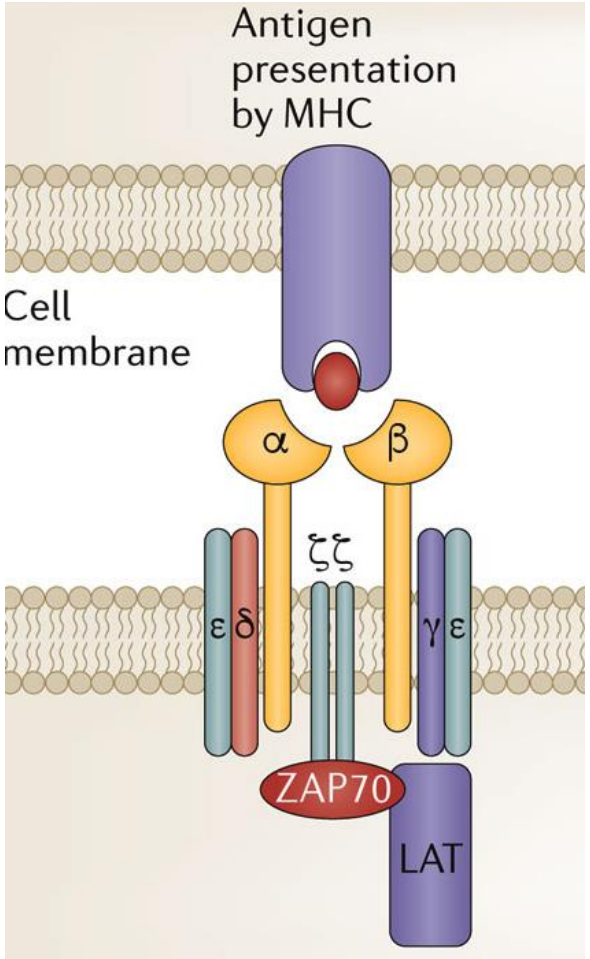
The concept of adoptive T cell therapy

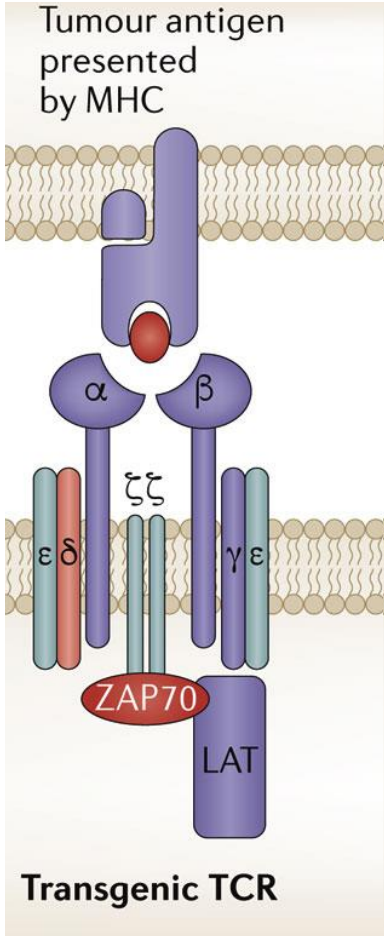
- Adoptive T cell therapy is a unique immunotherapy with living cells
- Pioneered by allogeneic hematopoietic cell transplant: donor lymphocytes produce GvL (1990s)
- Technology developments allow us to specifically direct T cells to cancer

How to redirect T cell specificity against cancer?

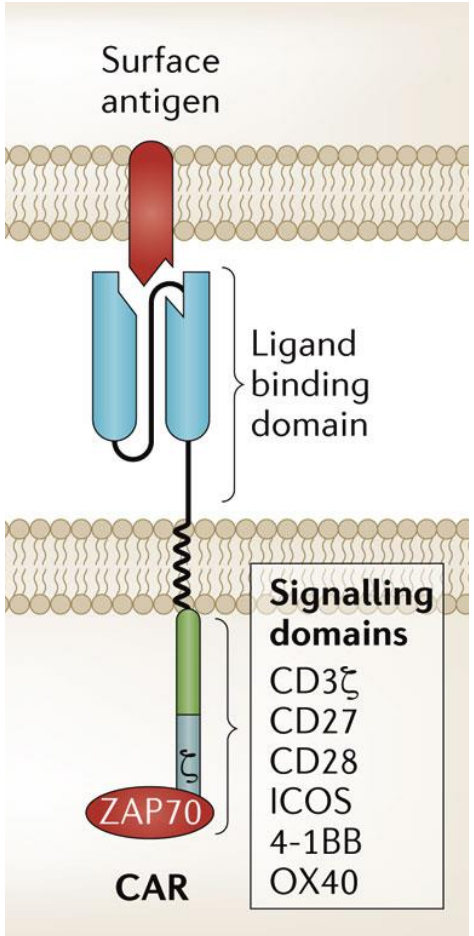
Native TCR



Transgenic TCR

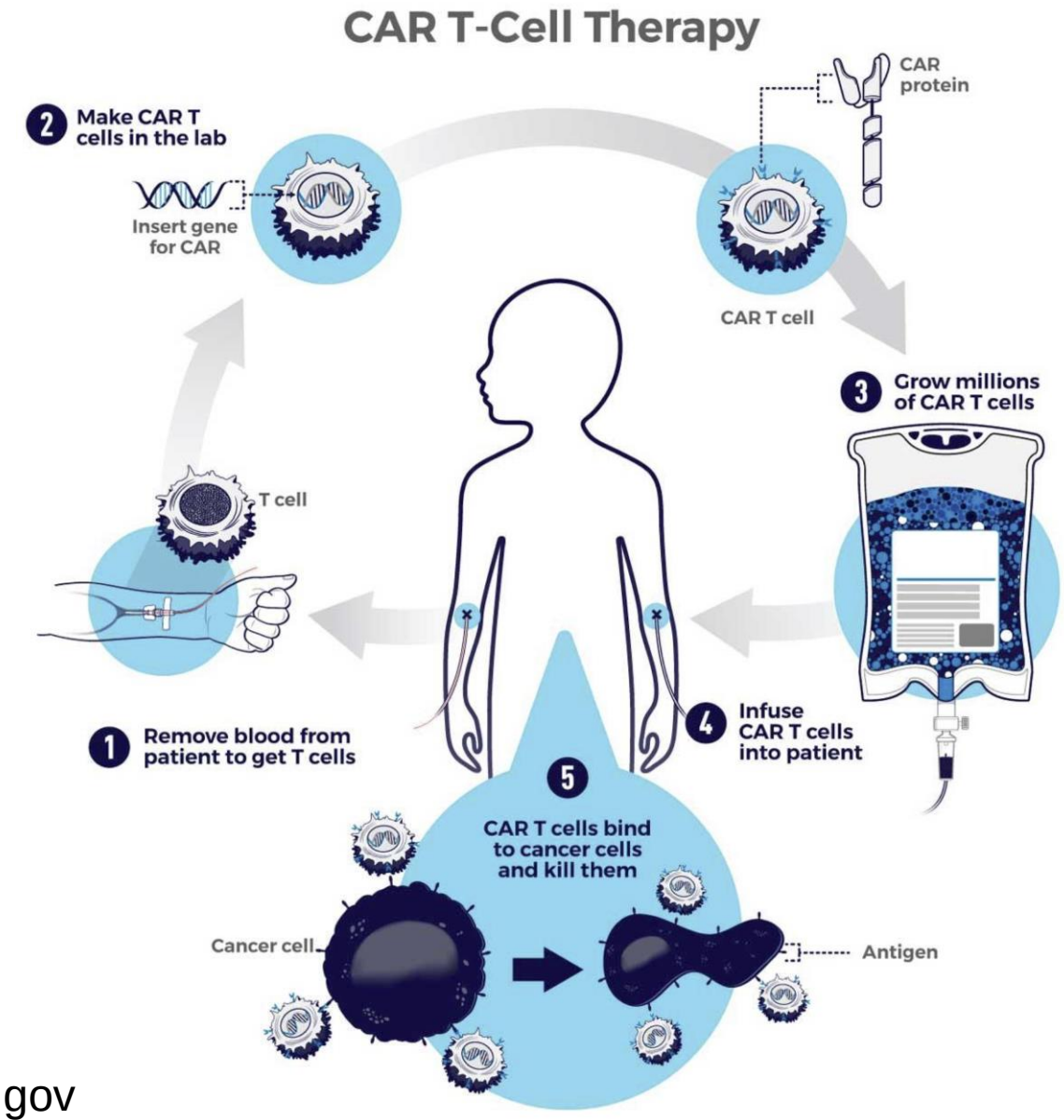


Synthetic CAR



Fesnak et al, Nat Rev Cancer, 2016

Overview of CAR T cell therapy



cancer.gov

Approved therapies on the market:

- CD19 CAR T cells for B cell lymphoma in adults
- CD19 CAR T cells for B cell acute lymphoblastic leukemia (ALL) in children and young adults

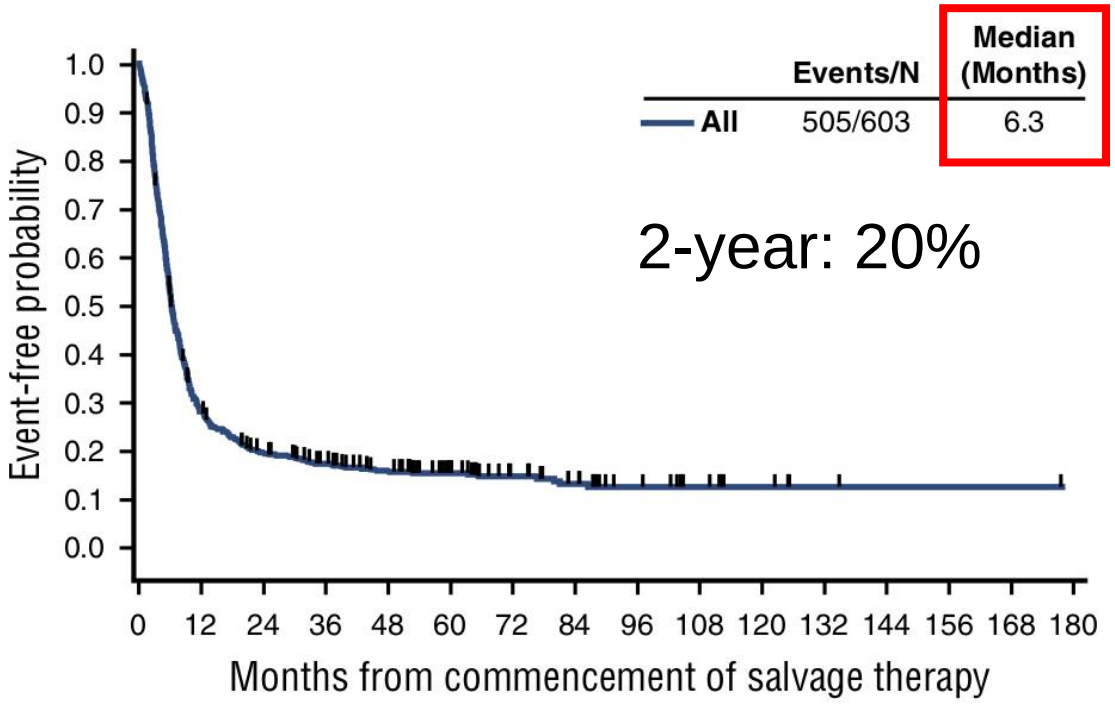
Coming soon:

multiple myeloma

Outcomes in refractory diffuse large B cell lymphoma – status in 2017 before CAR T

- SCHOLAR-1: multicohort retrospective study with patient-level pooled analysis to evaluate response rates and OS in RR NHL
- 4 sources: MDACC observational cohort, IA/MC, Canadian Cancer trials group study LY.12, CORAL LYSARC
- 636 pts included as ”refractory” into the analysis

Overall survival



SCHOLAR-1 Study, Blood 2017, 1800-08

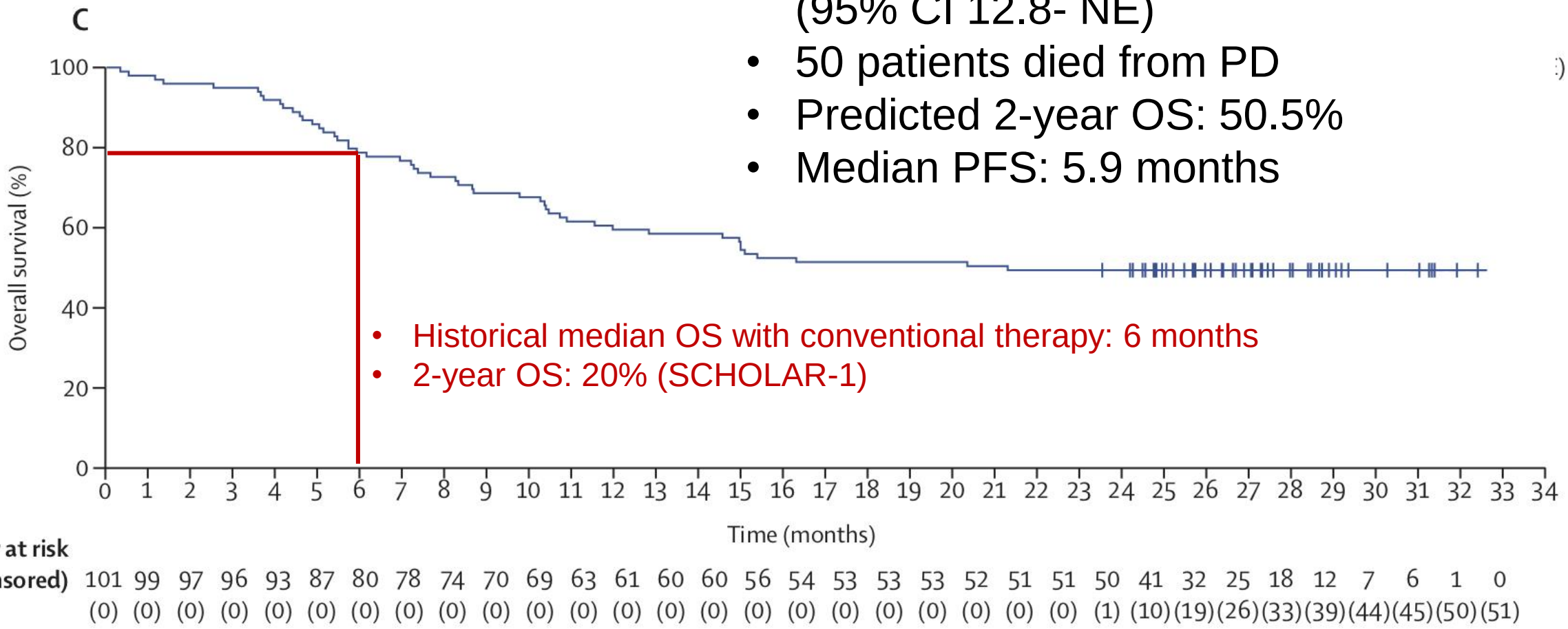
Registration trials: ZUMA-1 (axi-cel, Yescarta®), JULIET (tisa-cel, Kymriah®), TRANSCEND (liso-cel, Breyanzi®)

study	product	references
ZUMA-1 (Kite/ Gilead) Axi-Cel	CD28ζ Retrovirus, CD28 TM Activated T cells	• Academic Ph 1: Kochenderfer J et al., Molecular Therapy, 2017; 25: 2245-53 • Neelapu SS et al., NEJM, Dec 28, 2017, 2531-2544 • Locke et al., Lancet Oncology, 2019, Jan,20(1):31-42
JULIET (Novartis) Tisa-Cel	41BBζ Lentivirus, CD8 TM Activated T cells	• Academic Ph 1: Schuster SJ et al., NEJM, Dec 28, 2017, 2545-2554 • Schuster SJ et al, NEJM, 2019, Jan 3,380(1):45-56 • Schuster et al, NEJM 2021, Feb, first 5-year outcomes
TRANSCEND (Juno/ Celgene/ BMS) Liso-Cel	41BBζ Lentivirus, CD28 TM CD4:CD8 1:1 activated T cells	• Academic Ph 1: Turtle CJ et al., Science Translational Medicine 2016, 8(355):355ra116 • Abramson et al, The Lancet, Sep 2020, 839-852

ZUMA-1 results – FDA approval 2017

Overall survival

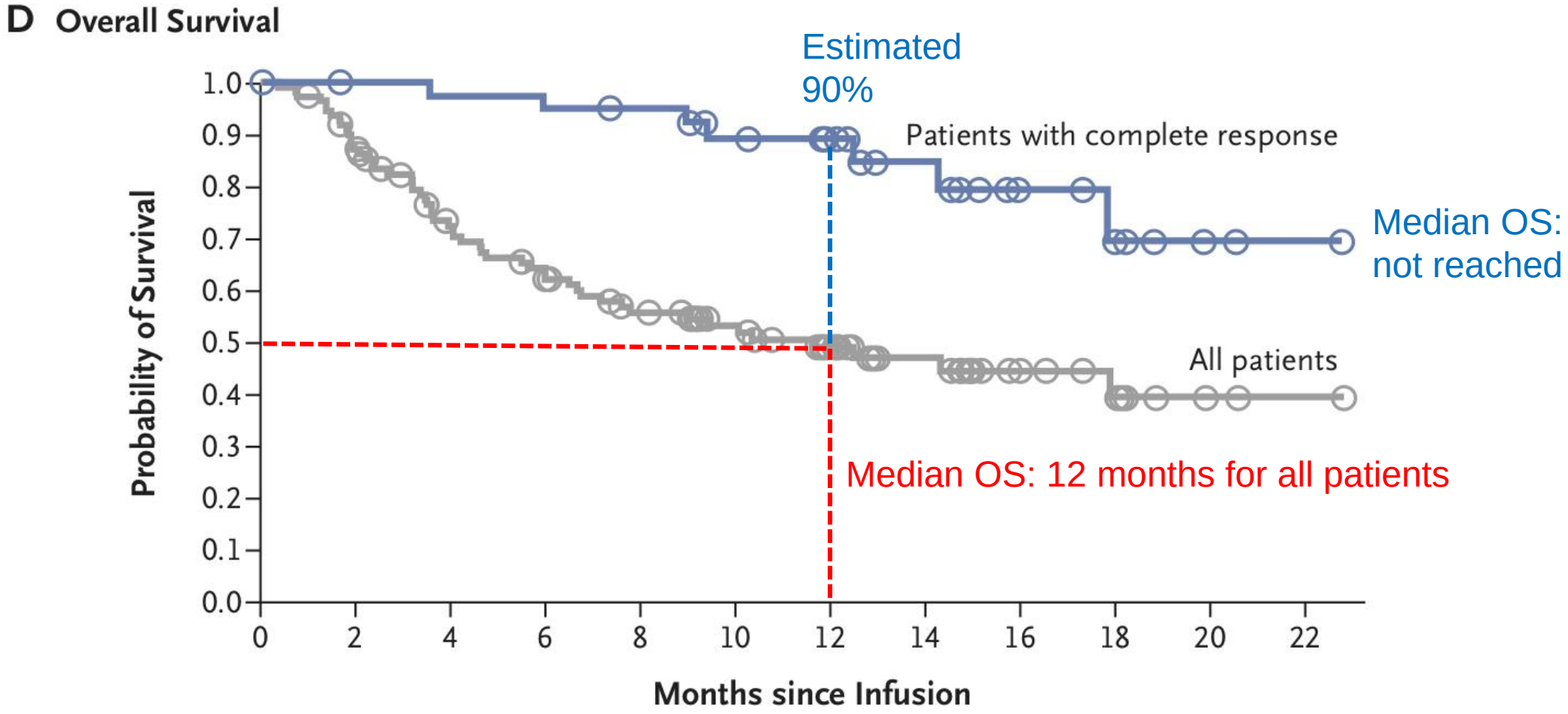
- Median OS: not reached (95% CI 12.8- NE)
- 50 patients died from PD
- Predicted 2-year OS: 50.5%
- Median PFS: 5.9 months



- Historical median OS with conventional therapy: 6 months
- 2-year OS: 20% (SCHOLAR-1)

Neelapu SS, et al., NEJM 2017, Locke FL, et al., The Lancet Oncology, 2018

JULIET Results – FDA approval 2018

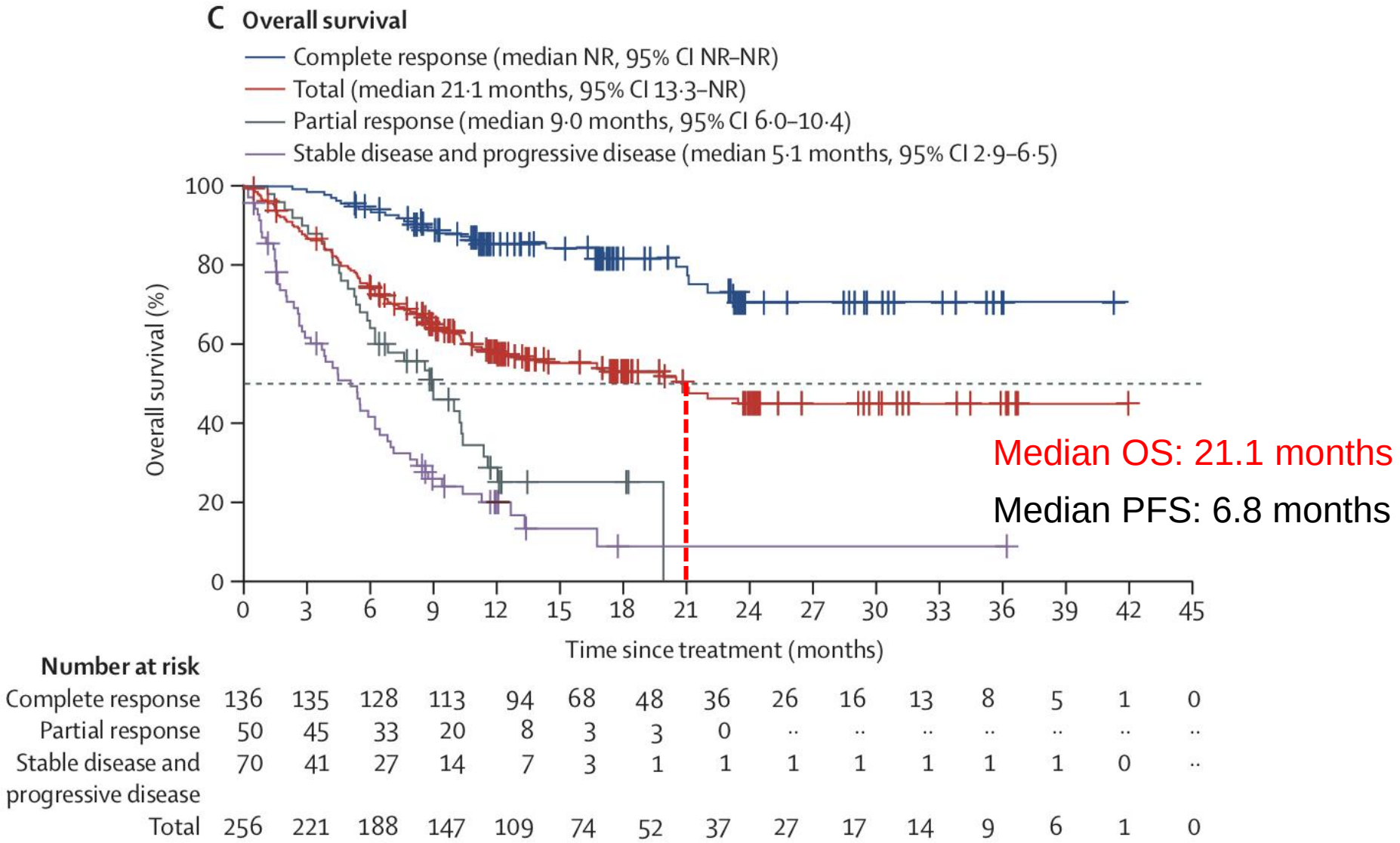


No. at Risk

Patients with complete response	40	40	40	40	39	39	38	38	37	36	30	29	23	16	16	12	9	9	7	3	2	1	1
All patients	111		94		71		60		50		40		28		19		11		8		2		1

Schuster SJ et al., NEJM 2019

TRANSCEND Results – FDA approval 2021



Median OS: 21.1 months

Median PFS: 6.8 months

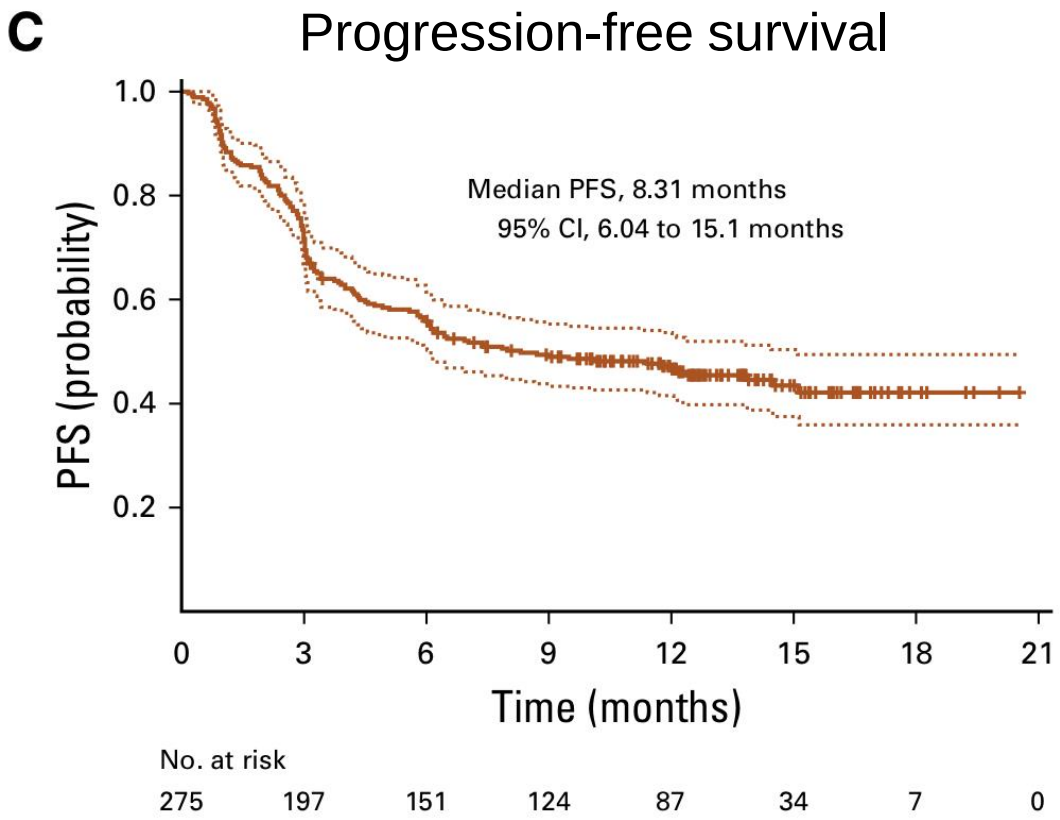
Abramson JS et al., The Lancet, 2020

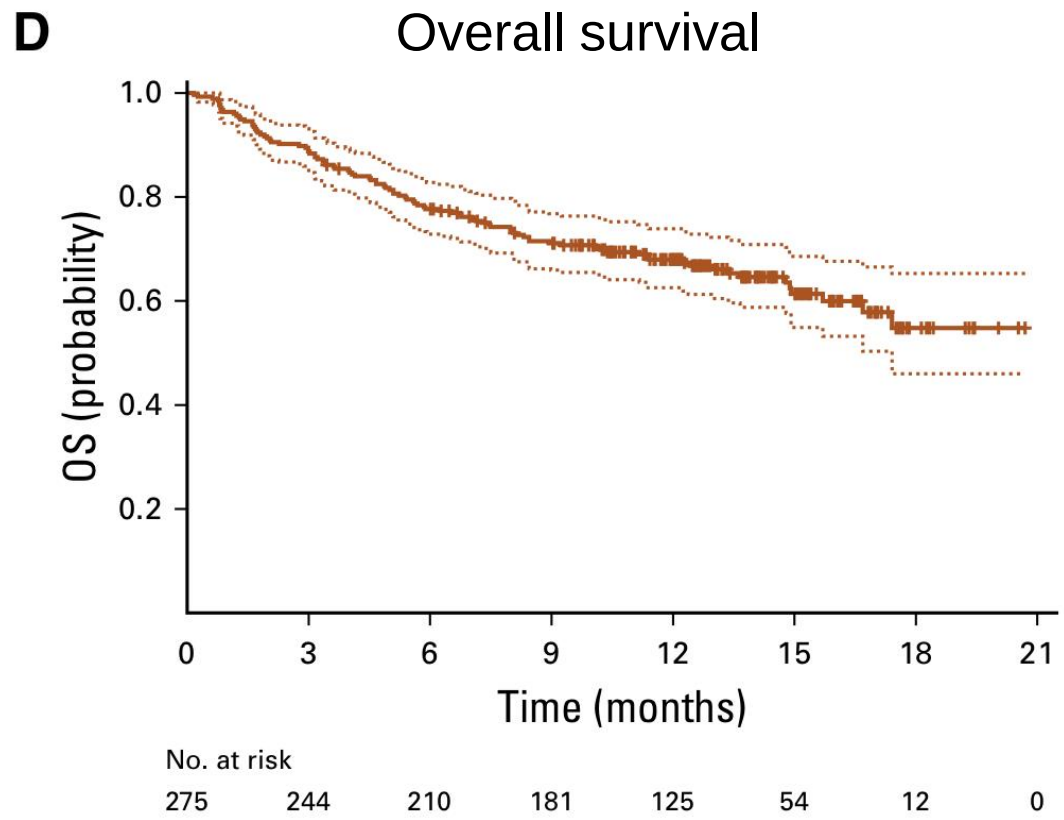
Toxicities after CAR T cell therapy

- Cytokine release syndrome (CRS):
  - fever, hypotension, respiratory insufficiency and other organ failures
  - different degrees of severity
- Neurotoxicity (CAR T cell therapy related encephalopathy syndrome, CRES):
  - confusion, delir, epilepsia, coma
  - different degrees of severity
- General: cytopenias
- On-target toxicity: elimination of normal B cells -> susceptibility to infections
- Management: supportive care, IL6Rα blockade (tocilizumab), steroids

Real world experience – Axi-cel (Yescarta®)

17 US centers, ITT 298 pts (275 infused) with commercial Axi-Cel
43% of patients did not meet ZUMA-1 criteria - Outcomes and toxicities are comparable





Nastoupil LJ et al., JCO, 2020

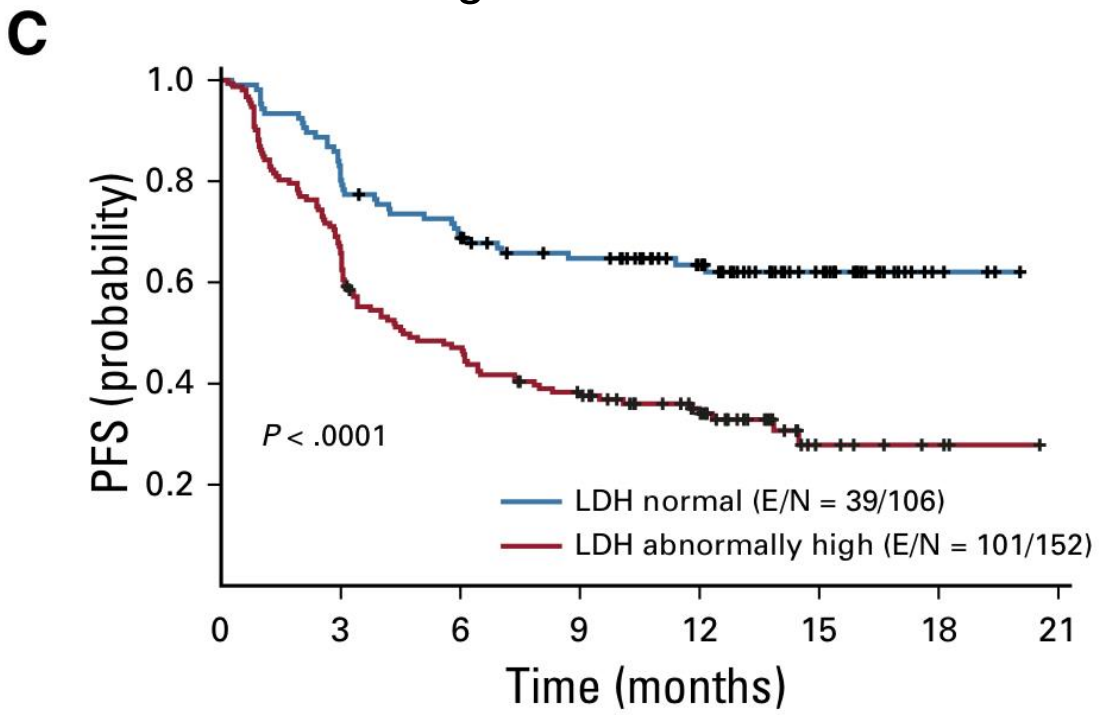
Overall response and CR, PR rates

Study	No. of Patients	ORR (%)	CR Rate (%)	Median PFS, Months (95% CI)	PFS Rate, % (95% CI)		OS Rate, % (95% CI)	
					6 Month	12 Month	6 Month	12 Month
ZUMA-1[6]								
Phase I and II (cohorts 1 and 2)	108	82	58	5.8 (3.3 to NE)	49 (39 to 58)	44 (34 to 53)	78 (69 to 85)	59 (49 to 68)
SOC cohort								
Total infused	275	82	64	8.3 (6.0 to 15.1)	56 (50 to 62)	47 (41 to 53)	78 (73 to 83)	68 (63 to 74)
Infused with comorbidities that were ZUMA-1 exclusion criteria[a]	110	74	56	5.3 (3.4 to 8.0)	48 (40 to 58)	34 (26 to 44)	70 (62 to 79)	58 (50 to 69)
Infused without comorbidities that were ZUMA-1 exclusion criteria[a]	165	87	69	NE (9.0 to NE)	61 (54 to 69)	55 (48 to 64)	83 (77 to 87)	74 (68 to 82)

Nastoupil LJ et al., JCO, 2020

Baseline LDH levels impact outcome

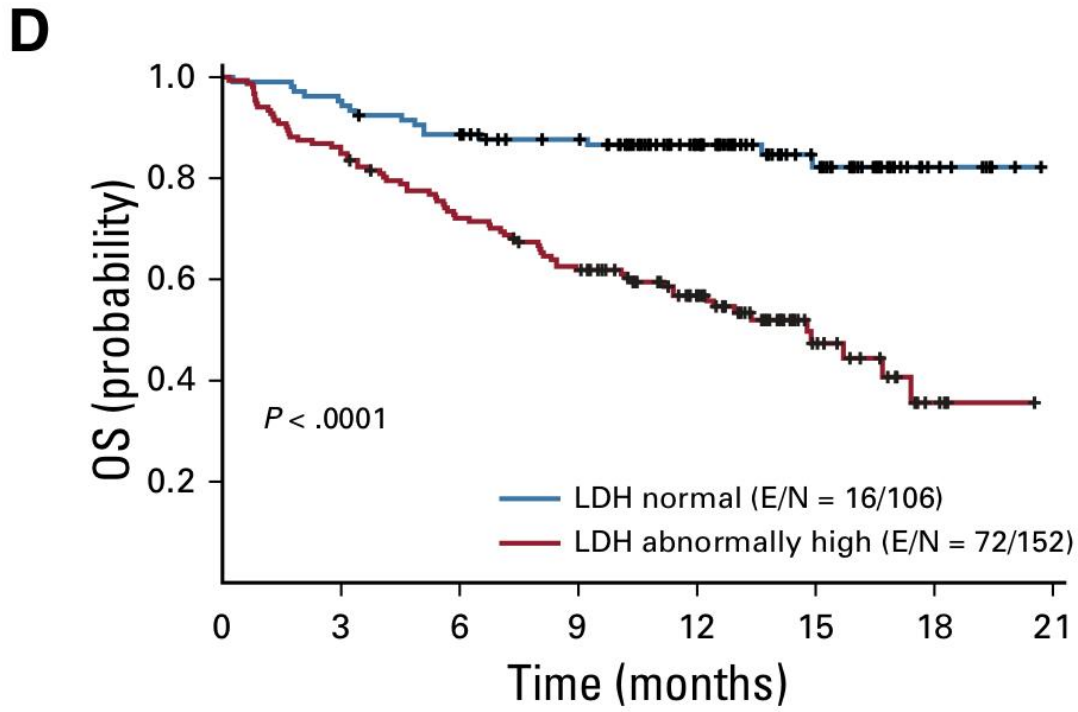
Progression-free survival



No. at risk:

LDH normal	106	85	72	62	48	24	4	0
LDH abnormally high	152	100	70	53	32	7	3	0

Overall survival



No. at risk:

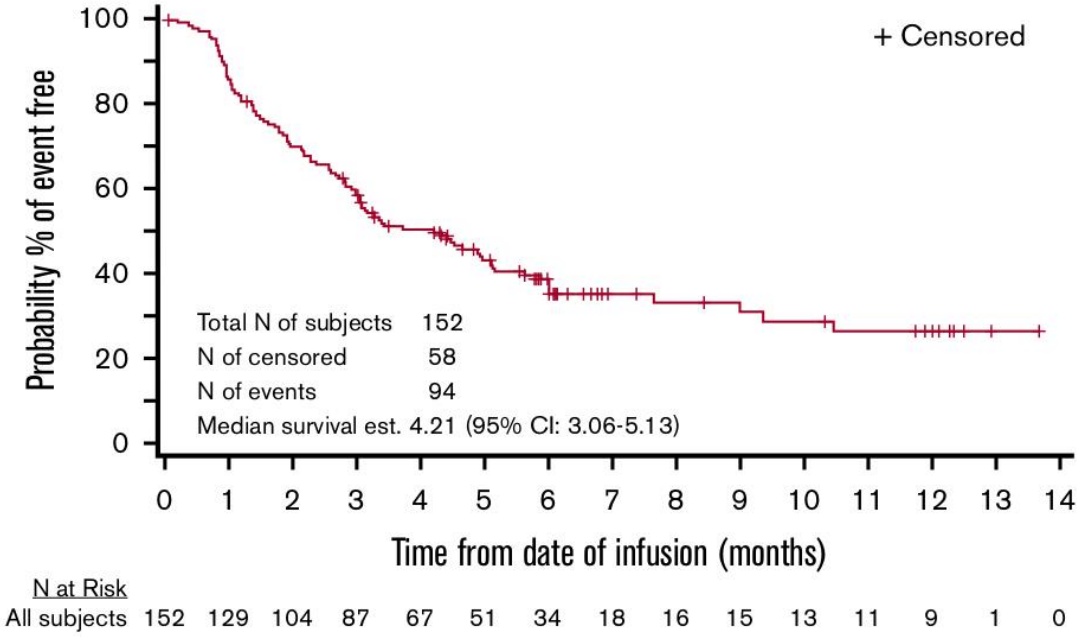
LDH normal	106	101	93	84	61	32	8	0
LDH abnormally high	152	129	107	88	57	19	4	0

Nastoupil LJ et al., JCO, 2020

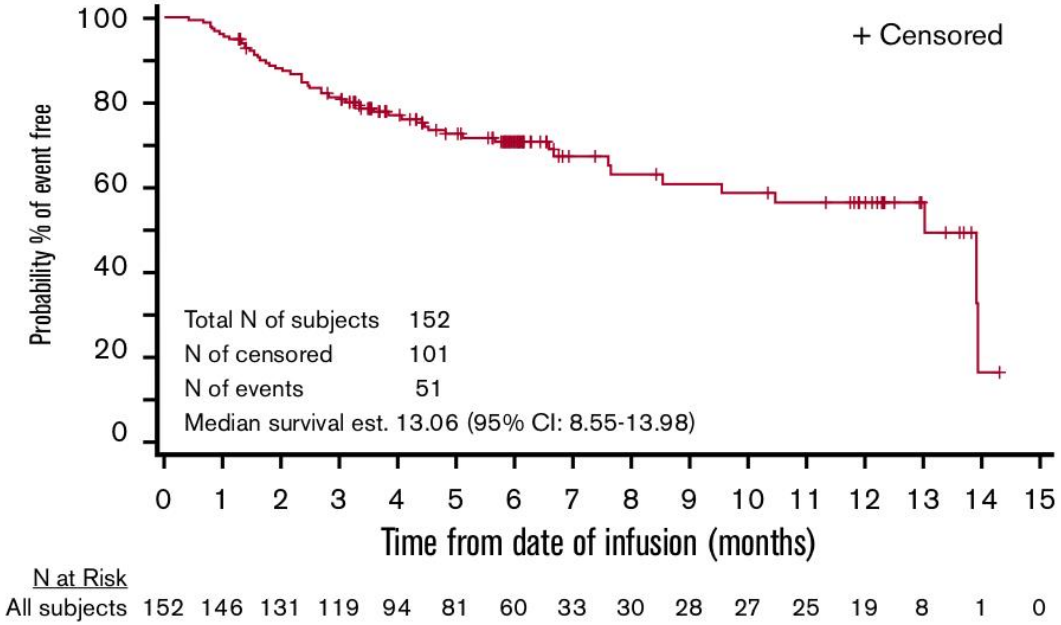
Real world experience – Tisa-cel (Kymriah®)

CIBMTR registry data, 130 centers in the US and Canada
255 pts with ALL, 155 pts with **lymphoma**

Progression-free survival lymphoma



Overall survival lymphoma



Pasquini MC et al., Blood Advances, 2020 / CIBMTR analysis

Outcomes CIBMTR real life vs JULIET : comparable results

	CIBMTR	JULIET
CIBMTR vs JULIET	(n = 152)	(n = 115)
ORR (CR + PR)	61.8 (53.6-69.6)	52.2 (42.7-61.6)
BOR of CR	39.5 (31.6-47.7)	38.3 (29.4-47.8)
DOR		
At 6 mo	55.3 (42.2-66.6)	66.6 (52.8-77.3)
At 12 mo	48.4* (33.9-61.5)	62.7 (48.7-73.9)
PFS		
At 6 mo	38.7 (30.5-46.9)	39.0 (29.7-48.2)
At 12 mo	26.4* (17.2-36.6)	34.7 (25.7-43.9)
OS		
At 6 mo	70.7 (62.2-77.6)	61.2 (51.6-69.5)
At 12 mo	56.3 (44.2-66.8)	48.2 (38.6-57.1)

* Less than 10 pts at risk

Pasquini MC et al., Blood Advances, 2020 / CIBMTR analysis

Conclusions

- CAR T cell therapies have profoundly impacted and changed patient management in B cell malignancies (B-ALL up to 25 yo, DLBCL and PMBCL)
- Real world experience recapitulates clinical trial results despite differences in patient selection
- Extension to other diseases awaited

Challenges

- Paucity of randomized studies
- Pharmacokinetics of living drug, relationship dose – response to treatment
- Predictors of response and toxicities at time of treatment decision
- Heterogeneity of
  - disease genetics
  - bridging therapies
  - lymphocyte quality (autologous products)
  - manufacturing time (time from treatment decision to infusion)
- Treatment options for patients that fail CAR T cell therapy
- Study design for next generation CAR Ts in existing indications