CAR-T CELL THERAPY

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DISCLOSURES

- None

OUTLINE

- Cases
- History of cellular therapy and blood cancer treatment
- What is CAR-T cell therapy?
- Indications
- Logistics
- Side effects
- Future directions

OBJECTIVE

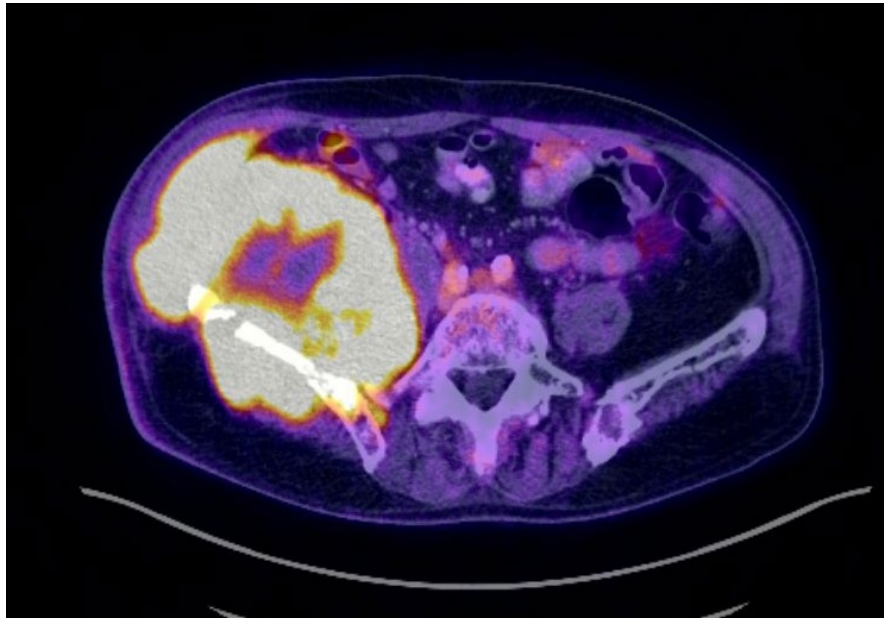
- Understand what CAR-T cell therapy is
- Understand current indications for CAR-T cell therapy
- Understand the risks and benefits of CAR-T cell therapy

CASE 1

- 64-year-old man with diffuse large B-cell lymphoma
- May 2020: Presented with fatigue and difficulty swallowing pills. Large neck mass noted, bx showed DLBCL of the thyroid with associated LA. Pt received 6 cycles of R-CHOP with remission.
- December 2021: Relapsed lymphoma with disease above and below diaphragm, pt received R-ICE x 2 cycles followed by autologous stem cell transplant, day 0 = 4/11/22
- October 2022: Relapsed disease

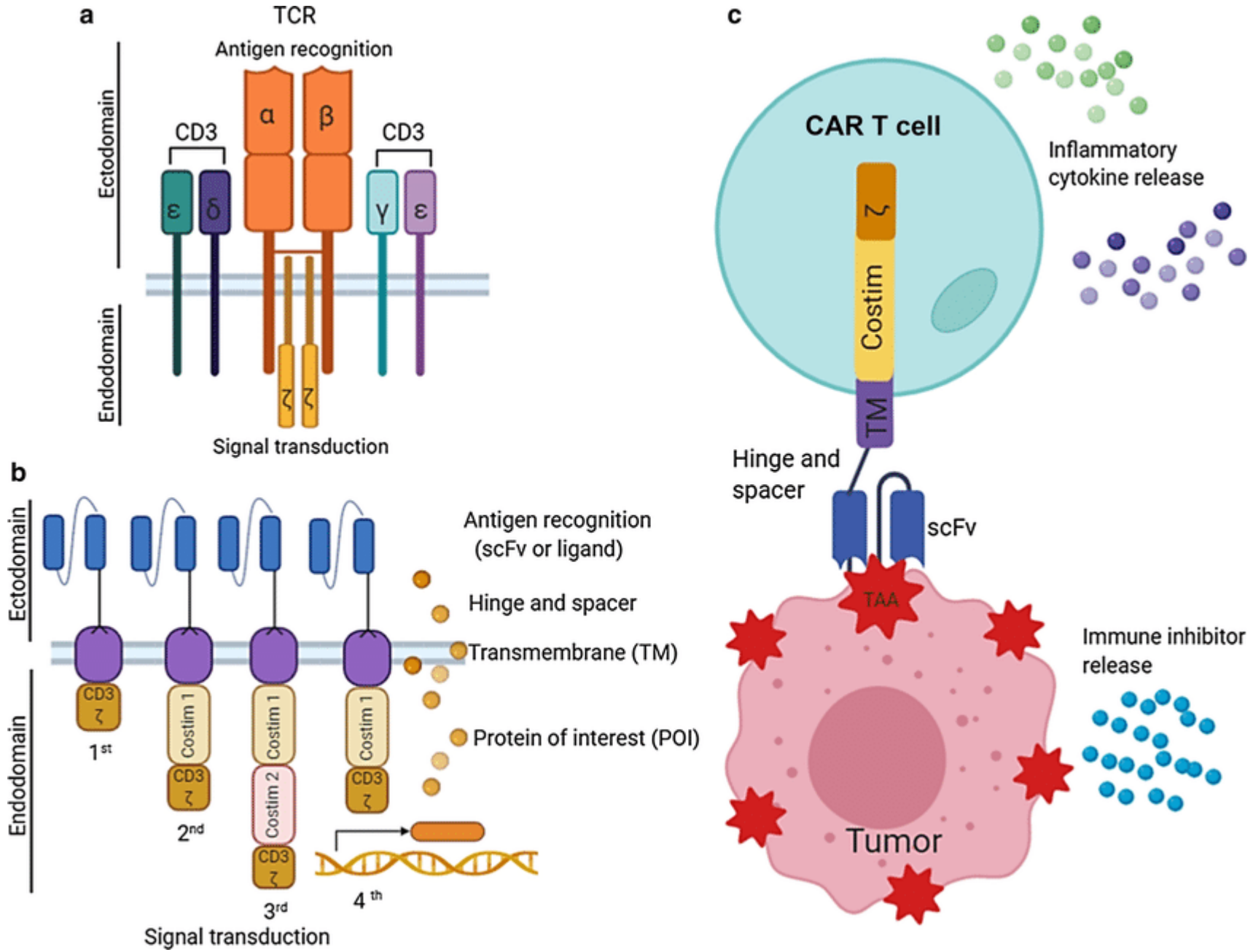
CASE 2

- 73-year-old man with multiple myeloma
- December 2020: Presented to the hospital with anemia, renal failure, lytic bone lesions. IgG kappa M-spike 4.1 gm/dL, FLC ratio 130, bone marrow with 50% plasma cells with poor risk cytogenetics
- Lines of therapy:
  - 1) VRd Dec 2020-March 2021
  - 2) DVRd March 2021-June 2021
  - 3) DPd June 2021- Sep 2022
  - 4) ERd Oct 2022- July 2023
- July 2023: Progression of disease,
  M-spike 2.6, FLC ratio 71



WHAT IS CAR-T CELL THERAPY?

- Chimeric antigen receptor T-cell therapy
- T-cells that are engineered in a lab to fight a specific cancer



Journal of Translational Medicine, Nov 2020

CAR-T CELL PRODUCTS

- Tisagenlecleucel (Kymriah)
- Axicabtagene ciloleucel (Yescarta)
- Lisocabtagene maraleucel (Breyanzi)
- Brexucabtagene autoleucel (Tecartus)
- Idecabtagene vicleucel (Abecma)
- Ciltacabtagene autoleucel (Carvykti)

CANCERS TREATED

- Acute lymphoblastic leukemia
- Diffuse large B-cell lymphoma
- Follicular lymphoma
- Marginal zone lymphoma
- Mantle cell lymphoma
- Chronic lymphocytic leukemia
- Multiple myeloma

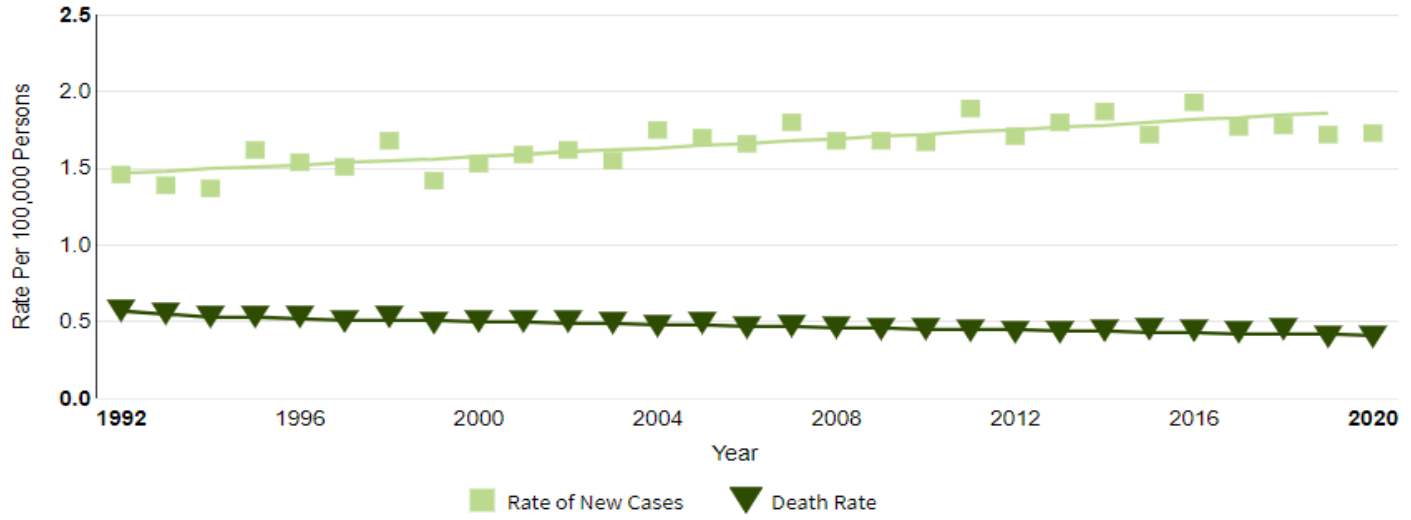
ACUTE LYMPHOBLASTIC LEUKEMIA

At a Glance

Estimated New Cases in 2023	6,540
% of All New Cancer Cases	0.3%

Estimated Deaths in 2023	1,390
% of All Cancer Deaths	0.2%

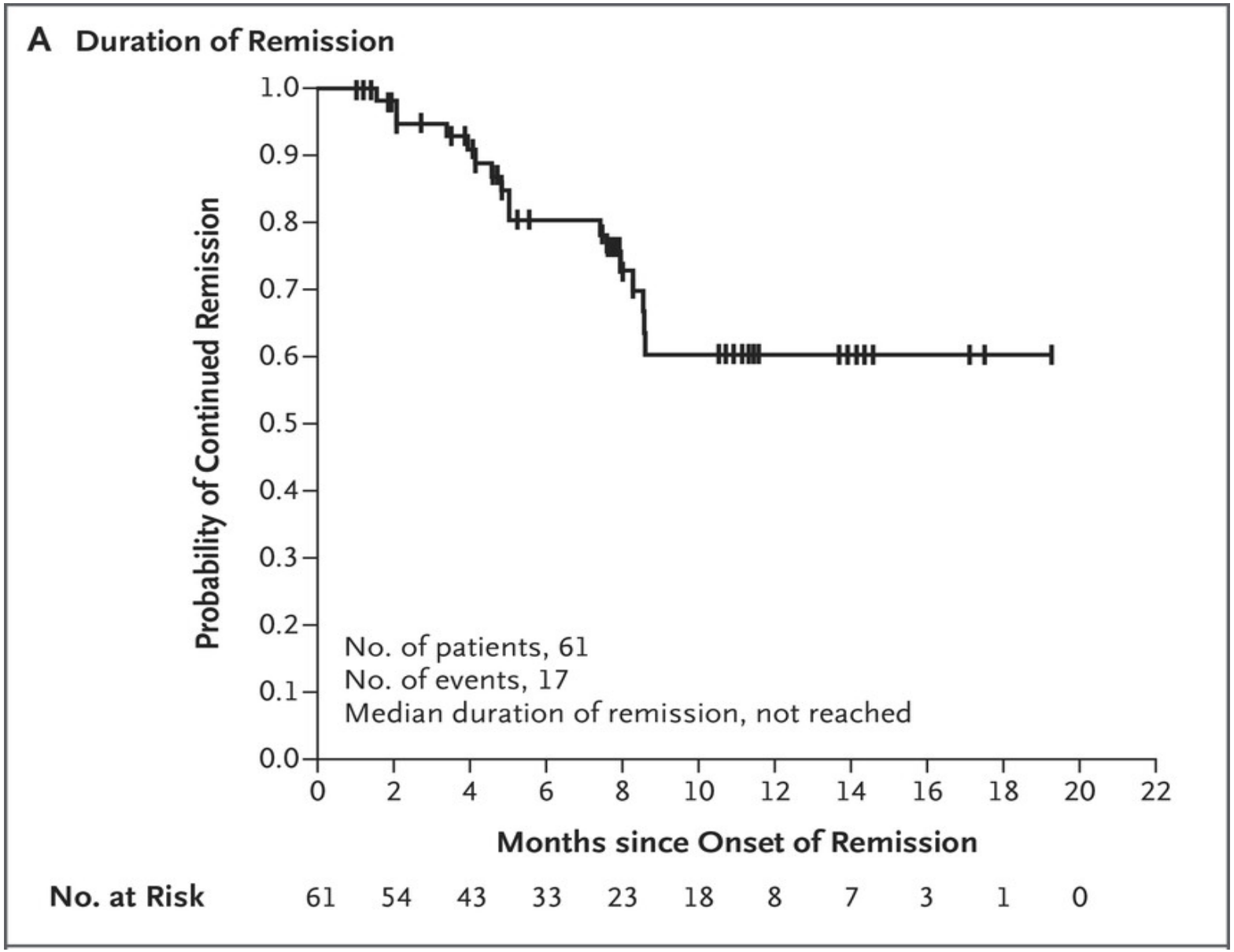
5-Year Relative Survival
71.3%
2013–2019

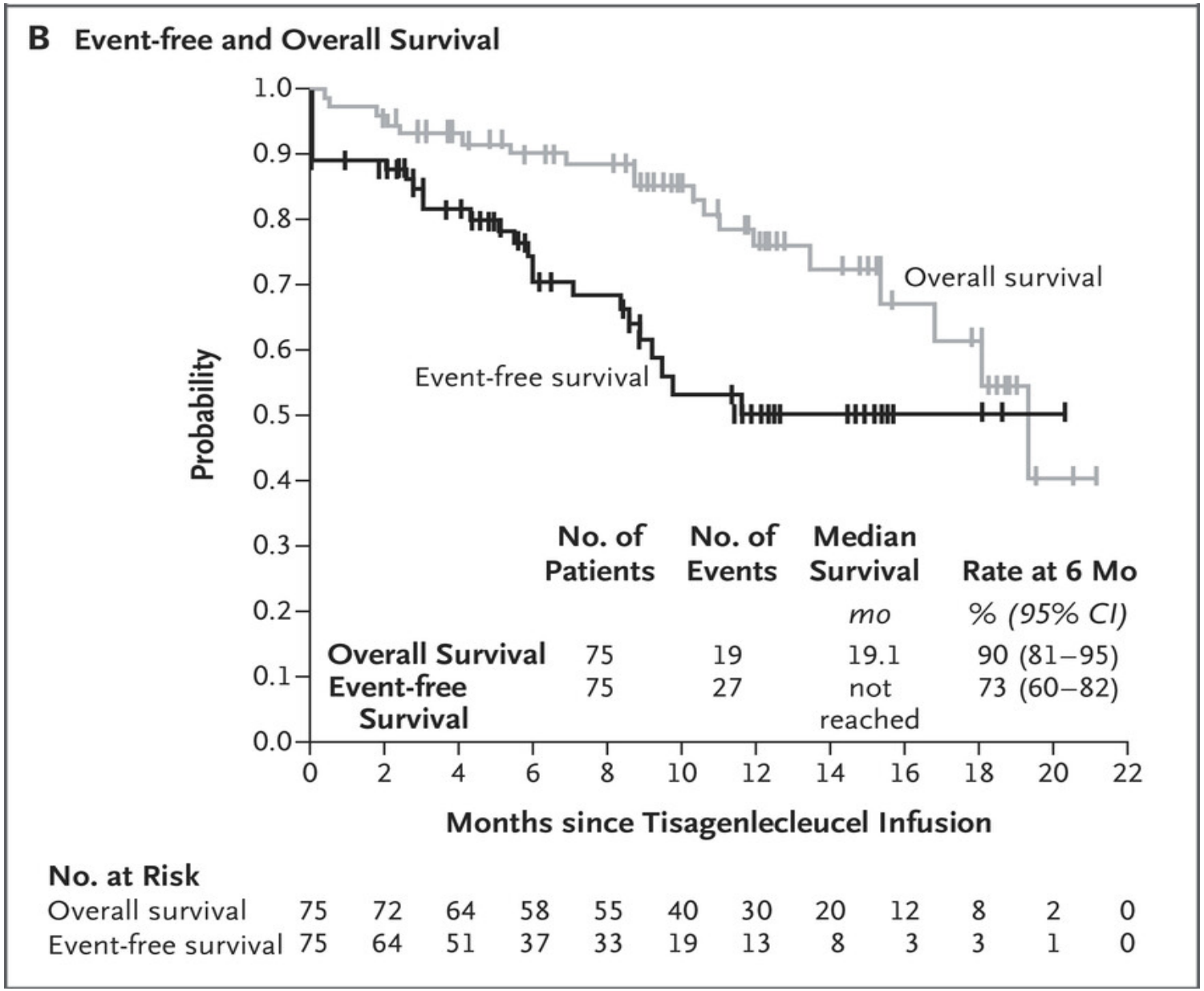


SEER database, 2024

ACUTE LYMPHOBLASTIC LEUKEMIA

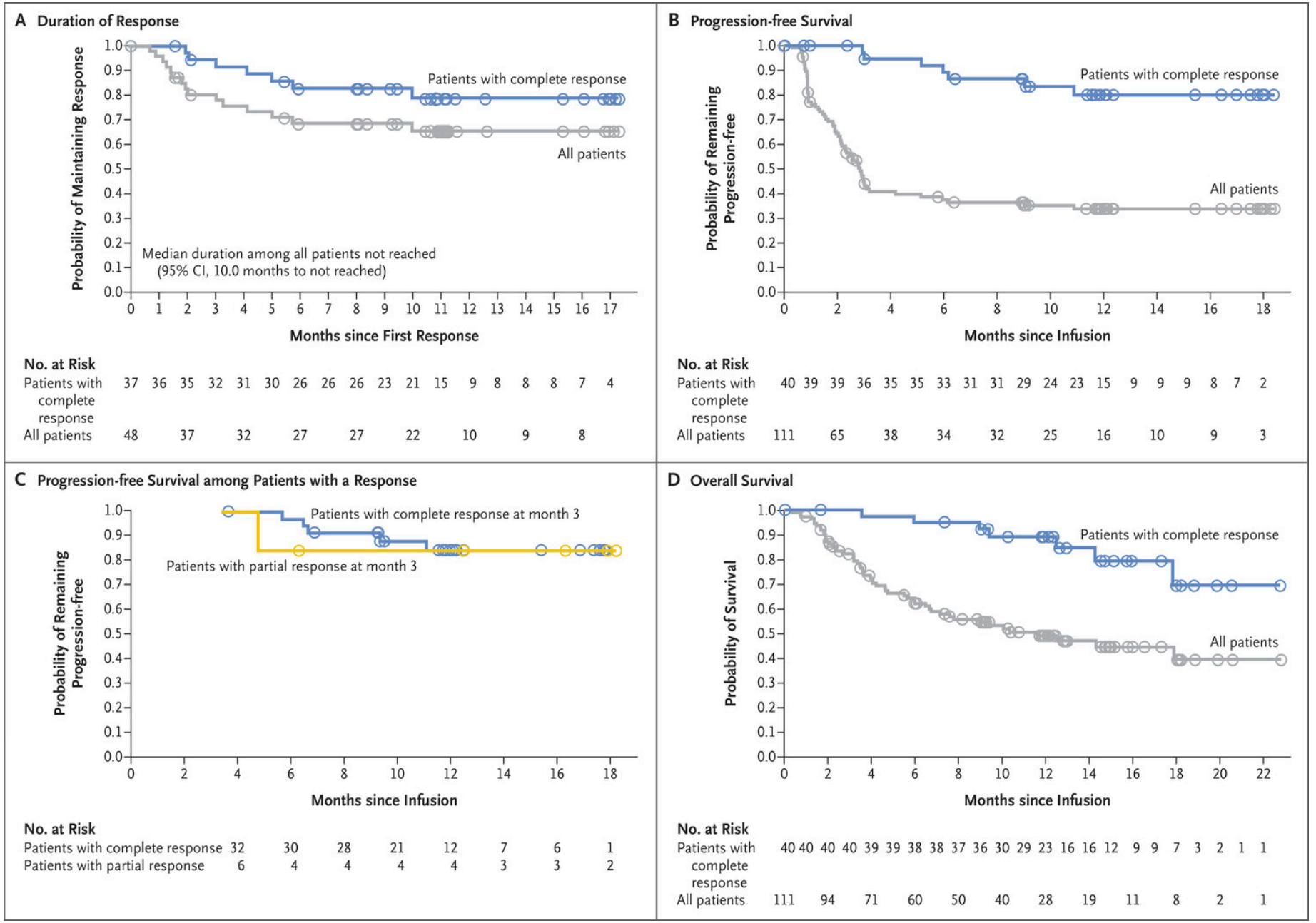
- First approval of CAR-T cell therapy in August 2017
- ELIANA trial for tisa-cel in children and young adults
  - Enrolled 92 patients, 75 underwent infusion
  - Median age: 11
  - Median previous lines of therapy: 3 (61% prior allo)
  - Median marrow blast percentage: 74%
- CR rate (CR+Cri) 81% at 3 months
- EFS 73% at 6 months, 50% at 12 months


A Duration of Remission
Probability of Continued Remission
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
No. of patients, 61
No. of events, 17
Median duration of remission, not reached
0
2
4
6
8
10
12
14
16
18
20
22
Months since Onset of Remission
No. at Risk
61
54
43
33
23
18
8
7
3
1
0


B Event-free and Overall Survival
Probability
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
Overall survival
Event-free survival
No. of Patients
No. of Events
Median Survival
Rate at 6 Mo
mo
% (95% CI)
Overall Survival 75 19 19.1 90 (81–95)
Event-free Survival 75 27 not reached 73 (60–82)
0 2 4 6 8 10 12 14 16 18 20 22
Months since Tisagenlecleucel Infusion
No. at Risk
Overall survival 75 72 64 58 55 40 30 20 12 8 2 0
Event-free survival 75 64 51 37 33 19 13 8 3 3 1 0

DIFFUSE LARGE B-CELL LYMPHOMA

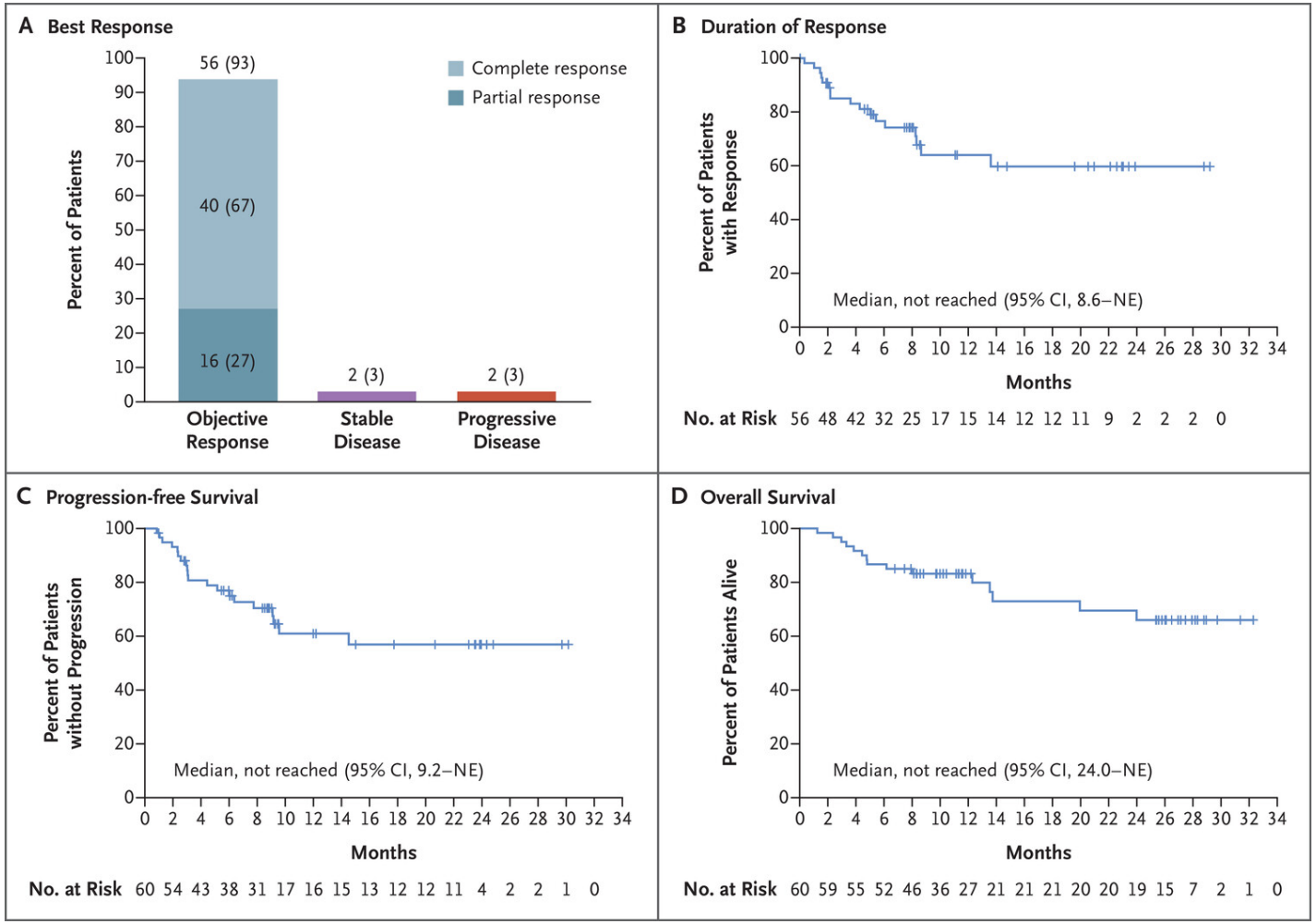
- First approval May 2018
- Approved third line or R/R DLBCL with response to first line <12 months
- JULIET trial for tisa-cel
  - 111 patients received infusion, 93 included in efficacy evaluation
  - Best ORR 52%: 40% CR, 12% PR
  - Patients who achieved a CR


A Duration of Response
Probability of Maintaining Response
Patients with complete response
All patients
Median duration among all patients not reached
(95% CI, 10.0 months to not reached)
Months since First Response
No. at Risk
Patients with complete response 37 36 35 32 31 30 26 26 26 23 21 15 9 8 8 8 7 4
All patients 48 37 32 27 27 22 10 9 8
B Progression-free Survival
Probability of Remaining Progression-free
Patients with complete response
All patients
Months since Infusion
No. at Risk
Patients with complete response 40 39 39 36 35 35 33 31 31 29 24 23 15 9 9 9 8 7 2
All patients 111 65 38 34 32 25 16 10 9 3
C Progression-free Survival among Patients with a Response
Probability of Remaining Progression-free
Patients with complete response at month 3
Patients with partial response at month 3
Months since Infusion
No. at Risk
Patients with complete response 32 30 28 21 12 7 6 1
Patients with partial response 6 4 4 4 4 3 3 2
D Overall Survival
Probability of Survival
Patients with complete response
All patients
Months since Infusion
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

MANTLE CELL LYMPHOMA

- First approved June 2020
- Brexu-cel
- Indication: R/R MCL who have progressed after BTK inhibitor
- ZUMA-2 trial
  - 74 patients evaluated, 60 ultimately enrolled
  - 87% ORR, 62% CR
  - 62% 3 year OS

MANTLE CELL LYMPHOMA



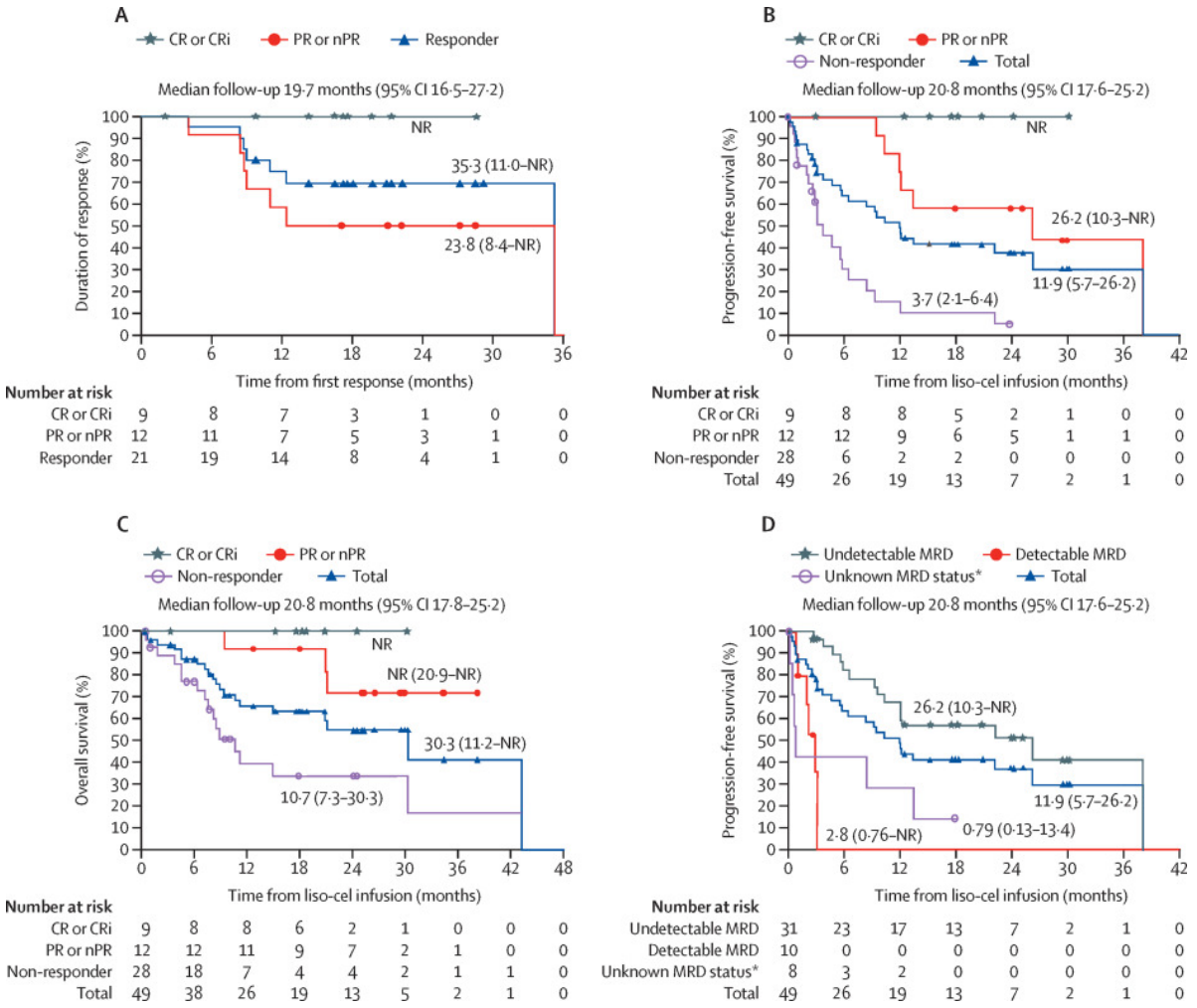
FOLLICULAR LYMPHOMA

- Axi-cel, first approval March 2021
- ZUMA-5
  - Evaluated 81 FL patients for efficacy
  - ORR 91%, CR rate 60%

CHRONIC LYMPHOCYTIC LEUKEMIA

- Most recent approval for CLL/SLL, March 2024
- Liso-cel
- At least two prior lines of therapy, including a BTKi and bcl2 inhibitor
- TRANSCEND CLL 004
  - 137 patients enrolled, 117 treated

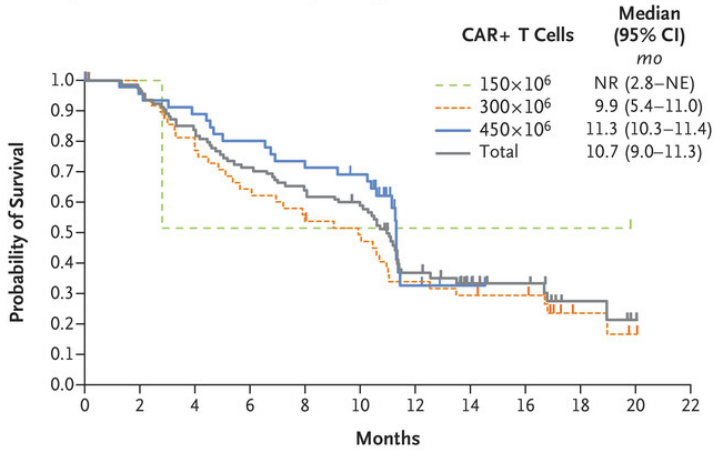
CHRONIC LYMPHOCYTIC LEUKEMIA



MULTIPLE MYELOMA

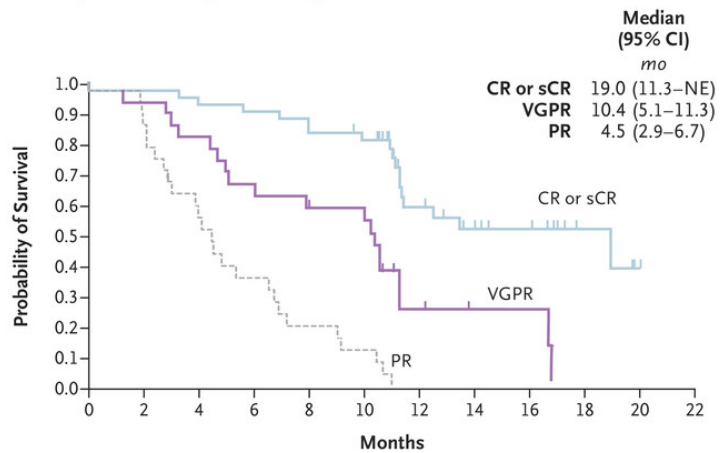
- Ide-cel approved March 2021
- KarMMa trial
  - 72% ORR, sCR 29%
  - mPFS 11.1 months
  - mOS 24 months

A Duration of Response, Overall and According to Target Dose



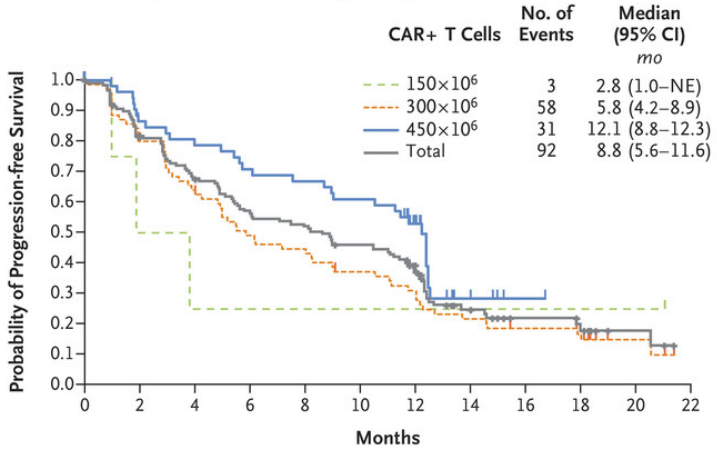
No. at Risk												
150×10⁶	2	2	1	1	1	1	1	1	1	1	0	
300×10⁶	48	45	35	29	24	21	14	12	11	3	1	0
450×10⁶	44	42	39	35	31	29	7	2	0	0	0	
Total	94	89	75	65	56	51	22	15	12	4	1	0

B Duration of Response According to Best Response



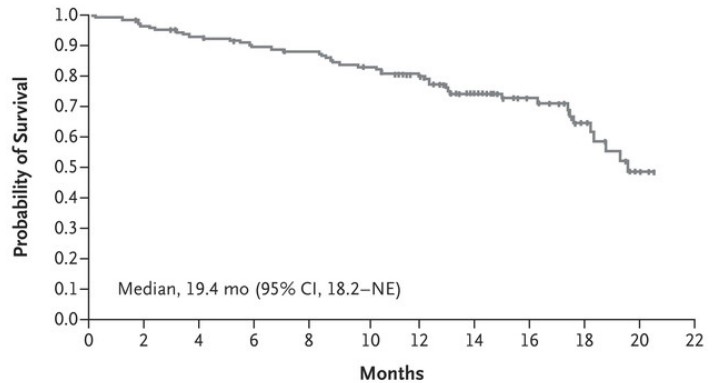
No. at Risk												
CR or sCR	42	42	40	39	36	34	18	13	10	4	1	0
VGPR	25	24	21	17	15	14	4	2	2	0	0	
PR	27	23	14	9	5	3	0	0	0	0	0	

C Progression-free Survival, Overall and According to Target Dose



No. at Risk												
150×10⁶	4	2	1	1	1	1	1	1	1	1	1	0
300×10⁶	70	56	42	33	29	24	17	14	11	7	3	0
450×10⁶	54	44	40	36	34	31	17	4	1	0	0	
Total	128	102	83	70	64	56	35	19	13	8	4	0

D Overall Survival



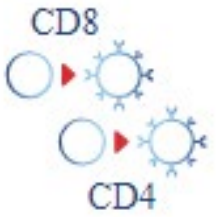
No. at Risk	128	122	114	108	104	97	82	55	38	27	12	0

LOGISTICS OF CAR-T

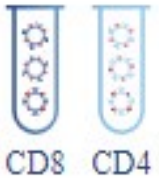
PROCESS

LEUKAPHERESIS

MANUFACTURING



INFUSION



MONITORING

LEUKAPHERESIS

- T-cells are collected via apheresis on our apheresis machines

BRIDGING THERAPY

- Chemotherapy that may be necessary between apheresis and infusion of CAR-T cell product due to rapid progression of disease
- Does bridging therapy increase the likelihood of treatment failure?
  - Jain et al identified inferior outcomes in 2019
  - Reevaluation in 2024 confirmed that pts with bridging therapy had worse outcomes, but on propensity score matching, outcomes were similar

MANUFACTURING

- Can take as little as 17 days or as much as six weeks
- Get an estimated manufacturing time at the time of apheresis
- Get an actual ship date ~one week prior

LYMPHODEPLETION

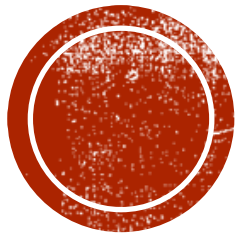
- Standard lymphodepletion fludarabine/Cytoxan
- Role is stunning the immune system to allow CAR-T cells in

CAR-T CELL INFUSION

- Different products are given slightly differently
- Looks like a blood transfusion or injection

MONITORING

- At WVU we administer all CAR-T cell therapy products as an outpatient
- 3x/day visits for vitals and ICE assessment (neurologic toxicity) for first 14 days, with labs once/day
- Daily visits for labs, vitals, ICE assessment for one week
- 3x/week visits for labs, vitals, ICE assessment for one week
- Discharge home ~day 28



SIDE EFFECTS

CYTOKINE RELEASE SYNDROME

- Syndrome of fevers, hypotension, SOB
- Grade 1-4
- Manage with steroids, tocilizumab

NEUROTOXICITY

- Immune effector cell-associated neurotoxicity syndrome (ICANS)
- Confusion, weakness, neuropathy, decreased level of consciousness, coma, seizures
- Grade 1-4, manage with steroids, levetiracetam, anakinra(?)

NEUROTOXICITY

ICE Scoring Worksheet	
Orientation to year, month, city, hospital (1 point for each correct, maximum of 4 p...	4
Name 3 objects - for example, point to clock, pen, and button (1 point for each cor...	3
Ability to follow simple commands (example "show me 2 fingers" or "close your ey...	1
Write a standard sentence (1 pt) for example "Our national bird is the bald eagle"	1
Count backwards from 100 in tens (1 point)	1
Score	10
Assessment Deferral Reason	

CYTOPENIAS

- Immune effector cell-associated hematotoxicity (ICAHT)
- Early and late (30 days)
- Most recent scoring system, ASH 2023
  - CAR-HEMATOX

CYTOPENIAS

Table 1.

ICAHT grading

Grading	1	2	3	4
Early ICAHT (day 0-30)				
ANC ≤500/μL	<7 d	7-13 d	≥14 d	Never above 500/μL
ANC ≤100/μL	—	—	≥7 d	≥14 d
Late ICAHT (after day +30)*				
ANC	≤1500/μL	≤1000/μL	≤500/μL	≤100/μL

* Measured ≥2 time points, or nontransient neutropenia.

CYTOPENIAS

Prior to lymphodepleting chemotherapy (day -5)

→ Determine patient-individual risk of heme-tox and infections using the **CAR-HEMATOTOX score**

- Leniency time period for lab values: 3 days

Features	0 Point	1 Point	2 Points
Platelet count	> 175.000/µl	75.000 - 175.000/µl	< 75.000/µl
Absolute neutrophil count (ANC)	> 1200/µl	≤ 1200/µl	-
Hemoglobin	> 9.0 g/dl	≤ 9.0 g/dl	-
C-reactive protein (CRP)	< 3.0 mg/dl	≥ 3.0 mg/dl	-
Ferritin	< 650 ng/ml	650-2000 ng/ml	> 2000 ng/ml
Low: 0-1 High: ≥2			

Low risk (HT 0-1)

High risk (HT 2-7)

Risk profile

	LBCL (n = 235)	MCL (n = 103)	MM (n = 113)
Median duration of severe neutropenia (ANC<500/µL, D0-60)	5.5 days (95% CI 5-8 days)	6 days (95% CI 5-7 days)	3 days (95% CI 2-5 days)
Aplastic phenotype	2.6%	0%	3%
Severe infection rate	8%	5%	5%
Severe bacterial infection rate	0.9%	5%	3%

	LBCL (n = 235)	MCL (n = 103)	MM (n = 113)
Duration of severe neutropenia (ANC<500/µL, day 0-60)	12 days (95% CI 10-16 days)	14 days (95% CI 9-18 days)	9 days (95% CI 7-13 days)
Aplastic phenotype	36%	47%	32%
Severe infection rate	40%	30%	40%
Severe bacterial infection rate	27%	28%	34%

LONG TERM TOXICITIES

- HLH
- Secondary malignancies
- Infection
- ?

LIMITATIONS OF CAR-T

- Is CAR-T cell therapy a cure?
- Competing drugs (BiTEs)

THE FUTURE OF CAR-T CELL THERAPY

- Additional disease indications (recent CLL approval)
- Moving up in lines of therapy
- CAR-T cell therapy as consolidation following transplant
- Allo-CAR T cells
- CAR-NK cell therapy

CASE 1

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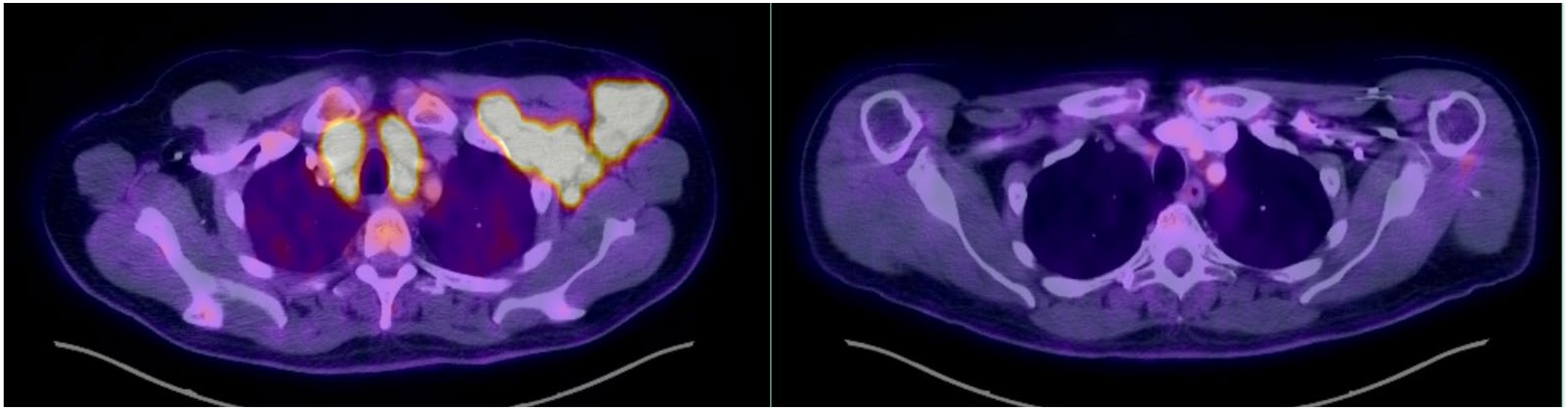
- October 2022: Relapsed disease

CASE 1

- 12/27/2022: Pt received liso-cel, CAR-T cell therapy complicated by grade 4 neurotoxicity with ICE score 0/10. Pt treated with steroids and levetiracetam with full recovery.
- 2/21/2022: PET/CT day 57 shows remission
- As of today, pt remains in remission

CASE 1



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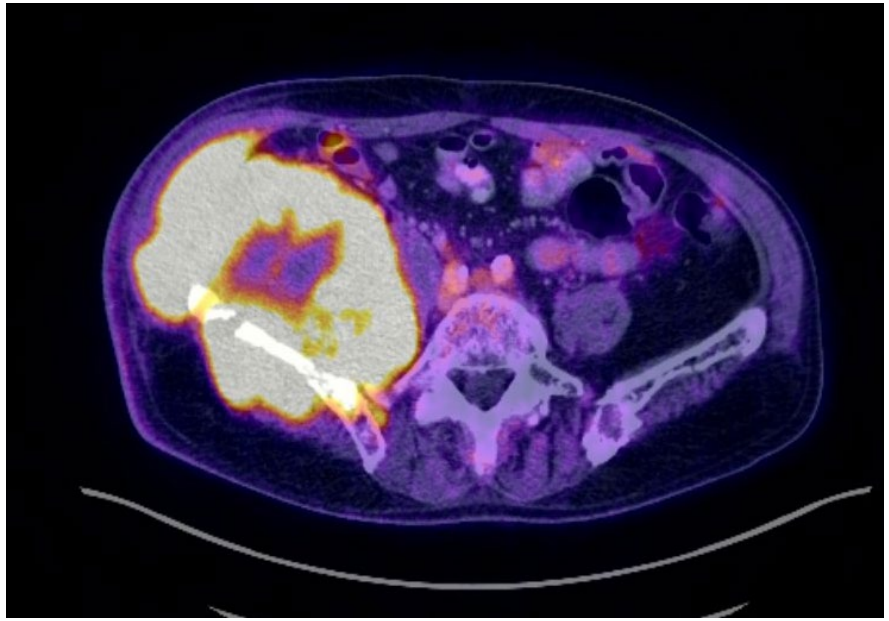
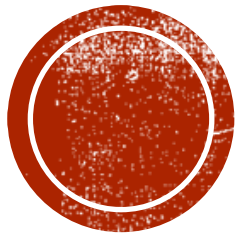


CASE 2

- Received CAR-T cell therapy with ide-cel 9/11/2023
- M-spike dropped from 2.5 gm/dL to 0.1 gm/dL



QUESTIONS?

SOURCES

- ELIANA trial - NEJM
- JULIET trial - NEJM
- TRANSCEND CLL 004
- ZUMA-2 - NEJM
- ZUMA-5 – Lancet Oncology
- Jain MD, Jacobs MT, Nastoupil LJ, et al. Characteristics and outcomes of patients receiving bridging therapy while awaiting manufacture of standard of care axicabtagene ciloleucel CD19 chimeric antigen receptor (CAR) T-cell therapy for relapsed/refractory large B-cell lymphoma: results from the US Lymphoma CAR-T Consortium. *Blood*. 2019;134(suppl 1):245.
- Jain MD, Jacobs MT, Gao F, et al. Bridging therapy with axicabtagene ciloleucel for large B-cell lymphoma: results from the US Lymphoma CAR-T Consortium. *Blood Adv*. 2024;8(4):1042-1050.