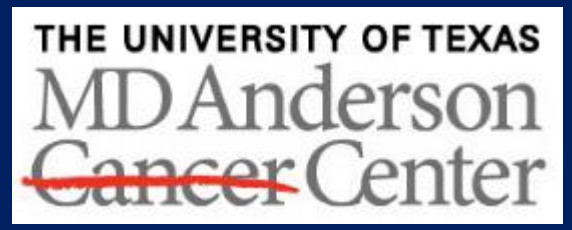
CAR T Cell Therapy in Multiple Myeloma

Krina Patel MD MSc

Associate Professor

Lymphoma Myeloma Department

UT MD Anderson Cancer Center



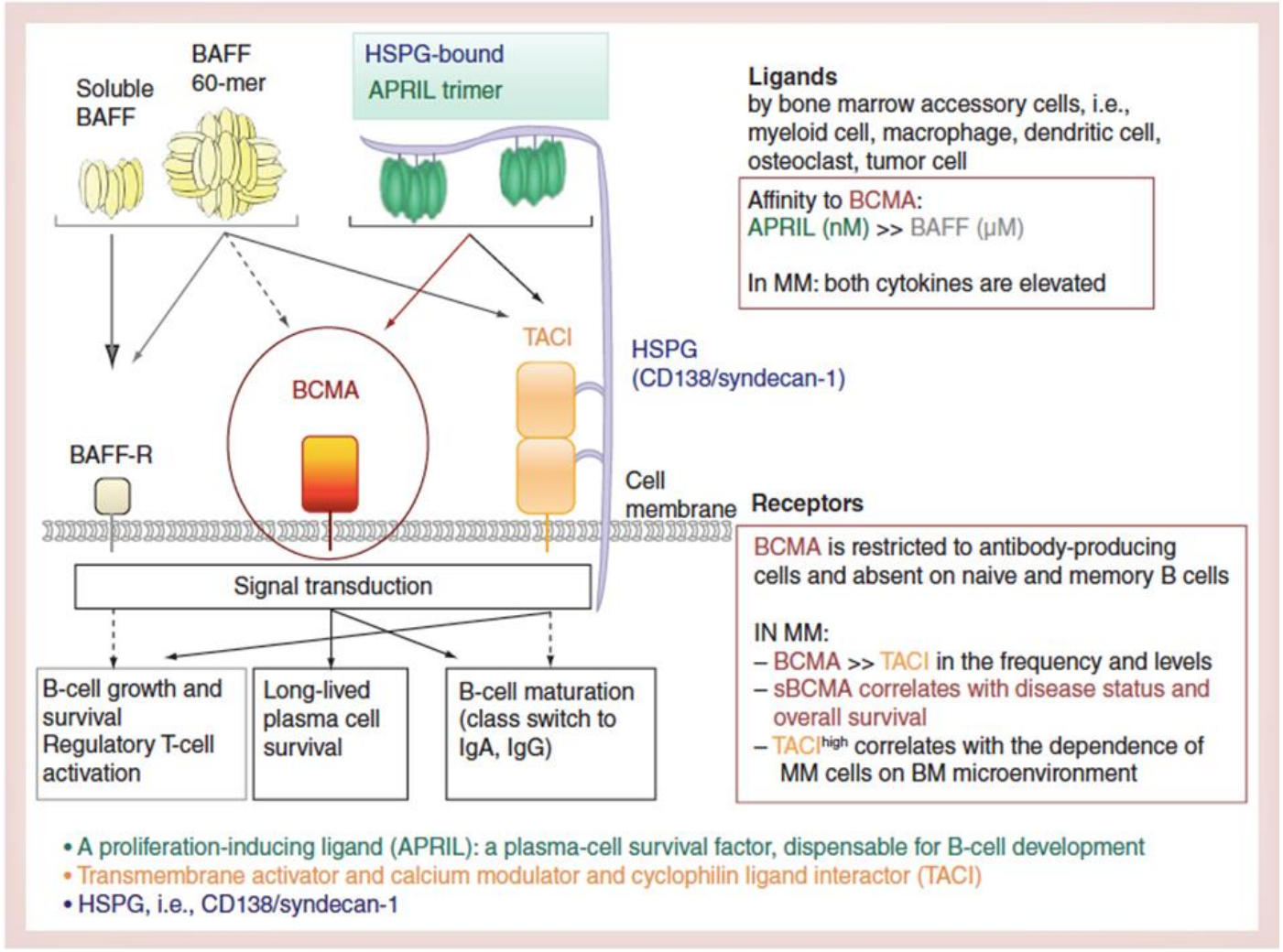
COI

Research: BMS, Janssen, Abbvie, Poseida, Cellectis, PrecisionBio, Allogene, Takeda

Honoraria: BMS/Celgene, Janssen, Oncopeptides, Pfizer, Abbvie, Arcellx

B Cell Maturation Antigen (BCMA)

- BCMA is a cell surface protein expressed on late-stage B cells and plasma cells but virtually absent on naïve and memory B cells[1-3]
- BCMA is highly expressed on malignant plasma cells in all patients with MM[3-5]
  - BCMA ligands, BAFF and APRIL, are detected in increased levels in the circulation of patients with MM[3,5]
- BCMA is essential for the proliferation and survival of malignant plasma cells[3]



APRIL, a proliferation-inducing ligand; BAFF, B-cell activating factor; BCMA, B-cell maturation antigen; sBCMA, serum BCMA.

1. Tai YT, et al. *Immunotherapy*. 2015;7(11):1187-1199. 2. Ryan MC, et al. *Mol Cancer Ther*. 2007;6(11):3009-3018. 3. Cho S-F, et al. *Front Immunol*. 2018;9:1821. doi:10.3389/fimmu.2018.01821.
4. Novak AJ, et al. *Blood*. 2004;103(2):689-694. 5. Tai YT, et al. *Blood*. 2014;123(20):3128-3138.

CAR T Therapy

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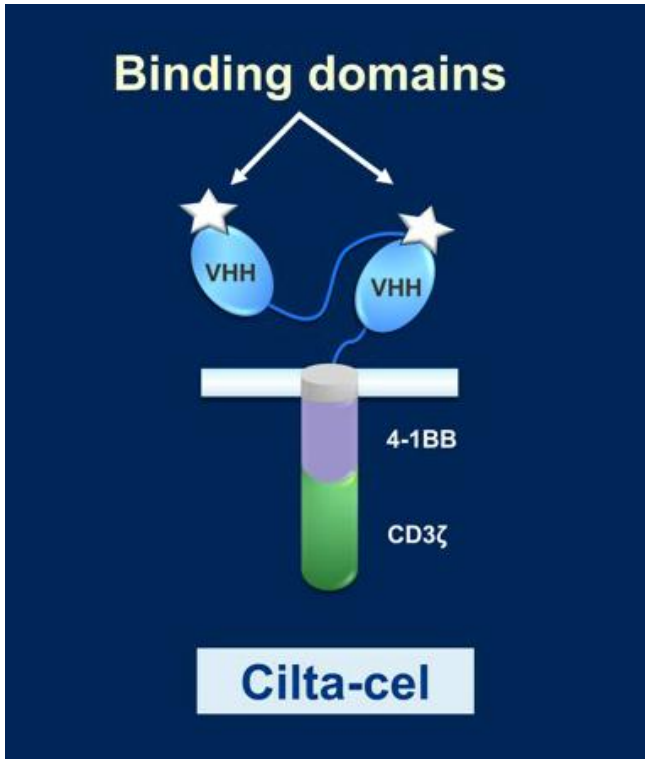
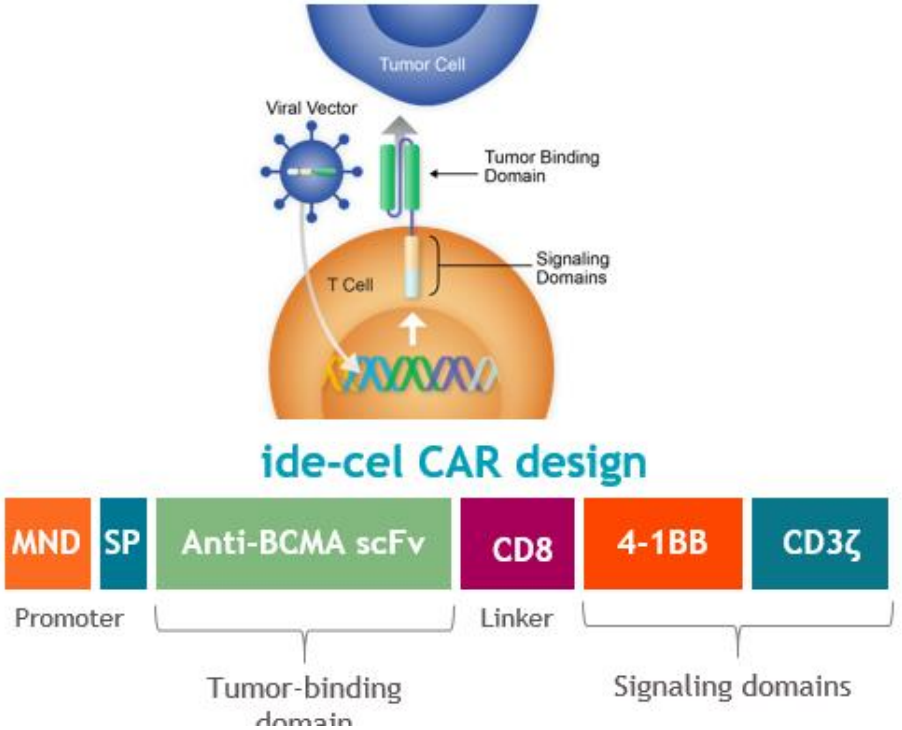




Characteristics and Efficacy

Characteristics	Ide-Cel (n=128)	Cilta-cel (n=97)	bb21217	CT103A (n=79)
Target Cell Dose	450 million	0.75 million/kg	450 million	1 million/kg
Median Prior Lines of Therapy	6	6	6	5
Triple class refractory	84%	88%	69%	16.5%
Penta class refractory	26%	42%	na	na
Extramedullary disease	39%	13.4%	29%	14%
Bone marrow disease	>50% PC = 51%	>60% PC = 21.9%	na	na
High Risk Cytogenetics	35%	23.7%	39%	35.4%

Efficacy	Ide-Cel (n=128)	Cilta-cel (n=97)	bb21217	CT103A
ORR	73%	98%	69%	95%
CR	33%	80%	39%	58%
MRD neg (10^{-5})	26%	58%	67%	94%
PFS	8.8 (CR = 19 months)	22.8	12.8	71% at 12 mo
OS	19 months	NR	na	na

Safety

Toxicity	Ide-Cel (n=128)	Cilta-cel (n=97)	bb21217	CT103A
CRS (all, g3/4)	84% (5%)	95% (5%)	75%(4%)	95%(2.5%)
Median onset CRS	1 day	7 days	2	6 days
ICANS (all, g3/4)	18% (3%)	17% (2%)	15% (4%)	1.3%
Infections (all; g3/4)	69% (22%)	58% (20%)	> G3 = 29%	na
Grade 3/4 neutropenia > 1 month	41%	10%	na	na
Grade 3/4 thrombocytopenia > 1 month	48%	25%	na	na
Delayed neurotoxicity (all;g3/4)	None*	12% (9%)	na	na

Mechanisms of response and resistance

Tumor Related

- Antigen expression levels
- Presence of soluble antigen
- Antigen loss or diminished antigen expression
- Tumor load
- High risk cytogenetics
- Extramedullary disease
- Resistance to effector mechanisms of T cells
- Inhibitory receptors and ligands which suppress T cell function

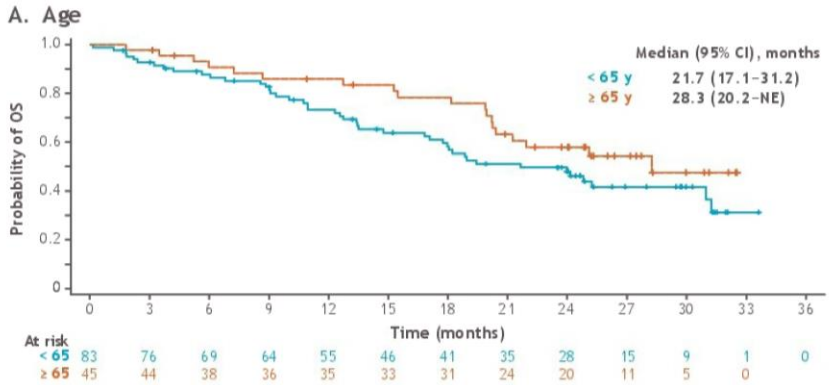
OS in high risk patient subgroups

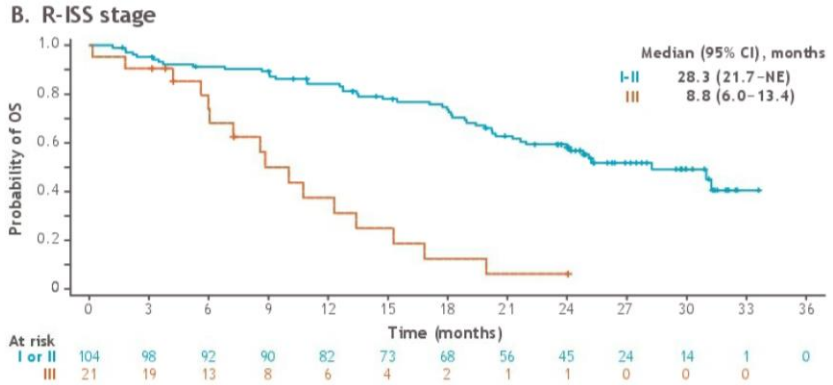
KarMMa-2 Phase 2 study of ide-cel in triple-class-exposed patients and patients with high-risk MM (PD ≤ 18 months of 1L or inadequate response to ASCT); NCT03601078

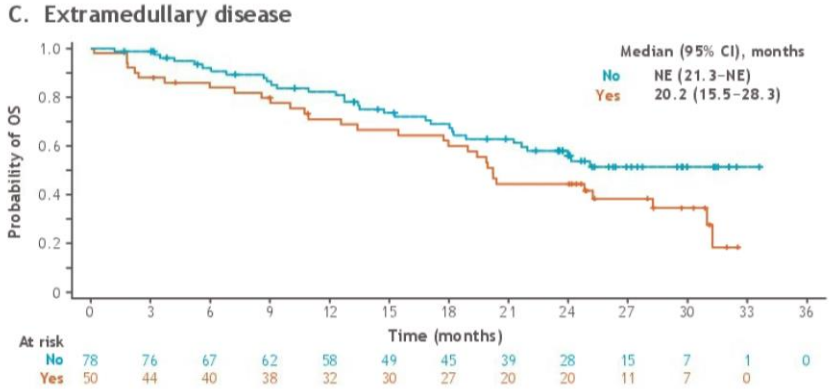
KarMMa-3 Phase 3 study of ide-cel vs standard regimens in triple-class-exposed patients with 2-4 prior lines of therapy; NCT03651128[8]

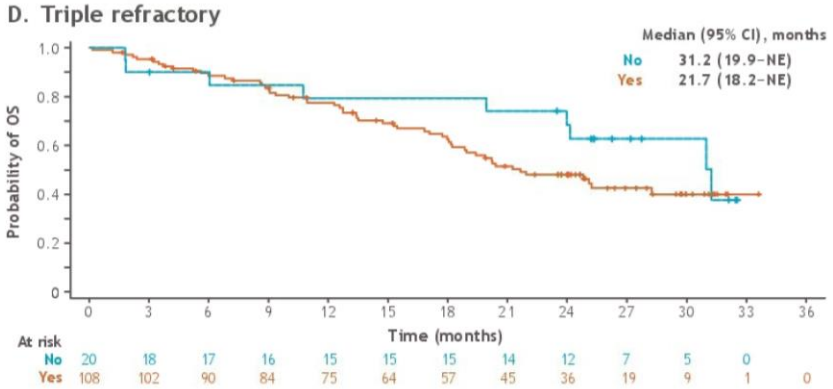
KarMMa-4 Phase 1 study of ide-cel in patients with high-risk NDMM (R-ISS stage III disease per IMWG criteria); NCT04196491[9]

KarMMa-7 Exploratory phase 1/2 study of ide-cel combination therapies in patients with RRMM; NCT04855136



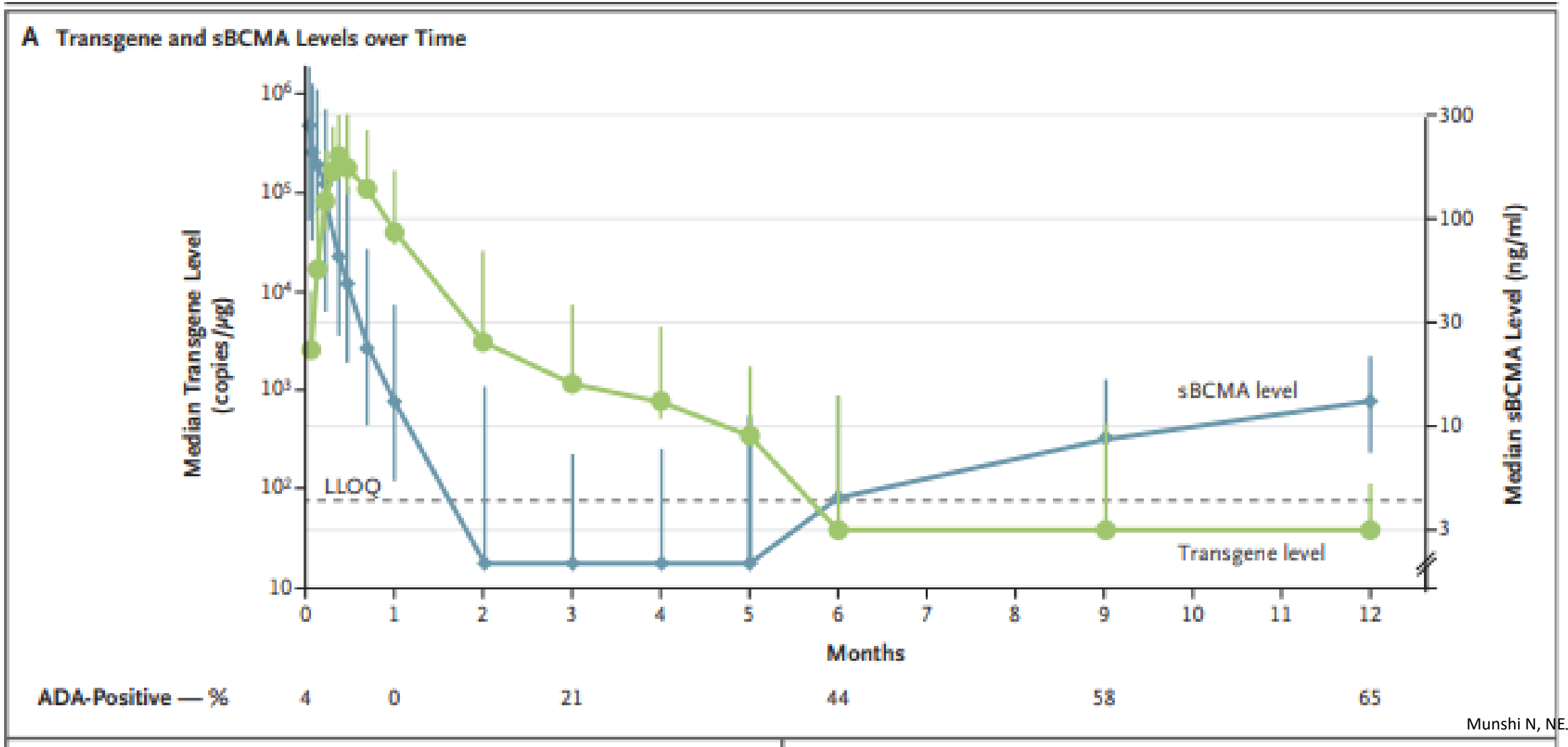






Anderson L, et al. ASCO 2021

sBCMA – biomarker?



Munshi N, NEJM 2021.

Sequencing of Therapy - BCMA

EXCEPTIONAL CASE REPORT

blood advances

Serial treatment of relapsed/refractory multiple myeloma with different BCMA-targeting therapies

Adam D. Cohen,[1] Alfred L. Garfall,[1] Ahmet Dogan,[2] Simon F. Lacey,[1] Chris Martin,[3] Nikoletta Lendvai,[2] Dan T. Vogl,[1] Matthew Spear,[3] and Alexander M. Lesokhin[2,4]

nature communications

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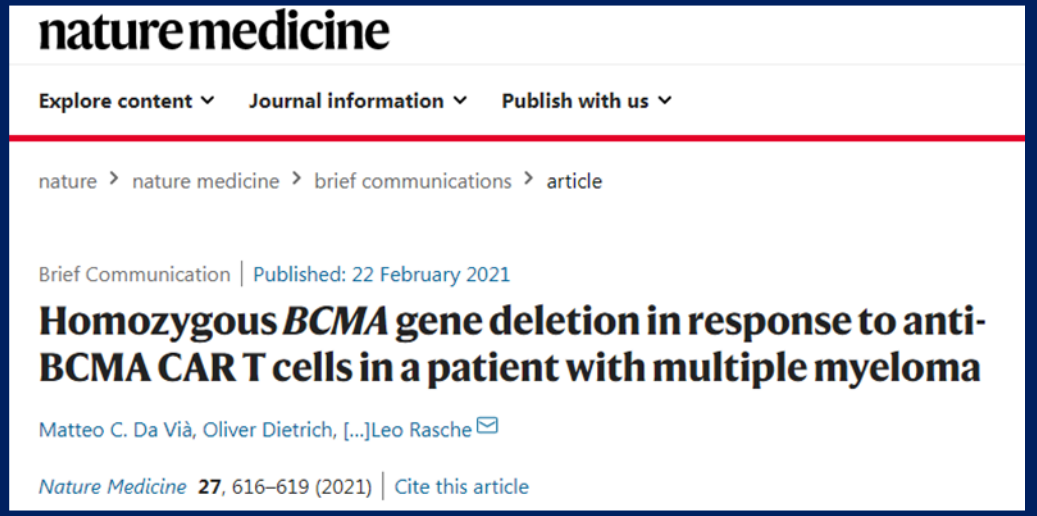
Article | Open Access | Published: 08 February 2021

Biallelic loss of BCMA as a resistance mechanism to CAR T cell therapy in a patient with multiple myeloma

Mehmet Kemal Samur, Mariateresa Fulciniti, Anil Aktas Samur, Abdul Hamid Bazarbachi, Yu-Tzu Tai, Rao Prabhala, Alejandro Alonso, Adam S. Sperling, Timothy Campbell, Fabio Petrocca, Kristen Hege, Shari Kaiser, Hervé Avet Loiseau, Kenneth C. Anderson & Nikhil C. Munshi

Nature Communications **12**, Article number: 868 (2021) | Cite this article



nature medicine

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nature > nature medicine > brief communications > article

Brief Communication | Published: 22 February 2021

Homozygous *BCMA* gene deletion in response to anti-BCMA CAR T cells in a patient with multiple myeloma

Matteo C. Da Vià, Oliver Dietrich, [...]Leo Rasche

Nature Medicine **27**, 616–619 (2021) | Cite this article

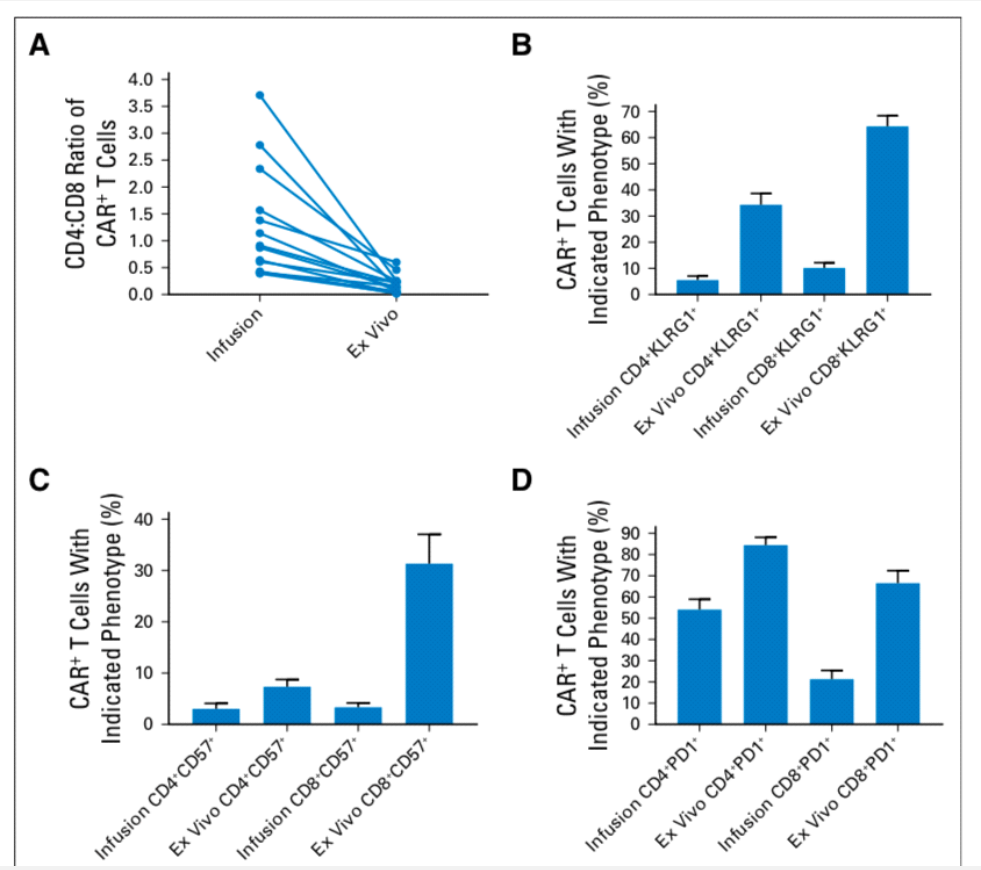
Microenvironment Related

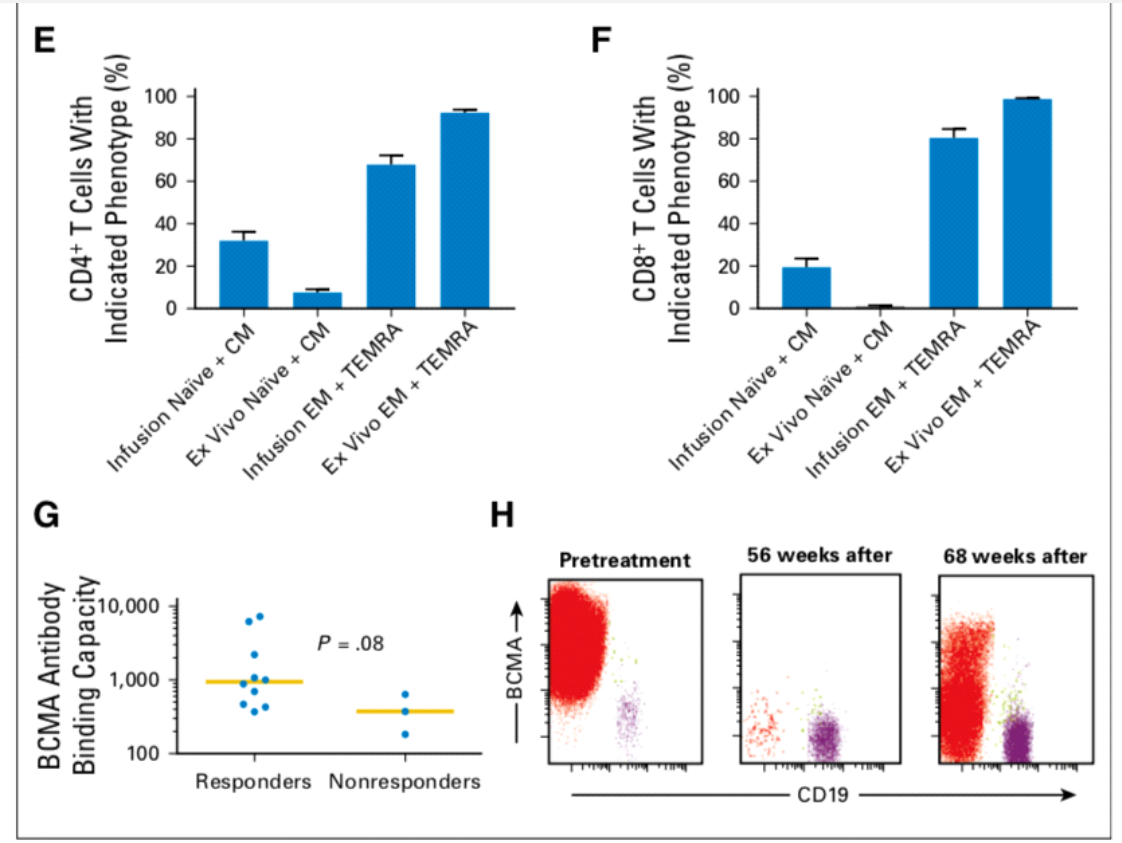
- Bone marrow stromal cells
- Immune suppressor cells
- Immunosuppressive molecules
- Type of Bridging therapy
- Lymphodepleting conditioning regimen

Endogenous T cell characteristics

- Absolute T cell count
- Early memory phenotype
- CD4/CD8 ratio
- Impact of prior therapy on T cell fitness

T CELL





Brudno, et al. JCO 2018

Sequencing of Therapy – Prior to CAR T

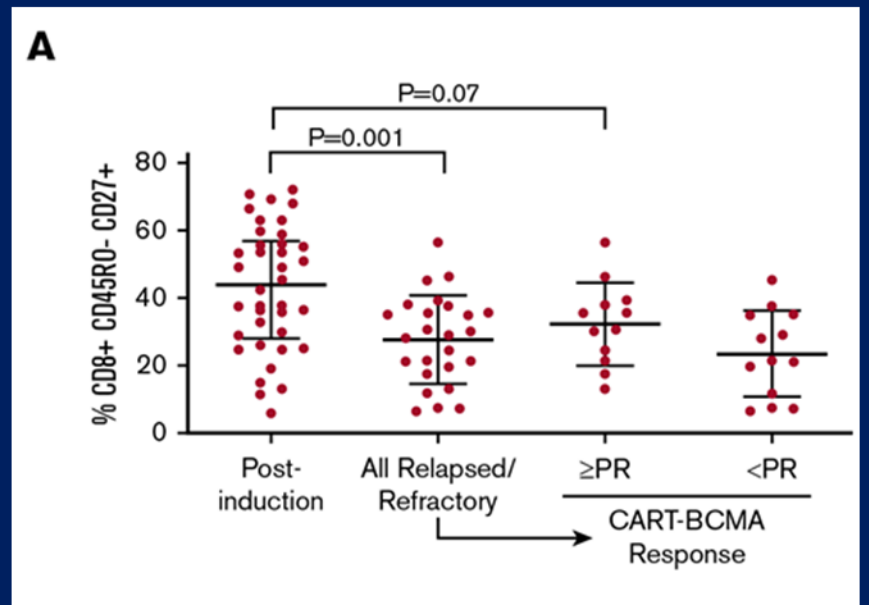
blood advances® ISSUES LATEST ARTICLES GUIDELINES COLLECTIONS AUTH

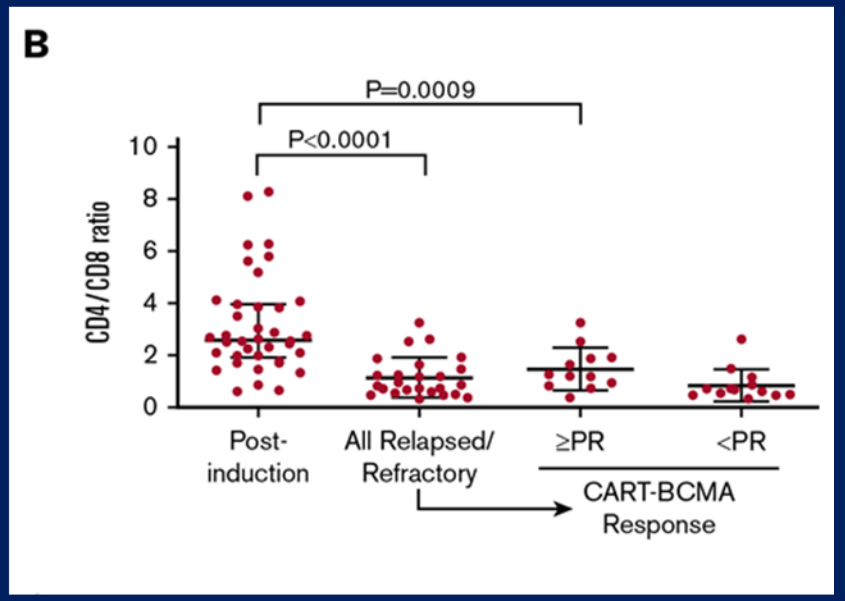
STIMULUS REPORT | OCTOBER 1, 2019

T-cell phenotypes associated with effective CAR T-cell therapy in postinduction vs relapsed multiple myeloma

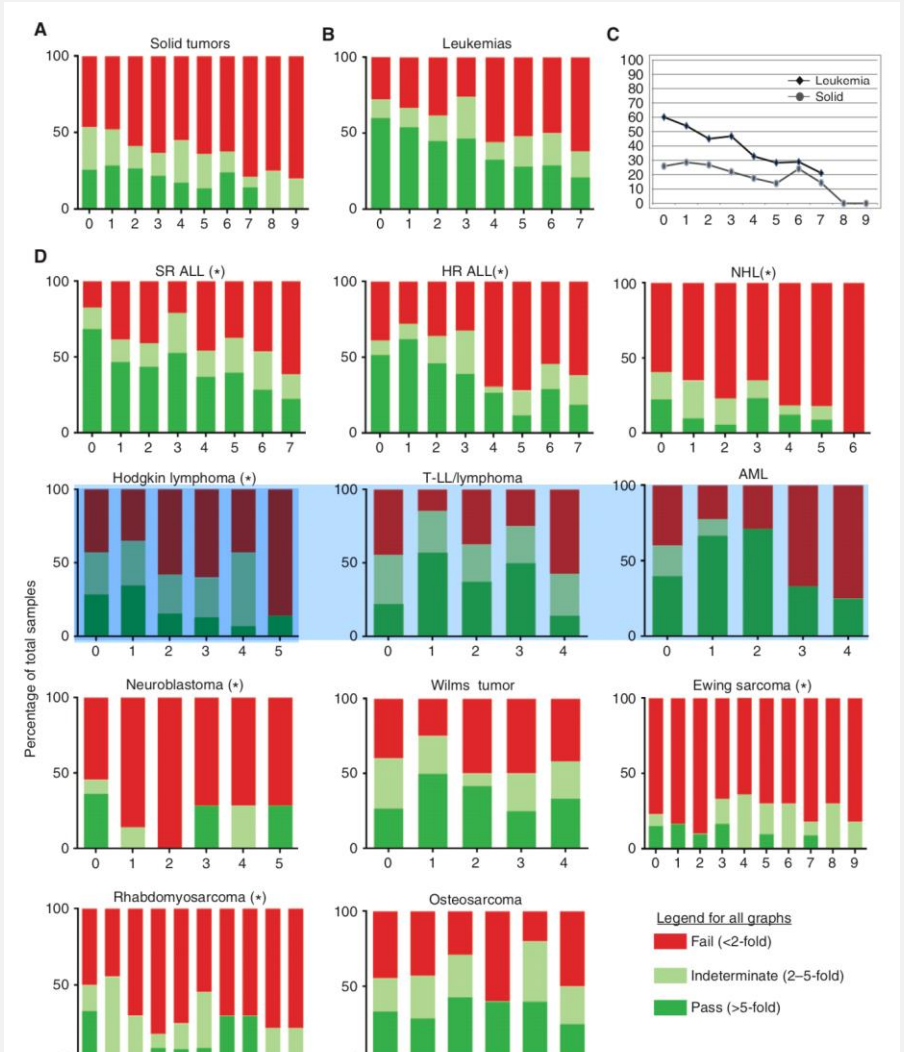
Alfred L. Garfall, Ehren K. Dancy, Adam D. Cohen, Wei-Ting Hwang, Joseph A. Fraietta, Megan M. Davis, Bruce L. Levine, Don L. Siegel, Edward A. Stadtmauer, Dan T. Vogl, Adam Waxman, Aaron P. Rapoport, Michael C. Milone, Carl H. June, J. Joseph Melenhorst

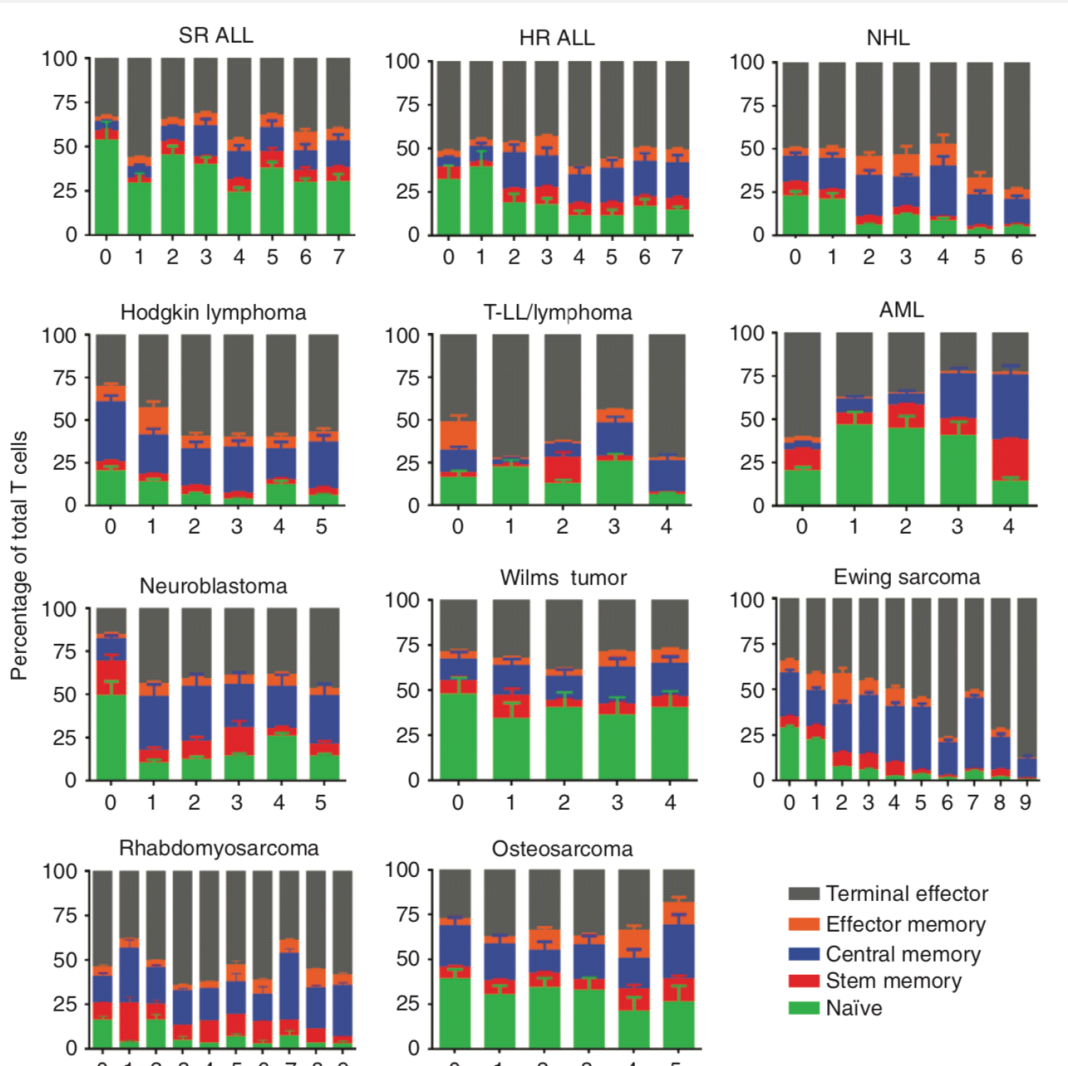
Check for updates





T CELL

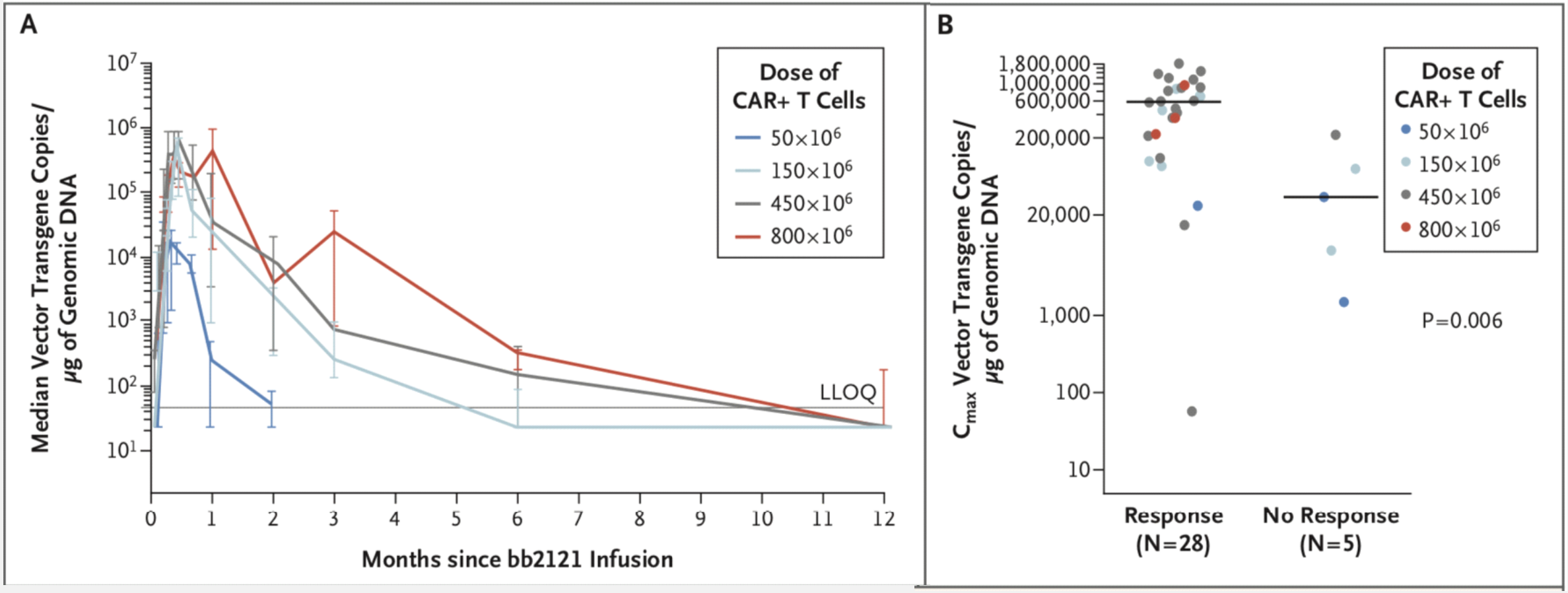

A
Solid tumors
B
Leukemias
C
Leukemia
Solid
D
SR ALL (*)
HR ALL(*)
NHL(*)
Hodgkin lymphoma (*)
T-LL/lymphoma
AML
Neuroblastoma (*)
Wilms tumor
Ewing sarcoma (*)
Rhabdomyosarcoma (*)
Osteosarcoma
Percentage of total samples
Legend for all graphs
Fail (<2-fold)
Indeterminate (2–5-fold)
Pass (>5-fold)


SR ALL
HR ALL
NHL
Hodgkin lymphoma
T-LL/lymphoma
AML
Neuroblastoma
Wilms tumor
Ewing sarcoma
Rhabdomyosarcoma
Osteosarcoma
Percentage of total T cells
Terminal effector
Effector memory
Central memory
Stem memory
Naïve

CAR T cell related

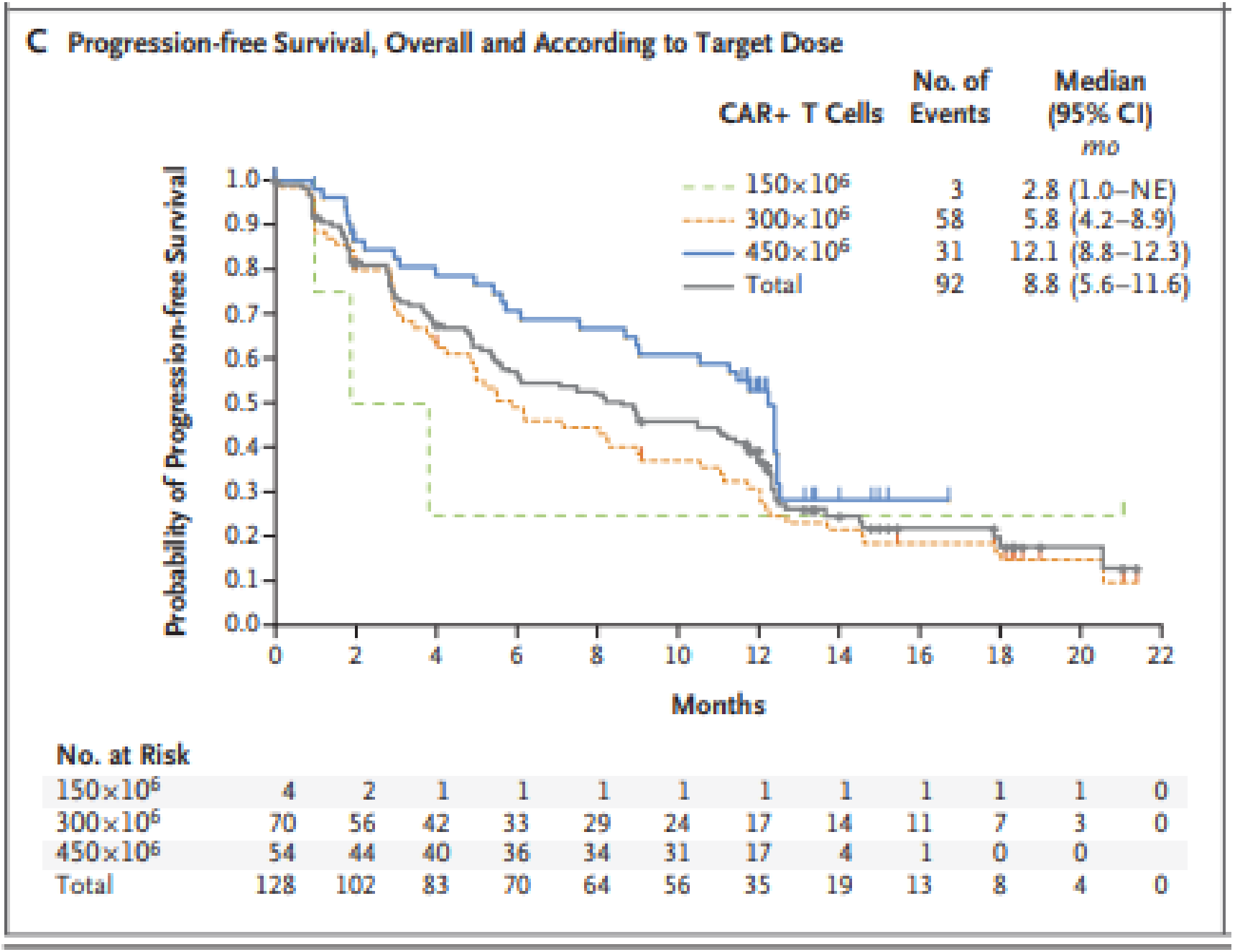
- Quality
- Dosing
- Affinity of antigen binding domain
- Costimulatory domain
- Immunogenecity
- Persistence?

T CELL



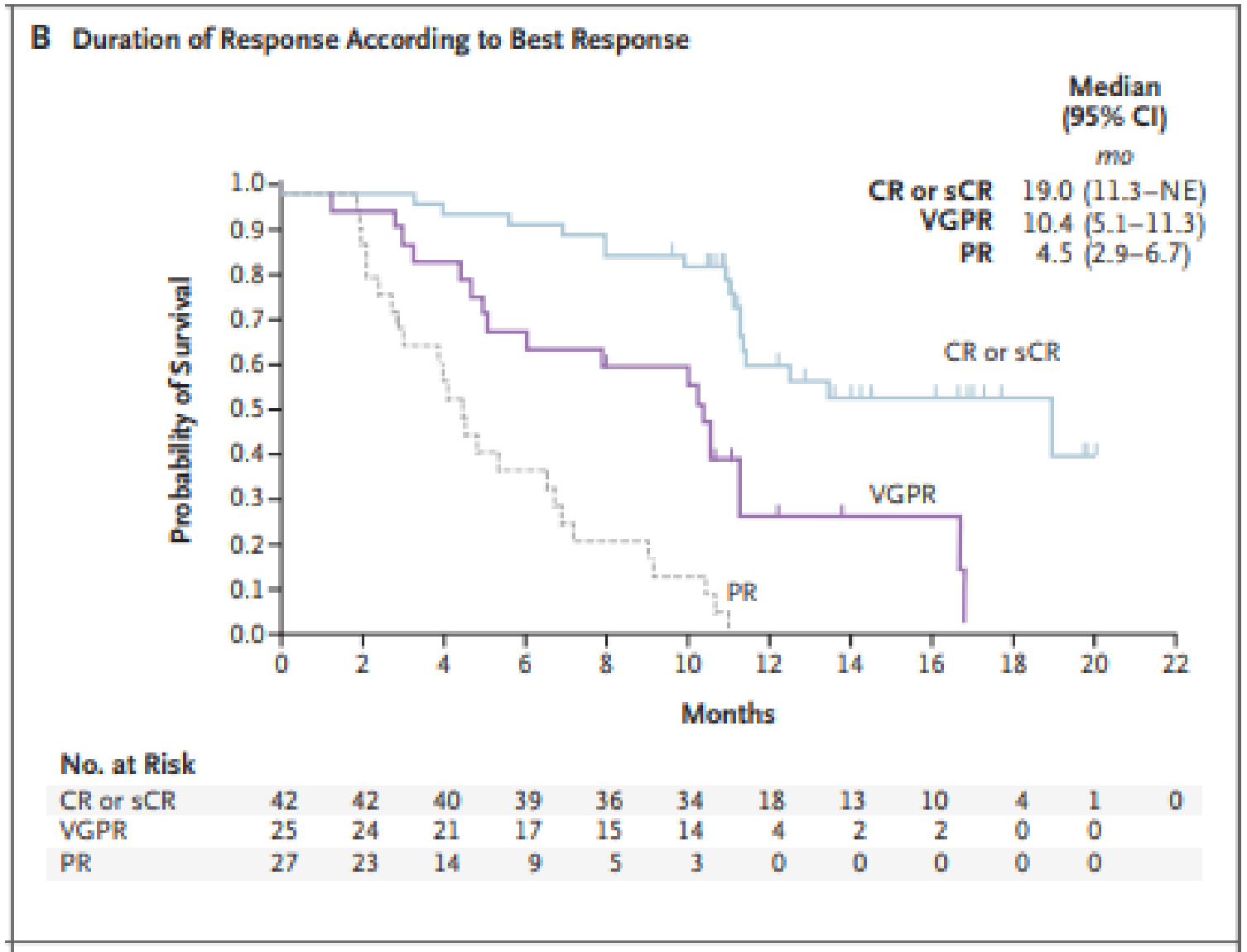
Raje N, NEJM 2019

Ide-Cel PFS



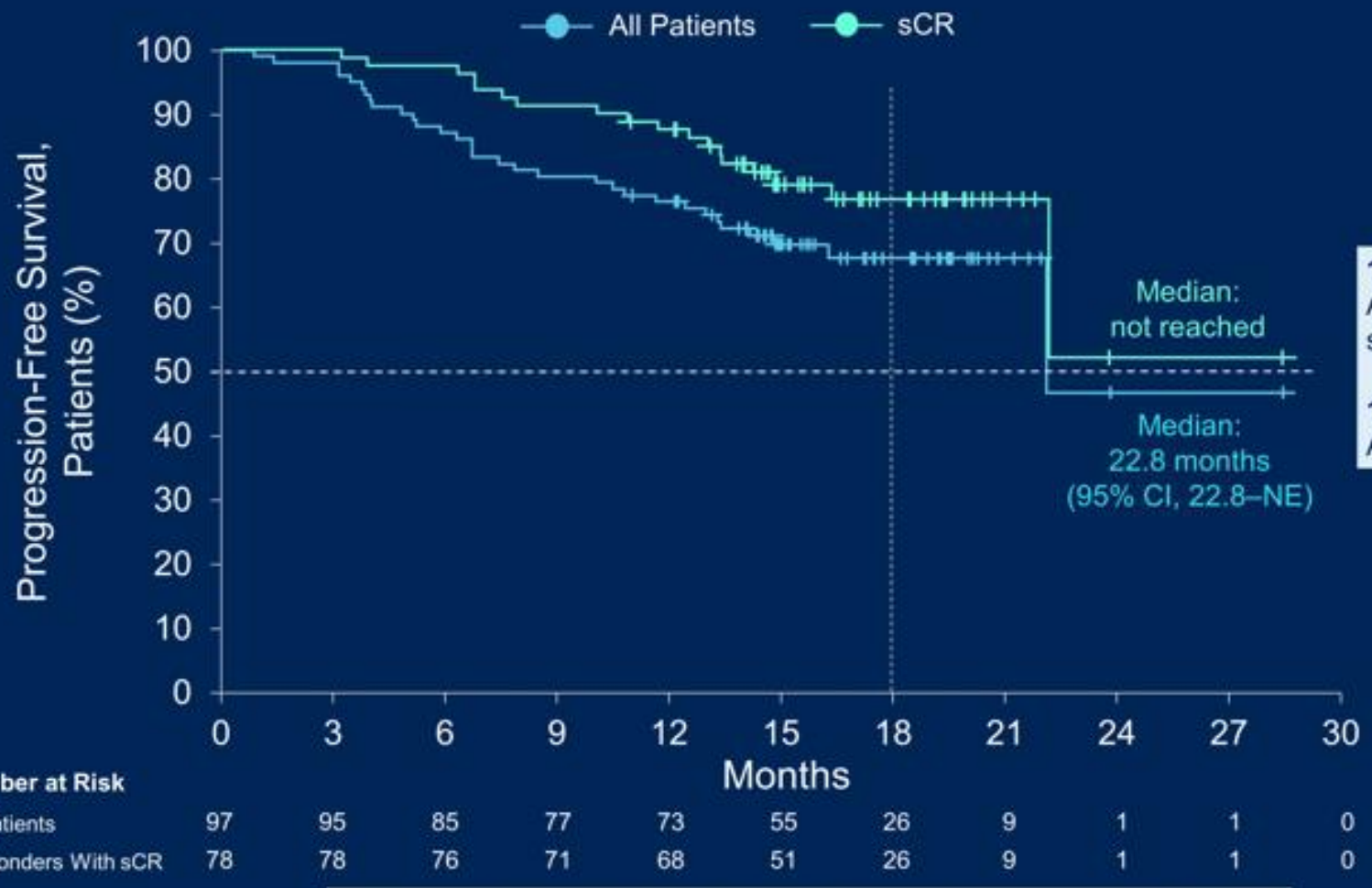
Munshi N, NEJM 2021.

Ide-Cel DOR based on response



Munshi N, NEJM 2021.

CARTITUDE-1: Progression-Free Survival



Number at Risk

All Patients	97	95	85	77	73	55	26	9	1	1	0
Responders With sCR	78	78	76	71	68	51	26	9	1	1	0

18-month PFS
All Patients: 66.0% (95% CI, 54.9–75.0)
sCR: 75.9% (95% CI, 63.6–84.5)

18-month OS
All patients: 80.9% (95% CI, 71.4–87.6)

Median duration of follow-up: 18 months (range, 1.5–30.5)

NE, not estimable; PFS, progression-free survival; OS, overall survival; sCR, stringent complete response.

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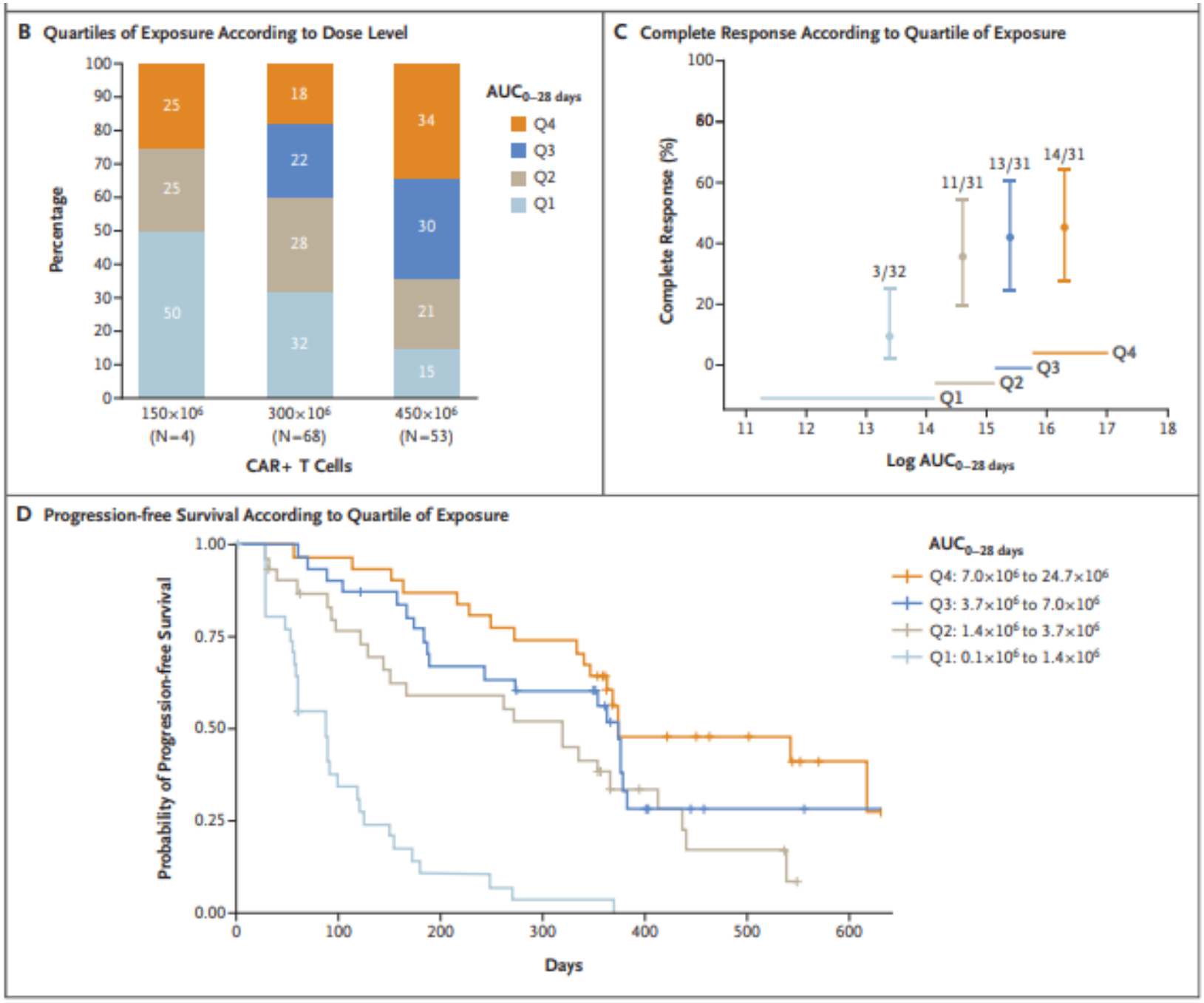
Quartile of exposure



Munshi N, NEJM 2021.

Efficacy and Safety of Idecabtagene Vicleucel (ide-cel, bb2121) in Elderly Patients with Relapsed and Refractory Multiple Myeloma: KarMMa Subgroup Analysis

		Age ≥65 Years (n=45)	Age ≥70 Years (n=20)	All ide-cel Treated (N=128)
Efficacy Outcomes				
ORR, n (%) [95% CI]		38 (84) [70.5–93.5]	18 (90) [76.9–100]	94 (73) [65.8–81.1]
CR rate, n (%) [95% CI]		14 (31) [18.2–46.6]	7 (35) [14.1–55.9]	42 (33) [24.7–40.9]
PFS, median (95% CI), mo		8.6 (4.9–12.2)	10.2 (3.1–12.3)	8.8 (5.6–11.6)
DOR,[a] median (95% CI), mo		10.9 (4.5–11.4)	11.0 (3.9–11.4)	10.7 (9.0–11.3)
Adverse Events of Interest[b]				
CRS, n (%)	Overall	40 (89)	20 (100)	107 (84)
	Grade ≥3	2 (4)	2 (10)	7 (5)
NT, n (%)	Overall	11 (24)	6 (30)	23 (18)
	Grade ≥3	4 (9)	1 (5)	4 (3)

CR, complete response; CRS, cytokine release syndrome; DOR, duration of response; NT, investigator-identified neurotoxicity; ORR, overall response rate; PFS, progression-free survival.
[a]Duration of response among responders.
[b]NT was graded according to NCI CTCAE v4.03. CRS was graded according to Lee et al. criteria (*Blood* 2014; 124:188-95).

Berdeja ASH 2020

Allo-715, allo 647

- FCA vs FC for LD treatment
- Dose level 320 million with standard LD of FC
- 5 prior lines of therapy, 100% refractory to last line
- 91% triple refractory, 42% penta-refractory
- Safety 1 patient with grade 3 CRS, neutox 14% grade ½, no GVHD
- 23 patients with infections, 3 with grade 5
- 71% ORR, CR/sCR 25%
- Median DOR 8.3 months

Unmet Need MM Population

- Those who don’t have access to appropriate health care or clinical trials
- High risk disease/plasma cell leukemia
- Relapsed refractory with aggressive disease
- Renal failure
- CNS involvement
- Frail Patients/Increased Co-Morbidities

The multiple possible pathways to cure. . .

- Patient A → CD38 monoclonal ab PI, IMID, dex as induction and CAR T
- Patient B → induction and autoSCT + CAR T
- Patient C → induction (+/- ASCT), multi-antigen PD1^{-} CAR T, +/- different antigen specific bispecific
- Patient D → induction (+/- ASCT), off the shelf multi-antigen CAR T, +/-consolidation/maintenance, cytokines, bispecifics
- Patient E → induction, off the shelf CAR T with repeat infusions or bridge to allogeneic transplant followed by repeat CAR T infusion, +/- maintenance, cytokines, bispecifics

+ Targeted therapies (i.e. venetoclax for t(11;14)) where applicable

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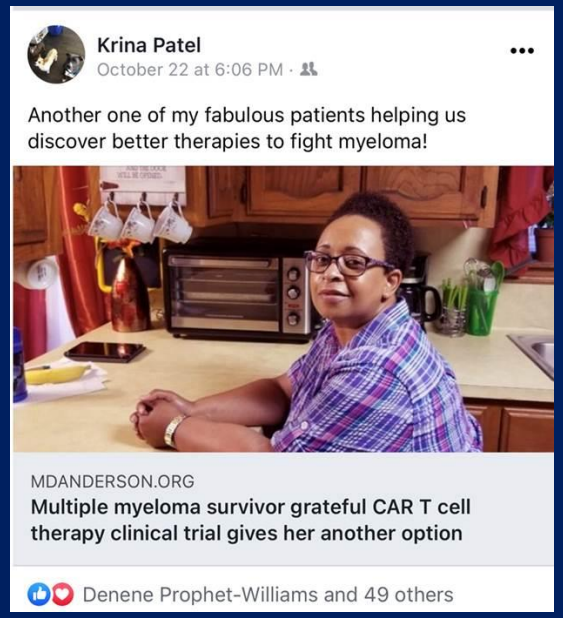
Take Home Points

- Multiple mechanisms of response and resistance exist for each type of anti-BCMA therapy. The following are the most important in my opinion:
  - antigen density versus antigen affinity
  - immune cell health
  - tumor load and high risk disease
- Soluble BCMA/BCMA expression should be evaluated in between different anti BCMA therapies.
- Sequencing matters!
  - avoid alkylators prior to CAR T manufacturing and likely prior to bispecific therapy
  - Refer patients early – if you save it for later, less patients will actually get treatment.

Thank you to our patients, caregivers and research teams!



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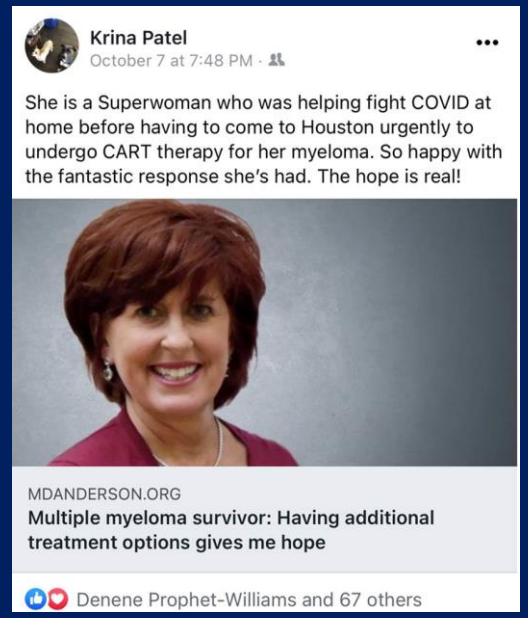

Any questions?

kpatel1@mdanderson.org