Penn Medicine

CAR T Cells for Myeloma: Clinical Results in Late Lines

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3rd Meeting on T-cell and NK-cell based Immunotherapies for Lymphoid Malignancies
Bologna, Italy

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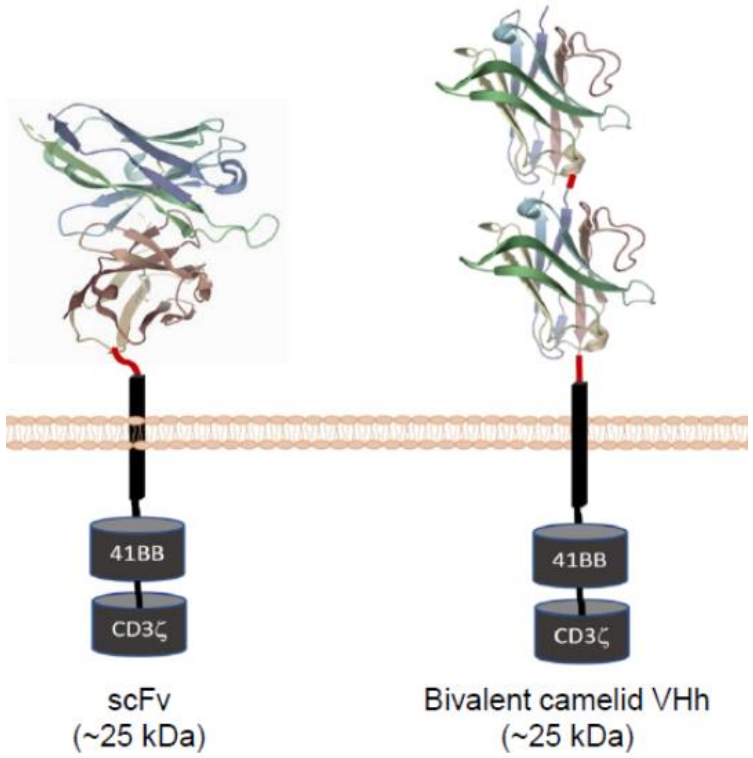
Disclosures

- Consulting/Advisory Boards: Celgene, BMS, Takeda, Janssen, Genentech/Roche, GlaxoSmithKline, Arcellx, Ichnos, Abbvie, Pfizer, iTeos, AstraZeneca, Legend, Sanofi
- Research support: Novartis, GlaxoSmithKline, Genentech, Janssen
- Intellectual property licensed by institution to: Novartis

Approved BCMA-directed CAR T cell products

Ide-cel **Cilta-cel**



scFv
(~25 kDa)

Bivalent camelid VHh
(~25 kDa)

Mar. 2021

FDA Approves First Cell-Based Gene Therapy for Adult Patients with Multiple Myeloma

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For Immediate Release: March 27, 2021

The U.S. Food and Drug Administration approved Abecma (idecabtagene vicleucel), a cell-based gene therapy to treat adult patients with multiple myeloma who have not responded to, or whose disease has returned after, at least four prior lines (different types) of therapy. Abecma is the first cell-based gene therapy approved by the FDA for the treatment of

Feb. 2022

U.S. FDA Approves CARVYKTI™ (ciltacabtagene autoleucel), Janssen's First Cell Therapy, a BCMA-Directed CAR-T Immunotherapy for the Treatment of Patients with Relapsed or Refractory Multiple Myeloma

In the pivotal clinical study, 98 percent of patients with relapsed or refractory multiple myeloma responded to a one-time treatment with ciltacabtagene autoleucel and 78 percent of patients who responded experienced a stringent complete response

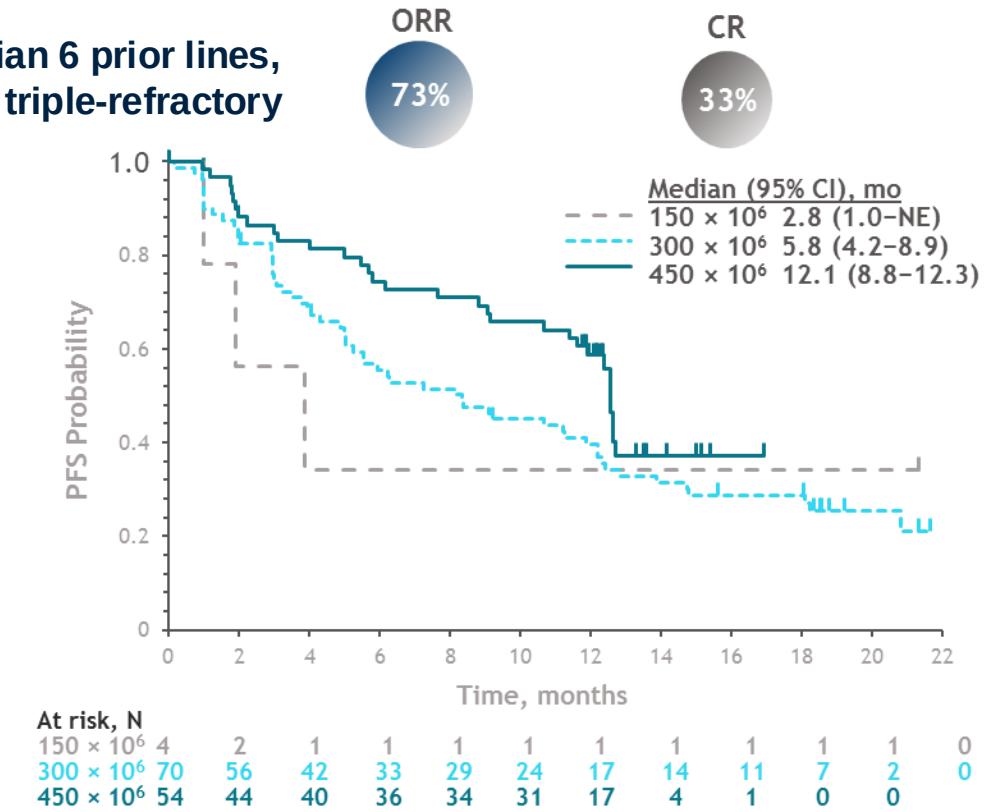
Frigault et al, ASH 2023, #1023

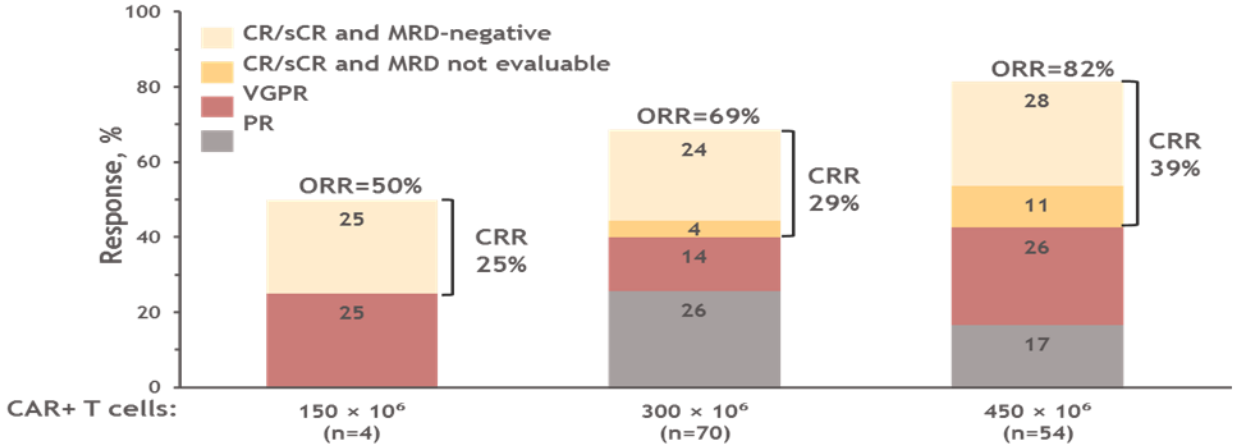
KarMMa Phase 2 study: summary key findings

Ide-cel

Median 6 prior lines, 84% triple-refractory

Efficacy





Adverse events of interest

Target Dose, × 10⁶ CAR+ T cells	150 (n=4)	300 (n=70)	450 (n=54)	Ide-cel Treated (N=128)
≥1 CRS event, n (%)	2 (50)	53 (76)	52 (96)	107 (84)
Grade ≥ 3 (Lee Criteria)[a]	0	4 (6)	3 (6)	7(5)
≥1 NT event, n (%)	0	12 (17)	11 (20)	23 (18)
Grade 3 (CTCAE)[a]	0	1 (1)	3 (6)	4 (3)

Primary (ORR >50%) and key secondary (CRR >10%) endpoints met
PFS increased with higher target dose; median PFS was 12.1 mo at 450 × 10⁶ CAR+ T cells

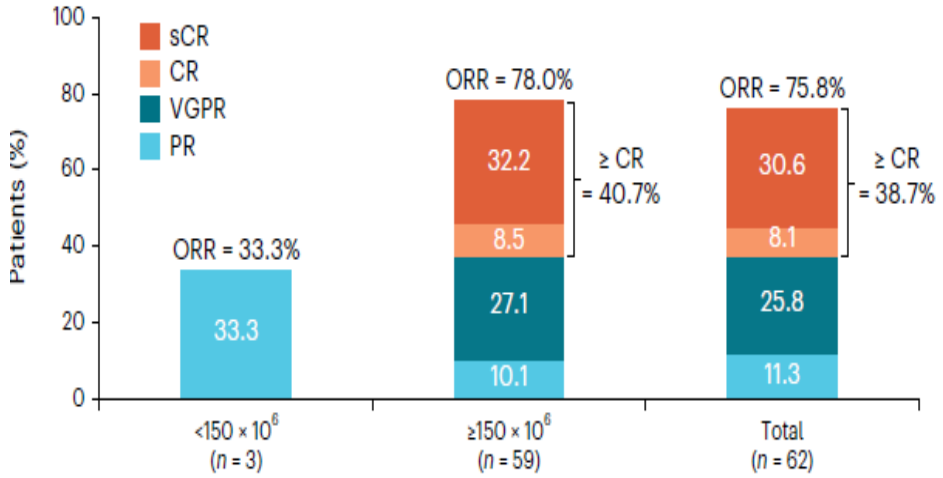
52% got tocilizumab

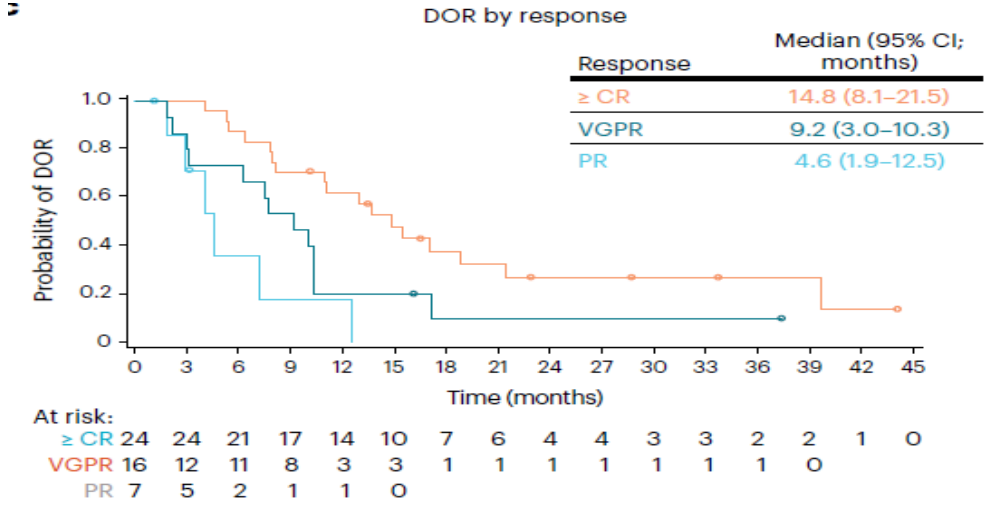
CAR, chimeric antigen receptor; CR, complete response; CRR, complete response rate; CRS, cytokine release syndrome; CTCAE, common criteria for adverse events; MRD, minimal residual disease; NE, not evaluable; ORR, overall response rate; PR, partial response; sCR, stringent complete response; CAR

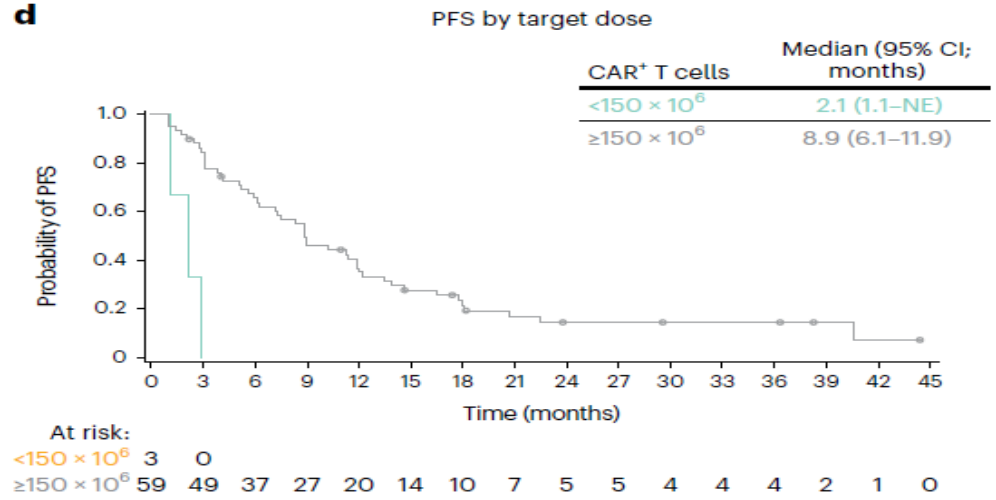
Munshi et al. ASCO 2020; abstract 8503 (oral presentation); NEJM 2021

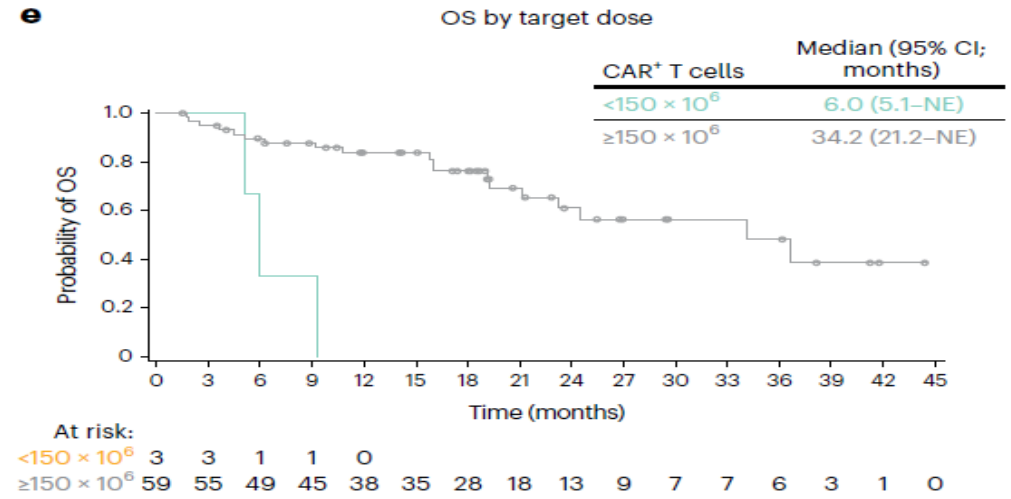
Long-term follow-up of bb2121 phase 1

Median 6 prior lines,
69% triple-refractory







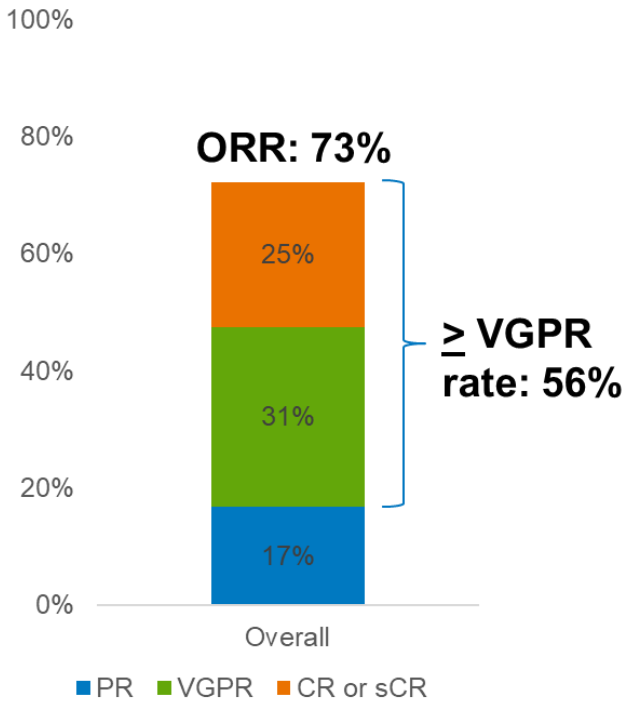


Lin et al, Nat Med 2023

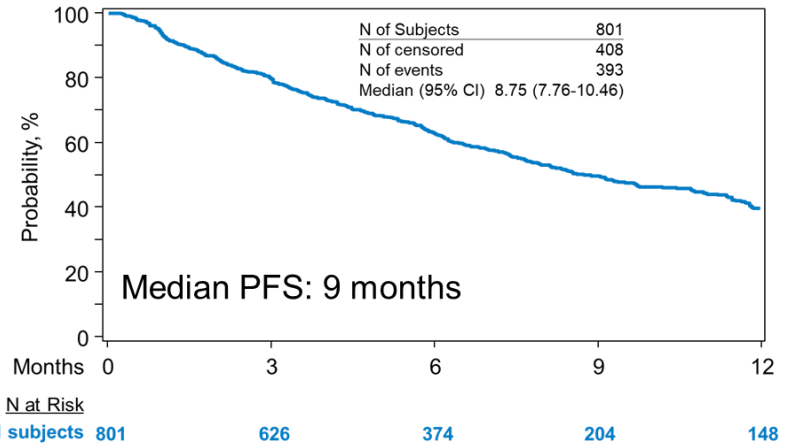
Penn Medicine

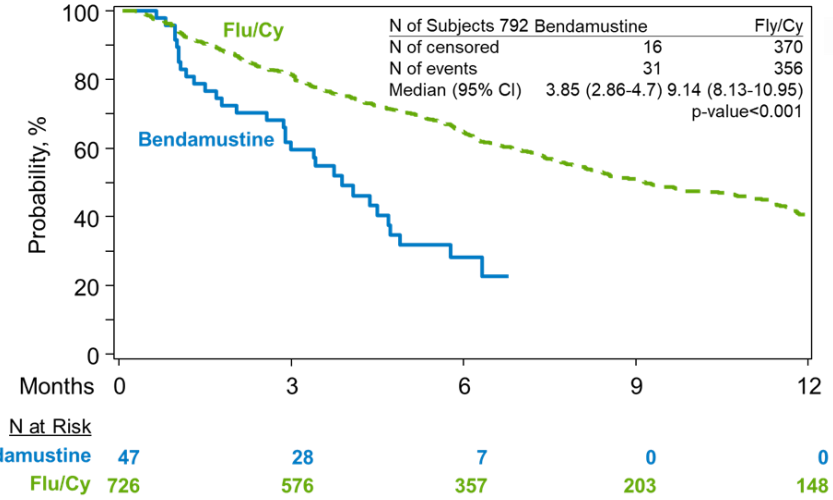
Ide-cel in RRMM: CIBMTR real-world cohort (n=821)

Median 7 prior lines,
69% triple-exposed
18% prior BCMA tx

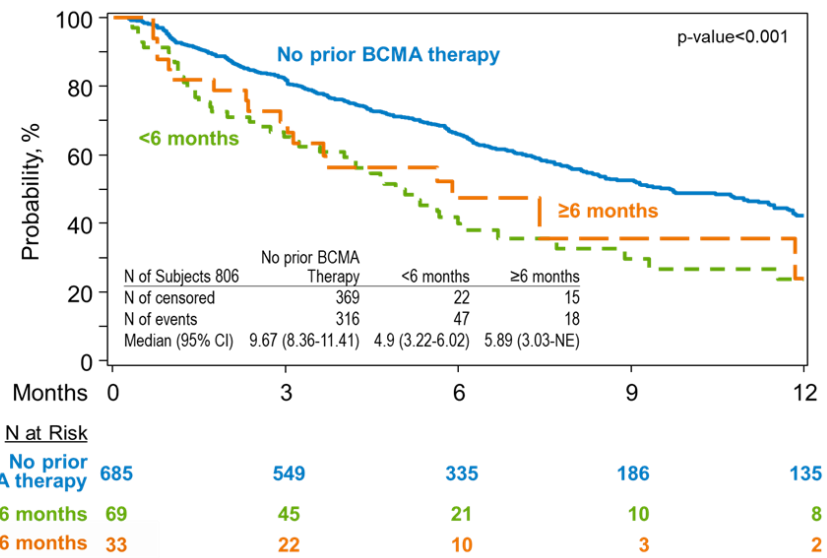


Progression-free Survival





Progression-free Survival



SPM (N=33)	N(%)
Basal cell/Squamous cell skin cancer	20 (61)
AML/MDS	8 (24)
Malignant Melanoma	2 (6)
Breast Cancer	1 (3)
CNS malignancy	1 (3)
Genitourinary malignancy	1 (3)

No T cell malignancies reported

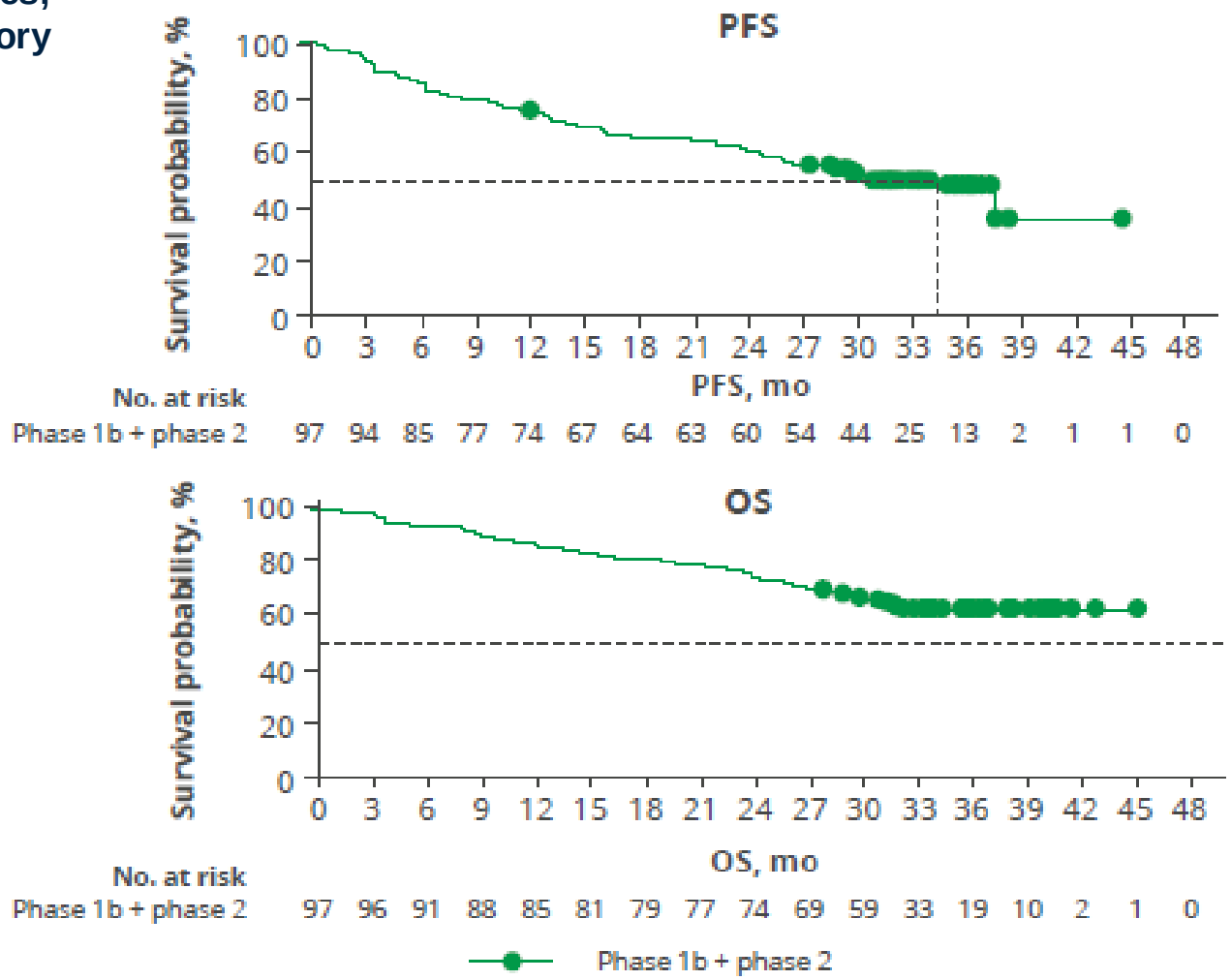
Sidana et al, ASH 2023, #1027

CARTITUDE-1: Long-term follow-up (med 33 mos.) with cilta-cel

Median 6 prior lines,
88% triple-refractory

- ORR = 98%
  - CR/sCR = 83%
- Median PFS = 34.9 mos.
- Median DOR = 33.9 mos.
- Median OS = not reached

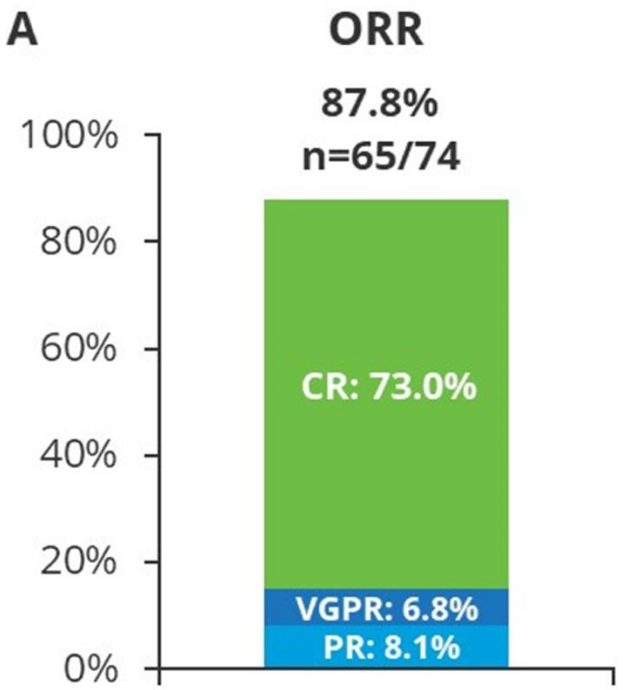
Subgroups	mPFS (95% CI), mo	30-mo PFS rate	36-mo PFS rate
All patients	34.9 (25.2–NE)	54.2%	47.5%
≥CR[a]	38.2 (34.9–NE)	66.8%	59.8%
12-mo sustained MRD negativity[b]	NR (NE–NE)	74.9%	NE
12-mo sustained MRD-negative ≥CR[b]	NR (NE–NE)	78.5%	NE



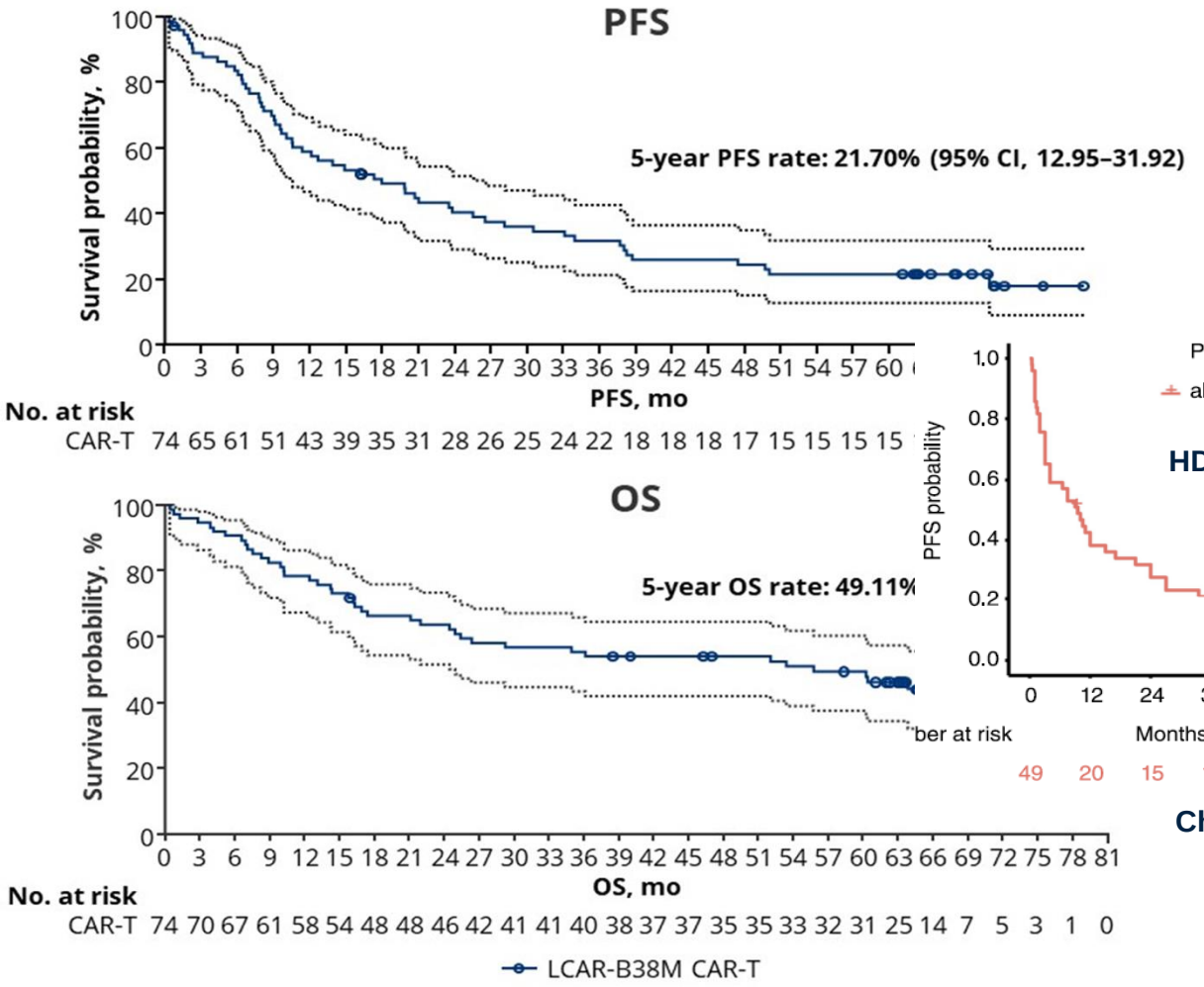
Lin et al, ASCO 2023, #8009

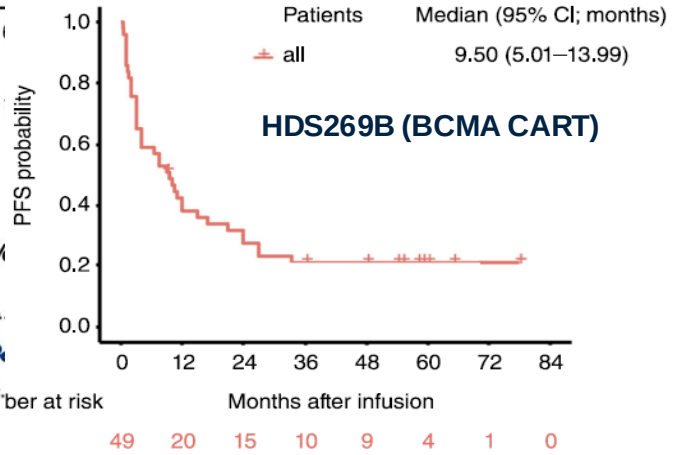
LEGEND-2: Long-term follow-up (med. 65 mos.) with LCAR-B38M

Median 3 prior lines,
0% triple-refractory



Median PFS = 18.0 mos.
Median DOR = 23.3 mos.
Median OS = 55.8 mos.



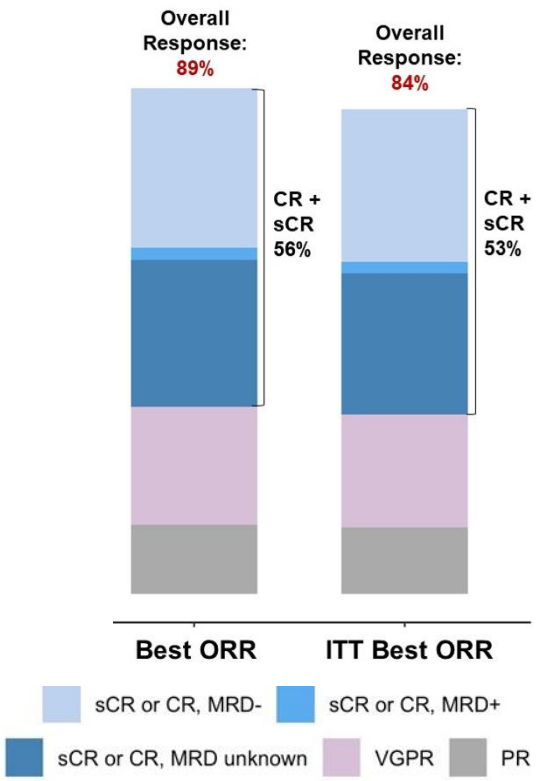


Chen et al, Clin Can Res 2024

Mi et al, ASCO 2023, #8010

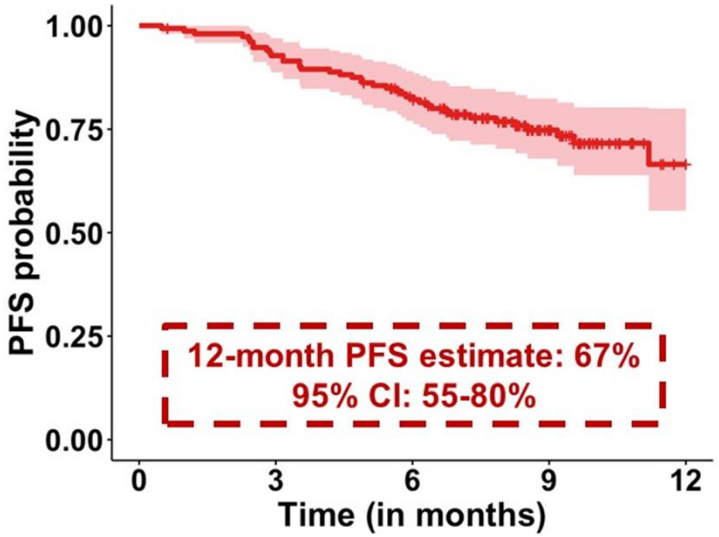
Cilta-cel in RRMM: Real-world cohort (n=143 infused)

Median 6 prior lines,
71% Triple-refractory
12% prior BCMA tx
22% OOS product

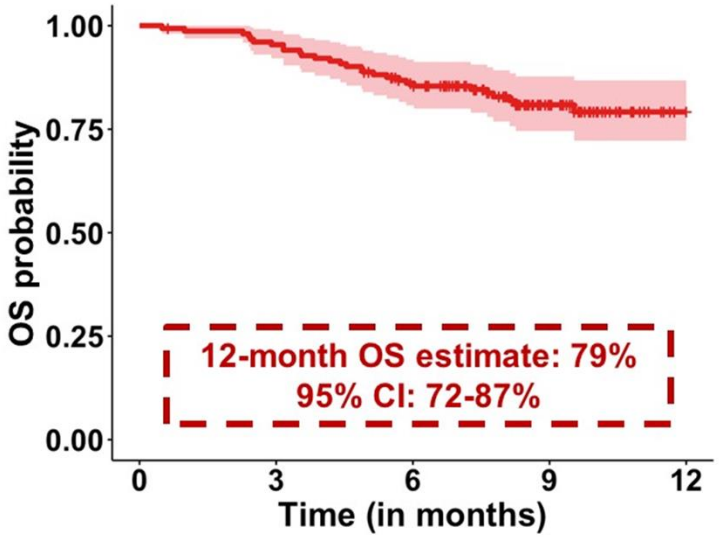


Median f/up 8.4 mos

Real World PFS



Real World OS



Total of 22 deaths (15%) in SOC population:
- **N=8 due to myeloma progression**
- **N=14 (10%) due to NRM**
  - **Gr5 CRS (N=3), concomitant CRS/infection (N=1), Gr5 ICANS (N=1), delayed NT (N=2), IEC-associated HLH-like syndrome (N=1), and infections (N=6)**

Hansen et al, ASCO 2023, #8012

BCMA CAR T Cells: Cytokine release syndrome

Ide-cel

Target Dose, × 10^6 CAR+ T cells	150 (n=4)	300 (n=70)	450 (n=54)	Ide-cel Treated (N=128)
≥1 CRS event, n (%)	2 (50)	53 (76)	52 (96)	107 (84)
Max. grade (Lee Criteria)*				
1/2	2 (50)	49 (70)	49 (91)	100 (78)
3	0	2 (3)	3 (6)	5 (4)
4	0	1 (1)	0	1 (<1)
5	0	1 (1)	0	1 (<1)
Median onset, d (range)	7 (2–12)	2 (1–12)	1 (1–10)	1 (1–12)
Median duration, d (range)	5 (3–7)	4 (2–28)	7 (1–63)	5 (1–63)
Tocilizumab, n (%)	1 (25)	30 (43)	36 (67)	67 (52)
Corticosteroids, n (%)	0	7 (10)	12 (22)	19 (15)

Cilta-cel

Characteristic	Total, N=97
Patients with a CRS event	92 (95%)
Maximum toxicity grade	
Grade 1	49 (51%)
Grade 2	38 (39%)
Grade 3	3 (3%)
Grade 4	1 (1%)
Grade 5	1 (1%)
Time to onset, days, median (IQR)	7·0 (5–8)
Duration, days, median (IQR)	4·0 (3–6)*
Supportive measures	88 (91%)
Tocilizumab	67 (69%)
Corticosteroids	21 (22%)
Anakinra	18 (19%)

Munshi et al. ASCO 2020; #8503; Berdeja et al, Lancet 2021

BCMA CAR T Cell toxicities: Neurotoxicity

Ide-cel

Parameter	Ide-cel Target Dose, CAR+ T Cells			
	150×10^6 (N=4)	300×10^6 (N=70)	450×10^6 (N=54)	Total (N=128)
Patients with a neurotoxicity event—no. (%)*	0	12 (17)	11 (20)	23 (18)
Grade 1	0	7 (10)	5 (9)	12 (9)
Grade 2	0	4 (6)	3 (6)	7 (5)
Grade 3	0	1 (1)	3 (6)	4 (3)
Median (range) time to onset—days	NA	3 (1–10)	2 (1–5)	2 (1–10)
Median (range) duration—days†	NA	3 (2–26)	5 (1–22)	3 (1–26)
Glucocorticoid use—no. (%)	0	2 (3)	8 (15)	10 (8)
Tocilizumab use—no. (%)	0	0	3 (6)	3 (2)
Anakinra use—no. (%)	0	0	1 (2)	1 (<1)

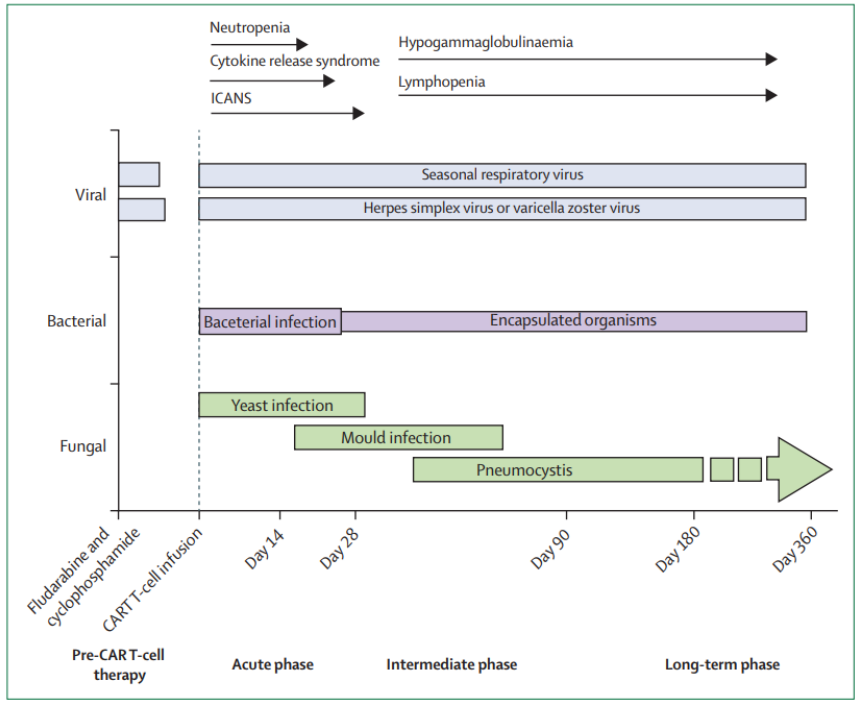
Cilta-cel

Any neurotox=21% (n=20)
Gr 3-5 = 9% (n=9)

Characteristic	ICANS*	Other neurotoxicities
Patients with a neurotoxic event	16 (17%)	12 (12%)
Maximum toxicity grade		
Grade 1	10 (10%)	0
Grade 2	4 (4%)	3 (3%)
Grade 3	1 (1%)	7 (7%)
Grade 4	1 (1%)	1 (1%)
Grade 5	0	1 (1%)
Time to onset, days, median (IQR)	8·0 (6–8)	27·0 (16–73)
Duration, days, median (IQR)	4·0 (3–7)	(··)
Time to recovery, days, median (IQR)	(··)	74·5 (28–159)
Supportive measures‡	16 (17%)	(··)
Corticosteroids	9 (9%)	(··)
Tocilizumab	4 (4%)	(··)
Anakinra	3 (3%)	(··)

Munshi et al. NEJM 2021; Berdeja et al, Lancet 2021

IMWG Consensus Guidelines for Infection Prevention Post-CAR T Cells



	EBMT[75] recommendation	IMWG recommendation	Comments
Antiviral prophylaxis	Valacyclovir 500 mg twice a day and acyclovir 800 mg twice a day from lymphodepletion for 1 year post-CAR T-cell therapy	Valacyclovir 500 mg twice a day and acyclovir 400–800 mg twice a day from lymphodepletion for 1 year post-CAR T-cell therapy	Late varicella zoster virus has been described
Antibacterial prophylaxis	Not recommended	Levofloxacin 500 mg daily (or equivalent)	To start at neutropenia (ANC <500 per uL) or during high steroid or multiple immunosuppressive medication use
Antifungal prophylaxis	Not recommended	Fluconazole 400 mg daily (or equivalent); prophylaxis against mould (eg, aspergillus) should be considered in high-risk situations	To start at neutropenia (ANC <500 per uL) or during high steroid or multiple immunosuppressive medication use
Anti-pneumocystis prophylaxis	Co-trimoxazole 480 mg daily or 960 mg three times a week pre-lymphodepletion for 1 year post-CAR T-cell therapy	Sulfamethoxazole 800 mg and trimethoprim 160 mg three times a week pre-lymphodepletion until 6 months post-CAR T-cell therapy; alternatives could be considered in settings of cytopenia, allergy, or regional drug access; alternatives include monthly pentamidine nebuliser or atovaquone (1·5 g daily)	Late infections occur and continue therapy until CD4+ count >200 cells per uL
Intravenous gamma globulin	Consider in adults who have had encapsulated organism infections	Consider IgG replacement if IgG <400 mg/dL with 400–500 mg/kg intravenous immunoglobulin every 4–6 weeks	No formal studies, consider replacement if recurrent infections and IgG is 400–600 mg/dL*
G-CSF use	Consider G-CSF to shorten duration of neutropenia from 14 days after CAR T-cell infusion	Should be used to maintain ANC >1000 per uL in the first 3 months after CAR T-cell infusion	Avoid during cytokine release syndrome or ICANS, or if presenting with macrophage activation syndrome-like symptoms

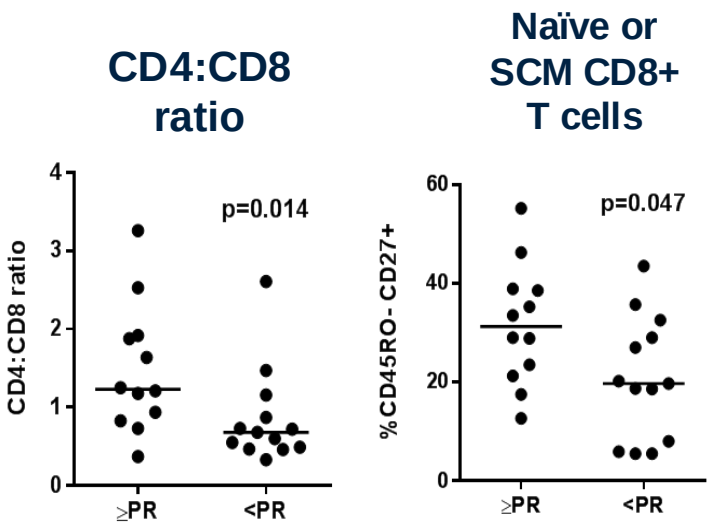
ANC=absolute neutrophil count. EBMT=European Society for Blood and Marrow Transplantation. G-CSF=granulocyte-colony stimulating factor. ICANS=immune effector cell-associated neurotoxicity syndrome. IMWG=International Myeloma Working Group. *Correct IgG level for IgG paraprotein—eg, if a residual M-spike of 0·4 g/dL IgG-kappa exists and the total IgG level is 700 mg/dL, then the correct IgG would be estimated around 300 mg/dL.

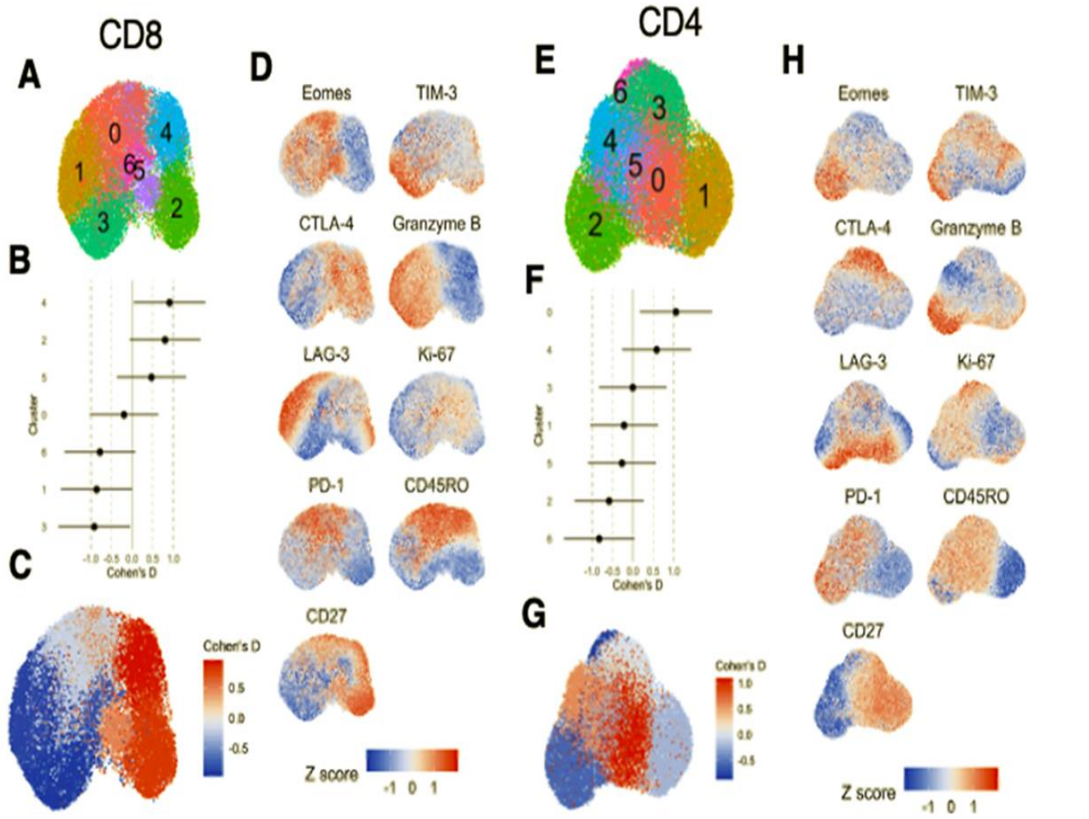
Table 1: **Antimicrobial prophylaxis**

Lin Y, Qiu L, Usmani S, et al. Lancet Oncol. 2024;25(8):e374-e387.

Challenge: How to increase proportion with durable response?

- Factors associated with response: T cell quality/fitness



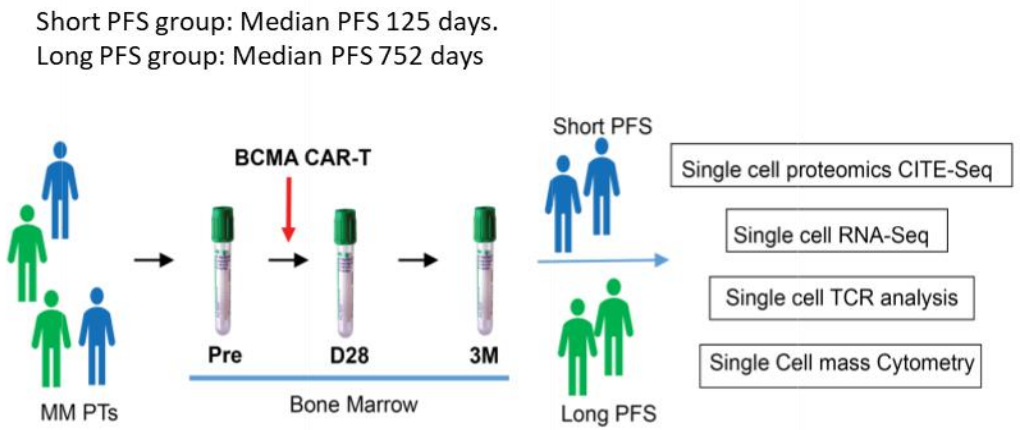


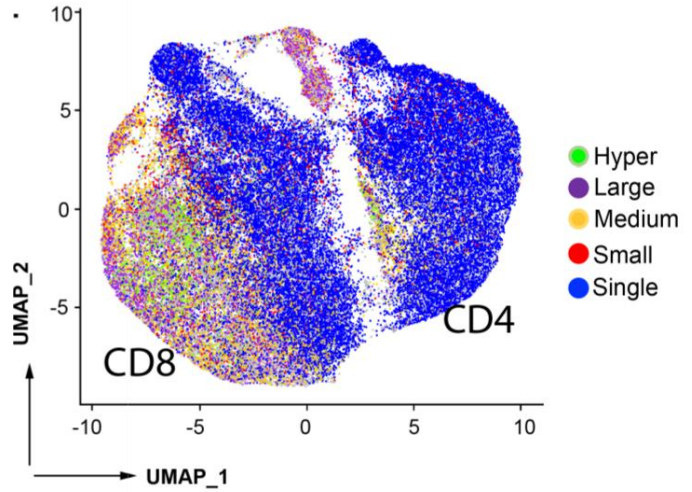
- Responders
  - Naïve, Tcm, Tscm
  - Non-activated
  - Granzyme B low
  - PD-1 low
  - TIM-3/LAG-3 low-int
- Non-responders
  - Teff or Tem
  - Highly-activated (HLA-DR+)
  - Granzyme B hi
  - PD-1 low
  - TIM-3 hi +/- LAG-3 hi

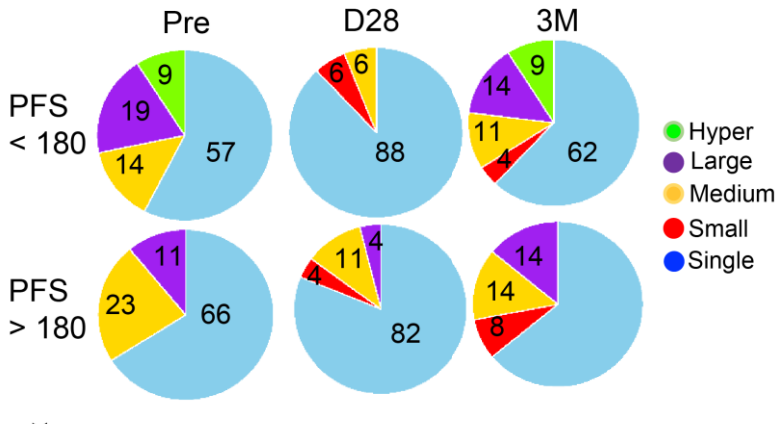
Cohen et al, J Clin Invest 2019; Wang et al, ASH 2019, #1909

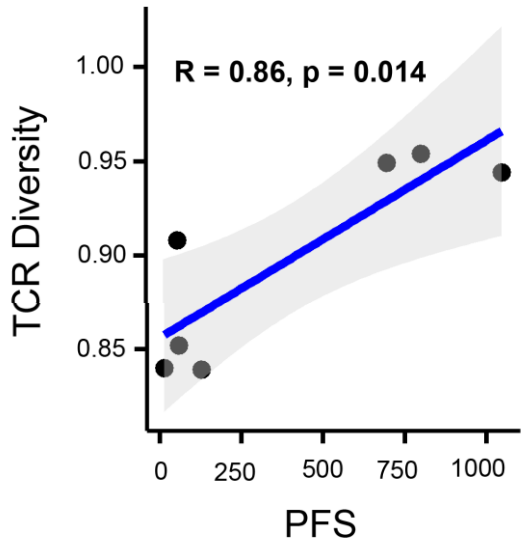
Challenge: How to increase proportion with durable response?

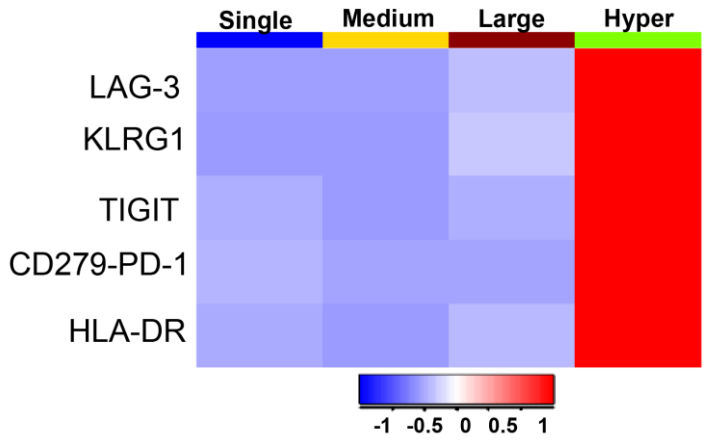
- Factors associated with response: T cell quality/fitness





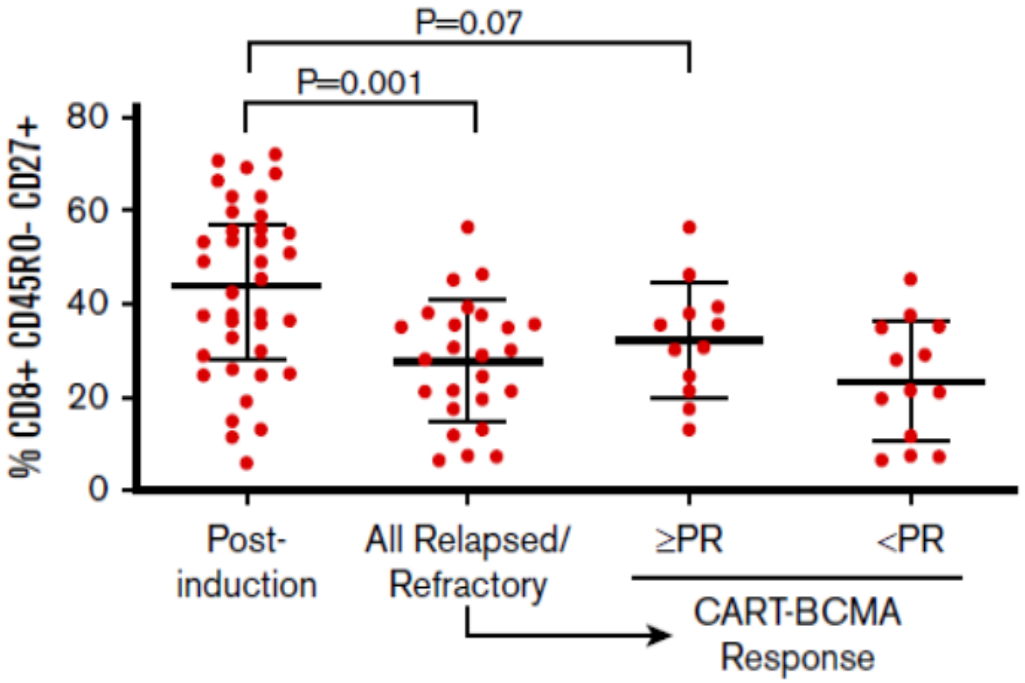






Dhodapkar, Cohen et al, Blood Cancer Disc 2022

Overcoming poor T cell fitness: Treat earlier in disease course?



Garfall et al, Blood Advances 2019

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