Penn Medicine

Novel CAR T cells and combinations for myeloma

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

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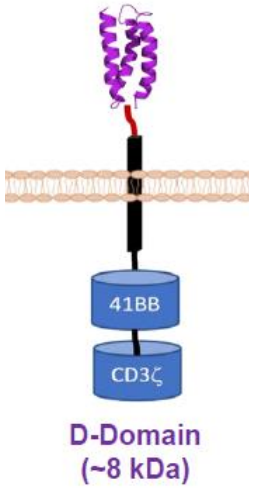
Disclosures

- 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

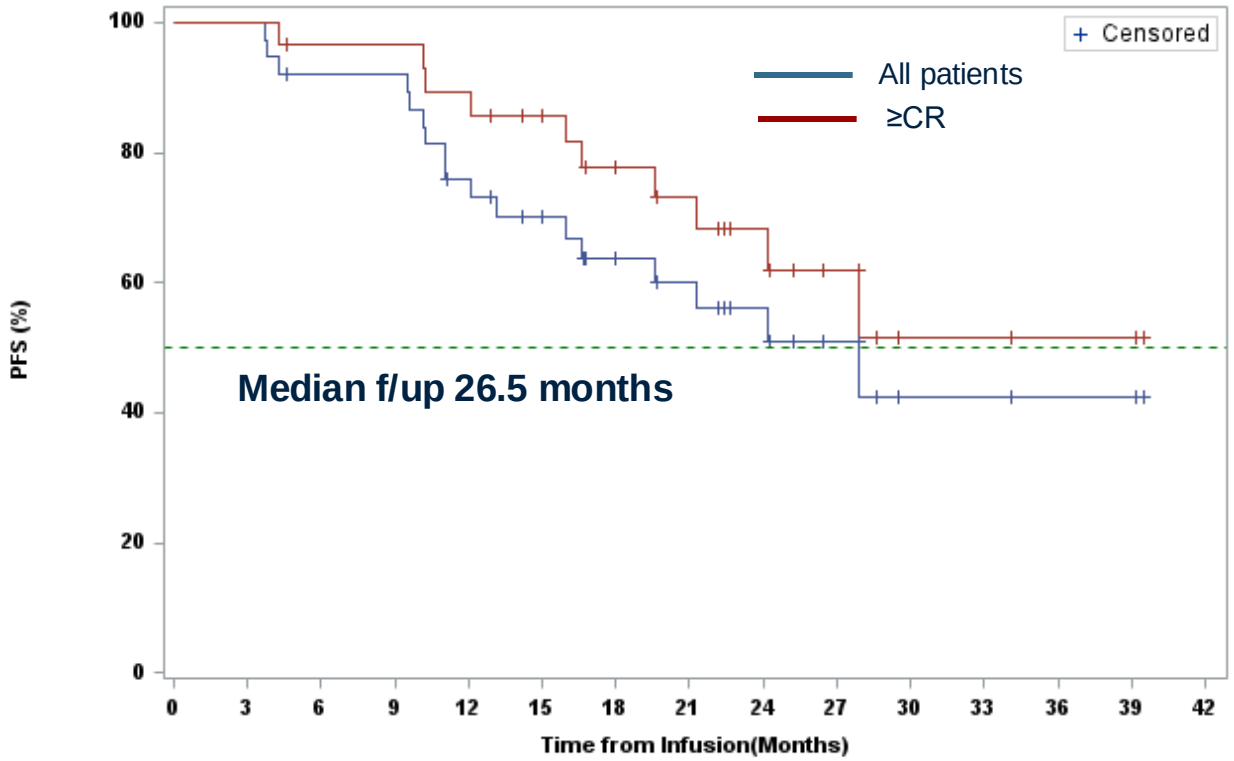
Other autologous BCMA CAR T Cell products

- Equ-cel (CT103A) – approved in China
- Zevor-cel (CT53) – approved in China
- Cesni-cel (ARI0002h) – approved in Spain
- Anito-cel (CART-ddBCMA)
- PHE885

CART-ddBCMA (anito-cel) phase1 for RRMM (n=40, n=38 dosed)



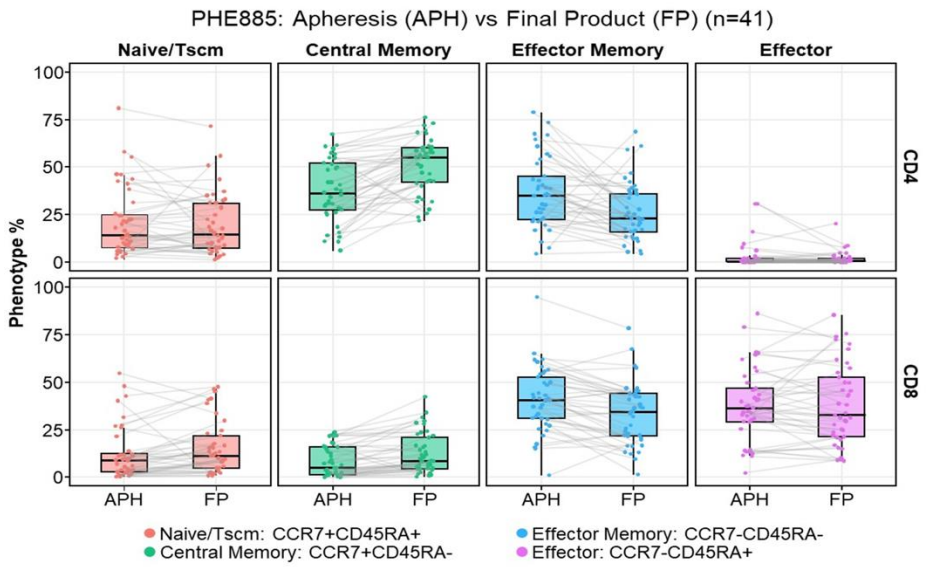
- Med 4 priors, 100% TCR, 34% EMD
  - ORR 100%, sCR/CR 76%
  - CRS 95% (2.5% Gr3)
  - ICANS 18% (2.5% Gr3)
  - No delayed neurotoxicity

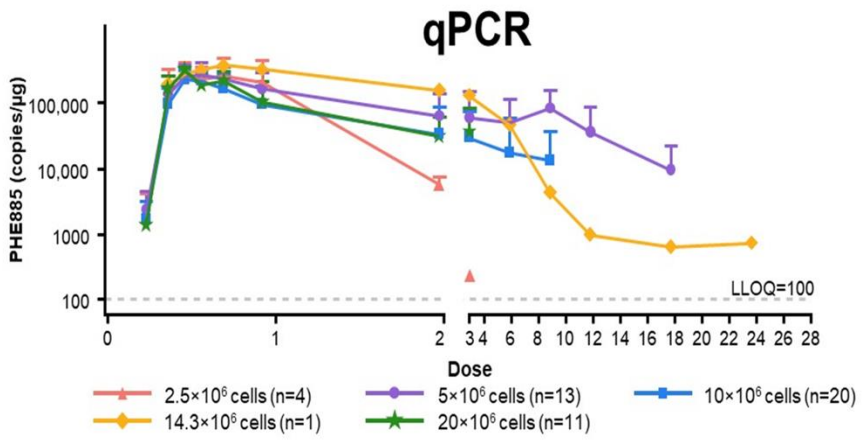


- Phase 2 completed
- Phase 3 anito-cel vs SOC in 1-3 priors open late 2024

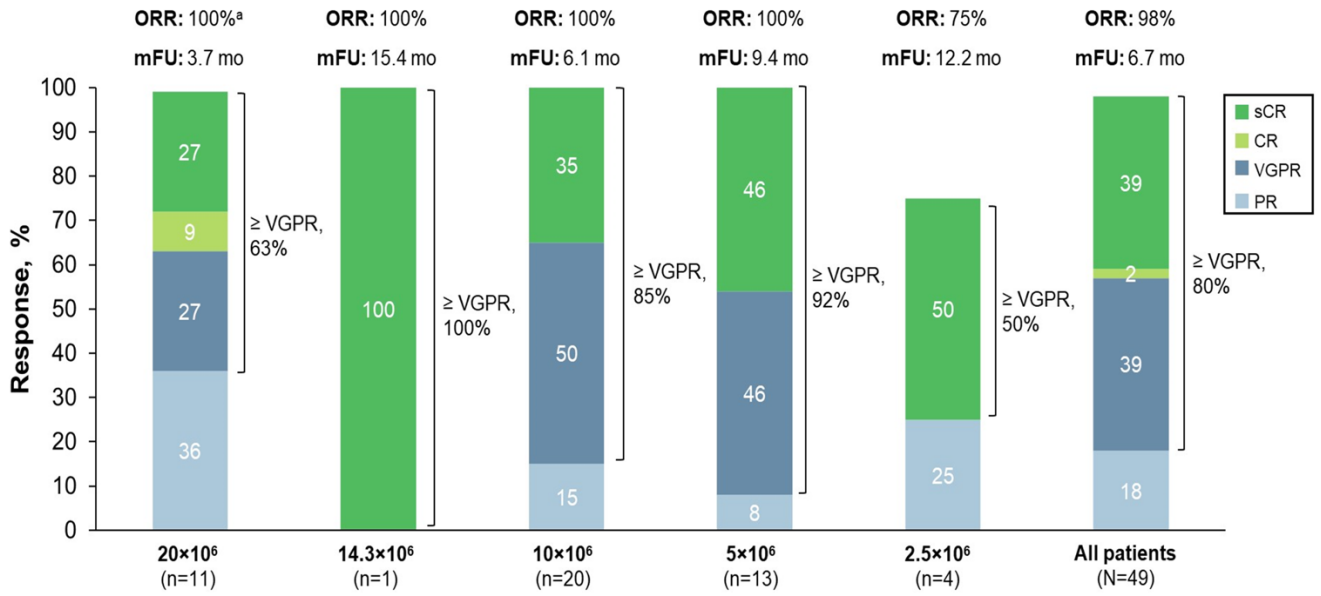
Frigault et al, ASH 2023, #1023

PHE885: rapid manufacturing BCMA CAR T product (<2 days)





- Med 4 priors, 94% TCR, 33% EMD
- 34% got bridging



- CRS 96% (10% Gr3)
- ICANS 20% (6% Gr3)
- No delayed neurotoxicity

Sperling et al, ASCO 2023, #8004

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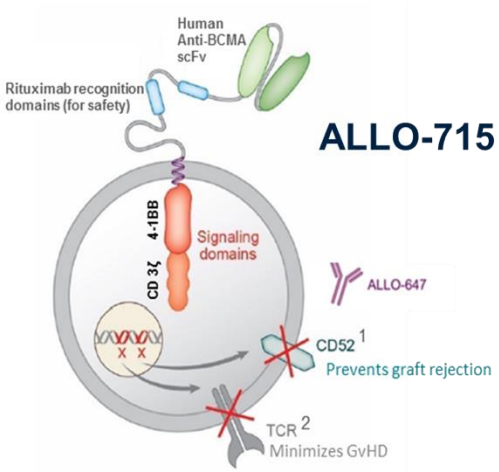
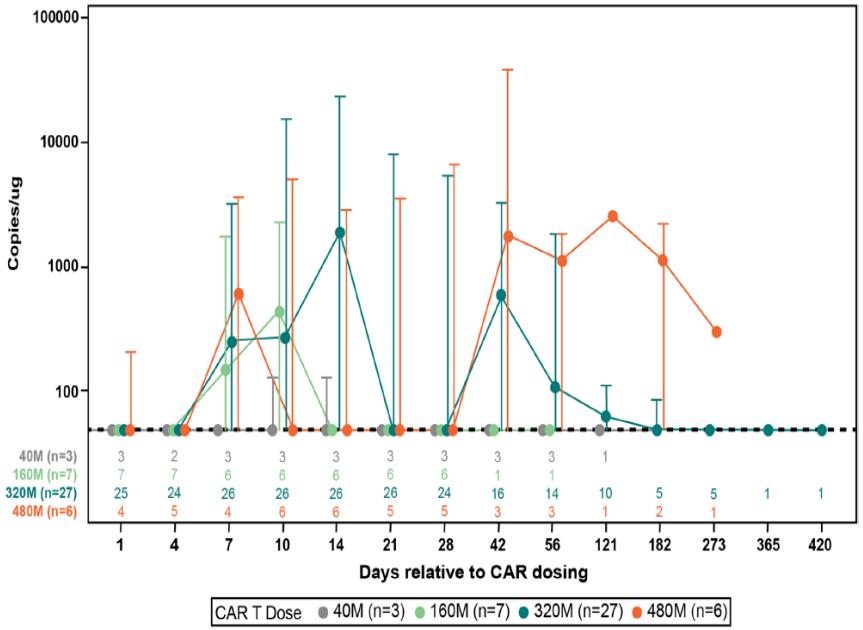
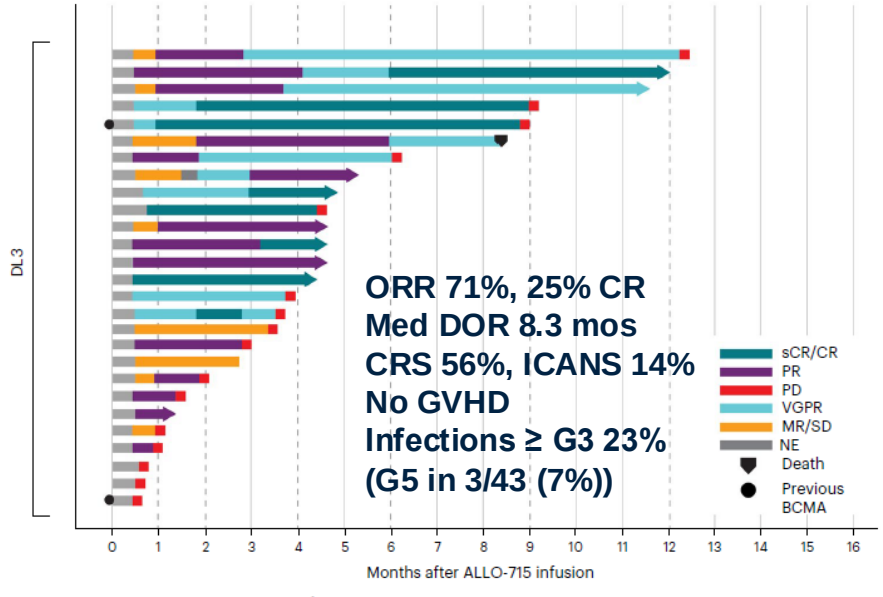
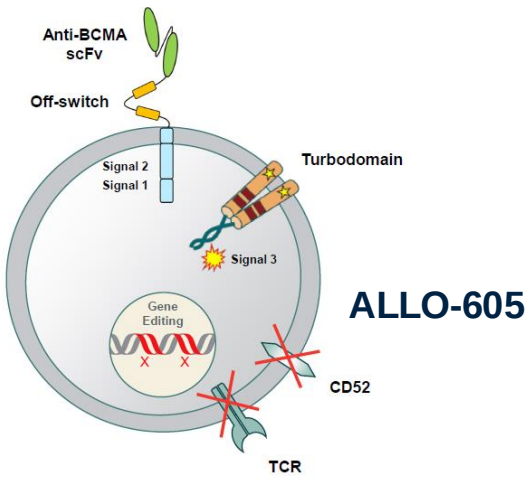
Allogeneic BCMA CAR-T products



ALLO-715

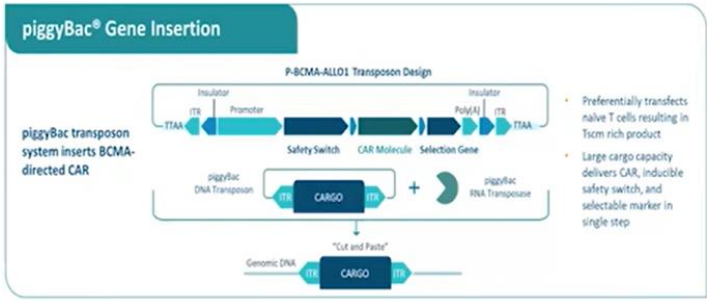


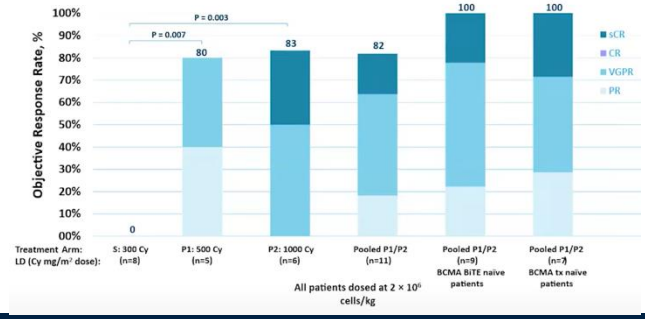




ALLO-605

P-BCMA-ALLO1 phase 1: activity seen with augmented cytoxan/flu LD



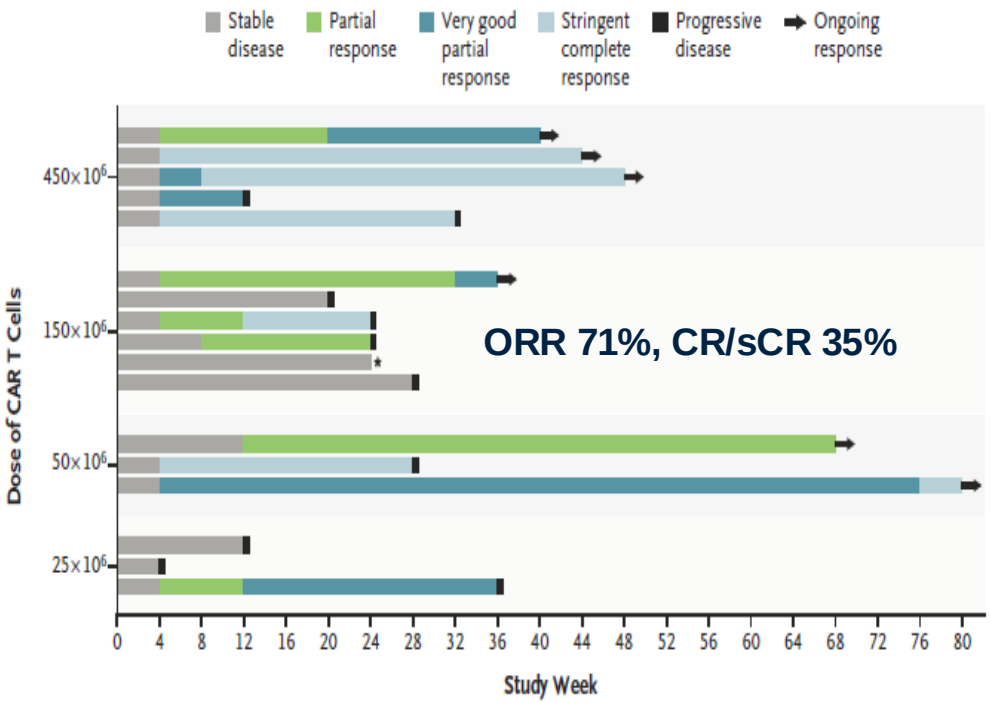


Mailankody et al, Nat Med 2023; Lin et al, Sci Advances 2023; Dholaria et al, ASH 2023, #3479

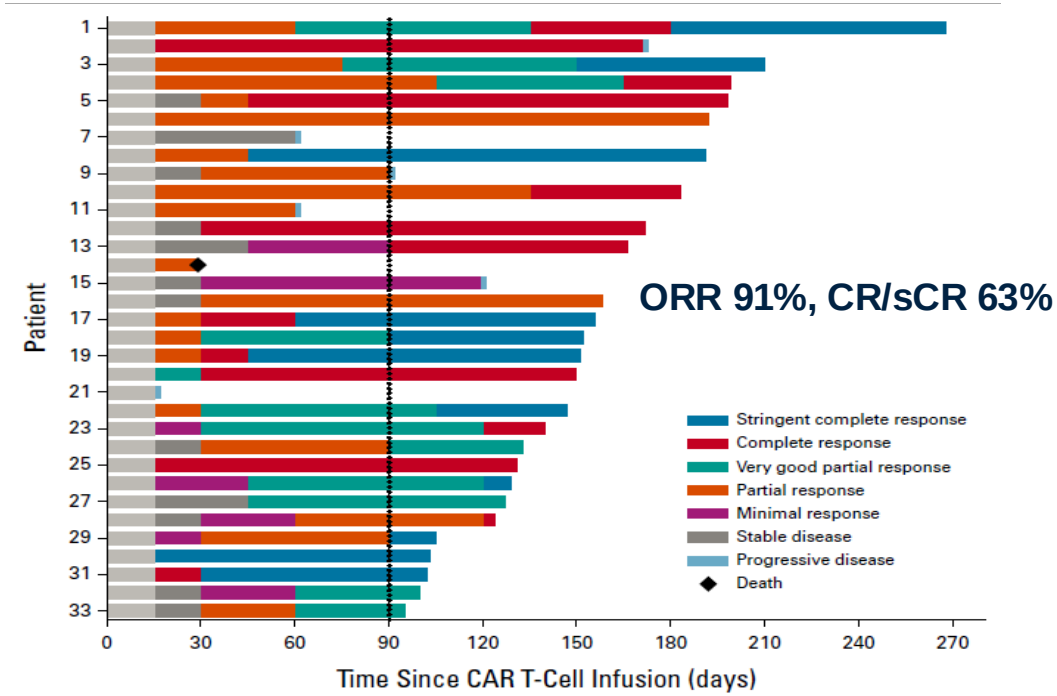
Other immunotherapy target for myeloma

- CD19
- CD138
- CD38
- SLAMF7
- CD44v6
- TACI
- CD229
- TnMUC1
- FcRH5

GPRC5D targeted CAR – MSKCC



GPRC5D targeted CAR – Xuzhou Med Univ.



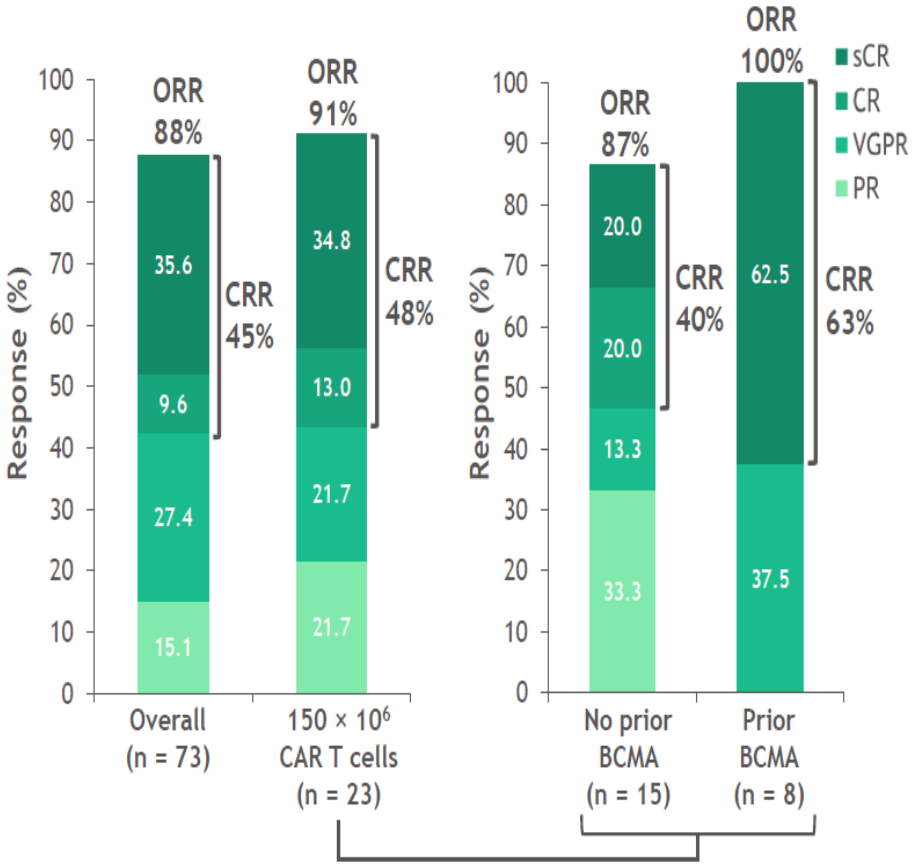
Responses seen in patient with prior BCMA-targeted therapies

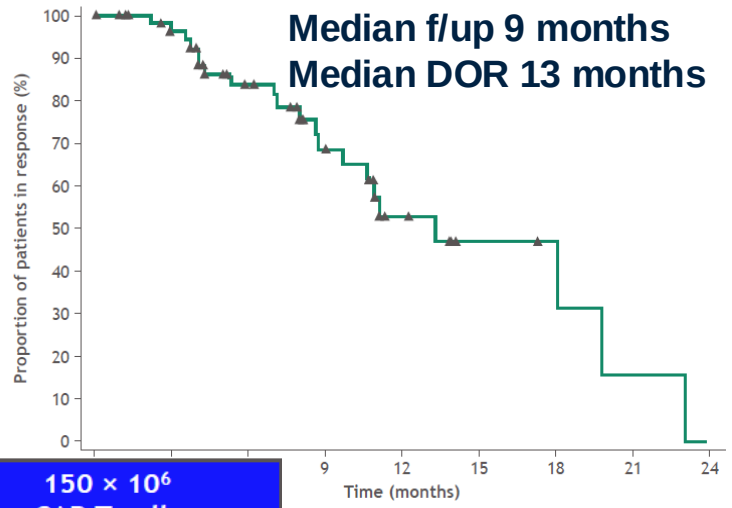
Toxicities: CRS, ICANS, cytopenias, dysguesia, skin/nail changes
2 cerebellar toxicities in MSKCC study

Mailankody et al, NEJM 2022; Xia et al, J Clin Oncol 2023

BMS-986393 (GPRC5D CART) in RRMM: multicenter phase 1

- Med 5 priors, 74% TCR, 44% EMD, 46% prior BCMA-targeted tx





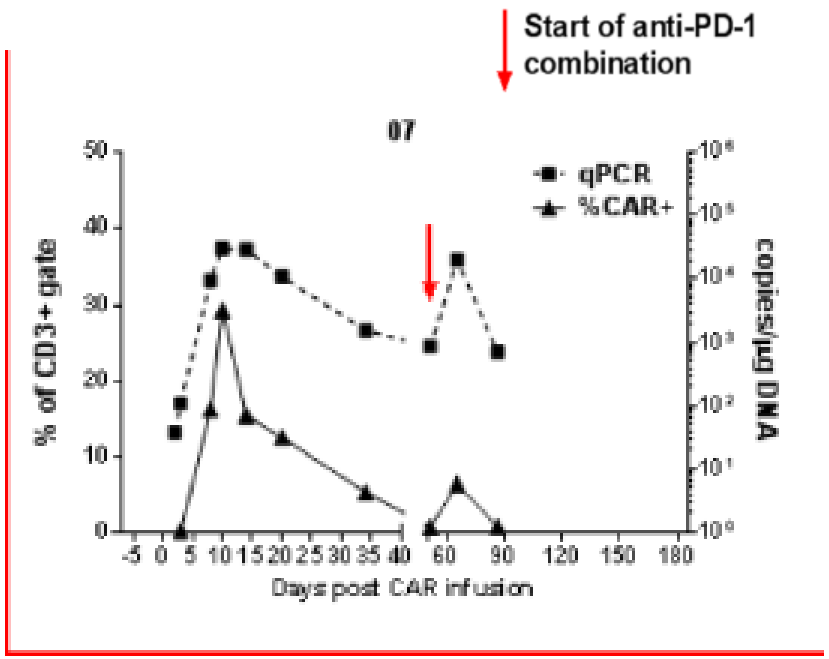
	All treated patients (n = 84)		150 × 10⁶ CAR T cells (n = 26)	
	Any grade	Grade 3/4	Any grade	Grade 3/4
CRS	64 (76.2)	3 (3.6)	23 (88.5)	0 (0)
Infections and infestations	34 (40.5)	11 (13.1)	9 (34.6)	3 (11.5)
Dysgeusia/taste disorder	21 (25.0)	0	8 (30.8)	0
Skin[a]	17 (20.2)	0	4 (15.4)	0
Nails[b]	11 (13.1)	0	3 (11.5)	0
Dysphagia	3 (3.6)	0	1 (3.8)	0
Neurotoxicity, n (%)	Any grade	Grade 3 only	Any grade	Grade 3 only
ICANS-type neurotoxicity[c]	8 (9.5)	2 (2.4)	1 (3.8)	0
Non-ICANS-type neurotoxicity[d]	9 (10.7)	3 (3.6)	4 (15.4)	1 (3.8)

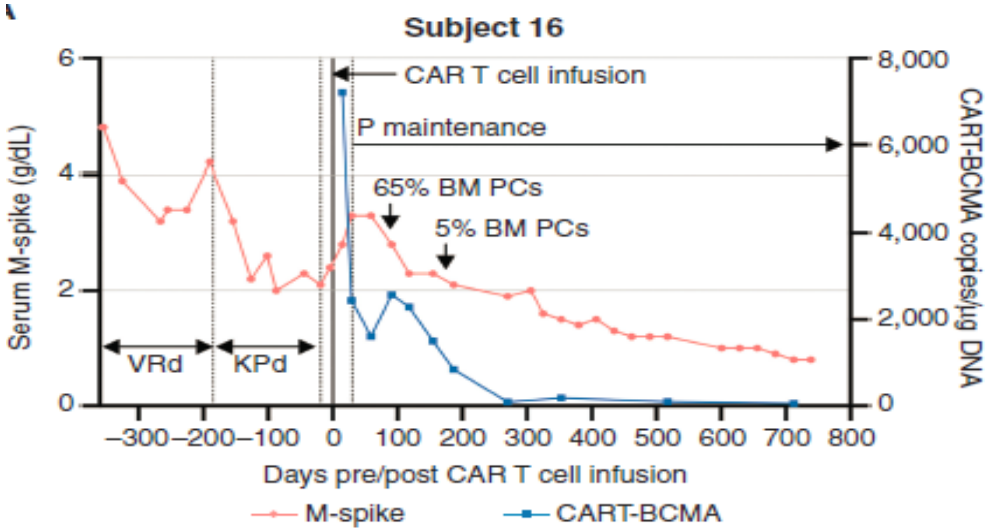
Bal et al, ASH 2023, #219

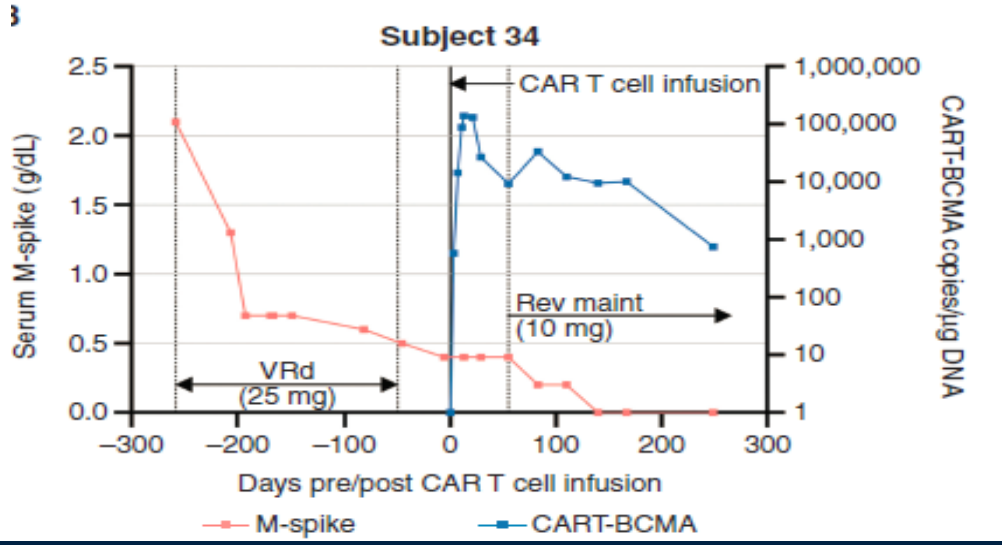
CAR T cell combinations in myeloma

- CAR T + gamma-secretase inhibitor
- CAR T + IMIDs
- CAR T + anti-PD-1
- CAR + CAR
- CAR T + bispecific Ab

BCMA CAR T cells can re-expand in vivo following immune-stimulating drugs

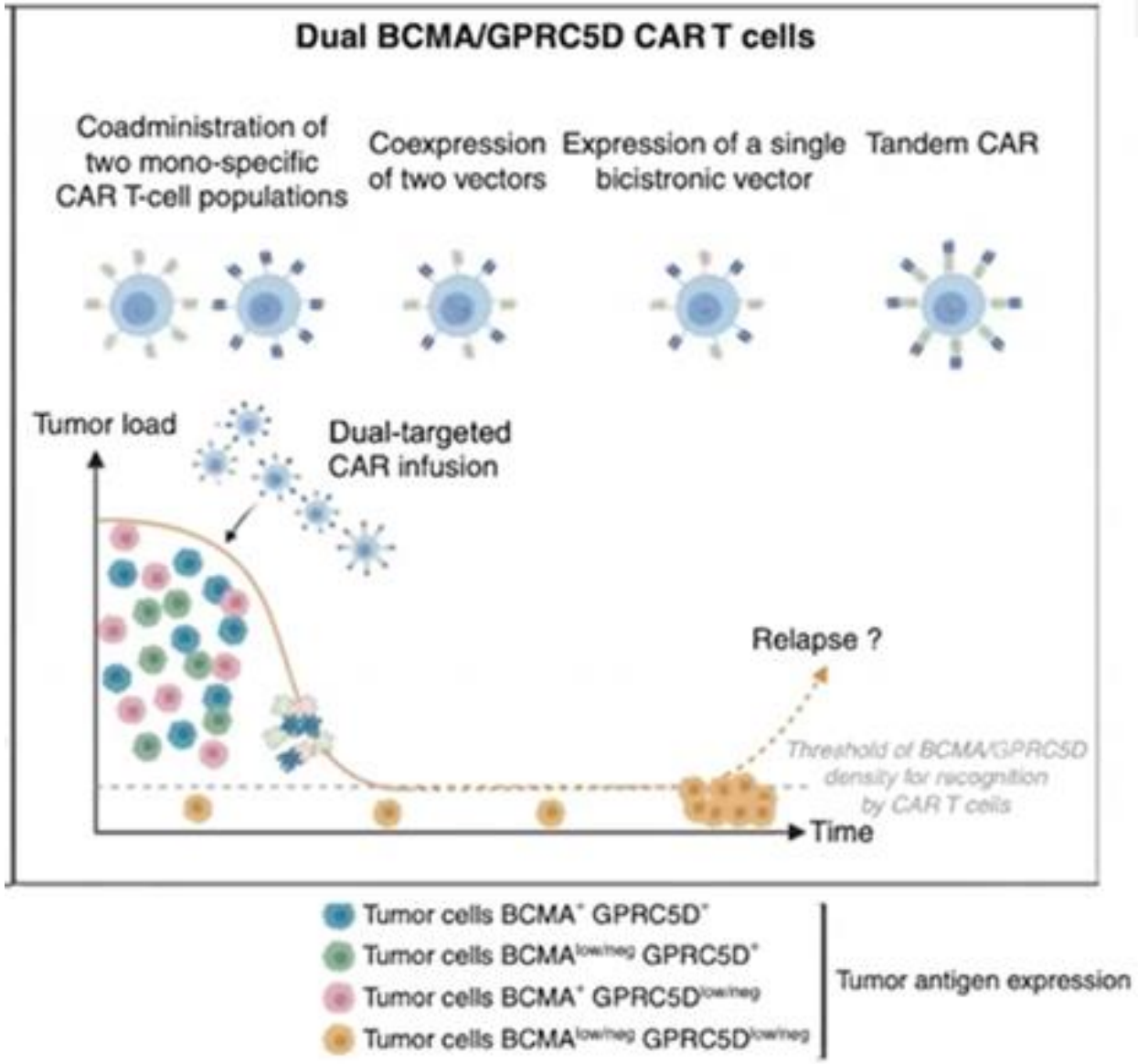






Bernabei et al, Brit J Haematol 2021; Garfall et al, Blood Canc Disc 2023

CAR + CAR



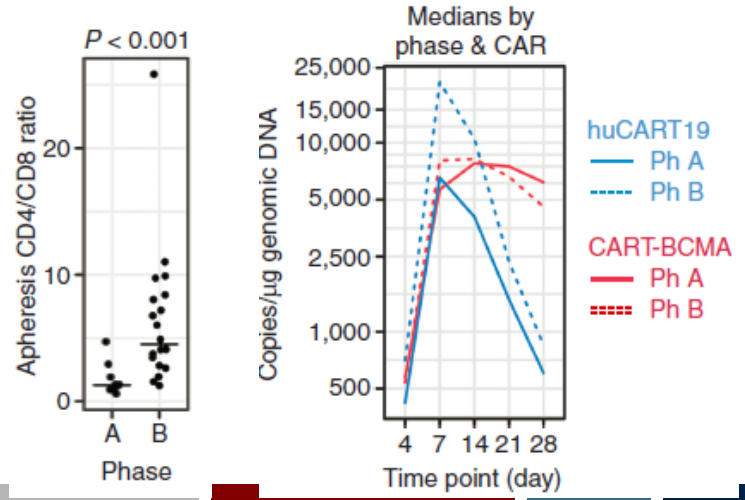
Simon and Riddell, Blood Cancer Discov 2020

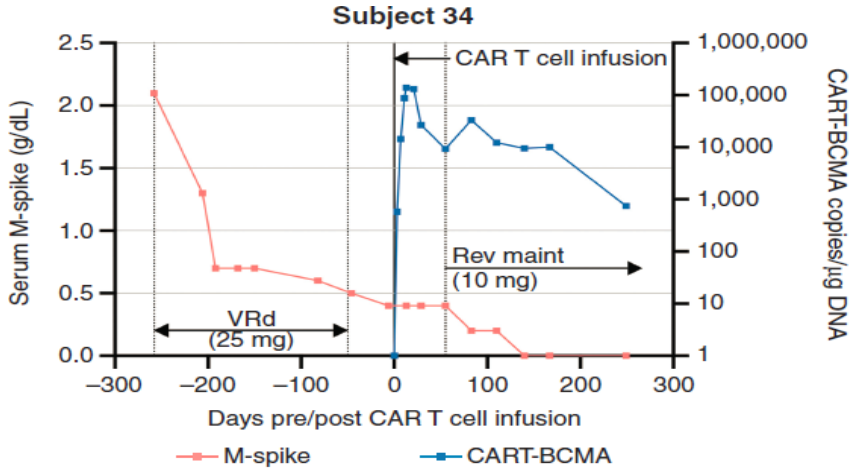
CART-BCMA +/- CTL019 for high-risk NDMM (or relapsed MM)

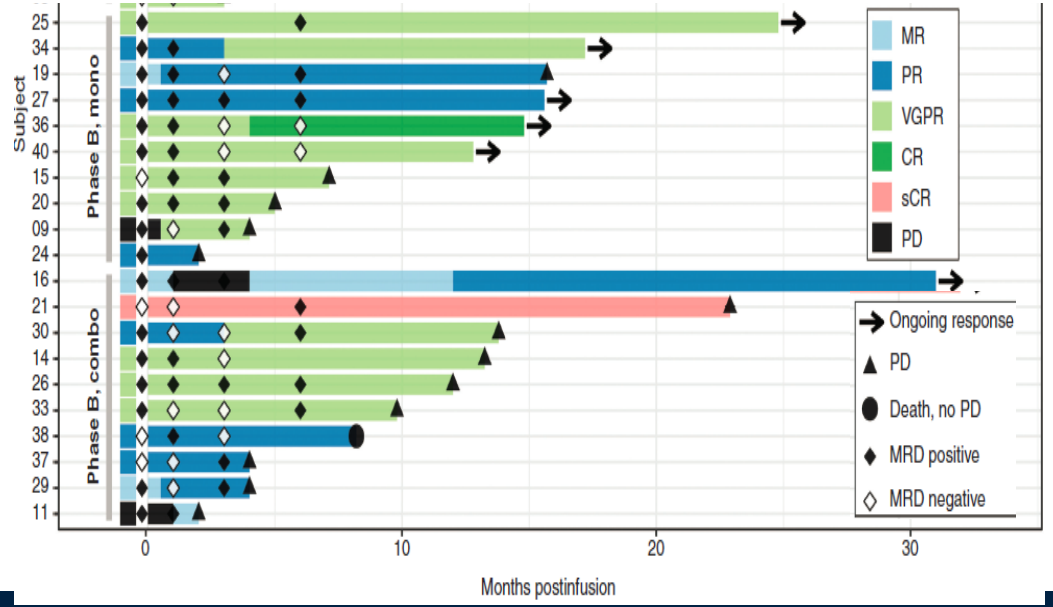
- Consolidate response to induction (B) or salvage therapy (A)
- Maintenance with IMIDs

	Grade 3/4 CRS	Any grade ICANS
CART-BCMA phase 1*	16%	32%
CART-BCMA + CTL019**	0%	3%

*in progressing, relapsed/refractory patients
**in responding patients in first-line (high-risk) or early relapse

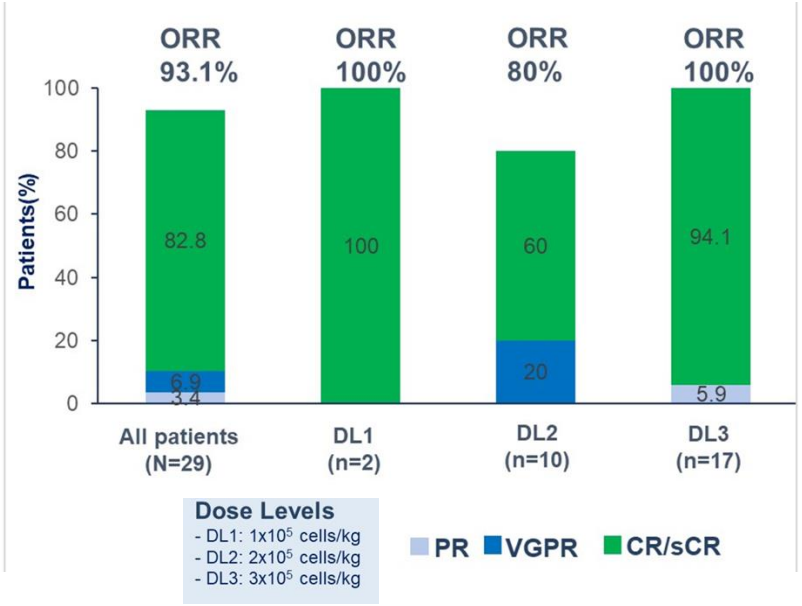






Garfall, Cohen et al, Blood Canc Disc 2023

GC012F FastCAR dual CD19/BCMA-targeted product

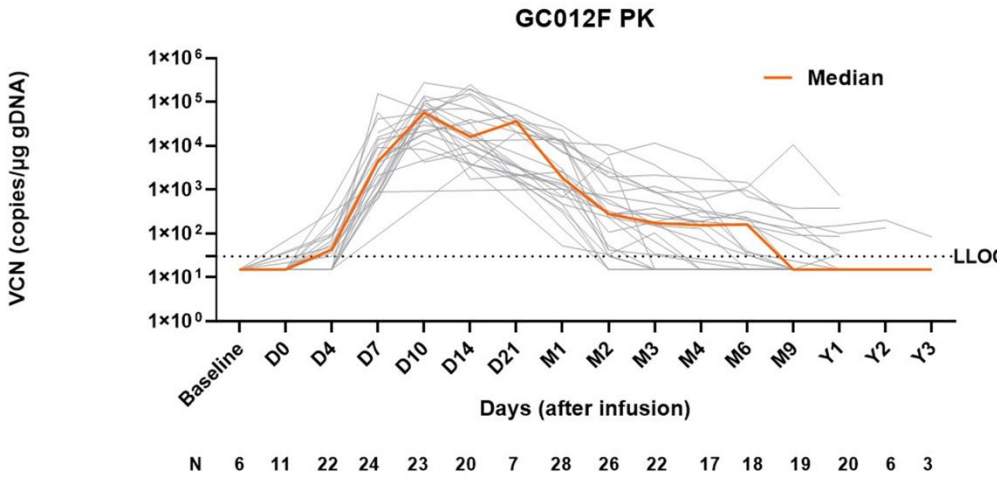


Subgroup	n	PFS, Median (95% CI, mo)	12-month PFS rate	36-month PFS rate
All patients	29	38.0 (11.8, NE)	69.0%	50.5%
sCR	24	38.0 (13.7, NE)	83.3%	61.0%
12-month sustained MRD negativity	10	NE (38.0, NE)	100%	100%
12-month sustained MRD negative CR	10	NE (38.0, NE)	100%	100%

N=29	CRS[1], n (%)	ICANS[2], n (%)
Grade 1	14 (48)	0 (0)
Grade 2	9 (31)	0 (0)
Grade 3	2 (7)	0 (0)
Grade 4-5	0 (0)	0 (0)

[1]CRS treated with Tocilizumab, vasopressors and dexamethaso

CRS any grade	Median (days)	Range (days)
Time to onset	6	2-10
Duration	3	1-8

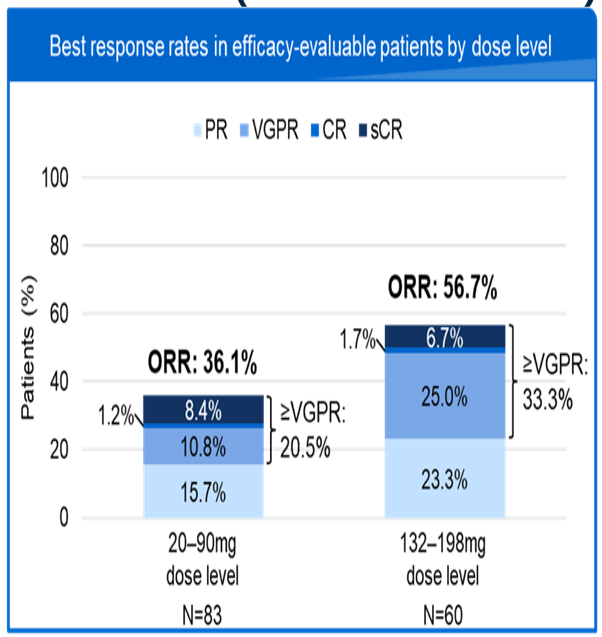


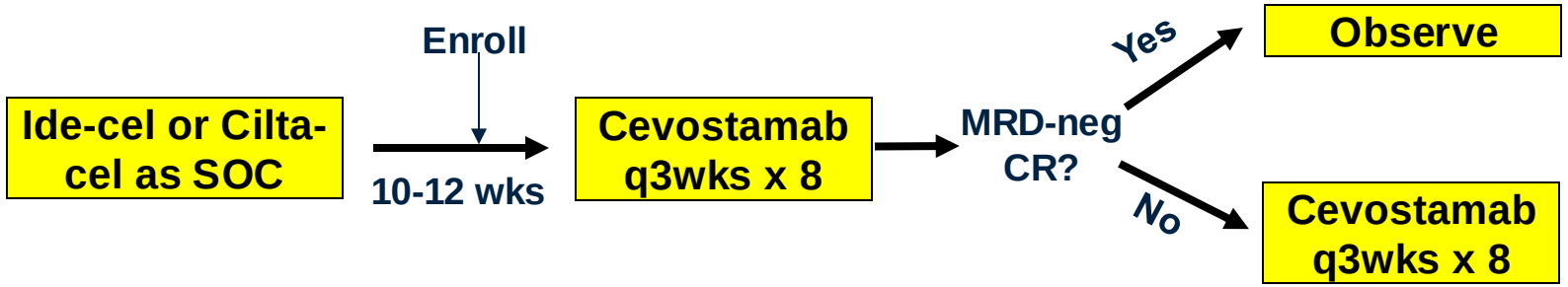
- Median Cmax = 96,438 copies/μg gDNA
- Median Tmax = Day 10
- Long-Term Persistence (≥LLOQ):
- 6 months: 72.2% (13/18)
- 12 months: 47.1% (8/17)

Du et al, ASCO 2023, #8005

Phase 2 study of cevostamab consolidation following BCMA CAR T cell therapy for relapsed/refractory multiple myeloma

Cevostamab (FcRH5 x CD3 bsAb)

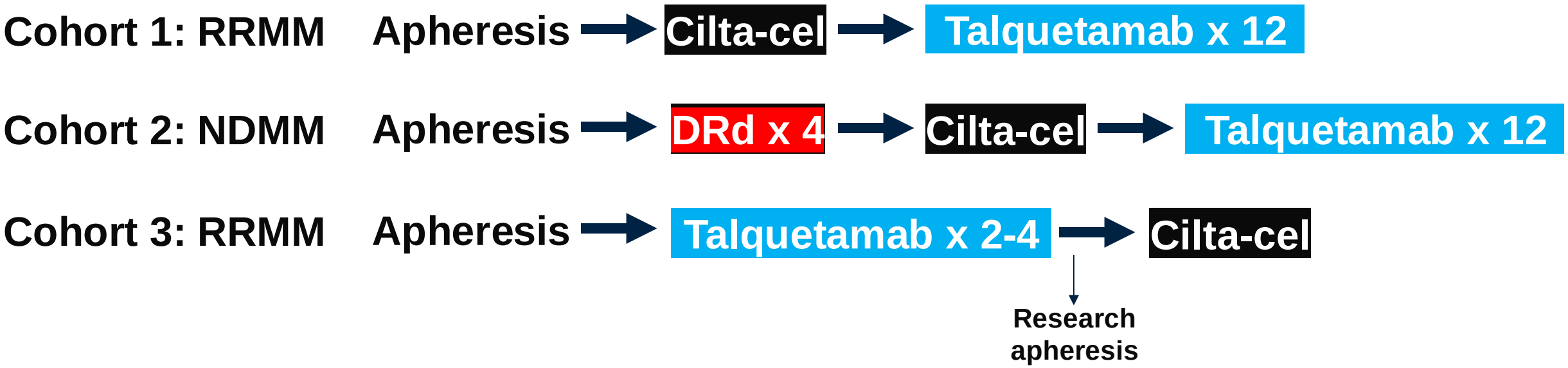




Primary endpoint: MRD-negative CR rate at 12 months post-CAR T cells
Planned n=26 evaluable

Trudel et al, ASH 2021, #157; Cohen et al, ASH 2023, #TIP 3389

MonumenTAL-8: ph2 of cilta-cel + talquetamab for MM



Also: MSKCC Phase 2 study of Talequetamab consolidation after ide-cel for RRMM

www.clinicaltrials.gov (NCT06550895, NCT06066346)

Penn Myeloma Program

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NIH P01 CA214278-01

Extra slides

CD38 CAR T cells

- Concern about off-tumor effects on T, B, NK cells, monocytes, and hematopoietic progenitors
  - Can generate low affinity CD38-targeted CARs→ impact on efficacy? (Drent et al, Clin Can Res 2019)
- Anti-**CD38** A2 **CAR-**T Cells phase 1 (Sorrento, NCT03464916) closed to accrual (n=9)
- 3 combo BCMA and CD38 targeted CAR trials in China

Trial	CARs	n	Med prior Tx	CRS	ORR	CR	PFS
Tianjian Hosp.	Separate BCMA and CD38 CARs	22	8	100% (Gr 3-5 27%)	91%	55%	49% @ 2 yrs
Jingzhou Hosp.	Bi-specific BCMA/CD38 CAR	16	3	75% (Gr 3-5 31%)	88%	81%	69% @ 1 yr
Union Hosp.	Bi-specific BCMA/CD38 CAR	23	4	87% (Gr 3-4 22%)	87%	52%	Med. 17 mos.

Zhang et al, Leuk Lymphoma 2022; Tang et al, J Exp Clin Can Res 2022; Mei et al, J Hematol Oncol 2021

Sequencing Bispecific Antibodies (BsAb) with CAR T cells