Current Role of Chimeric Antigen Receptor (CAR) T-Cell Therapy for MM

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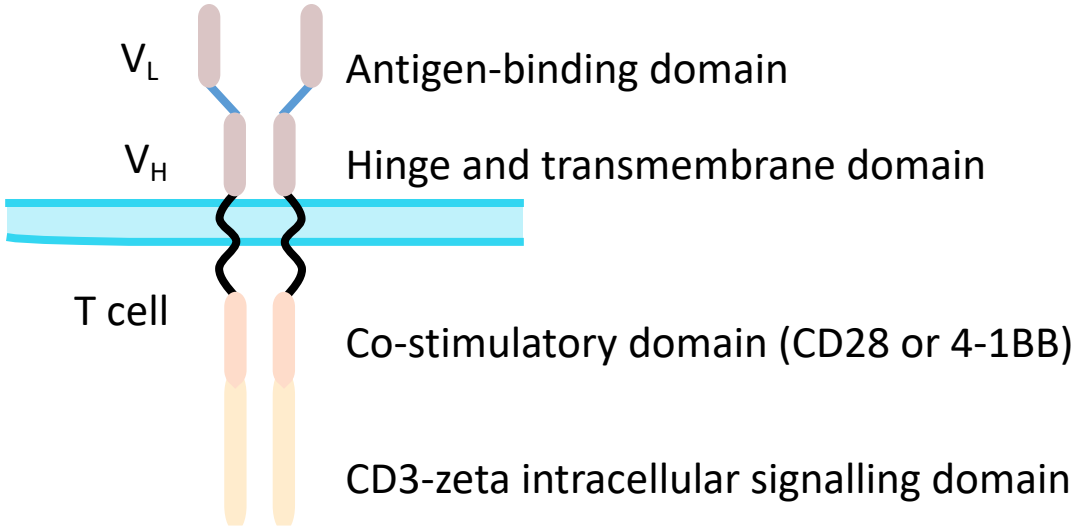
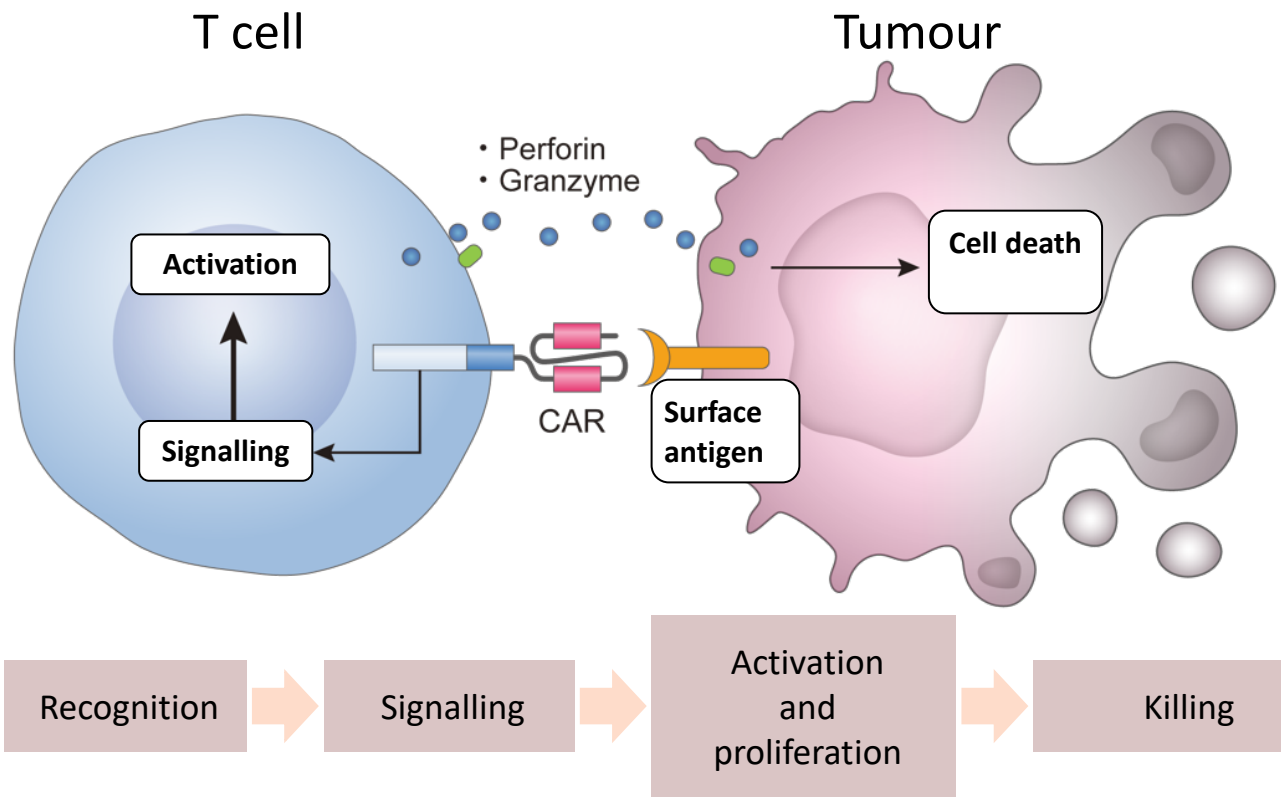
CANCER CENTER

Current Role of Chimeric Antigen Receptor (CAR) T-Cell Therapy for MM — Dr Raje

Structural makeup and manufacturing of available BCMA-directed CAR T-cell platforms
Results from the Phase II KarMMa trial evaluating idecabtagene vicleucel (ide-cel) for R/R MM
Key data from the CARTITUDE-1 trial of ciltacabtagene autoleucel (cilta-cel) for pretreated MM
Available and emerging data with ide-cel and cilta-cel in earlier lines of treatment
Spectrum, incidence and severity of toxicities with BCMA-targeted CAR T-cell therapies
Early data with non-BCMA CAR T-cell platforms (eg, BMS-986393)

CAR T cell therapy: mechanism of action





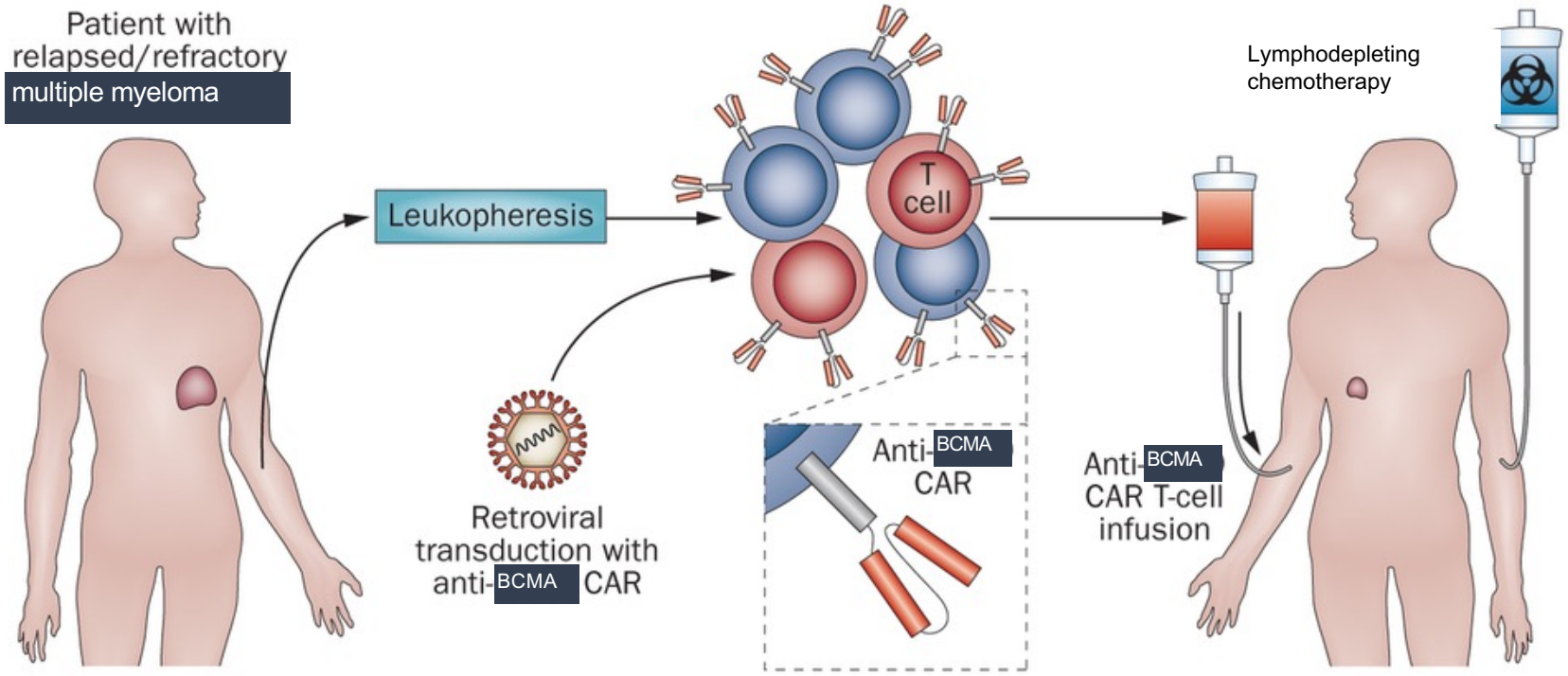
- Confer the high-affinity antigen specificity of an antibody to an autologous cytotoxic T cell
- Living drug, single infusion
- No need for immune suppression
- No risk of graft-versus-host disease

CAR, chimeric antigen receptor; V_H, variable heavy chain; V_L, variable light chain.

Abramson JS. Transfus Med Rev. 2020;34:29-33.

Images adapted from Shinshu University. Available from: www.shinshu-u.ac.jp/english/topics/research/shinshu_university_a_1.html.

CAR T-cell Therapy



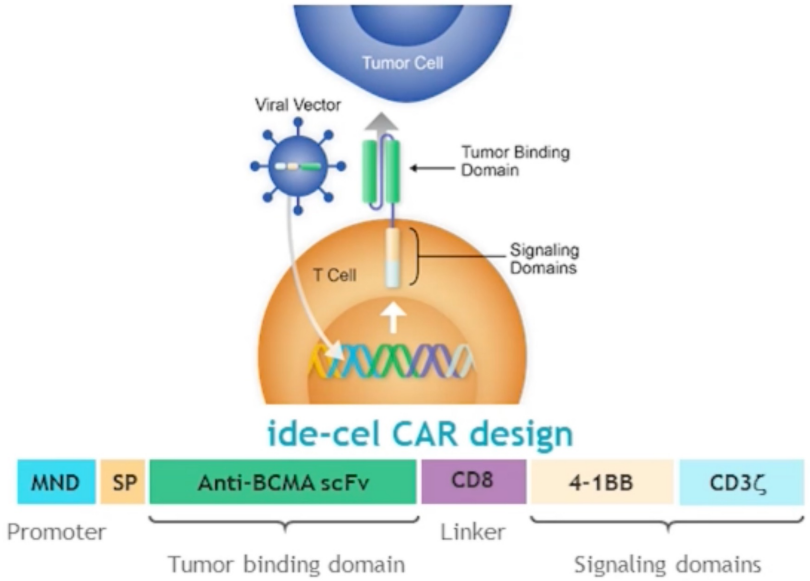
Klebanoff et al., *Nature Rev. Clin. Oncol* 2014

In ALL and lymphoma, patient's T-cells are collected and engineered to target CD19

In myeloma, CAR T-cells target myeloma-specific antigens, e.g. BCMA

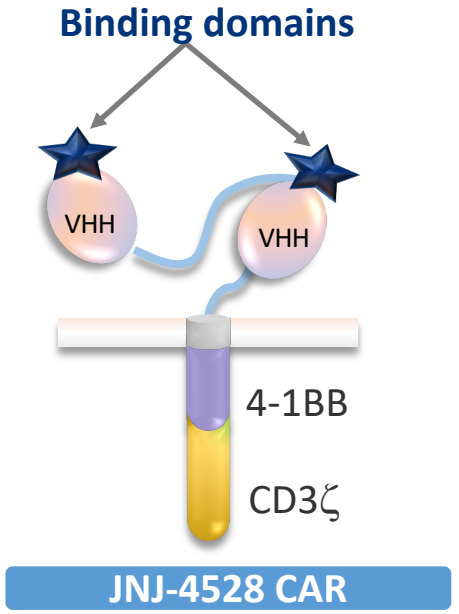
Idecabtagene-Vicleucel (ide-cel): Approved March 2021

- Autologous CAR T-cell
- Anti-BCMA scFv
- 4-1BB costimulatory domain
- CD3z intracellular signaling domain



Ciltacabtagene Autoleucel (JNJ-4528): Approved Feb 2022

- Autologous CAR T-cell
- **Two BCMA-targeting sites (increased avidity)**
- 4-1BB signaling domain
- CD3z intracellular signaling domain



****FDA Label:**

- **Four Prior Lines of Therapy**
- **Previously treated with IMID, PI and anti-CD38 monoclonal antibody**

Ide-cel vs. Cilta-cel

	Cilta-Cel	Ide-Cel
	SAFETY	
CRS (all; grade 3 or 4)	95% (5%)	84% (5%)
Median Onset CRS	**7 days**	**1 day**
ICANS (all, gr 3 or 4)	17% (2%)	18% (3%)
Infections (all, gr 3 or 4)	58% (20%)	69% (22%)
Grade 3 or 4 neutropenia > 1 mo	10%	41%
Grade 3 or 4 thrombocytopenia > 1 mo	25%	48%
Delayed neurotoxicity (all, gr 3 or 4)	**12% (9%)**	None
	EFFICACY	
ORR: CR rate	**98%; 82.5%**	**73%; 33%**
MRD negativity	92% (evaluable)	26%
PFS	NR; 24 mo 60.5%	Median 8.8 months
OS	NR; 24 mo: 74%	Median 19 mo

Administration kinetics and manufacturing failure

FDA Approved CAR-T cell product	Reference Publication	Number enrolled	Median interval between apheresis and CAR-T infusion	Manufacturing failure rate	Feasibility (% of enrolled patients receiving CAR-T product)
Ide-cel (MM)	Munshi NEJM 2021	N= 140	15 days	1%	92%
Cilta-cel (MM)	Berdeja Lancet 2021	N=113	29 days	0%	86%

Dhakal B B J Haem 2021

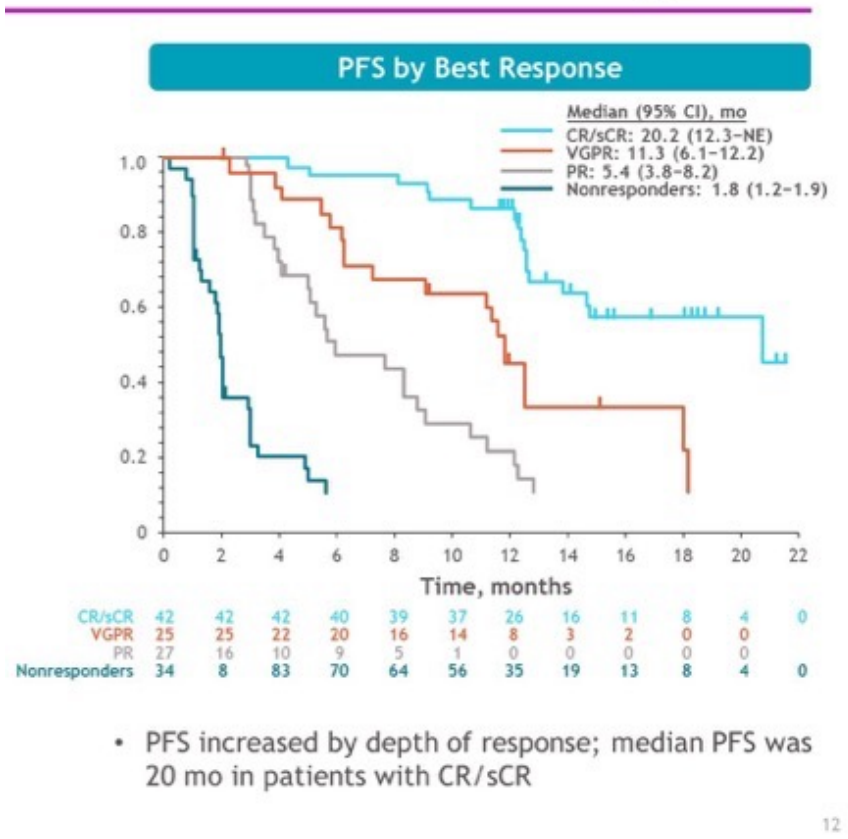
Practical Real-World Considerations

- Most commonly used first line regimen **RVD** +/- **ASCT**, with increasing use of quadruplets with the addition of **daratumumab**
- Patients frequently on **multiagent maintenance therapy** with lenalidomide +/- a proteasome inhibitor +/- daratumumab depending on risk of disease
- Increasing numbers of patients are **refractory to CD38 monoclonal antibodies** earlier in the disease course
- Thus, a patient may become **triple class refractory** as early as second line and frequently in 3rd line
- This would be ideal time for referral so subsequent **salvage therapy** can be planned in anticipation of CAR T-cell therapy
- Supply constraints with CAR T-cell therapy ongoing and demand is likely to exceed supply for the foreseeable future
- Other BCMA-directed therapy with bispecific antibodies and antibody-drug conjugates and optimal sequence remains an open question

PFS of CAR T-cells in multiple myeloma compared with diffuse large B-cell lymphoma

Idecabtagene vicleucel (KarMMa)

KarMMa™



- PFS increased by depth of response; median PFS was 20 mo in patients with CR/sCR

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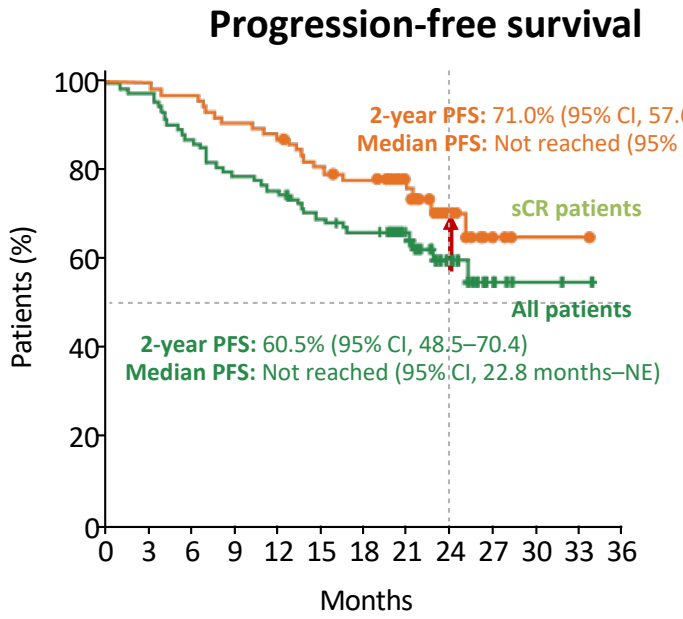
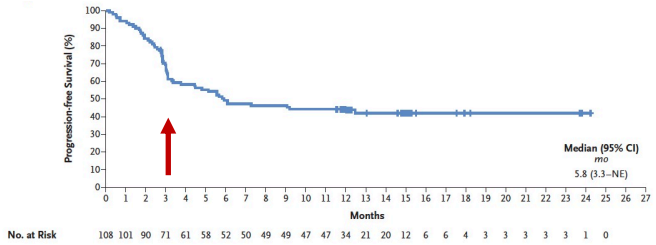
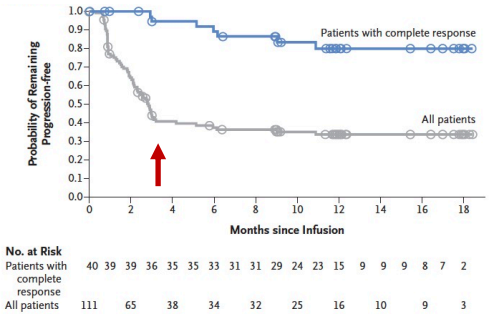
Cilta-cel (CARTITUDE)



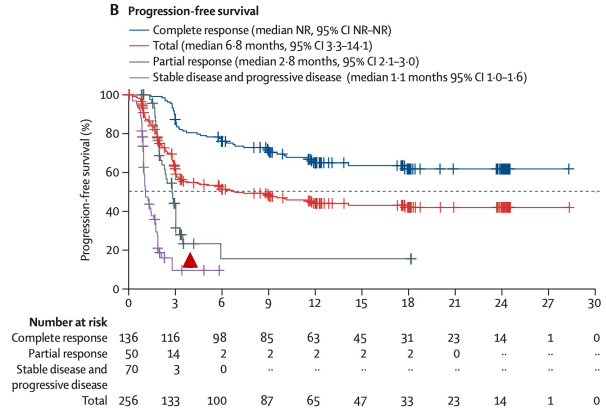
Axicabtagene ciloleucel (ZUMA-1)



Tisagenlecleucel (JULIET)



Lisocabtagene maraleucel (TRANSCEND NHL 001)



Room for improvement with CAR T….
Different biology of myeloma v. lymphoma….

Early Phase Trials:

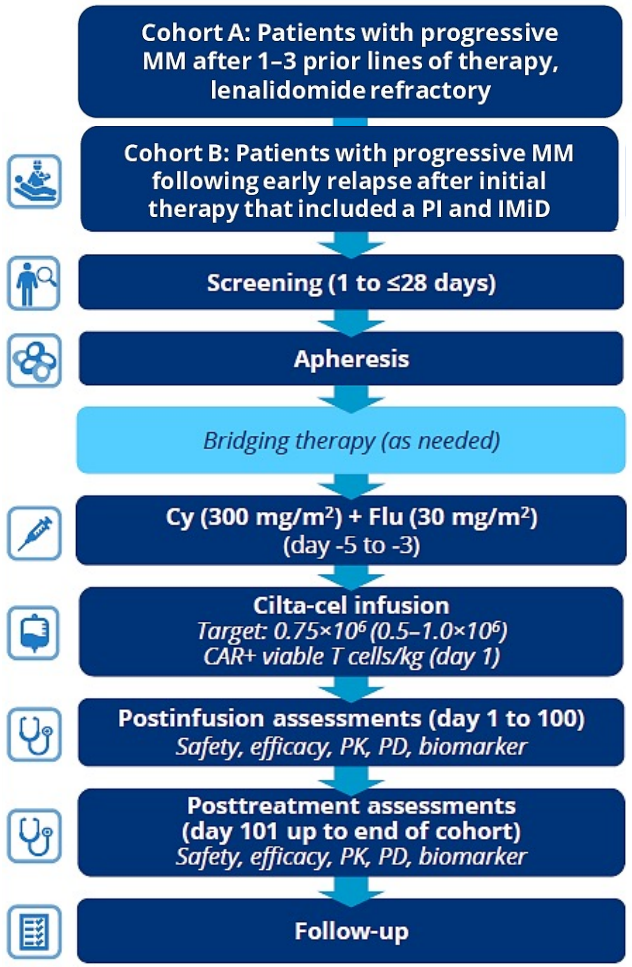
- KarMMa 3: 2-4 lines of treatment
- KarMMa 2: early relapse
- KarMMa 4: High risk

- CARTITUDE 2: early relapse
- CARTITUDE 4: 1-3 lines of treatment
- CARTITUDE 5: Upfront NT patients
- CARTITUDE 6: Upfront TE

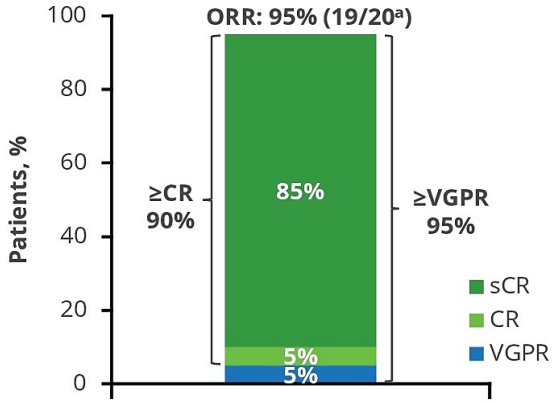
Combination Trials:

- KarMMa 7

Using CAR T-cell therapy at earlier lines of therapy: CARTITUDE-2

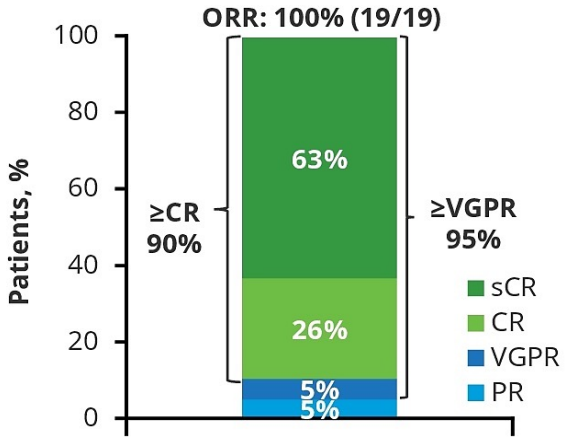


Cohort A



[a]One patient demonstrated a minimal response.
sCR, stringent CR

Cohort B



AEs ≥20%, n (%)	N=20	
	Any Grade	Grade 3/4
Hematologic		
Neutropenia	19 (95)	19 (95)
Thrombocytopenia	16 (80)	7 (35)
Anemia	15 (75)	9 (45)
Lymphopenia	14 (70)	14 (70)
Leukopenia	11 (55)	11 (55)
CAR-T–related AEs		
CRS	19 (95)	2 (10)
Neurotoxicity	6 (30)	1 (5)
ICANS	3 (15)	0
Other	3 (15)[a]	1 (5)

[a]One patient had peripheral sensorimotor neuropathy, one had anosmia and dysgeusia, and one had facial paralysis.

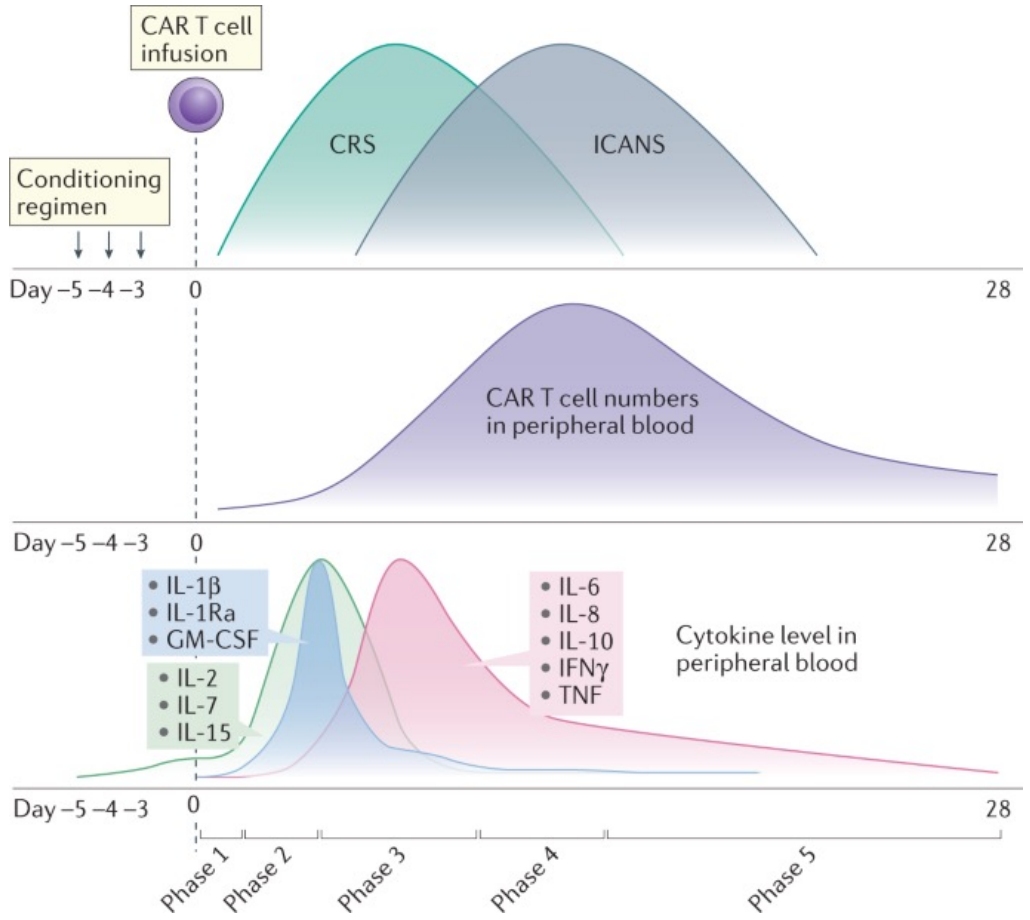
AEs ≥20%, n (%)	N=19	
	Any Grade	Grade 3/4
Hematologic		
Neutropenia	18 (95)	17 (90)
Anemia	11 (58)	9 (47)
Thrombocytopenia	11 (58)	5 (26)
Lymphopenia	6 (32)	6 (32)
Leukopenia	5 (26)	5 (26)
CAR-T–related AEs		
CRS	16 (84)	1 (5)
Neurotoxicity	5 (26)	1 (5)
ICANS	1 (5)	0
Other	4 (21)	1 (5)
Parkinsonism	1 (5)	1 (5)

CR, complete response; CRS, cytokine release syndrome; Cy, cytarabine; Flu, fludarabine; ORR, overall response rate; PD, pharmacodynamics; PK, pharmacokinetics; PR, partial response; sCR, stringent CR; VGPR, very good partial response

Hillengass J et al. EHA 2022;abstract P959 (poster presentation)
Agha M et al. EHA 2022;abstract S185 (oral presentation)

Cytokine Release Syndrome

- Triggered by: Activation of T-cells → release cytokines/ chemokines (esp. IL-6, IFN-gamma)
- Onset: typically within first week
- Risk factors: Bulky disease, comorbidities, sepsis
- Suspect if: 1+ of the following
  - **Fever**
  - **Hypotension < 90 mm Hg**
  - **Hypoxia < 90%**
  - **Evidence of organ toxicity**



Neelapu et al. *Nat Rev Clin Oncol* 2018
Morris et al. *Nat Rev Immunology* 2021

CRS Grading and Management

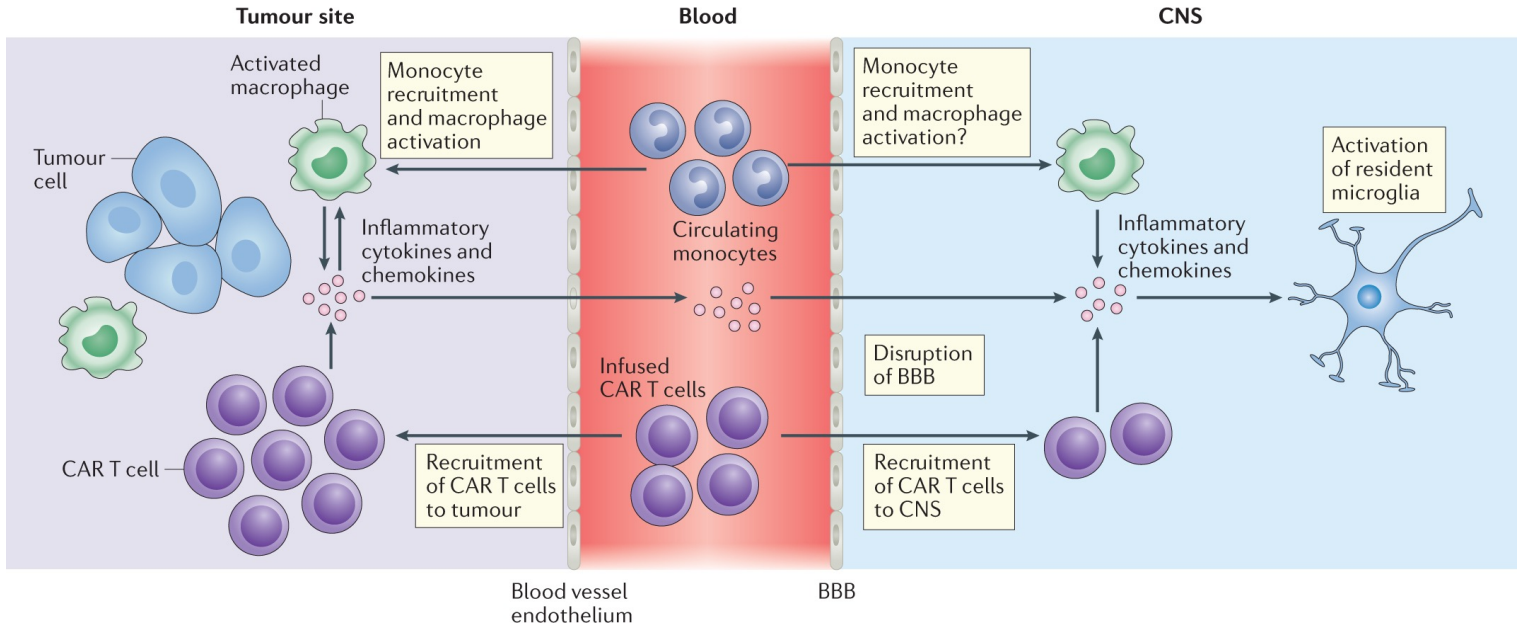
	CRS Grade 1	CRS Grade 2	CRS Grade 3	CRS Grade 4
Fever	Temperature ≥38°C			
With either:				
Hypotension	None	Not requiring vasopressors	Requiring one vasopressor (w/ or w/o vasopressin)	Requiring multiple vasopressors (excluding vasopressin)
and/or:				
Hypoxia	None	O2 NC (≤6 L/min) or blow-by	High-flow NC (>6 L/min), facemask, non-rebreather, or venturi mask	CPAP, BiPAP, intubation
MANAGEMENT				
	- Antipyretics - Infectious w/u - Antibiotics *<24 hrs: Consider tocilizumab if not responsive to antipyretics	- IV Fluids - Tocilizumab q8hr up to 2-3 doses - If early onset or no response to toci: Dexamethasone 10 mg IV	- ICU monitoring - Tocilizumab - Dexamethasone 10 mg q8-12 hrs until ≤ grade 1	- ICU management - Tocilizumab - Dexamethasone 20 mg IV q6 hrs - If no improvement after 24 hours: Methylpred 1g/d and/or anakinra

UChicago Medicine

Lee et al., BBMT 2019

Immune effector cell-associated neurotoxicity syndrome: ICANS

- Triggered by: Passive diffusion of cytokines into the brain, trafficking of CAR T-cells into CNS, monocyte recruitment and macrophage activation
- Onset: Biphasic (early or after CRS resolved)
- Suspect if:
  - **Diminished attention**
  - **Language disturbance**
  - **Impaired handwriting**
  - **Confusion, disorientation**
  - **Agitation**
  - **Aphasia, somnolence**
  - **Tremors, seizures**
  - **Motor weakness, incontinence**



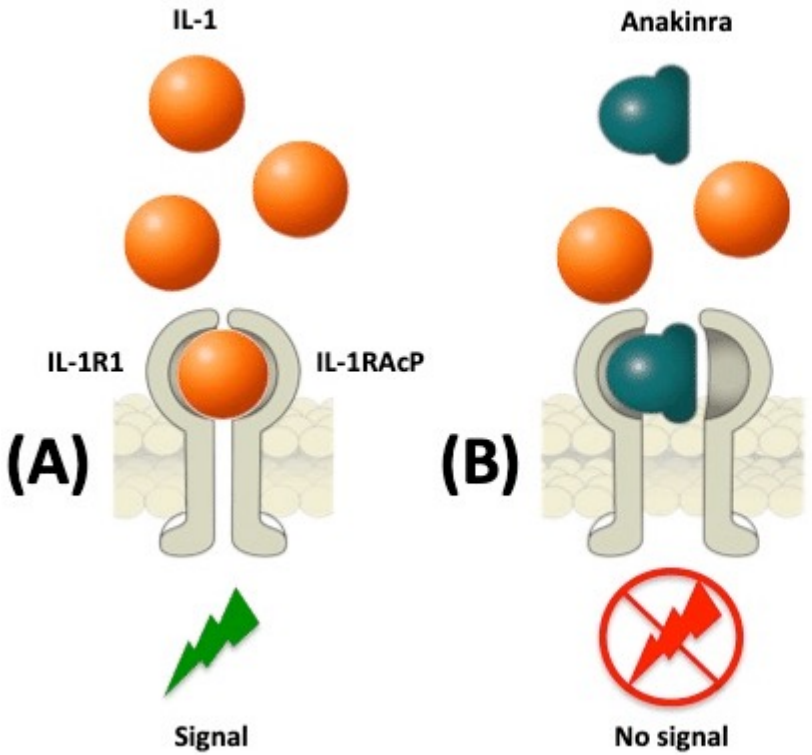
Neelapu et al. *Nat Rev Clin Oncol* 2018
Morris et al. *Nat Rev Immunology* 2021

ICANS Grading and Management

Lee et al., BBMT 2019	Grade 1	Grade 2	Grade 3	Grade 4
ICE Score	7-9	3-6	0-2	0 (unarousable or unable to perform)
Depressed level of consciousness	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Unarousable or requires repetitive tactile stimuli to arouse; stupor or coma
Seizure	N/A	N/A		Prolonged seizure / status epilepticus
Motor findings	N/A	N/A		Paralysis
Raised ICP/ cerebral edema	N/A	N/A	Focal/local edema on imaging	Diffuse edema on imaging; posturing; CN6 palsy; papilledema; Cushing's triad
MANAGEMENT	- Head CT - MRI? LP? EEG? - Dex if high-risk	G1 + - Dex 10 mg q8-12 hours until grade $\leq$ 1, then taper	G2 + - Dex 10-20 mg IV q6-12 hrs until grade $\leq$ 1 - Cerebral edema management - Antiepileptics	G3 + - Dex 20 mg q6hrs until grade $\leq$1 - Methlpred 1g/d if no improvement - Anakinra? Siltuximab? IT chemo?

Other CAR-T toxicities

- Cytopenias
  - Supportive care
- Macrophage activation-like syndrome
  - Measure ferritin, IL-2R, NK cell activation, coags
  - Anakinra
- Immunosuppression
  - IVIg
  - Antimicrobial prophylaxis



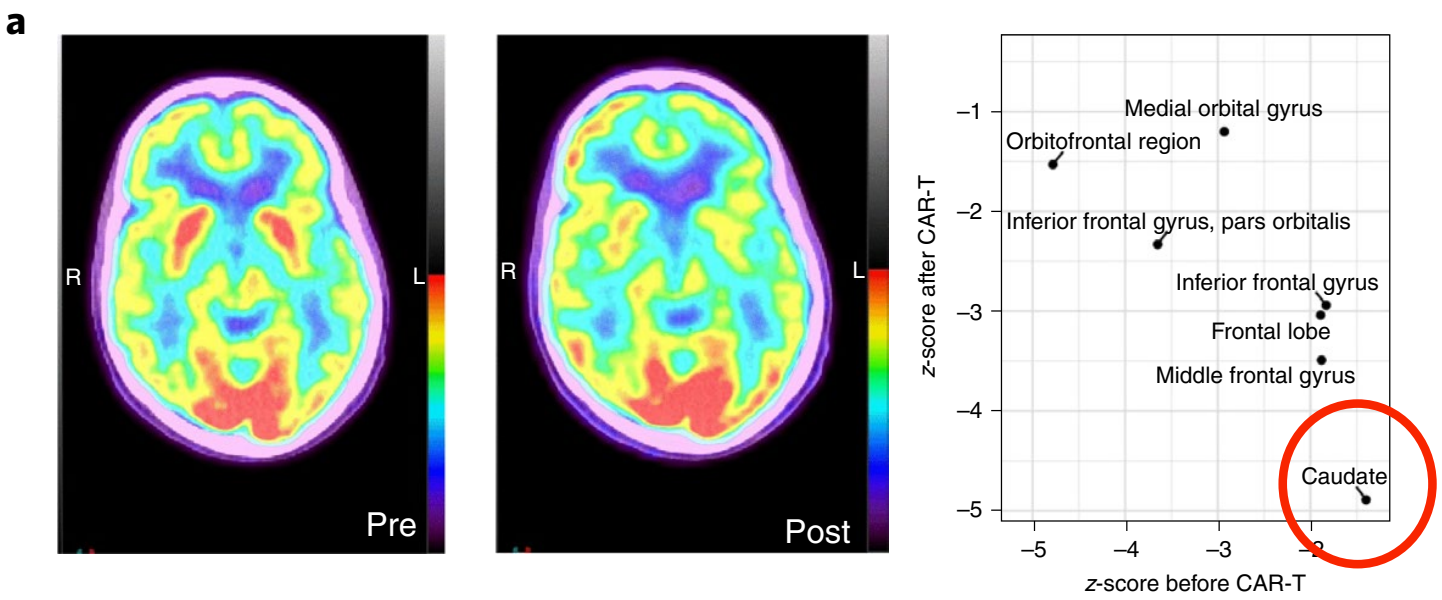
nature medicine

BRIEF COMMUNICATION

https://doi.org/10.1038/s41591-021-01564-7

Neurocognitive and hypokinetic movement disorder with features of parkinsonism after BCMA-targeting CAR-T cell therapy

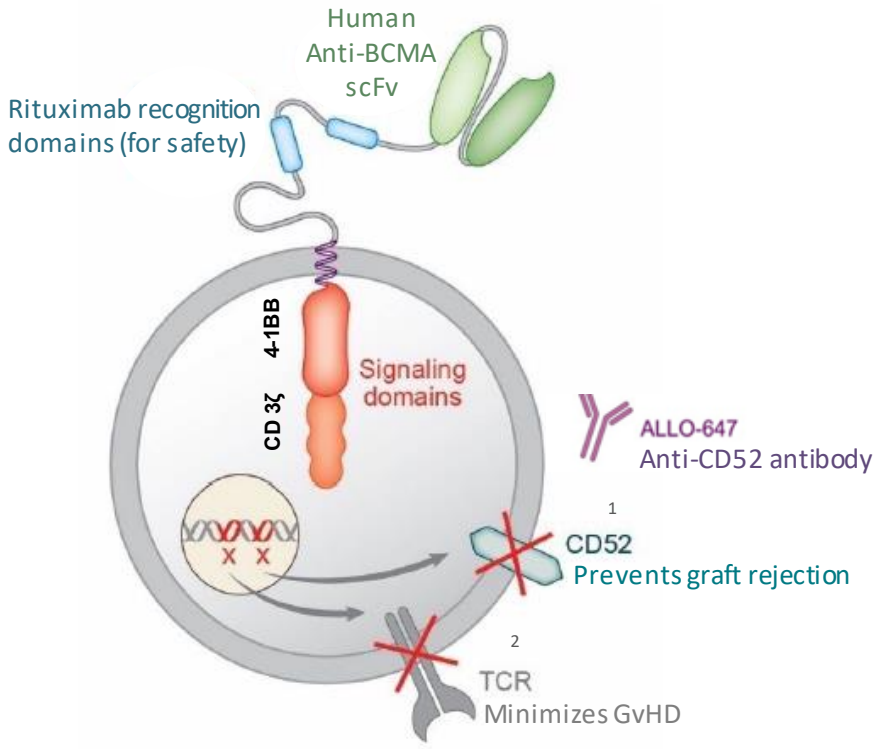
Oliver Van Oekelen[1,2,17], Adolfo Aleman[1,2,17], Bhaskar Upadhyaya[2,3,4], Sandra Schnakenberg[5,6], Deepu Madduri[2,3], Somali Gavane[7], Julie Teruya-Feldstein[5], John F. Crary[5,6,8,9,10,11], Mary E. Fowkes[5,6,18], Charles B. Stacy[12], Seunghee Kim-Schulze[3,4,13,14], Adeeb Rahman[3,4,13,14,15], Alessandro Laganà[3,13,16], Joshua D. Brody[2,3,13,14], Miriam Merad[3,4,13,14], Sundar Jagannath[2,3] and Samir Parekh[2,3,13,14] ✉



What's next?

The First Allogeneic anti-BCMA CAR T Study for R/R Multiple Myeloma

- BCMA cell therapy has demonstrated unprecedented efficacy, but is not readily available to all patients
- Allogeneic chimeric antigen receptor (CAR) T cell therapy has the potential for all eligible patients to receive therapy on demand and supports re-dosing
- ALLO-715 (anti-BCMA) is an allogeneic CAR T cell product utilizing TALEN® gene editing specifically designed to
  - Disrupt TCRα constant gene – to reduce the risk graft-versus-host disease (GvHD)
  - Edit CD52 gene – permits use of ALLO-647 (a humanized anti-CD5 mAb) to selectively deplete host T cells while protecting donor cell



1. TALEN-mediated CD52 KO allows selective lymphodepletion with ALLO-647
2. TALEN-mediated TRAC KO eliminates TCRα expression to minimize risk of GvHD

Abstract #3832

Phase I study of CART-ddBCMA: a CART-Therapy Utilizing a Novel Synthetic Binding Domain for the Treatment of Subjects with Relapsed or Refractory Multiple Myeloma

Matthew J. Frigault, MD[1], Jacalyn Rosenblatt, MD[2], Noopur S. Raje, MD[3], Gabriel Depinho, B.S.[4], Daniella Cook, BS[5], Emma K. Logan[2], Christopher R. Heery, MD[6], Christine Cornwell[6], Melissa Sheppard[7], Marcela V. Maus, MD, PhD[1], David Avigan, MD[2], Andrzej Jakubowiak[8], and Michael R. Bishop, MD[9]

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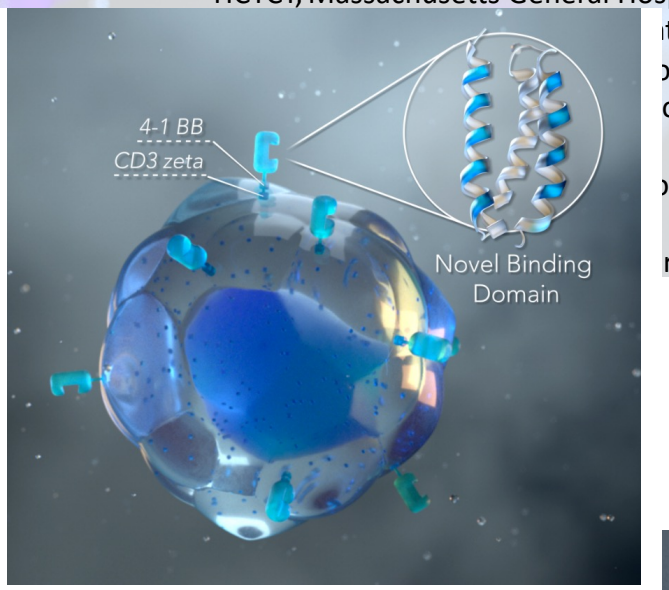
oston, MA; [5]Cancer Center, Massachusetts General Hospital, Boston, MA;

f Hematology and Oncology, University of Chicago Medical Center, Chicago, IL;

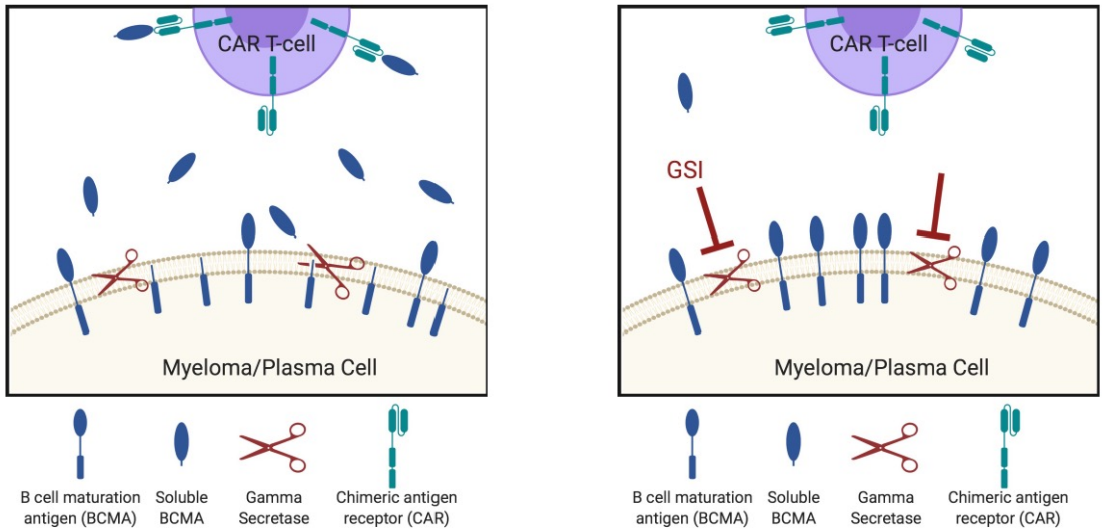
r Cellular Therapy, University of Chicago, Chicago, IL

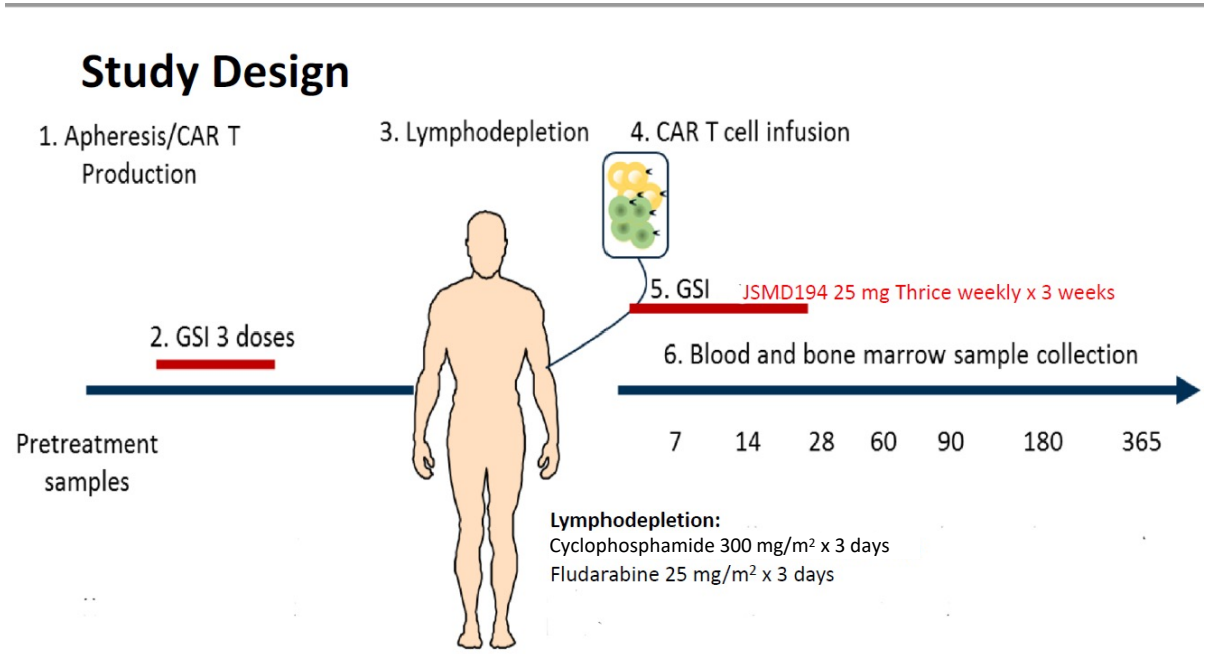


CAR-T containing a novel computationally designed synthetic protein binding domain (non-scFv) engineered to increase stability and decrease immunogenicity

Fully Human BCMA CAR T cells in Combination with a Gamma Secretase Inhibitor to Increase BCMA Expression in R/R Multiple Myeloma

Gamma Secretase Cleaves BCMA from Plasma Cells

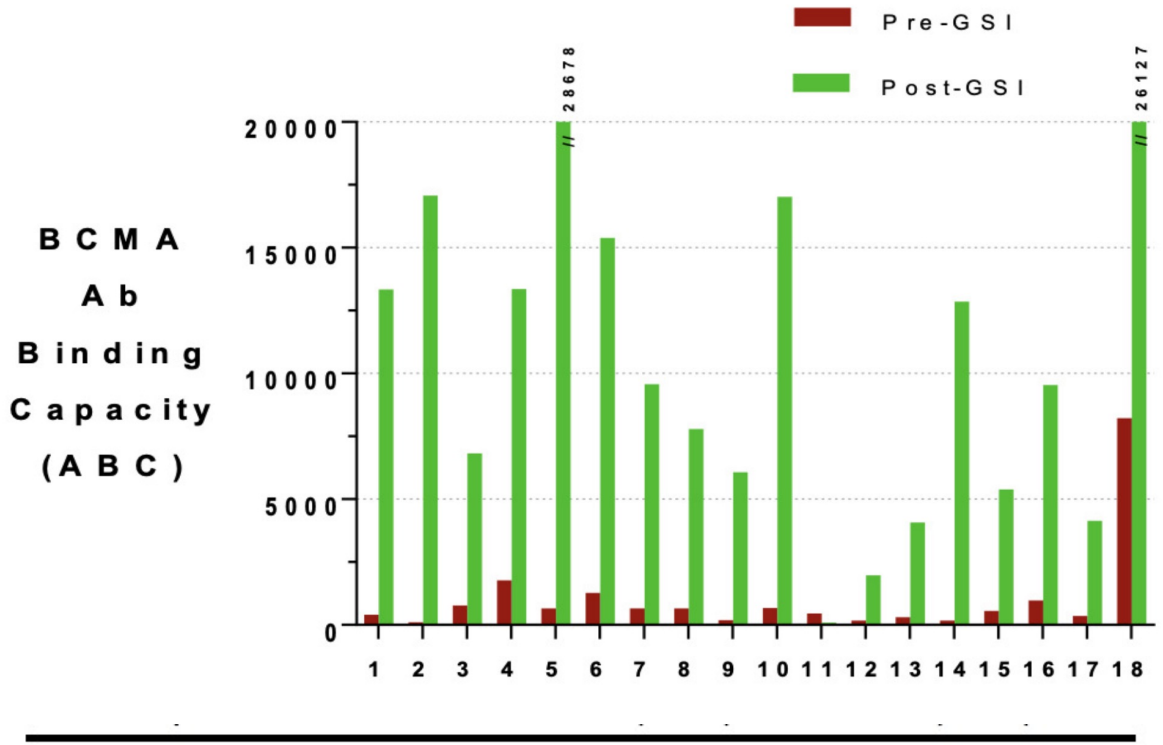




Cowan et al, ASH 2021

GSI in BCMA CAR T cells

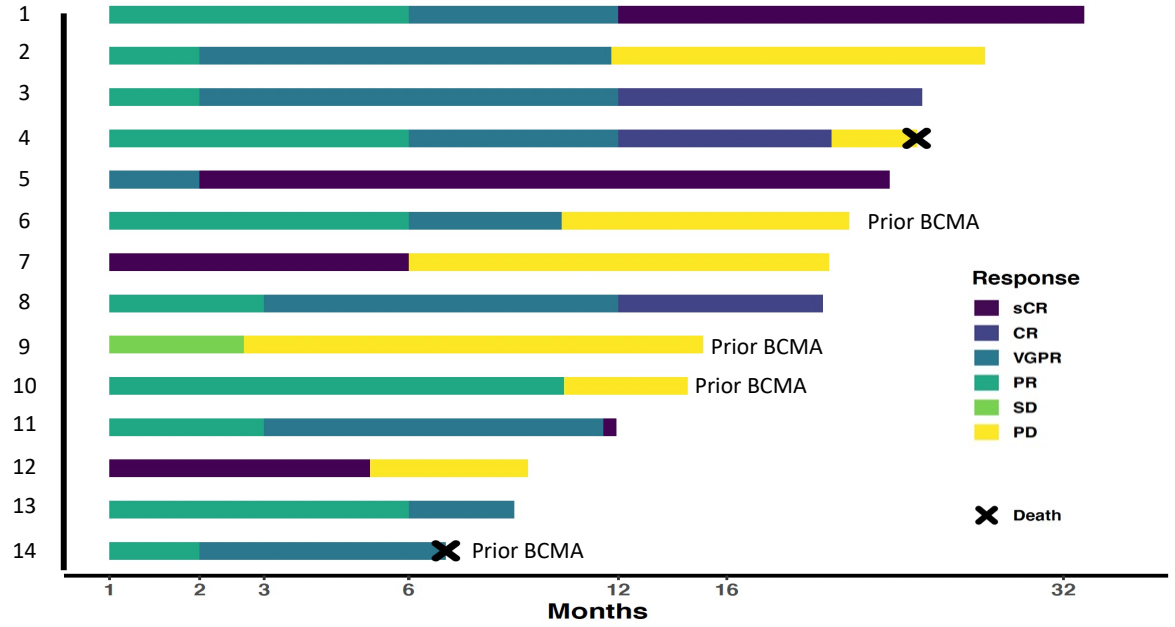
Gamma Secretase Inhibition Increases BCMA Surface Density



CRS (any grade)	17 (94%)
Neurologic Δ from baseline*	12 (66%)

Cowan et al, ASH 2021

Depth and Duration of Response

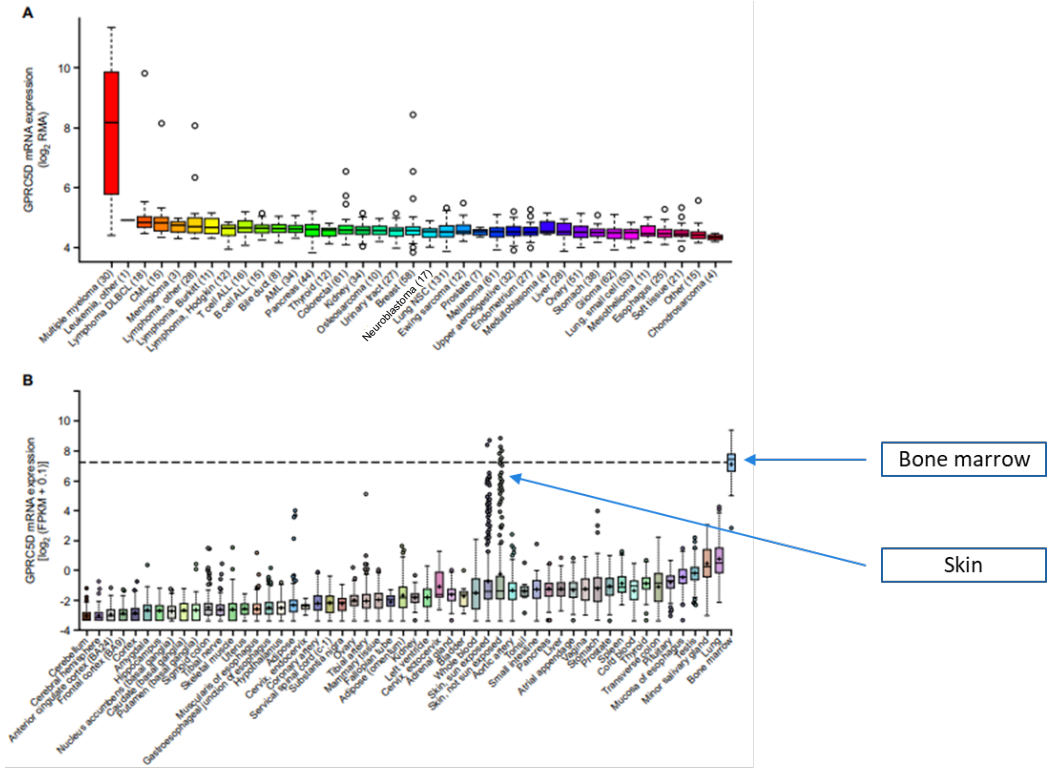


Cytokine Release Syndrome (ASTCT Grading)

Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
9 (50%)	6 (33%)	4 (22%)	1 (6%)	0 (0%)

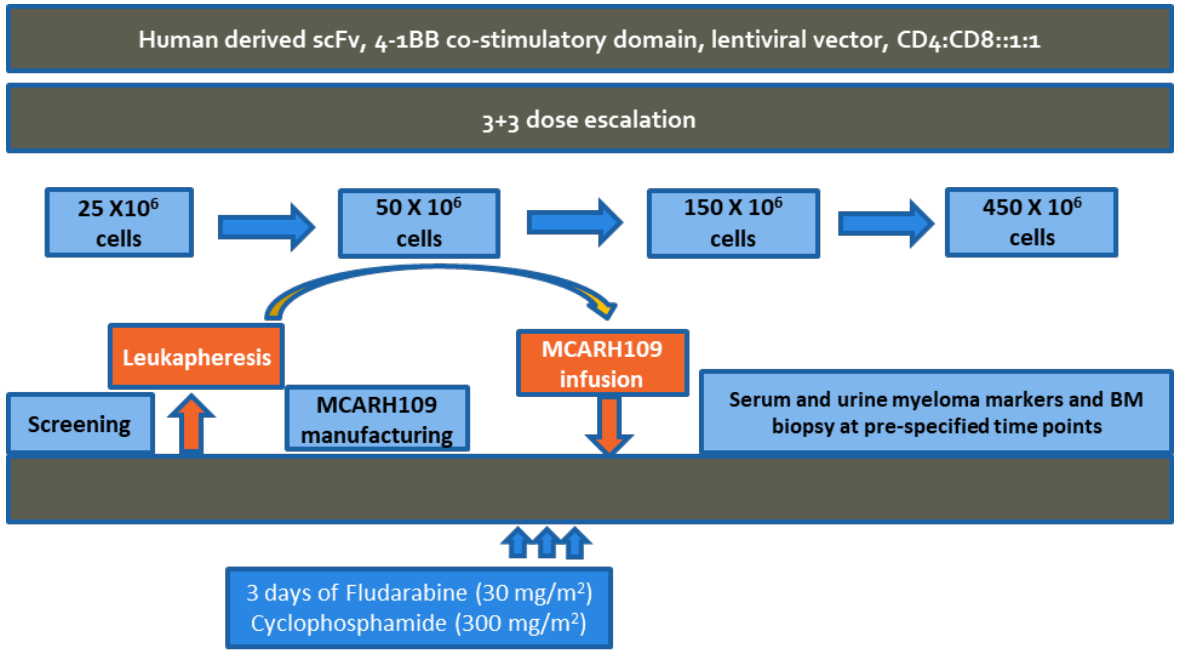
- Needs to be studied in prior BCMA therapy
- Concern for increased neurotoxicity

Phase I First-in-Class Trial of MCARH109, a G Protein Coupled Receptor Class C Group 5 Member D (GPRC5D) Targeted CAR T Cell Therapy in Relapsed or Refractory Multiple Myeloma



Smith EL. et al. Science Translational Medicine 2019

Study Design



Key eligibility criteria:

- 3 or more lines of therapy; Prior PI, IMiD, CD38 antibody-based therapy
- Prior BCMA and CART allowed; Non-secretory myeloma allowed

GPRC5D Targeted CAR T Cell Therapy in RR Multiple Myeloma Clinical Response (N=16)

Response	25 X10^6 CAR+ T cells (n=3)	50 X10^6 CAR+ T cells (n=3)	150 X10^6 CAR+ T cells (n=5)	450 X10^6 CAR+ T cells (n=5)	Total (N=16)
PR or better, n (%)	1 (33)	3 (100)	2 (40)	5 (100)	11 (69)
VGPR or better, n (%)	1 (33)	2 (67)	0 (0)	4 (80)	7 (44)
CR or better (%)	0 (0)	1 (33)	0 (0)	3 (60)	4 (25)
MRD negativity, n (%)	2 (67)	2 (67)	2 (40)	2 (50)	8 (50)

Response	Prior BCMA therapy (n=10)	Prior CAR T therapy (n=8)
Partial Response or better, n (%)	8 (80)	6 (75)
Complete Response or better	3 (30)	3 (38)
BM MRD negativity*, n (%)	5 (50)	2 (25)

Opportunities for combination treatment: biological rationale

IMiD effect on T cells

⬆ T cell proliferation
IL2 production
Th1-type cytokines (IFN-γ)
Costimulation (CD28)

⬇ Th2-type cytokines (IL4)
Immunosuppressive cytokines (IL10)
FOXP3 expression

- Lenalidomide enhances CAR T Cell function in MM preclinical models

Anti-CD38 mAbs:
- Induction of T cell expansion
- Depletion of CD38+ T regulatory cells
- Depletion of CD38+ MDSCs
- Depletion of CD38+ B regulatory cells

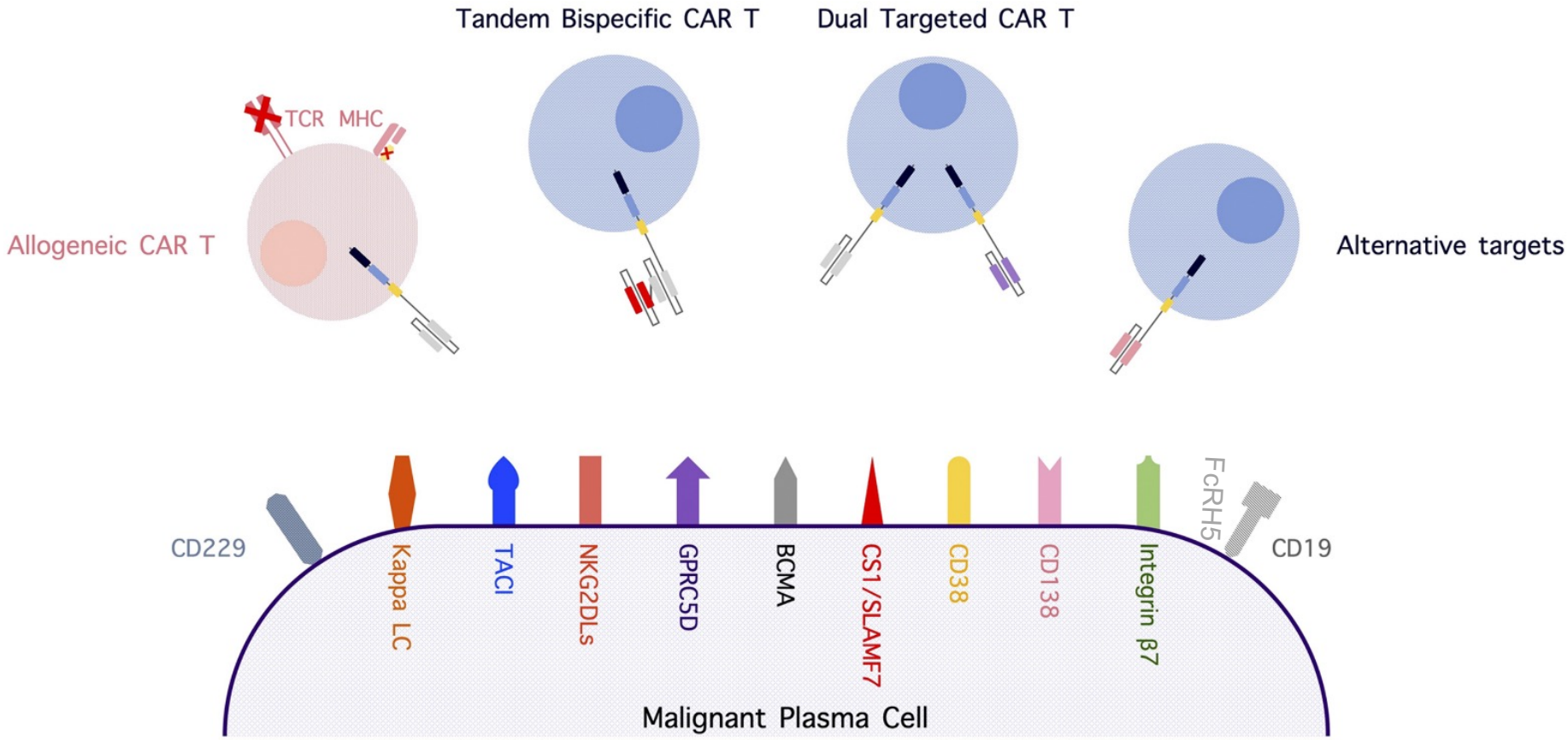
Anti-SLAMF7 mAbs:
- CD8+ T cells express SLAMF7
- Synergize with anti-PD1 mAbs in activating T cells

Checkpoint Axis:

- PD1 engagement on activated T cells induces a functionally exhausted state

- Anti-PD-1 mAbs augment CAR T cell activity in preclinical models

Future of CAR T cells and/or BiTES in Multiple Myeloma



Kitsada Wudhikarn,Sham Mailankody,Eric L. Smith, Future of CAR T cells in multiple myeloma, Hematology Am Soc Hematol Educ Program, 2020, Figure 1.

Current Understanding and Future Directions

- CAR T cells are an effective strategy in RR MM
- BCMA is a validated target
- Future will be to define how to combine/sequence with other immunotherapies
- Bring upfront
- Next generation approaches will focus on improving efficacy and DOR

Acknowledgements

Our Patients

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Appendix

Editorial Review

- Structural makeup and manufacturing of available BCMA-directed CAR T-cell platforms
  - Slides 4-8
- Results from the Phase II KarMMa trial evaluating idecabtagene vicleucel (ide-cel) for R/R MM
  - Slides 7, 10
- Key data from the CARTITUDE-1 trial of ciltacabtagene autoleucel (cilta-cel) for pretreated MM
  - Slides 7, 10
- Available and emerging data with ide-cel and cilta-cel in earlier lines of treatment
  - Slides 11-12
- Spectrum, incidence and severity of toxicities with BCMA-targeted CAR T-cell therapies
  - Slides 13-18
- Early data with non-BCMA CAR T-cell platforms (eg, BMS-986393)
  - Slides 20-27

- CONTENT NOTE: Circle back to potential ASH 2022 titles slides when time permits – DB/ASH 2022/MM/Faculty Assignments

RTP RESEARCH TO PRACTICE

Appendix Slides – None