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CAR-T Cells: Constructs & Target Antigens

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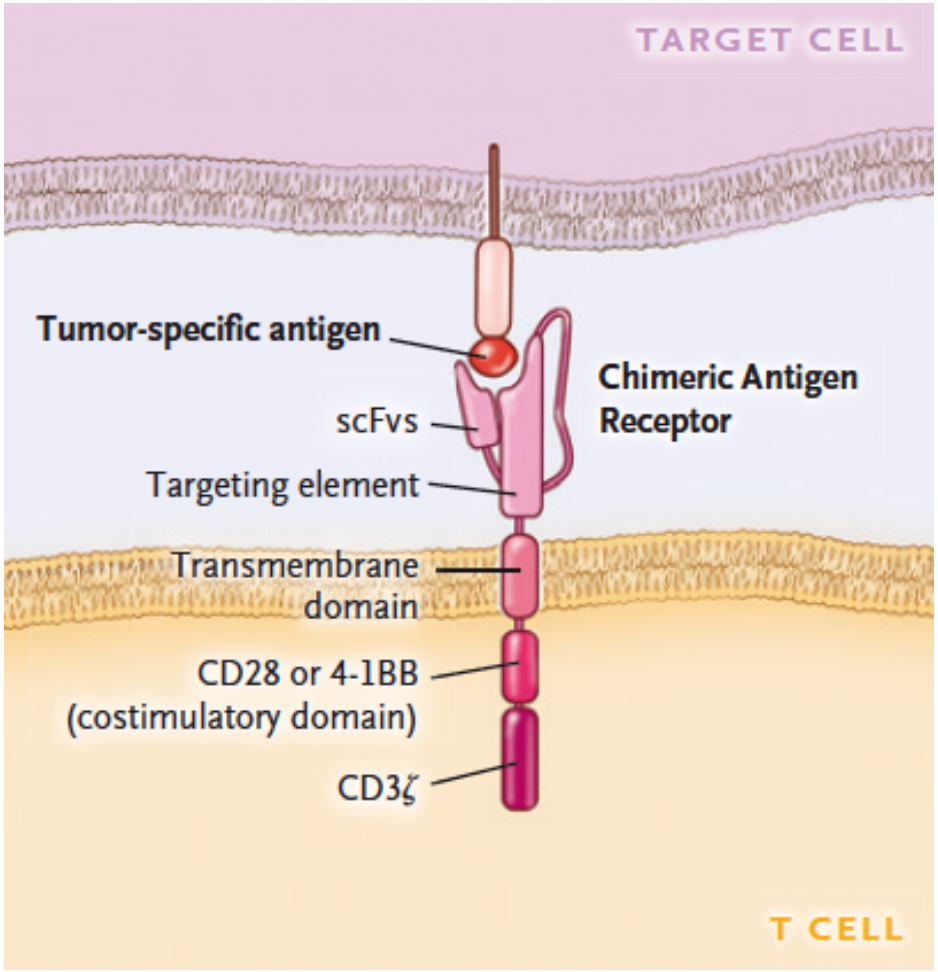
Disclosures

- Consulting or Advisory Role
  - ADC Therapeutics, Sanofi, Genenta Science, Novartis, Servier, Boehringer Ingelheim
- Honoraria
  - BMS, MSD, Servier, Janssen Oncology, Roche, Takeda

Chimeric Antigen Receptor

- The antigen binding site derived from *single-chain variable fragments (scFv)* of an Ab
- The hinge domain followed by the *transmembrane domain*
- The *intracellular signaling domain* [costimulatory domains, such as CD28 and 4-1BB, T-cell activation domain] which drive signal activation and expansion of CAR T cells



June CH, Sadelain M. N Engl J Med 2018;379:64-73

Original Article

Anti-BCMA CAR T-Cell Therapy bb2121 in Relapsed or Refractory Multiple Myeloma

Noopur Raje, M.D., Jesus Berdeja, M.D., Yi Lin, M.D., Ph.D., David Siegel, M.D., Ph.D., Sundar Jagannath, M.D., Deepu Madduri, M.D., Michaela Liedtke, M.D., Jacalyn Rosenblatt, M.D., Marcela V. Maus, M.D., Ph.D., Ashley Turka, Lyh-Ping Lam, Pharm.D., Richard A. Morgan, Ph.D., Kevin Friedman, Ph.D., Monica Massaro, M.P.H., Julie Wang, Pharm.D., Ph.D., Greg Russotti, Ph.D., Zhihong Yang, Ph.D., Timothy Campbell, M.D., Ph.D., Kristen Hege, M.D., Fabio Petrocca, M.D., M. Travis Quigley, M.S., Nikhil Munshi, M.D., and James N. Kochenderfer, M.D.

N Engl J Med
Volume 380(18):1726-1737
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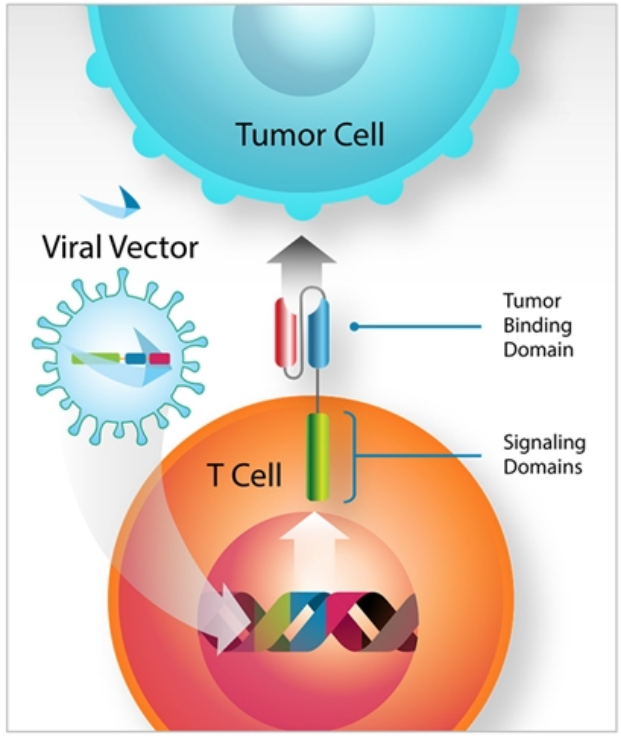
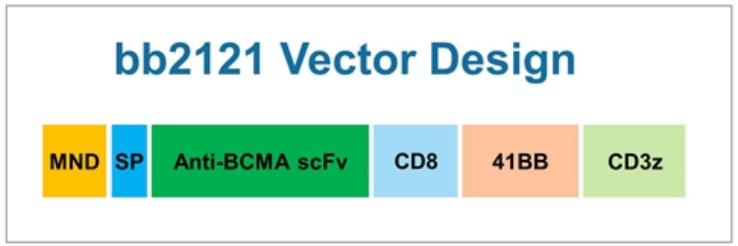
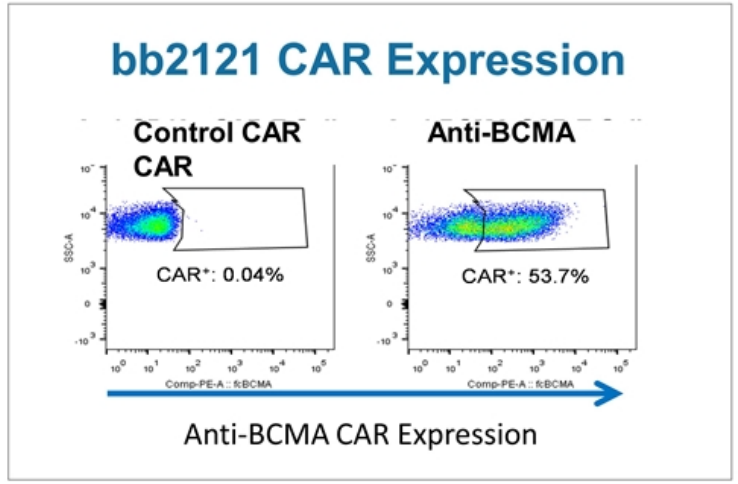
The NEW ENGLAND JOURNAL of MEDICINE

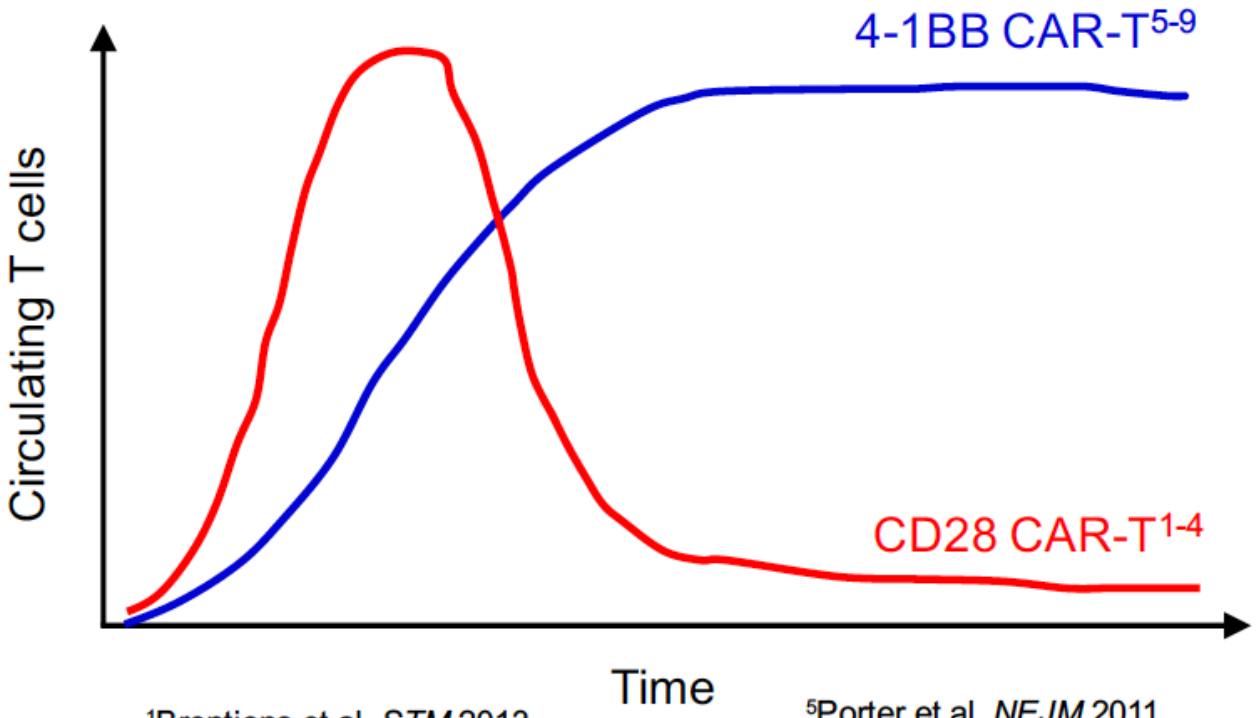
bb2121 Vector







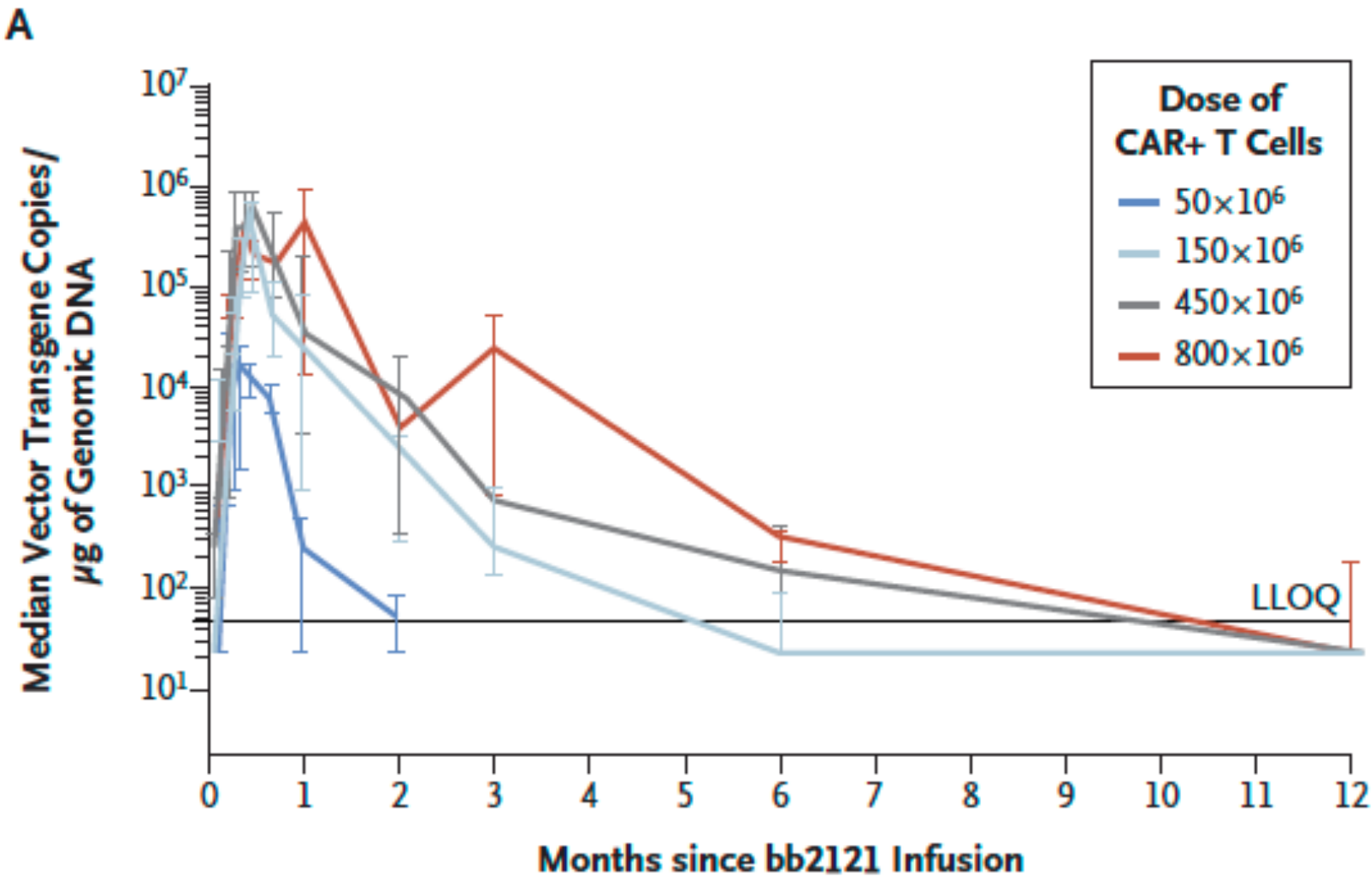
CD28 and 4-1BB Differently Affects the PK of CAR T cells



[1]Brentjens et al, *STM* 2013
[2]Kochenderfer et al, *JCO* 2014
[3]Lee et al, *Lancet Oncol* 2015
[4]Wang et al, *Blood* 2016

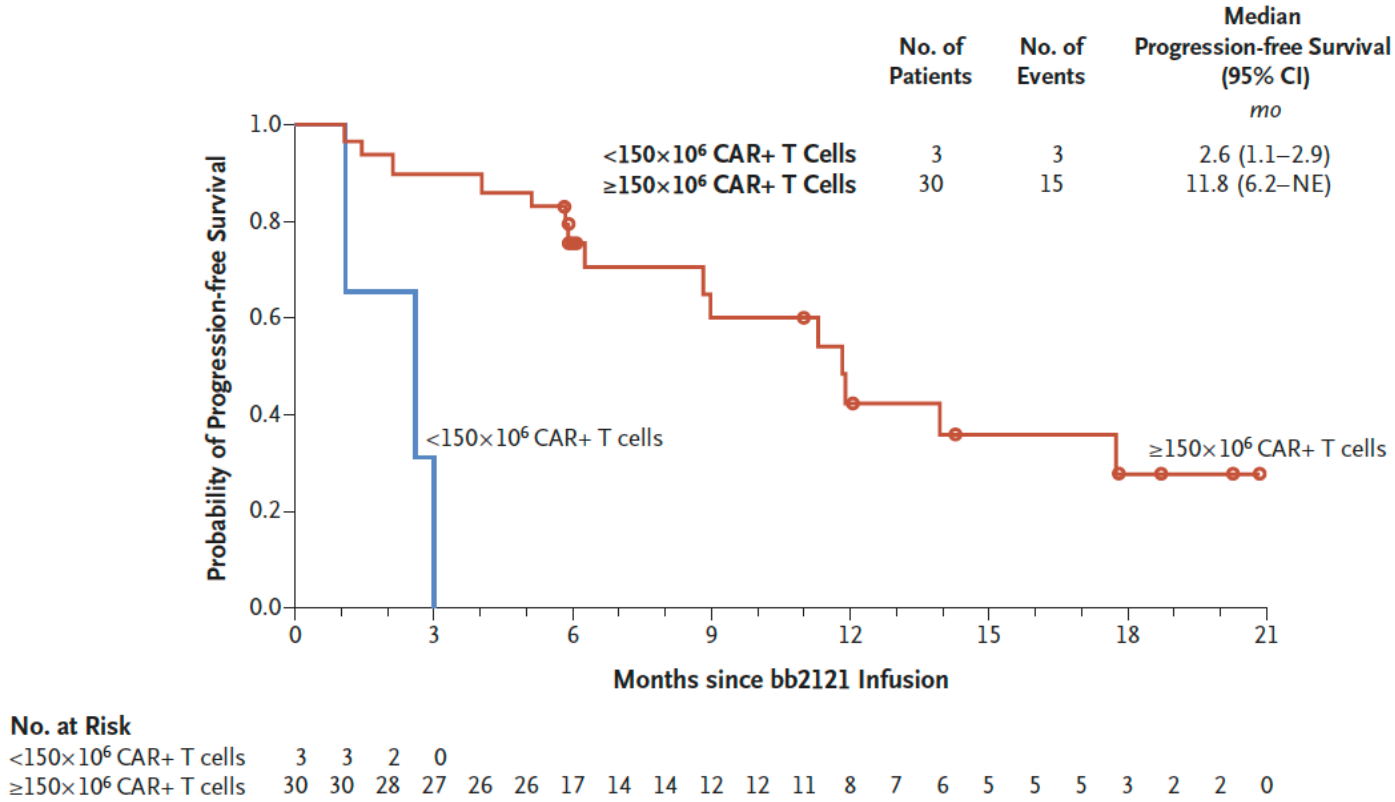
[5]Porter et al, *NEJM* 2011
[6]Porter et al, *STM* 2011
[7]Grupp et al, *NEJM* 2013
[8]Turtle et al, *JCI* 2015
[9]Maude et al, *NEJM* 2014

Courtesy of A. Bondanza


A
Median Vector Transgene Copies/ μg of Genomic DNA
10^7
10^6
10^5
10^4
10^3
10^2
10^1
Dose of CAR+ T Cells
50×10^6
150×10^6
450×10^6
800×10^6
LLOQ
0
1
2
3
4
5
6
7
8
9
10
11
12
Months since bb2121 Infusion

Progression-Free Survival

B



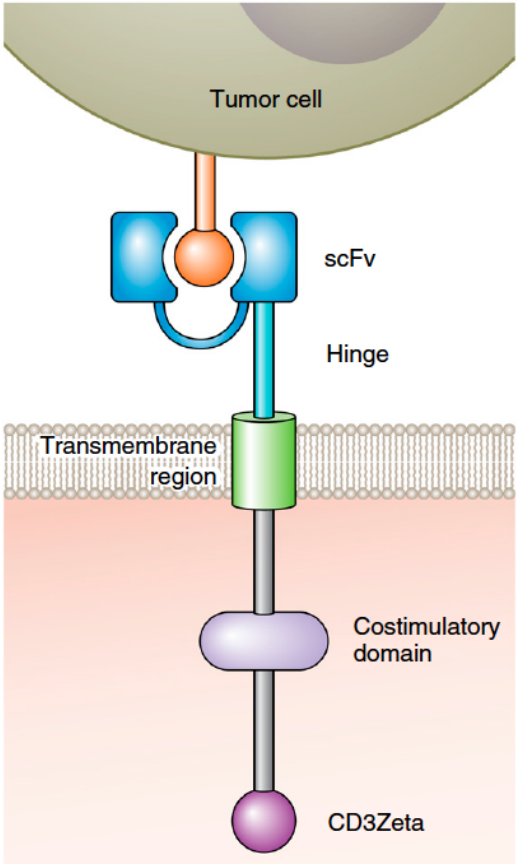
Loss or downregulation of BMCA expression following CART cell therapy

Trials of CAR-T Cells Targeting BMCA

CAR-T cell product (ref.)	*n* =	ORR (*n* =)	median PFS (95% CI)
bb2121 (22)	33	85% (28)	11.8 months (6.2–n.e.)[$]
CART-BCMA Upenn (23)	25	48% (12)	2.0 months (ND)
NCI CAR BCMA-T (24)[#]	10	20% (2)	1.5 months (ND)
NCI CAR BCMA-T (25)*	16	81% (13)	7.25 months (ND)
LCAR-B38M (26)	17	88% (15)	12.2 months (ND)
LCAR-B38M (27)	57	88% (50)	15.0 months (11.0–n.e.)

These data show ORR of 60% to 100%, including MRD-negative CR, after lymphodepleting conditioning. Response durability has been more variable, likely related to differences in CAR T-cell products, lymphodepleting regimens, and/or underlying biology/prognostic factors.

Modifications in CAR/Vector Design



- Overcoming resistance to CART cells
  - Optimize co-stimulatory domains
  - Novel target antigens
  - Bispecific surface targeting

Strategies for Generating CART Cells in MM

Variable	Examples
Targeted antigens[55,62,66,72]	BCMA, CD19, CD38, SLAMF-7, GPRC5D
Transfection system[41,44,52]	Lentivirus, retrovirus, nonviral systems
Manufacturing[50,76]	CD4/CD8 ratio, use of selected T lymphocyte subsets
Costimulatory signals	4-1BB, CD28z, OX40
Prevention of antigen loss[73]	Bispecific CARs, gamma secretase inhibitor
Armored CAR[90]	Cytokine release, CD40L, BiTEs
Other[82,89]	Allogeneic CAR T cells

Target Antigen Selection

- The optimal antigen should be expressed broadly in tumors of a given type, but should not be present in essential healthy tissues, as to avoid “on-target/off-tumor” effects and associated toxicity
- My SC antigen + My maturation antigen

- Rituximab-based experience is however conflicting with this assumptions

Published Clinical Trials

- CD138
- CD19
- CD19 & BMCA
- NKGD2
- Ig Light Chains

n = (ref.)	Antigen	Signaling domains	Cell source/type	Transfer method	Conditioning	T-cell dosage	Therapy-related side effects	Clinical effects
n = 1 (31)	CD138	ND	Autologous T cells	ND	CP/Flu	1.5×10^8	• CRS gr. 2 (1)	• PR (1)
n = 5 (32)	CD138	4-1BB/CD3ζ	Autologous T cells	Lentiviral	PCD, CP or VAD	0.756×10^7/kg	• Infusion-related fever (4) • Nausea and vomiting (3) • ↑ Liver function tests (1) • Possible TLS (1)	• SD > 3 m (4) • ↓ circulating PCL cells (1)
n = 10 (33)	CD19	4-1BB/CD3ζ	Autologous T cells	Lentiviral	HDM + ASCT	$1–5 \times 10^7$	• Hypogammaglobulinemia (1) • Autologous GvHD (1) • Mucositis (1)	• CR (1) • VGPR (6/10) at d100 post-ASCT • PR (2/10) at d100 post-ASCT
n = 5/8 (34)	CD19 + BCMA	OX40/CD28	Autologous or allogeneic T cells	Lentiviral	CP/Flu	1×10^7/kg	• CRS gr. 1–2 (7), gr.≥3 (1) • Prolonged cytopenias (5/5) • Coagulopathy (5) • ↑ Liver function tests (4) • Pulmonary edema (3) • Pleural effusion and ascites (1)	• sCR (1/5) • VGPR (1/5) • PR (2/5) • SD (1/5)
n = 10 (35)	CD19 + BCMA	OX40/CD28	Autologous T cells	Lentiviral	Bu-CP + ASCT	1×10^7/kg	• CRS gr. 1–2 (10) • Coagulopathy (7) • ↑ Troponin levels (4) • Atrial flutter (1)	• CR (7/10) • VGPR (3/10)
n = 5 (36)	NKG2D ligands	CD3ζ	Autologous T cells	Retroviral	None	$1–3 \times 10^{6–7}$	• None	• None
n = 7 (37)	κLC	CD28/CD3ζ	Autologous T cells	Retroviral	CP (4) or none (3)	$0.92–1.9 \times 10^8/m^2$	• Lymphopenia gr. 3 (1)	• SD 6 wk–24m (4)

Ongoing Clinical Trials

- CD38 (@Daratumumab - but expression on HSC and NK cells)
- SLAMF7/CS1 (marker for malignant plasma cells - but also T cells)
- CD44v6
- CD56
- GPRC5D (MM Ag; can rescue ag-loss relapse under BMCA-CART)
- TACI
- Lewis Y
- NY-ESO-1

BCMA-iNKT CAR Cell Therapy

- Toxicity reduction by expressing CAR proteins on invariant natural killer T cells (iNKTs) and the efficacy enhanced with long-acting IL-7 coexpression
- Median survival of mice was higher in the group receiving BCMA-iNKT-CAR therapy compared to CD19-iNKT-CAR (163 days versus 45 days)
- iNKTs can be an alternative source of off-the-shelf CAR cell therapies

Julie O'Neal from Washington University School of Medicine, Washington

Conclusions

- BCMA CAR-T cells show promising activity in MM patients with highly refractory disease, including patients across trials with ongoing durable remissions lasting >1-yr
- However, sample size is small and heterogeneity among the trials makes it difficult to draw firm conclusions about relative efficacy among CAR constructs

Conclusions

- Open Questions
  - BMCA expression (assays, level of expression, modulation)
  - Collection of less exhausted T cells
  - Improving CAR constructs
    - Novel target antigens
    - Novel costimulation
    - Dual-antigen targeting