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Cellicon Valley 2021

CAR T Cell Therapy for Multiple Myeloma

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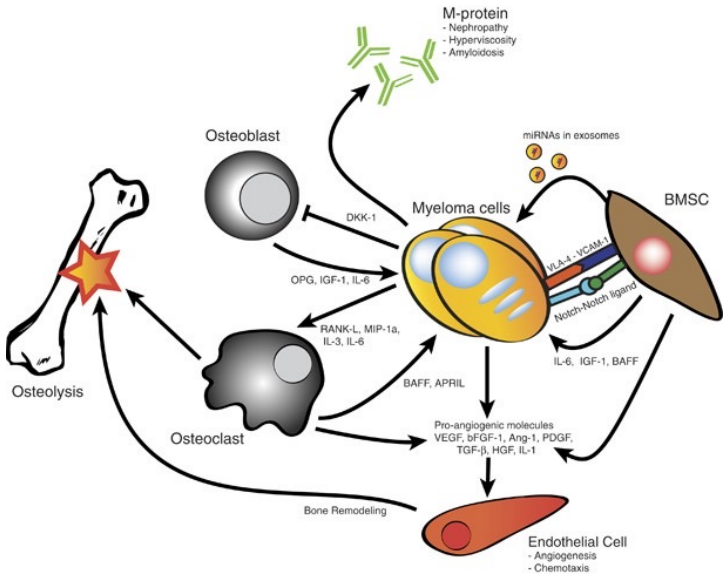
Disclosures

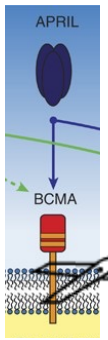
- Research funding to institution: Novartis, Janssen, Tmunity, CRISPR Therapeutics
- Honoraria: Janssen, GlaxoSmithKline, Amgen

FDA approves idecabtagene vicleucel for multiple myeloma

On March 26, 2021, the Food and Drug Administration approved idecabtagene vicleucel (Abecma, Bristol Myers Squibb) for the treatment of adult patients with relapsed or refractory multiple myeloma after four or more prior lines of therapy, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal antibody. This is the first FDA-approved cell-based gene therapy for multiple myeloma.

BCMA

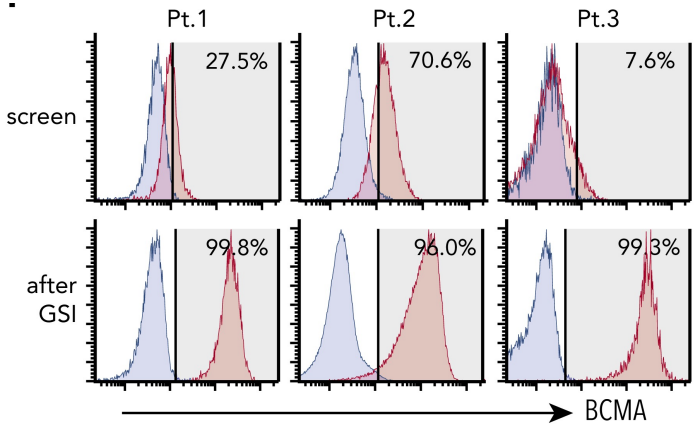


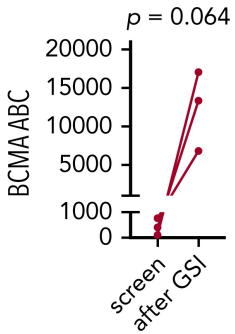


Gamma secretase

Soluble BCMA
- Potential biomarker of MM disease burden
- Potential biomarker of anti-BCMA therapy activity

MM patients treated with gamma secretase inhibitor





Pont et al., Blood. 2019 Nov 7;134(19):1585-1597
Hengeveld & Kersten, Blood Cancer Journal (2015) 5:282

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BCMA is a safe, validated target

Targeting B-cell maturation antigen with GSK2857916 antibody–drug conjugate in relapsed or refractory multiple myeloma (BMA117159): a dose escalation and expansion phase 1 trial

Lancet Oncol 2018; 19: 1641–53

Suzanne Trudel, Nikoletta Lendvai, Rakesh Popat, Peter M Voorhees, Brandi Reeves, Edward N Libby, Paul G Richardson, Larry D Anderson Jr, Heather J Sutherland, Kwee Yong, Axel Hoos, Michele M Gorczyca, Soumi Lahiri, Zangdong He, Daren J Austin, Joanna B Opalinska, Adam D Cohen

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 2019;380:1726-37.

T Cells Genetically Modified to Express an Anti–B-Cell Maturation Antigen Chimeric Antigen Receptor Cause Remissions of Poor-Prognosis Relapsed Multiple Myeloma

Jennifer N. Brudno, Irina Maric, Steven D. Hartman, Jeremy J. Rose, Michael Wang, Norris Lam, Maryalice Stetler-Stevenson, Dalia Salem, Constance Yuan, Steven Pavletic, Jennifer A. Kanakry, Syed Abbas Ali, Lekha Mikkilineni, Steven A. Feldman, David F. Stroncek, Brenna G. Hansen, Judith Lawrence, Rashmika Patel, Frances Hakim, Ronald E. Gress, and James N. Kochenderfer *J Clin Oncol 36:2267-2280.*

B cell maturation antigen–specific CAR T cells are clinically active in multiple myeloma

Adam D. Cohen,[1] Alfred L. Garfall,[1] Edward A. Stadtmauer,[1] J. Joseph Melenhorst,[2] Simon F. Lacey,[2] Eric Lancaster,[3] Dan T. Vogl,[1] Brendan M. Weiss,[1] Karen Dengel,[2] Annemarie Nelson,[2] Gabriela Plesa,[2] Fang Chen,[2] Megan M. Davis,[2] Wei-Ting Hwang,[4] Regina M. Young,[2] Jennifer L. Brogdon,[5] Randi Isaacs,[5] Iulian Pruteanu-Malinici,[5] Don L. Siegel,[2,6] Bruce L. Levine,[2,6] Carl H. June,[2,6] and Michael C. Milone[6]

J Clin Invest. 2019;129(6):2210-2221

[1]Abramson Cancer Center, [2]Center for Cellular Immunotherapies, [3]Department of Neurology, and [4]Department of Biostatistics, Epidemiology and Informatics, University of Pennsylvania, Philadelphia, Pennsylvania, USA. [5]Novartis Institute for Biomedical Research, Cambridge, Massachusetts, USA. [6]Department of Pathology and Laboratory Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, USA.

- Off-target or on-tumor/off-target toxicity has not been conclusively identified.
- However, some central and peripheral nervous system toxicities are emerging in CAR T and bispecific antibody studies.

Idecabtagene Vicleucel

- Autologous anti-BCMA CAR T cell with 4-1BB costimulatory domain
- Phase 2 study (KARMMA)
  - 3 prior regimens including a thalidomide analog, proteasome inhibitor, and anti-CD38 Ab
  - 140 enrolled, 128 treated, 1 unsuccessful manufacturing
  - Cy/flu 300/30 x 3 lymphodepletion
  - Dose: 150 (N=4), 300 (N=70), or 450 (N=54) x 10^6 cells
  - 84% triple-refractory, 26% penta-refractory

Munshi, Anderson, Shah et al., N Engl J Med 2021; 384:705-716

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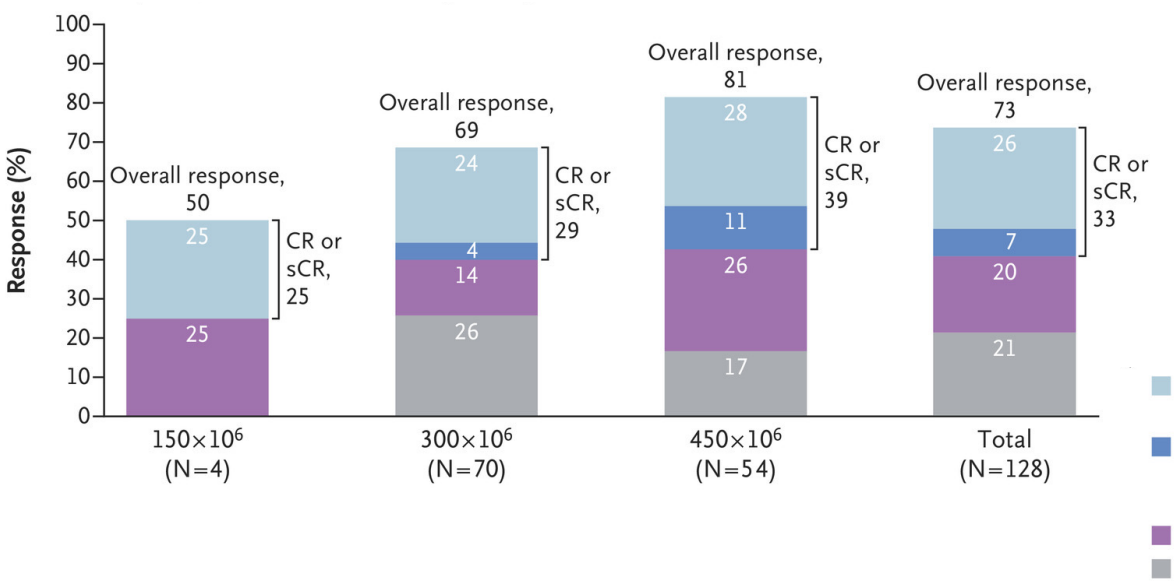
Idecabtagene Vicleucel



Similar RR in patients with…

- Triple- and penta-refractory MM
- Extramedullary disease
- High-risk cytogenetics
- High disease burden (>50% BM)

Munshi, Anderson, Shah et al., N Engl J Med 2021; 384:705-716

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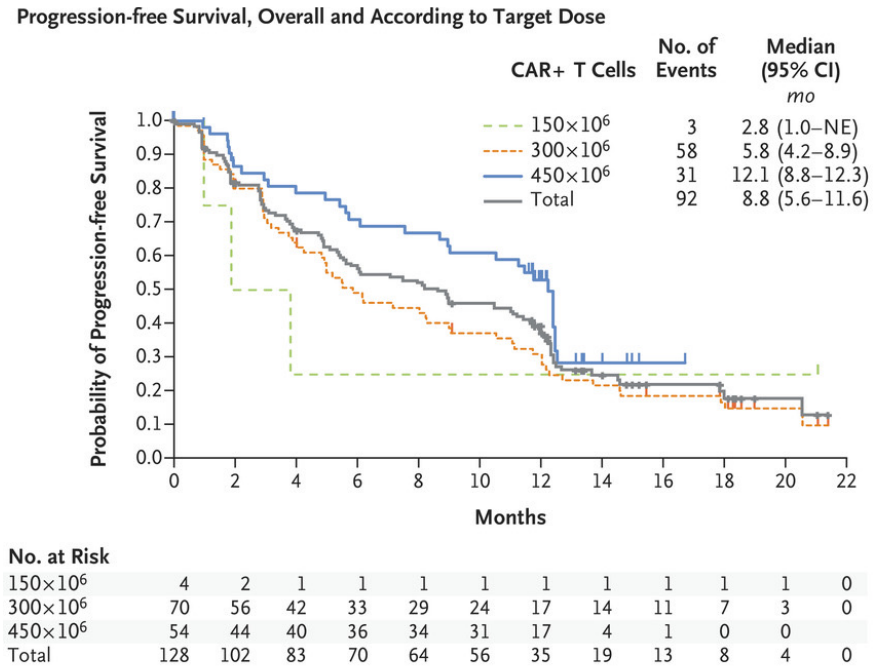
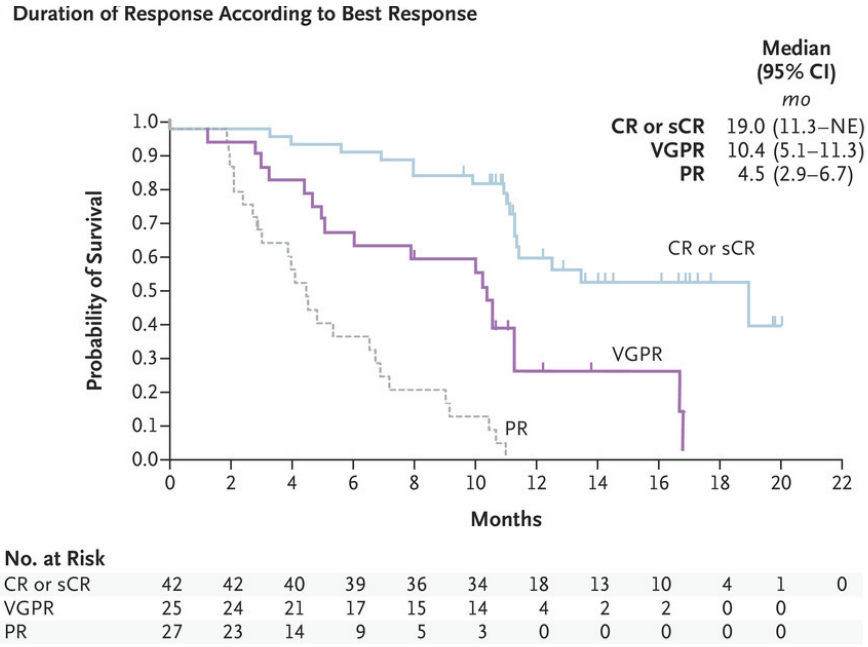
Idecabtagene Vicleucel





Munshi, Anderson, Shah et al., N Engl J Med 2021; 384:705-716

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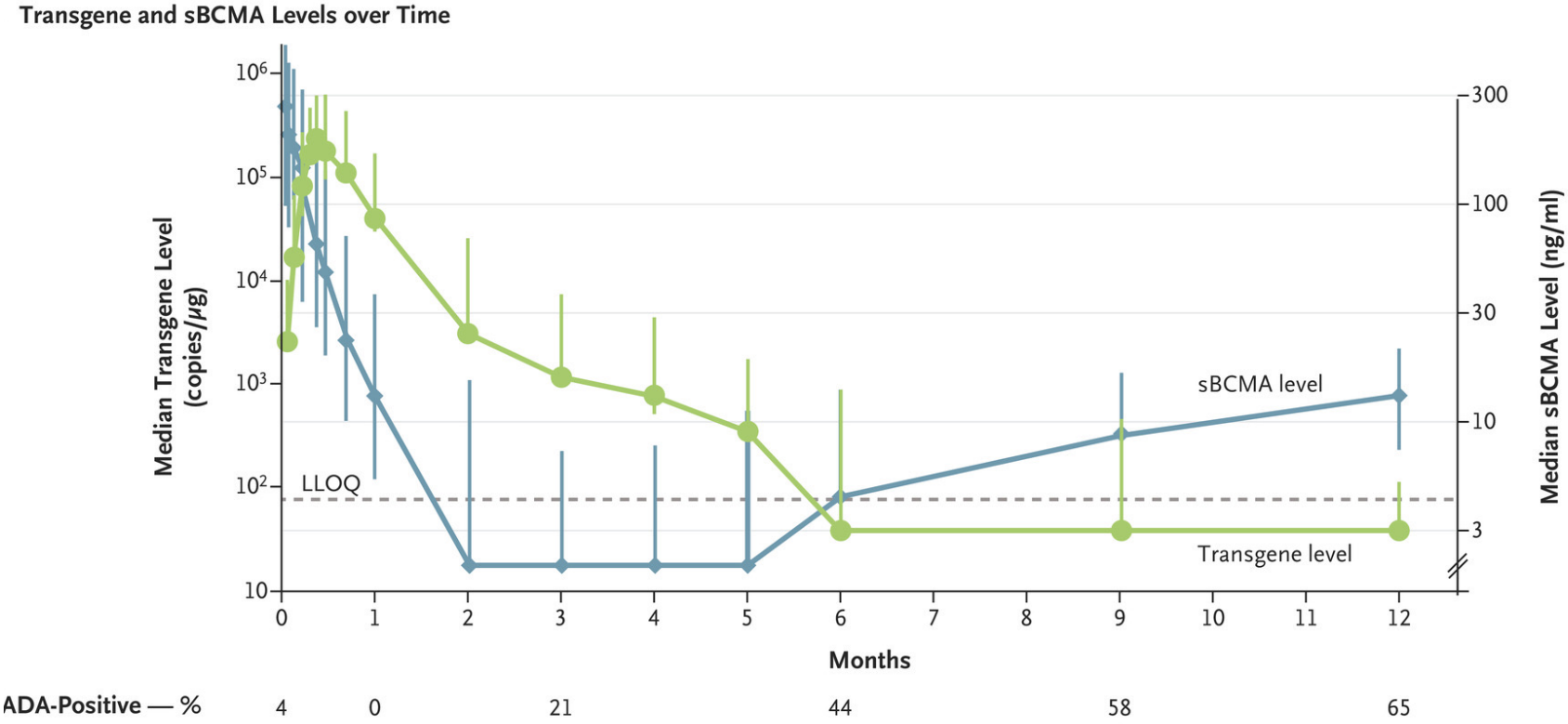
Idecabtagene Vicleucel

- Cytokine release syndrome:
  - 84% overall, 4% G3, N=1 G4, N=1 G5
  - 96% of patients at $450x10^6$ dose
  - Median onset day 1 (range 1-12), median duration 5d
- Neurologic toxicity:
  - 18% overall, 3% grade 3, no grade 4/5
  - Median onset day 2 (range 1-10), median duration 3d

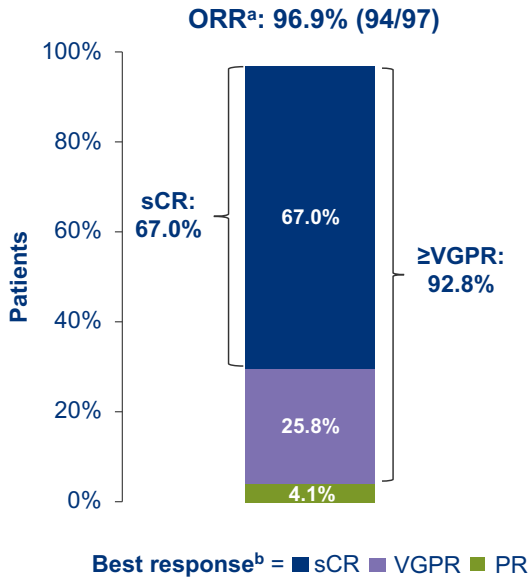
Idecabtagene Vicleucel

- 97% had rising soluble BCMA at time of disease progression
- 4% of patients with suspected BCMA loss at progression (1 with proven bi-alleleic BCMA loss)

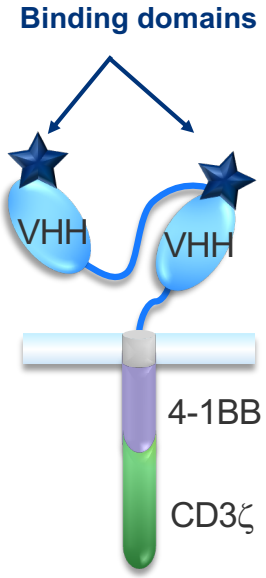


Ciltacabtagene autoleucel

- Camelid-derived tandem single-domain BCMA binders
- CARTITUDE-1 study (Phase 1b/2) (N=97)



	N	Frequency in evaluable patients n=57[c]	Frequency in all treated n=97[d]
Overall MRD-	53	93.0%	54.6%
MRD- and sCR	33	57.9%	34.0%
MRD- and ≥VGPR	49	86.0%	50.5%



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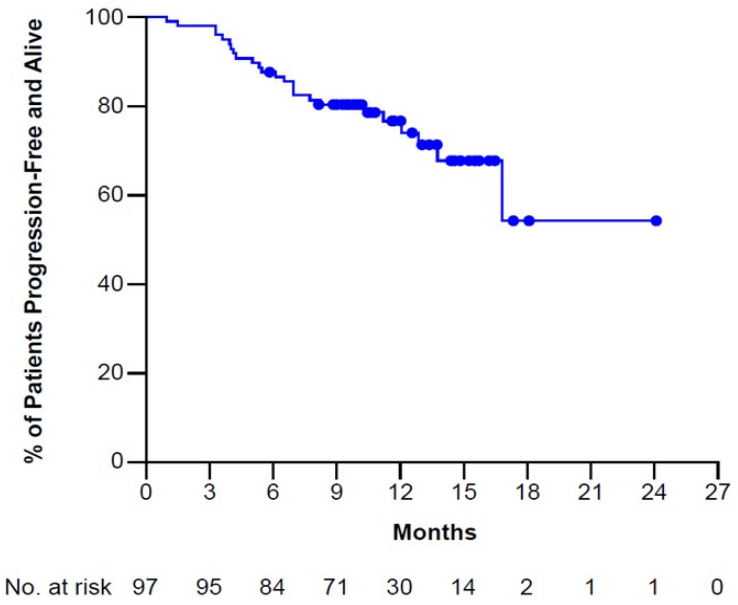
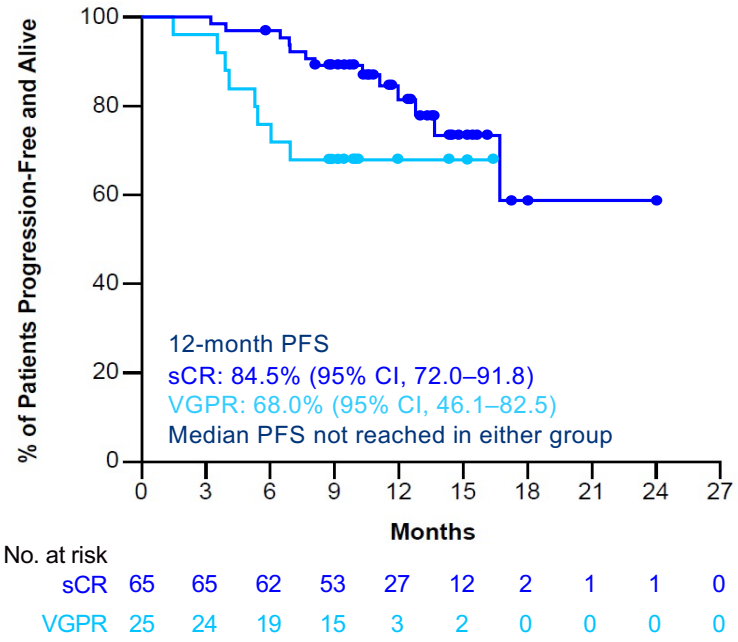
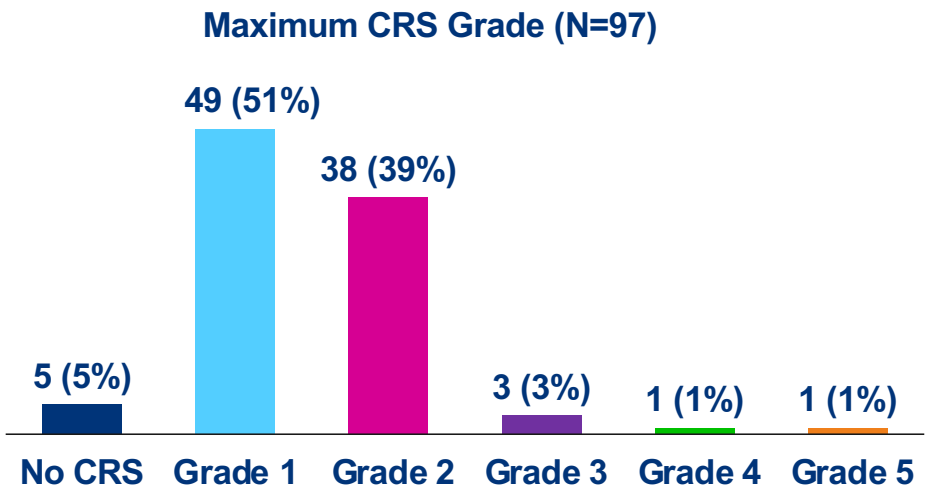




Cilta-cel: Cytokine Release Syndrome



- CRS onset
  - Day 4 or later: 89.1% (n=82)
  - Day 6 or later: 73.9% (n=68)
- CRS resolved in 91 (98.9%) patients within 14 days of onset

62nd ASH Annual Meeting 2020, Madduri D et al. #177

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Cilta-cel neurologic toxicities

- ICANS
  - Any grade: 16 (16.5%)
  - Grade ≥3: 2 (2.1%)
  - Resolved in all patients
- Other neurologic toxicities
  - Any grade: 12 (12.4%)
  - Grade ≥3: 9 (9.3%)
  - 5 pts: movement and/or neurocognitive
  - 7 pts: nerve palsy, peripheral motor neuropathy
  - Outcomes
    - 1 ongoing
    - 1 died due to neurotoxicity complications
    - 4 died due to other problems

	ICANS	Other neurotoxicities
Time to onset, median (range) days	8 (3–12)	27 (11–108)
Time to recovery, median (range) days	4 (1–12)	75 (2–160)

Other phase 1/2 autologous BCMA CAR T cell studies

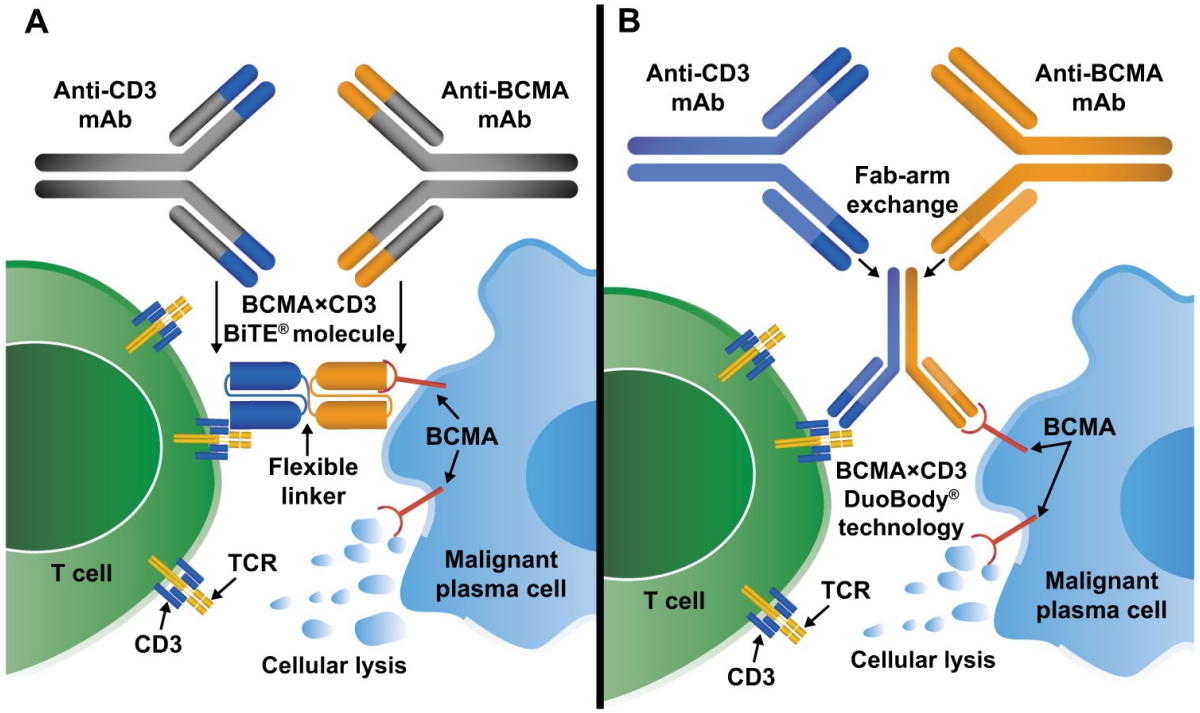
Abstract	Product	n	ORR	CR	Comment
ASCO 8504	orva-cel	62	92%	36%	1:1 CD4:CD8 ratio, T_{cm}-enriched
ASH 130	bb21217	69	68%*	29%	PI3K inhibitor during manufacturing
ASH 133	CT053	20	94%	28%	8-10 day manufacturing
ASH 134	P-BCMA-101	55	60%**	?	Transposon-based, T_{scm}+T_{cm}-enriched. Single and serial administration. Combos w/ ritux and len
ASH 178	GC012F	16	94%	56%	Dual BCMA/CD19 CAR. 24-36 hour manufacturing
ASH 498	FHVH-BCMA-T	20	90%	?	heavy chain-only binding domain

*84% (16/19) ORR w/ new manufacturing process
**original manufacturing process (n=30)

Mailankody et al, ASCO 2020, #8504; Alsina et al, ASH 2020, #130; Kumar et al, ASH 2020, #133; Costello et al, ASH 2020, #134; Jiang et al, ASH 2020, #178; Mikkilineni et al, ASH 2020, #498 Slide courtesy of Dr. Adam Cohen

Anti-BCMA/CD3 bispecific antibodies

AMG-420

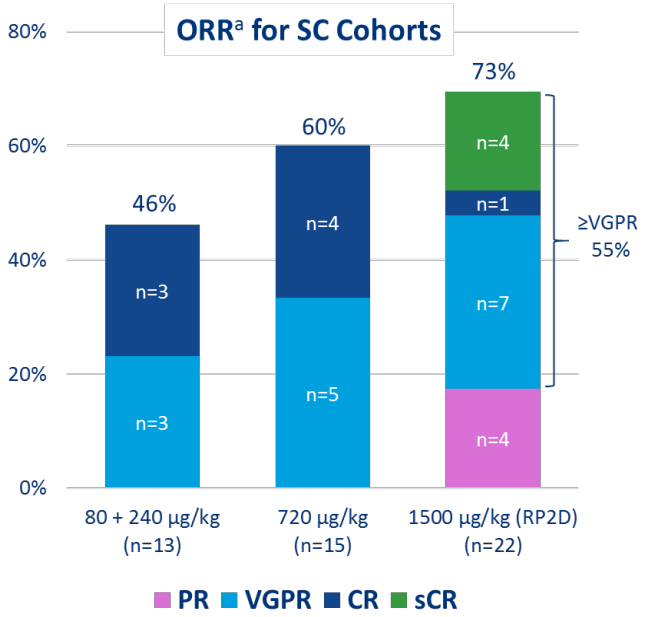


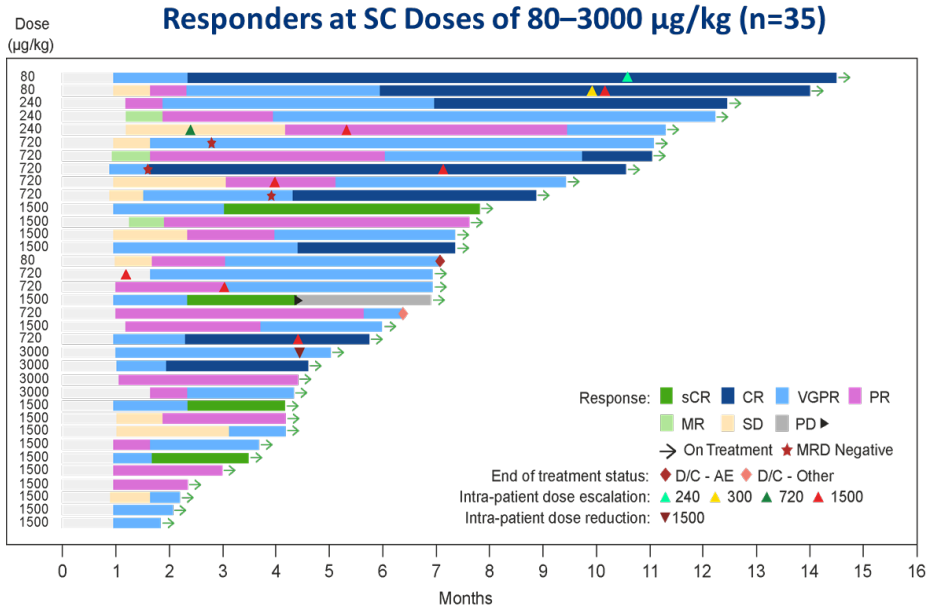
AMG701
PF-06863135
Teclistamab
EM801
CC-93269/EM901
REGN5458
HPN217
TNB-383B
AFM26

Image from Shah et al. (2020) Leukemia 34:985

Full-size anti-BCMA/CD3 bispecific antibodies

- Teclistamab, weekly subcutaneous dosing
- At most active IV/SC cohorts: 69% ORR, 94% of responses ongoing after mF/U 6.5 months





Garfall et al., ASH 2020, abstract 180

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Bispecific antibodies against other targets

- Talquetamab: anti-GPRC5D/CD3 (Chari et al., ASH 2020 abstract #290)
  - Dysgeusia as a notable AE
  - ORR 66% at active doses
- Cevostamab: anti-FCRH5/CD3 (Cohen et al., ASH 2020 abstract #292)
  - ORR 61% at active doses

Summary

- Very exciting time for multiple myeloma immunotherapy
- Ide-cel: FDA-approved anti-BCMA CAR T cell
- Other potent anti-BCMA CAR T cells are in clinical development
- Response durability remains a challenge; in vivo activity of CAR T cells appears limited
- Most patients progress with BCMA+ disease → potential for serial anti-BCMA therapies
- Neurologic toxicity may accompany more potent therapies
- Bispecific antibody responses rival CAR T cell responses
- New cell-surface targets: GPRC5D and FCRH5


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