Penn Medicine

Potential Role of CAR T Therapy in Patients with MM

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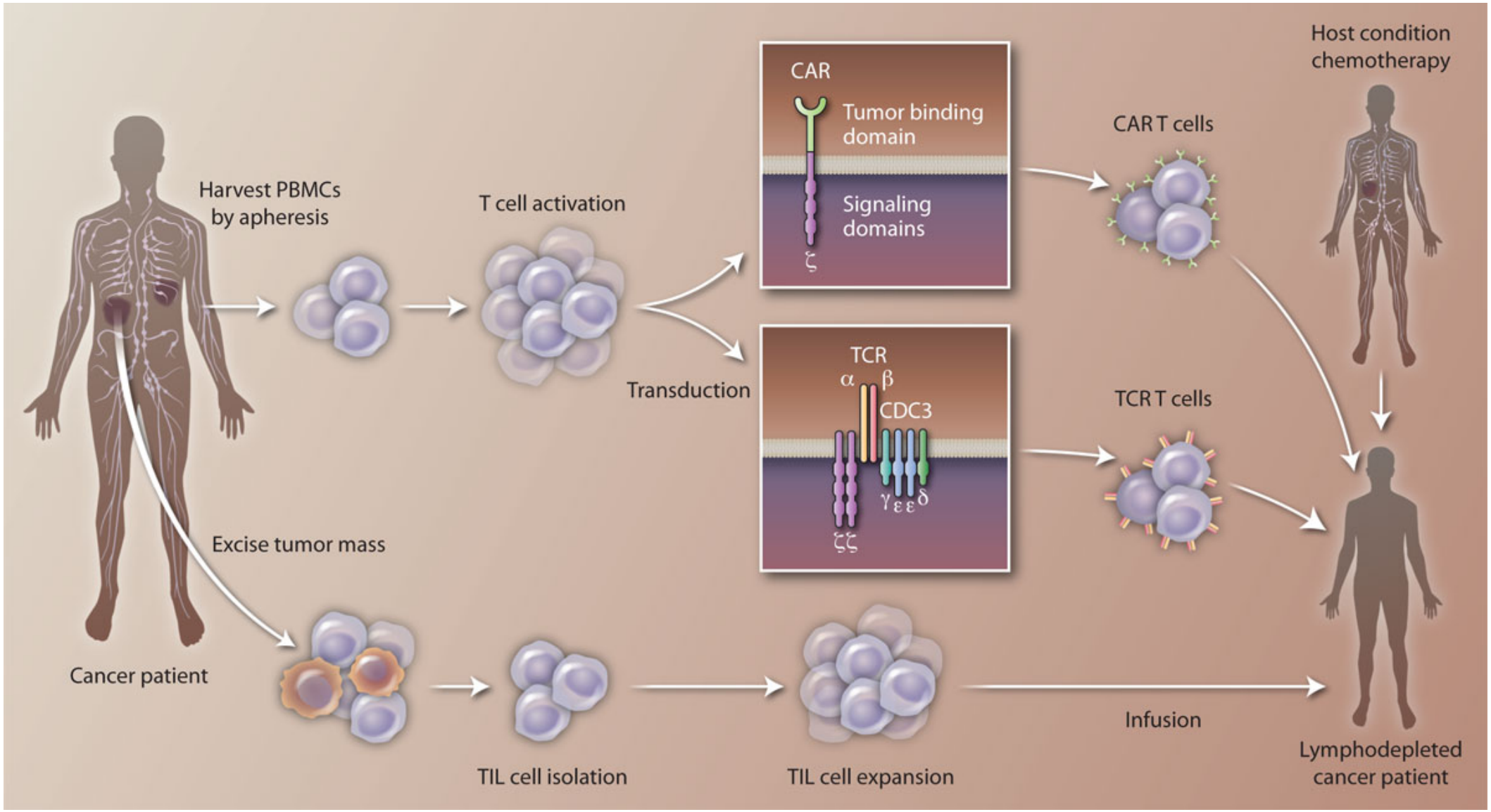
the cure is within
ABRAMSON CANCER CENTER

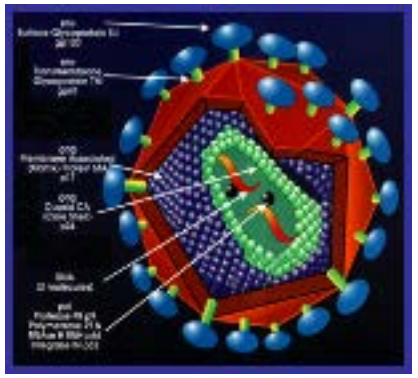
Adoptive T-cell therapy (three major approaches)



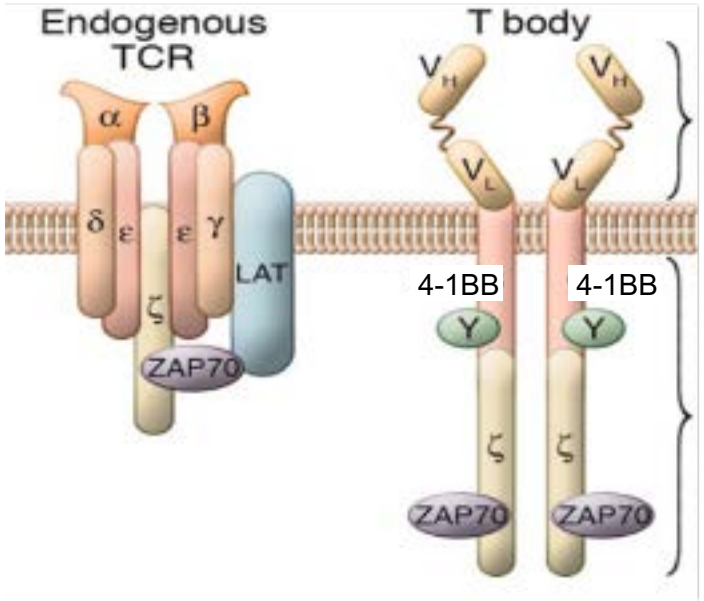
June et al *Sci Trans Med 2015*

Courtesy of Edward A Stadtmauer, MD

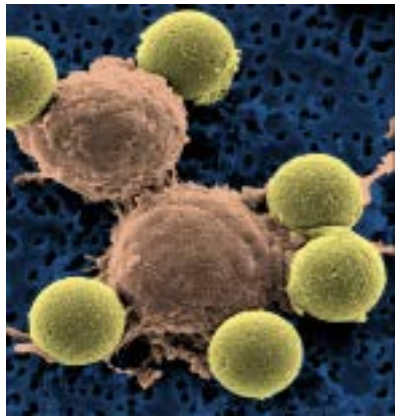
CAR for Plasma Cell Malignancy:
Autologous T Cells Transduced w/ Anti-BCMA Receptor Spliced to CD3 zeta and 4-1BB Signaling Domains



Lentiviral vector to deliver construct



CD3-z and 4-1BB signaling domains augments proliferation and survival



Anti-CD3/anti-CD28 mab coated bead stimulation (artificial DC) Expands the cells

Adapted from: Maus MV, et al. Blood. 2014;123:2625-35.

Courtesy of Edward A Stadtmauer, MD

Anti-BCMA CAR T cells – initial studies, refractory pts

Trial (Sponsor)	n	CAR	Condi-tioning	# lines	% hi risk†	Dosing	ORR	ORR (optimal doses)	VGPR/CR (optimal doses)
Phase I (NCI)[1]	26*	Murine, CD3/CD28	Cy/Flu	7.5	42%	0.3 – 9 x 10^6/kg	58%	81% (13/16)	63% (10/16)
Phase I (Penn)[2]	25	Human, CD3/41BB	None or Cy	7	76%	0.5 – 5 x 10^8	48%	64% (7/11)	36% (4/11)
Phase I (Pharma)[3]	43	Human, CD3/41BB	Cy/Flu	7.5	40%	0.5 – 8 x 10^8	77% (30/39)	96% (21/22)	86% (19/22)

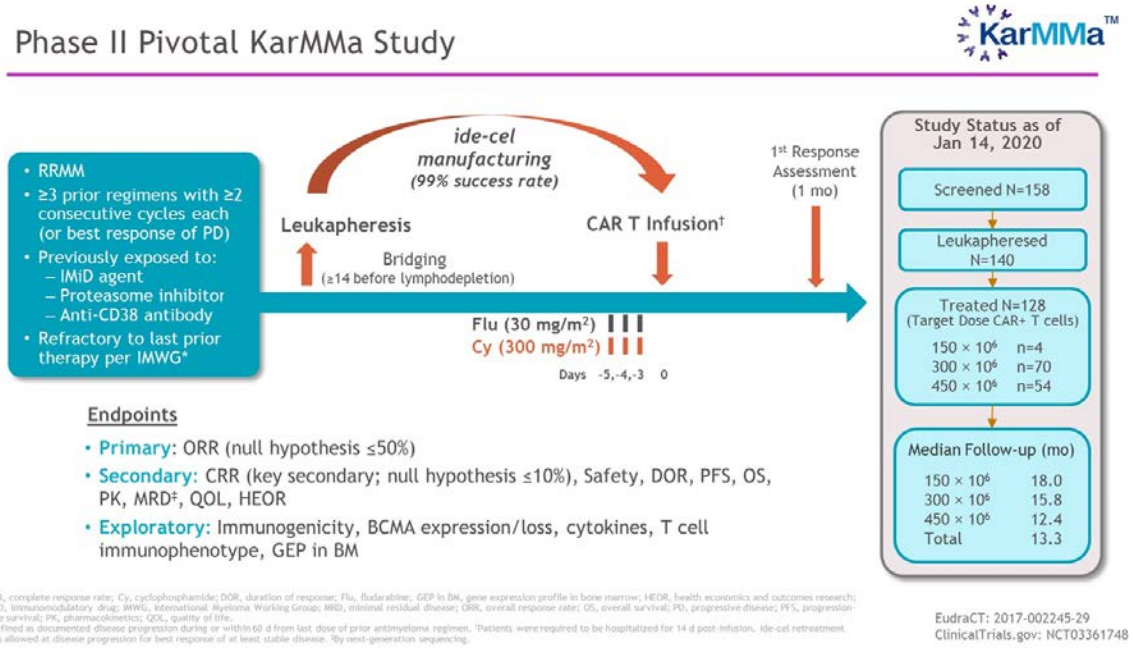
***2 treated twice; counted separately for response. † FISH +t(4;14), t(14;16), del 17p**

Trial (Sponsor)	n	CRS %	CRS G3-4 %	Neurotox %	Neuro tox G3-4 %	Tocilizumab
Phase I (NCI)[1]	26*	73%	23%	NR	12%	19%
Phase I (Penn)[2]	25	88%	32%	32%	12%	28%
Phase I (Pharma)[3]	43	63%	5%	33%	2%	21%

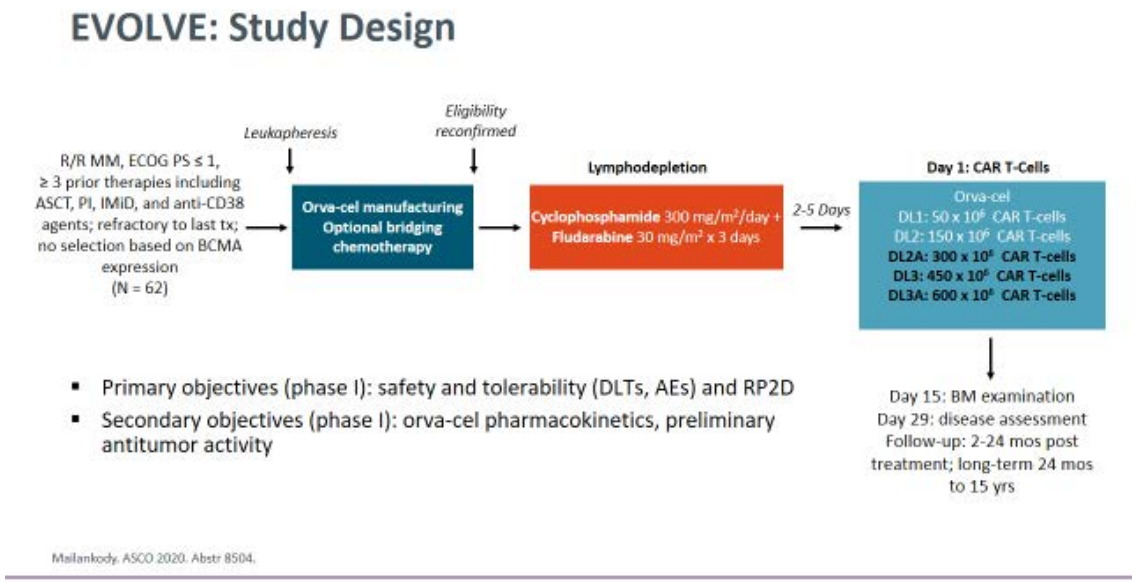
***excluded high tumor burden in last 14 pts. NR = not reported**

[1]Ali, Blood 2016 and Brudno, J Clin Oncol 2018; [2]Cohen, ASH 2017. 2018; and JCI 2019 in press [3]Raje, ASCO 2018

BCMA Directed CAR T Studies: ASH 2019, ASCO 2020



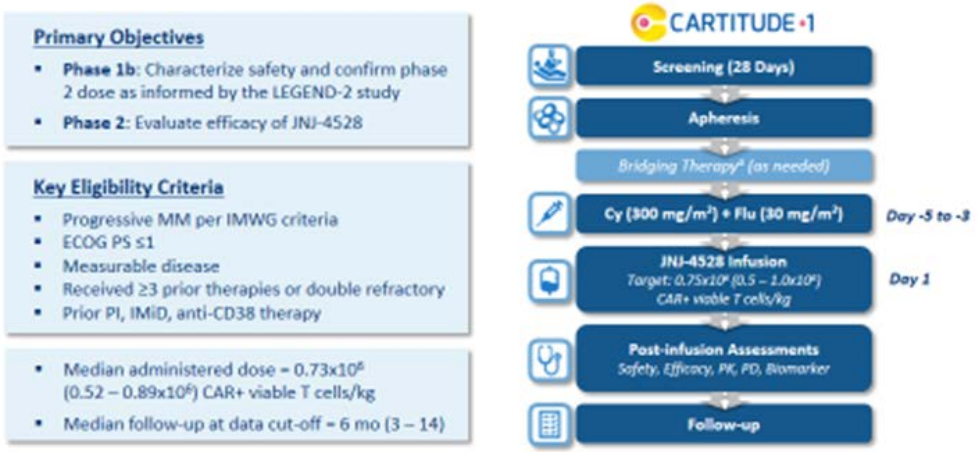
EudraCT: 2017-002245-29
ClinicalTrials.gov: NCT03361748



Mailankody. ASCO 2020. Abstr 8504.

Similar approach in 3 studies:

R/R MM
Steady state T cell collection
CY/FLU lymphodepletion
Single infusion



BCMA Directed CAR T Studies: ASH 2019, ASCO 2020

Patient Characteristics

	KarMMa: idecabtagene vicleucel (n=128)	EVOLVE: orvacabtagene autoleucel (n=62)	CARTITUDE-1: JNJ-4528 (n = 29)
Age	61 (33-78)	61 (33-77)	60 (50-75)
High Risk Cytogenetics, %	35	41*	27
Tumor Burden in BM, %	>50% PC = 51	—	≥60% PC = 24
Extramedullary PCs, %	39	23	10
Median prior lines of therapy	6 (3-16)	6 (3-18)	5 (3-18)
Triple refractory, %	84	94	86
Bridging therapy, %	88	63	79
Unique properties	Human BCMA, 4-1BB, CD3z	Modified spacer, CD4:CD8 enriched for CM	Median cell dose **$0.72x10^6$** cells/kg 2 BCMA single chain antibodies

BCMA Directed CAR T Studies: ASH 2019, ASCO 2020

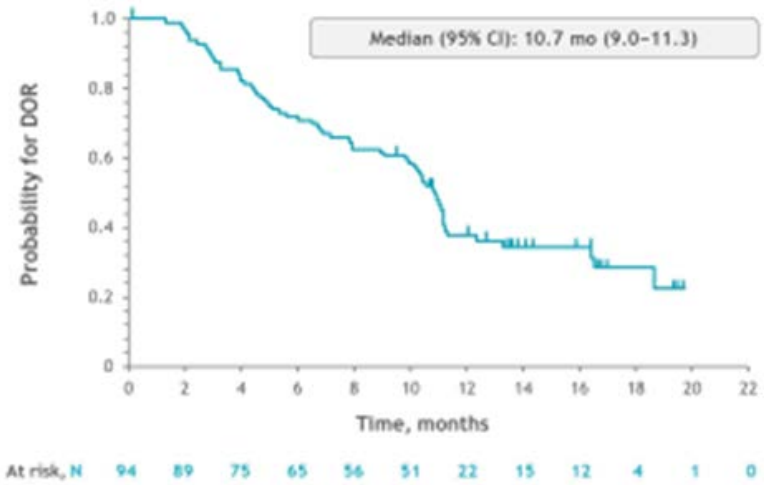
Response Rates

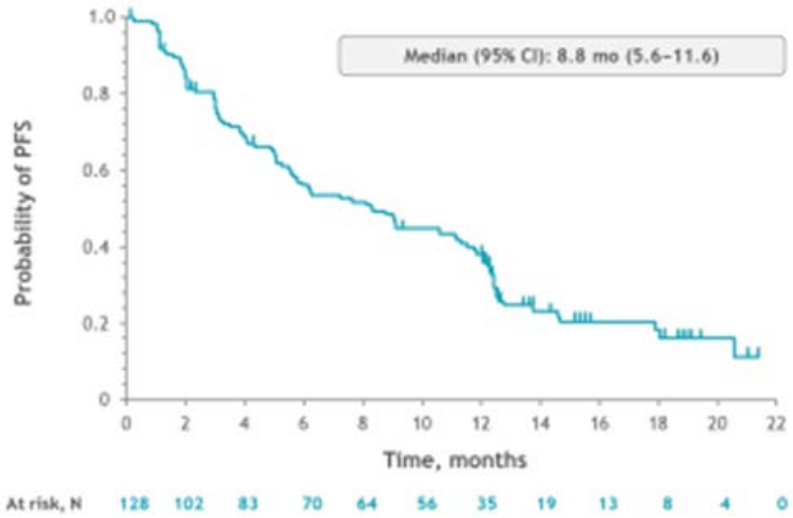
	KarMMa	EVOLVE	CARTITUDE-1
↓ANC ≥G3, %	89	90	100
↓plts ≥G3, %	52	47	69
CRS: all, ≥G3,%	84, 6	89, 3	93, 7
Med. time to CRS, duration, days	1 (1-12) 5 (1-63)	2 (1-4) 4 (1-10)	7 (2-12) 4 (2-64)
ICANS: all, ≥G3,%	17, 3	13, 3	10, 3
HLH/MAS, %	--	5	? 7 (lfts)
Infections: all, ≥G3 %	69, --	40, 13	--, 19
Toci/steroid/ anakinra use, %	52/15/0	76/52/23	79/21/21

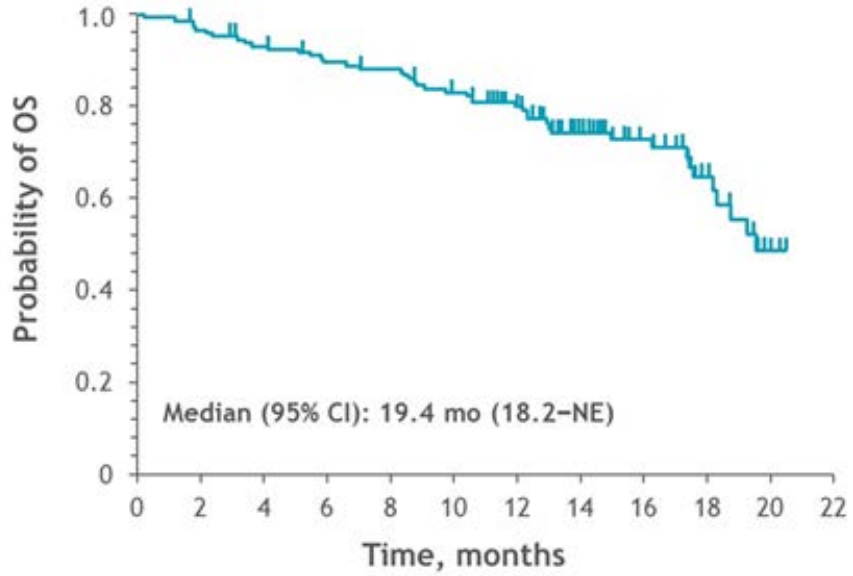
	KarMMa (n = 128)	EVOLVE (n = 62)	CARTITUDE-1 (n = 29)
ORR, %	73 (66-81)	92	100
sCR/CR, %	33	36	86
MRD neg ≥10^{-5}, % (of evaluable)	94	84	81
PFS/DoR, months	8.8/10.7	NR*	NR**
Screened Apheresed Treated	150 140 128	--	35 35 29

BCMA Directed CAR T Studies: KarMMa

Duration of Response, Progression Free and Overall Survival





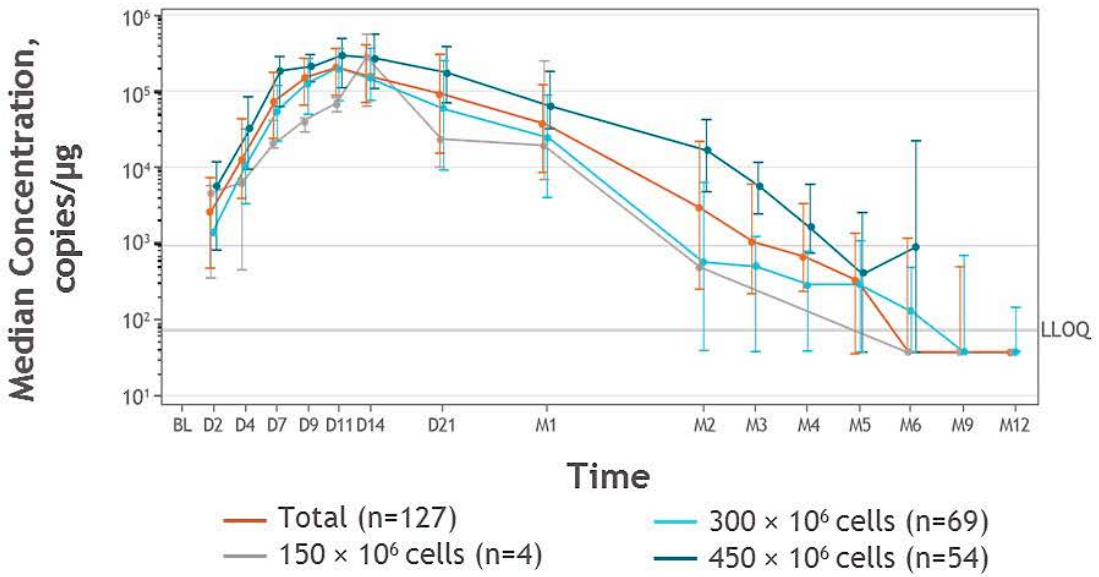


Munshi, ASCO 2020, Abstract 8503

Courtesy of Edward A Stadtmauer, MD

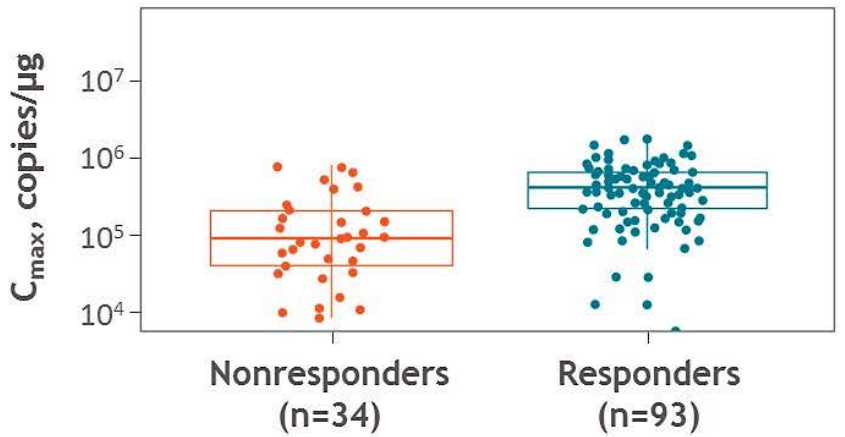
CAR+ T Cell Expansion, Persistence, and Peak Exposure

CAR+ T Cell Expansion and Persistence



	Mo 1	Mo 3	Mo 6	Mo 9	Mo 12
Evaluable patients, n	118	100	49	27	11
Patients with detectable vector, n (%)	117 (99)	75 (75)	29 (59)	10 (37)	4 (36)

Peak Vector Copies in Responders (≥PR) vs Nonresponders (<PR)



- Median peak CAR+ T cell expansion was at 11 d
- Median expansion increased at higher target doses with overlapping profiles
- Peak exposure higher in responders than nonresponders
- Durable persistence was observed up to 1 y

Data cutoff: 19 April 2019. Pharmacokinetic (PK) analysis population (N=127). One patient died on day 4 and had no evaluable PK samples and was therefore excluded. Error bars represent interquartile range. BL, baseline; C_{max}, maximum concentration; LLOQ, lower limit of quantitation; M, month.

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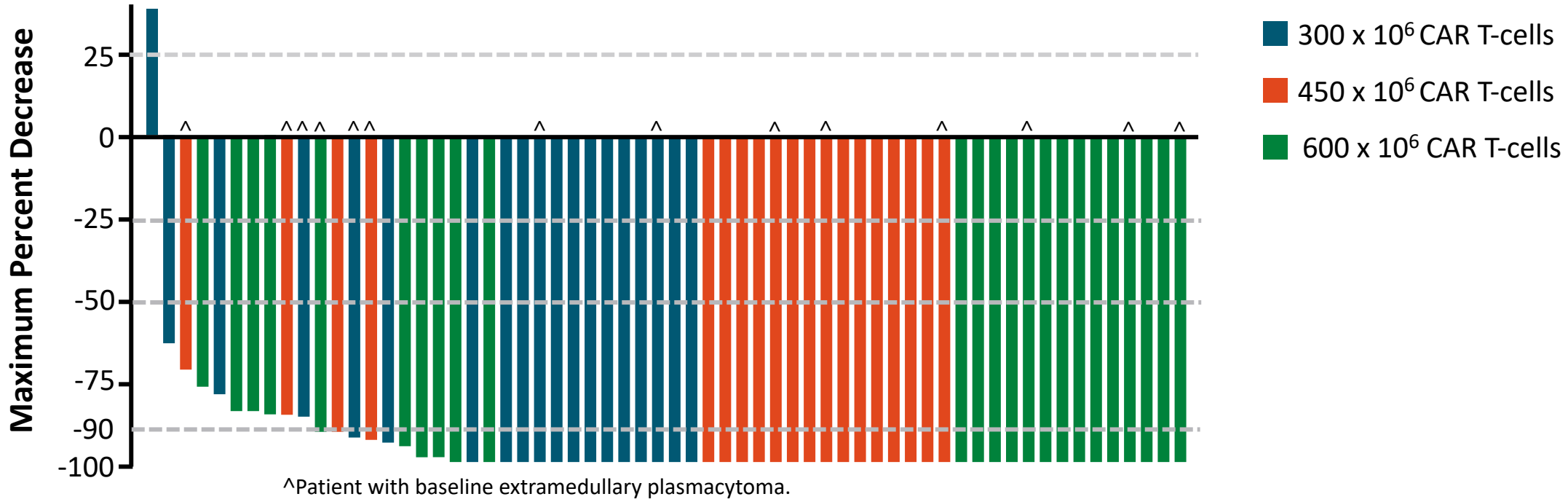
Munshi, ASCO 2020, Abstract 8503

Courtesy of Edward A Stadtmauer, MD

EVOLVE: Tumor Burden Reduction According to Dose



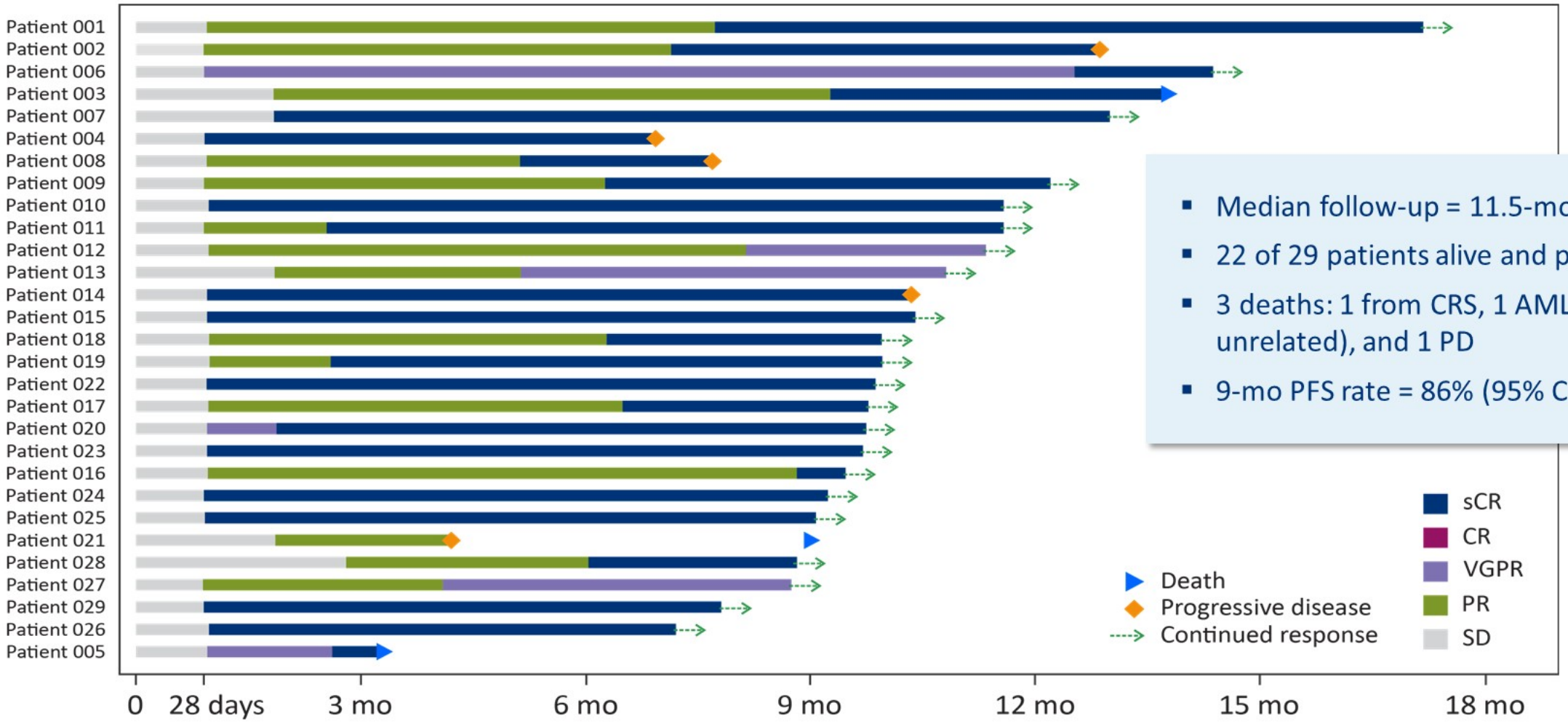
^Patient with baseline extramedullary plasmacytoma.

- Serologic responses (serum or urine paraprotein, free light chains) were observed in all patients treated at 450 x 10^6 and 600 x 10^6 dose levels
- Orva-cel activity not impacted by high baseline sBCMA
  - 12/12 patients achieved ≥ PR; 8/12 ≥ VGPR

Mailankody. ASCO 2020. Abstr 8504.

Courtesy of Edward A Stadtmauer, MD

CARTITUDE-1: Duration of Response



- Median follow-up = 11.5-mo (3 – 17)
- 22 of 29 patients alive and progression-free
- 3 deaths: 1 from CRS, 1 AML (treatment unrelated), and 1 PD
- 9-mo PFS rate = 86% (95% CI, 67 – 95)

AML=acute myeloid leukemia (biphenotypic); PD=progressive disease; PFS=progression-free survival

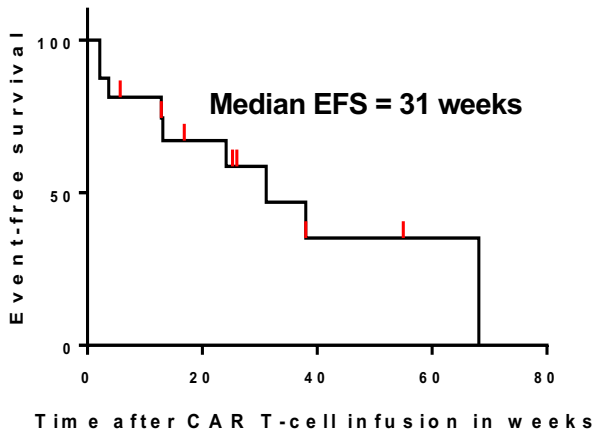
Courtesy of Edward A Stadtmauer, MD

Presented By Jesus Berdeja at TBD

Anti-BCMA CAR T cells – lessons from initial studies

- **Probably not curative in refractory patients**

NCI – 9x10e6/kg



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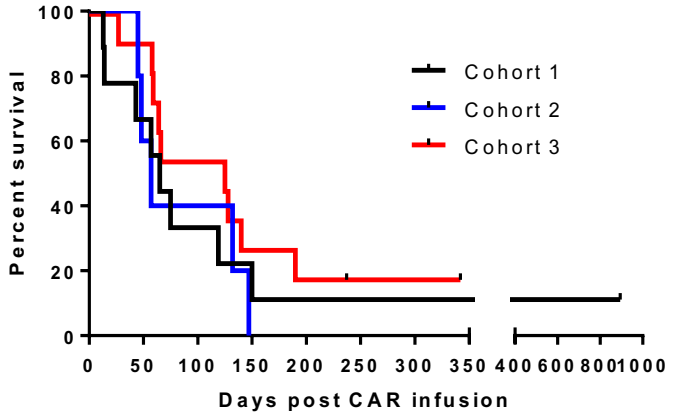
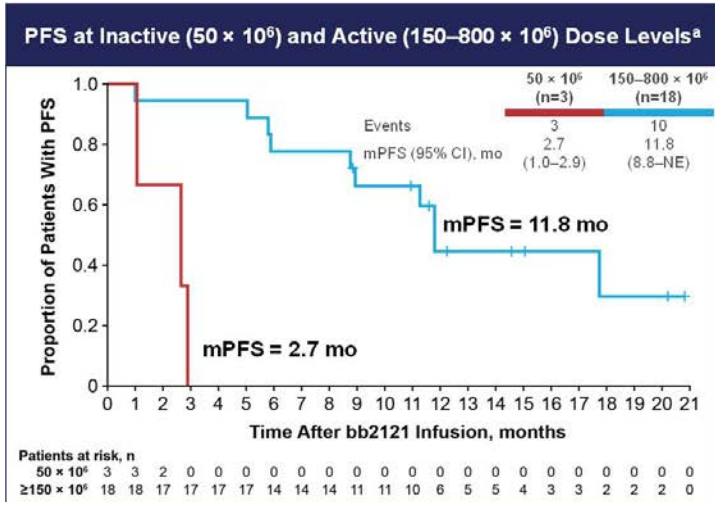
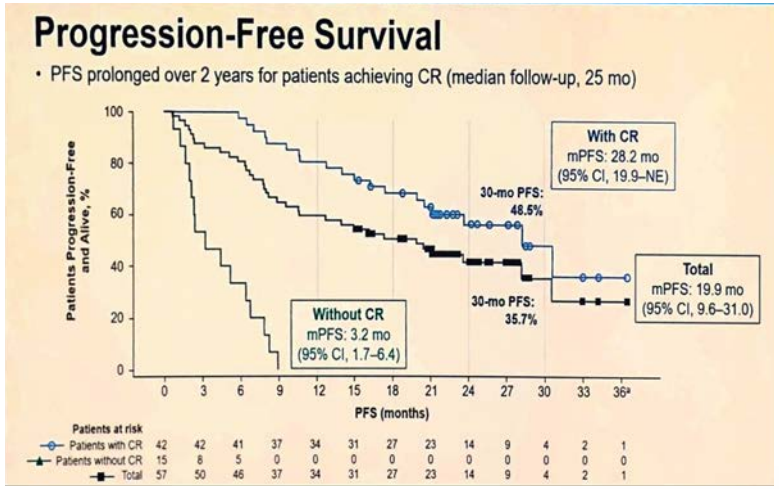


Phase I Trial – dose escalation



Phase I/II Trial



Anti-BCMA CAR T cells – lessons from initial studies

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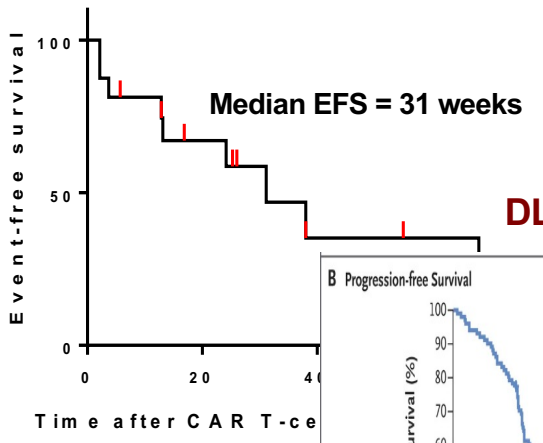
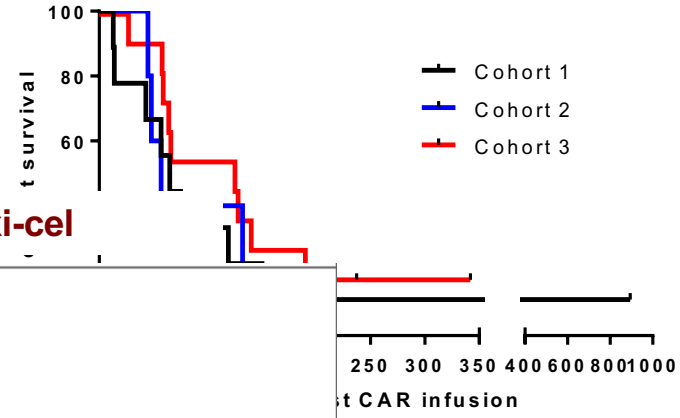
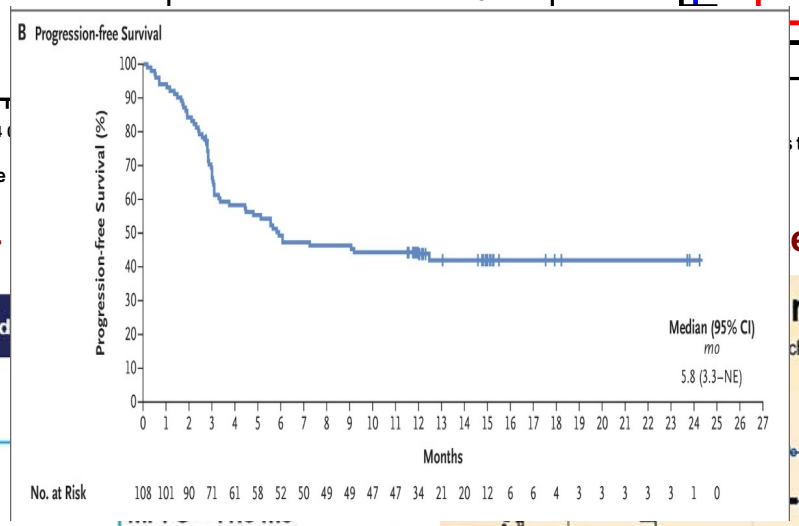


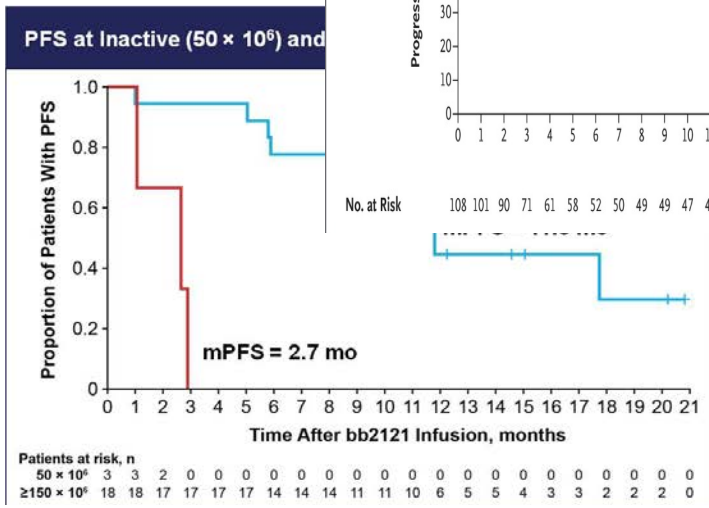
Penn



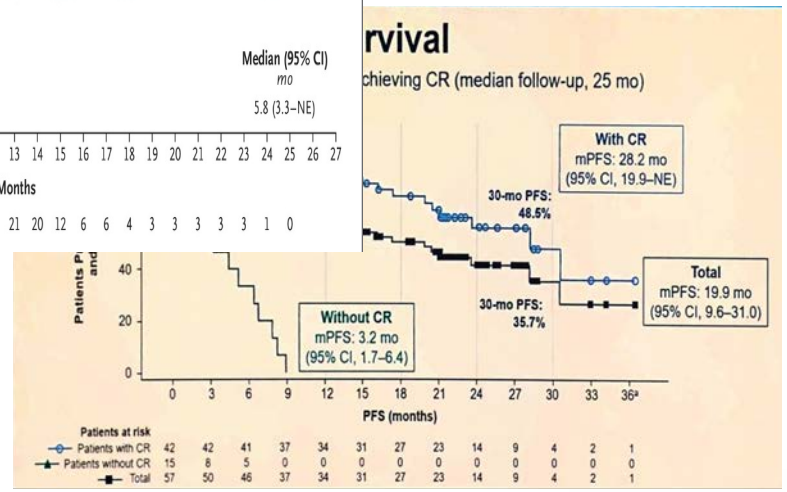
DLBCL ph2 Axi-cel



Bluebird –



egend



Why not more durable responses?

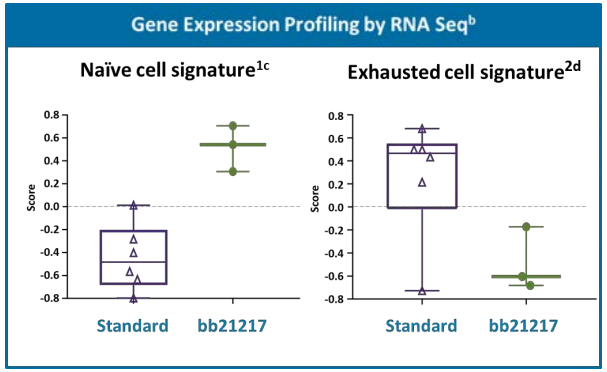
- **CAR-intrinsic factors**
  - Binding affinity, epitopes
  - Tonic signaling
  - Co-stimulation
- **T-cell intrinsic factors**
  - Pre-manufacturing
  - Post-manufacturing
  - Post-infusion
- **Tumor-intrinsic factors**
  - Myeloma cell
  - Microenvironment
- **Other**
  - Lymphodepletion regimen?

Courtesy of Edward A Stadtmauer, MD

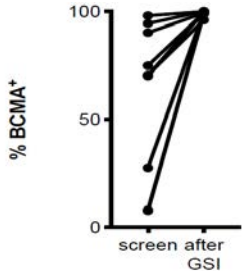
Cohen et al, J Clin Invest 2019; Brudno et al, J Clin Oncol 2018; Wang et al, ASH 2019, #1909

How to improve clinical outcomes?

- Optimize CAR T product?
  - Dual epitope or dual antigen binding
  - Novel costimulatory domains
  - Transposon-based
  - Suicide genes/safety switches
  - Gene editing (e.g. PD-1 knockdown, allogeneic CARTs)
- Optimize manufacturing?
  - Defined CD4:CD8 ratios? Start with Tn or Tcm? PI3K inhibitors?
- Optimize target expression?
  - Gamma-secretase inhibitors for BCMA?
- Optimize infusion schedule?
  - Serial infusions? Retreatment at progression?
- Patient selection?
  - Only high expressors? Earlier lines of therapy? High-risk?
- Lymphodepletion?
  - Is Cy/Flu the best?
- Rational combinations?
  - Immune checkpoint inhibitors? IMiDs? Other CAR

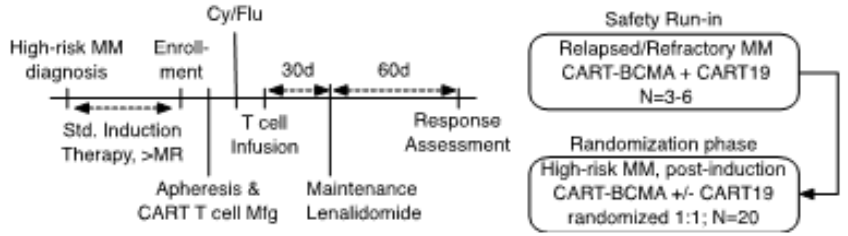


Berdeja et al, ASH 2019, #927



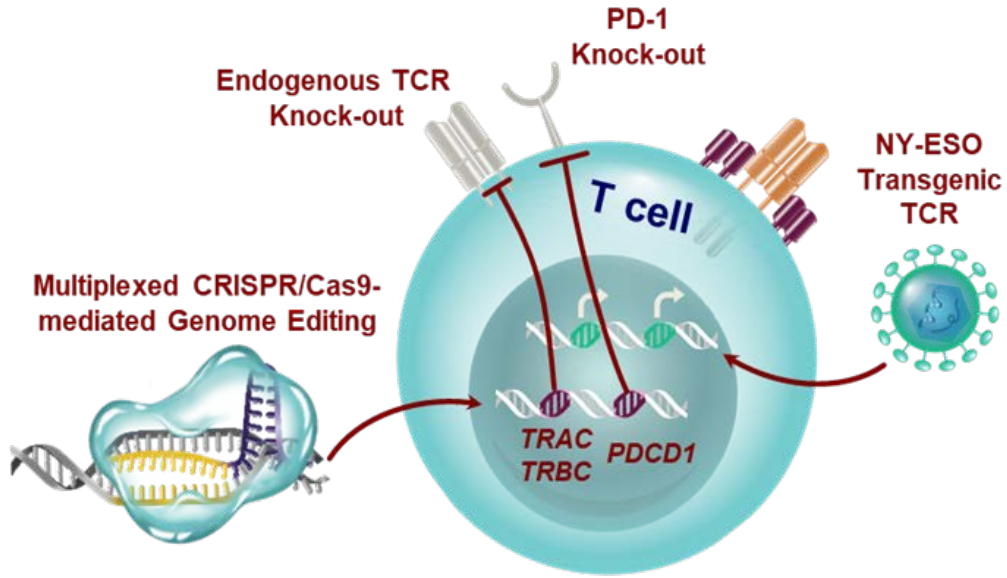
Cowan et al, ASH 2019, #204

UPCC 46417 (PI: Al Garfall)



Manufacturing NYCE T cells: *Multiplexed Genomic Editing*

- Autologous T cells
- Anti-CD3/CD28 bead stimulation
- Electroporation with ribonucleoprotein (RNP) complexes:
  TRAC/*TRBC*/*PDCD1* gRNAs + Cas9 Protein
- Transduction with NY-ESO-1 TCR lentiviral vector
- Expansion of engineered T cells



Cell Product Release Criteria

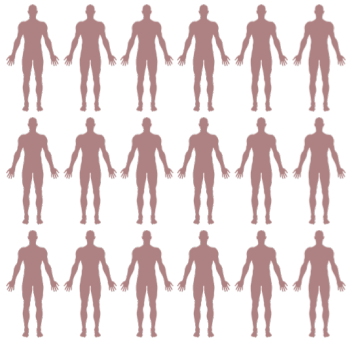
- Viability: ≥ 70%
- NY-ESO TCR Transduction Efficiency (Vβ8 Flow Cytometry): ≥ 2%
- NY-ESO TCR Transduction Efficiency (WPRE qPCR): ≥ 0.02 - ≤ 5 Avg. copies / cell
- Residual Beads: ≤ 100 beads / 3 x 10^6 cells
- Endotoxin Content: ≤ 3.5 EU / mL
- Microbial Contamination: Negative
- Long-term Culture: No growth in the presence of IL-2 (no cell transformation)
- Replication Competent Lentivirus (VSV-G): < 50 Avg. copies / µg DNA
- *TRAC, TRBC, PDCD1* Disruption: Detectable
- Residual Cas9 Protein: Decreasing concentration from Day 0 to cell harvest

Stadtmauer *et al, Science,* 2020

Courtesy of Edward A Stadtmauer, MD

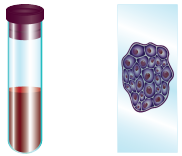
Study Schema: *NY-ESO-1-redirected CRISPR Edited T Cells (NYCE T Cells)*

ClinicalTrials.gov Identifier: NCT03399448



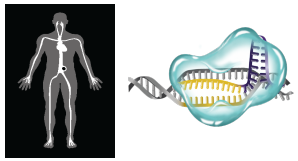
Confirmed Malignancy
- Multiple Myeloma
- Synovial Sarcoma
- Myxoid/Round Cell Liposarcoma

→



HLA-A*0201 Positive & Tumor NY-ESO-1 or LAGE-1 Positive by IHC and/or RT-PCR

→

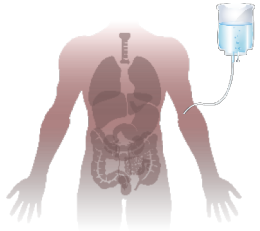


Study screening, Enrollment, Apheresis, Manufacturing

→

Multiple Myeloma, & Sarcoma Lymphodepletion
300 mg/m^2 cyclophosphamide + 30 mg/m^2 fludarabine
Days -5, -4, -3

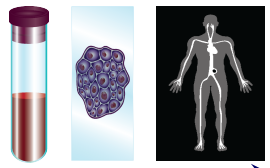
→



NYCE T cell Infusion
(1 × 10^8 total T cells/kg)
Day 0

→

Follow-up: Safety & Research
- Day 1
- Day 3
- Day 7
- Day 10
- Day 14
- Day 21
- Day 28 (Staging, Biopsy)
- Month 2
- Month 3 (Staging)
- Months 4, 5, 6
- Follow-up every 3 months until 2 years



Long-term Follow-up
Up to 15 years; every 6 months for up to 5 years annually thereafter for up to 10 additional years

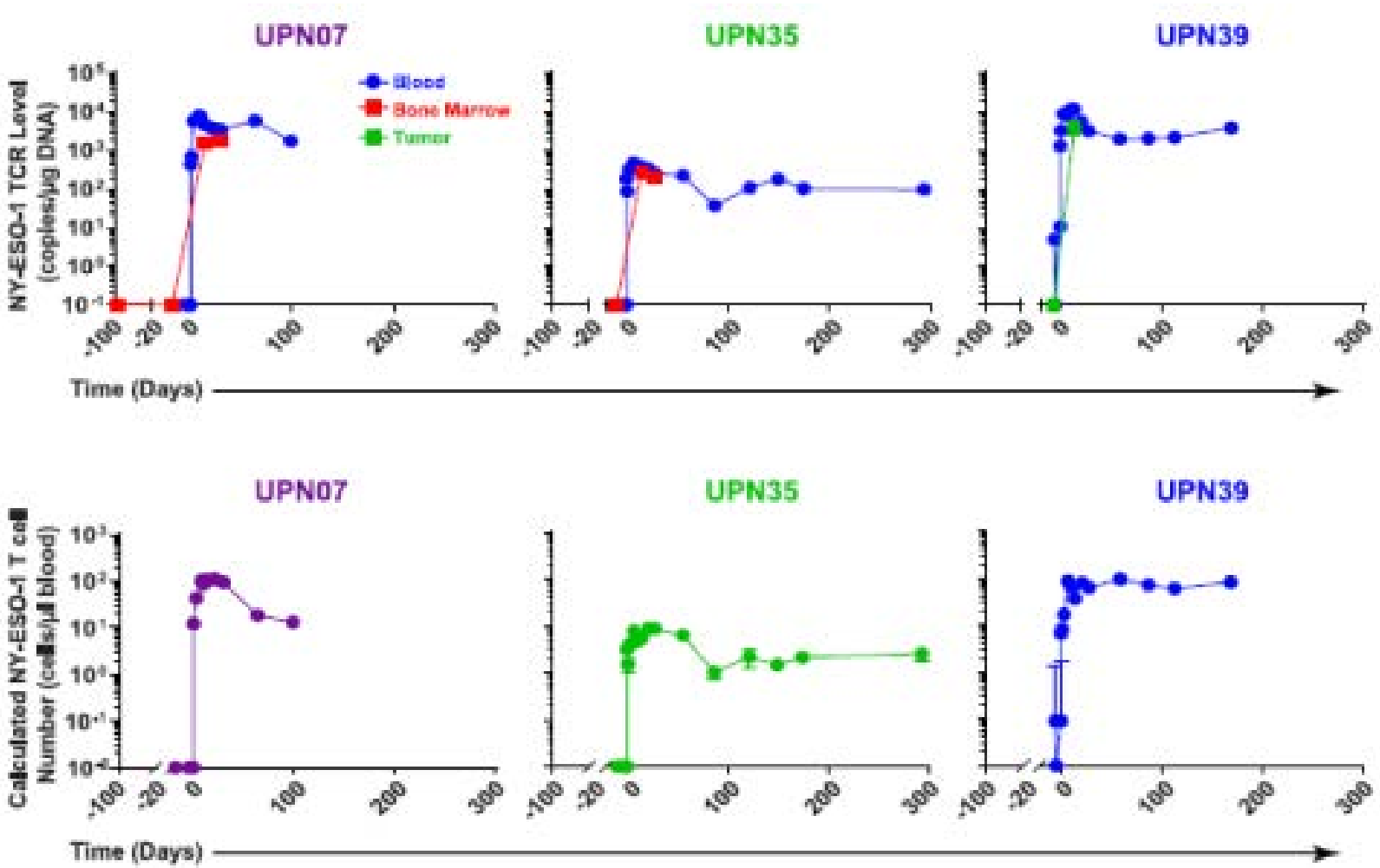
Time

Peripheral Blood *Tumor Biopsy* *Imaging* CRISPR/Cas9 *Lymphodepletion* *NYCE T cell Product*

Stadtmauer *et al, Science*, 2020

Courtesy of Edward A Stadtmauer, MD

Expansion, Persistence and Trafficking of NYCE T cells: *NY-ESO-1 TCR T cells (PCR)*



- There is rapid expansion and stable persistence of T cells expressing the NY-ESO-1 transgenic TCR as measured by qPCR in all 3 patients
  - The stable PK of NY-ESO-1 expressing T cells is very different from the PK of CAR T cells which tends to decrease more quickly

- Clear trafficking of T cells to the tumor
  - The levels of T cells expressing the NY-ESO-1 TCR in bone marrow and tumor is similar to blood

Stadtmauer *et al, Science,* 2020

Courtesy of Edward A Stadtmauer, MD

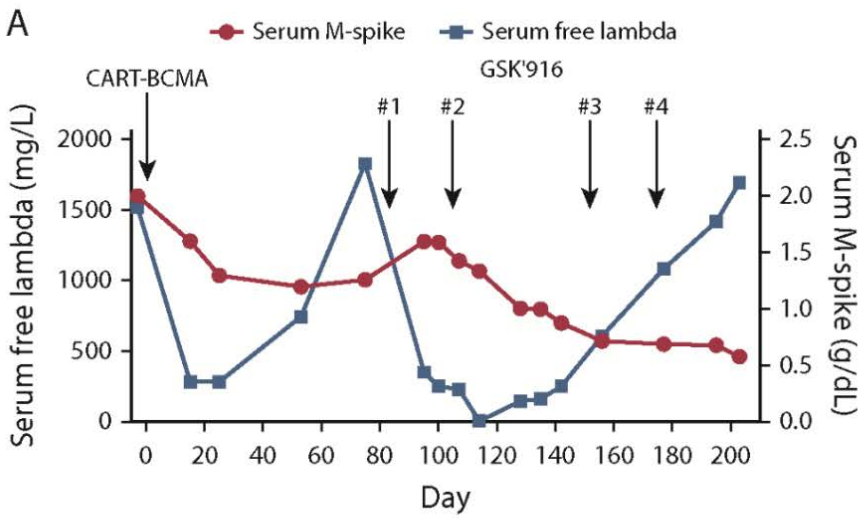
Conclusions (NYCE T Cells Study)

- Generation of multiplexed genetic engineering of autologous T cells expressing NY-ESO-1 TCR and CRISPR/Cas9 gene edited to eliminate endogenous TCR and PD-1 (NYCE T cells) is feasible
- Three patients with advanced cancer have safely received NYCE T cells after lymphodepletion
- Engineered T cells expand, survive and persist long-term in patients
- Best overall response achieved after NYCE T cell infusion to date is stable disease
- May allow for engineering of off-the-shelf allogeneic CAR T cells

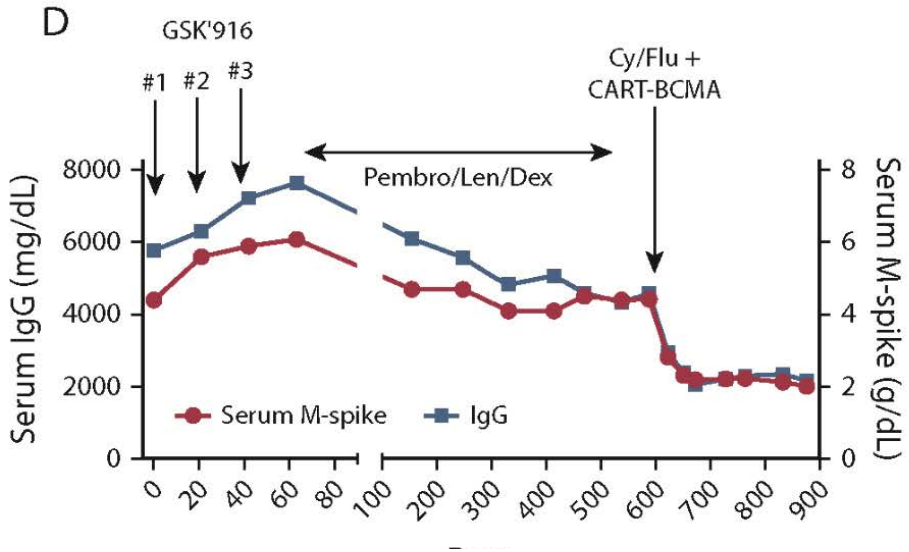
Courtesy of Edward A Stadtmauer, MD

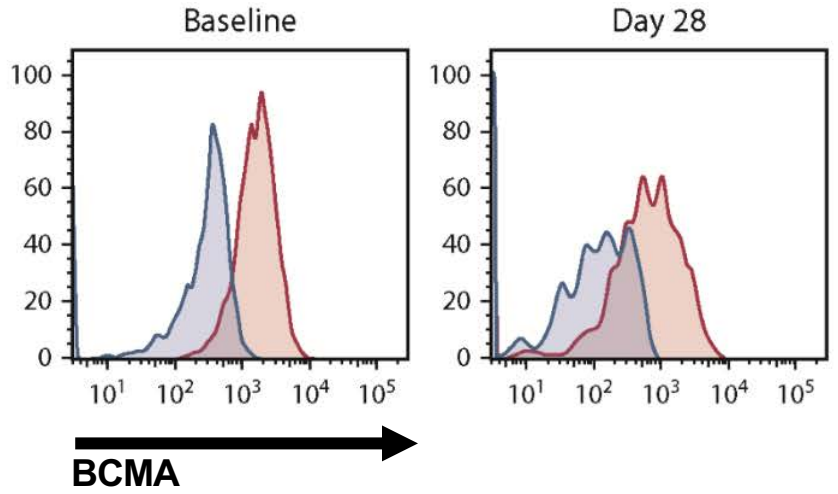
Serial treatment with BCMA-targeted therapies

Patient 1



Patient 2





Cohen et al, Blood Advances 2019

Courtesy of Edward A Stadtmauer, MD

What's Happening in 2020 for Engineered T cells for Myeloma?

- **Anti-BCMA CAR registration trials in rel/ref MM**
  - Not perfect, still lots of relapses within 1 year, but remarkable responses in R/R MM without other options
  - Ongoing ph 1/2 for next-gen CAR products

- **CAR T cells against CD38, SLAMF7 (CS1), GPRC5D, NY-ESO-1**
  - These are all reasonable targets, but much more limited experience

- **Anti-BCMA CAR trials for less-heavily treated patients**
  - 1-3 priors
  - Post-induction in hi risk
    - CART-BCMA +/- CART-19
  - Post-autoSCT
    - ASCT + CAR T in High Risk or Poor Response

- **Anti-BCMA CAR combo trials**
  - Other CAR T cells, IMiDs, checkpoint inhibitors

- **Gene-edited T cells**
  - "Off-the-shelf" allogeneic CAR T cells
  - PD-1 deficient, endogenous TCR edited T cells (*Science* 2020)

Courtesy of Edward A Stadtmauer, MD

Case #1 CAR-T Related CRS

- 66-year-old man with an 11-year history of IgG kappa multiple myeloma.
- VTD → VRD, stem cell harvest, HD Melphalan and stem cell transplant → revlimid maintenance therapy x 5 years.
- PD → radiation to T2 and S4, → RVD and biaxin, → CAR/REV/DEX → CYBOR → one cycle of VD-PACE → CAR/POM/CY/DEX → ELO/POM/DEX → filanesib clinical trial → pomalidomide and decadron, with relatively stable disease
- Hgb 13.8, WBC 5.3, Plt 146,000, ANC of 2300, ALC of 1700, Creatinine 1.44, IgA 43, IgG 2292, IgM 20, Kappa 63, Lambda 11.5, Ratio 5.5, SPEP 1.7
- Enrolled on BCMA CAR-T protocol

Courtesy of Edward A Stadtmauer, MD

Case # 1 CAR-T Patient cont.

- Steady state T-cell harvest and during manufacturing continued pomalidomide and dexamethasone. As per protocol, he received no lymphodepleting therapy. He then received the CAR T infusion in planned 3 daily doses of 10%, 30% and 60% total dose. He successfully received as an outpatient the first 2 doses.
- D+3 (11/5/15) he was admitted, with fever and hypotension. He did not receive Day 3 infusion.
- He was begun on empiric antibiotics. Chest X-ray showed interval development of bilateral patchy opacities. He gradually improved and lost his oxygen requirement with diuretics.
- Initially he had low ferritin, but by D+8, his ferritin had peaked to 4453 and CRP 5.3. He developed further fever and hypotension and received tocilizumab. When he developed worsening hypoxia and persistent fevers, he received a second dose a day later. He had worsening renal insufficiency. His creatinine peaked 11/10/15 at 2.85. He did have some mild elevation of his AST and ALT 11/11/10, most consistent with some mild toci related reaction. He symptomatically improved substantially and was discharged D+12.
- D+28 No fevers, shortness of breath or CRS
- Hgb 12.3, WBC 6.0 platelet 151,000. A normal differential. All other serum chemistries are within normal limits. His CRP is normal at 0.7. A ferritin is WNL
- IgA <2, IgG 765, IgM <10. He has immune paresis. An SPEP shows an M-spike of 0.6 (significantly decreased from 1.7 prior to treatment)

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Case # 1 CAR-T Patient cont.

- D + 60 No fevers, no neurotoxicity or CRS and is feeling great. Hgb 13, WBC 9.6, platelets 225,000. Normal differential. Serum chemistries WNL. Ferritin that is down to 27 CRP is 1.3. SPEP 0.4 g/dl. BMBx biopsy which shows a 55% cellular marrow with no evidence of myeloma
- +11 mos, Hgb 13.4, WBC 7.4, platelet 174,000. ANC of 4,200. IgA 47, IgG 699, IgM 89. Kappa 10.2, Lambda 11.2, Ratio 0.91. SPEP is negative
- Did well untill biochemical progression +32 months. +35 months received Flu-Cy lymphodepleting therapy followed by infusion of the remaining 60% dose of BCMA directed CAR T-cell infusion.
- The patient required admission D+5 for cough and fatigue with fever. Evaluation revealed a new oxygen requirement, mild tachycardia, and borderline hypotension. He received intravenous fluids and admitted for further evaluation, which included a chest x-ray, which showed bibasilar infiltrates. His ferritin peaked at 94, and a CRP peaked at 14.3. He was felt to have a grade 1 CRS and a pneumonia. He became afebrile and was discharged D+8.
- D+28 clear signs of continued progression.

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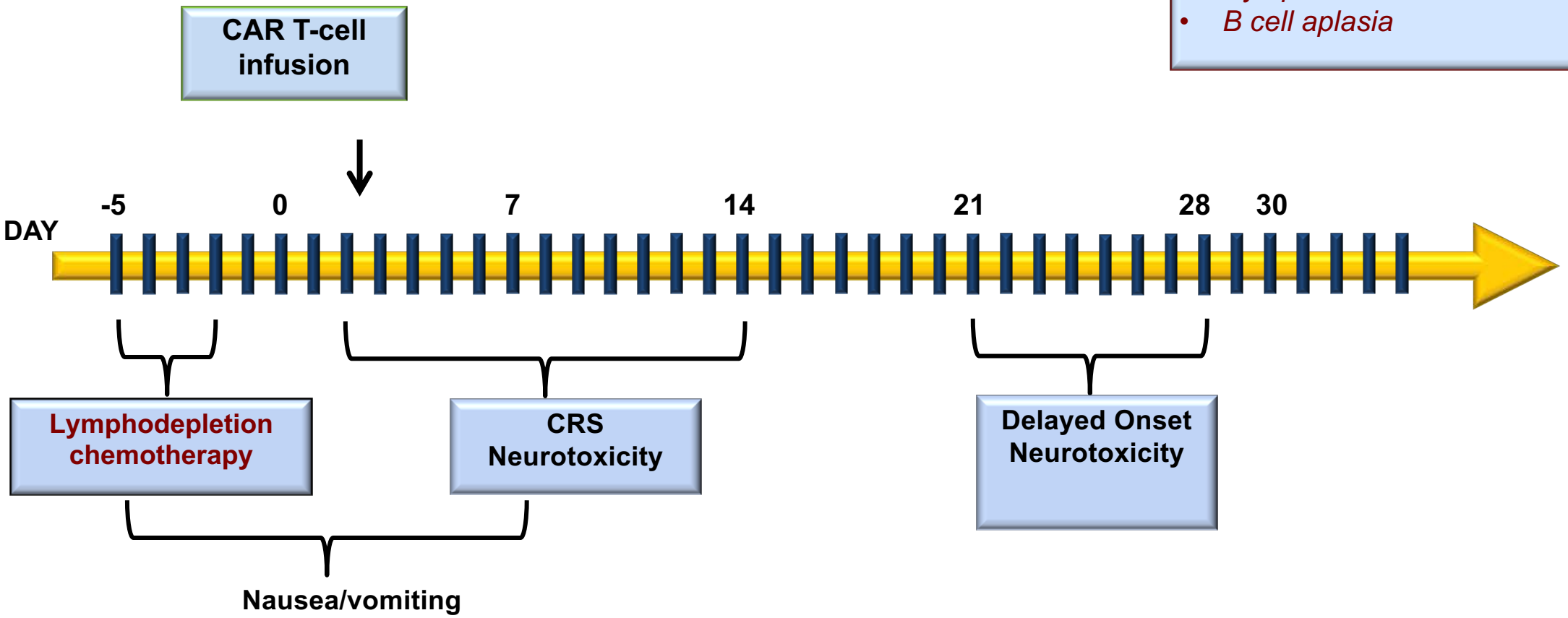
CAR-T Toxicities Timeline

Adverse Events > Day 30:
- *Infection*
- *Cytopenias*
- *B cell aplasia*



Brudno JN, et al. Blood. 2016;127:3321-30. Neelapu SS, et al. Nat Rev Clin Oncol. 2018; 15:47-62.

Courtesy of Edward A Stadtmauer, MD

CAR T-Cell Toxicity/Treatments

Cytokine Release Syndrome

Cause:
Activation/expansion of CAR T-cells increased levels of cytokines (IL-6, IL-15, INF-γ, GM-CSF, others)

Onset: variable; 1 to 3 days CD28; 3 to 5 days 4-1BB

Duration: 3 to 5 days

Risk: variable up to 30% grade 3

- Disease burden
- Peak CAR T-cell levels
- Pre-treatment and peak cytokine levels

Neurotoxicity

Cause:
Mechanism less understood

- High CSF: blood cytokine levels
- CAR-positive and CAR-negative T-cells in CSF

Onset: 5 to 7 days; later than CRS

Duration: 5 to 10 days

- Fully reversible except in cases of fatal cerebral edema

Risk: variable, up to 40% grade 3

- Disease burden
- Peak CAR T-cell levels
- Early and high-grade CRS
- Pre-treatment and peak cytokine levels
- DIC

- Santomasso B, et al. *Am Soc Clin Oncol Educ Book.* 2019;39:433-444.

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ASTCT Consensus Grading of CRS

CRS Parameter*	Grade 1	Grade 2	Grade 3	Grade 4
Fever#†	Temperature ≥38°C	Temperature ≥38°C	Temperature ≥38°C	Temperature ≥38°C
		With		
Hypotension#	None	Not requiring vasopressors	Requiring one vasopressor with or without vasopressin	Requiring multiple vasopressors (excluding vasopressin)
		And/ or‡		
Hypoxia#	None	Requiring low-flow nasal cannula^ or blow-by	Requiring high-flow nasal cannula^, facemask, non-rebreather mask, or Venturi mask	Requiring positive pressure (eg: CPAP, BiPAP, intubation and mechanical ventilation)

#Not attributable to any other cause

†In patients who have CRS then receive tocilizumab or steroids, fever is no longer required to grade subsequent CRS severity

‡CRS grade is determined by the more severe event

^Low-flow nasal cannula is ≤ 6 L/min and high-flow nasal cannula is > 6 L/min

*Organ toxicities associated with CRS may be graded according to CTCAE v5.0 but they do not influence CRS grading

Lee et al. *Biol Blood Marrow Transplant,* 2019 Apr;25 (4):625-638

Courtesy of Edward A Stadtmauer, MD

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Management of CRS

ASTCT CRS Grade	Management
Grade 1	• Antipyretics and IV hydration • Diagnostic work-up to rule out infection • Consider growth factors and antibiotics if neutropenic
Grade 2	• Supportive care as in grade 1 • IV fluid boluses and/or supplemental oxygen • Tocilizumab +/- dexamethasone or its equivalent of methylprednisolone
Grade 3	• Supportive care as in grade 1 • Consider monitoring in ICU • Vasopressor support and/or supplemental oxygen • Tocilizumab + dexamethasone 10 mg to 20 mg IV every 6 h or its equivalent of methylprednisolone
Grade 4	• Supportive care as in grade 1 • Monitoring in ICU • Vasopressor support and/or supplemental oxygen via positive pressure ventilation • Tocilizumab + methylprednisolone 1000 mg/day

◆ Neelapu SS, et al. *Nat Rev Clin Oncol.* 2018;15:47-62; Neelapu SS. *Hematol Oncol.* 2019;37:48-52.

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Case # 2 CAR T Related Neurotoxicity

- 55-year-old man with a heavily treated IgA lambda MM manifested by bone marrow plasmacytosis, lytic bone lesions, serum and urine monoclonal protein and an 11;14 translocation
- VRD → HD melphalan and autologous stem cell transplant → VRd maintenance therapy for 2 years → VGPR
- Progressed and received following regimens: Cy-Pom-Dex → VPD → bendamustine, daratumumab → Dara-Rev-Dex → Car-Pom-Pred with biochemical progression.
- Enrolled on a BCMA directed CAR T protocol, underwent steady-state harvest. Did not require bridging therapy. Successful manufacturing, fludarabine/cyclophosphamide lymphodepleting therapy followed by infusion of target dose of CAR T cells 5/6/19.

Case # 2 Continues

- On D+ 2 had fevers to 103, rigors, hypotension, desaturations to 83%, and altered mental status of lethargy. Ferritin slightly increased to 480 with CRP significantly increased to 13.
- Empirically started on cefepime and was given tocilizumab x1 dose (CRS was thought to be more likely etiology of his symptoms).
- Transferred to the MICU for worsening mental status. Persistent profound agitated delirium. Neuro workup included LP, CT and MRI which were unrevealing for a source of his agitation and as such his agitation was thought to be due to neurotoxicity.
- Started on dexamethasone 10 mg q6h. Anakinra (D+4 - D+11) for CRS treatment and heavily
- Intubated for airway protection (D+3 - D+12)

Case # 2 Continues

- D+12
  - Hgb 10.4, WBC 20.4, platelet 99,000
  - Ferritin of 184, CRP of 0.30
  - SPEP shows an M-spike of 2.1 g/dl (decreased from 2.8) IgA 1,856 (decreases from 2,416).
  - CT scan of his head → no evidence of an acute process, and numerous bone lesions in his skull.
- D+22 Neurologic symptoms resolved. Performance status improved rapidly. Discharged D +28
- D+60 IgA 323
- PD 11.9 months later (IgA 667) started Car-Pom-Dex →NR
- Enrolled on a BCMA bispecific Ab protocol. Well tolerated without neurotoxicity. PR.
- May 2020 IgA 287 → high-dose melphalan 200 mg/m^2 and autologous transplantation. D+ 75 IgA 179
- +4 months from his salvage stem-cell transplant in remission and started on maintenance Elo-Rev-Dex

ASTCT Consensus Grading of ICANS for Adults

(IEC-Associated Neurotoxicity Syndrome)

Neurotoxicity Domain‡	Grade 1	Grade 2	Grade 3	Grade 4
ICE Score	7-9	3-6	0-2	0 (patient is unarousable and unable to perform ICE)
Depressed level of consciousness	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse or stupor or coma
Seizure	N/A	N/A	Any clinical seizure focal or generalized that resolves rapidly ; or Non-convulsive seizures on EEG that resolve with intervention	Life-threatening prolonged seizure (>5 min); or Repetitive clinical or electrical seizures without return to baseline in between
Motor findings	N/A	N/A	N/A	Deep focal motor weakness such as hemiparesis or paraparesis
Raised intracranial pressure / Cerebral edema	N/A	N/A	Focal/local edema on neuroimaging#	Diffuse cerebral edema on neuroimaging; Decerebrate or decorticate posturing; or Cranial nerve VI palsy; or Papilledema; or Cushing's triad

‡ICANS grade is determined by the most severe event (ICE score, level of consciousness, seizure, motor findings, raised ICP/cerebral edema) not attributable to any other cause

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