CAR-T: una nuova frontiera terapeutica nel mieloma multiplo

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T-cells and MM and GVM effect

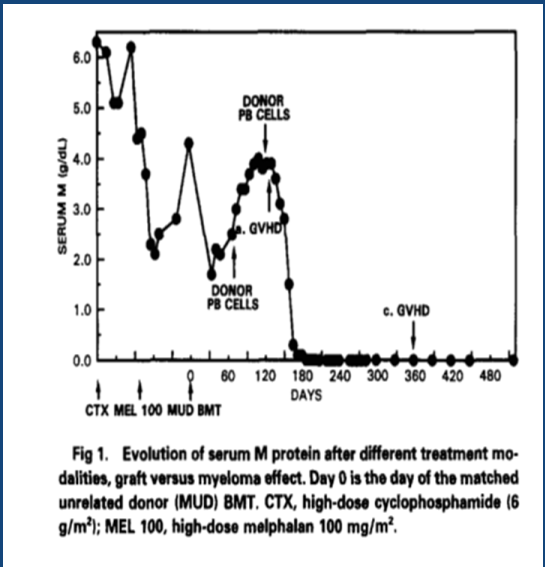


Fig 1. Evolution of serum M protein after different treatment modalities, graft versus myeloma effect. Day 0 is the day of the matched unrelated donor (MUD) BMT. CTX, high-dose cyclophosphamide (6 g/m²); MEL 100, high-dose melphalan 100 mg/m².

Date	Procedure	Clinical variable	
		Serum M protein (g/L)	Bone marrow plasma cells (%)*
April, 1992	BMT	32	55
August, 1992	Evaluation	Absent†	8‡
December, 1992	Evaluation	4	ND
July, 1993	Evaluation	13	15
October, 1993	Infusions	20	40
January, 1994	Evaluation	8	2‡
May, 1994	Evaluation	Absent†	<1§
October, 1994	Evaluation	Absent†	<1§
March, 1995	Evaluation	Absent†	<1§
September, 1995	Evaluation	Absent†	<1§

*In bilateral biopsy samples and aspirates. †Analysed by immunofixation in serum and in 10 × concentrated urine. ‡Merely IgA/lambda-positive plasma cells. §Polyclonal plasma cells (normal κ/λ ratio within IgA). ND=not done

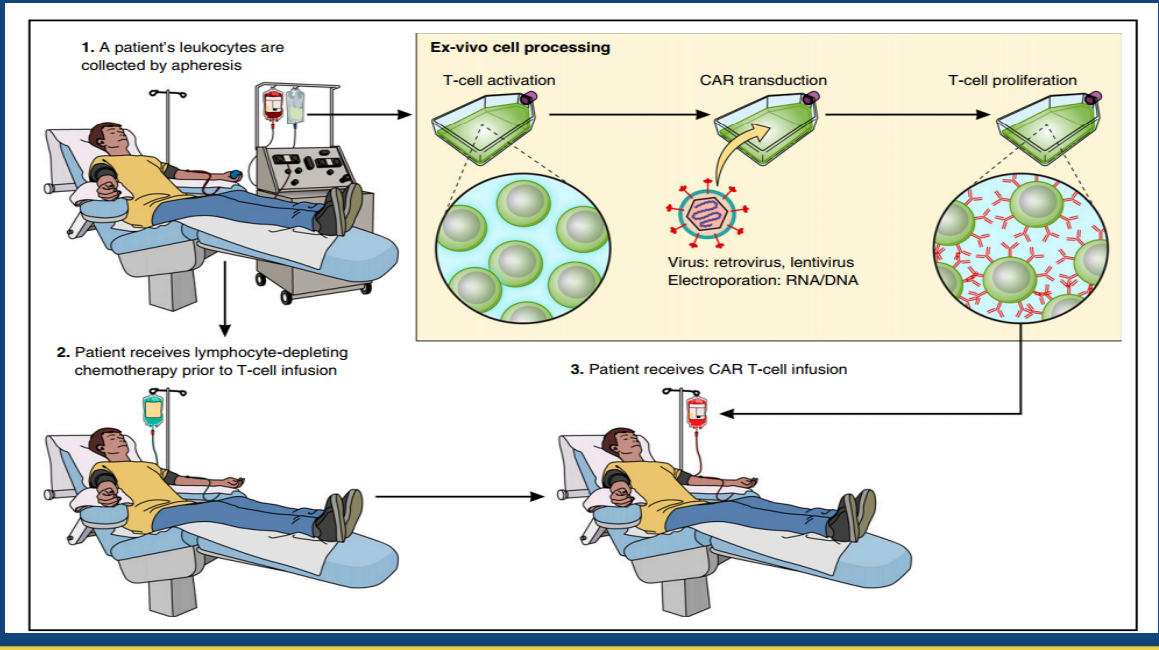
Table 1: **Response of the multiple myeloma (IgA/lambda) in patient 1 before and after donor leucocyte infusions**

- Cytotoxic T lymphocytes (CTL) can mediate antitumoral immunity in an HLA- dependent way
- The presence of TILs represents a positive prognostic factor; however tumor induces **T cell exhaustion**
- Long-term remissions with allogeneic SCT / responses with donor lymphocyte infusions suggest graft-versus-myeloma effect mediated by donor T-cells at cost of GVHD, infections and TRM
- New options of T-cell-mediated immunotherapy are needed

Tricot Blood 1996 1196; Verdonck Lancet 1996 800; Lokhorst Blood 2004 4362; Van De Donk BMT 2006 1135

Novel immunotherapies in MM: adoptive T-cell therapy

- Expansion of tumor-infiltrating lymphocytes (TILs) / BM-infiltrating lymphocytes (MILs)
- Immune cells engineered to possess high-affinity receptors specific for particular antigens expressed on tumor cells
- Gene transfer of chimeric antigen receptor by lentiviral or retroviral trasduction

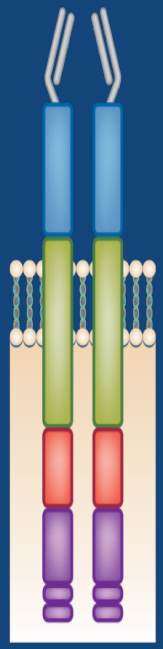


PRESENTED A

June Sci Trans Med 2015; Noonan Sci Transl Med 2015; Linette Blood 2013; Rapoport Nat Med 2015; Ghosh Leuk Lymph 2017

CAR-T (chimeric antigen receptor-T cells)
Structure and functions

- 2 main components:
  - **Extracellular domain** that recognizes a cell-surface antigen specific for the target
  - **Intracellular signalling domain** that initiates signal transduction necessary for T cell activation upon antigen binding



-**Extracellular domain** that can bind specifically to a target molecule expressed on the tumor cell surface:
-Single-chain antibody or ligand of cell surface receptor
-Recognize tumor-associated antigens in a non-MHC-specific manner
-Molecular **hinge region** derived from CD8 provides flexibility to allow reorientation to bind antigen

-**Costimulatory domain (II and III generation CAR-T)**:
CD28 or 4-1BB
More robust cytokine production and enhanced cytolytic activity of CAR-Ts

-**T-cell activation domain**: CD3ζ

- **Antigen recognition** via extracellular domain and **HLA-independent activation of T cells** with powerful cytotoxic and memory functions via intracellular domain
- **Remodelling of tumor suppressive microenvironment**

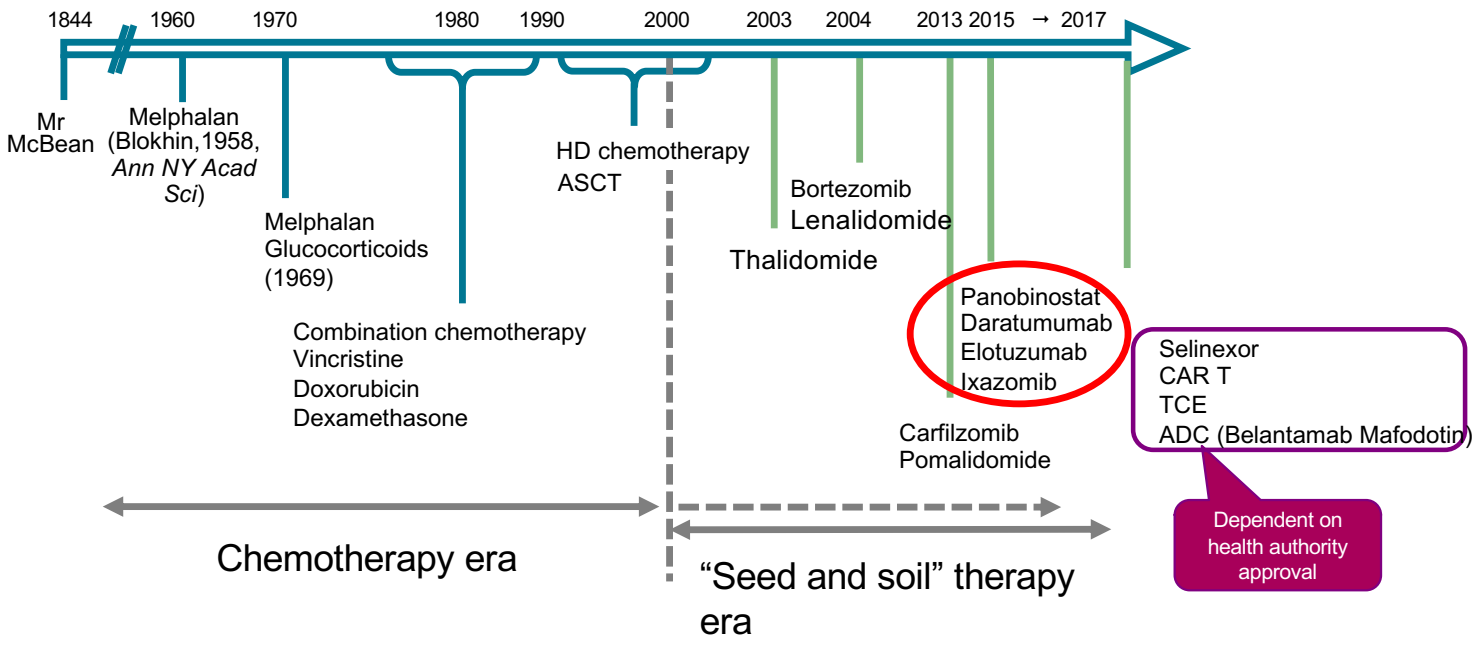
Ye B et al, Molecular cancer 2018; 15;17(1):32

Adapted from Kershaw MH et al. Nat rev Cancer 2013

PRESENTED A

- CAR, chimeric antigen receptor; MHC, major histocompatibility complex; MM, multiple myeloma; NK, natural killer.

Do we need new treatments for patients with MM?



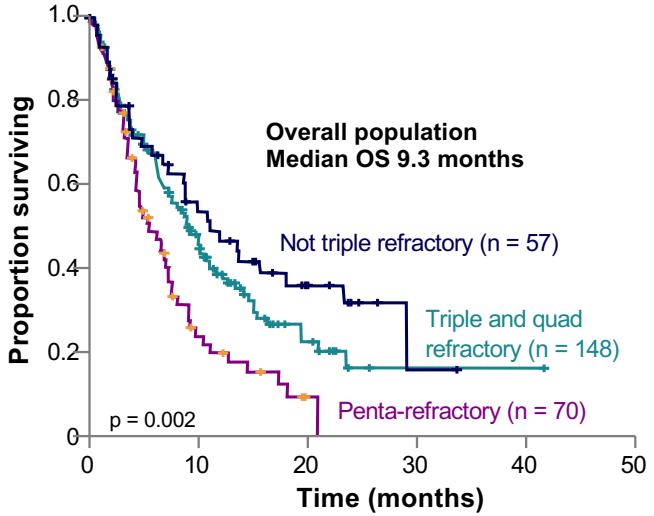
ADC, antibody drug conjugate; ASCT, autologous stem cell transplantation; CAR T, chimeric antigen receptor T cell; HD, high-dose; MM, multiple myeloma; TCE, T-cell engager.

Adapted from Rodríguez Otero P, et al. Haematologica. 2017;102:423-32.

MAMMOTH study: suboptimal outcomes in patients refractory to anti-CD38 monoclonal antibodies

275 patients refractory to anti-CD38 mAbs

	Median OS months	
Not triple refractory	11.2	Refractory to 1 CD38 mAb, and not both PI and IMiD
Triple and quad refractory	9.2	Refractory to 1 CD38 mAb + 1 PI + 1 or 2 IMiD compounds, etc.
Penta refractory	5.6	Refractory to 1 CD38 mAb + 2 PIs + 2 IMiD compounds
Overall cohort	8.6	



249 patients received further treatment
ORR 31%
mPFS 3.4 months
mOS 9.3 months

Gandhi UH et al., *Leukemia*. 2019

First CAR-T in MM: CD-19

Rational: a minor component of the MM clone with drug-resistant, disease-propagating properties has a B-cell phenotype (99% PCs negative for CD19)

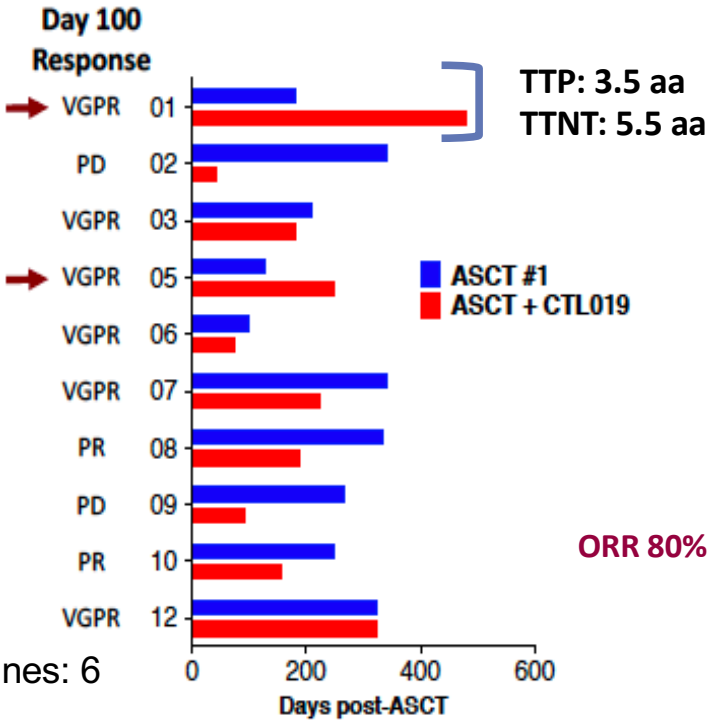
Study Design and Patient Characteristics

Eligibility Criteria
- Multiple Myeloma Progression within one year of prior ASCT
- Age <70
- Fit for 2nd ASCT

Salvage High-dose Melphalan + Auto-SCT → 12-14 DAYS → CTL019 5 x 10^7 cells → FOLLOW FOR PFS

Primary Endpoints
- Safety (CRS, neurotoxicity)
- Feasibility (manufacturing success)

Secondary Endpoints
- CTL019 engraftment and B cell aplasia
- Day 42 and day 100 response
- Progression-free survival (vs. last ASCT)
- Correlation of response to CD19 expression

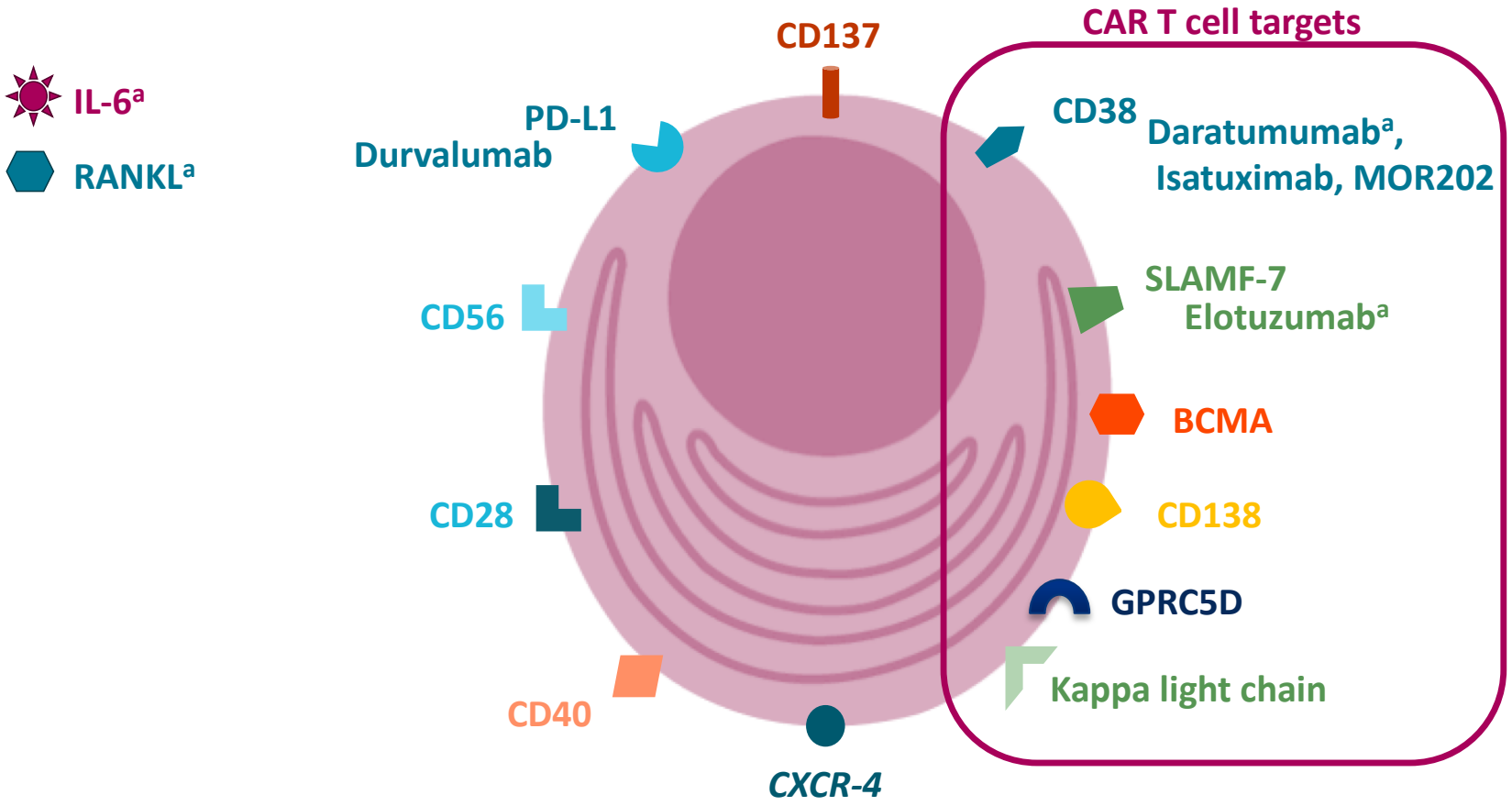


•**12** pts enrolled → **10 pts** treated. Median of prior lines: 6

Garfall AL, et al. N Engl J Med 2015; 373:1040-1047

Garfall AL, et al. JCI Insight, 2018; 3(8):e120505

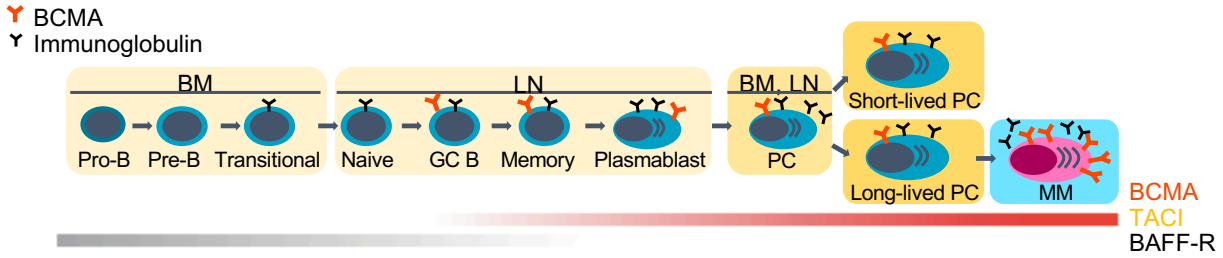
Surface antigens on clonal plasma cells

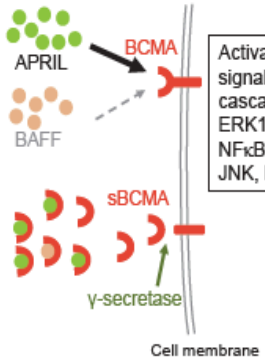


[a]Approved by the FDA and EMA.
BCMA, B-cell maturation antigen; IL-6, interleukin-6; PD-L1, programmed cell death-ligand; RANKL, receptor activator of nuclear factor kappa-B ligand.

Bhatnagar V, et al. Oncologist. 2017;22:1347-53. Gormley NJ, et al. Clin Cancer Res. 2017;23:6759-63. Jelinek T, et al. Front Immunol. 2018;9:2431. Moreno L, et al. Clin Cancer Res. 2019;epub. Raab MS, et al. Blood. 2016;128:1152. Rawstron AC, et al. Haematologica. 2008;93:431-8. Smith EL et al. Sci Tras Med 2019; 11(485).

BCMA: a good target





- BCMA is an antigen expressed specifically on PCs and myeloma cells
  - Member of TNFR superfamily. Binds 2 ligands (BAFF e APRIL)
  - higher expression in myeloma cells than normal PCs
  - key role in B-cell maturation and differentiation
  - promotes myeloma cell growth, chemoresistance, and immunosuppression in the BM microenvironment
- Expression of BCMA increases as the disease progresses from MGUS to advanced myeloma

APRIL, a proliferation-inducing ligand; BAFF-R, B-cell activating factor receptor; GC, germinal centre; LN, lymph node; MGUS, monoclonal gammopathy of unknown significance; sBCMA, soluble BCMA; TACI, transmembrane activator and CAML interactor.

Cho SF, et al. Front Immunol. 2018;9:1821. Moreaux J, et al. Blood. 2004;103:3148-57. Sanchez E, et al. Br J Haematol. 2012;158:727-38.

BCMA CAR T cells in MM

46 clinical trials with BCMA CAR T in clinicaltrials.gov

Trial site	ScFv	Co-s domain	Gene transfer	Conditioning therapy	T-cell dose CAR+ T cells/kg
NCI[1,2]	11D5-3	**CD28**	**ϒ- retroviral**	Cy 300 mg/m^2 × 3 + Flu 30 mg/m^2 × 3	0.3–9.0 × 10^6
[redacted]	NR, murine	4-1BB	Lentiviral	Cy 300 mg/m^2 × 3 + Flu 30 mg/m^2 × 3	50, 150, 450, and 800 × 10^6
University of Pennsylvania[4]	NR, human	4-1BB	Lentiviral	**None or Cy 1.5 g/m^2**	10–50 × 10^6 or 100–500 × 10^6
[redacted]	NR, human	4-1BB	Lentiviral	**Cy 300 mg/m^2 × 3**	1.5–7.0 × 10^6
MSKCC[7,8]	NR, human	4-1BB	**ϒ- retroviral**	Cy 3000 mg/m^2 or Cy 300 mg/m^2 × 3 + Flu 30 mg/m^2 × 3	1, 150, 450, and 800 × 10^6
[redacted]	NR[a], human	4-1BB	Transposon	Cy 300 mg/m^2 × 3 + Flu 30 mg/m^2 × 3	0.75, 2, 6, 10, and 15 × 10^6

[a] Small human ibronectin domain.
Cy, cyclophosphamide; Flu, fludarabine.

1. Brudno JN, et al. J Clin Oncol. 2018;36:2267-80. 2. Ali SA, et al. Blood. 2016;128:1688-700. 3. Berdeja JG, et al. Blood. 2017;130:740. 4. Cohen AD, et al. Blood. 2017;130:505. 5. Aili H, et al. EHA abstract. 6. Fan FX, et al. J Clin Oncol. 2017;35:18. 7. Smith EL, et al. Blood. 2017;130:742. 8. Hermanson DL, et al. Blood. 2016. 9. Gregory T, et al. Blood. 2018;132:1012. Presented at ASH 2018.

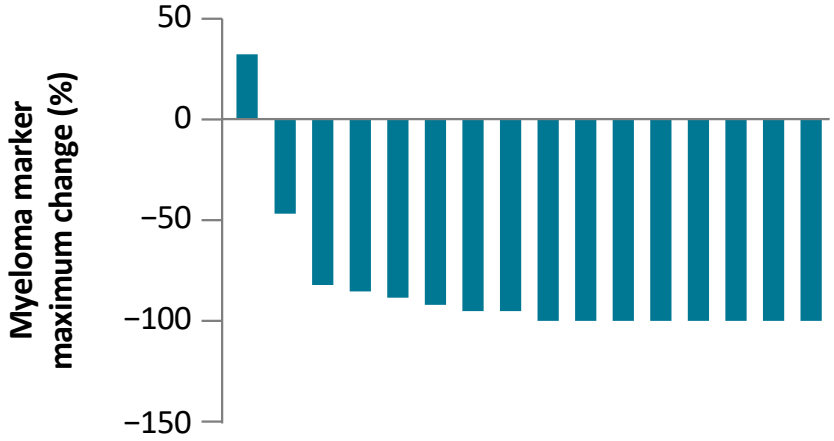
BCMA-CAR T cells in MM
Phase I study NCI: efficacy (N = 16)

Study Design:

- **Cy** 300mg/mq + **Flu** 30mg/mq gg -5, -4, -3
- **Dose escalation: 0.3 x 10^6** CART cells/kg → **1 x 10^6 → 3 x 10^6 → 9 x 10^6**

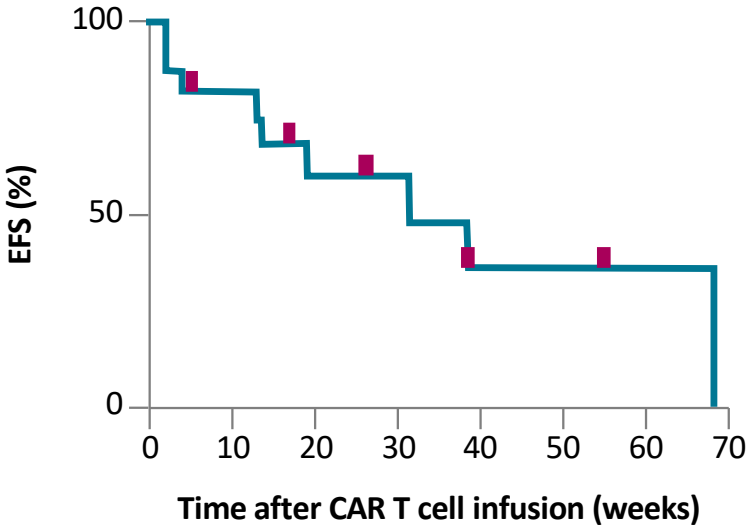
ORR: 13/16 (81%) at 9 × 10^6 cells/kg dose level

11/14 (79%) evaluable pts at 9 × 10^6 cells/kg achieved MRD-neg status



Median EFS = 31 weeks

(6 pts with ongoing response)



CRS minimal at lower doses but substantial at 9 × 10^6/kg

- 6 pts grade 3–4 CRS
- 10 pts grade 1–2 CRS
- 5/16 pts (31%) received tocilizumab
- 4/16 pts (25%) received steroids

Brudno JN, et al. J Clin Oncol. 2018;36:2267-80.

CAR-T cell therapy (and other T-cell redirected therapies): unique acute toxicities

- Cytokine release syndrome (CRS)
  - Inflammatory process related to exponential T cell proliferation and activation
  - Release of supra-physiological levels of pro-inflammatory cytokines (e.g, IL-6, INFγ, TNFα)
  - IL-6 believed to be central mediator
- Time to onset: expected in first 14 days (mostly first 7 days)
- Fever, hypotension, hypoxia, multi-organ failure
- Diagnosed based on clinical symptoms; CRP used as surrogate

- Encephalopathy/Neurological toxicity
  - Exact mechanism remains unclear but pathophysiology thought to include endothelial activation/dysfunction and microangiopathy
  - May occur together with CRS or independently (after CRS).
  - Time to onset: expected in first 14 days
  - Diminished attention, language disturbance, confusion, disorientation, and occasionally seizures/cerebral oedema , delirium

Citopenie persistenti/infezioni

Neelapu Nat Rev Clin Oncol 2018 Jan;15(1):47-62; Drent PloS One 2018

Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

https://doi.org/10.1016/j.bbmt.2018.12.758

ASBMT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells

Daniel W. Lee

The goal

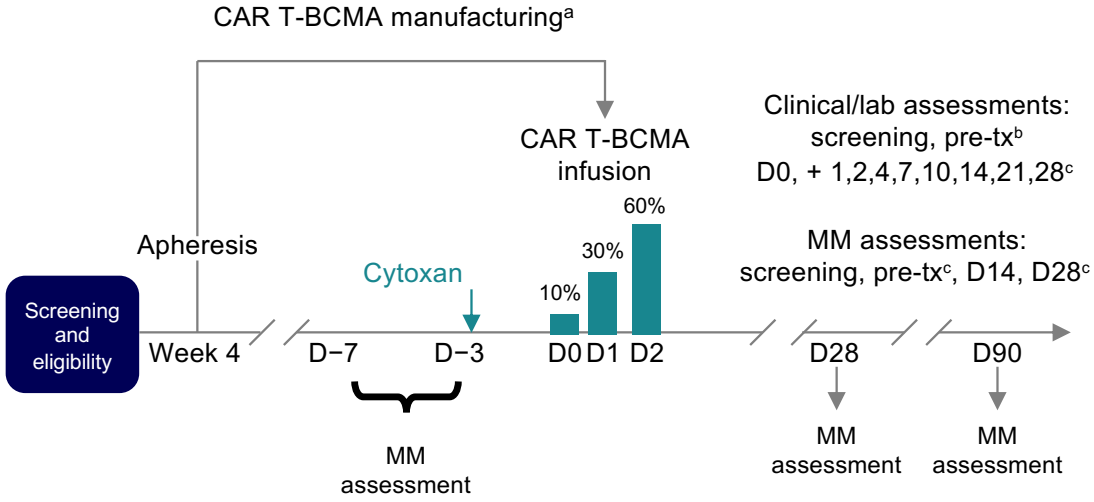
to provide a uniform consensus grading system for CRS and neurotoxicity associated with immune effector cell therapies, for use across clinical trials and in the post-approval clinical setting

Penn/Novartis BCMA CAR-T Phase I trial

- Lentiviral vector-based + 4-1BB co-stimulatory domain
- **Fully human** scFV fused to hinge and TM CD8

Inclusion criteria:

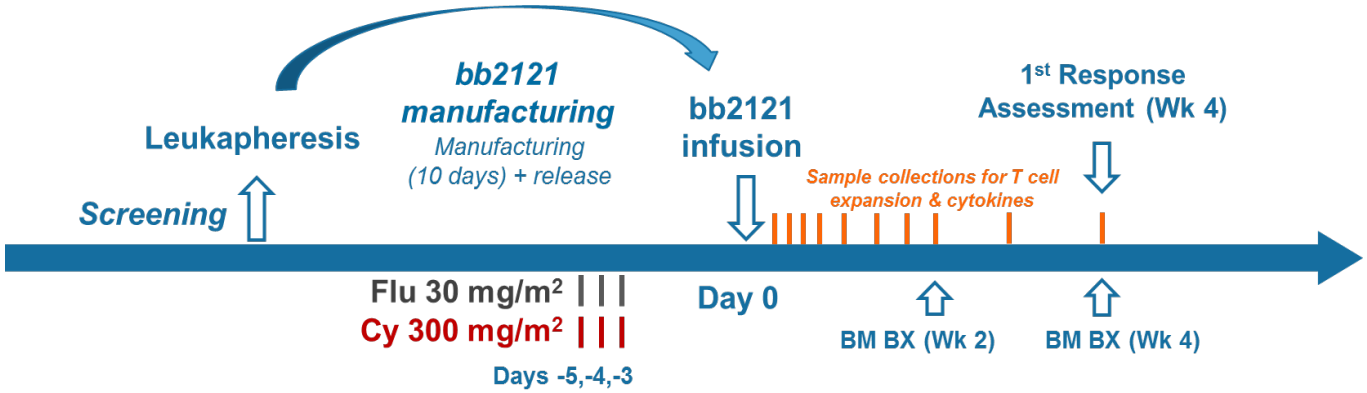
- RRMM with ≥ 3 prior lines of therapy (including PI and immunomodulatory drugs), or 2 prior regimens if double refractory **(median: 7 lines)**



	Cohort 1 (n = 9)	Cohort 2 (n = 5)	Cohort 3 (n = 11)
Treatment	1–5 × 10^8 CAR+ T cells	Cy 1.5 g/m^2 + 1–5 × 10^7 CAR+ T cells	Cy 1.5 g/m^2 + 1–5 × 10^8 CAR+ T cells
ORR, n (%)	4 (44)	1 (20)	7 (64)
mPFS, days	65	57	125

Cohen AD, et al. J Clin Invest. 2019;129:2210-21

BCMA CAR T cell
Ide-cel (bb2121) CRB-401 phase 1 trial



Dose escalation

≥ 50% BCMA expression

50×10^6 → 150×10^6 → 450×10^6 → 800×10^6

Inclusion criteria:

- RRMM with ≥ 3 prior lines of therapy (including PI and IMiD compounds), or double-refractory
- Measurable disease
- ≥ 50% BCMA expression
- Adequate organ function

Primary endpoint: safety (AEs, CRS, neurological toxic events)
Secondary endpoints: response rate and duration

Dose expansion

< 50% BCMA expression
≥ 50% BCMA expression
Dose range: $150–450 \times 10^6$ CAR+ cells

Inclusion criteria:

- No BCMA expression required
- **Previous exposure** to PI, IMiD compounds, and **daratumumab**
- Refractory to last line of therapy

AE, adverse event; RRMM, relapsed/refractory MM.

Raje N, et al. N Engl Med. 2019;380:1726-37.

Ide-cel CRB-401 phase 1 trial: baseline demographics and patient characteristics

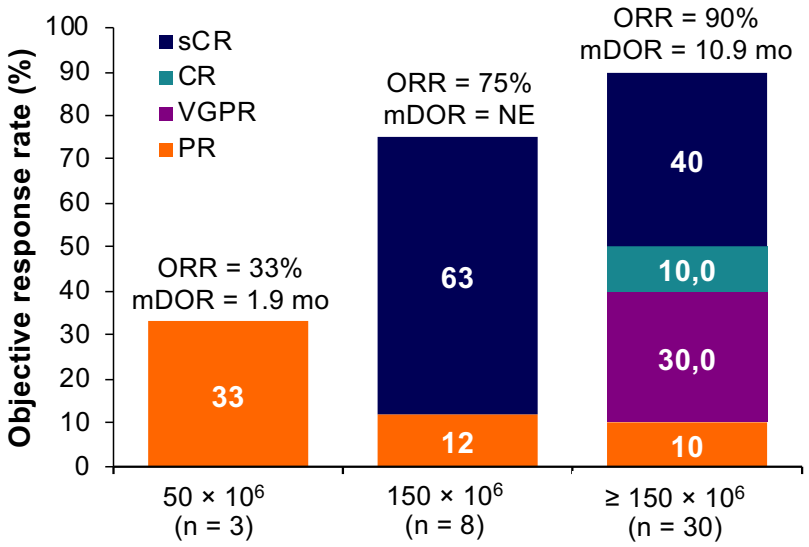
Characteristic	Dose escalation (N = 21)	Expansion (N = 12)
Prior anti-myeloma regimens, median (range)	7 (3–14)	8 (3–23)
Prior ASCT, no. (%)		
0	0	1 (8)
1	15 (71)	8 (67)
≥ 2	6 (29)	3 (25)

Characteristic	Dose escalation (N = 21)		Expansion (N = 12)	
	Exposed	Refractory	Exposed	Refractory
Prior therapies, n (%)				
Bortezomib	21 (100)	13 (62)	12 (100)	7 (58)
Carfilzomib	19 (91)	12 (57)	11 (92)	7 (58)
Lenalidomide	21 (100)	17 (81)	12 (100)	7 (58)
Pomalidomide	19 (91)	14 (67)	12 (100)	12 (100)
Daratumumab	15 (71)	9 (43)	12 (100)	9 (75)
Bortezomib / Lenalidomide	21 (100)	12 (57)	12 (100)	5 (42)
Bortezomib / Lenalidomide / Carfilzomib / Pomalidomide / Daratumumab	15 (71)	3 (14)	11 (92)	3 (25)

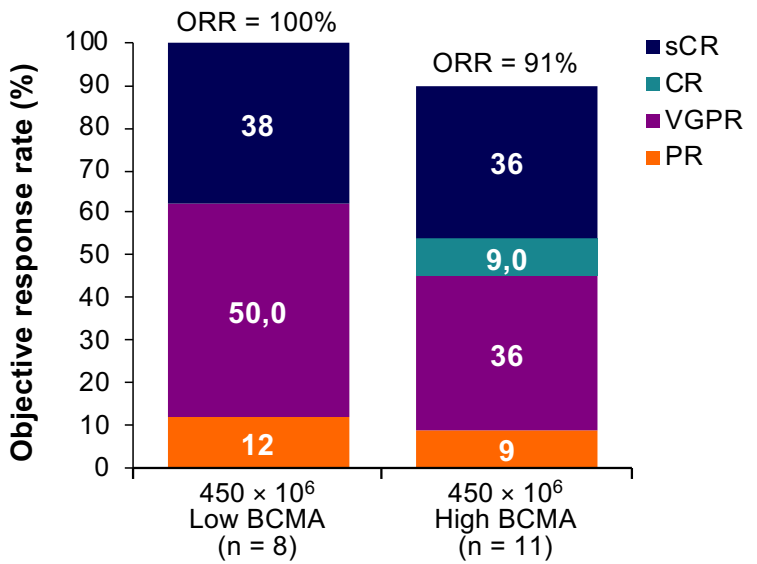
Raje N, et al. N Engl Med. 2019;380:1726-37.

Ide-cel CRB-401 phase 1 trial: tumour response is dose-related and independent of tumour BCMA expression

Tumour response by dose



Tumour response by BCMA expression[a]

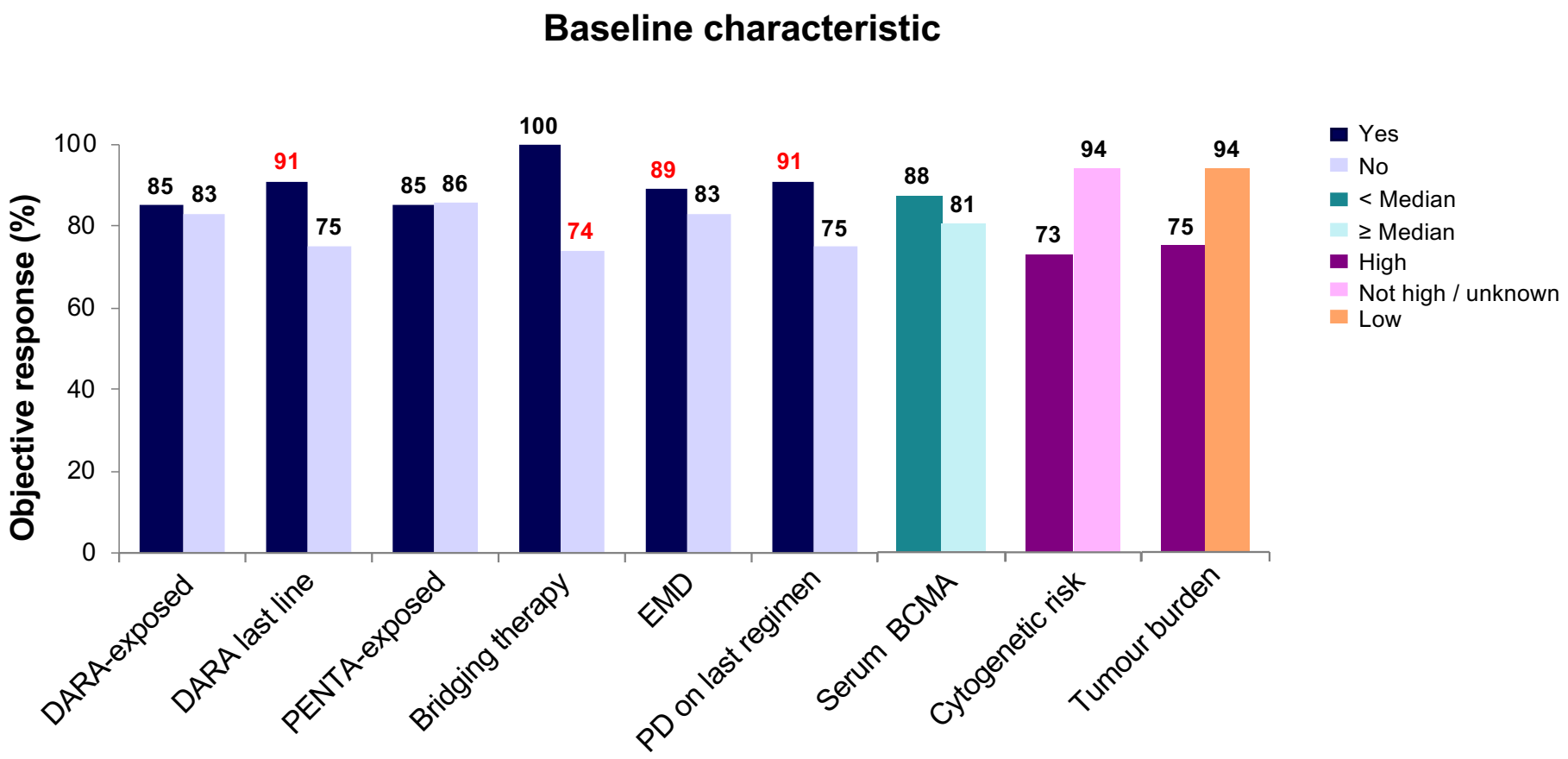


Response	50 × 10⁶	150 × 10⁶	450 × 10⁶	800 × 10⁶	Total
MRD-evaluable responders	0	4	11	1	16
MRD-neg[a]	0	4 (100)	11 (100)	1 (100)	16 (100)

mDOR, median duration of response; NE, not evaluable.

Raje N, et al. N Engl Med. 2019;380:1726-37.

Ide-cel CRB-401 phase 1 trial: tumour response by baseline characteristics



DARA, daratumumab; EMD, extramedullary disease; PD, progressive disease.

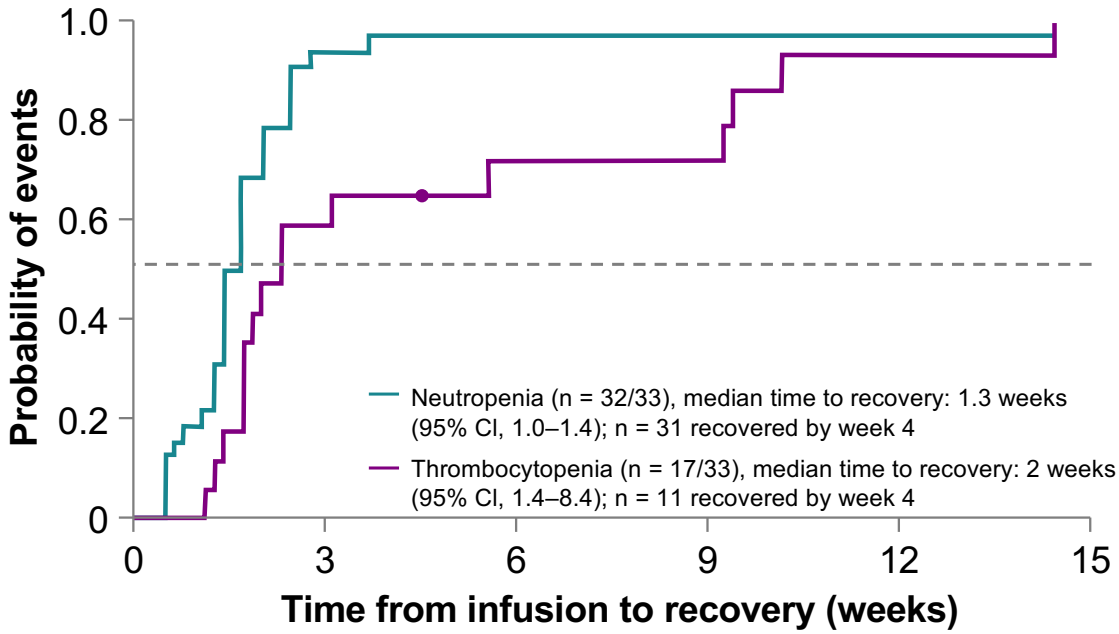
Raje N, et al. N Engl Med. 2019;380:1726-37.

Ide-cel CRB-401 phase 1 trial: AEs of special interest

CAR T cell therapy TEAEs
All infused patients (N = 33)

TEAE, n (%)	Any Grade	Grade 3	Grade 4
CRS	25 (76)	2 (6)	0
Neurological toxic effect[a]	14 (42)	0	1 (3)[b]
Neutropenia	28 (85)	2 (6)	26 (79)
Thrombocytopenia	19 (58)	5 (15)	10 (30)
Anaemia	19 (58)	15 (45)	0
Infection	12 (36)	2 (6)	0

Time to recovery of grade 3/4 cytopenia[c]



[a] Events occurring in first 90 days and including dizziness, bradyphrenia, brain oedema, somnolence, confusional state, nystagnmus, insomnia, memory impairment, neurotoxicity, lethargy, tremor and hallucination. [b] Patient with high tumour burden; neurological effect resolved within a month. [c] Includes patients with grade 3/4 cytopenia on or before month 1 are included.
Median and 95% CI from Kaplan–Meier estimate. CI, confidence interval; TEAE, treatment-emergent adverse event.

Raje N, et al. N Engl Med. 2019;380:1726-37.

Cytokine release syndrome and neurotoxicity of bb2121 compared with anti-CD19 CAR T

	bb2121 CRB 401	Axi-cel ZUMA-1	Tisa-cel JULIET
Target	BCMA	CD19	CD19
Co-stimulatory domain	4-1BB	CD28	4-1BB
Grade 3-4 cytokine release syndrome	6%	13%	22%
Grade 3-4 neurotoxicity	3%	28%	12%

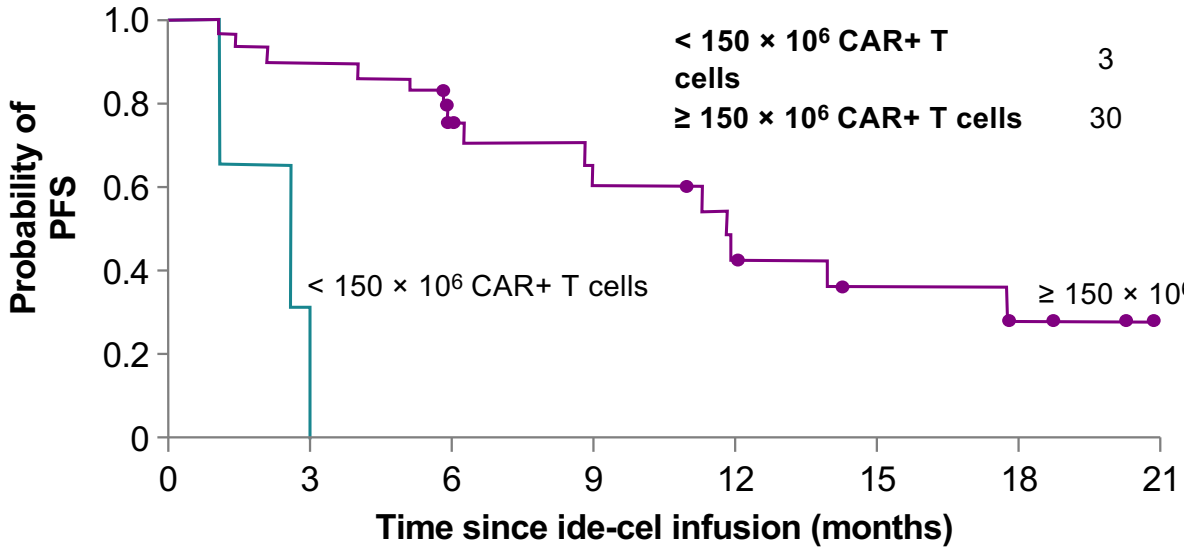
n.b. KITE-585, anti-BCMA CAR T using CD28, no longer in development

- **Relationship tumor burden-CRS risk**
- **Possible but not sure relationship CAR-T dose-CRS risk**

Raje N et al., *N Engl J Med* 2019
Neelapu SS et al., *N Engl J Med* 2017
Schuster SJ et al., *N Engl J Med* 2019

Ide-cel CRB-401 phase 1 trial: PFS

PFS at <150 × 10^6 and ≥ 150 × 10^6 CAR T cells



	No. of patients	No. of events	Median PFS (95% CI), months
< 150 × 10^6 CAR+ T cells	3	3	2.6 (1.1−2.9)
≥ 150 × 10^6 CAR+ T cells	30	15	11.8 (6.2−NE)

No. at risk

< 150 × 10^6 CAR+ T cells	3	3	2	0																	
≥ 150 × 10^6 CAR+ T cells	30	30	28	27	26	26	17	14	14	12	12	11	8	7	6	5	5	5	3	2	2	0

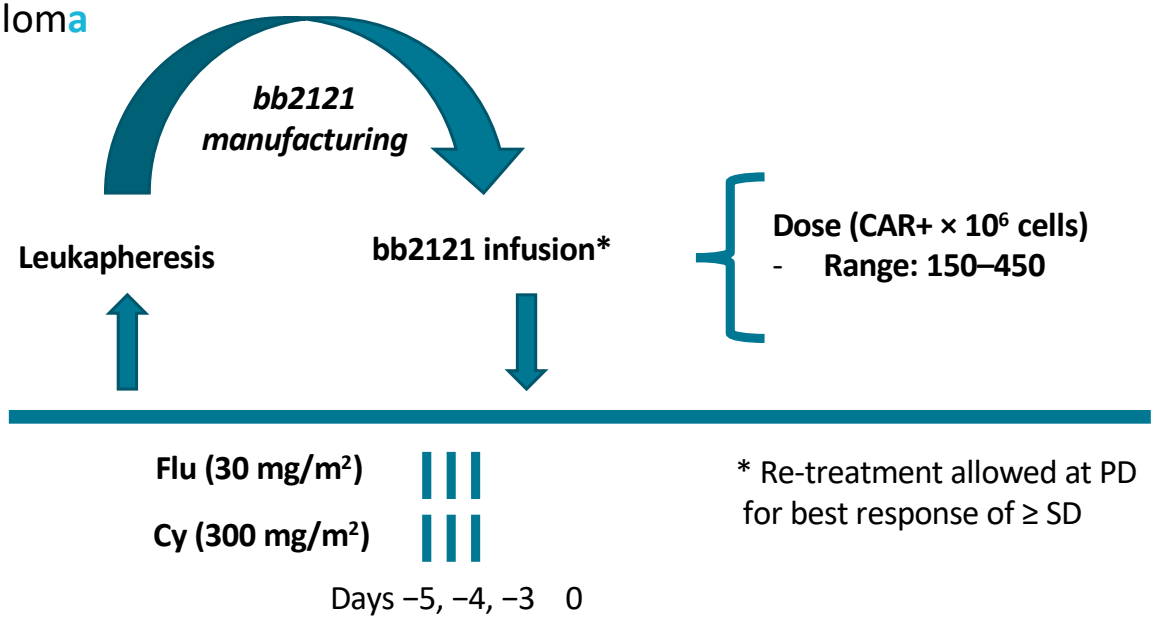
Raje N, et al. N Engl Med. 2019;380:1726-37.

KarMMa
Ide-cel pivotal phase 2 single-arm study

KarMMa — Kar T In Multiple Myeloma

RRMM

- ≥ 3 prior treatment regimens with ≥ 2 consecutive cycles each
- **Received prior IMiD, PI, and anti-CD38**
- Refractory (per IMWG criteria) to last treatment regimen



Endpoints

Primary: ORR

Secondary: CR (key secondary), TTR, DOR, PFS, TTP, OS, safety, bb2121 expansion and persistence, MRD (genomic and flow assays), QoL, immunogenicity, cytokines

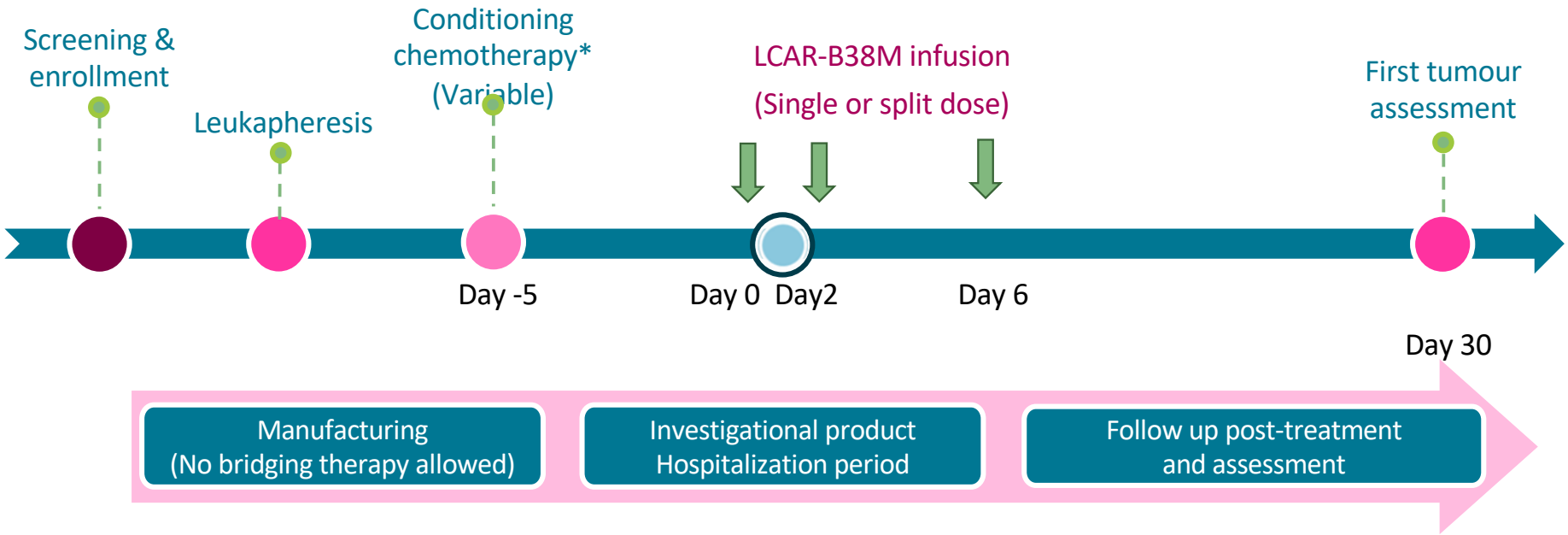
Exploratory: BCMA expression/loss, T cell immunophenotype, GEP in BM, HEOR

GEP, gene expression profile; HEOR, health economics and outcomes research; IMWG, International Myeloma Working Group; QoL, quality of life; TTP, time to progression; TTR, time to response.

ClinicalTrials.gov Identifier: NCT03361748.

LCAR-B38M BCMA CAR T
Phase I study: design

- Lentiviral vector based + 4-1BB co-stimulatory domain
- BCMA catching domain target **two different epitopes simultaneously**



Key inclusion: resistant to > 3 prior lines, BCMA expression in >10% clonal PCs

Median number of prior lines of therapy: **3 (1–9)**

Prior bort: 68%; prior len: 44%; prior PI + IMiD: 60%; prior SCT: 18%

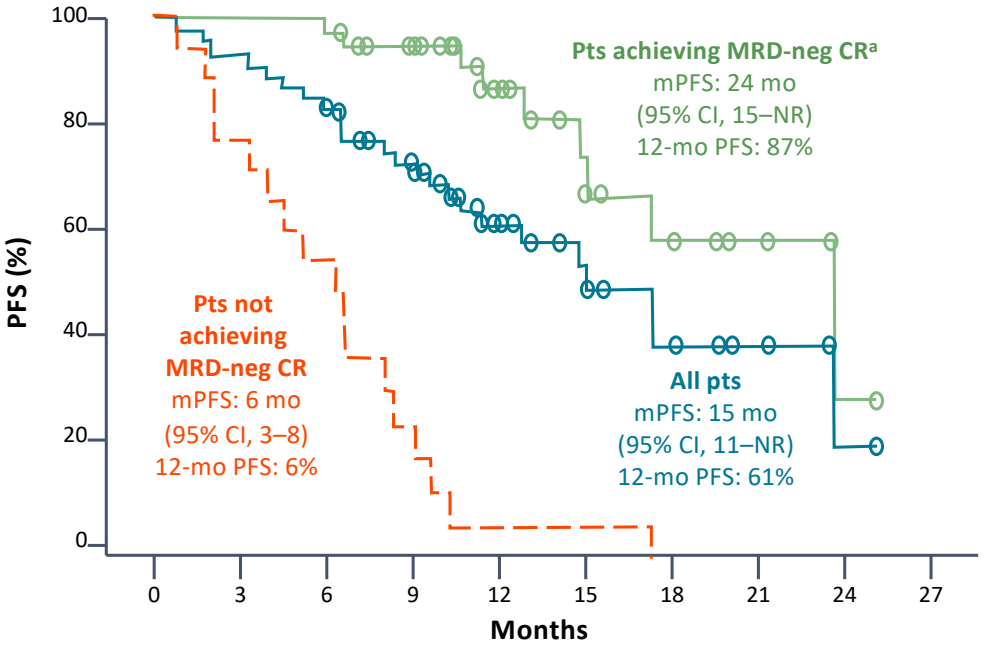
Zhao WH, et al. Presented at ASH 2018; abstract 955.

LCAR-B38M: Legend Biotech phase I trial - updated single-centre experience (LEGEND 2)

- **Conditioning**: Cyclophosphamide 300mg/m^2

- **CAR-T cells**/kg: 0.07 – 2.1 x 10^6. Median dose: 0.5 x 10^6 cells/kg
- **Split infusion** (Day 1 20%, Day 3 30%, Day 7 50%)

ORR = 88% 74% CR and 68% MRD-neg CR)



All pts:	57	53	48	37	21	11	7	4	1	0
Pts achieving MRD-neg CR:	39	39	38	33	20	10	7	4	1	0
Pts not achieving MRD-neg CR:	18	14	10	4	1	1	0	0	0	0

Zhao WH, et al. Presented at ASH 2018; abstract 955.

- mDOR = 16 mo (95% CI, 12 mo–NR)
- mDOR for MRD-neg CR: 22 mo (95% CI, 14 mo–NR)
- 12 mo OS: 75%; 94% for pts achieving MRD-neg CR
- Pts not achieving MRD-neg CR had poor outcome: mPFS 6 mo, mOS 8 mo, 12-mo OS 29%

Toxicity profile

- 35% grade 2 CRS; 7% grade 3; no grade 4
- Tocilizumab use: 46%

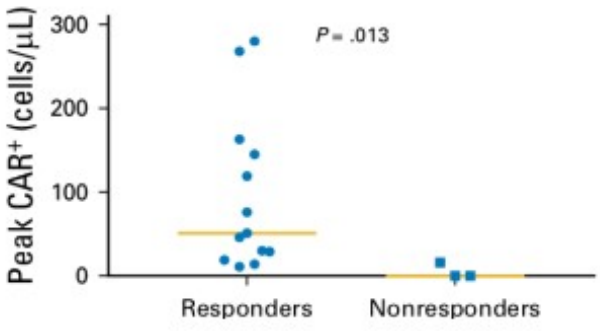
Ongoing trial, **phase 1b/2 CARTITUDE-1 study** (NCT03548207) evaluating **JNJ-68284528** (**same CAR as LCAR-B38M**)

Evaluate effectiveness of LCAR-B38M in more typically heavily treated US (and ex-US) patients compared to Chinese cohort

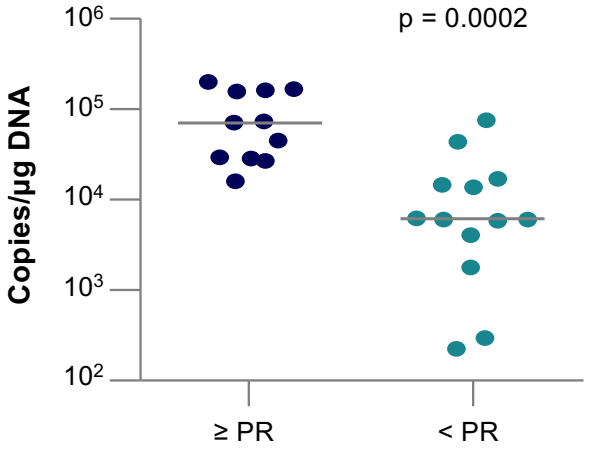
What we know: lessons from initial studies

CAR-T cell expansion correlates with response across different trials

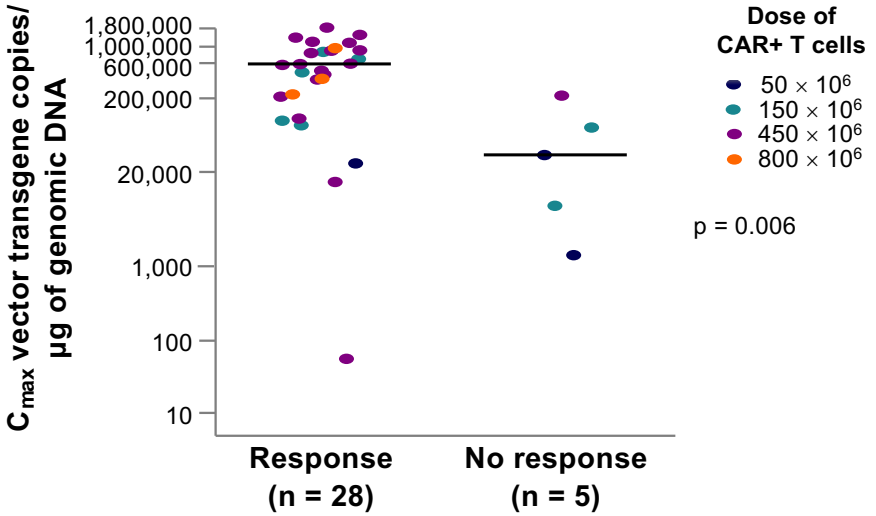
NCI[2]



UPenn[3]



Peak ide-cel vector copies in responders vs non-responders[1]



Patients with at least 1 month of cellular kinetics data (N = 33).
The p value is based on a 2-sided Wilcoxon rank-sum test.

- Comparable C_{max} in active dose cohorts (≥ 150 × 10^6 CAR+ T cells)
- Durable ide-cel persistence (≥ 6 months) in 57%
- Higher peak expansion in patients with response

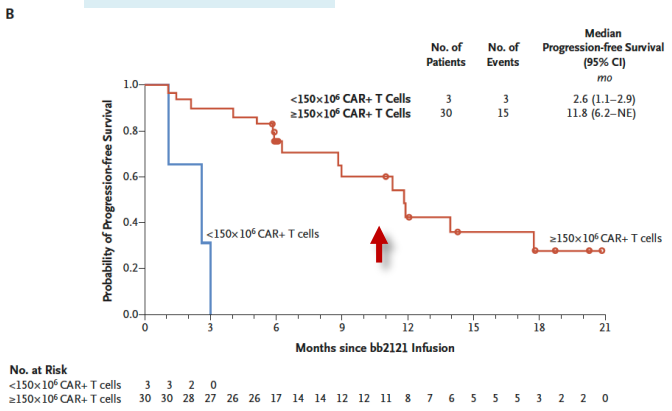
[1]Raje N, et al. N Engl Med. 2019;380:1726-37; [2]Brudno JN, et al. J Clin Oncol. 2018;36:2267-80; [3]Cohen AD, et al. J Clin Invest. 2019;129:2210-21.

What we know: lessons from initial studies

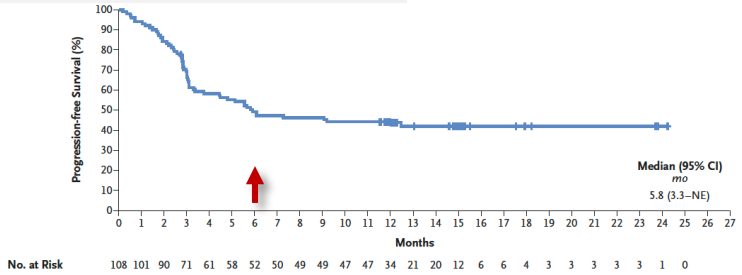
PFS of CAR-T cells in multiple myeloma compared with lymphoma:

Despite very high ORR and CR rates, patients continue to relapse....

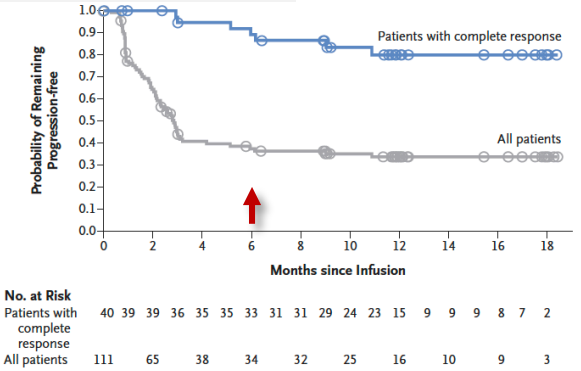
bb2121 (CRB 401)



Axicabtagene ciloleucel (ZUMA-1)



Tisagenlecleucel (JULIET)



Room for improvement with CAR-T....

Different biology of myeloma v. lymphoma....

What we know: lessons from initial studies
CAR-T vs other therapies

CAR-T therapy may allow patients to step off the "treadmill" of continuous treatment

CAR T

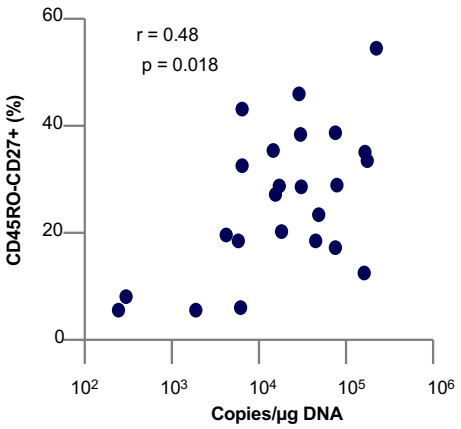
Current paradigm of myeloma therapy:
continuous *treatment until progression*

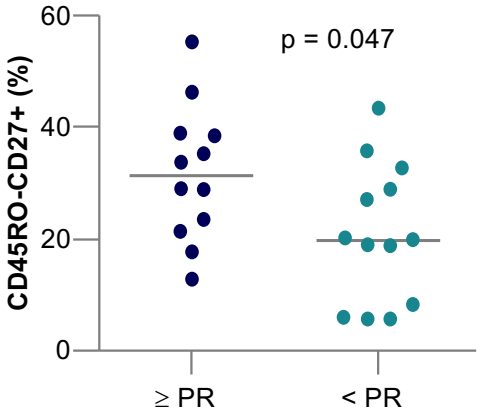
One *treatment (then observation)*

What we know:

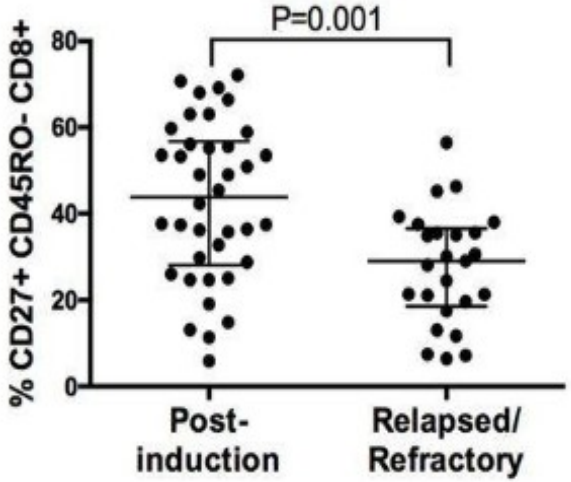
Not all T-cells are the same. T-cell fitness matters

% of naive-memory CD8+ cells in the apheresis product correlates with in vivo expansion and response





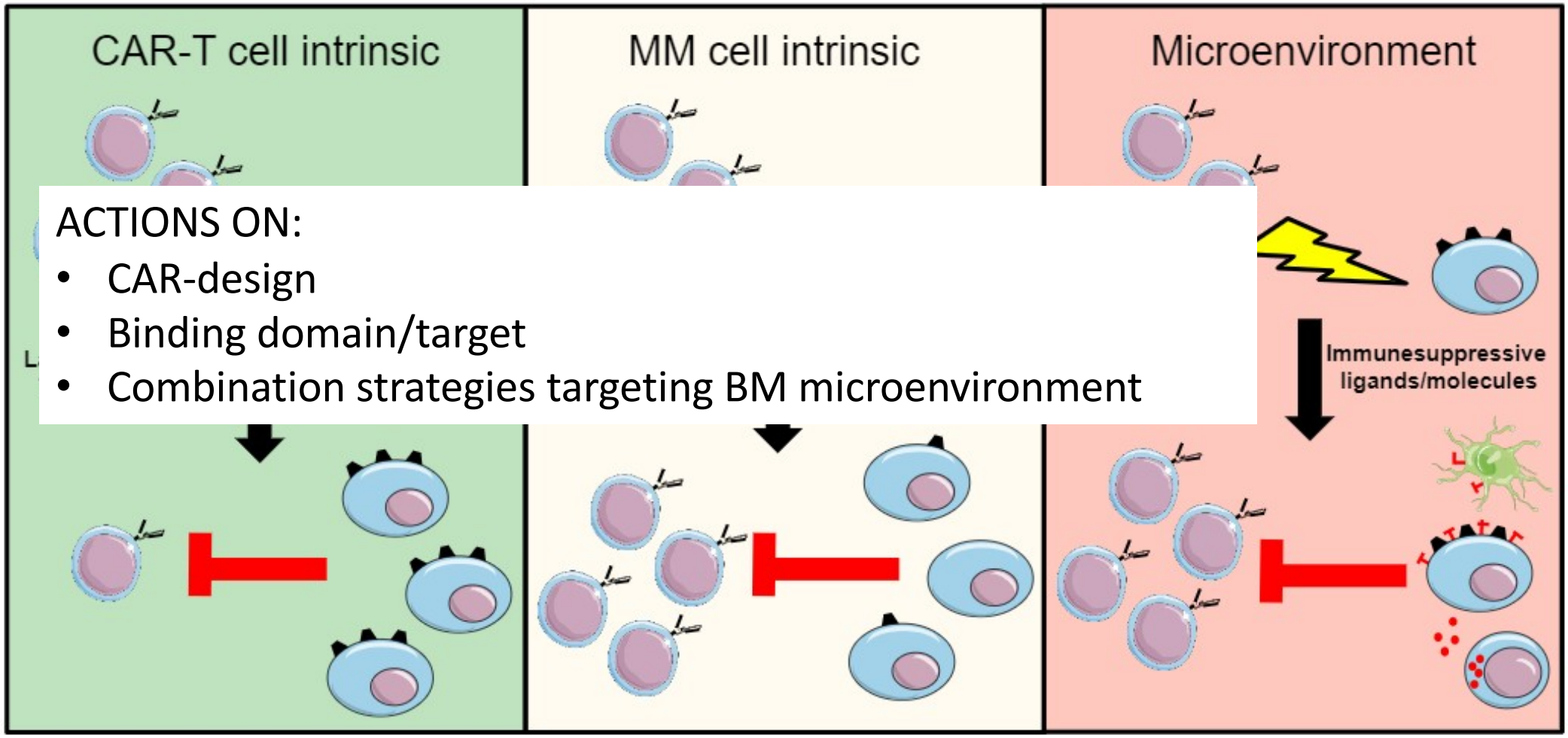
Patient selection: early RRMM patients after induction treatment compared to highly pretreated RRMM patients[2]



	Post-induction	Relapsed/ Refractory
Median lines of terapy (range)	1 (1-4)	7 (3-15)

Gattinoni L et al. Nature Medicine (2017); Cohen AD, et al. J Clin Invest. 2019;129:2210-21; Dancy E et al, ASH 2018, Blood 132:1886

What we do not know yet?
Understanding the non-responders and the resistance



Slide presented by N. Raje at IMS Boston meeting

Not all T cells are the same

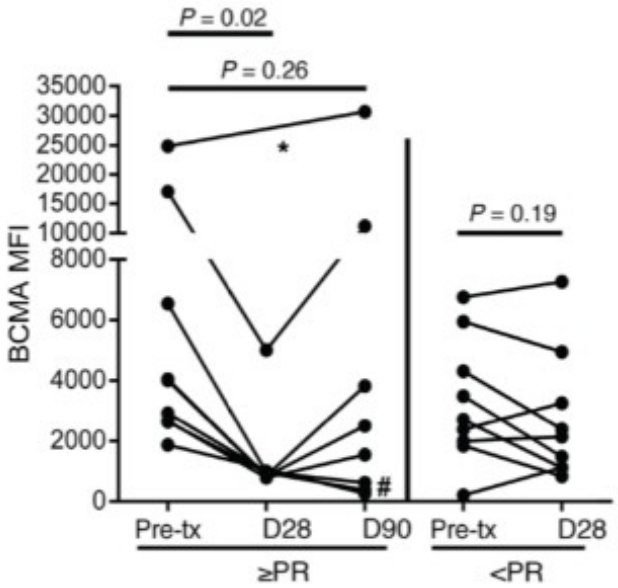
Next generation of products trying to increase the % of memory Tcells

	bb21217	JCARH125
Binder	Murine	Human
Costimulatory domain	4-1BB	4-1BB
Vector	Lentivirus	Lentivirus
Manufacturing Process	Unselected T cells at culture initiation + **PI3K inhibitor during T cell culture**	1:1 ratio of CD4/CD8 T cells at culture initiation
T Cell Phenotype	Enriched for T_n and T_{cm} cells	Enriched for T_n and T_{cm} cells
Preclinical	Low tonic signaling No inhibition by sBCMA	Low tonic signaling No inhibition by sBCMA
Stage of Development	Phase I trial initiated Q3 2017	Phase I trial initiated Q1 2018
Preliminary efficacy results	ORR 83% $150x10^6$ CAR T 4/4 MRDneg	ORR (n=44) 79%; CR 43%

Shah N et al. Presented at ASH 2018; abstract 488
ASH 2018 [redacted] investor relations event, december 2, 2018:
https://s22.q4cdn.com/728481125/files/doc_presentations/2019/03/ASH-2018-IR-Event_FINAL_website-version_updated.pdf
Mailankody S et al.Blood;132:957. Presented at ASH 2018

MM-cell intrinsic mechanisms:
BCMA loss or modulation has been described after anti-BCMA CAR T therapy

Residual MM cells from responding patients show a lower BCMA expression 1 month after CAR-T cell infusion[2]



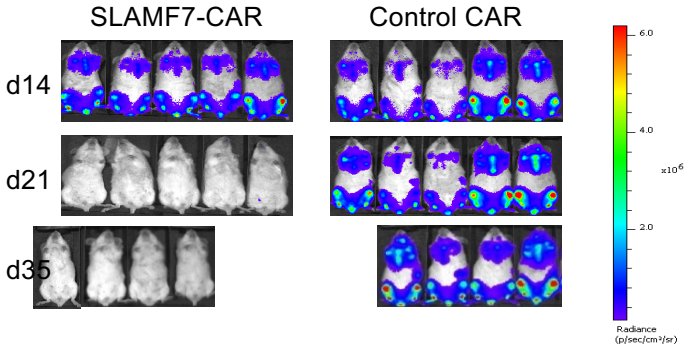
CARAMBA project: SLAMF-7 CAR T

SLAMF-7 targeting, virus-free Sleeping Beauty gene transfer

Expressed on a fraction of NK, T & B cells: activating or inhibitory function

High-level expression is retained in malignant plasma cells in MM and MGUS

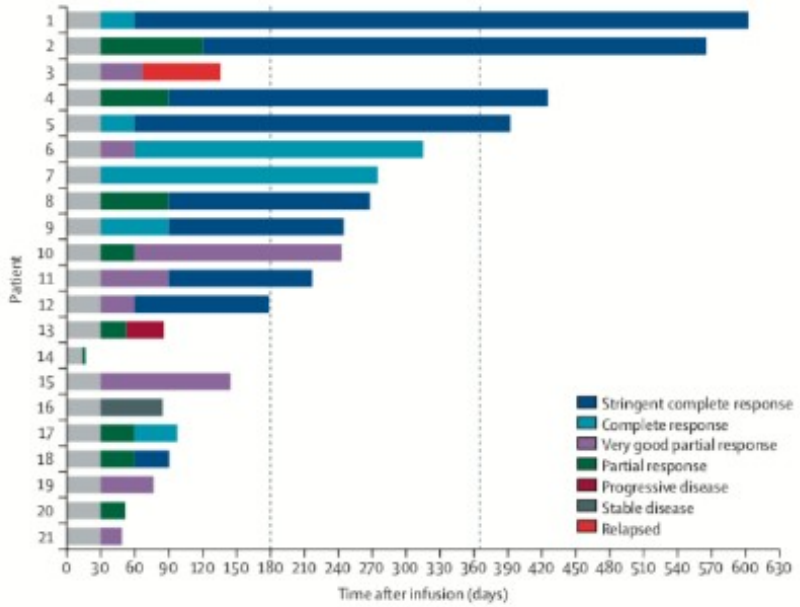
Eradication of extra-/medullary myeloma after single dose of SLAMF7 CAR T



Cohen AD, et al. J Clin Invest. 2019;129:2210-21, Gogishvili T, et al. Blood 2017;130:2838–47.

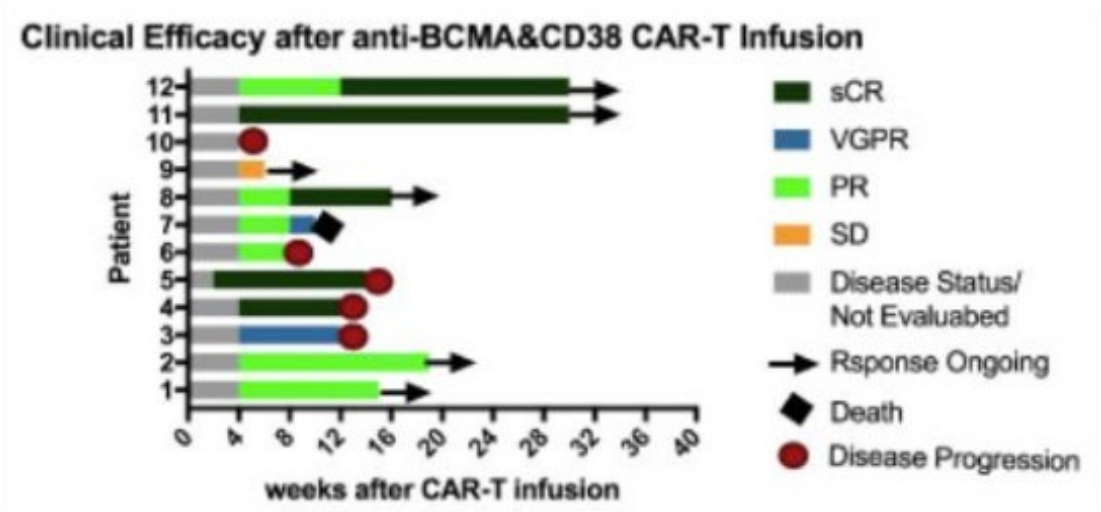
New targets and dual-target CAR-T

Infusion of anti-CD19 and anti-BCMA CAR T cells[1]



ORR 95%
(≥CR 57%)

Dual targeting anti-BCMA/anti-CD38 CAR T cells[2]

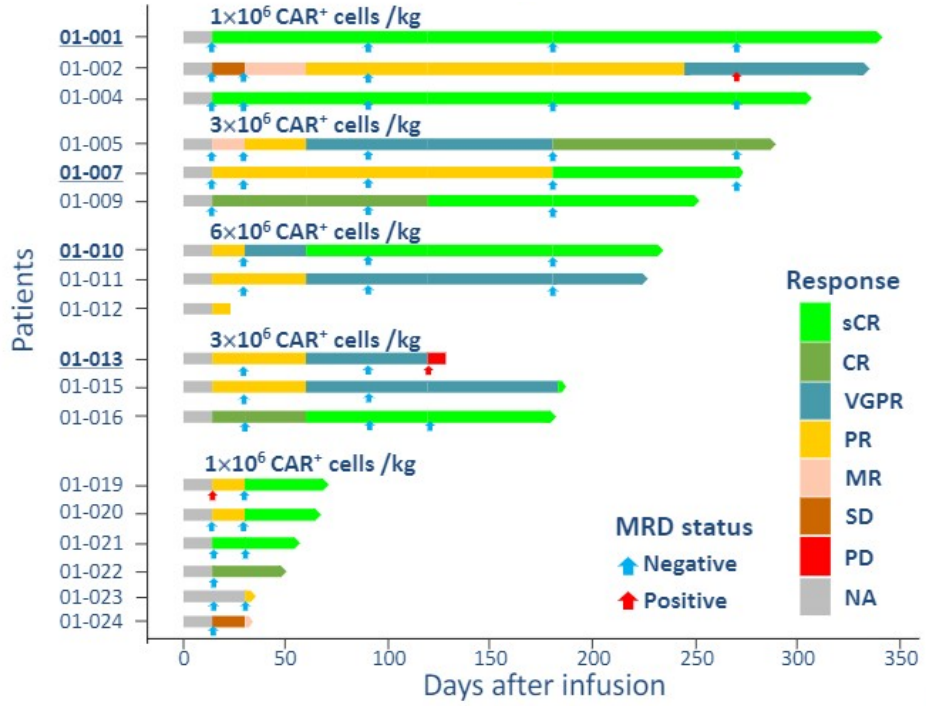


ORR 83%
(≥CR 42%)

Yan Z et al. Lancet Haematol. 2019 Aug 1; Mei H et al EHA 2019 Jun 15, 2019; 267409; S826.
ORR: overall response rate; CR: complete response. sCR: stringent complete response. VGPR: very good partial remission. PR: partial response. SD: stable disease.

However, most patients relapse with persistent but non-functional CAR-T

- Is there a role of host anti-CAR immunity?. Since most of the CARs have non-human domains
  ➔ Role of **fully humanized CAR-T**



The data are cut off 2019-08-29
The sensitivity of MRD assessment is $1/10^4$ cells

Best Response Achieved

ORR 100%

sCR/CR 70.6%**

VGPR or better 88.2%**

BOLD Numbers- Patients relapsed from a prior CAR-T treatment

* Patient 12 died during the trial probably due to respiratory failure resulting from a lung infection.
**For evaluable patients (n=17)

Li C. et al. Oral presentation at IMW meeting in Boston, September 2019

Future development of CAR T in multiple myeloma

- **This is just the beginning of anti BCMA CAR T**, "version 1.0"
  - Deep responses, but room for improvement with durability of response
- Currently, CAR T reserved for patients with refractory, heavily pretreated disease

- Potential **advantages to CAR T earlier in patient course**
  - **Less clonal heterogeneity**, less clonal evolution: less resistance to therapy (note better responses seen with e.g., daratumumab or dexamethasone earlier in disease course)
  - **Lower tumor burden** at first or earlier relapse may respond better to CAR T
  - **Better functional status,** less comorbidities, better renal function
  - CAR T-cells created from less heavily treated patients may be more effective
    - **Source of CAR T-cells may be less "exhausted**," see also comparison of T cells in healthy donors v. MGUS/myeloma patients (Bailur JK et al., *JCI Insight* 2019)
- **KarMMa-2 (**NCT03601078) in early relapse with bb2121
  - Early relapse defined as progressive disease <18 months since start of initial therapy (with or without auto SCT)
- **KarMMa-3** (NCT03651128), randomized study of bb2121 v. standard of care in patients with 2-4 prior lines of treatment

CAR-T trials ongoing (2019-2020)

- **BCMA CAR pivotal trials in RRMM (≥ 3 prior lines)**
  - [redacted]
  - **Regulatory approval by 2020?? (FDA)**

- **Ongoing ph 1/2 trials for next generation CAR productos (i.e. BB21217)**

- **BCMA CAR trials in patients in earlier lines of therapy**
  - 1-3 prior lines (randomized with SoC regimens)
  - Early relapse after optimized frontline treatment (high-risk disease)
  - Consolidation in non-CR patients with HR disease

- **Combination trials**
  - Gammasecretase inhibitors, checlpoint, IMIDs, dual CAR-T (CD19 + BCMA, CD38 + BCMA)

- **Off-the shelf allogeneic CAR-T**

- **New targets: SLAMF7 (CARAMBA trial), GPRC5D …**

Conclusion

- Despite continuous improvement in survival thanks to the incorporation of novel treatments, MM patients still relapse, and survival after failure to IMiDs and PIs remains poor. Therefore, there is a **need for new treatment strategies in these patients**
- BCMA is a promising therapeutic target and clinical results with the new BCMA-directed treatments are encouraging among patients with RRMM
- Adoptive cell therapy, especially **with CAR T cells, is revolutionizing the treatment of haematological malignancies**
  - In MM, **promising results** have been reported so far with very high CR and MRD-neg rates in an end-stage population. However, **no plateau** has yet been seen in the curve
- **Outcomes will be improved by understanding the mechanisms of action, immune response and cell biology**
- **There is a need to define which patient may benefit from each strategy. Can they live together in the MM portfolio?? Is there a specific place for BiTes or CAR-T???**
- Adequate patient selection and earlier use in the course of the disease may surely impact the long-term outcome of these novel therapies.