Penn Medicine

Cellular Immunotherapy for Myeloma

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IMF Symposium
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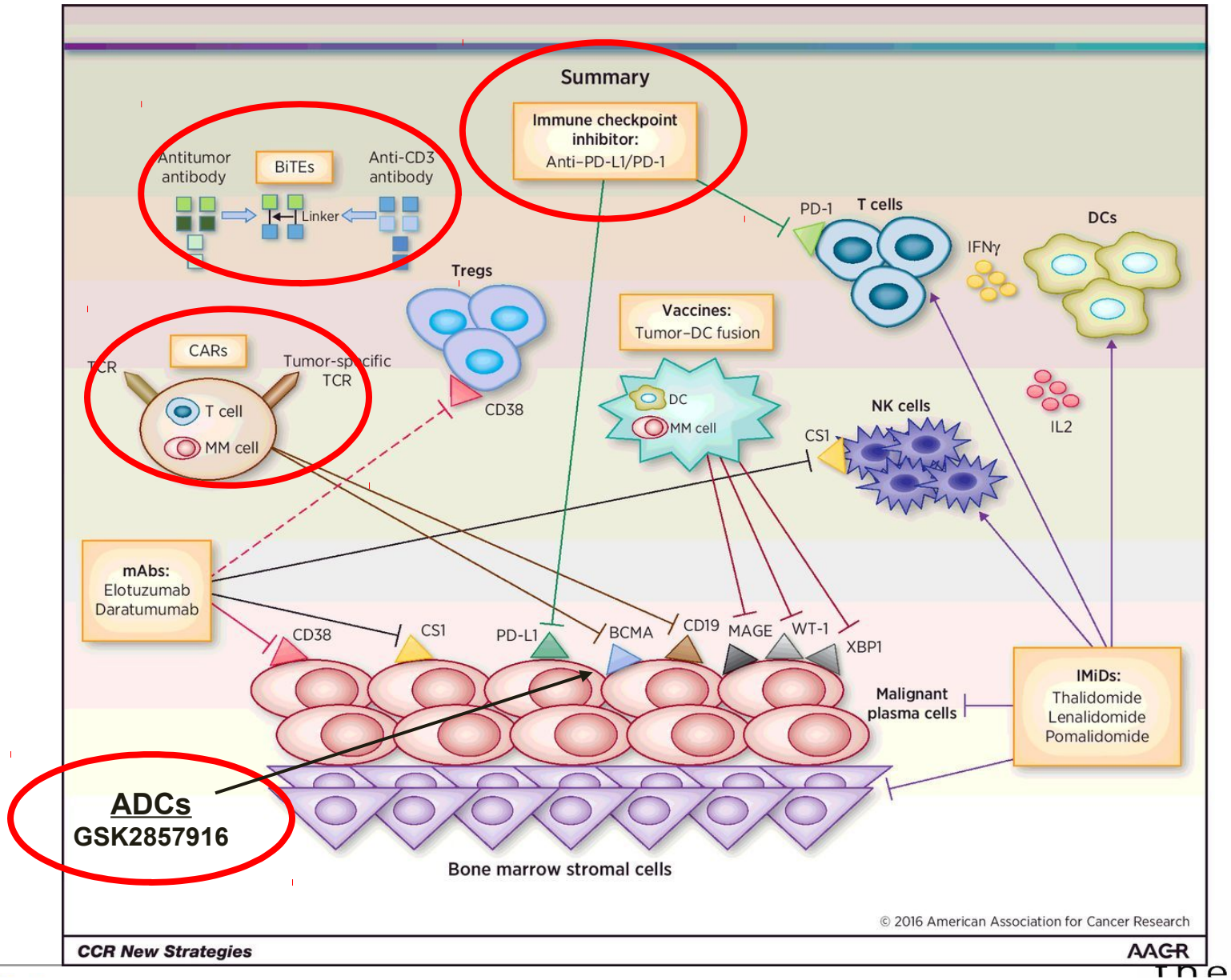
the cure is within
ABRAMSON CANCER CENTER

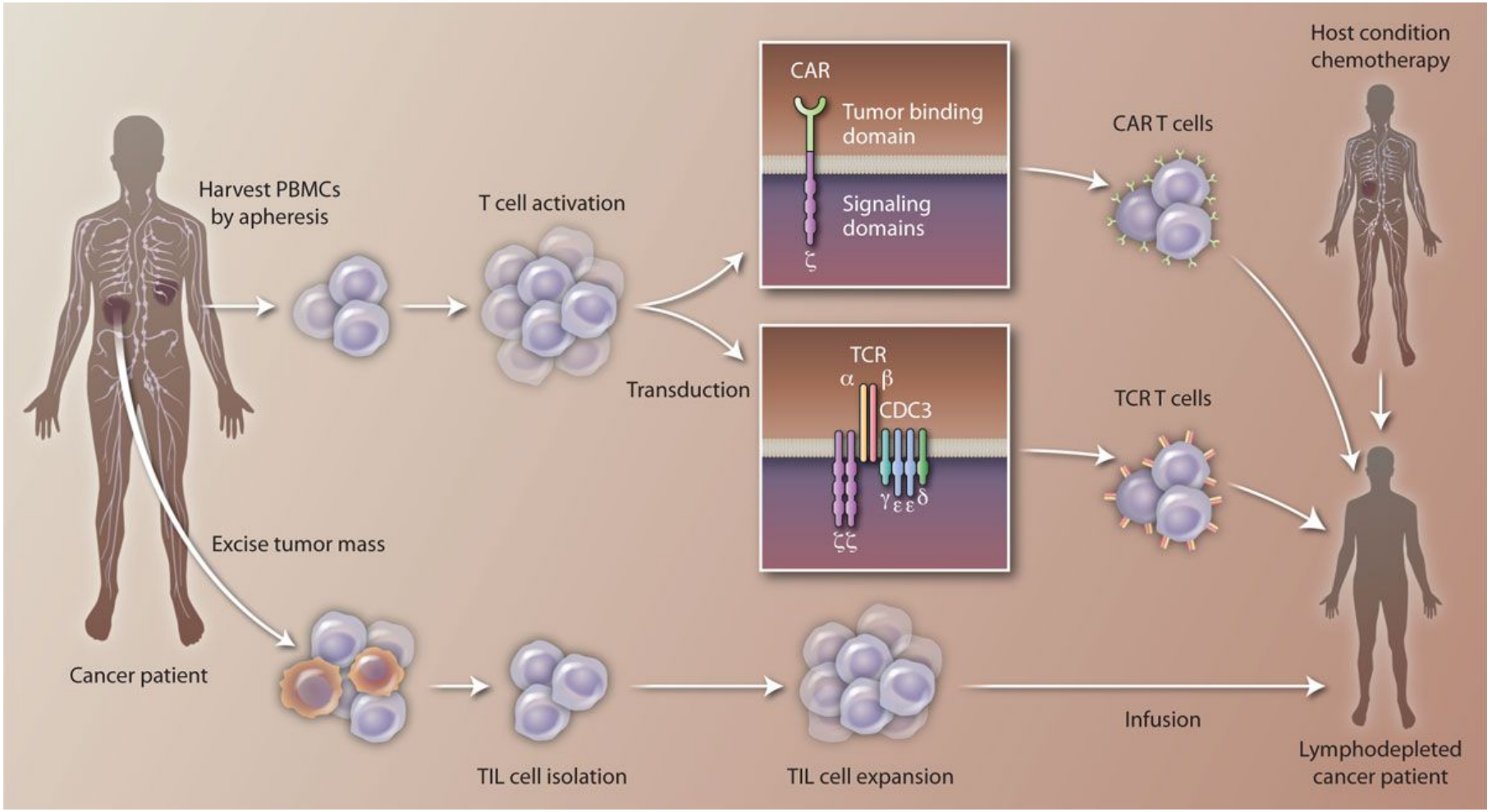
Immunotherapy for MM: Targets and Tools



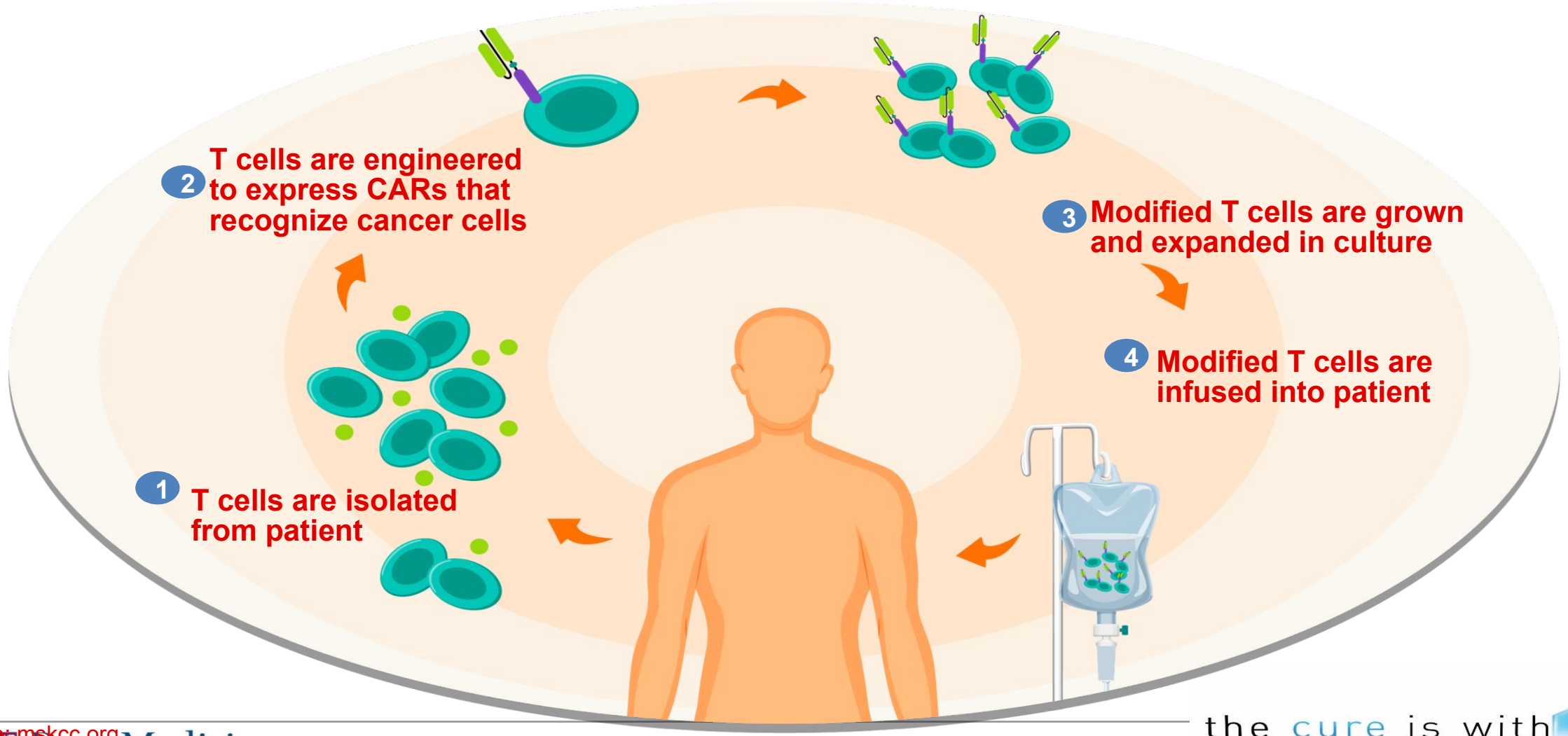
Neri et al, Clin Can Res 2016

Adoptive T cell therapy (three major approaches)

- June et al *Sci Trans Med 2015*

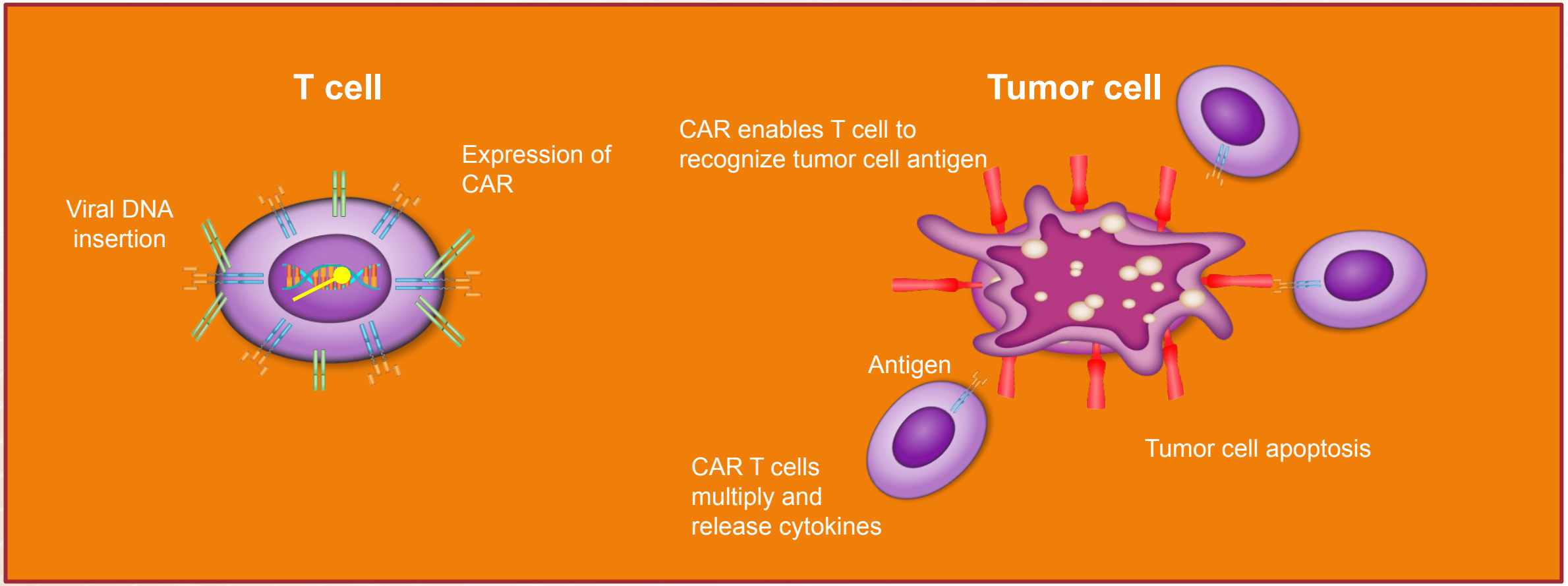


Making CAR T-Cells



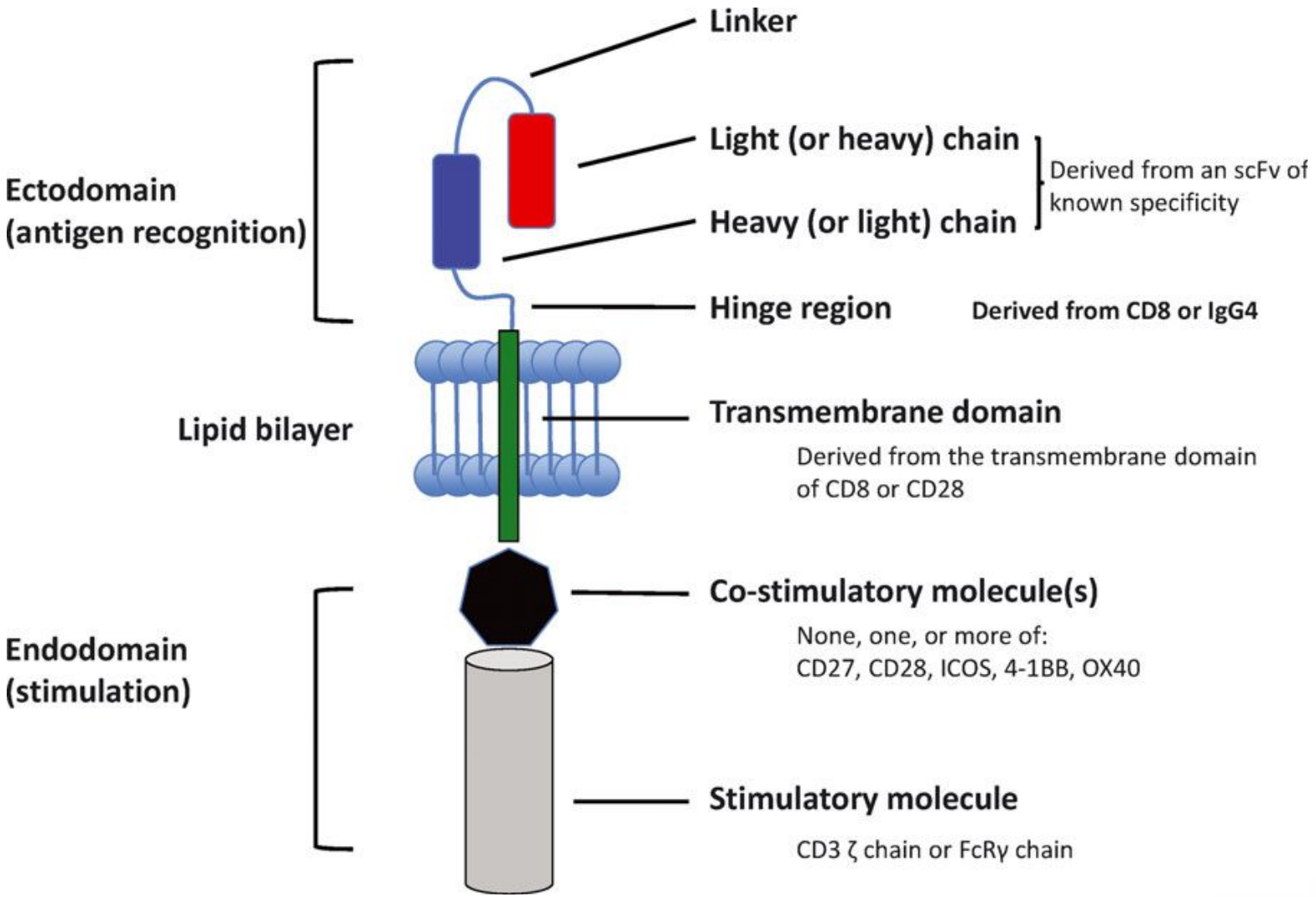
Source: mskcc.org

How CAR T-Cell Therapy Works



Anatomy of a Chimeric Antigen Receptor (CAR)

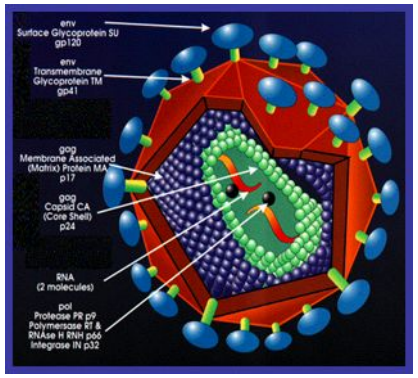
Gill S, June C Immunol Rev. 2015 Jan;263(1):68-89

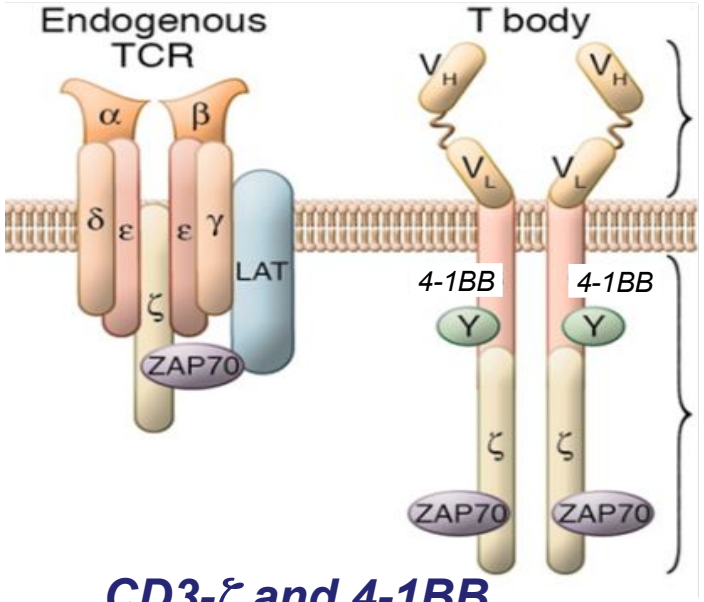


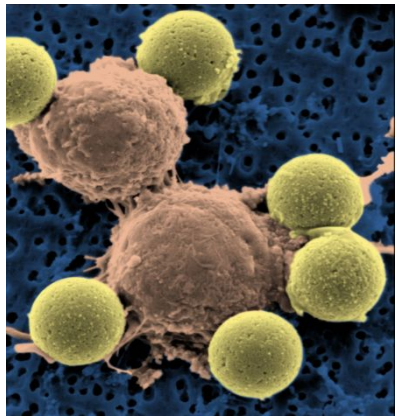
A single-chain variable fragment (scFv) is not actually a fragment of an antibody, but instead is a fusion protein of the variable regions of the heavy and light chains of immunoglobulins, connected with a short linker peptide

2nd Generation CAR for B Cell Malignancy:

Autologous T Cells Transduced w/ Anti-CD19 Receptor
Spliced to CD3 zeta and 4-1BB Signaling Domains







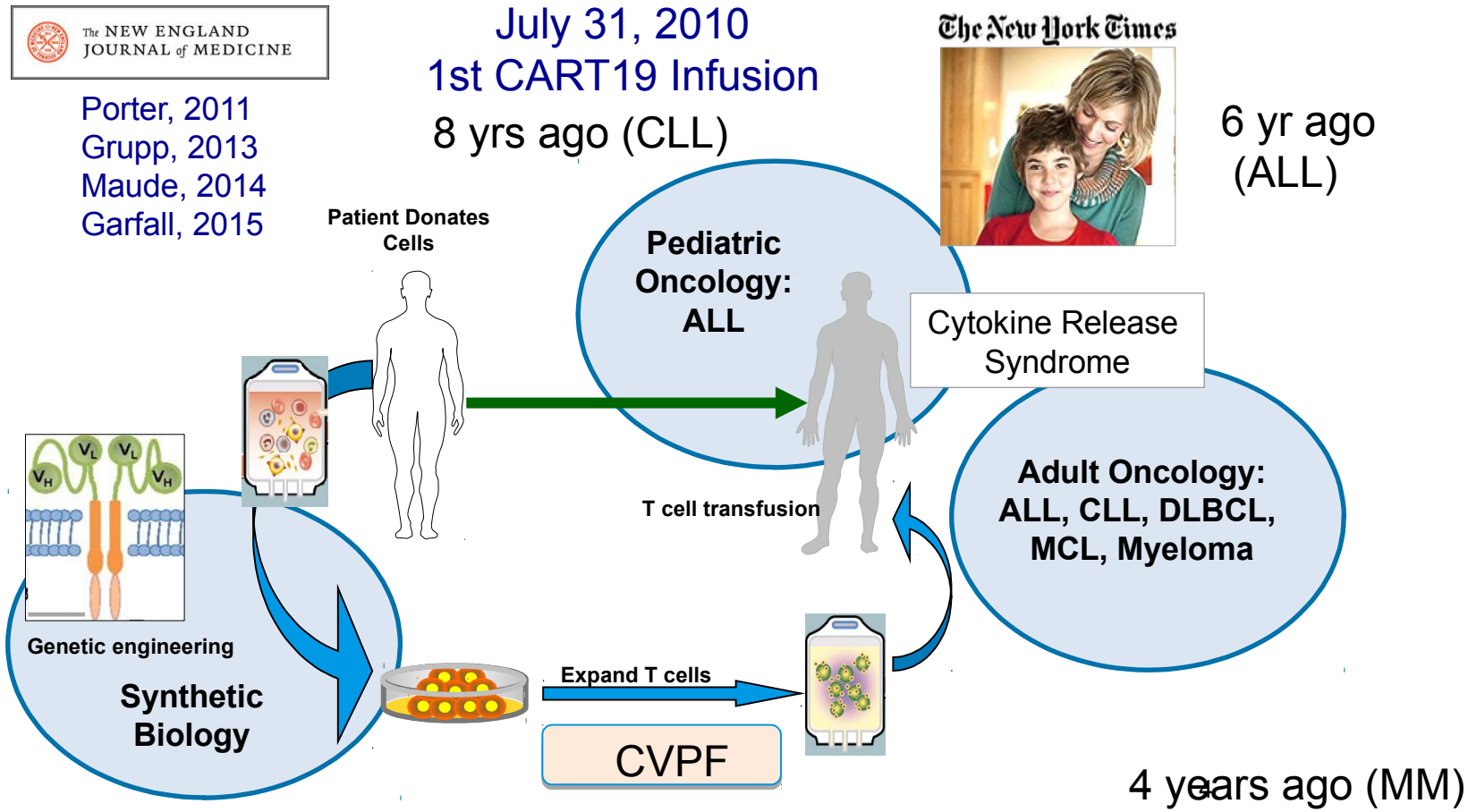
Lentiviral vector to deliver construct

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

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

CARs directed against CD19 have been tested in CLL and ALL

CART19 (tisagenlecleucel-T): Penn Med Overview



Slide courtesy of Carl June

CD19-targeted CAR T cells for B cell malignancies

- **Experience from numerous national and international trials**
  - autologous and allogeneic T cells

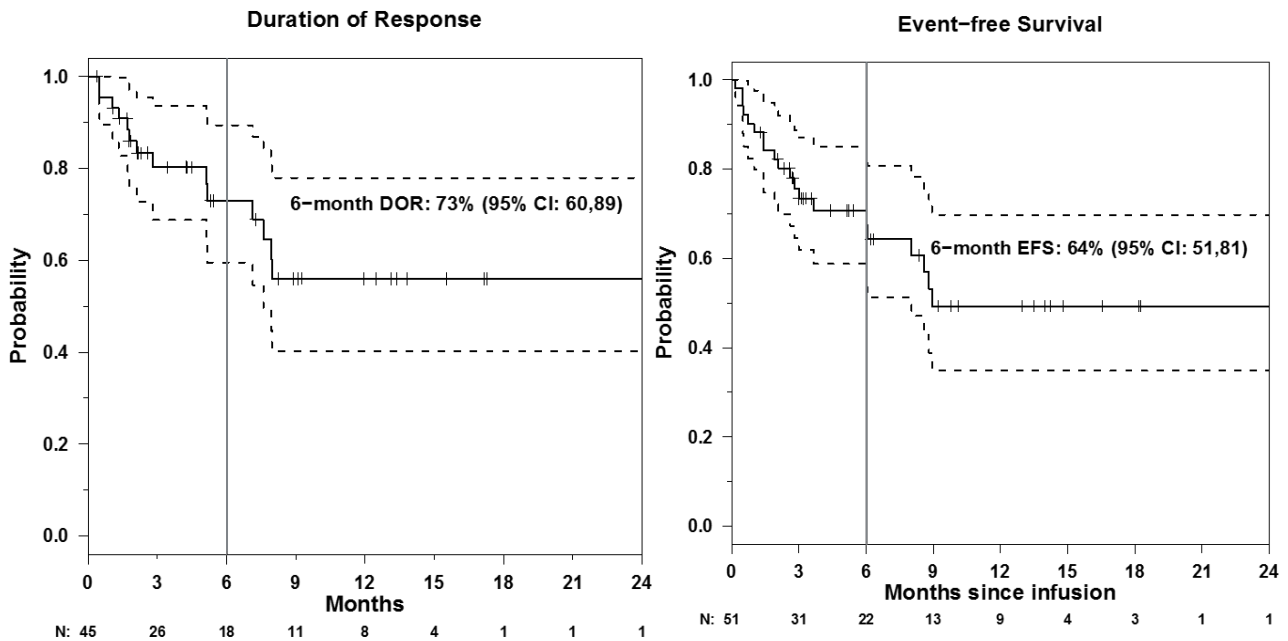
- **Responses seen in heavily-pretreated CLL, ALL, and B-cell NHL**
  - ORR 40-50% in CLL, 80% in ALL, 50-80% in NHL
  - some durable CRs > 5 years

Summary of CTL019 Efficacy in R/R ALL (n = 51)

39 Pediatric and 12 Adult

FDA Breakthrough Designation for ALL

Maude, et al, *NEJM* 2014



Davila et al, Science Trans Med 2014; Porter et al, ASH 2013; #873; Maus et al, Blood 2014,

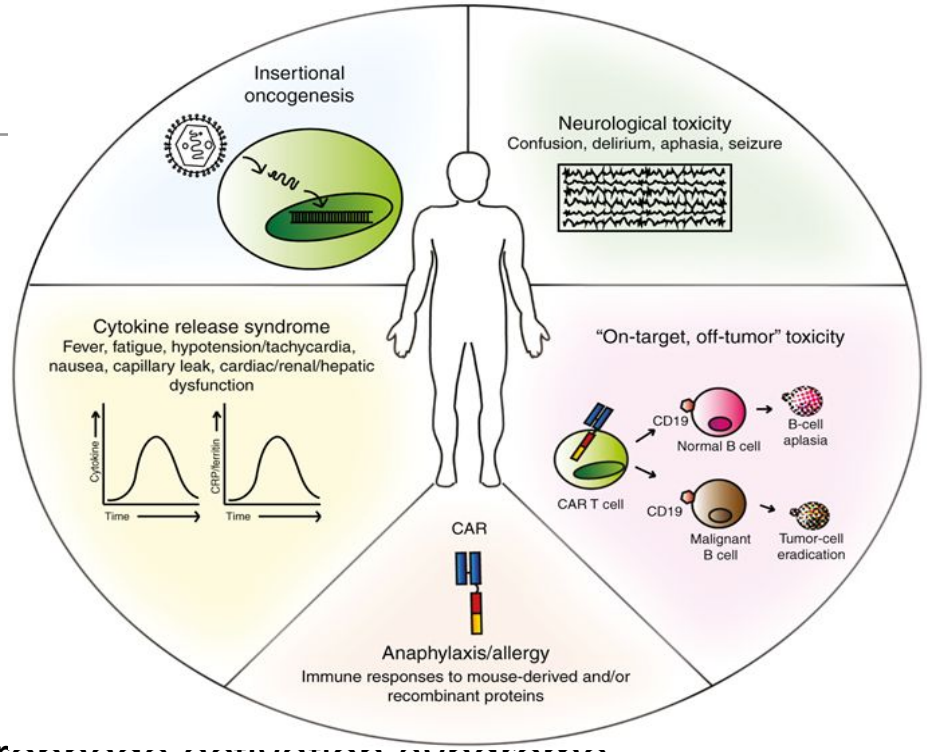
F.D.A. Approves First Gene-Altering Leukemia Treatment,

Costing $475,000 R/R ALL (age <25 yr)
CD19 Driected CAR
New York Times, 8/30/2017
AND AGAIN 5/2/18 in R/R B-NHL
AND AGAIN 10/18 in R/R B-NHL

Flash Mob at Penn Medicine FDA Approval CAR T

But not without toxicity

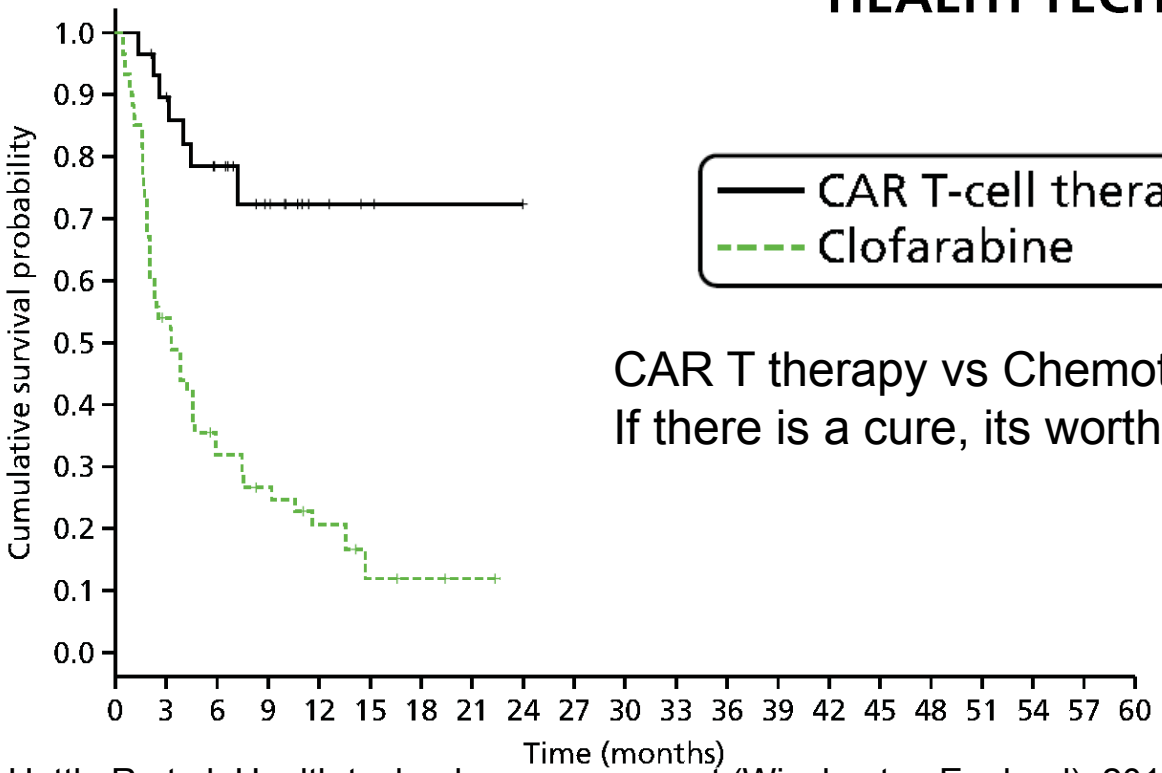
- **On target toxicities:**
  - Tumor lysis syndrome
  - B cell aplasia
  - hypogammaglobulinemia
- **Off target toxicities:**
  - Cytokine release syndrome
    - persistent high fevers, rigors,
    - myalgias, hypotension, hypoxia,
    - neurologic dysfunction, HLH/macrophage activation syndrome
    - very high IL6, also IFN-gamma, TNF
    - responds to steroids → but lose CAR T cells
    - tocilizumab (anti-IL6 receptor mAb) can abrogate CRS
  - CNS toxicity
    - The causative pathophysiology of these neurologic side effects is unknown, though given similar events reported with blinatumomab administration
    - The neurologic toxicity has been reversible in a majority of cases



Bonifant et al, Molecular Therapy — Oncolytics (2016) 3, 16011;

And Not Without Cost

CAR T Therapy is Complicated and Expensive
Is the Juice Worth the Squeeze?



HEALTH TECHNOLOGY ASSESSMENT

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CAR T therapy vs Chemotherapy for R/R ALL
If there is a cure, its worth it!

NHS
National Institute for Health Research

Hettle R et al. Health technology assessment (Winchester, England). 2017;21(7):1-204.

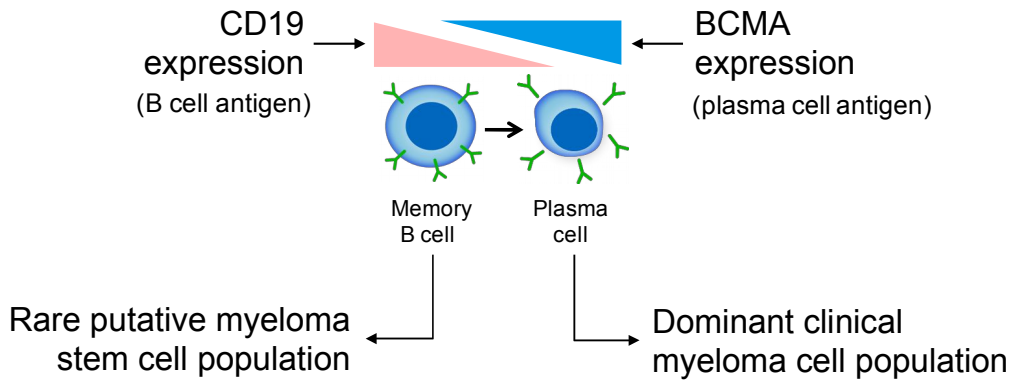
The classics:

- CD138
- CD38
- CD56
- kappa light chain

And… CD19 as a target in myeloma?

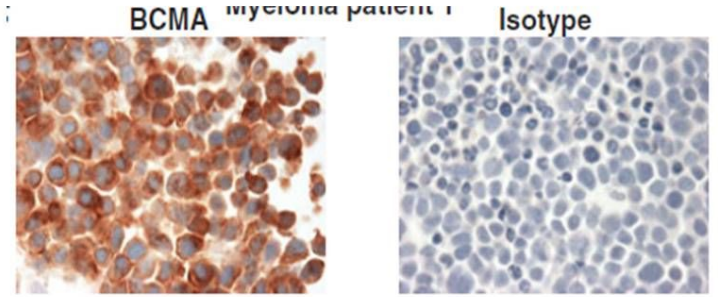
The new models:

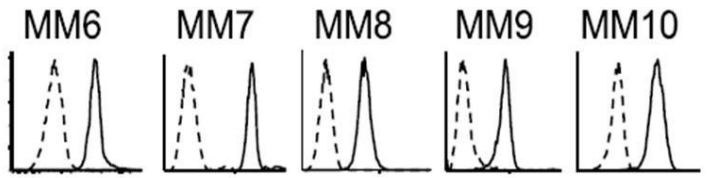
- Lewis Y
- CD44v6/CD229
- MAGE A3/NY-ESO-1
- CS1/SLAMF7
- BCMA (B-cell Maturation Antigen)
- Integrin beta 7

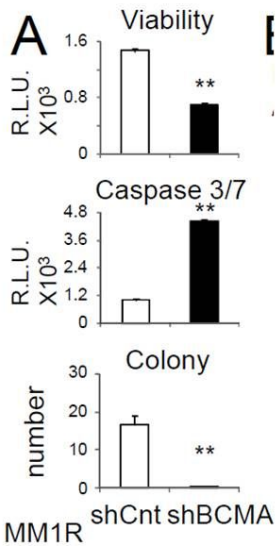


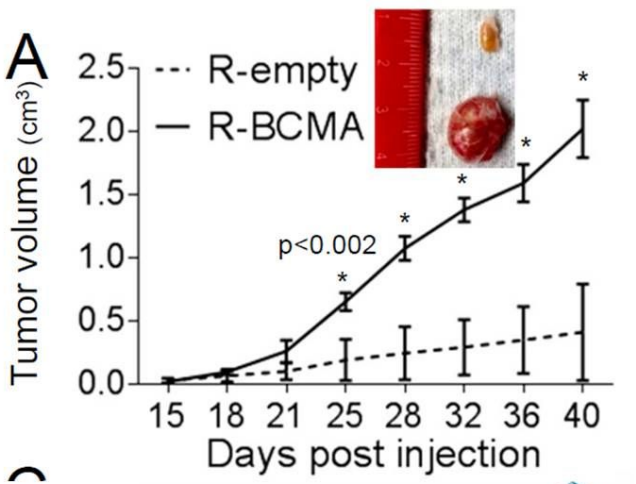
BCMA (*B-cell Maturation Antigen*)

- **Receptor for BAFF (Blys) and APRIL**
- **Expressed on plasma cells, some mature B cell subsets, and plasmacytoid DC's**
  - Maintains plasma cell homeostasis
- **Highly expressed on myeloma cells**
- **Soluble BCMA in patient serum**
- **Promotes MM pathogenesis**



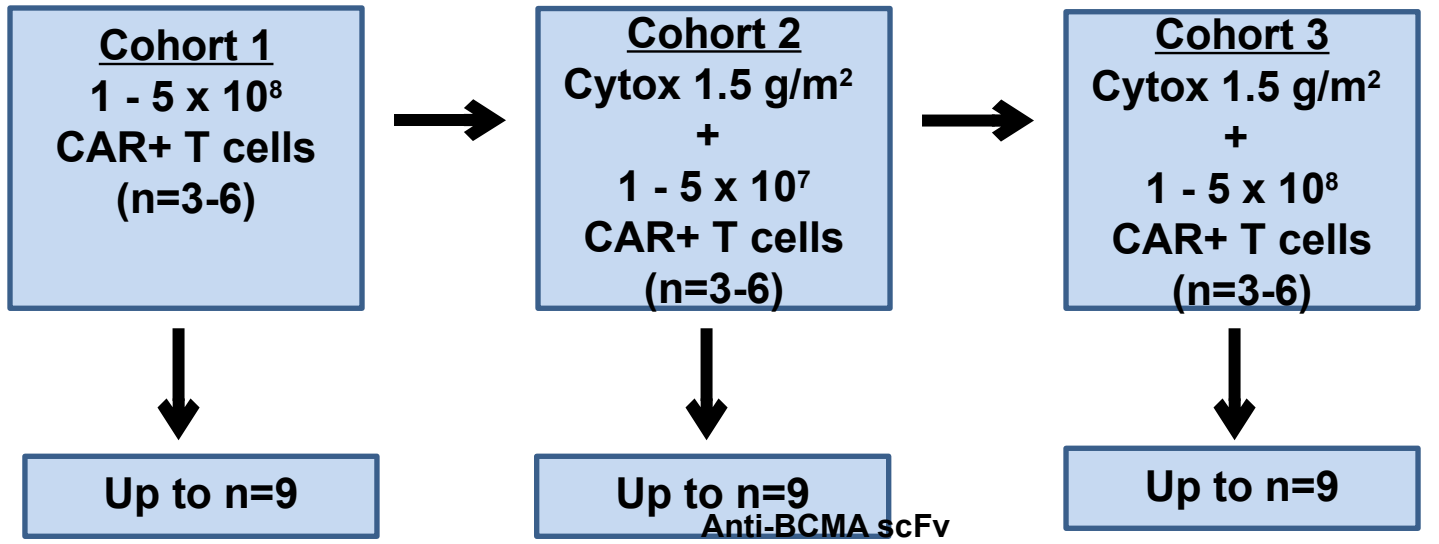






Frigyesi et al, Blood 2014; Tai et al, Blood 2014; Carpenter et al, Clin Can Res 2013; Tai et al, Blood 2016

Study design: Adam Cohen, MD PI



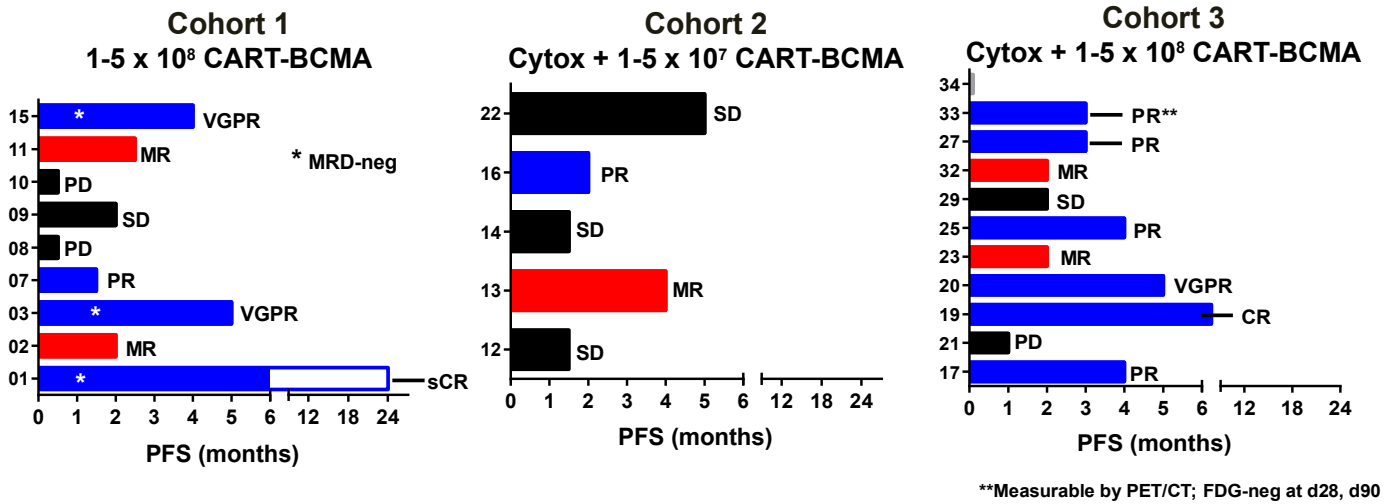
- **Primary objective**
  - Safety
- **Secondary**
  - Feasibility
  - Efficacy (response rates, PFS, OS, MRD)
- **Exploratory:**
  - CART-BCMA expansion, persistence, phenotype
  - Impact on normal B cell and PC compartments
  - BCMA expression pre- and post-treatment
  - Cytokine/chemokine levels
  - Soluble BCMA, BAFF, APRIL levels
  - Assess for anti-CAR immune responses
  - Impact on tumor microenvironment

Cohen et al, ASH 2017, #505

Treated Patient characteristics

	All patients (n=24)	Cohort 1 (n=9)	Cohort 2 (n=5)	Cohort 3 (n=10)
Age	58 (44-75)			
Gender	67% M; 33% F			
Yrs from diagnosis	4.6 (1.8 – 14.5)			
Prior lines of therapy	7 (3-13)			
Lenalidomide	100%			
Bortezomib	100%			
Pomalidomide	92%			
Carfilzomib or Oprozomib	96%			
Daratumumab	75%	44%	80%	100%
Dual- / Quad- / Penta-refractory	96% / 54% / 42%	89% / 56% / 33%	100% / 60% / 40%	100% / 50% / 50%
Autologous / Allogeneic SCT	92% / 4%			
Cyclophosphamide	100%			
Anti-PD1	29%			
High-risk genetics -17p or *TP53* mutation	96% 71%			
Extramedullary dz	29%			
% BM plasma cells	70% (0 - 95)			

Clinical activity



**Measurable by PET/CT; FDG-neg at d28, d90

ORR = 4/9 (44%)

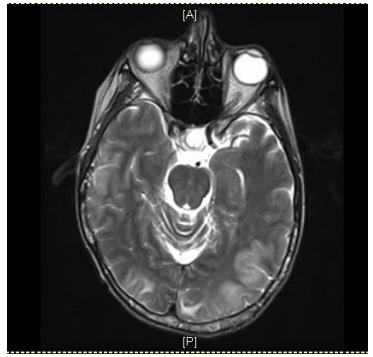
ORR = 1/5 (20%)

ORR = 6/10 (60%)

ORR (≥PR) @ 10e8 = 10/19 (53%)

Median DOR = 4 months

Safety BCMA CAR



- **Cytokine release syndrome in 8/9 (89%)**
  - Grade 1 (n=1); Grade 2 (n=4); Grade 3 (n=2); Grade 4 (n=1)
  - 4/9 received tocilizumab
  - Median hospital stay = 9 days (range 3 – 40)

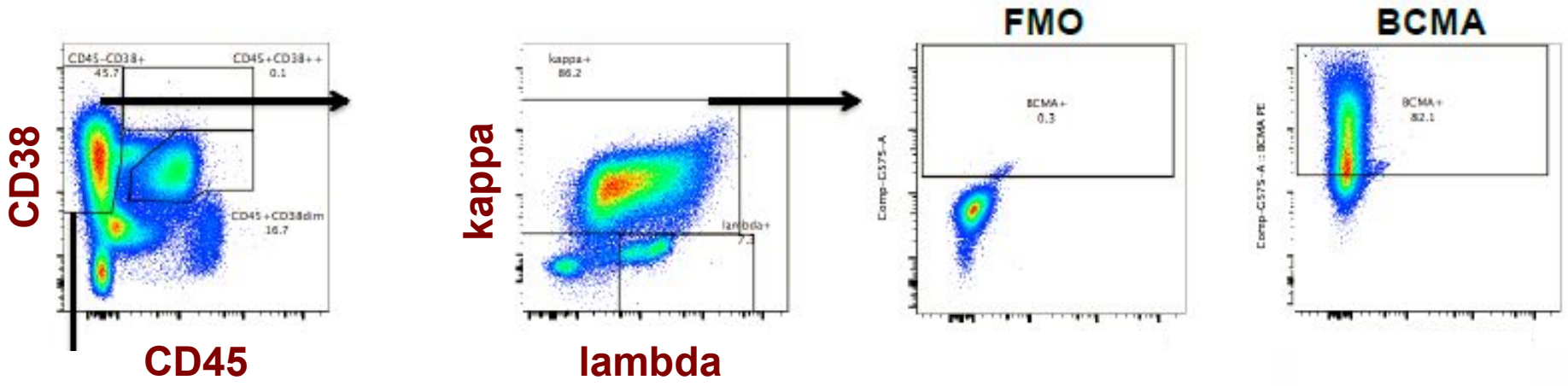
- **Dose-limiting toxicity (pt. 03):**
  - Grade 4 PRES (posterior reversible encephalopathy syndrome)
    - Recurrent seizures, obtundation
    - MRI brain: diffuse enhancement w/ swelling and sulcal effacement.
    - Rapid peripheral CART expansion
    - Solumedrol 1 g/d x 3→Cytoxan 1.5 g/m2 day 17
    - Rapid improvement, resolution of MRI changes and neuro deficits
      - Garfall et al, ASH 2016, #5702

CART-BCMA Cells for Multiple Myeloma

Subject 1

- **66M, IgG kappa MM dx'd April 2006**
  - 11 prior lines, PD on last therapy
  - Pre-treatment bone marrow bx:
  - 70% MM cells
  - FISH: gain CCND1, del17p,
  - loss of MAF (16q)
  - NGS: mutations in *NRAS, TP53, TP53*

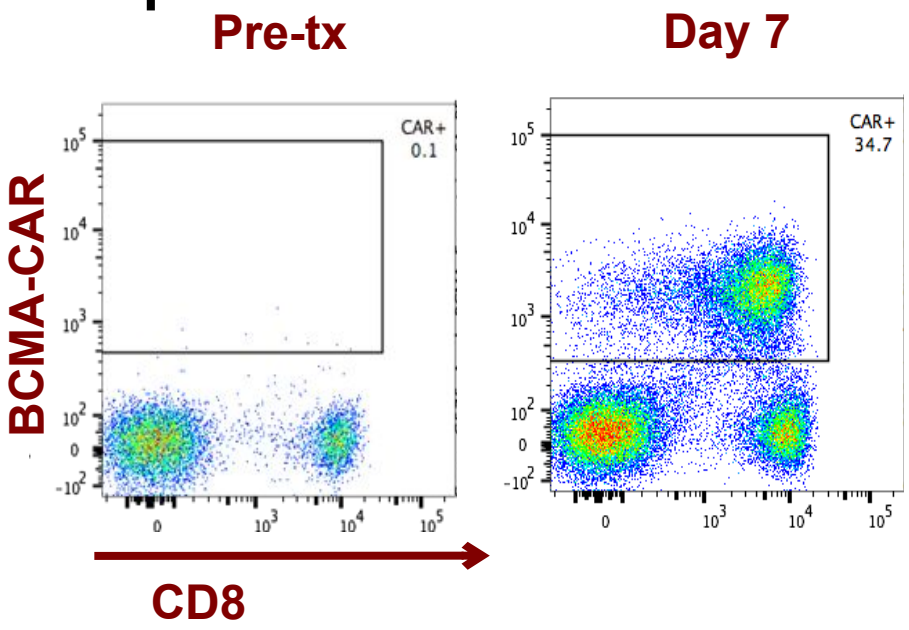
Pre-treatment marrow

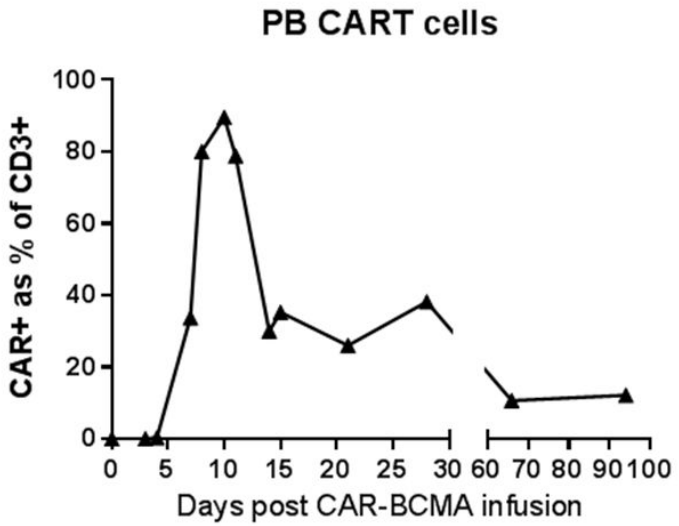


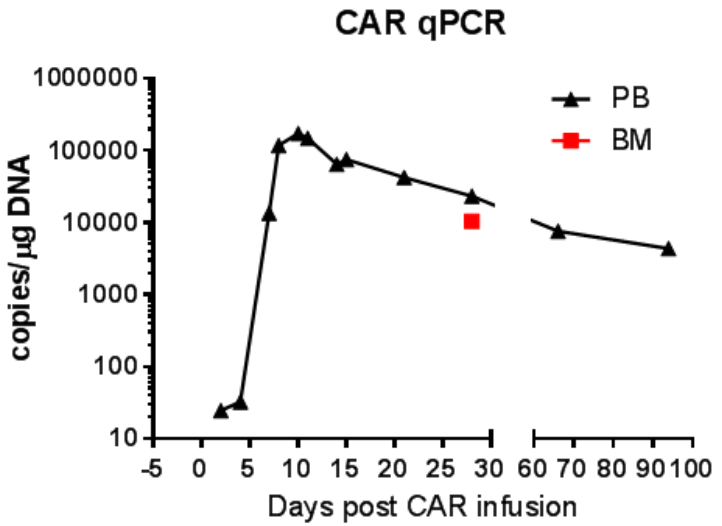
BCMA CAR Cells for Multiple Myeloma

Subject 1

- **2 x 10^8 BCMA CAR cells**
  - no lymphodepletion
- **Grade 3 CRS→ responded to tocilizumab**
- **Robust BCMA CAR expansion and persistence**



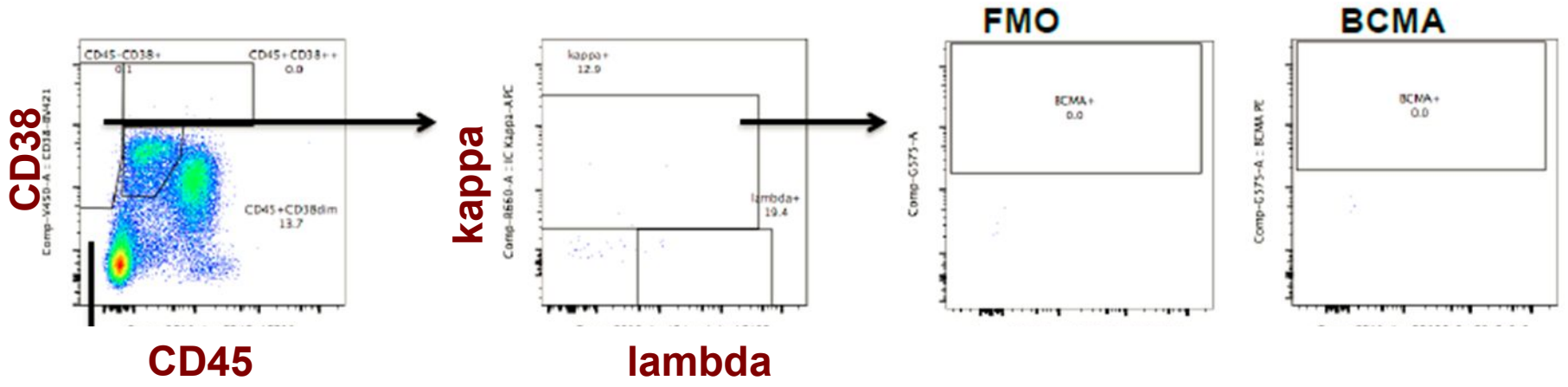


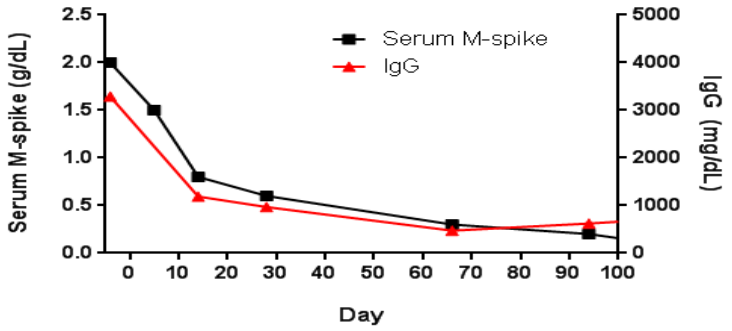


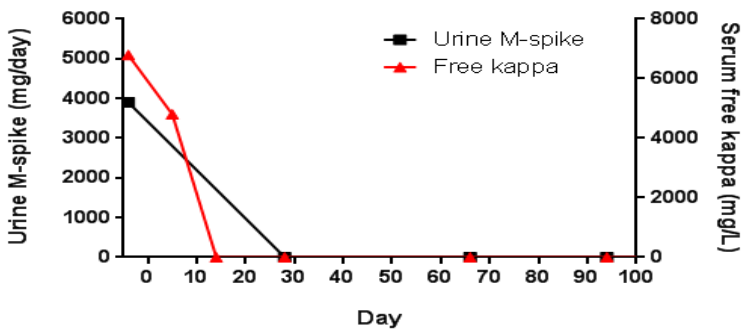
BCMA CAR Cells for Multiple Myeloma

Subject 1

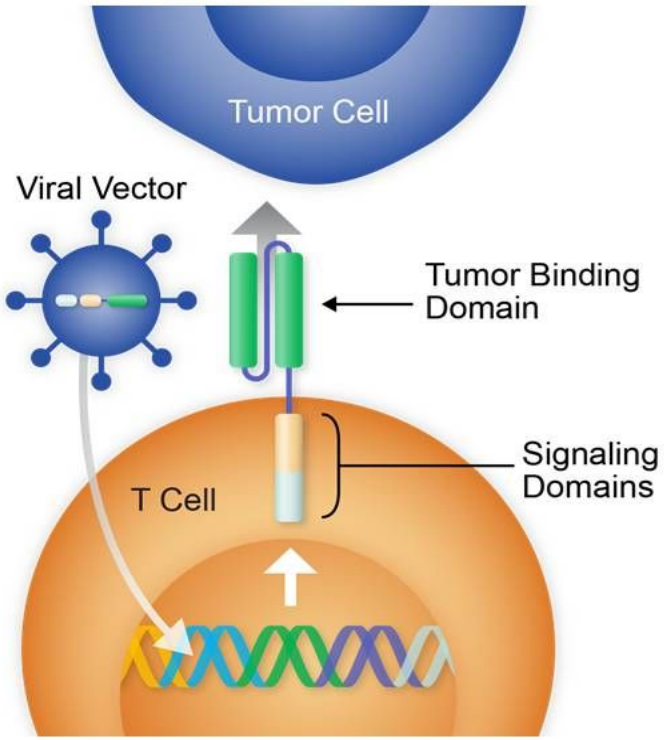
- Day 28 marrow: negative by IHC and flow
- VGPR-> sCR (continued 2.5 years later!)

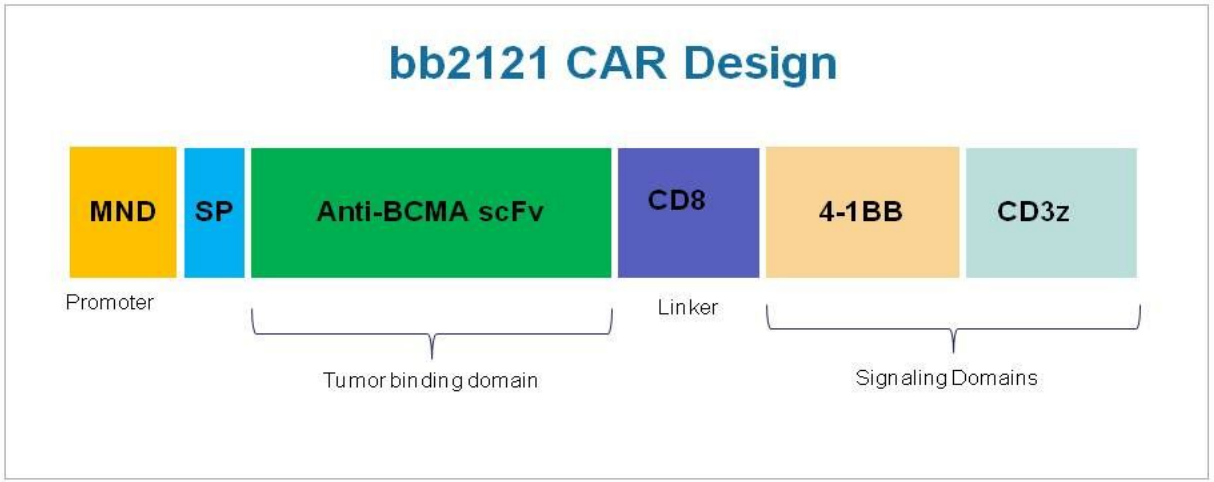






bb2121: AN OPTIMAL BCMA CAR T CELL DESIGN

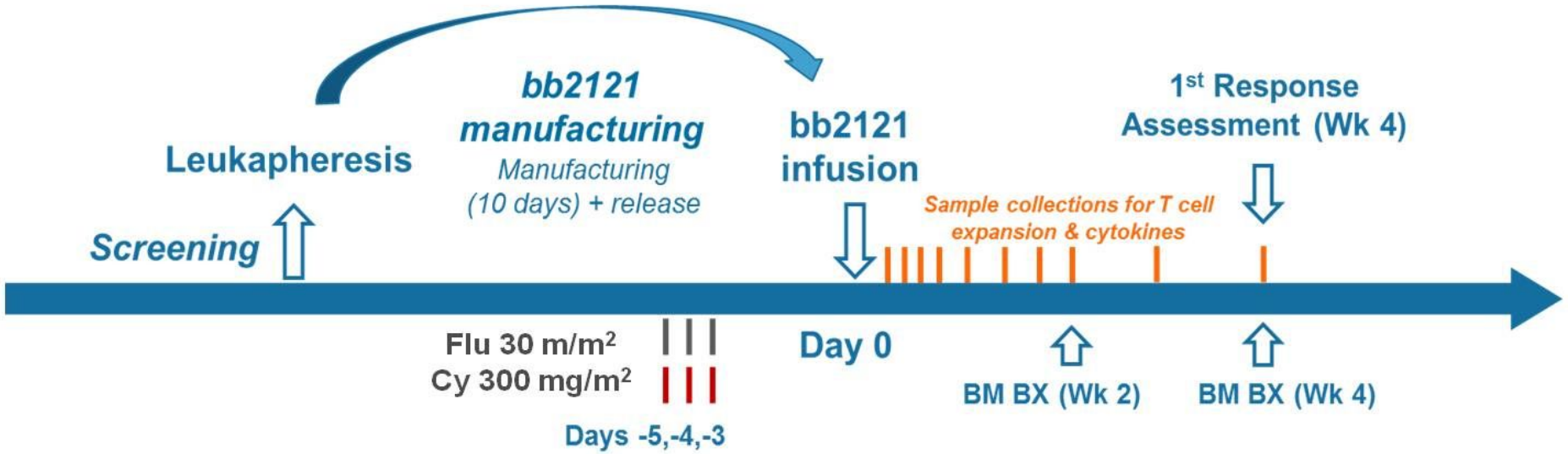




- Autologous T cells transduced with a lentiviral vector encoding a CAR specific for human BCMA
- State of the art lentiviral vector system
- Optimal 4-1BB costimulatory signaling domain: associated with less acute toxicity and more durable CAR T cell persistence than CD28 costimulatory domain[1]

1. Ali SI, et al. *Blood*. 2016;128(13):1688-700.

CRB-401 PHASE 1 STUDY DESIGN



Dose Escalation (N=21)

≥50% BCMA expression

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

Dose Expansion (N=22)

<50% BCMA expression (n=10)

≥50% BCMA expression (n=12)

Dose range: 150–450 × 10^6 CAR+ cells

Manufacturing success rate of 100%

TREATMENT HISTORY

	Escalation (N=21)	Expansion (N=22)
Median (min, max) prior regimens	7 (3, 14)	8 (3, 23)
Prior autologous SCT, n (%)	21 (100)	19 (86)
0	0	3 (14)
1	15 (71)	14 (64)
>1	6 (29)	5 (23)

	Escalation (N=21)		Expansion (N=22)	
	Exposed	Refractory	Exposed	Refractory
Prior therapies, n (%)				
Bortezomib	21 (100)	14 (67)	22 (100)	16 (73)
Carfilzomib	19 (91)	12 (57)	21 (96)	14 (64)
Lenalidomide	21 (100)	19 (91)	22 (100)	18 (82)
Pomalidomide	19 (91)	15 (71)	22 (100)	21 (96)
Daratumumab	15 (71)	10 (48)	22 (100)	19 (86)
Exposed/Refractory, n (%)				
Bort/Len	21 (100)	14 (67)	22 (100)	14 (64)
Bort/Len/Car/Pom/Dara	15 (71)	6 (29)	21 (96)	7 (32)

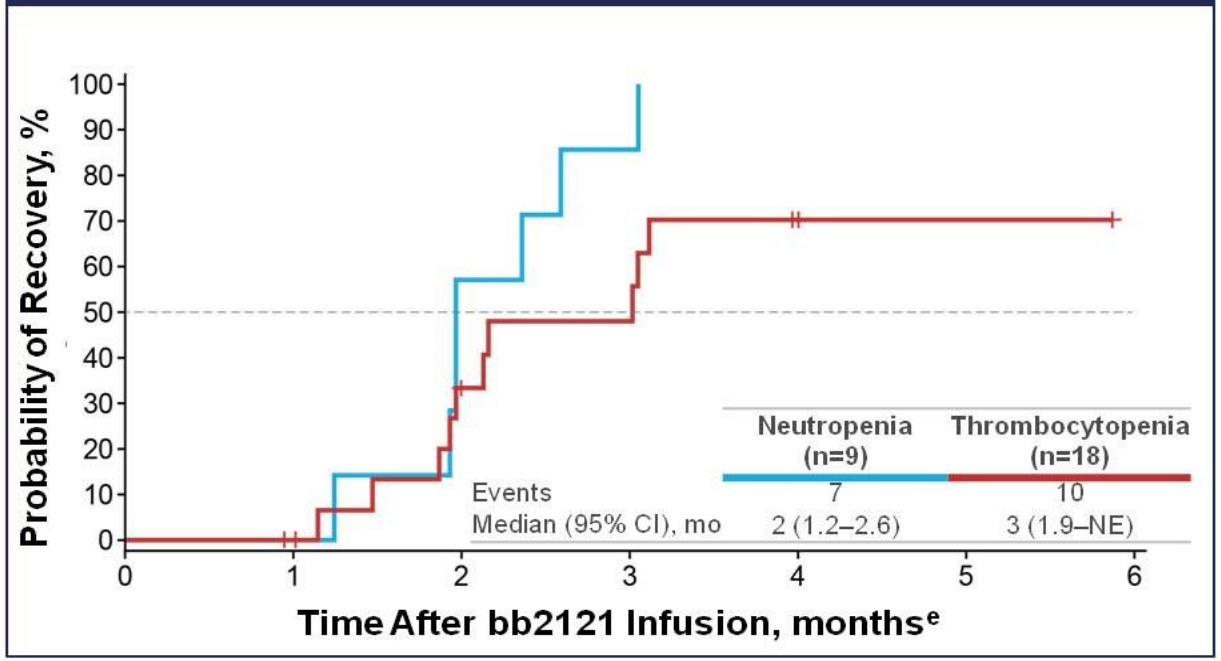
Data cutoff: March 29, 2018. SCT, stem cell transplant.

ADVERSE EVENTS OF SPECIAL INTEREST

CAR T Treatment-Emergent Adverse Events All Infused Patients (N=43)

TEAE, n (%)	Overall	Grade ≥3
Cytokine release syndrome[a]	27 (63)	2 (5)
Neurotoxicity[b]	14 (33)	1 (2)
Neutropenia	35 (81)	34 (79)
Thrombocytopenia	26 (61)	22 (51)
Anemia	24 (56)	19 (44)
Infection[c]		
Overall	26 (61)	9 (21)
First Month	10 (23)	2 (5)

Time to Recovery of Grade 3/4 Cytopenias in Patients Without Recovery by Month 1[d]



- No grade 4 CRS events
- No fatal CRS or neurotoxicity events

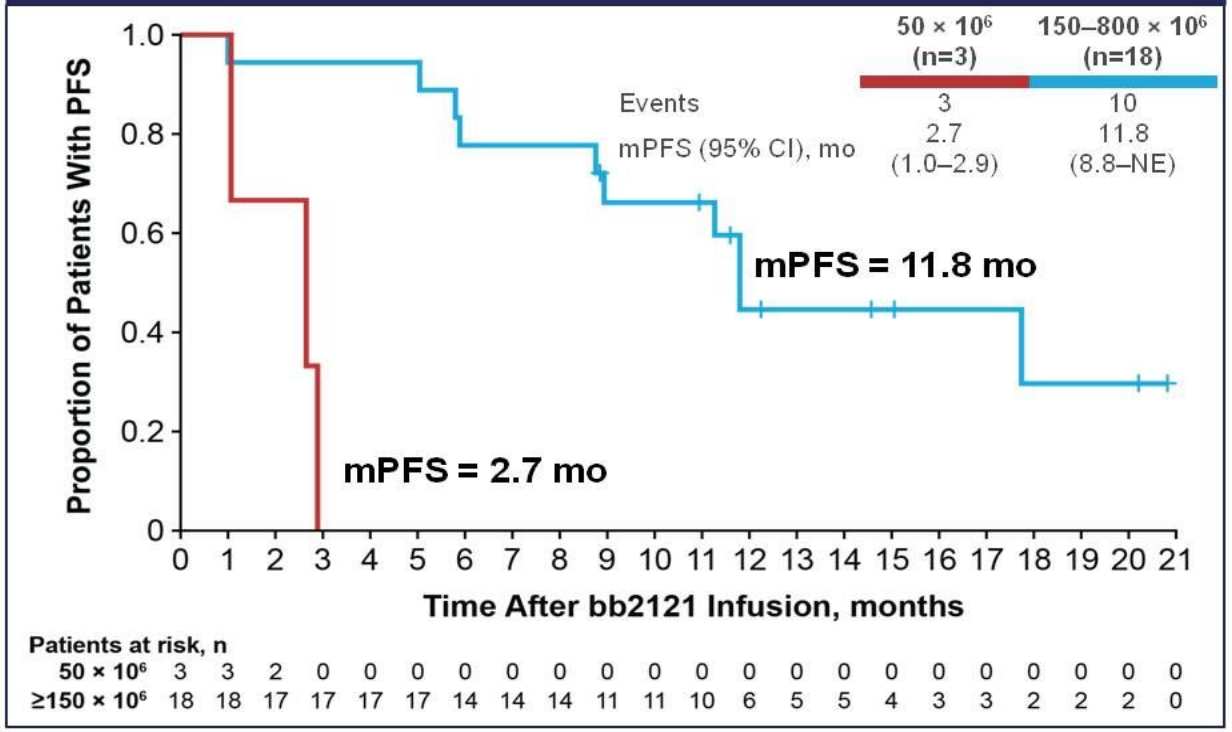
- 31/40 (78%) recovered ANC to ≥1000/μL by Day 32
- 22/40 (55%) recovered PLT to ≥50,000/μL by Day 32

Data cutoff: March 29, 2018. NE, not estimable. [a]CRS uniformly graded per Lee DW, et al. *Blood.* 2014;124(2):188-195. [b]Events occurring in first 28 d and including dizziness, bradyphrenia, somnolence, confusional state, nystagnmus, insomnia, memory impairment, depressed level of consciousness, neurotoxicity, lethargy, tremor and hallucination. [c]Includes the SOC Infections and Infestations. Events observed in >10% include upper respiratory tract infection and pneumonia. [d]Includes patients treated with active doses (150–800 × 10^6 CAR+ T cells; N=40). Median and 95% CI from Kaplan-Meier estimate. [e]Time from first bb2121 infusion to the first grade ≤2 event after day 32.

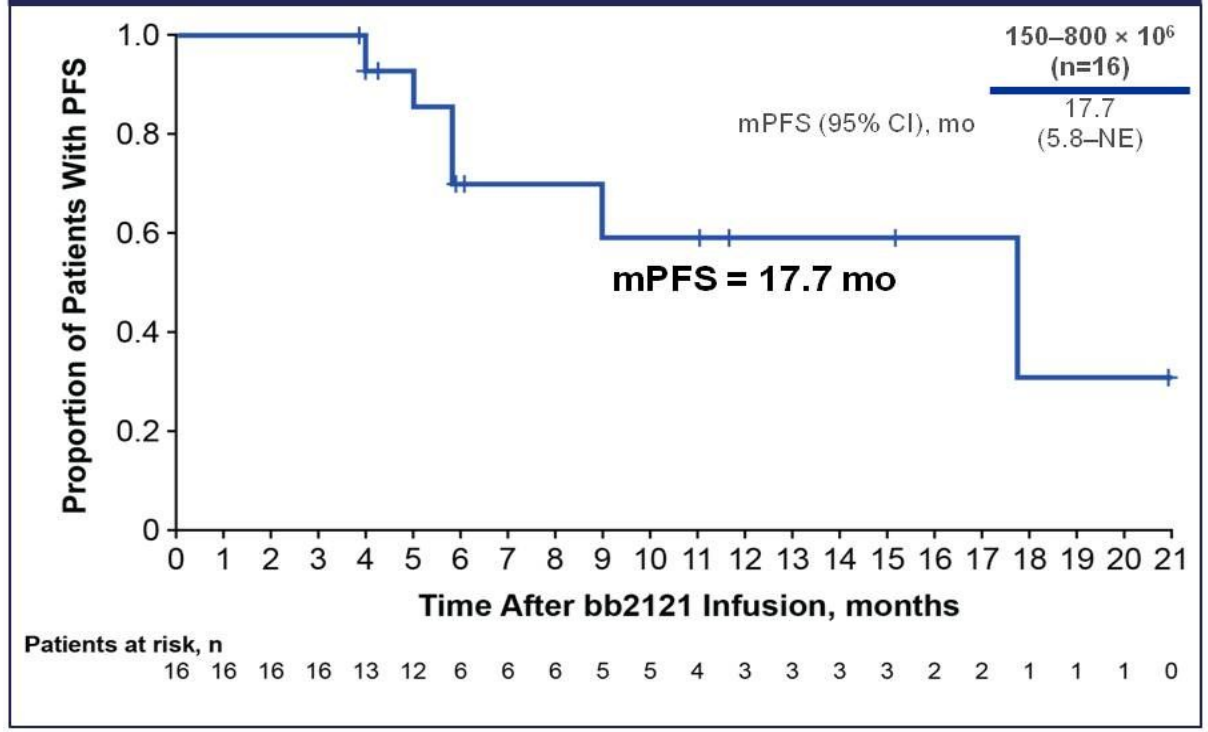
PROGRESSION-FREE SURVIVAL

- mPFS of 11.8 months at active doses (≥150 × 10^6 CAR+ T cells) in 18 subjects in dose escalation phase
- mPFS of 17.7 months in 16 responding subjects who are MRD-negative

PFS at Inactive (50 × 10^6) and Active (150–800 × 10^6) Dose Levels[a]



PFS in MRD-Negative Patients



Data cutoff: March 29, 2018. Median and 95% CI from Kaplan-Meier estimate. NE, not estimable. [a]PFS in dose escalation cohort.

OVERALL SUMMARY

bb2121 at active doses (≥150 × 10^6 CAR+ T cells) induces deep and durable responses in a heavily pretreated population with R/R MM

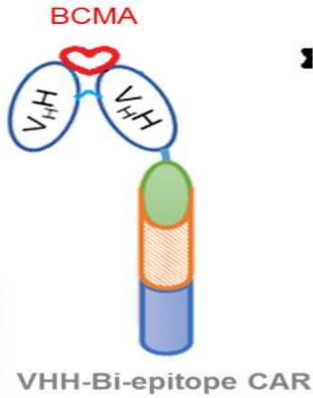
- Median PFS of 11.8 months for patients in the dose escalation cohort
- MRD-negative results in 100% of 16 evaluable responding patients; median PFS of 17.7 months
- Comparable ORR in patients with low and high BCMA-expressing MM
- Dose response relationship observed across the active dose ranges
- Higher peak CAR T expansion in responders versus nonresponders

To date, the safety profile of bb2121 has been manageable at doses as high as 800 × 10^6 CAR+ T cells

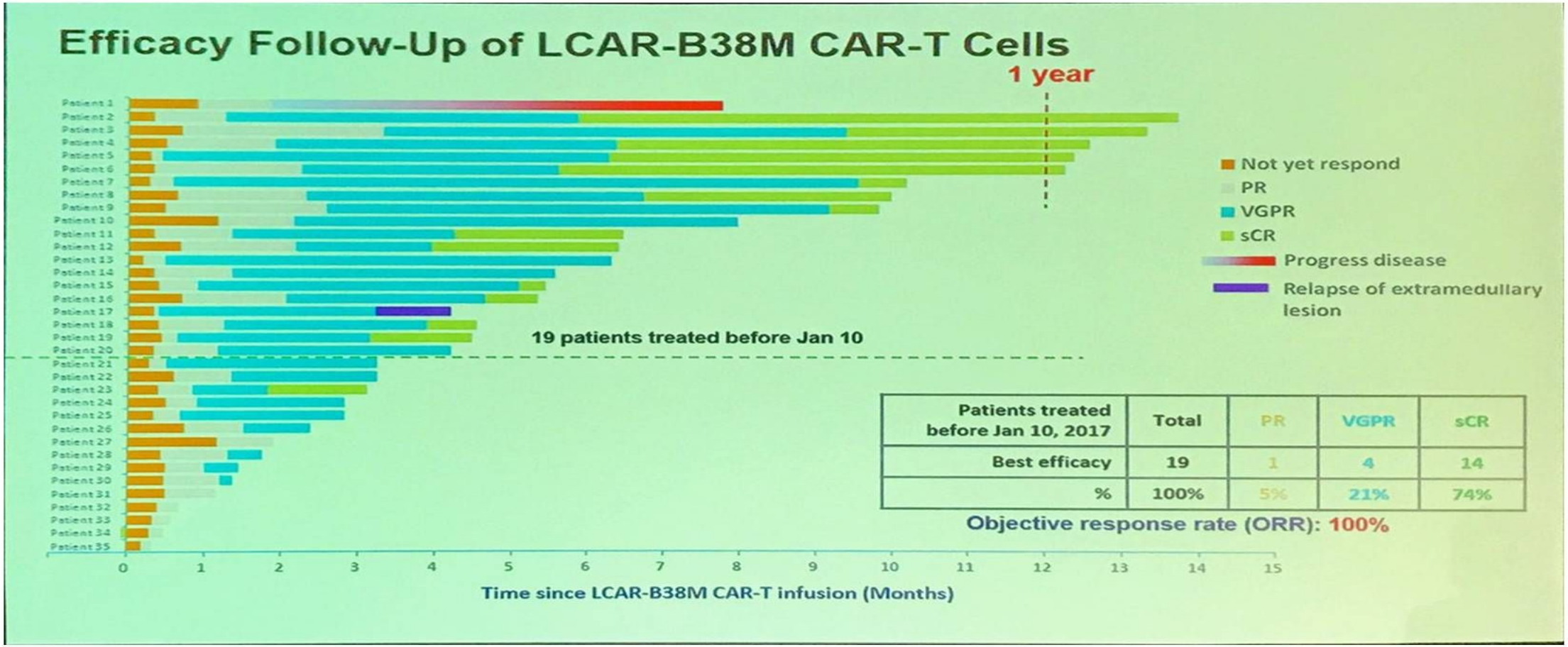
- Mostly grade 1/2 CRS observed with infrequent tocilizumab and corticosteroid use
- The 2 events of grade 3 CRS resolved within 24 hours
- 1 case of reversible grade 4 neurotoxicity without additional events during expansion

Legend Biotech: Phase 1 LCAR-B38M (anti-BCMA CAR T cells) in RRMM

- Novel CAR construct – 2 binding sites for BCMA
- BCMA+ MM cells by flow required
- n=35 enrolled, 19 evaluable for response
- median 3-4 lines (?prior therapies)
- 100% evaluable responded, 74% sCR



VHH-Bi-epitope CAR



Fan et al, ASCO 2017, #LBA3001

Presented By Adam Cohen at 2018 ASCO Annual Meeting

the cure is within
ABRAMSON CANCER CENTER

Comparison of CART-BCMA trials

	NCI	Penn/NVS	Bluebird	Legend
Sites	Single	Single	Multi-center	Multi-center
scFv	Murine	Human	Murine	Camelid
Vector	Gamma-retroviral	Lentiviral	Lentiviral	??
Domains	CD3/CD28	CD3/41BB	CD3/41BB	CD3/41BB
BCMA+ required	Yes (IHC) (52/85 (62%+)	No	Yes (IHC) (60%+)	Yes (flow) (??)
Dosing	0.3 – 9x10⁶/kg 1 day	5 x 10⁸ 3 days	0.5 – 8 x10⁸ 1 day	0.6 – 7x10⁶/kg 3 days
Conditioning	Flu/Cy	None or Cy	Flu/Cy	Cy
Med # priors	7*	7	6	3-4
*includes XRT				

Ali et al, Blood 2016; Cohen et al, ASH 2016; Lin et al, EHA 2017; Fan et al, ASCO 2017

Designing Better CARS

- **Targets**
  - Single vs multiple
- **Constructs**
  - antigen recognition
  - stimulatory molecules
- **Vectors**
  - Viral
  - Non-viral approaches
- **Dose**
- **Off switches**
- **Lympho-depletion**
- **Single vs serial infusions**
- **Patient selection**
  - Test for target
  - Early vs heavily pre-treated disease
  - Early vs dysfunctional T-cells
  - Early vs late dysfunctional host

CAR T cells for MM in 2018

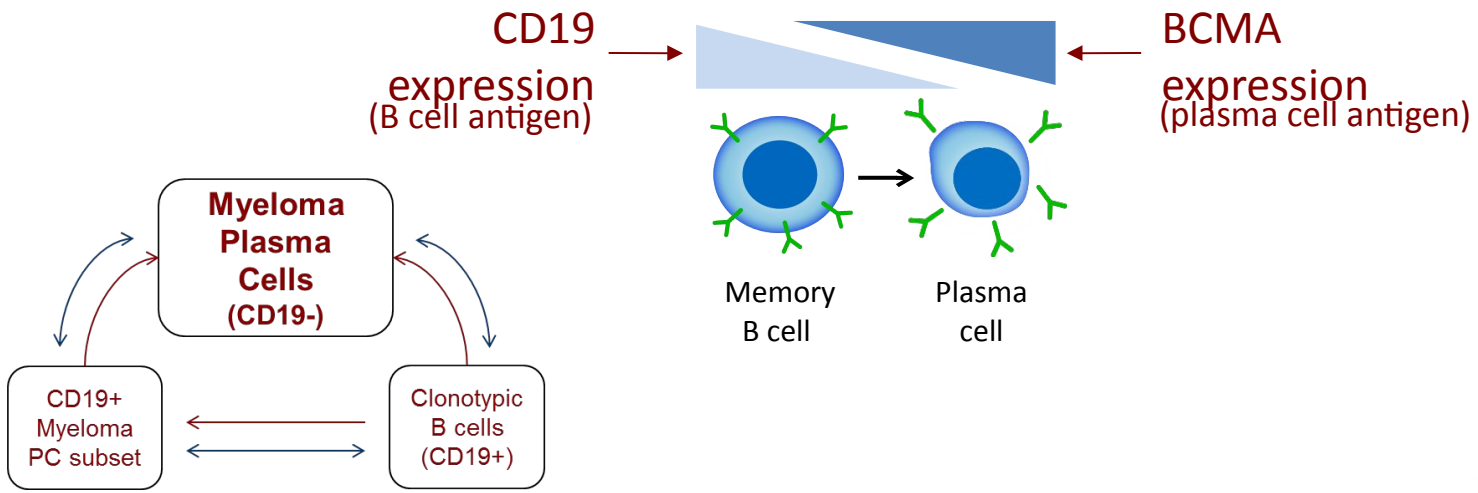
Antigen	Trial Site/Company	Accrual
BCMA	National Cancer Institute	completed (n=26)
BCMA	University of Pennsylvania / Novartis	completed (n=25)
BCMA	Multi-site phase 1/ Bluebird	ongoing (n=21 reported)
BCMA	Multi-site phase 2/ Bluebird	ongoing
BCMA	Multi-site phase 1 / Bluebird (bb21217 product)	ongoing
BCMA	Multi-site phase 1/2, Nanjing Legend	ongoing (n=19 reported)
BCMA	Memorial Sloan-Kettering / Juno	ongoing (n=6 reported)
BCMA	Fred Hutchinson / Juno	ongoing
BCMA	Multi-site phase 1/2, Juno	ongoing
BCMA	Multi-site phase 1, Poseida	ongoing
BCMA	Multi-site phase 1, Kite	ongoing
BCMA	Multiple hospital sites in China	ongoing
BCMA	Multi-site phase 1/2, Autolus Limited	ongoing
BCMA	Virginia Cancer Specialists, Cartesian Therapeutics	ongoing

Antigen	Trial Site/Company	Accrual
CD19	University of Pennsylvania / Novartis	completed (n=10)
CD19 + BCMA	University of Pennsylvania / Novartis	open 2018
CD19 + BCMA	Soochow University, China	ongoing (n=10 reported)
CD138	General Hospital of PLA, China	completed (n=5)
CD138	Soochow University, China	ongoing
Kappa LC	Baylor University	completed (n=7 MM)
CD38	Multi-site phase 1, Sorrento Therapeutics	ongoing
CD38	Shenzhen Geno-Immune Medical Institute, China	ongoing
CD38	n/a	pre-clinical
SLAMF7/ CS1	n/a	pre-clinical

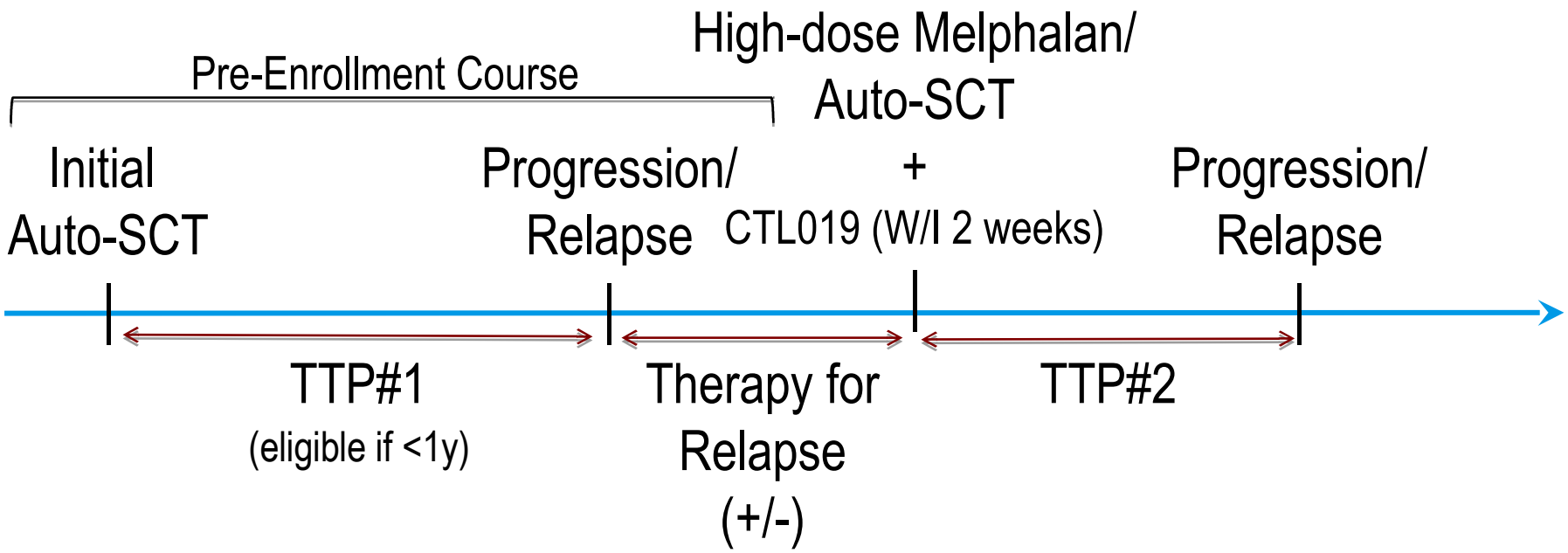
www.clinicaltrials.gov, March 2018

Rationale for anti-CD19 therapy in myeloma

- **Plasma cells are derived from B-lymphocytes so malignant precursors likely are CD19 + even if the majority of plasma cells are CD19 neg by conventional flow cytometry**
- **Intraclonal heterogeneity (and plasticity) in myeloma**
  - Genetic: somatic mutations, copy number abnormalities, cytogenetic features.
  - Phenotypic: B cell ⟷ Plasma cell
  - Functional: Stem-cell/clonogenic ⟷ Non-clonogenic
- **The B cell phenotype may be associated with stem-cell/clonogenic properties and CD19+ cells may be a reservoir of resistant precusors**
- **Specifically targeting B cells may improve durability of response to PC-directed therapies**



Pilot Study of CART19 in Multiple Myeloma: Al Garfall PI (Support of hypothesis design)



Eligibility Criteria

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

Primary Endpoints

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

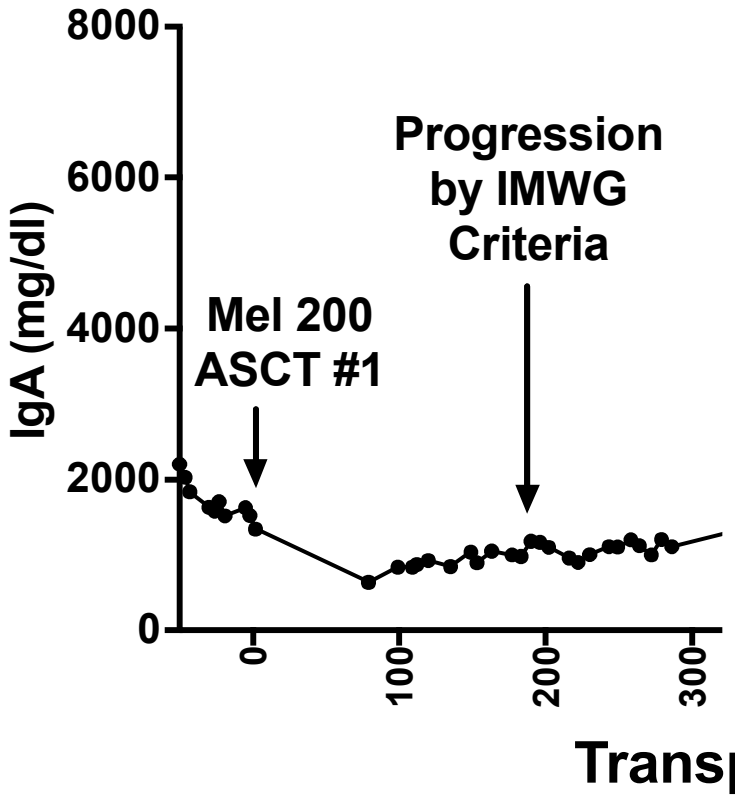
Secondary Endpoints

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

In our retrospective analysis of second salvage ASCT for r/r MM in "modern era", 56% response (≥PR), no remission inversions.

Garfall et al, NEJM September 10 2015

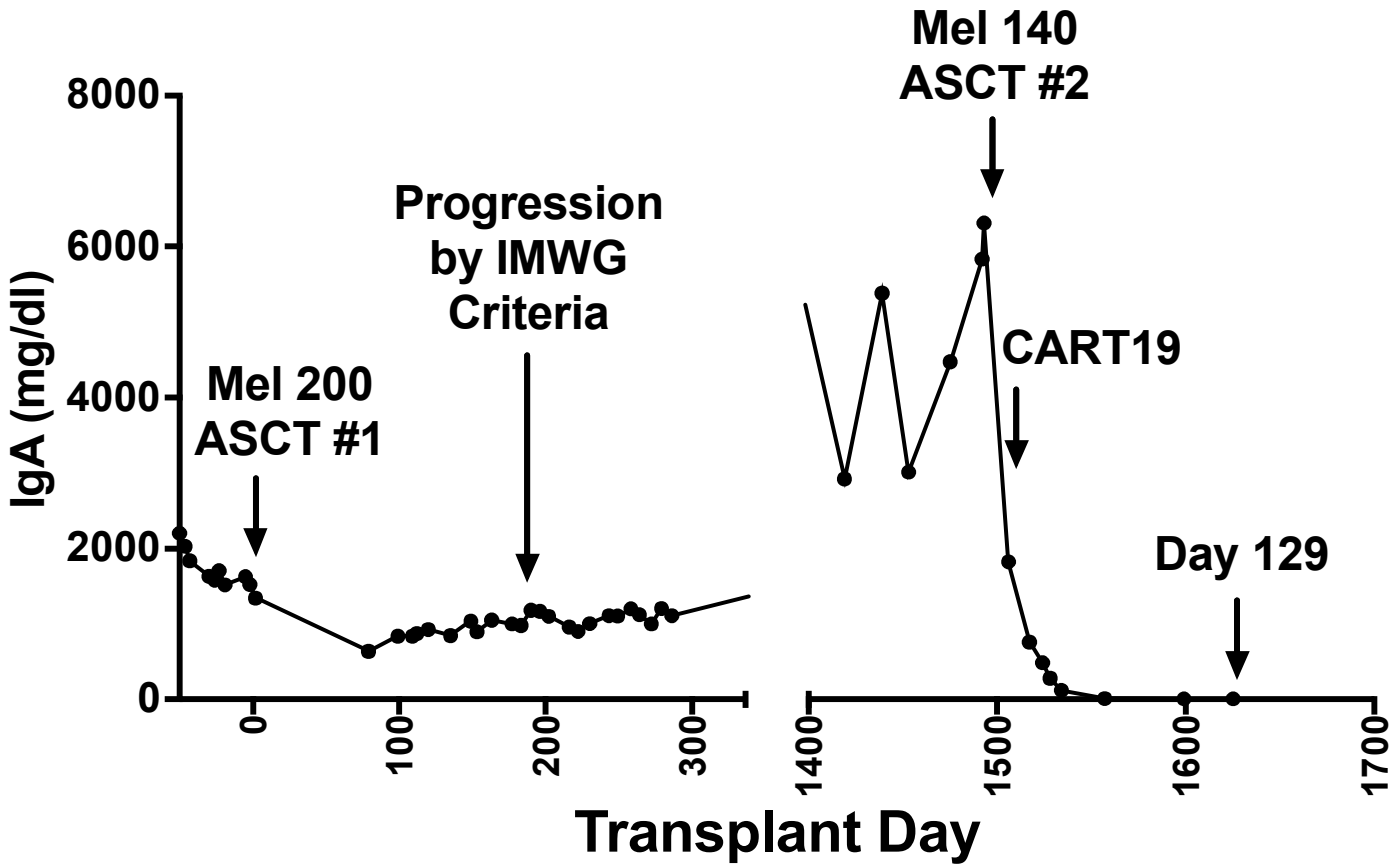
Pilot Study of CTL019 in Advanced Multiple Myeloma: Pt - 01



48 y/o F
IgA kappa
TTP 6 mo after ASCT #1
10 prior lines of therapy over 5 years
Lenalidomide, pomalidomide, Bortezomib, carfilzomib, MEL 200 SCT, Vorinostat, elotuzumab, cyclophosphamide

Garfall et al, NEJM September 10 2015

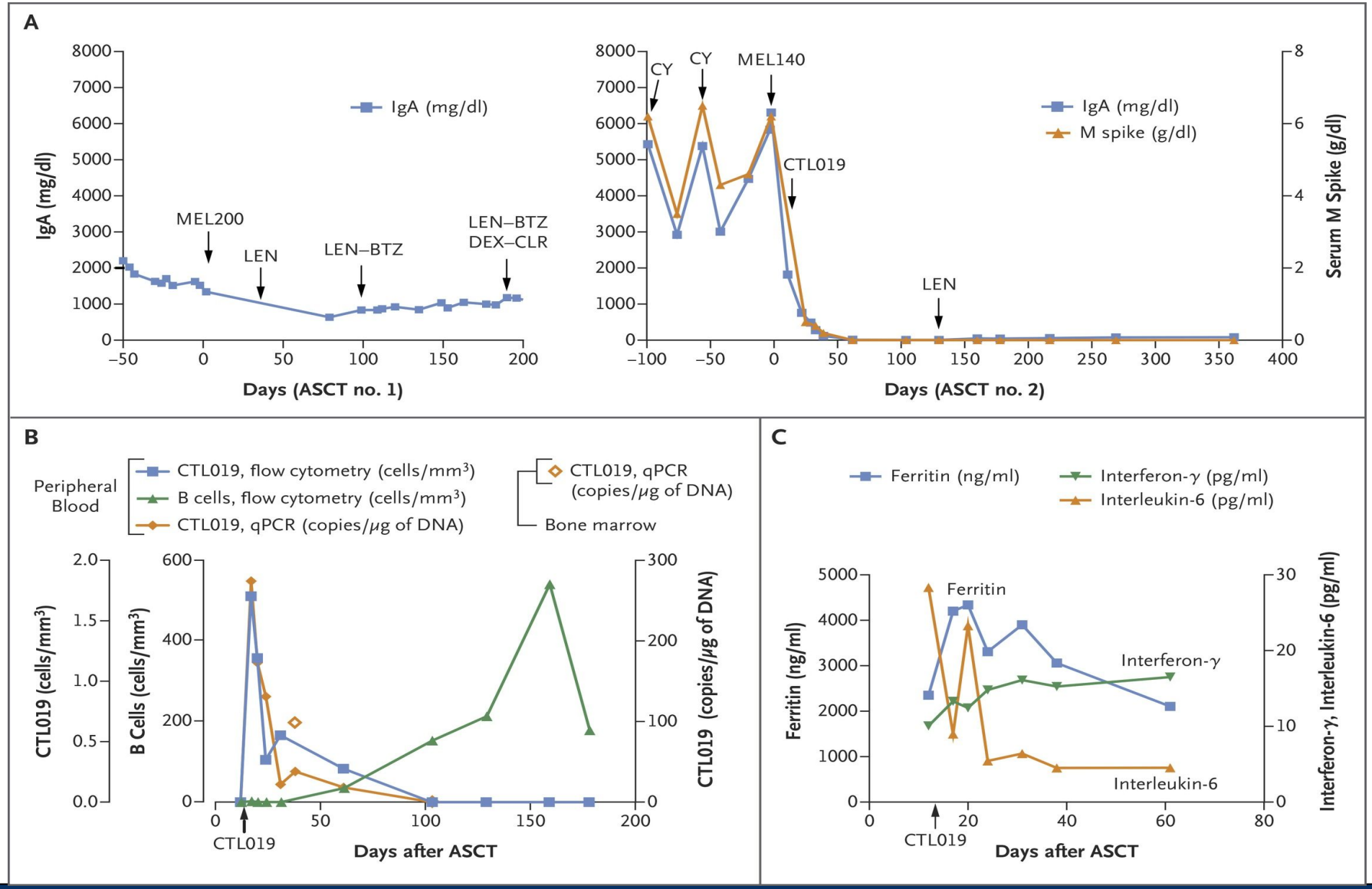
Pilot Study of CTL019 in Advanced Multiple Myeloma: Pt 02413-01



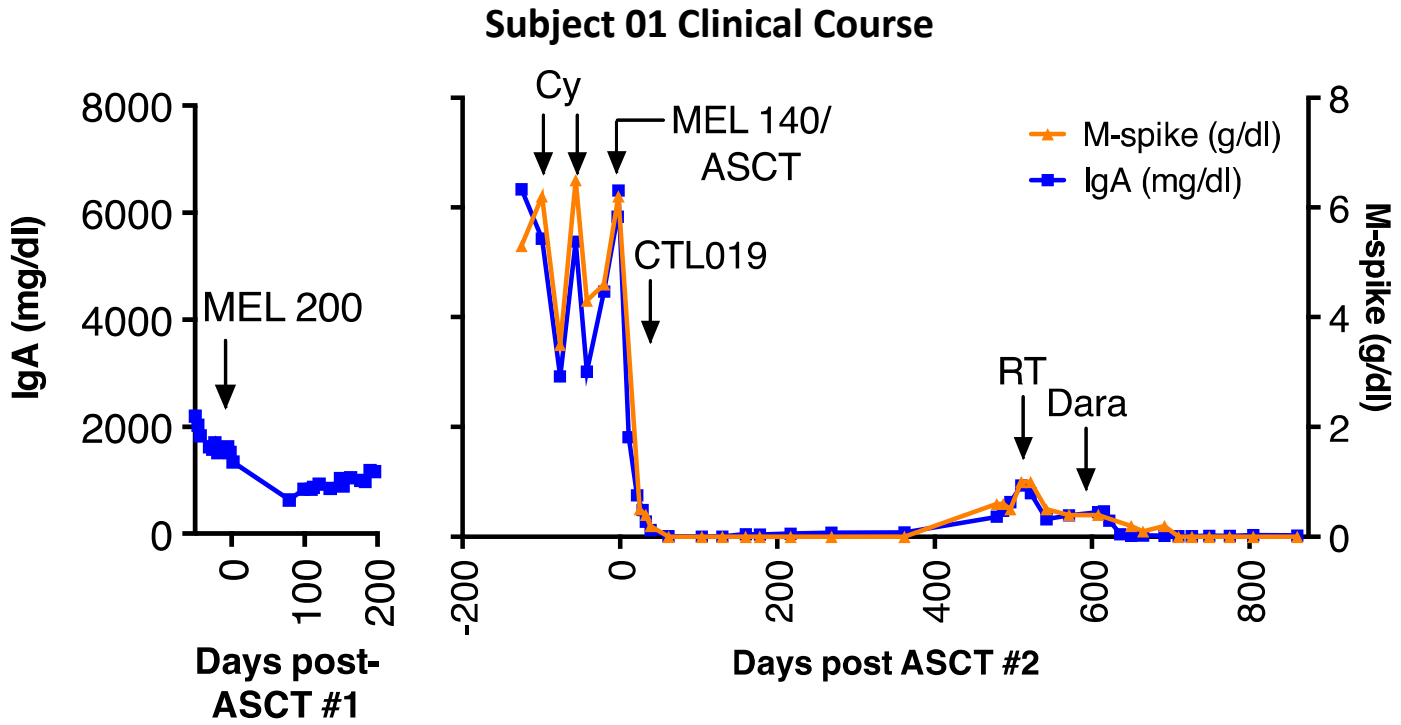
Garfall et al, NEJM September 10 2015

CD19 negative PCs
Clinical CR
MRD neg (flow/deep sequencing)

Pilot Study of CTL019 in Advanced Multiple Myeloma: Pt 02413-01



Clinical responses after ASCT + anti-CD19 CAR T cells

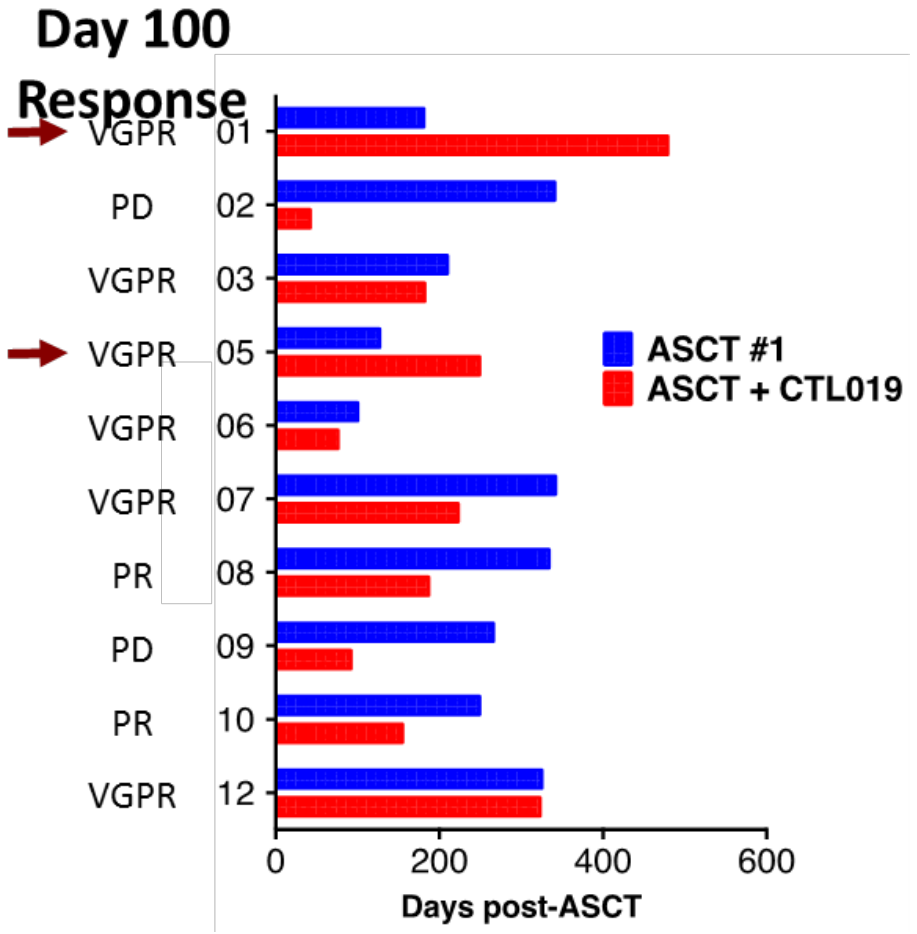


Subjects 01 (and 05) progressed with isolated extramedullary plasmacytomas and negative bone marrows.

Garfall et al, ASH 2016, #974

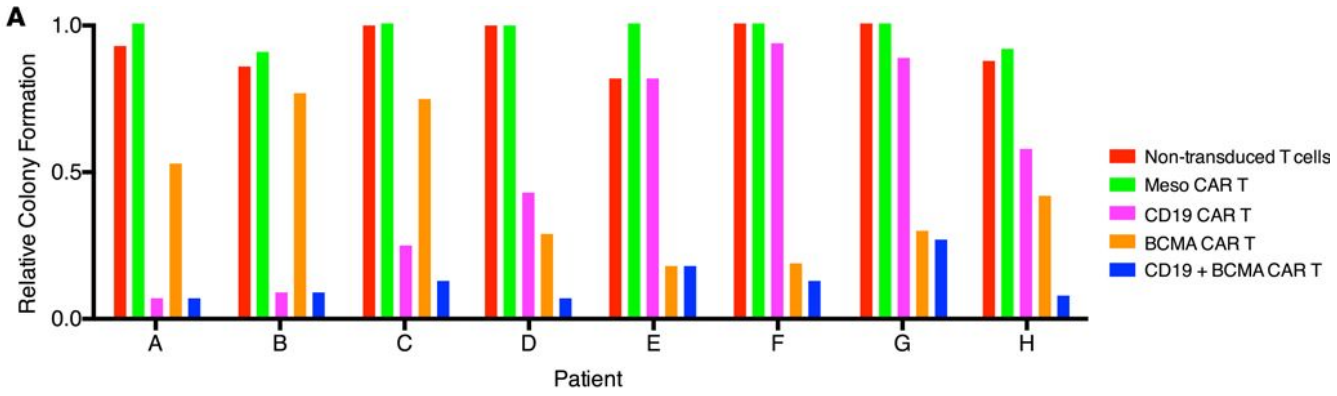
Patient Characteristics and Outcomes

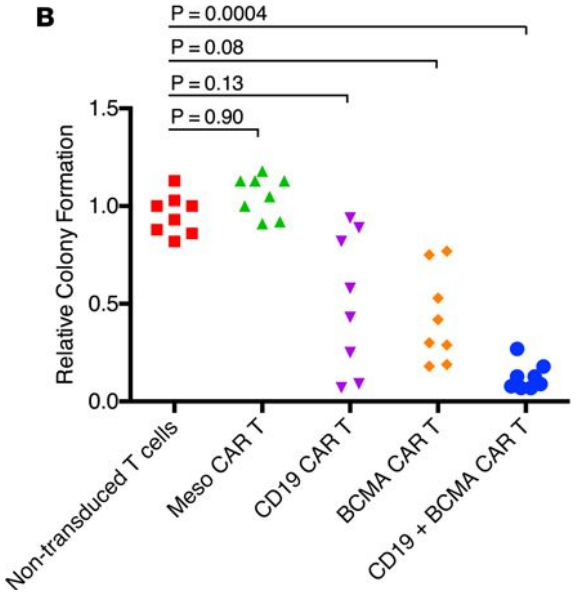
ID	Age/ Sex	TTP1 (days)	Prior Tx	Baseline Prognostic Features	Mel. Dose
1	48F	181	10	Complex karyotype, t(4;14), del17p, +1q21	140
2	58M	341	7	Complex karyotype, BRAFV600E	200
3	65F	210	3	Plasma cell leukemia	140
5	64F	127	7	t(4;14), +1q, <PR to induction	140
6	53M	100	2	BRAF V600E mutation	140
7	62F	342	6	Not available	140
8	57F	334	4	t(4;14), +1q	200
9	62M	266	4	t(4;14), +1q	140
10	68F	249	10	del(17p), +1q	140
12	59M	325	6	Not available	200



Garfall et al, ASH 2016, #974

Dual BCMA/CD19 Directed CAR Myeloma Trial





Correlates of favorable clinical outcome

- peak CTL019 frequency in bone marrow
- emergence of humoral and cellular immune responses against the stem-cell antigen Sox2.

- **Ex-vivo treatment of primary myeloma samples with a combination of CTL019 and BCMA CAR T**
  - reliably inhibited myeloma colony formation in vitro while either alone inhibited colony formation inconsistently.

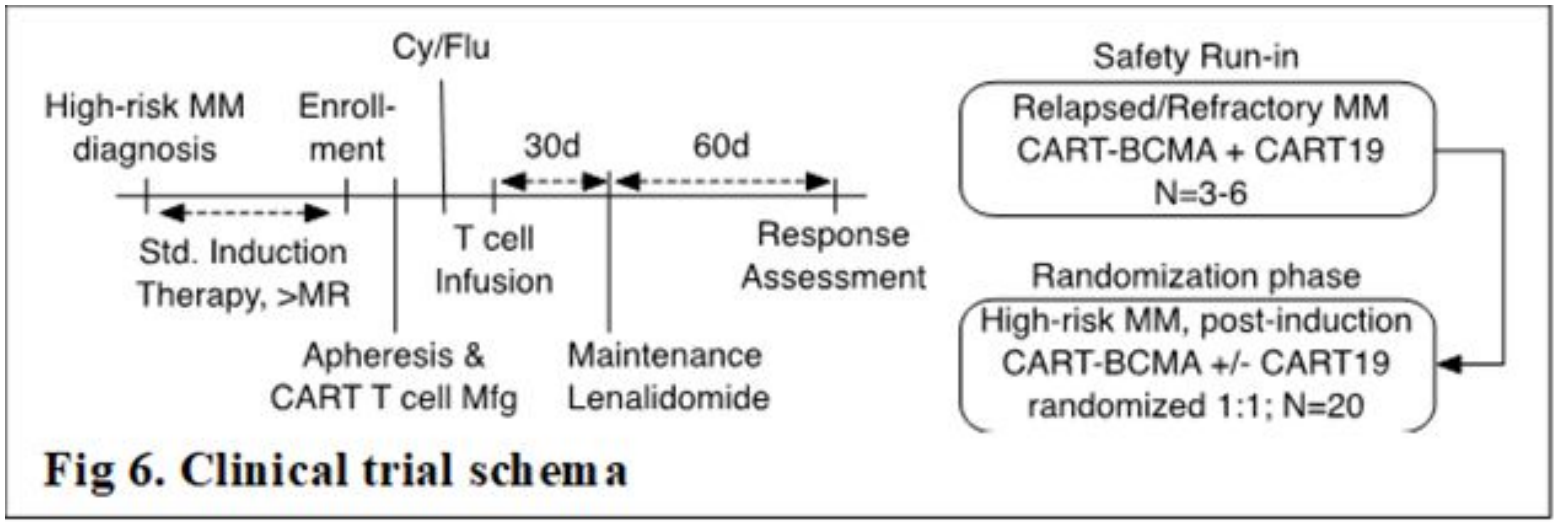


Fig 6. Clinical trial schema

Garfall et al, NEJM 2015, JCI Insight 2018

NY-ESO1 TCR T cells

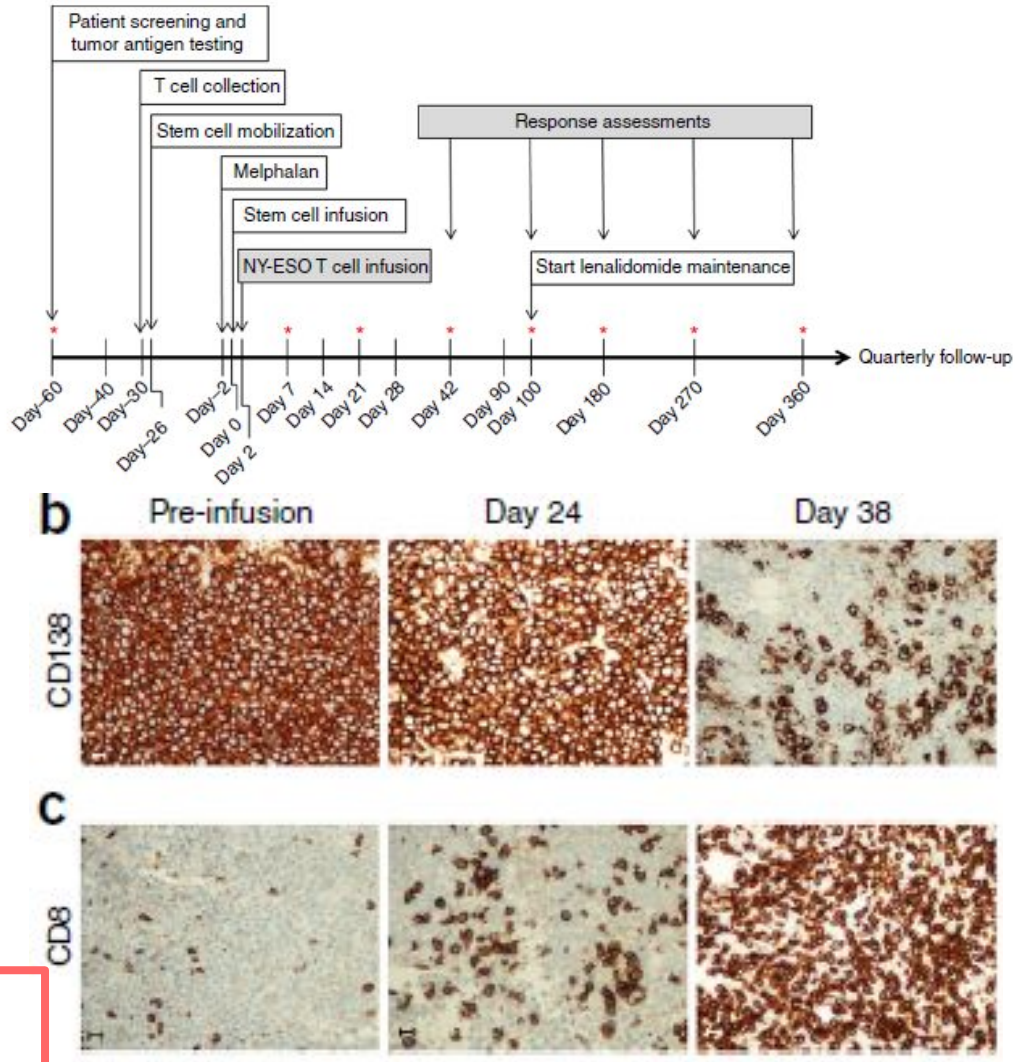
Phase 1/2 of autologous NY-ESO1-specific T cells after autoSCT in MM (n=25)

- **Well-tolerated**
- **T cells expanded, homed to BM, persisted in some**
- **70% nCR/CR**

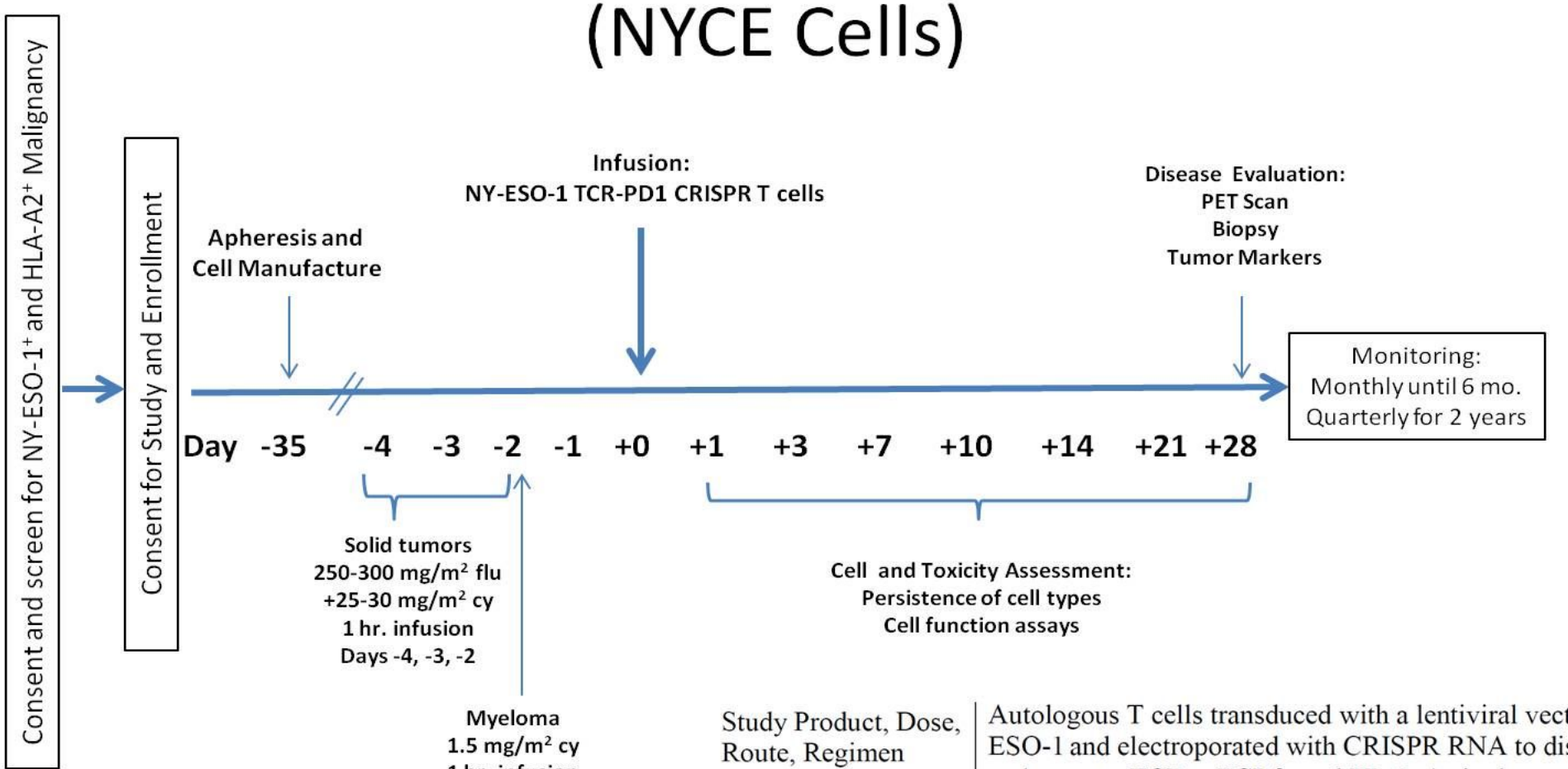
- **Median progression-free survival 19.1 mos**

- **Relapse assoc. with loss of NYESO1 or T cells**

Pilot study of CRISPR gene-edited, NY-ESO1-specfic T cells in MM, sarcoma, and melanoma
- **To open 2018**
  - **Penn, MDACC, UCSF**



NY-ESO-1 CRISPR (TCR-PD1) Triple Edited T Cell Study Schema (NYCE Cells)



Study Product, Dose, Route, Regimen	Autologous T cells transduced with a lentiviral vector to express NY-ESO-1 and electroporated with CRISPR RNA to disrupt expression of endogenous TCRα, TCRβ, and PD-1. A single manufacturing site at UPENN will be used for all subjects enrolled into this study. A single dose of $1x10^8$cells/kg will be given i.v.

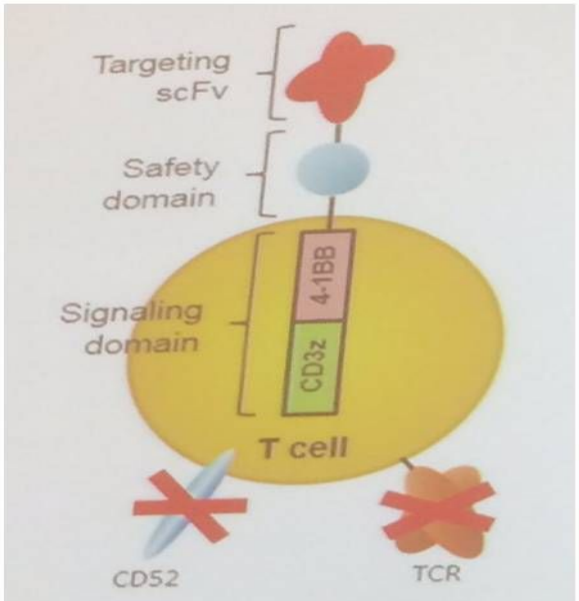
IND 17297 and Clinicaltrials.gov NCT03399448
Sponsor: Tmunity and Parker Institute for Cancer Immunotherapy

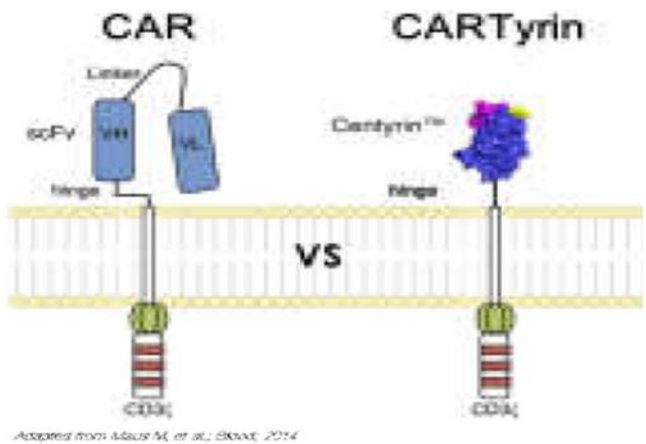
What's next for cellular therapy?

- **Gene-editing**
  - "Universal" CAR T cells
  - PD-1 knock-out
    - Ph 1 of CRISPR/Cas9 gene-edited NY-ESO1 TCR T cells
- **Suicide genes/safety domains**
- **Novel constructs, vectors**
- **Serial infusions/re-treatment**
- **Combinations**
  - IMiDs
  - Checkpoint blockade
  - Cytokines
  - Vaccines
  - Multiple CARs
- **Earlier treatment**

CANCER

Molecular remission of infant B-ALL after infusion of universal TALEN gene-edited CAR T cells





Qasim et al, Sci Trans Med 2017; Hermanson et al, ASH 2016, #383; Boldajipour et al, ASH 2016, #381; Chong et al, Blood 2016

Myeloma Cellular and Vaccine Immunotherapy:

- **Investigation of cellular and vaccine therapy for myeloma has been ongoing for almost 2 decades**
- **Myeloma specific targeted vaccinations show immune responses but limited clinical responses**
  - Dendritic cell vaccines most promising
- **Cellular vaccine approaches have been most frequently added after myeloablative alkylating agent chemotherapy and AHCT**
  - Frequent evidence for immune response but limited evidence for incremental clinical benefit
- **Multiple promising targets for CARs, MILs and affinity enhanced TCRs:**
  - BCMA, NY-ESO-1, CD19, CD138, CD38, CD56, kappa, Lewis Y, CD44v6, CS1
- **Functional CAR and affinity enhanced TCR T cells can be generated from MM patients**
- **CAR T and TCR T and NK cells have in vitro and in vivo activity against MM**
- **Remarkable clinical responses have been seen with BCMA and CD19 genetically modified T Cells**
  - Not all patients
  - CRS, CNS, GVHD and on target-off tumor toxicities have generally been limited in frequency, duration and severity
  - Need to study approaches to engineer improved activity, persistence and decreased toxicity
- **The age of cellular immunotherapy for myeloma is upon us!**

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Penn Medicine

the cure is within
ABRAMSON CANCER CENTER