Cellular Immunotherapy for Myeloma

Edward A. Stadtmauer, MD
Chief, Hematologic Malignancies Section
Professor of Medicine
Abramson Cancer Center
University of Pennsylvania
Philadelphia, Pa

IMF Symposium
October 13, 2018
Immunotherapy for MM: Targets and Tools

ADCs
GSK2857916

Summary

Immune checkpoint inhibitor:
Anti–PD-L1/PD-1

ADCs

mAbs:
Eotuzumab
Daratumumab

CARS

Tumor-specific TCR

mAbs:

Bone marrow stromal cells

Malignant plasma cells

IMIDs:
Thalidomide
Lenalidomide
Pomalidomide

NK cells

DCs

Vaccines:
Tumor–DC fusion

DC

NK cell

IL-2

IFNγ

T cells

PD-1

Tregs

CD38

BCMA

CD19

MAGE

WT-1

XSP1

CCR New Strategies

© 2016 American Association for Cancer Research

Adoptive T cell therapy (three major approaches)

- June et al Sci Trans Med 2015
Making CAR T-Cells

1. T cells are isolated from patient
2. T cells are engineered to express CARs that recognize cancer cells
3. Modified T cells are grown and expanded in culture
4. Modified T cells are infused into patient
How CAR T-Cell Therapy Works

Viral DNA insertion

Expression of CAR

CAR enables T cell to recognize tumor cell antigen

Antigen

CAR T cells multiply and release cytokines

Tumor cell apoptosis
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

July 31, 2010
1st CART19 Infusion
8 yrs ago (CLL)

6 yr ago
(ALL)

Porter, 2011
Grupp, 2013
Maude, 2014
Garfall, 2015

Genetic engineering
Synthetic Biology
Patient Donates Cells

Pediatric Oncology: ALL
Cytokine Release Syndrome

T cell transfusion

Expand T cells

CVPF

Adult Oncology: ALL, CLL, DLBCL, MCL, Myeloma

4 yrs ago (MM)

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-Editing Leukemia Treatment,
Costing $475,000 R/R ALL (age <25 yr)
CD19 Directed 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
CAR T Therapy is Complicated and Expensive
Is the Juice Worth the Squeeze?

HEALTH TECHNOLOGY ASSESSMENT

VOLUME 21  ISSUE 7  FEBRUARY 2017
ISSN 1366-5278

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

Designing a Myeloma CAR: Candidate antigen targets

❖ The classics:
  - CD138
  - CD38
  - CD56
  - kappa light chain

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

And… CD19 as a target in myeloma?
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

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

Cohort 1
1 - 5 x 10^8 CAR+ T cells (n=3-6)
Up to n=9

Cohort 2
Cytox 1.5 g/m^2 + 1 - 5 x 10^7 CAR+ T cells (n=3-6)
Up to n=9

Cohort 3
Cytox 1.5 g/m^2 + 1 - 5 x 10^8 CAR+ T cells (n=3-6)
Up to n=9

4 week delay between subjects

Cohen et al, ASH 2017, #505
### Treated Patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>All patients (n=24)</th>
<th>Cohort 1 (n=9)</th>
<th>Cohort 2 (n=5)</th>
<th>Cohort 3 (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>58 (44-75)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td>67% M; 33% F</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Yrs from diagnosis</strong></td>
<td>4.6 (1.8 – 14.5)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Prior lines of therapy</strong></td>
<td>7 (3-13)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lenalidomide</td>
<td>100%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bortezomib</td>
<td>100%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pomalidomide</td>
<td>92%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carfilzomib or Oprozomib</td>
<td>96%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daratumumab</td>
<td>75%</td>
<td>44%</td>
<td>80%</td>
<td>100%</td>
</tr>
<tr>
<td>Dual- / Quad- / Penta-refractory</td>
<td>96% / 54% / 42%</td>
<td>89% / 56% / 33%</td>
<td>100% / 60% / 40%</td>
<td>100% / 50% / 50%</td>
</tr>
<tr>
<td>Autologous / Allogeneic SCT</td>
<td>92% / 4%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>100%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-PD1</td>
<td>29%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>High-risk genetics</strong></td>
<td>96%</td>
<td>6%</td>
<td>33%</td>
<td>42%</td>
</tr>
<tr>
<td>-17p or TP53 mutation</td>
<td>71%</td>
<td>6%</td>
<td>33%</td>
<td>42%</td>
</tr>
<tr>
<td>Extramedullary dz</td>
<td>29%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>% BM plasma cells</strong></td>
<td>70% (0 - 95)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Clinical activity

Cohort 1
1-5 x 10⁸ CART-BCMA

Cohort 2
Cytox + 1-5 x 10⁷ CART-BCMA

Cohort 3
Cytox + 1-5 x 10⁸ CART-BCMA

ORR (≥PR) @ 10e8 = 10/19 (53%)
Median DOR = 4 months

Cohen et al, ASH 2017, #505

**Measurable by PET/CT; FDG-neg at d28, d90
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
Subject 1

- $2 \times 10^8$ 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

CRB-401 PHASE 1 STUDY DESIGN

Dose Escalation (N=21)

≥50% BCMA expression

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

Dose Expansion (N=22)

<50% BCMA expression (n=10)
≥50% BCMA expression (n=12)
Dose range: 150–450 x 10^6 CAR+ cells

Manufacturing success rate of 100%
### TREATMENT HISTORY

<table>
<thead>
<tr>
<th></th>
<th>Escalation (N=21)</th>
<th>Expansion (N=22)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median (min, max)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>prior regimens</td>
<td>7 (3, 14)</td>
<td>8 (3, 23)</td>
</tr>
<tr>
<td>Prior autologous SCT, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>21 (100)</td>
<td>19 (86)</td>
</tr>
<tr>
<td>1</td>
<td>15 (71)</td>
<td>14 (64)</td>
</tr>
<tr>
<td>&gt;1</td>
<td>6 (29)</td>
<td>5 (23)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Escalation (N=21)</th>
<th>Expansion (N=22)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior therapies, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bortezomib</td>
<td>21 (100)</td>
<td>22 (100)</td>
</tr>
<tr>
<td>Carfilzomib</td>
<td>19 (91)</td>
<td>21 (96)</td>
</tr>
<tr>
<td>Lenalidomide</td>
<td>21 (100)</td>
<td>20 (91)</td>
</tr>
<tr>
<td>Pomalidomide</td>
<td>19 (91)</td>
<td>20 (91)</td>
</tr>
<tr>
<td>Daratumumab</td>
<td>15 (71)</td>
<td>18 (82)</td>
</tr>
<tr>
<td>Exposed/Refractory, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bort/Len</td>
<td>21 (100)</td>
<td>22 (100)</td>
</tr>
<tr>
<td>Bort/Len/Car/Pom/Dara</td>
<td>15 (71)</td>
<td>21 (96)</td>
</tr>
</tbody>
</table>

Data cutoff: March 29, 2018. SCT, stem cell transplant.
ADVERSE EVENTS OF SPECIAL INTEREST

<table>
<thead>
<tr>
<th>CAR T Treatment-Emergent Adverse Events</th>
<th>Overall</th>
<th>Grade ≥3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytokine release syndrome(^a)</td>
<td>27 (63)</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Neurotoxicity(^b)</td>
<td>14 (33)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>35 (81)</td>
<td>34 (79)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>26 (61)</td>
<td>22 (51)</td>
</tr>
<tr>
<td>Anemia</td>
<td>24 (56)</td>
<td>19 (44)</td>
</tr>
<tr>
<td>Infection(^c)</td>
<td>26 (61)</td>
<td>9 (21)</td>
</tr>
<tr>
<td>First Month</td>
<td>10 (23)</td>
<td>2 (5)</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Time to Recovery of Grade 3/4 Cytopenias in Patients Without Recovery by Month 1(^d)</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="#" alt="Graph showing time to recovery of grade 3/4 cytopenias" /></td>
</tr>
</tbody>
</table>

- 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 estimaible. \(^a\)CRS uniformly graded per Lee DW, et al. Blood 2014;124(2):188-195. \(^b\)Events occurring in first 28 d and including dizziness, bradypnea, somnolence, confusion, state, nystagmus, 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 × 10⁶ 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 × 10⁶ CAR+ T cells) in 18 subjects in dose escalation phase
- mPFS of 17.7 months in 16 responding subjects who are MRD-negative

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

bb2121 at active doses (≥150 × 10⁶ 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 × 10⁶ 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
# Comparison of CART-BCMA trials

<table>
<thead>
<tr>
<th></th>
<th>NCI</th>
<th>Penn/NVS</th>
<th>Bluebird</th>
<th>Legend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sites</td>
<td>Single</td>
<td>Single</td>
<td>Multi-center</td>
<td>Multi-center</td>
</tr>
<tr>
<td>scFv</td>
<td>Murine</td>
<td>Human</td>
<td>Murine</td>
<td>Camelid</td>
</tr>
<tr>
<td>Vector</td>
<td>Gamma-retroviral</td>
<td>Lentiviral</td>
<td>Lentiviral</td>
<td>??</td>
</tr>
<tr>
<td>BCMA+ required</td>
<td>Yes (IHC) (52/85 (62%+)</td>
<td>No</td>
<td>Yes (IHC) (60%+)</td>
<td>Yes (flow) (??)</td>
</tr>
<tr>
<td>Dosing</td>
<td>0.3 – 9x10^6/kg 1 day</td>
<td>5 x 10^8 3 days</td>
<td>0.5 – 8 x10^8 1 day</td>
<td>0.6 – 7 x10^6/kg 3 days</td>
</tr>
<tr>
<td>Conditioning</td>
<td>Flu/Cy</td>
<td>None or Cy</td>
<td>Flu/Cy</td>
<td>Cy</td>
</tr>
<tr>
<td>Med # priors</td>
<td>7*</td>
<td>7</td>
<td>6</td>
<td>3-4</td>
</tr>
</tbody>
</table>

*includes XRT

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

<table>
<thead>
<tr>
<th>Antigen</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCMA</td>
</tr>
<tr>
<td>BCMA</td>
</tr>
<tr>
<td>BCMA</td>
</tr>
<tr>
<td>BCMA</td>
</tr>
<tr>
<td>BCMA</td>
</tr>
<tr>
<td>BCMA</td>
</tr>
<tr>
<td>BCMA</td>
</tr>
<tr>
<td>BCMA</td>
</tr>
<tr>
<td>BCMA</td>
</tr>
<tr>
<td>BCMA</td>
</tr>
<tr>
<td>BCMA</td>
</tr>
<tr>
<td>BCMA</td>
</tr>
<tr>
<td>BCMA</td>
</tr>
<tr>
<td>BCMA</td>
</tr>
<tr>
<td>BCMA</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Trial Site/Company</th>
<th>Accrual</th>
</tr>
</thead>
<tbody>
<tr>
<td>National Cancer Institute</td>
<td>completed (n=26)</td>
</tr>
<tr>
<td>University of Pennsylvania / Novartis</td>
<td>completed (n=25)</td>
</tr>
<tr>
<td>Multi-site phase 1/ Bluebird</td>
<td>ongoing (n=21 reported)</td>
</tr>
<tr>
<td>Multi-site phase 2/ Bluebird</td>
<td>ongoing</td>
</tr>
<tr>
<td>Multi-site phase 1 / Bluebird (bb21217 product)</td>
<td>ongoing</td>
</tr>
<tr>
<td>Multi-site phase 1/2, Nanjing Legend</td>
<td>ongoing (n=19 reported)</td>
</tr>
<tr>
<td>Memorial Sloan-Kettering / Juno</td>
<td>ongoing (n=6 reported)</td>
</tr>
<tr>
<td>Fred Hutchinson / Juno</td>
<td>ongoing</td>
</tr>
<tr>
<td>Multi-site phase 1/2, Juno</td>
<td>ongoing</td>
</tr>
<tr>
<td>Multi-site phase 1, Poseida</td>
<td>ongoing</td>
</tr>
<tr>
<td>Multi-site phase 1, Kite</td>
<td>ongoing</td>
</tr>
<tr>
<td>Multiple hospital sites in China</td>
<td>ongoing</td>
</tr>
<tr>
<td>Multi-site phase 1/2, Autolus Limited</td>
<td>ongoing</td>
</tr>
<tr>
<td>Virginia Cancer Specialists, Cartesian Therapeutics</td>
<td>ongoing</td>
</tr>
<tr>
<td>University of Pennsylvania / Novartis</td>
<td>completed (n=10)</td>
</tr>
<tr>
<td>Soochow University, China</td>
<td>ongoing (n=10 reported)</td>
</tr>
<tr>
<td>General Hospital of PLA, China</td>
<td>completed (n=5)</td>
</tr>
<tr>
<td>Soochow University, China</td>
<td>ongoing</td>
</tr>
<tr>
<td>Baylor University</td>
<td>completed (n=7 MM)</td>
</tr>
<tr>
<td>Multi-site phase 1, Sorrento Therapeutics</td>
<td>ongoing</td>
</tr>
<tr>
<td>Shenzhen Geno-Immune Medical Institute, China</td>
<td>ongoing</td>
</tr>
<tr>
<td>n/a</td>
<td>pre-clinical</td>
</tr>
<tr>
<td>n/a</td>
<td>pre-clinical</td>
</tr>
</tbody>
</table>

[www.clinicaltrials.gov](http://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 precursors
- 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

Mel 200
ASCT #1

Progression by IMWG Criteria

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

Garfall et al, NEJM September 10 2015
Subjects 01 (and 05) progressed with isolated extramedullary plasmacytomas and negative bone marrows.

Garfall et al, ASH 2016, #974
## Patient Characteristics and Outcomes

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

**Day 100 Response**

<table>
<thead>
<tr>
<th>Response</th>
<th>Days post-ASCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>VGPR</td>
<td>01</td>
</tr>
<tr>
<td>PD</td>
<td>02</td>
</tr>
<tr>
<td>VGPR</td>
<td>03</td>
</tr>
<tr>
<td>VGPR</td>
<td>05</td>
</tr>
<tr>
<td>VGPR</td>
<td>06</td>
</tr>
<tr>
<td>VGPR</td>
<td>07</td>
</tr>
<tr>
<td>PR</td>
<td>08</td>
</tr>
<tr>
<td>PD</td>
<td>09</td>
</tr>
<tr>
<td>PR</td>
<td>10</td>
</tr>
<tr>
<td>VGPR</td>
<td>12</td>
</tr>
</tbody>
</table>

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.

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-specific T cells in MM, sarcoma, and melanoma
- To open 2018
  - Penn, MDACC, UCSF

Rapoport et al, Nature Med 2015, ASH 2017
NY-ESO-1 CRISPR (TCR-PD1) Triple Edited T Cell Study Schema (NYCE Cells)

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**

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!
Acknowledgements

**Principle Investigators**
- Adam Cohen
- Alfred Garfall
- Edward Stadtmauer
- Carl June

**Penn Myeloma/BMT**
- Dan Vogl
- Brendan Weiss
- Patricia Mangan
- Emilie Tilhou
- Colleen Erb
- Mary Sanchez
- Tim Holtz
- Kelly Kraus
- Kathy Cunningham

**Heme/Onc Division**
- David Porter
- Noelle Frey
- Lynn Schuchter
- Alison Loren
- Steve Schuster
- Jakub Svoboda

**ACC TRP**
- Karen Dengel
- Naseem Kerr
- Holly McConneville
- Elizabeth Veloso
- Lester Lledo
- Anne Chew

**CCI**
- Jos Melenhorst
- Simon Lacey
- Yolanda Mahnke
- Chris Carlson
- Nina Luning Prak
- Martin Carroll
- Mike Malone

**CVPF**
- Bruce L. Levine
- Zoe Zheng
- Julio Cotte
- Dawn Meier
- Alexey Bersenev

**U Maryland**
- Aaron Rapoport
- Ashraf Z. Badros
- Saul Yanovich
- Gorgun Akpek
- Sunita Phillips
- Kelly-Marie Betts
- Phillip Miller
- Sandra Westphal

**Adaptimmune**
- Gwen K Binder-Scholl
- Bent K Jakobsen
- Dominic P Smethurst
- Helen K Tayton-Martin
- Joanna E Brewer
- Alan D Bennett
- Andrew B Gerry
- Nick J Pumphrey
- Lilliam Ribeiro

**Funding**
- Novartis, Adaptimmune
- Leukemia & Lymphoma Society
- NIH: K12 CA076931
- The Parker Institute
- ACC Pilot funds: Heme Malignancies TCE, GREG WOLF Foundation
- ACC Shared Resources (Human immunology Core, CRU, Biostatistics, etc)

**Special Thanks To:**
- THE PATIENTS AND THEIR FAMILIES
- THE INPATIENT AND OUTPATIENT NURSING STAFF, REFERRING MDs
- THE MYELOMA AND CELLULAR IMMUNOTHERAPY COMMUNITY