Adoptive Cell Therapies: Keeping Pace With New and Emerging Therapies

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Abramson Cancer Center
University of Pennsylvania
Learning Objectives

1. Review the approved indications for use of chimeric antigen receptor (CAR) T-cell therapy and studies in hematologic malignancies
2. Gain understanding of the CAR T-cell process
3. Understand the strategies for monitoring and managing emerging toxicities in patients receiving CAR T-cell therapy
4. Describe some of the future directions in the use of this therapy
Adoptive Cellular Therapy: Rationale

• Overcomes limitations of chemotherapy

• Combines advantages of:
  • Antibody therapy (specificity)
  • Cellular therapy (amplified response)
  • Vaccine therapy (memory activity)
Adoptive T cell therapy (three major approaches)

June et al. Sci Trans Med 2015
Anatomy of a Chimeric Antigen Receptor

- Gene transfer technology is used to stably express CARs on T cells, conferring novel antigen specificity.
- CARs combine antigen recognition domain (Anti-CD19, BCMA, CD38, CS1) with intracellular signaling domain.
- Intracellular signaling domain:
  - Same functionality as endogenous T cells.
  - Co-stimulatory endodomain mediates potent anti-tumor effects & promotes persistence (4-1BB, CD28).

CD19: An ideal tumor target

- CD19 is expressed on surface of most B cell malignancies
- CD19 expression is restricted to B cells and their precursors
- CD19 is not expressed on pluripotent bone marrow stem cells
- On target expected SE is B cell aplasia

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

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

Therapeutic Overview

Cellular Immunotherapy with CAR T cells (CTL019)

1. Leukapheresis / Apheresis

2. Antibody-coated beads

3. T-cell activation / Transduction (gene transfer using retroviral transposon or RNA as vector)

4. Lymphodepleting Chemotherapy

5. Modified T-cell infusion

Bead removal

Modified T-cell expansion

Courtesy of Noelle Frye, MD
## Successes of CART19 Therapy

<table>
<thead>
<tr>
<th>Ref</th>
<th>Program/CAR</th>
<th>Population</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acute Lymphoblastic Leukemia</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maude et al. NEJM 2014</td>
<td>PENN 4-1BB</td>
<td>N=30(ALL) Peds&amp;Adults</td>
<td>CR=90%</td>
</tr>
<tr>
<td>Davila et al. SciTrMed 2014</td>
<td>MSK CD28</td>
<td>N=16 (ALL) Adults</td>
<td>CR=88%</td>
</tr>
<tr>
<td>Lee et al. Lancet 2015</td>
<td>NCI CD28</td>
<td>N=21 (ALL) Peds&amp;AYA</td>
<td>CR=67% Intent to Treat</td>
</tr>
<tr>
<td>Turtle et al. JCI 2016</td>
<td>Seattle 4-1BB</td>
<td>N=30 Adults</td>
<td>CR=93%</td>
</tr>
<tr>
<td><strong>Non-Hodgkin Lymphoma &amp; Chronic Lymphocytic Leukemia</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kochenderfer JCO 2015</td>
<td>NCI CD28</td>
<td>N=15 (NHL/CLL)</td>
<td>CR=53% PR=27%</td>
</tr>
<tr>
<td>Porter et al. SciTrMed 2014</td>
<td>PENN 4-1BB</td>
<td>N=14(PLL)</td>
<td>CR=29% PR=29%</td>
</tr>
</tbody>
</table>
### ALL: Overall Response to CART19

<table>
<thead>
<tr>
<th>Response</th>
<th>N=30</th>
<th>%</th>
</tr>
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<tbody>
<tr>
<td>Complete Response</td>
<td>27/30</td>
<td>90%</td>
</tr>
<tr>
<td>No response</td>
<td>3/30</td>
<td>10%</td>
</tr>
</tbody>
</table>

CART19 for Rel/Ref ALL: Survival

Overall Survival

6-month OS: 78% (95% CI: 64,95)

Maude, Frey et al. NEJM 2014;371:1507-1517.
ELIANA: CAR T-cell Therapy in ALL

- Phase II trial of CAR T-cell therapy: tisagenlecleucel
- 79 pediatric/young adult patients (age 3-23) with relapsed or refractory CD19+ B-cell acute lymphoblastic leukemia (ALL)
- Median duration of remission and median overall survival remain unreached

24 month follow up analysis ➔

Survival at a Median Follow-Up of 13.1 Months

<table>
<thead>
<tr>
<th>Months since Tisagenlecleucel Infusion</th>
<th>Event-Free Survival</th>
<th>Overall Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>12 months</td>
<td>66%</td>
<td>76%</td>
</tr>
<tr>
<td>18 months</td>
<td>66%</td>
<td>70%</td>
</tr>
<tr>
<td>24 months</td>
<td>62%</td>
<td>66%</td>
</tr>
</tbody>
</table>
First Gene Therapy Approval: Tisagenlecleucel

- FDA approved for B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse in the treatment of patients up to 25 years of age
- Approval date: August 30, 2017
- Lymphodepletion regimen:
  - Fludarabine 30 mg/m² D-6, D-5, D-4, D-3
  - Cyclophosphamide 500 mg/m² D-6, D-5
- Black box warning for CRS and neurotoxicity
Successes of CART19 Therapy

<table>
<thead>
<tr>
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<td>PENN 4-1BB</td>
<td>N=14 (CLL)</td>
<td>CR=29% PR=29%</td>
</tr>
</tbody>
</table>
ZUMA-1: Axicabtagene Ciloleucel in DLBCL Survival at a Median of 27.1 Months

Phase II trial of axicabtagene ciloleucel anti-CD19 CAR-T therapy in 101 patients with refractory large B-cell lymphoma

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>Progression Free Survival</th>
<th>Overall Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 months</td>
<td>49%</td>
<td>78%</td>
</tr>
<tr>
<td>12 months</td>
<td>44%</td>
<td>59%</td>
</tr>
<tr>
<td>24 months</td>
<td>39%</td>
<td>51%</td>
</tr>
</tbody>
</table>

Median overall survival not reached (95% CI 12.8-NE)

Overall Survival
Progression Free Survival

6 month plateau largely maintained
Only 10 patients progressed beyond 6 month follow up

Axicabtagene Ciloleucel

- FDA approved for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after 2 or more lines of systemic therapy - including DLBCL not otherwise specified, primary mediastinal large B-cell lymphoma, high grade B-cell lymphoma, and DLBCL arising from follicular lymphoma

- Lymphodepletion regimen:
  - Fludarabine 30 mg/m² D-5, D-4, D-3
  - Cyclophosphamide 500 mg/m² D-5, D-4, D-3

- Black box warning for CRS and neurotoxicity
JULIET: Tisagenlecleucel in DLBCL

- Phase II trial of CAR T-cell therapy: tisagenlecleucel in 93 adult patients with relapsed or refractory DLBCL

<table>
<thead>
<tr>
<th>Response Rate (%)</th>
<th>Best Overall (n = 81)</th>
<th>3 Months (n = 81)</th>
<th>6 months (n = 46)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR (CR + PR)</td>
<td>52</td>
<td>38</td>
<td>33</td>
</tr>
<tr>
<td>CR</td>
<td>40</td>
<td>32</td>
<td>29</td>
</tr>
<tr>
<td>PR</td>
<td>12</td>
<td>6</td>
<td>4</td>
</tr>
</tbody>
</table>
Tisagenlecleucel: Second Indication

• FDA approved for adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy - including DLBCL not otherwise specified, high grade B-cell lymphoma and DLBCL arising from follicular lymphoma

• Lymphodepletion regimen options:
  – Fludarabine 25 mg/m² D-5, D-4, D-3
  – Cyclophosphamide 250 mg/m² D-5, D-4, D-3
  – Bendamustine 90 mg/m² D-4, D-3
    Previously experienced hemorrhagic cystitis with cyclophosphamide or demonstrate resistance to a cyclophosphamide regimen
  – Omit lymphodepletion if WBC ≤ 1x 10⁹/L within one week of CAR T infusion

• Black box warning for CRS and neurotoxicity
# CD19 CAR T-Cell Products

<table>
<thead>
<tr>
<th></th>
<th>Axicabtagene Ciloleucel (axi-cel)</th>
<th>Tisagenlecleucel (CTL019)</th>
<th>Lisocabtagene Maraleucel* (liso-cel)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>US FDA Indication</strong></td>
<td>Adult DLBCL</td>
<td>Ped/young adult ALL</td>
<td>Pending – adult DLBCL</td>
</tr>
<tr>
<td><strong>CAR Type</strong></td>
<td>CD19/CD28/CD3z</td>
<td>CD19/4-1BB/CD3z</td>
<td>CD19/EGFRt/4-1BB/CD3z</td>
</tr>
<tr>
<td><strong>Costimulatory Domain</strong></td>
<td>CD28</td>
<td>4-1BB (CD 137)</td>
<td>4-1BB (CD 137)</td>
</tr>
<tr>
<td><strong>scFv</strong></td>
<td>FMC63</td>
<td>FMC63</td>
<td>FMC63</td>
</tr>
<tr>
<td><strong>Vector</strong></td>
<td>Retrovirus</td>
<td>Lentivirus</td>
<td>Lentivirus</td>
</tr>
<tr>
<td><strong>Defined Cells</strong></td>
<td>No</td>
<td>No</td>
<td>CD4:CD8</td>
</tr>
<tr>
<td><strong>Pivotal Trial</strong></td>
<td>ZUMA-1 (LBCL)</td>
<td>ELIANA (ALL), JULIET (DLBCL)</td>
<td>TRANSCEND (LBCL)</td>
</tr>
</tbody>
</table>

*Not FDA-approved

Summary: CART19 in CD19+ Disease

- 80-90% CR rate in rel/ref ALL & 50% ORR in CLL
  - MRD negative
  - Successful bridge to ALLO SCT
  - Some pts with prolonged remissions from CART19 alone

- CAR T cells can persist for >48 months (Penn experience)
  - Cells remain functional
  - Correlates with remission & B cell aplasia (IVIG replacement)

- CRS is most significant toxicity
  - Responsive to supportive care and anti-cytokine therapy

- Relapses
  - CD19 negative: combination strategies/baseline predictors?
  - CD19 positive: loss of persistence

Designing a Myeloma CAR: Candidate antigen targets

CD19 expression (B cell antigen) → Memory B cell
BCMA expression (plasma cell antigen) → Plasma cell

Rare putative myeloma stem cell population
Dominant clinical myeloma cell population
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

### BCMA CAR T cells – initial studies, refractory pts

<table>
<thead>
<tr>
<th>Trial</th>
<th>n</th>
<th>Conditioning</th>
<th># lines</th>
<th>% hi risk†</th>
<th>ORR</th>
<th>ORR (optimal doses)</th>
<th>VGPR/CR (optimal doses)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCI¹</td>
<td>26*</td>
<td>Cy/Flu</td>
<td>7.5</td>
<td>42%</td>
<td>58%</td>
<td>81% (13/16)</td>
<td>63% (10/16)</td>
</tr>
<tr>
<td>Penn²</td>
<td>25</td>
<td>None or Cy</td>
<td>7</td>
<td>76%</td>
<td>48%</td>
<td>64% (7/11)</td>
<td>36% (4/11)</td>
</tr>
<tr>
<td>Bluebird³</td>
<td>43</td>
<td>Cy/Flu</td>
<td>7.5</td>
<td>40%</td>
<td>77% (30/39)</td>
<td>96% (21/22)</td>
<td>86% (19/22)</td>
</tr>
<tr>
<td>Janssen⁴</td>
<td>57</td>
<td>Cy</td>
<td>NA</td>
<td>NA</td>
<td>88%</td>
<td></td>
<td>78%</td>
</tr>
</tbody>
</table>

*2 treated twice; counted separately for response. †FISH +t(4;14), t(14;16), del 17p  *excluded high tumor burden in last 14 pts. NR = not reported

<table>
<thead>
<tr>
<th>Trial</th>
<th>n</th>
<th>CRS %</th>
<th>CRS G3-4 %</th>
<th>Neurotox %</th>
<th>Neurotox G3-4 %</th>
<th>Toci</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCI¹</td>
<td>26*</td>
<td>73%</td>
<td>23%</td>
<td>NR</td>
<td>12%</td>
<td>19%</td>
</tr>
<tr>
<td>Penn²</td>
<td>25</td>
<td>88%</td>
<td>32%</td>
<td>32%</td>
<td>12%</td>
<td>28%</td>
</tr>
<tr>
<td>Bluebird³</td>
<td>43</td>
<td>63%</td>
<td>5%</td>
<td>33%</td>
<td>2%</td>
<td>21%</td>
</tr>
<tr>
<td>Janssen⁴</td>
<td>57</td>
<td>76%</td>
<td>7%</td>
<td>42%</td>
<td>2%</td>
<td></td>
</tr>
</tbody>
</table>

¹Ali, Blood 2016 and Brudno, J Clin Oncol 2018; ²Cohen, JCI 2019 ³Raje, NEJM 2019 ; ⁴Zhao. ASH 2018
BCMA CAR T cells – lessons from initial studies

• Probably not curative in refractory patients

Median EFS = 31 weeks

Bluebird – dose escalation

DLBCL ph2 Yescarta

1Ali, Blood 2016 and Brudno, J Clin Oncol 2018; 2Cohen, JCI 2019 3Raje, NEJM 2019; 4Zhao. ASH 2018
Interpretation:
Dose matters, Not Fixing everyone

• 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.

Raje, NEJM 2019
Designing Better BCMA 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
CART-BCMA manufacturing with PI3 kinase inhibition

bb21217: Next-Generation Anti-BCMA CAR T Cell Therapy Product for Multiple Myeloma

- bb21217 uses the same CAR construct design as bb2121
- bb21217 is cultured with PI3 kinase inhibitor, bb007, to enrich for T cells displaying a memory-like phenotype
- CAR T cells enriched for this phenotype may persist and function longer than non-enriched CAR T cells
- Persistence of functional CAR T cells after infusion may be one determinant of duration of response

Shah et al, ASH 2018, #488
CART-BCMA manufacturing with PI3 kinase inhibition

- Toxicities similar to bb2121 (CRS, neurotox)
- ?any difference in memory phenotype, persistence?

Clinical Responses and Duration of Response at the 150 x 10^6 CAR+ T Cell Dose

Shah et al, ASH 2018, #488
Legend Biotech: Phase 1 LCAR-B38M (BCMA CAR T cells)

- Single institution experience (n=57)
- CD3/41BB dual-binding CAR, Cy conditioning, med 3 prior

ORR 88%
CR 68%

CRS 90% (7% Gr 3-4)
Neurotox 2% (Gr 1)

Med PFS = 15 mos?
Transposon-based BCMA CAR construct

- Non-viral gene delivery system, larger cargo capacity
  - Cheaper/faster manufacturing, positive selection gene, suicide gene

P-BCMA-101: Comprised of a High Percentage of Desirable $T_{SCM}$ Cells

We believe $T_{SCM}$ cells in product is the key to increase duration of response and reduce toxicity

- high percentage of $T_{SCM}$ cells is a distinct advantage
- piggyBac™ preferentially transposes in $T_{SCM}$ cells
- $T_{SCM}$ cells engraft and live longer than more differentiated T cells
- $T_{SCM}$ cells can produce potentially unlimited waves of effector cells
- $T_{SCM}$ cells should lead to better duration of response, potential for re-response and efficacy in solid tumors, with more gradual tumor killing producing less toxicity

Gregory et al, ASH 2018, #1012
Transposon-based BCMA CAR construct

Slower in vivo expansion (peak day 14-21)

Cytokine Release Syndrome By Dose Level

Tumor Response in Evaluable Patients by Dose

ORR = 63% (12/19 evaluable)

Gregory et al, ASH 2018, #1012
MSKCC/Juno Vectors in clinical trials

- **MCARH171**
  - Retrovirus
  - No Pre-defined CD4:CD8 ratio

- **JCARH125 (EVOLVE)**
  - Lentivirus
  - 1:1 CD4:CD8 ratio prior to transduction and expansion

- **FCARH143**
  - Lentivirus
  - 1:1 CD4:CD8 ratio after transduction

ASH 2018 abstracts 959, 957 and 1011.
Ph 1/2 JCARH125 (defined CD4:CD8 pre-manufacturing)

- CRS 80% (Gr 3-4 9%)
- Neurotox 25% (Gr 3-4 7%)

Mailankody et al, ASH 2018, #957
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
A combination of humanized anti-CD19 and anti-BCMA CAR T cells in patients with relapsed or refractory multiple myeloma: a single-arm, phase 2 trial (21 pts)

Zhiling Yan*, et al Lancet Oncology 2019
Designing a Myeloma CAR: Candidate antigen targets

• The classics
  • CD138
  • CD38
  • CD56
  • Kappa light chain
  • CD19

♦ The new models:
  • Lewis Y
  • CD44v6
  • MAGE A3
  • NY-ESO-1
  • CS1/SLAMF7
  • BCMA
  • Integrin beta 7
  • FcRH5
  • CD48
  • CD46
  • CD229
  • GPRC5D
## CAR T cells for MM in 2018

<table>
<thead>
<tr>
<th>Antigen</th>
<th>Trial Site/Company</th>
<th>Accrual</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCMA</td>
<td>National Cancer Institute</td>
<td>completed (n=26)</td>
</tr>
<tr>
<td>BCMA</td>
<td>University of Pennsylvania / Novartis</td>
<td>completed (n=25)</td>
</tr>
<tr>
<td>BCMA</td>
<td>Multi-site phase 1/ Bluebird</td>
<td>ongoing (n=21 reported)</td>
</tr>
<tr>
<td>BCMA</td>
<td>Multi-site phase 2/ Bluebird</td>
<td>ongoing</td>
</tr>
<tr>
<td>BCMA</td>
<td>Multi-site phase 1 / Bluebird (bb21217 product)</td>
<td>ongoing</td>
</tr>
<tr>
<td>BCMA</td>
<td>Multi-site phase 1/2, Nanjing Legend</td>
<td>ongoing (n=19 reported)</td>
</tr>
<tr>
<td>BCMA</td>
<td>Memorial Sloan-Kettering / Juno</td>
<td>ongoing (n=6 reported)</td>
</tr>
<tr>
<td>BCMA</td>
<td>Fred Hutchinson / Juno</td>
<td>ongoing</td>
</tr>
<tr>
<td>BCMA</td>
<td>Multi-site phase 1/2, Juno</td>
<td>ongoing</td>
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<tr>
<td>BCMA</td>
<td>Multi-site phase 1, Poseida</td>
<td>ongoing</td>
</tr>
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<td>BCMA</td>
<td>Multi-site phase 1, Kite</td>
<td>ongoing</td>
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<tr>
<td>BCMA</td>
<td>Multiple hospital sites in China</td>
<td>ongoing</td>
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<tr>
<td>BCMA</td>
<td>Multi-site phase 1/2, Autolus Limited</td>
<td>ongoing</td>
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<tr>
<td>BCMA</td>
<td>Virginia Cancer Specialists, Cartesian Therapeutics</td>
<td>ongoing</td>
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<tr>
<td>CD19</td>
<td>University of Pennsylvania / Novartis</td>
<td>completed (n=10)</td>
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<tr>
<td>CD19 + BCMA</td>
<td>University of Pennsylvania / Novartis</td>
<td>open 2018</td>
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<tr>
<td>CD19 + BCMA</td>
<td>Soochow University, China</td>
<td>ongoing (n=10 reported)</td>
</tr>
<tr>
<td>CD138</td>
<td>General Hospital of PLA, China</td>
<td>completed (n=5)</td>
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<td>CD138</td>
<td>Soochow University, China</td>
<td>ongoing</td>
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<tr>
<td>Kappa LC</td>
<td>Baylor University</td>
<td>completed (n=7 MM)</td>
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<tr>
<td>CD38</td>
<td>Multi-site phase 1, Sorrento Therapeutics</td>
<td>ongoing</td>
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<tr>
<td>CD38</td>
<td>Shenzhen Geno-Immune Medical Institute, China</td>
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<td>CD38</td>
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</tr>
<tr>
<td>SLAMF7/ CS1</td>
<td>n/a</td>
<td>pre-clinical</td>
</tr>
</tbody>
</table>

[www.clinicaltrials.gov](http://www.clinicaltrials.gov), March 2018
Cancer Testis Antigens (NY-ESO-1, LAGE-1)

- Expressed in a wide variety of cancers, including multiple myeloma
- Good immunotherapy targets due to limited expression on normal somatic tissue
- Restricted expression decreases the likelihood of ‘on-target off-tumor’ effects
- The frequency of CTA expression tends to increase with cancer stage and recurrence
- NY-ESO-1 and LAGE-1a have been detected at higher levels in advanced multiple myeloma

Ghafouri-Fard et al, Iran J Cancer Prev 2015
van Rhee et al, Blood 2005
Gjerstorff et al, Oncotarget 2015
NY-ESO-1<sup>c259</sup>TCR : Enhanced Affinity
(PENN, MARYLAND, ADAPTIMMUNE/GSK)

- Lentiviral vector. All domains of the natural TCR are intact, with no added intracellular signaling domains.
- The engineered TCR targets NY-ESO-1 and LAGE-1a, as the same epitope (SLLMWITQC) is present on both CTAs.
- The CDRs (complementary determining regions) are modified to enhance the recognition of the SLLMWITQC peptide in the context of HLA-A*02.
Overview of Study Design

* High dose: 200mg/m²
Conclusions

• NY-ESO-1\textsuperscript{c259} T-cell therapy in the setting of ASCT has promising efficacy and acceptable safety

• Long-term survival demonstrated in a refractory population

• It is possible to achieve negative MRD with this therapy

• TCR-transduced T-cells persist long term and are not exhausted

• Persisting cells produce multiple cytokines in response to antigen

• Persisting cells include highly differentiated effector subsets and a population of self-renewing stem cell/memory cells

• BUT inconclusive:

• Partnered with MEL 200 ASCT; no long-term progression-free survival

Multiplexed genetic engineering of autologous T cells expressing NY-ESO-1 TCR and CRISPR/Cas9 gene edited to eliminate endogenous TCR and PD-1 (PENN, TMUNITY, PARKER)

- **Overall Rationale:**
  
  - Increase safety and efficacy by increasing engineered TCR expression and checkpoint inhibition

- **Rationale for endogenous TCRα (TRAC) and TCRβ (TRBC) genes editing:**
  
  - Reduce endogenous TCR mispairing with exogenous NY-ESO-1 TCR thereby reducing risk of auto-reactivity enhancing recombinant NY-ESO-1 TCR expression on the cell surface for improved potency

- **Rationale PDCD1 gene editing (generate checkpoint resistant T cells)**
  
  - Gain resistance to PD1 induced suppression thereby improve potency, delay T cell exhaustion
NY-ESO-1 CRISPR (TCR-PD1) Triple Edited T Cell Study Schema (NYCE Cells)

Consent and screen for NY-ESO-1 and HLA-A2: Malignancy

Consent for Study and Enrollment

Day -35 → -4 → -3 → -2 → -1 → +0 → +1 → +3 → +7 → +10 → +14 → +21 → +28

Infusion: NY-ESO-1 TCR-PD1 CRISPR T cells

Disease Evaluation:
- PET Scan
- Biopsy
- Tumor Markers

Monitoring:
- Monthly until 6 mo.
- Quarterly for 2 years

- Solid tumors
  - 250-300 mg/m² flu
  - +25-30 mg/m² cy
  - 1 hr. infusion
  - Days -4, -3, -2

- Myeloma
  - 1.5 mg/m² cy
  - 1 hr. infusion
  - Day -2

Cell and Toxicity Assessment:
- Persistence of cell types
- Cell function assays

Study Product, Dose, Route, Regimen

<table>
<thead>
<tr>
<th>IND 17297</th>
<th>Clinicaltrials.gov NCT03399448</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sponsor: Tmunity and Parker Institute for Cancer Immunotherapy</td>
<td></td>
</tr>
</tbody>
</table>

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 $1 \times 10^6$ cells/kg will be given i.v.
Toxicities

Associated with CAR T therapy
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, 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

*Potential Life threatening toxicities

Bonifant et al, Molecular Therapy — Oncolytics (2016) 3, 16011
Cytokine Release Syndrome (CRS)

• Correlates with:
  • CAR-T activation and expansion
  • Dramatic cytokine elevations (very high levels of IL6, IL10, IFNγ, CRP, ferritin)
  • Many responding patients developed a CRS

• Clinical syndrome:
  • Onset: 1-14 days after infusion
  • Duration: 1-10 days
  • Monitor: VS, ferritin level, and CRP level
  • Fevers come first and get very high (105°F/41°C)
  • Myalgias, fatigue, anorexia
  • Capillary leak, hypoxia and hypotension
    • May require ICU support
  • Altered mental status, seizures, DIC

• Self-limited or anti-cytokine intervention
CRS After CAR T Cells: Risk Factors

Disease Characteristics
• Disease Burden (ALL)\textsuperscript{1-4}

Therapeutic Characteristics
• Infusional Dose\textsuperscript{3,4,6}
• Product variance
• LD chemotherapy\textsuperscript{4}

Correlates with Severe Course
• Cytokines and CRP\textsuperscript{1,5}
• Concurrent infectious illness\textsuperscript{6}

\textsuperscript{1}Maude et al. NEJM 2014
\textsuperscript{2}Davila et al. SciTranMed 2014
\textsuperscript{3}Lee et al. TheLancet 2015
\textsuperscript{4}Turtle et al. JCI 2016
\textsuperscript{5}Teachey et al. CancerDisc. 2016
\textsuperscript{6}Frey et al. ASCO 2016
CRS: Cytokine Profiles

• Clinical Laboratory Correlates:
  • Ferritin and CRP

• Investigational Correlates: Direct Impact on Care\(^1\)
  • Cytokine Profiles: IFN\(\gamma\), IL6, IL2R, IL10

\(^1\)Grupp et al. NEJM 2013
CRS After CAR T Cells: Anti-cytokine Management

CRS with high IL6

Tocilizumab for CRS$^1$:

- Humanized monoclonal antibody to IL6-R
- FDA approved adult RA, JIA
- Limited inherent toxicity
- Adopted by most programs
- Effective for most patients

$^1$Grupp et al. NEJM 2013
“The Antidote”: Tocilizumab

- Humanized monoclonal antibody to IL-6
- Can rapidly reverse CRS\(^1\)
- Ensure that 2 doses of tocilizumab are available prior to infusion of CAR-T cells
- Monitor patients closely at least daily for 7 days following infusion for signs and symptoms of CRS
- May be admitted for this close observation then closely as outpatient for 4 weeks following the CAR T infusion.
- Counsel patients to seek immediate medical attention should signs or symptoms of CRS occur at any time
- At the first sign of CRS, institute treatment with supportive care, tocilizumab or tocilizumab and corticosteroids as indicated

## CRS With CART19 Therapy

<table>
<thead>
<tr>
<th>Ref</th>
<th>Program/ CAR</th>
<th>Population</th>
<th>Response</th>
<th>CRS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acute Lymphoblastic Leukemia</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maude et al. NEJM 2014</td>
<td>PENN 4-1BB</td>
<td>N=30 (ALL) Peds&amp;Adults</td>
<td>CR=90%</td>
<td>100% CRS 27% Severe</td>
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<td>Davila et al. SciTrMed 2014</td>
<td>MSK CD28</td>
<td>N=16 (ALL) Adults</td>
<td>CR=88%</td>
<td>43% Severe</td>
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<td>N=21 (ALL) Peds&amp;AYA</td>
<td>CR=67% Intent to Treat</td>
<td>76% CRS 28% Severe</td>
</tr>
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<td>Turtle et al. JCI 2016</td>
<td>Seattle 4-1BB</td>
<td>N=30 Adults</td>
<td>CR=93%</td>
<td>83% CRS</td>
</tr>
<tr>
<td><strong>Non-Hodgkins Lymphoma &amp; Chronic Lymphocytic Leukemia</strong></td>
<td></td>
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<td>27% Severe</td>
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<td>Porter et al. SciTrMed2014</td>
<td>PENN 4-1BB</td>
<td>N=14 (CLL)</td>
<td>CR=29% PR=27%</td>
<td>42% Severe</td>
</tr>
</tbody>
</table>
CRS: Clinical Response to Tocilizumab

![Graph showing Temp over time with a peak during Tocilizumab treatment.](image-url)
CRS: Ferritin Response to Tocilizumab

Tocilizumab: d10

Ferritin

CRS, Pt 04409-09
Mild CRS: Case #1

NHL History
- 59 yo male
- R CHOP x 6 cycles -> CR
- Relapsed 5 mo later
- Salvage with R-ICE x 2 cycles followed by AutoBMT
- Relapsed 3 mo later by radiographic PD

<table>
<thead>
<tr>
<th>Timing</th>
<th>Key events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Month-3</td>
<td>Re-induction with R ICE (response)</td>
</tr>
<tr>
<td>Month -2</td>
<td>T cells collected</td>
</tr>
<tr>
<td>Week -1</td>
<td>lymphodepleting chemotherapy (fludarabine/cyclophosphamide)</td>
</tr>
<tr>
<td>Day -1</td>
<td><strong>PET/CT with PR</strong> BM blasts, no peripheral blasts</td>
</tr>
</tbody>
</table>

*Note: PR = Peripheral Response*
Mild CRS: Case #1

- Antibiotics (days 1-7)
- Myalgias (days 2-7)
- Anti-pyretics (days 3-6)
- CTL019 Infusion
- D/C home
Severe CRS: Case #2

**ALL History**

- 22 yo male ALL
- 1st relapse in maintenance therapy
- Refractory to reinduction

<table>
<thead>
<tr>
<th>Timing</th>
<th>Key notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Month -2</td>
<td>T cells collected after failed re-induction</td>
</tr>
<tr>
<td>Month -1</td>
<td>Started hydroxyurea</td>
</tr>
<tr>
<td>Week -1</td>
<td>lymphodepleting chemotherapy (fludarabine/cyclophosphamide)</td>
</tr>
<tr>
<td>Day -1</td>
<td>97% BM blasts, no peripheral blasts</td>
</tr>
</tbody>
</table>
Severe CRS: Case #2

- CTL019 infusion
- Tocilizumab (days 5 and 8)
- Confusion (day 2-11)
- Respiratory support (days 3-10)
- High-dose vasopressors (days 5-9)
- High-dose steroids (days 7-11)
- Transfusion support (days 2-15)
- FFP (days 2 and 8)
- Cryoprecipitate (days 10-15)
- Rasburicase (Day 9)
# ASBMT Consensus Grading for CRS Associated with Immune Effector Cells (IEC)

<table>
<thead>
<tr>
<th>CRS Parameter</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fever</strong>*</td>
<td>$T_m &gt; 100.4^\circ F$</td>
<td>$T_m &gt; 100.4^\circ F$</td>
<td>$T_m &gt; 100.4^\circ F$</td>
<td>$T_m &gt; 100.4^\circ F$</td>
</tr>
<tr>
<td><strong>With either:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Hypotension</strong></td>
<td>None</td>
<td>Responsive to fluids</td>
<td>Requiring 1 vasopressor (w/ or w/o vasopressin)</td>
<td>Requiring multiple vasopressors (excluding vasopressin)</td>
</tr>
<tr>
<td><strong>And/or</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Hypoxia</strong></td>
<td>None</td>
<td>Low-flow nasal cannula or blow-by</td>
<td>High-flow nasal cannula, face mask, non-rebreather mask, or Venturi mask</td>
<td>Requiring positive pressure (CPAP, BiPAP Intubation and mechanical ventilation)</td>
</tr>
</tbody>
</table>

- Organ toxicities associated with CRS may be graded according to CTCAE v5.0, but they do not influence CRS grading.
- Low-flow nasal cannula: O2 delivered at <6 L/minute.
CRS Management

- Hypotension SBP < 90 mm Hg refractory to IVF challenge and requiring vasopressors OR
- Respiratory distress/hypoxia requiring ventilatory support OR
- Acute coronary syndrome with positive troponin and/or ECG changes OR
- Seizure, clinically suspected and/or documented on EEGC

Tocilizumab 8 mg/kg IV once

- Worsening CRS within 12 hrs
  - Increasing vasopressors dose OR
  - Increasing ventilatory support OR
  - Persistent seizure activity

- No clinical improvement ≥ 24 hrs

Dexamethasone 10 mg IV Q6H

- Taper as clinically indicated

Clinical improvement < 24 hrs
- Decreasing vasopressor dose OR
- Decreasing ventilatory support OR
- No further seizure activity

Observe

- Worsening CRS
  - Increasing vasopressors OR
  - Increasing ventilatory support OR
  - New seizure

Park. ASCO 2016. Abstr 7003
CAR T cells for ALL: Optimizing Risk: Benefit Ratio

- **Delivery of CAR T cells:**
  - Dose adjustment based on disease burden
  - Fractionated dosing: Real time dose modification by CRS symptoms

- **CAR T modifications:**
  - Create CARTs with targets for destruction:
    (CD20, EGFR, HSV thymidine kinase, caspase 9)
  - “On switch”: additional signal (drug) to be activated

---

1. Gardner et al. ASH2016-586
2. NCT02906371(CHOP)
3. Frey et al. ASCO. 2016
4. DiStasi et al, NEJM. 2011
5. Casucci et al, Molecular Therapy. 2013
Neurotoxicity
Second Most Common Toxicity Associated with CAR T-cell Therapy

• Range of Symptoms
diminished attention, language disturbance, confusion, disorientation, agitation, aphasia, tremors, seizures, encephalopathy

• Pathophysiology
  – Unclear; however is likely related to T-cell
  – Passive diffusion of cytokines
  – Expansion of CAR T-cells into CNS

• Predictors
  – High Disease Burden
  – High IL6 on Day1

• Neurotoxicity and CRS follow a different course of onset and resolution
• Onset varies and can be biphasic:
  – Early – Symptoms occur concurrently with CRS symptoms (~within first 5 days)
  – Late – Begins after CRS symptoms have resolved
  – Delayed – Most neurotoxicity events (88-98%) occur within 8 weeks after cell infusion (seizures, episodes of confusion)
### Immune Effector Cell-Associated Encephalopathy (ICE) Score

<table>
<thead>
<tr>
<th>ICE Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Score 10:</td>
<td>No impairment</td>
</tr>
<tr>
<td>Score 7-9:</td>
<td>Grade 1</td>
</tr>
<tr>
<td>Score 3-6:</td>
<td>Grade 2</td>
</tr>
<tr>
<td>Score 0-2:</td>
<td>Grade 3</td>
</tr>
</tbody>
</table>

*Combine with other ICANS assessments for final grade*

- How many of the following is the patient oriented to: year, month, city, hospital
- Identify 3 objects. How many can the patient name?
- Can follow commands
- Can write a standard sentence
- Can count backwards from 100 by 10

### Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS)

<table>
<thead>
<tr>
<th>Neurotoxicity Domain</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ICE SCORE</strong></td>
<td>7-9</td>
<td>3-6</td>
<td>0-2</td>
<td>0 (patient is unarousable and unable to perform ICE)</td>
</tr>
<tr>
<td>Depressed LOC</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>attributed to no other cause</td>
<td>Awakens spontaneously</td>
<td>Awakens to voice</td>
<td>Awakens only to tactile stimulus</td>
<td>Patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse. <strong>Stupor or coma</strong></td>
</tr>
<tr>
<td>Seizure</td>
<td>N/A</td>
<td>N/A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Motor findings</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Raised ICP / Cerebral edema</td>
<td>N/A</td>
<td>N/A</td>
<td>Focal/local edema on neuroimaging</td>
<td><strong>Diffuse cerebral edema</strong> on neuroimaging; Decerebrate or decorticate posturing; or Cranial nerve VI palsy; or Papilledema; or Cushing’s triad</td>
</tr>
</tbody>
</table>

Managing Neurotoxicity of CAR T-Cell Therapy

- **Tocilizumab** might reverse neurotoxicity during first phase but not second phase
- **Corticosteroids** may be used to manage neurotoxicity if tocilizumab is not effective[1]
- **Seizure prophylaxis**

---

Management of CRES

**CAR-Related Encephalopathy Syndrome**

- **Grade 1/2**
  - Requires vigilant supportive care
  - Neuro consult with diagnostic imaging
  - Daily monitoring with EEGs
  - Consider tocilizumab
  - **Grade 2:** tocilizumab/siltuximab or high-dose corticosteroids and consider ICU transfer

- **Grade 3/4**
  - Vigilant supportive care and neuro workup
  - ICU transfer
  - Consider tocilizumab/siltuximab
  - Corticosteroid taper for worsening
  - **Grade 4:** ICU monitoring and consider mechanical ventilation
    - Anakinra (IL1 inhibitor)

Adapted from MD Anderson Cancer Center. Chimeric Antigen Receptor (CAR) Cell Therapy Toxicity Assessment and Management - Adult.
## Neurotoxicity of CART19 Therapy

### Acute Lymphoblastic Leukemia

<table>
<thead>
<tr>
<th>Ref</th>
<th>Program CAR</th>
<th>Population</th>
<th>Response</th>
<th>CRS</th>
<th>Neurotoxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maude et al. NEJM 2014</td>
<td>PENN 4-1BB</td>
<td>N=30(ALL) Peds&amp;Adults</td>
<td>CR=90%</td>
<td>100% CRS 27% Severe</td>
<td>43% Total Encephalopathy Aphasia Seizure (1)</td>
</tr>
<tr>
<td>Davila et al. SciTrMed 2014</td>
<td>MSK CD28</td>
<td>N=16 (ALL) Adults</td>
<td>CR=88%</td>
<td>43% Severe</td>
<td>25% Gr3-4 Encephalopathy Seizure</td>
</tr>
<tr>
<td>Lee et al. Lancet 2015</td>
<td>NCI CD28</td>
<td>N=21 (ALL) Peds&amp;AYA</td>
<td>CR=67% Intent to Treat</td>
<td>76% CRS 28% Severe</td>
<td>29% Total hallucinations Dysphasia encephalopathy</td>
</tr>
<tr>
<td>Turtle et al. JCI 2016</td>
<td>Seattle 4-1BB</td>
<td>N=30 Adults</td>
<td>CR=93%</td>
<td>83% CRS</td>
<td>50% Severe</td>
</tr>
</tbody>
</table>

### Non-Hodgkins Lymphoma & Chronic Lymphocytic Leukemia

<table>
<thead>
<tr>
<th>Ref</th>
<th>Program CAR</th>
<th>Population</th>
<th>Response</th>
<th>CRS</th>
<th>Neurotoxicity</th>
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</thead>
<tbody>
<tr>
<td>Kochenderfe JCO 2015</td>
<td>NCI CD28</td>
<td>N=15 (NHL/CLL)</td>
<td>CR=53% PR=27%</td>
<td>27% Severe</td>
<td>40% Total Encephalopathy Aphasia, R facial par</td>
</tr>
<tr>
<td>Porter et al. SciTrM2015</td>
<td>PENN 4-1BB</td>
<td>N=14(CLL)</td>
<td>CR=29% PR=29%</td>
<td>42% Severe</td>
<td>43% Total 1/14 Grade 4</td>
</tr>
</tbody>
</table>
# Toxicities in BCMA Trials for Myeloma

<table>
<thead>
<tr>
<th>Trial</th>
<th>n</th>
<th>CRS %</th>
<th>CRS G3-4 %</th>
<th>Neurotox %</th>
<th>Neurotox G3-4 %</th>
<th>Tocilizumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCI¹</td>
<td>26*</td>
<td>73%</td>
<td>23%</td>
<td>NR</td>
<td>12%</td>
<td>19%</td>
</tr>
<tr>
<td>Penn²</td>
<td>25</td>
<td>88%</td>
<td>32%</td>
<td>32%</td>
<td>12%</td>
<td>28%</td>
</tr>
<tr>
<td>Bluebird³</td>
<td>43</td>
<td>63%</td>
<td>5%</td>
<td>33%</td>
<td>2%</td>
<td>21%</td>
</tr>
<tr>
<td>Janssen⁴</td>
<td>57</td>
<td>76%</td>
<td>7%</td>
<td>42%</td>
<td>2%</td>
<td></td>
</tr>
</tbody>
</table>

¹Ali, Blood 2016 and Brudno, J Clin Oncol 2018; ²Cohen, JCI 2019 ³Raje, NEJM 2019; ⁴Zhao. ASH 2018
Premedication and Prophylaxis Considerations

- Cell-infusion pre-medications: acetaminophen and diphenhydramine. Use of uric acid lowering medications to prevent TLC.
- No steroids from the start of lymphodepleting chemotherapy.
- Infection prophylaxis:
  - Antiviral
  - Antifungal and fluoroquinolone during neutropenic period
  - PJP prophylaxis
- Seizure prophylaxis:
  - Examples: levetiracetam 500-750 mg PO BID day -1/0 to day 30.
B-cell Aplasia and Hypogammaglobulinemia

- On target expected SE is B cell aplasia
- Correlates with CART persistence
- Successfully managed with IVIG replacement
- No excessive or frequent infections

Additional Toxicities Associated with CAR T-cells

• Tumor lysis syndrome
  – Use of uric acid lowering meds with high burden of disease
• Infections (opportunistic)
  – IVIg
  – Antiviral, Antibacterial, Antifungal
• Prolonged cytopenias
  – Continued monitoring of CBC
  – Growth factor as needed
Cellular Therapy Coordination

- Logistical Navigation
- Financial Approval
- REMS
- Patient Assessment/Selection
- Patient Education
- Multi-disciplinary Coordination
What’s Next in Cellular Immunotherapy?

- Constructs
  - Antigen recognition
  - Stimulatory molecules
- Vectors
  - Viral
  - Non-viral approaches
- Dose
- Off switches
  - Suicide genes/safety domains
- Lympho-depletion
- Single vs serial infusions
- Patient selection
  - Test for target
  - Early vs heavily pretreated
- Toxicities
  - Timing of tocilizumab
- Gene editing
  - “Universal” or “Off the Shelf” CAR T cells
  - CRISPR gene edited NY-ESO1 TCR T cells
- Dual CARs
- Combinations with
  - IMIDs
  - Checkpoint inhibitors
- Use in other cancers

1 Grupp et al. ASHAbst221
2 Chang et al ASH Abst 587
3 Shah et al: ASHAbst 650
4 Neelapu et al. LBAbst 6
Clinical Pearls

• CAR T therapy is an effective form of cellular immunotherapy for ALL, NHL and multiple myeloma.
• It is multi-step process and requires great deal of coordination of care.
• There are unique toxicities associated with this therapy, which vary by product and disease being treated.
• We now are more comfortable with earlier intervention without loss of effectiveness or persistence of these cells
• This is just the beginning of adoptive immunotherapy!!
  • For use in other malignancies; with less toxicities and more persistence and availability.
More Questions?

Come see us in the Skybridge Lobby near Registration from 8:15 to 8:45 am tomorrow.
This has been a SMARTIE presentation.

To access your post-session questions, you can:
- Click on the link that was sent to you via email
- Visit the SMARTIE station
- Go to jadprolive.com/smartie2019