CARs to Armored CARs: T cell Treatment of Cancer

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Conflict of Interest Disclosure
Renier Brentjens MD PhD

• **Stockholder**: Juno Therapeutics (scientific co-founder)
• **Royalties**: Juno Therapeutics
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• **Research Funding**: Juno Therapeutics
• **Consultant fees**: Juno Therapeutics
• **Discussion of off-label drug use**: Tocilizumab
Generation of a tumor targeted chimeric antigen receptor (CAR)

α-TAA mAb

TCR complex

α-TAA scFv—CD8-ζ

CAR retroviral vector
Generation of TAA-targeted T cells for treatment of Cancer

1. Construct a chimeric antigen receptor (CAR)

2. Subclone CAR gene into a retroviral vector (SFG)

3. Transduce and expand patient T cells \textit{ex vivo}

4. Infuse transduced T cells to eradicate TAA$^+$ tumor cells
Advantages of CAR T cell therapy

- HLA-independent antigen recognition, therefore universal application
- Active in both CD4\(^+\) and CD8\(^+\) T cells
- Target antigens include proteins, carbohydrates and glycolipids
- Rapid generation of tumor specific T cells
- Minimal risk of autoimmunity or GvHD
- A living drug, single infusion
Expression of CD19 and other B cell markers on B lineage cells

Stem Cell → pro B → pre B → immature B → mature B → plasma cell

- CD19
- CD22
- CD20

preB-ALL

B cell lymphomas and leukemias

myelomas
Evolution in CAR design

First-Generation CAR
scFv-CD3ζ

Second-Generation CAR
scFv-CD28-CD3ζ

Third-Generation CAR
scFv-CD28-4-1BB-CD3ζ
scFv-CD28-OX40-CD3ζ
2nd generation CARs: *in vivo*

Brentjens et al Clin Cancer Res. 2007 Sep 15;13(18 Pt 1):5426-35
Clinical trials using CD19 targeted T cells in relapsed B cell ALL
A Phase I trial of precursor B cell Acute Lymphoblastic Leukemia (B-ALL) treated with autologous T cells genetically targeted to the B cell specific antigen CD19

• **Inclusion Criteria:**
  – Adult patients, age ≥18
  – Relapsed or refractory CD19+ B-ALL
  – Relapsed after allogeneic HSCT allowed

• **Exclusion Criteria:**
  – Active CNS disease
  – Active GvHD requiring immunosuppressants
  – Significant heart disease (MI ≤ 6 months or NYHA III/IV CHF or EF <40%)
Study Design

Leukapheresis

T Cell Production

Salvage Chemo

CTX Conditioning

19-28z CAR T Cell Infusion (1-3x10^6 CAR T cells/kg)

Day -2

BMB

LP + IT Chemo

Day 1

Disease Assessment

Post-Treatment Follow UP
Patient characteristics and treatment outcomes

<table>
<thead>
<tr>
<th>Patient ID</th>
<th>Age (years)</th>
<th>FISH/cytogenetics</th>
<th>Initial therapy</th>
<th>Duration of CR1</th>
<th>Salvage therapy</th>
<th>Disease response to salvage therapy</th>
<th>Disease response to cell therapy</th>
<th>Steroids</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>MSK-ALL01</td>
<td>66</td>
<td>Normal karyotype</td>
<td>Mito/Cy→Vinc/Pred→Cy→Etop/Cy</td>
<td>27 weeks</td>
<td>Vinc/Pred/Peg</td>
<td>MRD⁺</td>
<td>MRD⁻</td>
<td>N</td>
<td>Allo-SCT</td>
</tr>
<tr>
<td>MSK-ALL03</td>
<td>56</td>
<td>Normal karyotype</td>
<td>Hyper-CVAD</td>
<td>45 weeks</td>
<td>Inotuzumab ozogamicin→Vinc/Pred/Peg</td>
<td>MRD⁻</td>
<td>MRD⁻</td>
<td>N</td>
<td>Allo-SCT</td>
</tr>
<tr>
<td>MSK-ALL04</td>
<td>59</td>
<td>t(9;11), 9p21 deletion</td>
<td>ECOG2993 (24)</td>
<td>5 weeks</td>
<td>Vinc/Pred</td>
<td>Refractory disease, 63% blasts in BM</td>
<td>MRD⁻</td>
<td>Y</td>
<td>Ineligible for Allo-SCT, relapse 90 days</td>
</tr>
<tr>
<td>MSK-ALL05†</td>
<td>58</td>
<td>9p21 deletion</td>
<td>ECOG2993</td>
<td>28 weeks</td>
<td>HIDAC/Mito</td>
<td>Refractory disease, 70% blasts in BM</td>
<td>MRD⁻</td>
<td>Y</td>
<td>Allo-SCT</td>
</tr>
<tr>
<td>MSK-ALL06</td>
<td>23</td>
<td>Normal karyotype</td>
<td>NYII (25)</td>
<td>34 months</td>
<td>Modified NYII consolidation I (25)</td>
<td>MRD⁺</td>
<td>MRD⁻</td>
<td>N</td>
<td>Allo-SCT</td>
</tr>
</tbody>
</table>

*MSK-ALL02 patient was removed from the study before the planned T cell infusion because he deferred T cell infusion for an allo-SCT.  †Disease status within 1 week of infusion with CD19-targeted T cells.  ‡This patient's T cells were harvested while in remission. All other patients listed had their T cells harvested while they had relapsed disease.
Rapid tumor elimination and recovery of normal bone marrow after 19-28z CAR T cell therapy

Sci Transl Med. 2013 Mar 20;5(177):177ra38
Study Progress

• As of 30 March 2015, 39 adult patients with relapsed/refractory ALL treated with 19-28z CAR T cells at MSKCC
  – 39 patients evaluable for toxicity assessment
  – 38 patients evaluable for response assessment with ≥1 month follow up
## Baseline Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Number of Patients N=39 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>29 (76)</td>
</tr>
<tr>
<td>Female</td>
<td>10 (24)</td>
</tr>
<tr>
<td><strong>Age at infusion (years)</strong></td>
<td></td>
</tr>
<tr>
<td>18-29</td>
<td>10 (26)</td>
</tr>
<tr>
<td>30-59</td>
<td>19 (49)</td>
</tr>
<tr>
<td>≥60</td>
<td>10 (26)</td>
</tr>
<tr>
<td>Median (range)</td>
<td>45 (22-74)</td>
</tr>
<tr>
<td><strong>Disease burden immediately prior to T cells</strong></td>
<td></td>
</tr>
<tr>
<td>Morphologic disease (5-100%, median 52%)</td>
<td>21 (54)</td>
</tr>
<tr>
<td>Minimal residual disease (&lt;5%)</td>
<td>18 (46)</td>
</tr>
</tbody>
</table>
## Baseline Disease Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Number of Patients, N=39 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior Lines of Therapy</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>19 (49)</td>
</tr>
<tr>
<td>3</td>
<td>9 (23)</td>
</tr>
<tr>
<td>≥4</td>
<td>11 (28)</td>
</tr>
<tr>
<td>Prior allogeneic HSCT</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>14 (36)</td>
</tr>
<tr>
<td>No</td>
<td>25 (64)</td>
</tr>
<tr>
<td>Philadelphia chromosome (Ph)+ T315I mutation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>13 (33)</td>
</tr>
<tr>
<td></td>
<td>4 (11)</td>
</tr>
</tbody>
</table>
Summary of Clinical Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Number of Patients, N=38</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall CR Rate, n (%) [95% CI]</td>
<td>33/38 (87%) [72, 96]</td>
</tr>
<tr>
<td>MRD Negative CR Rate, n (%) [95% CI]</td>
<td>26/32 (81%) [64, 93]</td>
</tr>
<tr>
<td>Median Time to CR (Range)</td>
<td>23.0 days (8 – 46)</td>
</tr>
</tbody>
</table>
## CR Rates by Subgroups

<table>
<thead>
<tr>
<th>Subgroups</th>
<th>CR Rate (%)</th>
<th>MRD Negative CR Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pre-T cell Disease Burden</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morphologic disease</td>
<td>16/20 (80)</td>
<td>13/15 (87)</td>
</tr>
<tr>
<td>Minimal residual disease</td>
<td>17/18 (94)</td>
<td>13/17 (76)</td>
</tr>
<tr>
<td><strong>Prior Allogeneic HSCT</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>11/13 (85)</td>
<td>9/10 (90)</td>
</tr>
<tr>
<td>No</td>
<td>22/25 (88)</td>
<td>17/22 (77)</td>
</tr>
<tr>
<td><strong>Ph+ Status</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>12/13 (92)</td>
<td>8/12 (67)</td>
</tr>
<tr>
<td>No</td>
<td>21/25 (84)</td>
<td>18/20 (90)</td>
</tr>
<tr>
<td><strong>Age at infusion (years)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18-29</td>
<td>9/10 (90)</td>
<td>7/9 (78)</td>
</tr>
<tr>
<td>30-59</td>
<td>16/18 (89)</td>
<td>11/15 (73)</td>
</tr>
<tr>
<td>≥60</td>
<td>8/10 (80)</td>
<td>8/8 (100)</td>
</tr>
<tr>
<td><strong>Prior Lines of Therapy</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>16/18 (89)</td>
<td>13/16 (81)</td>
</tr>
<tr>
<td>3</td>
<td>7/9 (78)</td>
<td>5/7 (71)</td>
</tr>
<tr>
<td>≥4</td>
<td>10/11 (91)</td>
<td>8/9 (89)</td>
</tr>
</tbody>
</table>
Post-CAR T Cell Follow Up

- Median follow-up: 5.6 months (1-38+ months)
- Median duration of response or relapse free-survival: 5.3 months (95% CI: 3-9)
- 14 patients remain disease-free: 10 patients w/o HSCT
  - 6 patients with > 1 year follow up
- 11 patients proceeded to allogeneic HSCT
- 14 patients relapsed during follow-up
  - 3 relapses post-HSCT (2 patient with CD19 negative blasts)
  - 10 relapses without HSCT
Overall Survival: All Patients

All Patients
- Median OS = 8.5 months
- OS Rate at 6 mos: 59% (95% CI: 39-74)

MRD-CR Patients
- Median OS = 10.8 months
- OS Rate at 6 mos: 75% (95% CI: 50-89)

At Risk
- 38
- 22
- 12
- 7
- 5
- 5
- 2
- 2
- 1
- 1
- 0

Memorial Sloan Kettering Cancer Center
Overall Survival:
By Allo-SCT Status Among CR Subjects

Allo-SCT Post-CAR
mOS=9.9 mos
OS rate at 6 month: 70% (95% CI: 33-89)

No Allo-SCT Post-CAR
mOS=8.5 mos
OS rate at 6 month: 62% (95% CI: 34-81)

Log-rank p=0.5

At Risk
11 10 6 4 3 3 2 2 2 1 1 0
22 12 6 3 2 2 0 0 0 0 0 0
19-28z CAR T Cell Expansion & Persistence

- 19-28z CAR T cells were measured in PB and BM by qPCR and flow cytometry
- Maximum T cell expansion occurred between days 7 – 14, and correlated with occurrence of CRS
- T cells persisted 1 – 3 months following T cell infusion
Adverse Events

- Cytokine release syndrome (CRS)
  - Fever
  - Hypotension
  - Respiratory insufficiency

- Neurological changes
  - Delirium
  - Global encephalopathy
  - Aphasia
  - Seizure-like activities/seizure
## CRS & Neurological Toxicities

<table>
<thead>
<tr>
<th>Subgroups</th>
<th>Severe CRS*</th>
<th>Grade 3/4 Neurotoxicity</th>
<th>Grade 5 Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall (n=39)</td>
<td>9 (23)</td>
<td>11 (28)</td>
<td>3 (8)¶</td>
</tr>
<tr>
<td>Pre-T cell Disease Burden</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morphologic disease (n=21)</td>
<td>9 (43)</td>
<td>8 (38)</td>
<td>2 (10)</td>
</tr>
<tr>
<td>MRD (n=18)</td>
<td>0 (0)</td>
<td>3 (17)</td>
<td>1 (6)</td>
</tr>
</tbody>
</table>

*Requiring vasopressors and/or mechanical ventilation for hypoxia
¶1 pt with ventricular arrhythmia (DNR); 1 pt had seizure, but unknown cause of death; and 1 pt died of sepsis.

- Severity of CRS correlated with disease burden.
- CRS managed with IL-6R inhibitor (4 pts), steroid (2 pts), IL-6R inhibitor+steroid (9 pts)
- Neurological symptoms are reversible, and can occur independent of CRS
Adverse Events: Cytokine Release Syndrome

- Cytokine release syndrome (CRS)
  - fevers, hypotension, hypoxia, malaise

- Neurologic changes*
  - confusion, speech disorders, obtundation, seizure-like activities

- There is a strong correlation between sCRS and pre-T cell disease burden

- 0/10 sCRS in MRD patients
- 8/11 sCRS in Morphologic residual pts
Management of sCRS
Summary of CAR T cell in adult ALL at MSKCC

- 39 adult patients with relapsed or refractory B-ALL have been treated with 19-28z CAR T cells, and 38 patients are evaluable for response.
- High CR rate (87%) can be achieved in adults with R/R B-ALL.
  - Majority of CR is MRD negative (81%).
  - Similar CR rates regardless of disease status, Ph+, age or prior alloHSCT.
- Median time to CR is 23 days.
- 33% of patients proceeded to alloHSCT after achieving CR with CAR T cells.
- Durable responses have been observed in a subset of patients with no subsequent alloHSCT.
  - Depth of response (i.e. MRD negativity) is correlated with overall survival.
- Severe CRS (23%) and neurological toxicities (28%) have been observed and correlate with disease burden and response.
UPenn studies of relapsed B-ALL

- 25 pediatric and 5 adult relapsed or refractory B-ALL patients treated
- 19-4-1BBz CAR design
- 90% CR
- 6 month EFS 67%
- 6 month OSR 78%

NCI studies of relapsed B-ALL

- 20 pediatric and young adult relapsed or refractory B-ALL patients treated.
- 19-28z CAR design
- 70% CR (14/20)
- 60% MRD- CR
- 5 month EFS 78% in MRD- patients
Clinical trials using CD19 targeted T cells other B cell malignancies
Early NCI clinical trial results

Patient with relapsed follicular NHL

Prior Therapies:  PACE, idiotype vaccine, ipilimumab, EPOCH-R

Conditioning: high dose cyclophosphamide with fludarabine

Post infusion: IL-2 tid x 3 days

Response: PR with persistent B cell aplasias

Kochenderfer et al Blood 2010

An additional 7 patients plus retreatment of patient 1 with low grade B cell malignancies

Prior Therapies: Not Reported

Conditioning: high dose cyclophosphamide with fludarabine

Post infusion: IL-2 tid as tolerated

Response: 1/8 CR, 4/8 PR with persistent B cell aplasias in 4/8 patients treated

Kochenderfer et al Blood 2011
NCI studies of relapsed B cell lymphomas

- 15 patients with relapsed B cell lymphomas
  - 9 with DLBCL
  - 4 with CLL
  - 2 with low grade lymphomas

- 19-28z CAR design

- 8/15 CRs
  - 4/7 with DLBCL (3/4 ongoing 9-22 mo)
  - 3/4 with CLL
## UPenn clinical trial results

<table>
<thead>
<tr>
<th>Patient</th>
<th>Prior Chemotherapy</th>
<th>Conditioning Chemotherapy</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Fludarabine, Rituximab, Alemtuzumab, R-CVP, Lenolidomide, PCR</td>
<td>Bendamustine</td>
<td>CR (3+ years)</td>
</tr>
<tr>
<td>2</td>
<td>Alemtuzumab</td>
<td>Bendamustine/Rituximab</td>
<td>PR (7 months)</td>
</tr>
<tr>
<td>3</td>
<td>Rituximab/Fludarabine, Rituximab/Bendamustine, Alemtuzumab</td>
<td>Pentostatin/Cyclophosphamide</td>
<td>CR (3+ years)</td>
</tr>
</tbody>
</table>
Updated UPenn Trials in CLL (ASH 2013)

- **Abstract 4162**
  - CD19 CAR T cells treating relapsed/refractory CLL
    - Utilizing a 4-1BBz CAR construct, 14 CLL patients treated
    - 3/14 patients obtained CR (21%), 5/14 patients obtained PR (36%), 6/14 patients with no response (43%)
    - 6/14 patients with persistent detectable CAR T cells (5-35 months)
    - No CR patients with reported relapsed disease
    - No dose response reported

- **Abstract 873**
  - Dose randomized dose optimization trial of CLL patients with either high or low dose CAR T cell infusions
    - Utilizing a 4-1BBz CAR construct, 27 CLL patients treated
    - Patients randomized to either low dose ($5 \times 10^7$ CAR T cells) or high dose ($5 \times 10^8$ CAR T cells)
    - No dose response benefit seen in these treated patients
    - Overall response rate (CR + PR) was 40%
    - No correlation with CRS and RR was observed
MSKCC clinical trial results: CLL

Table 1. Patient characteristics

<table>
<thead>
<tr>
<th>Diagnosis-Patient</th>
<th>Age at Diagnosis (years)</th>
<th>Age at Treatment (years)</th>
<th>Sex</th>
<th>Indication for Treatment</th>
<th>Prior Therapies</th>
<th>Genetic Abnormalities/ IgV(_H) Mutation Status</th>
<th>WBC (x10(^3) /ul)</th>
<th>ALC (x10(^3) /ul)</th>
<th>Hgb (g/dL)</th>
<th>PLT (x10(^3) /ul)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLL-1</td>
<td>44</td>
<td>51</td>
<td>M</td>
<td>Bulky LAD</td>
<td>PCR, PCRM</td>
<td>deli1q</td>
<td>200.6</td>
<td>196.6</td>
<td>7.1</td>
<td>26</td>
</tr>
<tr>
<td>CLL-2</td>
<td>66</td>
<td>72</td>
<td>M</td>
<td>Bulky LAD</td>
<td>FR, RCVP, PCRM</td>
<td>Unmutated IgV(_H)</td>
<td>4.2</td>
<td>3.4</td>
<td>9.9</td>
<td>60</td>
</tr>
<tr>
<td>CLL-3</td>
<td>62</td>
<td>73</td>
<td>F</td>
<td>Bulky LAD</td>
<td>Chlorambucil, PCR, PCRM</td>
<td>Normal karyotype</td>
<td>136.4</td>
<td>132.3</td>
<td>8.9</td>
<td>100</td>
</tr>
<tr>
<td>CLL-4</td>
<td>63</td>
<td>69</td>
<td>M</td>
<td>Bulky LAD</td>
<td>R, PCRM</td>
<td>deli1q</td>
<td>187.1</td>
<td>174</td>
<td>9.9</td>
<td>189</td>
</tr>
<tr>
<td>CLL-5</td>
<td>65</td>
<td>68</td>
<td>M</td>
<td>Bulky LAD</td>
<td>PCR</td>
<td>deli1q, trisomy 12</td>
<td>76.3</td>
<td>66.4</td>
<td>10</td>
<td>162</td>
</tr>
<tr>
<td>CLL-6</td>
<td>56</td>
<td>68</td>
<td>M</td>
<td>Bulky LAD</td>
<td>RCVP, PCR, Bendamustine</td>
<td>deli1q, inv1, unmutated IgV(_H)</td>
<td>97.1</td>
<td>92.2</td>
<td>8.9</td>
<td>174</td>
</tr>
<tr>
<td>CLL-7</td>
<td>52</td>
<td>62</td>
<td>M</td>
<td>Bulky LAD</td>
<td>CVP, RC, PCR, PCRM</td>
<td>deli7p, unmutated IgV(_H)</td>
<td>1.9</td>
<td>1</td>
<td>10</td>
<td>61</td>
</tr>
<tr>
<td>CLL-8</td>
<td>58</td>
<td>61</td>
<td>M</td>
<td>Bulky LAD</td>
<td>RCVP, Alemtuzumab</td>
<td>deli7p, monosomy 14, monosomy 15</td>
<td>5.4</td>
<td>3.3</td>
<td>11.6</td>
<td>41</td>
</tr>
</tbody>
</table>

Table 5. Summary of patient responses

<table>
<thead>
<tr>
<th>Diagnosis-Patient</th>
<th>Response to T-cell infusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLL-1</td>
<td>No objective response</td>
</tr>
<tr>
<td>CLL-2</td>
<td>No objective response</td>
</tr>
<tr>
<td>CLL-3</td>
<td>No objective response</td>
</tr>
<tr>
<td>CLL-4</td>
<td>Not evaluable</td>
</tr>
<tr>
<td>CLL-5</td>
<td>Marked reduction in lymphadenopathy at 3 months subsequently stable for 6 months</td>
</tr>
<tr>
<td>CLL-6</td>
<td>Progressive disease</td>
</tr>
<tr>
<td>CLL-7</td>
<td>Stable disease, lasting 4 months</td>
</tr>
<tr>
<td>CLL-8</td>
<td>Stable disease, lasting &gt;8 weeks</td>
</tr>
</tbody>
</table>

Brentjens et al Blood. 2011 Nov 3;118(18):4817-28
Clinical Trial Treatment Schema I: Screening & CAR-modified T cell production

Previously untreated CLL with high-risk disease features
Unmutated IGHV del11q or del17p
Age ≥18 years

PCR x 6 cycles
Pentostatin
Cyclophosphamide
Rituximab

MRD-CR
MRD+CR
PR
Leukapheresis
T cell modification & production
SD
PD
## Summary of Response Rates

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Patient</th>
<th>Age</th>
<th>Disease Risk</th>
<th>Response after PCR</th>
<th>T Cell Dose</th>
<th>Response after T Cells</th>
<th>Follow-Up Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>59</td>
<td>UM IgHV</td>
<td>PR</td>
<td>$3 \times 10^6$ 19-28z/kg</td>
<td>MRD+CR</td>
<td>17 months</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>68</td>
<td>Del11q</td>
<td>PR</td>
<td>$3 \times 10^6$19-28z/kg</td>
<td>PR</td>
<td>14 months</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>45</td>
<td>UM IgHV</td>
<td>PR (LN &gt;3cm)</td>
<td>$3 \times 10^6$ 19-28z/kg</td>
<td>PD in LN only at 6 months (marrow CR)</td>
<td>13 months</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>56</td>
<td>UM IgHV</td>
<td>PR (LN &gt;5cm)</td>
<td>$1 \times 10^7$ 19-28z/kg</td>
<td>PD</td>
<td>11 months</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>66</td>
<td>UM IgHV</td>
<td>PR</td>
<td>$1 \times 10^7$ 19-28z/kg</td>
<td>PR</td>
<td>11 months</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>68</td>
<td>UM IgHV, trisomy 12</td>
<td>PR</td>
<td>$1 \times 10^7$ 19-28z/kg</td>
<td>CR</td>
<td>4 months</td>
</tr>
<tr>
<td>3</td>
<td>7</td>
<td>54</td>
<td>UM IgHV, del11q</td>
<td>PR (LN &gt;5cm)</td>
<td>$3 \times 10^7$ 19-28z/kg</td>
<td>CR</td>
<td>2 months</td>
</tr>
</tbody>
</table>

*No sCRS in any treated patients on this clinical trial*
Phase I Trial of 19-28z Chimeric Antigen Receptor Modified T cells (19-28z CAR-T) Post-High Dose Therapy and Autologous Stem Cell Transplant (HDT-ASCT) for Relapsed and Refractory (rel/ref) Aggressive B Cell Non-Hodgkin Lymphoma (B-NHL)

Craig S. Sauter PI
Advantages of 19-28z CAR T cells Post-Ablative Chemotherapy and ASCT

• Modulation of a hostile immune suppressive tumor microenvironment
  – elimination of regulatory T cells, myeloid derived suppressor cells

• Elimination of cytokine “sinks” for optimized proliferative expansion of 19-28z CAR T cells
Eligibility Criteria

- Patients ≥ 18 years old with relapsed or refractory aggressive histology B-NHL meeting at least one of the following criteria:
  - PET positive disease following ≥ 2 cycles of salvage chemotherapy, though still achieving chemosensitive status per 1999 IWG CT criteria.
  - Bone marrow involvement at the time of relapse or refractory disease and not appropriate for allogeneic transplantation.

Adequate organ function:
- cardiac function (LVEF > 40%)
- pulmonary function as assessed by DLCO of ≥ 45%
- renal function GFR ≥ 50 cc/min or serum creatinine ≤ 1.5 mg/dL
- liver function AST/ALT < 3x upper limit of normal bilirubin < 2 mg/dL
Schema

Salvage Chemotherapy, Leukapheresis, CAR T cell generation

Admission to BMT Service

BEAM Conditioning

-7 -6 -5 -4 -3 -2 -1 0 +1 +2 +3

Pegfilgrastim

ASCT

Infusion 19-28z CAR T cells

Anticipated engraftment

Dose Level -1 – 2x10^6 CAR/kg
Dose Level 1 – 5 x 10^6 CAR/kg
Dose Level 2 – 1 x 10^7 CAR/kg
Dose Level 3 – 2 x 10^7 CAR/kg

Days

+10
Objectives

Primary Objective:

• To assess the safety and maximum tolerated dose (MTD) of 19-28z CAR T cell infusion following high dose therapy and CD34+ autologous stem transplantation for CD 19+ relapsed and refractory aggressive histology B-NHL.

Secondary Objectives:

• 1 and 2 year PFS.
• Assess for modified T cell persistence.
<table>
<thead>
<tr>
<th>Patient #</th>
<th>Age</th>
<th>histology/ #lines of therapy</th>
<th>Status at HDT-ASCT</th>
<th>Dose CAR-T (x10^6/kg)</th>
<th>Clinically Relevant ≥ grade 3 non-heme AE</th>
<th>Cytokine release syndrome(^1) (CRS)/Rx</th>
<th>Peak CRP (mg/dL)</th>
<th>Best Response/PFS (months)</th>
<th>Cur Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>34</td>
<td>tFL/3</td>
<td>PET(+) PR</td>
<td>5</td>
<td>Gr3 CRS (mental status (MS) changes)</td>
<td>Yes/Toc(^*) x1</td>
<td>27.3 (D4)</td>
<td>CR/20+</td>
<td>CR</td>
</tr>
<tr>
<td>2</td>
<td>68</td>
<td>DLBCL/4</td>
<td>PET(+) PR</td>
<td>5</td>
<td>Gr3 febrile neutropenia, Gr3 MS changes</td>
<td>Yes/None</td>
<td>16.5 (D4)</td>
<td>CR/21+</td>
<td>CR</td>
</tr>
<tr>
<td>3</td>
<td>56</td>
<td>tMZL/2</td>
<td>PET(+) PR BM involved</td>
<td>5</td>
<td>Gr3 hypophosphatemia</td>
<td>No</td>
<td>17.6 (D3)</td>
<td>CR/12</td>
<td>Alive, POD</td>
</tr>
<tr>
<td>4</td>
<td>59</td>
<td>tFL/DHL/2</td>
<td>PET(+) PR</td>
<td>10</td>
<td>Gr3 hypocalcemia, Gr3 AST/ALT, Gr4 CRS (hypotension, AKI, MS changes)</td>
<td>Yes/Toc(^*) x1+dex</td>
<td>43.1 (D3)</td>
<td>CR/15+</td>
<td>CR</td>
</tr>
<tr>
<td>5</td>
<td>66</td>
<td>DLBCL/3</td>
<td>PET(+) PR</td>
<td>5</td>
<td>Gr3 hyperglycemia</td>
<td>No</td>
<td>5 (D3)</td>
<td>CR/13+</td>
<td>CR</td>
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<tr>
<td>6</td>
<td>64</td>
<td>CD5+ DLBCL/2</td>
<td>PET(+) PR</td>
<td>5</td>
<td>none</td>
<td>No</td>
<td>7.9 (D4)</td>
<td>SD/6</td>
<td>Alive, POD</td>
</tr>
<tr>
<td>7</td>
<td>65</td>
<td>BL/2</td>
<td>PET(+) PR BM involved</td>
<td>5</td>
<td>Gr3 CRS (MS changes,), Gr3 febrile neutropenia, Gr3 hyperglycemia</td>
<td>Yes/Toc(^*)x1</td>
<td>11.8 (D7)</td>
<td>CR/2</td>
<td>POD/ DOD</td>
</tr>
<tr>
<td>8</td>
<td>56</td>
<td>DLBCL/DHL/2</td>
<td>PET (+) PR</td>
<td>5</td>
<td>Gr3 electrolytes, Gr3 CRS (seizure) Gr3 respiratory failure, Gr3 febrile neutropenia, Gr 4 cytopenias, Gr 5 infection (mucormycosis)</td>
<td>Yes/Toc(^*) x1</td>
<td>18.1 (D4)</td>
<td>Not-evaluated (NE)</td>
<td>NRM /1 month</td>
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<tr>
<td>9</td>
<td>51</td>
<td>DLBCL/2</td>
<td>PET (+) PR</td>
<td>5</td>
<td>Gr3 febrile neutropenia</td>
<td>No</td>
<td>31.8 (D3)</td>
<td>POD/2</td>
<td>DOD</td>
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<tr>
<td>10</td>
<td>61</td>
<td>blastoid MCL/4</td>
<td>PET CR, leukemic phase</td>
<td>5</td>
<td>Gr3 CRS (MS changes)</td>
<td>Yes/Toc(^*) x 1+dex</td>
<td>16.5 (D5)</td>
<td>POD/2</td>
<td>Alive</td>
</tr>
<tr>
<td>11</td>
<td>75</td>
<td>Richter’s/2</td>
<td>PET (+) PR</td>
<td>5</td>
<td>Gr 3 febrile neutropenia, Gr 4 CRS (encephalopathy)</td>
<td>Yes/Toc(^*) x 1+dex</td>
<td>22.8 (D5)</td>
<td>NE current d30</td>
<td>NE</td>
</tr>
</tbody>
</table>

\(^1\) Lee et al Blood 124(2): 2014

Dose-limiting toxicity, \(^*\)tocilizumab, +continuous response
NRM: non-relapse mortality, POD: progression of disease, DOD: dead of disease
Summary

• 19-28z CAR T cells are safe post HDT-ASCT at 5x10^6/kg (DLT 1/10 patients)
• 7 of 11 patients experienced ≥ grade 3 CRS, predominately CNS toxicity, with full reversibility
• variable IL-6 and CRP with or without CRS
• 4 of 10 evaluable patients remain progression-free at 13-21 months post HDT-ASCT
• Currently expanding dose level #1 (5 x 10^6/kg 19-28z CAR T cells) to further establish safety
NCI studies of CAR T cell DLI

- 10 post-transplant patients with persistent B cell malignancies
  - 4 MCL
  - 4 CLL
  - 2 DLBCL
- 0-1 grade GvHD with prior unmodified DLI therapy
- Single infusion of 19-28z donor CAR T cells
- 3 PRs, 1 patient with CLL achieved a CR.
- No evidence of GvHD

Kochenderfer et al Blood 2013
Conclusions

• Marked anti-tumor efficacy of CD19 targeted CAR T cells in relapsed B-ALL across multiple centers serves as a proof of principle regarding the potential of this adoptive T cell approach to cancer.

• Markedly positive clinical outcomes in relapsed B-ALL with CD19 targeted CAR T cell therapy may dramatically alter the standard of care for this disease pending phase II registration clinical trials.

• More modest responses in the setting of low grade B cell malignancies suggests that additional modification of this CAR T cell approach is required to optimize this therapy in this setting.

• Assessment of the B cell tumor microenvironment and BM cellularity at the time of CAR T cell therapy may offer clues to optimizing CAR T cell therapy.

• The ultimate goal of this research is to expand this technology to the setting of solid tumor malignancies.
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