Pre-emptive infusion with CD19-directed, CAR-modified T cells infused after autologous or allogeneic hematopoietic cell transplantation for patients with advanced CD19+ malignancies


Session 723. Clinical Allogeneic and Autologous Transplantation: Late Complications and Approaches to Disease Recurrence: Relapse
American Society of Hematology
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Background

• Chimeric antigen receptor (CAR)-modified T cells have:
  – Eradicated tumor in relapsed disease setting

• CAR⁺ T cells can:
  – Be a bridge to hematopoietic stem-cell transplantation (HSCT)

• CAR⁺ T cells may:
  – Consolidate graft-versus-tumor effect after HSCT
    • Reduced tumor burden decreases the risk of cytokine storm and related toxicities
Objectives and rationale

• Implemented two clinical trials infusing T cells expressing CAR in adjuvant setting
  • Autologous
    • New data
  • Allogeneic
    • Updated

• Test *Sleeping Beauty* (SB) transposon/transposase system to express a CD19-specific CAR in patient- and donor-derived T cells
  – Nimble system
  – Cost-effective

• Enroll recipients at high risk of relapse after HSCT for advanced B-lymphoid malignancies
SB system to genetically modify T cells to target CD19 via CAR

2nd generation CD19-specific CAR (CD19RCD28) signaling through CD28 & CD3-ζ

Transposon (Donor) sequences flanked by inverted repeats are integrated into genome

Transposase (Helper) expression is transient

Plasterk RH, Cell 74(5):781, 1993
Produce clinical-grade CAR\(^+\) T cells

Two major manufacturing technologies:
1. SB system for gene transfer
2. Activating and propagating cells (AaPC) to retrieve CAR\(^+\) T cells in culture

Irradiated AaPC
Derived from K-562 cells and modified to co-express CD19, CD86, CD137L, membrane-bound IL-15 (and CD64)

Methods available, including at:
Characterization of manufactured T cells

Outgrowth of genetically modified T cells, and T-cell subsets, similar between patient and donor-derived products.
Quality of manufactured T cells

- Preserved telomere length
- Heterogeneous phenotype

No evidence for replicative senescence

Romero P. et al., JI 2007
Trial schema

• Study populations
  – CD19+ lymphoid malignancies beyond first remission, induction failure, or relapse at time of HSCT
  – 1-65 yrs-old for allo-HSCT; up to 75 yrs-old for auto-HSCT

• Preparative treatment
  – Auto-HSCT
    • BEAM prep
    • PBSC day 0, CAR T cells day +2
  – Allo-HSCT
    • HSCT prep per MD choice
    • Donor-derived T cells 6-12 weeks post HSCT
    • GVHD prophylaxis maintained

<table>
<thead>
<tr>
<th>Dose Level</th>
<th>Single T-cell dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>&gt;5 x 10^7/m^2 but ≤ 5 x 10^8/m^2</td>
</tr>
<tr>
<td>B</td>
<td>&gt;5 x 10^8/m^2 but ≤ 5 x 10^9/m^2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Dose Level</th>
<th>Single T-cell dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Not to exceed 10^6/m^2</td>
</tr>
<tr>
<td>B</td>
<td>&gt;10^6/m^2 but ≤ 10^7/m^2</td>
</tr>
<tr>
<td>C</td>
<td>&gt;10^7/m^2 but ≤ 5x10^7/m^2</td>
</tr>
<tr>
<td>D</td>
<td>&gt;5x10^7/m^2 but ≤ 10^8/m^2</td>
</tr>
</tbody>
</table>

Per body surface area
### Patient characteristics, outcomes of auto-CAR\(^+\) T cells

N=7 pts treated, 6 alive in CR with median 25.5 mo (range 6.4-32.7) follow-up

<table>
<thead>
<tr>
<th>P#</th>
<th>Age</th>
<th>Histo-logy</th>
<th>Stage at HCT</th>
<th>Prep</th>
<th>T-cell dose level (m(^2))</th>
<th>% CAR</th>
<th>Relapse</th>
<th>Status</th>
<th>Response duration (months) at last follow up</th>
<th>Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>P446</td>
<td>61</td>
<td>Follicular</td>
<td>DLBL, CR2, PET(^{-})</td>
<td>BEAM</td>
<td>5x10(^8)</td>
<td>87.5</td>
<td>No</td>
<td>CCR</td>
<td>32.7</td>
<td>None</td>
</tr>
<tr>
<td>P458</td>
<td>58</td>
<td>Nodular HL</td>
<td>DLBL, CR2, PET(^{-})</td>
<td>BEAM</td>
<td>5x10(^8)</td>
<td>77.2</td>
<td>No</td>
<td>CCR</td>
<td>29.7</td>
<td>None</td>
</tr>
<tr>
<td>P468</td>
<td>48</td>
<td>Follicular</td>
<td>Follicular, Rel1, PET(^{+})</td>
<td>BEAM</td>
<td>5x10(^8)</td>
<td>85.5</td>
<td>No</td>
<td>CCR</td>
<td>24.4</td>
<td>None</td>
</tr>
<tr>
<td>P471</td>
<td>55</td>
<td>DLBL</td>
<td>DLBL, Rel1, PET(^{+})</td>
<td>BEAM</td>
<td>5x10(^8)</td>
<td>90.4</td>
<td>No</td>
<td>CCR</td>
<td>27.4</td>
<td>None</td>
</tr>
<tr>
<td>*P509</td>
<td>59</td>
<td>DLBL with CNS</td>
<td>Residual CNS</td>
<td>BEAM</td>
<td>5x10(^8)</td>
<td>95.9</td>
<td>Yes</td>
<td>Alive</td>
<td>20.8</td>
<td>None</td>
</tr>
<tr>
<td>P708</td>
<td>36</td>
<td>DLBL</td>
<td>Recurrent in CNS</td>
<td>BEAM</td>
<td>5x10(^9)</td>
<td>92.2</td>
<td>No</td>
<td>CCR</td>
<td>12.4</td>
<td>None</td>
</tr>
<tr>
<td>P747</td>
<td>47</td>
<td>MCL</td>
<td>CR2, PET(^{-})</td>
<td>BEAM</td>
<td>5x10(^9)</td>
<td>91</td>
<td>No</td>
<td>CCR</td>
<td>6.4</td>
<td>None</td>
</tr>
</tbody>
</table>

* Patient 509 had decreased expression HLA-DR and PDL-1, increased expression of TIM3 and BTLA.
Survival for recipients of autologous CAR$^+$ T cells
## Outcomes for sibling donor-derived CAR⁺ T cells

N=11 pts treated, 4 in CR with median 7.4 mo (range 3.4-14.4) follow-up

<table>
<thead>
<tr>
<th>P#</th>
<th>Age</th>
<th>Histo-logy</th>
<th>Stage at HSCT</th>
<th>Prep. Regimen</th>
<th>Dose level (m²)</th>
<th>BSA (m²)</th>
<th>Total T cells</th>
<th>% CAR</th>
<th>Days to CAR</th>
<th>Relapse</th>
<th>Status</th>
<th>Response duration (months)</th>
<th>Tox.</th>
</tr>
</thead>
<tbody>
<tr>
<td>411</td>
<td>50</td>
<td>DLBL Refractory, PET⁺</td>
<td>BEAM</td>
<td>10^6</td>
<td>2.3</td>
<td>0.03</td>
<td>70.5</td>
<td>71</td>
<td>Y</td>
<td>Dead</td>
<td>1.0</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>410</td>
<td>21</td>
<td>B-ALL CR3, MRD⁺</td>
<td>BuClo</td>
<td>10^6</td>
<td>1.5</td>
<td>0.02</td>
<td>96.8</td>
<td>54</td>
<td>Y</td>
<td>Dead</td>
<td>2.3</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>396</td>
<td>23</td>
<td>B-ALL CR2, MRD⁺</td>
<td>BuClo</td>
<td>10^6</td>
<td>1.6</td>
<td>0.02</td>
<td>96.5</td>
<td>64</td>
<td>Y</td>
<td>Dead</td>
<td>6.0</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>617</td>
<td>41</td>
<td>B-ALL CR2, MRD⁺</td>
<td>VP16T BI12</td>
<td>10^7</td>
<td>2.3</td>
<td>0.28</td>
<td>66.6</td>
<td>43</td>
<td>Y</td>
<td>Dead</td>
<td>4.5</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>564</td>
<td>31</td>
<td>B-ALL CR2, MRD⁺</td>
<td>BuClo</td>
<td>10^7</td>
<td>2.3</td>
<td>0.23</td>
<td>91.2</td>
<td>64</td>
<td>Y</td>
<td>Dead</td>
<td>3.0</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>459</td>
<td>25</td>
<td>B-ALL CR2, MRD⁻</td>
<td>BuClo</td>
<td>10^7</td>
<td>2.4</td>
<td>0.28</td>
<td>90.5</td>
<td>64</td>
<td>N</td>
<td>Dead</td>
<td>14.1</td>
<td>GVHD liver</td>
<td>None</td>
</tr>
<tr>
<td>P713</td>
<td>47</td>
<td>B-ALL Prior Allo, CR2, MRD⁻</td>
<td>FM</td>
<td>5 x 10^7</td>
<td>2.07</td>
<td>1.02</td>
<td>65.8</td>
<td>56</td>
<td>N</td>
<td>CCR</td>
<td>8.8</td>
<td>None</td>
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</tr>
<tr>
<td>P641</td>
<td>38</td>
<td>B-ALL CR2, MRD⁻</td>
<td>BuClo</td>
<td>5 x 10^7</td>
<td>1.81</td>
<td>0.91</td>
<td>72.4</td>
<td>68</td>
<td>N</td>
<td>CCR</td>
<td>14.4</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>P647</td>
<td>28</td>
<td>B-ALL Ref Rel, MRD⁺</td>
<td>BuClo</td>
<td>5 x 10^7</td>
<td>1.45</td>
<td>0.76</td>
<td>82.3</td>
<td>57</td>
<td>Y</td>
<td>Dead</td>
<td>2.8</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>P753</td>
<td>56</td>
<td>B-ALL CR1, MRD⁻</td>
<td>FBVC</td>
<td>10^8</td>
<td>1.72</td>
<td>1.72</td>
<td>57.7</td>
<td>84</td>
<td>N</td>
<td>CCR</td>
<td>3.4</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>P718</td>
<td>44</td>
<td>B-ALL CR1, MRD⁺</td>
<td>BuClo</td>
<td>5 x 10^7</td>
<td>1.87</td>
<td>0.94</td>
<td>91.8</td>
<td>56</td>
<td>N</td>
<td>CCR</td>
<td>6.0</td>
<td>None</td>
<td></td>
</tr>
</tbody>
</table>

P718 underwent 1-antigen HLA-mismatched HSCT

Response duration based on last follow up
Survival for recipients of all allogeneic CAR⁺ T cells
## Patient characteristics, outcomes of haploidentical donor-derived CAR$^+$ T cells

N=8 pts treated, 6 alive in CR with median 5.2 mo. (range 2.7-18.1) follow-up

<table>
<thead>
<tr>
<th>P#</th>
<th>Age</th>
<th>Histology</th>
<th>Stage at HSCT</th>
<th>Prep. regimen</th>
<th>T-cell dose level (m$^2$)</th>
<th>BSA (m$^2$)</th>
<th>Total T cells</th>
<th>% CAR</th>
<th>Days to CAR</th>
<th>Relapse</th>
<th>Status</th>
<th>Response duration (month)</th>
<th>Tox.</th>
</tr>
</thead>
<tbody>
<tr>
<td>580</td>
<td>31</td>
<td>B-ALL</td>
<td>Allo2, MRD neg</td>
<td>FluMel</td>
<td>$10^6$</td>
<td>2.03</td>
<td>0.02</td>
<td>70.4</td>
<td>81</td>
<td>N</td>
<td>CCR</td>
<td>18.1</td>
<td>None</td>
</tr>
<tr>
<td>513</td>
<td>25</td>
<td>B-ALL</td>
<td>Auto, MRD neg</td>
<td>FluMel</td>
<td>$10^6$</td>
<td>1.74</td>
<td>0.02</td>
<td>93.3</td>
<td>66</td>
<td>N</td>
<td>CCR</td>
<td>7.2</td>
<td>GVHD, skin</td>
</tr>
<tr>
<td>P732</td>
<td>36</td>
<td>B-ALL</td>
<td>CR2, MRD pos</td>
<td>FluMel</td>
<td>$10^7$</td>
<td>2.04</td>
<td>0.2</td>
<td>67.8</td>
<td>46</td>
<td>Y</td>
<td>Alive</td>
<td>4.5</td>
<td>None</td>
</tr>
<tr>
<td>671</td>
<td>52</td>
<td>Follicular</td>
<td>Transformed DLBL, PET$^{&lt;}$</td>
<td>FluCy-TBI 2Gy</td>
<td>$10^7$</td>
<td>2.2</td>
<td>0.21</td>
<td>95.2</td>
<td>45</td>
<td>N</td>
<td>CCR</td>
<td>13.2</td>
<td>None</td>
</tr>
<tr>
<td>P723</td>
<td>23</td>
<td>B-ALL</td>
<td>PIF in CR, MRD neg</td>
<td>FluMel</td>
<td>$10^7$</td>
<td>2.04</td>
<td>0.21</td>
<td>58.8</td>
<td>54</td>
<td>N</td>
<td>CCR</td>
<td>6.0</td>
<td>GVHD, skin</td>
</tr>
<tr>
<td>P771</td>
<td>46</td>
<td>B-ALL</td>
<td>CR1, MRD neg</td>
<td>FM-TBI 2Gy</td>
<td>$5 \times 10^7$</td>
<td>1.92</td>
<td>0.96</td>
<td>56.8</td>
<td>67</td>
<td>N</td>
<td>CCR</td>
<td>3.9</td>
<td>None</td>
</tr>
<tr>
<td>P783</td>
<td>21</td>
<td>B-ALL</td>
<td>PIF, MRD pos</td>
<td>FluMel Thio</td>
<td>$10^8$</td>
<td>2.27</td>
<td>1.14</td>
<td>90.3</td>
<td>49</td>
<td>Y</td>
<td>Alive</td>
<td>2.9</td>
<td>None</td>
</tr>
<tr>
<td>P788</td>
<td>37</td>
<td>B-ALL</td>
<td>Allo,, MRD neg</td>
<td>FM-TBI 2Gy</td>
<td>$10^8$</td>
<td>1.74</td>
<td>1.14</td>
<td>83.8</td>
<td>74</td>
<td>N</td>
<td>CCR</td>
<td>2.7</td>
<td>None</td>
</tr>
</tbody>
</table>

Response duration based on last follow up
Survival for recipients of haploidentical allogeneic CAR\(^+\) T cells
Low levels of cytokines that signal through common \(\gamma\)-chain receptor at time of T-cell infusions

Lack of T-cell pro-survival cytokines in recipients
Persistence of infused CAR$^+$ T cells

<table>
<thead>
<tr>
<th>T-cell Dose Level and recipients (allo versus auto)</th>
<th>Number of patients infused</th>
<th>Average time (days) transgene detected</th>
<th>Maximum time (days) transgene detected</th>
</tr>
</thead>
<tbody>
<tr>
<td>MSD (allo)*</td>
<td>10</td>
<td>52</td>
<td>90</td>
</tr>
<tr>
<td>Haplo (allo)</td>
<td>8</td>
<td>54</td>
<td>180</td>
</tr>
<tr>
<td>All Auto patients</td>
<td>7</td>
<td>201</td>
<td>360</td>
</tr>
<tr>
<td>All Allo patients</td>
<td>19</td>
<td>51</td>
<td>180</td>
</tr>
</tbody>
</table>

*Excluding P718
Re-infusion of CAR$^+$ T cells

- Safely re-infuse CAR$^+$ T cells from patient-specific cryopreserved banks
  - 4 patients re-treated
- Two patients with ongoing responses to re-treatment
  - One patient re-treated and responded to 5x10$^7$/m$^2$ CAR T cells without prior lympho-depleting chemotherapy
First-in-human use of SB system: Summary I

• Successful manufacture of T-cell products
  – 200 mL of peripheral blood (avoiding costs & inconvenience of apheresis)

• Safely infuse patients
  – No immediate or late toxicity
  – Decreased GVHD rate at 11%
    – Administered up to $10^8$/m² genetically modified haplo-identical T cells
  – Decreased CMV reaction, 24% vs. 41%¹
  – Outpatient infusions

• Cytokines
  – Low levels of cytokine at time of T-cell infusion
  – Mild elevation, peak at ~2 weeks
  – No cytokine storm

First-in-human use of SB system: Summary II

• Survival of CAR$^+$ T cells

<table>
<thead>
<tr>
<th></th>
<th>Average, days</th>
<th>Max, days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autologous</td>
<td>201</td>
<td>360</td>
</tr>
<tr>
<td>Allogeneic</td>
<td>51</td>
<td>180</td>
</tr>
</tbody>
</table>

- CAR$^+$ T cells exhibit longer persistence in the auto group
- No apparent positive correlation with T-cell dose
- No apparent correlation with disease burden

• Survival of recipients after CAR$^+$ T cells

<table>
<thead>
<tr>
<th></th>
<th>PFS</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autologous</td>
<td>83%, 3-yr</td>
<td>100% 3-yr</td>
</tr>
<tr>
<td>Allogeneic (all)</td>
<td>53%, 1-yr</td>
<td>63%, 1-yr</td>
</tr>
<tr>
<td>Allogeneic (haploidentical)</td>
<td>75%, 1-yr</td>
<td>100%, 1-yr</td>
</tr>
</tbody>
</table>

- **Auto**: Compared with ~49% 3-year PFS reported for patients receiving auto-HSCT for advanced DLBL$^1$
- **Allo**: Compared with 1-year OS 20 to 34% reported for this patient group$^2$

$^1$Sauter, C.S. *et al*., Blood 125, 2579-2581 (2015)
First-in-human use of SB system: Conclusions

• CAR\(^+\) T cells appear effective in the adjuvant disease setting
  – Overall survival doubled compared with historical controls

• Absence of GVHD
  – Large doses of HLA-mismatched CAR\(^+\) (TCR\(^+\)) T cells can apparently be safely infused; encouraging for use of third party T cells as off-the-shelf allogeneic therapy
Future

• Next-generation *Sleeping Beauty* trial safe-to-proceed (IND 16474, clinical trial.gov NCT02529813)
  – Infuse patients with active CD19+ lymphoid malignancy
  – Lymphodepletion followed by administration of CD19-specific CAR+ T cells
  – Altered CAR stalk to improve persistence
It takes a village….

**Adult Transplant Faculty**
- Richard Champlin
- Elizabeth Shpall
- Katy Rezvani
- Amanda Olson
- Yago Nieto
- Qaiser Bashir
- Jeffrey Molldrem
- Ian McNiece
- Martin Korbling
- Uday Popat
- Rima Saliba
- Muzaffar Qazilbash
- Krina Patel

**Pediatric Transplant Faculty**
- Borje Andersson
- Simrit Parmar
- Stefan Ciurea
- Roy Jones
- Nina Shah
- Saira Ahmed
- Paolo Anderlini
- Chitra Hosing
- Issa Khouri
- Amin Alousi
- Gabriela Rondon
- Gheath Al-Atrash

**CooperLab**
- Laurence Cooper
- Laura Worth
- Demetrios Petropoulos

**GMP**
- Dean Lee
- Priti Tewari

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**UTHealth**
**The University of Texas**
**MD Anderson Cancer Center**
**National Cancer Institute**
**PACT**
**Ziopharm Oncology, Inc.**

**Graduate School of Biomedical Sciences**