Targeting Lymphomas Using Non-Engineered, Multi-Antigen Specific T Cells

Infusion

Tumor-specific T cells

Patient

Adoptive T cell transfer

Blood draw

PBMCs

Antigen Specificity

Tumor-specific T cells

Infusion
Our approach

• Simultaneously target multiple TAAs

• Target multiple epitopes (CD4 and CD8) within each antigen

• T cells with native T cell receptor specificity (non-engineered)
MultiTAA T cell therapy for lymphoma

MAGEA4
PRAME
Survivin
NYESO1
SSX2

MultiTAA T cells
MultiTAA-T Cell manufacture

Overlapping pepmixes

DC
MultiTAA-T Cell Specificity

![Graph showing SFC/2x10^5 cells for PRAME, SSX2, MAGEA4, NYESO1, and Survivin.](image)

- **PRAME**
- **SSX2**
- **MAGEA4**
- **NYESO1**
- **Survivin**
Multi TAA-T Cell Autoreactivity

% Specific Lysis

E:T of 20:1
Clinical Trial: Eligibility

Any patient ≥18 yrs with HL or NHL

Active disease
- in 2nd or subsequent relapse
- in 1st relapse for indolent lymphoma after 1st line therapy for relapse
- in 1st relapse if immunosuppressive chemotherapy contraindicated
- primary refractory disease or persistent disease after 1st line therapy
- multiply relapsed patients in remission at a high risk of relapse
- lymphoma as a second malignancy e.g. Richters

After autologous or syngeneic SCT (adjuvant therapy)

Infusion of multiTAA-T cells specific for PRAME, SSX2, MAGEA4, NYESO1, Survivin
Antigen Escalation Phase = fixed dose $5 \times 10^6/m^2 - 2$ pts/stage:
Day 0: PRAME-specific T cells
Day 28: PRAME and SSX-specific T cells

Stage Two:
Day 0: PRAME and SSX-specific T cells
Day 28: PRAME/SSX/MAGE-specific T cells

Stage Three:
Day 0: PRAME/SSX/MAGE-specific T cells
Day 28: PRAME/SSX/MAGE/NYESO1-specific T cells

Stage Four:
Day 0: PRAME/SSX/MAGE/NYESO1-specific T cells
Day 28: PRAME/SSX/MAGE/NYESO1/Survivin-specific T cells
Safety of MultiTAA T cells - Dose escalation

PRAME/SSX/MAGE/NYESO1/Survivin-specific T cells:
2-4 pts at each level, 2 infusions 14 days apart

**Dose Level 1:**
Day 0 and 14: 5x10^6 cells/m²

**Dose Level 2:**
Day 0 and 14: 1x10^7 cells/m²

**Dose Level 3:**
Day 0 and 14: 2x10^7 cells/m²
Clinical Trial: Treatment

- 33 patients infused
Clinical Trial: Treatment

- 33 patients infused

Group A: In remission

Group B: Active lymphoma (failed prior lines)

Antigen escalation (n=4)

Dose escalation (n=14)

Dose escalation (n=11)

Antigen escalation (n=4)
Clinical Trial: Treatment

- 33 patients infused (0.5-2x10^7 cells/m^2)
  - 12 HL
  - 19 aggressive NHL (DLBCL/mantle/peripheral T)
  - 2 with composite lymphoma

- No lymphodepletion
- No adverse events
Pt1 (HL) – Clinical and Immune effects

Pre T cells

Post T cells

Targeted antigens

SSX2
PRAME

Non-targeted antigens

AFP
NYESO1

SFC/2x10^5

Pre
Post
Pt2 (NHL) - Clinical and Immune effects

Targeted antigens
- MAGEA4
- SSX2
- PRAME
- Survivin

Non-targeted antigen
- SFC/2x10^5

Clinical and Immune effects

Pre-Mth Fusion

SFC/2x10^5

- MAGEC1

Pre Mth3 Mth9

0 5 10 15 20 25 30 35 40 45

Pt2 (NHL)
Clinical Outcomes – Adjuvant

- 18 patients infused as adjuvant
  - 15/18 in remission (median 19 months)
<table>
<thead>
<tr>
<th>ID</th>
<th>Age/Sex</th>
<th>Disease</th>
<th>Prior Therapies</th>
<th>Response to T cell therapy (duration)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1*</td>
<td>39/M</td>
<td>HL &amp; DLBCL</td>
<td>ABVD → RICE → ASCT</td>
<td>CCR (&gt;3 years)</td>
</tr>
<tr>
<td>2*</td>
<td>78/F</td>
<td>DLBCL</td>
<td>R → RCHOP</td>
<td>In remission (8 mo) → relapse</td>
</tr>
<tr>
<td>3*</td>
<td>78/F</td>
<td>DLBCL</td>
<td>R → RCHOP → multiTAA T cells → R-Bendamustine</td>
<td>CCR (&gt;3 years)</td>
</tr>
<tr>
<td>4*</td>
<td>21/M</td>
<td>HL</td>
<td>ABVD → Brentuximab → Nav/Gem → ASCT</td>
<td>CCR (&gt;4 years)</td>
</tr>
<tr>
<td>5</td>
<td>34/M</td>
<td>HL</td>
<td>ABVD → ICE → ASCT + XRT → Brentuximab</td>
<td>In remission (12 mo) → relapse</td>
</tr>
<tr>
<td>6</td>
<td>54/M</td>
<td>DLBCL</td>
<td>RCHOP → R-EPOCH → R-DHAP → ASCT</td>
<td>In remission (19 mo) → relapse</td>
</tr>
<tr>
<td>7</td>
<td>61/M</td>
<td>DLBCL</td>
<td>R-EPOCH → ASCT → XRT</td>
<td>CCR (&gt;2 years)</td>
</tr>
<tr>
<td>8</td>
<td>41/F</td>
<td>HL</td>
<td>ABVD + XRT → ICE → ASCT + XRT → Brentuximab → DHAP</td>
<td>CCR (&gt;4 years)</td>
</tr>
<tr>
<td>9</td>
<td>62/M</td>
<td>T cell</td>
<td>CHOP + XRT → ASCT</td>
<td>CCR (&gt;3 years)</td>
</tr>
<tr>
<td>10</td>
<td>53/M</td>
<td>Mantle</td>
<td>R-HyperCVAD → R-Bendamustine → R-Ibrutinib → ASCT + XRT</td>
<td>CCR (&gt;2 years)</td>
</tr>
<tr>
<td>11</td>
<td>39 not 67/M</td>
<td>Mantle</td>
<td>R-Bendamustine-Ara-C → ASCT</td>
<td>CCR (&gt;3 years)</td>
</tr>
<tr>
<td>12</td>
<td>65/F</td>
<td>DLBCL</td>
<td>R-EPOCH → ASCT</td>
<td>CCR (&gt;2 years)</td>
</tr>
<tr>
<td>13</td>
<td>35/M</td>
<td>HL</td>
<td>ABVD → Brentuximab + Bendamustine → ASCT → XRT</td>
<td>CCR (&gt;2 years)</td>
</tr>
<tr>
<td>14</td>
<td>73/F</td>
<td>DLBCL</td>
<td>R-CHOP → XRT → ESHAP → RIE</td>
<td>CCR (&gt;1 year)</td>
</tr>
<tr>
<td>15</td>
<td>50/F</td>
<td>DLBCL</td>
<td>HyperCVAD → ASCT</td>
<td>CCR (9 mo)</td>
</tr>
<tr>
<td>16</td>
<td>41/M</td>
<td>DLBCL</td>
<td>ABVD → R-ICE → ASCT</td>
<td>CCR (&gt;1 year)</td>
</tr>
<tr>
<td>17</td>
<td>32/F</td>
<td>T cell ALCL</td>
<td>CHOP → Brentuximab → Crizotinib → CD30 CAR T cells → Crizotinib</td>
<td>CCR (9 mo)</td>
</tr>
<tr>
<td>18</td>
<td>25/M</td>
<td>HL</td>
<td>ABVD → Brentuximab → ICE → ASCT</td>
<td>CCR (&gt;1 year)</td>
</tr>
</tbody>
</table>
Clinical Outcomes – Active disease

- 15 patients treated for active disease
  - 6 CRs; 4 SD; 5 PD
## Clinical Outcomes – Active disease

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<thead>
<tr>
<th>ID</th>
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<th>Prior Therapies</th>
<th>Response to multiTAA T cells (duration)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1*</td>
<td>31/F</td>
<td>HL</td>
<td>ABVD → ICE → Cis-Gem → XRT → ASCT → EBV T cells → Brentuximab → Yttrium90 → CART-CD30</td>
<td>Stable disease (5 mo) → Off study [Revlimid (5 mo) → PD1]</td>
</tr>
<tr>
<td>2*</td>
<td>55/F</td>
<td>HL/NHL</td>
<td>RCHOP + XRT → ICE → ASCT</td>
<td>CR (4 mo) Died of pneumonia</td>
</tr>
<tr>
<td>3*</td>
<td>38/M</td>
<td>HL</td>
<td>ABVD → XRT → IGEV → ESHAP → ASCT → GVD → XRT</td>
<td>CR (&gt;2 years ongoing)</td>
</tr>
<tr>
<td>4*</td>
<td>44/F</td>
<td>HL</td>
<td>ABVD → ICE → ASCT → Brentuximab</td>
<td>CR (&gt;5 years ongoing)</td>
</tr>
<tr>
<td>5</td>
<td>46/M</td>
<td>HL</td>
<td>ABVD → ICE → ASCT + XRT → Brentuximab</td>
<td>CR (&gt;2 years ongoing)</td>
</tr>
<tr>
<td>6</td>
<td>46/F</td>
<td>DLBCL</td>
<td>RCHOP → GDC → ASCT</td>
<td>CR (&gt;3 years ongoing)</td>
</tr>
<tr>
<td>7</td>
<td>31/F</td>
<td>HL</td>
<td>ABVD → XRT → ICE → Nav/Gem → ASCT → HDACi → Brentuximab → Bendamustine → PD1i</td>
<td>Stable disease (5 mo) → PD</td>
</tr>
<tr>
<td>8</td>
<td>69/M</td>
<td>NHL</td>
<td>EPOCH → Romidepsin → ASCT</td>
<td>Stable disease (&gt;2 years)</td>
</tr>
<tr>
<td>9</td>
<td>54/M</td>
<td>DLBCL</td>
<td>RCHOP → R-ICE → ASCT</td>
<td>Stable disease (6 mo) → PD → Started PD1i - &gt;2 years; Alive</td>
</tr>
<tr>
<td>10</td>
<td>18/F</td>
<td>HL</td>
<td>ABVE-PC → XRT → IVBoR → Brentuximab → PD1i</td>
<td>Stable disease (9 mo) → PD</td>
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<tr>
<td>11</td>
<td>48/M</td>
<td>DLBCL</td>
<td>EPOCH-R → R-ICE → ASCT → XRT</td>
<td>CR (&gt;1 year)</td>
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<tr>
<td>12</td>
<td>49/M</td>
<td>HL</td>
<td>ABVD → ICE → ASCT → XRT → Brentuximab → Nivolumab → Bendamustine</td>
<td>PD (3 mo)</td>
</tr>
<tr>
<td>13</td>
<td>54/M</td>
<td>DLBCL</td>
<td>EPOCH-R → ICE-R → XRT → ASCT</td>
<td>SD (9 mo)</td>
</tr>
<tr>
<td>14</td>
<td>64/M</td>
<td>DLBCL</td>
<td>R-CHOP → Bendamustine/Rituxan → RICE → RIE → ASCT</td>
<td>PD (9 mo)</td>
</tr>
<tr>
<td>15</td>
<td>68/M</td>
<td>DLBCL</td>
<td>RCHOP → GDP → ASCT</td>
<td>Stable disease (4 mo) → CD19-CAR-T</td>
</tr>
</tbody>
</table>
Summary to date

• Safe to date
• Feasible adjuvant and treatment
• In vivo expansion of T cells directed to targeted antigens
• Antigen/Epitope spreading
• Clinical benefit
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