T Cell Immunotherapy - Optimizing Trial Design

Session I

Current Status of Cancer Immunotherapy: Trials, Results, and Challenges

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### Overview of TCR Trials Sponsored by Adaptimmune

<table>
<thead>
<tr>
<th>Protocol number/title</th>
<th>Disease indication/Research Participant population</th>
<th>TCR or CAR product (ex vivo cell/ vector/transgene) and Dose</th>
<th>Trial initiation date/status /enrollment</th>
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<tbody>
<tr>
<td>NIH-OBA#1177/BB-IND 14603 “Phase I/Iia Open Label, Multiple Site Clinical Trial Evaluating the Safety and Activity of Engineered Autologous T Cells Expressing an Affinity-Enhanced TCR Specific for NY-ESO-1 in Patients with Relapsed or Progressive Disease Following Prior Auto-HSCT”</td>
<td>Relapsed or progressive disease in multiple myeloma (HLA-A201+; NY-ESO-1+ tumor)</td>
<td>TCR: NY-ESO-1(^{c259})-specific Cells: autologous T cells Vector: Lentivirus Target Dose: 10(^9) to 10(^{10}) total cells</td>
<td>Initiated September 2013 Enrolling September 2013</td>
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<tr>
<td>NIH-OBA#118/BB-IND 14603 “Phase I, Open Label, Dual Cohort, Triple Center Trial Evaluating the Safety and Efficacy of Autologous T Cells Expressing Enhanced TCRs Specific for NY-ESO-1 in Patients with Recurrent or Treatment Refractory Ovarian Cancer”</td>
<td>Recurrent or treatment refractory ovarian cancer (HLA-A201+; NY-ESO-1+ tumor)</td>
<td>TCR: NY-ESO-1(^{c259})-specific Cells: autologous T cells Vector: Lentivirus Target Dose: 10(^9) to 10(^{10}) total cells</td>
<td>Initiated June 2013 Currently Enrolling</td>
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# Overview of CD19-CAR Trials for Lymphoma Following HSCT

| Protocol number/title | NIH-OBA#1062/BB-IND 14645  
“Phase I/II Study of Cellular Immunotherapy Using Central Memory-Enriched CD8+ T Cells Lentivirally Transduced to Express a CD19 CAR Following HSCT for patients with High Risk Intermediate Grade, B-lineage NHL.” | NIH-OBA#1183/BB-IND 15490  
“Phase I Study of Cellular Immunotherapy Using Central Memory Enriched T Cells Lentivirally Transduced to Express a CD19-Specific, CD28-Costimulatory CAR and a Truncated EGFR Following HSCT for Patients with High-Risk Intermediate Grade B-Lineage NHL.” |
| Disease indication/Research Participant population | Relapsed B cell lymphoma  
(Diffuse large B cell and recurrent mantle cell lymphoma) | Relapsed B cell lymphoma  
(Diffuse large B cell, transformed B cell and recurrent mantle cell lymphoma) |
| TCR or CAR product (ex vivo cell/vector/transgene) and Dose | CAR: CD19-specific, CD3\(\zeta\) (1st Gen)  
Cells: Autologous CD8+ Tcm  
Vector: Lentivirus, epHIV7  
Dose escalation: 5x10^7 to 10^9 CAR+ | CAR: CD19-specific, **CD28**, CD3\(\zeta\) (2nd Gen)  
Additional Transgene: **EGFRt**  
Cells: Autologous **CD4**+CD8+Tcm  
Vector: Lentivirus, epHIV7  
Dose escalation: 5x10^7 to 8x10^8 CAR+ |
| Trial initiation date/status/enrollment | Initiated June 2012  
11 Enrolled  
6 treated (2 pending)  
5 of 6 w/ active disease at time of HSCT | Initiated June 2013  
Enrolling Oct 2013 |
NIH-OBA#1062 (NHL-1)
Phase I/II Study of Cellular Immunotherapy Using Central Memory-Enriched CD8+ T Cells Lentivirally Transduced to Express a CD19CAR Following HSCT for patients with High Risk Intermediate Grade, B-lineage NHL.”

Dose Schedule

<table>
<thead>
<tr>
<th>CAR+ Dose</th>
<th>≤ 50M</th>
<th>100M</th>
<th>500M</th>
<th>1000M</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treated Patients</td>
<td>5</td>
<td>1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Enrollment: Relapsed B Cell Lymphoma (recurrent large cell & mantle cell lymphoma); Poor prognosis with auto-transplant.

Infuse cells on day +2/+3 after HSCT
- Lymphopenic environment for homeostatic expansion
- Engraft cells as a component of the reconstituted immune system
Lessons Learned

- NIH-OBA#1062/NHL-1
  - Feasibility of manufacturing CD8+ CD19Rζ+ Tcm [Wang et al J Immunother 2012]
  - No infusional toxicities (T cells D+2 after HSCT)
  - No interference with HSC engraftment
  - Low levels of T cells detected by flow cytometry/qPCR in a subset of patients
  - B cell aplasia observed (up to 6 mos)
  - 4/5 currently in remission (6-13 mos); 1/6 too early to evaluate.