T Cell Immunotherapy- Optimizing Trial Design

Session I

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

Brentjens/Sadelain
Memorial Sloan Kettering Cancer Center

September 10, 2013
## Overview of Trials

<table>
<thead>
<tr>
<th>Protocol number/title</th>
<th>MSKCC IRB# 06-138</th>
<th>MSKCC IRB #11-048</th>
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</thead>
<tbody>
<tr>
<td><strong>Protocol number/title</strong></td>
<td><strong>A Phase I/IIa Trial For The Treatment of Relapsed or Chemotherapy Refractory Chronic Lymphocytic Leukemia or Indolent B Cell Lymphoma Using Autologous T Cells Genetically Targeted to the B Cell Specific Antigen CD19</strong></td>
<td><strong>A Phase I Trial of Consolidation Therapy with Autologous T Cells Genetically Targeted to the B Cell Specific Antigen CD19 in Patients with Chronic Lymphocytic Leukemia Following Upfront Chemotherapy with Pentostatin, Cyclophosphamide and Rituximab</strong></td>
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<tr>
<td><strong>Disease indication/Research</strong></td>
<td><strong>Relapsed or refractory CD19+ leukemia or lymphoma, including CLL/SLL, follicular, Waldenstrom’s, marginal zone, and mantle cell lymphoma</strong></td>
<td><strong>CLL patients who have achieved PR, nPR, or MRD+CR following frontline therapy with PCR</strong></td>
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<td><strong>Participant population</strong></td>
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<tr>
<td><strong>TCR or CAR product (ex vivo cell/ vector/transgene) and Dose</strong></td>
<td><strong>CAR</strong></td>
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<td></td>
<td><strong>Phase I: γ-retrovirus, 19-28z, 1x10^7 – 3x10^7 CAR+ T cells/kg</strong></td>
<td><strong>γ-retrovirus</strong></td>
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<td><strong>Phase IIa: 1:1 mixture of γ-retrovirus (19-28z) and lentivirus transduced (CART19:CD3z-4-1BB), 3x10^7 CAR+ T cells/kg</strong></td>
<td><strong>19-28z</strong></td>
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<td><strong>3x10^6 – 3x10^7 CAR+ T cells/kg</strong></td>
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<tr>
<td><strong>Trial initiation date/status /enrollment</strong></td>
<td><strong>March, 2007 Open to enrollment 13 patients treated (10 in phase I and 3 in phase Iia)</strong></td>
<td><strong>August, 2011 Open to enrollment 10 enrolled, 6 treated</strong></td>
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Lessons Learned

• Brief summary of important trial results...
  • 06-138:
    – T cell collection and transduction feasible in these heavily pretreated patients
    – Results of 8 treated patients published (Blood 2011;118(18):4817-28)
    – Of the 5 remaining patients, 2 treated under phase I and 1 achieved MRD negative CR and remains in remission over one year; 3 patients treated under STRAP, and 1 patient achieved MRD negative CR (also had CRS).
  • 11-048:
    – T cell collection and transduction feasible after completion of PCR
    – Acceptable safety profile observed with no DLT
    – CRS observed in 2 patients with a positive correlation between the development of CRS and the modified T cell persistence
    – 2 patients who had PR following PCR achieved CR after the T cell infusion; 2 patients maintained PR; and 2 patients had progressive disease (one in LN only).
• Summary of unexpected results (e.g., AE management)...
  – Unlike in ALL, we have not observed mental status changes despite patients developing CRS, although to a lesser degree.
  – For patients treated under STRAP, two fever curves were observed, one immediately following the T cell infusion that lasts 2-7 days, and then a second wave of fever approximately 3 weeks thereafter.
## Overview of Trials

| Protocol number/title | NCT01044069  
|-----------------------|---------------------------------------------------------------|

| Disease indication/Research | Relapsed/Refractory B-ALL  
| Participant population | Adults ≥ 18 years old |

| TCR or CAR product (ex vivo cell/vector/transgene) and Dose | CAR: 1928z  
| Vector: SFG  
| Gene-Transfer: gammaretrovirus  
| Cells: autologous bulk transduced T cells  
| Dose: $3 \times 10^6$ CAR+ T cells |

| Trial initiation date/status/enrollment | Trial Initiation: 9/9/2009  
| Enrollment: 14 patients treated to date (12 have been treated in the last 14 months) |
Lessons Learned

• Impressive MRD- induction rate (11/14 patients had an optimal MRD- response). Compared to a 20% salvage CR rate in a similar population.

• Cytokine Release Syndromes (CRS) strongly correlate with leukemia burden at time of CAR T cell infusion.

• Neurologic adverse events are common as part of the CRS, but ultimately are reversible.

• CAR T cells migrate to the CNS but its unknown if the migration is related to disease status.
Lessons Learned

- CRS is manageable with steroids or IL6 blockade, but relapses have occurred after steroids.
- CAR T cell lifespan is limited and B cell aplasia is reversible so long-term immune system support is unnecessary
**Overview of Trials (continued)**

<table>
<thead>
<tr>
<th>Protocol number/title</th>
<th>MSKCC IRB# 12-117 A Phase I Trial of High Dose Therapy and Autologous Stem Cell Transplantation Followed by Infusion of Chimeric Antigen Receptor (CAR) Modified T-Cells Directed Against CD19+ B-Cells for Relapsed and Refractory Aggressive B Cell Non-Hodgkin Lymphoma</th>
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<tbody>
<tr>
<td>Disease indication/Research Participant population</td>
<td>relapsed and refractory aggressive B-cell non-Hodgkin’s lymphoma</td>
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</table>
| TCR or CAR product (ex vivo cell/ vector/transgene) and Dose | 19-28z CAR  
Dose level #1: 5x10^6/kg  
Dose level #2: 1x10^7/kg  
Dose level #3: 2x10^7/kg |
| Trial initiation date/status /enrollment | 4/23/13  
2 patients enrolled and treated |
Lessons Learned

• Brief summary of important trial results
• Patient #1: fevers and MS changes during nadir. LP revealed lymphocytosis and protein >400 w/ evidence of 19-28z CAR-T on PCR. Symptoms abated with one dose of tocilizumab
• Patient #2: febrile neutropenia. No further complications.
• Both patients awaiting d100 restaging imaging.
• No DLT at current 5 x10e6/kg dose level
# Overview of Trials (continued)

| Protocol number/title | MSKCC IRB# 13-052  
A Phase I Trial of Autologous T-Lymphocytes Genetically Targeted to the B-Cell Specific Antigen CD19 in Pediatric and Young Adult Patients with Relapsed B-Cell Acute Lymphoblastic Leukemia | MSKCC IRB# 11-038  
A Phase I Dose Escalation Trial Using In Vitro Expanded Allogeneic Epstein-Barr Virus Specific Cytotoxic T-Lymphocytes (EBV-CTLs) Genetically Targeted to B-Cell Specific Antigen CD19 Positive ALL |
|-----------------------|-------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------|
| **Disease indication/Research Participant population** | B-ALL  
Pediatric Patients (0-26 years) | B-ALL (post-HSCT)  
Pediatric Patients (0-19 years) |
| **TCR or CAR product (ex vivo cell/ vector/transgene) and Dose** | CAR  
Autologous T cells  
γ-retrovirus  
19-28z  
3x10⁶ – 1x10⁷ – 3x10⁷ | CAR  
EBV-CTLs (donor)  
γ-retrovirus  
19-28z  
1x10⁶ – 3x10⁶ – 1x10⁷ (Total T cells) |
| **Trial initiation date/status /enrollment** | May 2013  
Open to Enrollment  
2 patients treated | September 2011  
Open to Enrollment  
4 patients treated |
Lessons Learned

- Brief summary of important trial results... EBV CAR T cell trial
- EBV CAR T cells well tolerated (GVHD)
- Very limited persistence of T cells noted in these patients
- No objective responses
- No cytokine release syndrome noted