T Cell Immunotherapy- Optimizing Trial Design

Session I

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

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Pediatric Oncology Branch
National Cancer Institute

September 10, 2013
<table>
<thead>
<tr>
<th><strong>NCI 12-C-0112</strong></th>
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<tbody>
<tr>
<td><strong>Phase I Study of T Cells Expressing an Anti-CD19 Chimeric Receptor in Children and Young Adults with B Cell Malignancies</strong></td>
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<td><strong>PI:</strong> Daniel Trey Lee</td>
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**PATIENT POPULATION:**
- Age 1-30
- Refractory CD19+ B cell malignancy
- Two strata—no hx of alloBMT, hx of alloBMT

**REGIMEN/PRODUCT:**
- Cyclophosphamide (900mg/m²)/fludarabine (75 mg/m²)
- Fresh or frozen T cells
  - anti-CD3/CD28 beads plus rhIL2
  - anti-CD19.zeta.28 CAR (Kochendorfer designed; supplied by S. Rosenberg)
  - Retrovirus (MSGV)
- No interleukin-2
- Dose Escalation: 1 x 10⁶/kg; 3 x 10⁶/kg

**PROTOCOL OPENED:** APRIL, 2012
Enrollment: 10 patients
Status: open to accrual
**NCI Pediatric Trial (FMC63-CAR.28.z)**

67% CR Rate Overall; 75% CR Rate in ALL

<table>
<thead>
<tr>
<th>Pt.</th>
<th>Age/Sex</th>
<th>Disease</th>
<th>Prior Allo BMT</th>
<th>CAR Dose (x10^6/kg)</th>
<th>% marrow blasts</th>
<th>Response</th>
<th>Status</th>
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<tbody>
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<tr>
<td>8</td>
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<td>1</td>
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<td>&lt;0.01%</td>
<td>CR</td>
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**Dose Level 2**

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<th>Prior Allo BMT</th>
<th>CAR Dose (x10^6/kg)</th>
<th>% marrow blasts</th>
<th>Response</th>
<th>Status</th>
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<tr>
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*MRD negative is defined as <0.01% blasts*
75% CR rate in Acute Lymphoblastic Leukemia

- Intent-to-Treat analysis
  - No preselection for ability for cells to expand:
  - Includes 2 patients in whom T cells expanded poorly
  - Antitumor effects observed even with doses \(<1 \times 10^6/\text{kg}\)
- CR in patient with primary refractory ALL confirms activity in chemoresistant disease

CD19-CAR traffic to tissues and mediate antitumor effects

- Observed CD19-CAR mediated clearance of CSF blasts
- Expansion in malignant effusion with no evidence for lymphoblasts

Toxicity

- Overall well tolerated with Gr \(\leq \text{I-II} \) Cytokine Release in 9/10 patients treated
- One dose limiting cytokine release syndrome
  - Hypotension treated successfully with anti-IL6r mAb
  - Anti-IL6R therapy resulted in rises in serum IL-6 levels
  - Persistent hallucinations \(5-6\)d, IL-6 levels present in CSF
  - Retreatment at lower disease burden with same cells resulted in no toxicity
- ? relationship between tumor burden and toxicity

Evidence for B cell recovery observed in all patients
NCI 11-C-0113
A Pilot Study of Genetically Engineered NY-ESO-1 Specific (c259) T cells in HLA-A2+ Patients with Synovial Sarcoma
NCI/Children’s Hospital of Philadelphia/MSKCC (pending)

Patient Population:
• HLA-A2+ Synovial Sarcoma, NY-ESO-1+
• Unresectable, metastatic, progressive or recurrent
• must have already received doxorubicin and/or ifosfamide
• must have measurable disease

Product:
Cyclophosphamide/fludarabine preparative regimen
Cryopreserved T cells
  - activated using anti-CD3/CD28 beads plus rhIL2
  - NY-ESO-1 (c259) T cell receptor
  - Lentivirus (pELNS backbone vector)
  - EF-1 alpha promoter, 2A cleavage between TCR alpha and beta
  - NO interleukin-2
Cell dose: 1 x 10^9/kg (max 4 x 10^10 cells)

IRB approval: 2/25/2011
Enrollment: 2 patients
Status: open to accrual
Patient 02 NY-ESO

NY-ESO T Cell infusion: $34 \times 10^9$

Cyclophosphamide
Fludarabine

Coronavirus
Fever, SOB, Hypotension

C- Reactive Protein

Absolute lymphocyte count

Activated CD8+ cells (CD25+)

Recurrent Synovial Sarcoma:
Metastatic to lung
Miliary pattern
Baseline 1/2/13 "miliary disease"
Day +2 1/10/13 "pseudoprogression"
Day +28 2/6/13 VGPR
6 months 7/18/13 Sustained CR
Complete Response to Adoptive Therapy with NY-ESO-1 Engineered T Cells

Baseline
January 2, 2013

6 months
July 19, 2013
Lessons Learned

• Proof-of-principle for efficacy of NY-ESO TCR therapy in synovial sarcoma
  – First sustained CR observed in synovial sarcoma treated with adoptive cell therapy
  – Factors determining response for individual patients remain unclear
  – Did the viral infection render the T cells more potent in patient #2?
• IL-2 is not necessary for antitumor effects using this approach
• Widespread T cell activation is associated with “inflammatory” toxicity
  – Pseudoprogression: The tumor appears worse before it appears better
  – Similar results seen with checkpoint inhibitors
• Major challenge is applying this therapy across the range of HLA-alleles present in the population
  – Many patients screened who do not meet the A2+/NYESO1+ eligibility criteria