T Cell Immunotherapy- Optimizing Trial Design

Session I

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

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# Overview of Trials

<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>
</tr>
</thead>
</table>
Research Participant Population:  
- KPS>70  
- 18 - 70 years of age  
- Candidates for AutoHSCT | Vector: plasmid pMG CD20CAR (1st Gen) and NeoR  
Dose: $10^7$ – $10^9$ cells/m²  
3 doses q 2 weeks intrapatient escalation  
Dosing post ANC recovery | Trial initiation date: 9/1999  
Status: closed  
Enrollment: 5 enrolled, 3 treated |
| NIH OBA # 0006-402: Phase I Study to Evaluate Safety of Cellular Immunotherapy for Recurrent/Refractory Neuroblastoma Using Genetically Modified Autologous CD8+ T Cell Clones | Disease Indication: Pediatric Relapsed/Refractory Neuroblastoma  
Research Participant Population:  
- KPS>60  
- 18 - 70 years of age  
- Non-resectable disease | Vector: plasmid pMG L1CAM CAR (1st Gen) and HyTK  
Dose: $10^7$ – $10^9$ cells/m²  
3 doses q 2 weeks intrapatient escalation  
No lymphodepletion | Trial initiation date: 8/2000  
Status: closed  
Enrollment: 10 enrolled, 6 treated |
## Overview of Trials

<table>
<thead>
<tr>
<th>Protocol number/title</th>
<th>NIH OBA# 496: Cellular Immunotherapy using Autologous CD8+ T-Cell Clones Genetically Modified to Express the IL13-Zetakine and HyTK for Recurrent Malignant Glioma</th>
<th>NIH OBA # 0207-543: Phase I Study to Evaluate the Safety of Cellular Immunotherapy for CD19+ Follicular Lymphoma Using Autologous T Cell Cytolytic Clones Genetically Modified to be CD19 Specific and Express HSVTK</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Disease indication/Research Participant population</strong></td>
<td>Disease Indication: Grade III and IV Malignant Glioma</td>
<td>Disease Indication: Refractory Follicular Lymphoma</td>
</tr>
<tr>
<td>Research Participant Population:</td>
<td>- KPS&gt;70</td>
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</tr>
<tr>
<td>- 18 - 70 years of age</td>
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<tr>
<td>- Resectable disease</td>
<td>- 18 - 70 years of age</td>
<td>- Multiple recurrent/refractory</td>
</tr>
<tr>
<td><strong>TCR or CAR product (ex vivo cell/ vector/transgene) and Dose</strong></td>
<td>Vector: plasmid pMG IL13zetakine (1st Gen) and HyTK Dose: $10^7 - 5 \times 10^7 - 10^8$ cells Intracavitary Infusions 12 Doses q M,W,F Intrapatient Dose Escalation</td>
<td>Vector: plasmid pMG CD19CAR (1st Gen) and HyTK Dose: $10^7-10^9$/m²</td>
</tr>
<tr>
<td><strong>Trial initiation date/status /enrollment</strong></td>
<td>Trial initiation date: 2/2002 Status: closed Enrollment: 13 enrolled, 3 treated</td>
<td>Trial initiation date: 4/2010 Status: follow up Enrollment: 11 enrolled, 6 treated, 1 remains in follow up.</td>
</tr>
</tbody>
</table>
## Overview of Trials (continued)

<table>
<thead>
<tr>
<th>Protocol number/title</th>
<th>NIH OBA #0704-848: Phase I Study of Intratumoral Administration of Cellular Immunotherapy for Recurrent/Refractory Malignant Glioma Using Alloclone-002 Modified for Glucocorticoid Resistance and Interleukin-2</th>
<th>NIH-OBA #1202-1150: A Phase I/II Study of Cellular Immunotherapy With Donor Central Memory Derived Virus Specific CD8+ T Cells Engineered to Target CD19 for CD19+ Malignancies After alloHSCT (C. Turtle)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TCR or CAR product (ex vivo cell/ vector/transgene) and Dose</td>
<td>Vector: plasmid pMG IL13zetakine (1st Gen) and HyTK Adenoviral mediated knockout of GR using zinc finger nuclease Dose: $10^8$</td>
<td>Vector: 3rd Gen. Self Inactivating Lenti CD19CAR (2nd Gen CD28:zeta) and EGFRt Cell dose infused &gt;30 days post alloHSCT</td>
</tr>
<tr>
<td>Trial initiation date/status /enrollment</td>
<td>Trial initiation date: 4/2010 Status: follow up Enrollment: 11 enrolled, 6 treated, 1 remains in follow up.</td>
<td>Trial Active Status: Enrolling, 1 treated</td>
</tr>
</tbody>
</table>
## Overview of Trials

|----------------------|----------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------|
| Disease indication/Research Participant population | Disease Indication: High Risk Relapsed/Refractory CD19+ ALL  
Research Participant Population:  
- no prior alloHSCT  
- KPS>60  
- 1yr-26yrs | Disease Indication: High Risk/Refractory B Cell Malignancies (CLL, ALL, NHL)  
Research Participant Population:  
- KPS>60  
- >17yrs  
- No prior alloHSCT |
| TCR or CAR product (ex vivo cell/ vector/transgene) and Dose | Vector: 3rd Gen. Self Inactivating Lenti CD19CAR (2nd Gen CD28:zeta) and EGFRt  
Cytoxan lymphodepletion 3gm/m2 x 2  
Escalating Cohorts starting at 10^6 EGFRt+ T cells/kg | Vector: 3rd Gen. Self Inactivating Lenti CD19CAR (2nd Gen 41BB:zeta) and EGFRt  
1:1 Mix of CD4+:Tcm CD8+  
Lymphodepletion  
Escalating Cohorts starting at 5x10^5 EGFRt+ T cells/kg |
| Trial initiation date/status /enrollment | Trial Active  
Status: Enrolling, 1 treated | Trial Active  
Status: Enrolling, 3 patients treated |
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<tr>
<td>NIH-OBA #1306-1233: Pediatric Leukemia Adoptive Therapy (PLAT)-02: A Phase I/II Feasibility and Safety Study of CD19-CAR T Cell Immunotherapy for CD19+ ALL</td>
<td>Disease Indication: Phase I Cohort- Post alloHSCT relapse Phase II Cohort- post alloHSCT + high risk relapse pre-HSCT</td>
</tr>
<tr>
<td><strong>TCR or CAR product (ex vivo cell/ vector/transgene) and Dose</strong></td>
<td><strong>Vector: 3rd Gen. Self Inactivating Lenti CD19CAR (2nd Gen 41BB:zeta) and EGFRt 1:1 CD4+:CD8+ Purified to &gt;95% EGFRt+ Cytoxan lymphodepletion Escalating Cohorts starting at 10^6 EGFRt+ T cells/kg</strong></td>
</tr>
<tr>
<td><strong>Trial initiation date/status/enrollment</strong></td>
<td>Trial IND authorization pend</td>
</tr>
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</table>
Lessons Learned

• Early trials established feasibility of non viral vector and derivation of clones, infusional toxicities mild but limited persistence

• Cellular rejection response to NeoR and HyTK, not CAR

• CNS can tolerate $>10^9$ T cells in intracavitary fractionated doses

• IL13zetakine CAR rx with documented regression of GBM
Lessons Learned

- Recent experience with CD19 G2 CAR’s in lenti transduced T cells expanded <28 days
  - ALL pt w self limited cytokine storm (IL-6 80X baseline), CR achieved
  - Lymphoma patient bulky refractory dz also CR without cytokine storm