

# **T Cell Immunotherapy- Optimizing Trial Design**

## **Session I**

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

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**September 10, 2013**



# Overview of Trials

<b>Protocol number/title</b>	NIH OBA# 9907-330: Pilot Ph I Study to Eval. Safety of Cellular ImmunoRx Using Auto Genetically Modified CD20-specific CD8+ T Cell Clones for Pts. With Recurrent/Refractory CD20+ Lymphomas Undergoing autoHSCT	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
<b>Disease indication/Research Participant population</b>	Disease Indication: Intermediate Grade B-Cell NHL  Research Participant Population: - KPS $\geq$ 70 - 18 - 70 years of age - Candidates for AutoHSCT	Disease Indication: Pediatric Relapsed/Refractory Neuroblastoma  Research Participant Population: - KPS $\geq$ 60 - 18 - 70 years of age - Non-resectable disease
<b>TCR or CAR product (ex vivo cell/ vector/transgene) and Dose</b>	Vector: plasmid pMG CD20CAR (1 <sup>st</sup> Gen) and NeoR Dose: 10 <sup>7</sup> – 10 <sup>9</sup> cells/m <sup>2</sup> 3 doses q 2 weeks inpatient escalation Dosing post ANC recovery	Vector: plasmid pMG L1CAM CAR (1 <sup>st</sup> Gen) and HyTK Dose: 10 <sup>7</sup> – 10 <sup>9</sup> cells/m <sup>2</sup> 3 doses q 2 weeks inpatient escalation No lymphodepletion
<b>Trial initiation date/status /enrollment</b>	Trial initiation date: 9/1999 Status: closed Enrollment: 5 enrolled, 3 treated	Trial initiation date: 8/2000 Status: closed Enrollment: 10 enrolled, 6 treated

# Overview of Trials

<b>Protocol number/title</b>	<b>NIH OBA# 496: Cellular Immunotherapy using Autologous CD8+ T-Cell Clones Genetically Modified to Express the IL13-Zetakine and HyTK for Recurrent Malignant Glioma</b>	<b>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</b>
<b>Disease indication/Research Participant population</b>	<p>Disease Indication: Grade III and IV Malignant Glioma</p> <p>Research Participant Population:</p> <ul style="list-style-type: none"> <li>- KPS<math>\geq</math>70</li> <li>- 18 - 70 years of age</li> <li>- Resectable disease</li> </ul>	<p>Disease Indication: Refractory Follicular Lymphoma</p> <p>Research Participant Population:</p> <ul style="list-style-type: none"> <li>- KPS<math>\geq</math>60</li> <li>- 18 - 70 years of age</li> <li>- Multiple recurrent/refractory</li> </ul>
<b>TCR or CAR product (ex vivo cell/ vector/transgene) and Dose</b>	<p>Vector: plasmid pMG IL13zetakine (1<sup>st</sup> Gen) and HyTK Dose: 10<sup>7</sup> – 5x 10<sup>7</sup> - 10<sup>8</sup> cells Intracavitary Infusions 12 Doses q M,W,F Inpatient Dose Escalation</p>	<p>Vector: plasmid pMG CD19CAR (1<sup>st</sup> Gen) and HyTK Dose: 10<sup>7</sup>-10<sup>9</sup>/m<sup>2</sup></p>
<b>Trial initiation date/status /enrollment</b>	<p>Trial initiation date: 2/2002 Status: closed Enrollment: 13 enrolled, 3 treated</p>	<p>Trial initiation date: 4/2010 Status: follow up Enrollment: 11 enrolled, 6 treated, 1 remains in follow up.</p>

# Overview of Trials (continued)

<b>Protocol number/title</b>	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	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)
<b>Disease indication/Research Participant population</b>	Disease Indication: Grade III and IV Malignant Glioma  Research Participant Population: - KPS $\geq$ 60 - 18 - 70 years of age - Non-resectable disease	Disease Indication: High Risk Adult B Cell Malignancies  Research Participant Population: - KPS $\geq$ 60 - 18 + years of age -HLA Matched Related Donor alloHSCT
<b>TCR or CAR product (ex vivo cell/ vector/transgene) and Dose</b>	Vector: plasmid pMG IL13zetakine (1 <sup>st</sup> Gen) and HyTK Adenoviral mediated knockout of GR using zinc finger nuclease Dose: 10 <sup>8</sup>	Vector: 3 <sup>rd</sup> Gen. Self Inactivating Lenti CD19CAR (2 <sup>nd</sup> Gen CD28:zeta) and EGFRt Cell dose infused >30 days post alloHSCT
<b>Trial initiation date/status /enrollment</b>	Trial initiation date: 4/2010 Status: follow up Enrollment: 11 enrolled, 6 treated, 1 remains in follow up.	Trial Active Status: Enrolling, 1 treated

# Overview of Trials

<b>Protocol number/title</b>	NIH-OBA #1204-1161: Phase I Feasibility and Safety Study of Cellular Immunotherapy for Relapsed Pediatric CD19+ ALL Using Autologous T Cells Lentivirally Transduced to Express CD19-Specific CAR	NIH-OBA #1303-1213: Phase I/II Study of Immunotherapy for Advanced CD19+ B Cell Malignancies with Defined Subsets of Autologous T Cells Engineered to Express CD19CAR (C. Turtle)
<b>Disease indication/Research Participant population</b>	Disease Indication: High Risk Relapsed/Refractory CD19+ ALL  Research Participant Population: -no prior alloHSCT - KPS $\geq$ 60 - 1yr-26yrs	Disease Indication: High Risk/Refractory B Cell Malignancies (CLL, ALL, NHL)  Research Participant Population: - KPS $\geq$ 60 - >17yrs -No prior alloHSCT
<b>TCR or CAR product (ex vivo cell/ vector/transgene) and Dose</b>	Vector: 3 <sup>rd</sup> Gen. Self Inactivating Lenti CD19CAR (2 <sup>nd</sup> Gen CD28:zeta) and EGFRt Cytoxan lymphodepletion 3gm/m <sup>2</sup> x 2 Escalating Cohorts starting at 10 <sup>6</sup> EGFRt+ T cells/kg	Vector: 3 <sup>rd</sup> Gen. Self Inactivating Lenti CD19CAR (2 <sup>nd</sup> Gen 41BB:zeta) and EGFRt 1:1 Mix of CD4+:Tcm CD8+ Lymphodepletion Escalating Cohorts starting at 5x10 <sup>5</sup> EGFRt+ T cells/kg
<b>Trial initiation date/status /enrollment</b>	Trial Active Status: Enrolling, 1 treated	Trial Active Status: Enrolling, 3 patients treated

# Overview of Trials

<b>Protocol number/title</b>	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
<b>Disease indication/Research Participant population</b>	Disease Indication: Phase I Cohort- Post alloHSCT relapse Phase II Cohort- post alloHSCT + high risk relapse pre-HSCT
<b>TCR or CAR product (ex vivo cell/ vector/transgene) and Dose</b>	Vector: 3 <sup>rd</sup> Gen. Self Inactivating Lenti CD19CAR (2 <sup>nd</sup> Gen 41BB:zeta) and EGFRt 1:1 CD4+:CD8+ Purified to >95% EGFRt+ Cytosan lymphodepletion Escalating Cohorts starting at 10 <sup>6</sup> EGFRt+ T cells/kg
<b>Trial initiation date/status /enrollment</b>	Trial IND authorization pend

# 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**