

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

## **Session I**

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

**Philip D. Greenberg  
Fred Hutchinson Cancer Research Center**

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# Overview of Trials

<b>Protocol number/title</b>	<b>#1655: Phase I/II Study of Adoptive Immunotherapy with CD8+ WT1-specific CTL Clones for Patients with Advanced AML, ALL, MDS, or CML after Allogeneic Hematopoietic Stem Cell Transplant</b>
<b>Disease indication/Research Participant population</b>	<u>High-risk Leukemias post HCT</u> : MDS RAEB or RAEB-T, CML beyond chronic phase, AML beyond first remission, Ph <sup>+</sup> ( <i>BCR-abl</i> ) ALL at any stage, any ALL beyond 1 <sup>st</sup> remission, primary refractory AML or ALL, and secondary AML.
<b>TCR or CAR product (ex vivo cell/vector/transgene) and Dose</b>	HLA A*0201 restricted, donor-derived WT1-specific (RMFPNAPYL) CD8 <sup>+</sup> clones. Escalating doses of WT1-specific CTL of 3.3x10 <sup>8</sup> , 1.0x10 <sup>9</sup> , 3.3x10 <sup>9</sup> , and 1 x 10 <sup>10</sup> CTL/m <sup>2</sup> with the last cell dose followed by low-dose s.c. IL-2 (250,000 IU/m <sup>2</sup> twice daily) x 14 days.
<b>Trial initiation date/status/enrollment</b>	From 03/2006 to 08/2010, 37 patient/donor pairs were enrolled <ul style="list-style-type: none"> <li>• 11 patients received CTL infusions</li> <li>• 3 patients alive at 42, 40 and 30 months after CTL infusion, and 47, 45 and 50 months after HCT respectively</li> <li>• Trial is closed to accrual.</li> </ul>

# Overview of Trials

<b>Protocol number/title</b>	<b>#2498: Phase I/II study of adoptive immunotherapy with virus specific CD8+ T cells transduced to express a WT1-specific TCR for patients with high risk or relapsed AML, MDS, or CML</b>
<b>Disease indication/Research Participant population</b>	<p><u>High-risk Leukemias post HCT</u>: AML beyond 1<sup>st</sup> remission and secondary AML, MDS RAEB or RAEB-T, CML beyond chronic phase,.</p> <ul style="list-style-type: none"> <li>• Arm 1/prophylaxis: no evidence of disease post-HCT.</li> <li>• Arm 2/treatment: refractory/relapsed disease post HCT.</li> </ul>
<b>TCR or CAR product (ex vivo cell/vector/transgene) and Dose</b>	<p>Virus (EBV/CMV)-specific CD8<sup>+</sup> T cells transduced to express a characterized HLA A*0201-restricted WT1-specific TCR (TCR<sub>C4</sub>).</p> <ul style="list-style-type: none"> <li>• Escalating doses of CTL<sub>C4</sub> of 1.0x10<sup>9</sup>, 3.3x10<sup>9</sup>, 1 x 10<sup>10</sup> and 1 x 10<sup>10</sup> CTL/m<sup>2</sup> followed by low-dose s.c. IL-2 (250,000 IU/m<sup>2</sup> twice daily) x 14 days (Arm 1: q4 weeks, Arms 2: q2 weeks).</li> </ul>
<b>Trial initiation date/status/enrollment</b>	<p>Trial is open to accrual and actively enrolling since 03/2013.</p> <ul style="list-style-type: none"> <li>• 10 patients are currently enrolled</li> <li>• 2 completed treatment on Arm 2 (3<sup>rd</sup> patient received only 3 of 4 planned infusions due to progression)</li> <li>• 1 completed treatment on Arm 1.</li> <li>• 2 additional patients scheduled to receive CTL<sub>C4</sub> in the next month</li> </ul>

# Lessons Learned

- **Protocol 1655:**

- Targeting WT1 does **not appear toxic** to tissues expressing physiological levels of WT1 (kidney, lung)
- **No new-onset GVHD** observed within 3 months of CTL infusions
- **Anti-leukemic activity** was observed in a subset of patients, and correlated with detection of CTL clones *in vivo*.
- **Long-term persistence of CTL** clones *in vivo* was observed in the subset of patients who both received clones primed with IL-21 and had no detectable leukemia/MRD at time of infusion
- The **avidities of the clones** obtained were **variable** (50% target lysis ranging over 4 logs, from  $10^{-1}$  to  $<10^{-4}$  ng/ml).
- More reproducible clinical results might be achieved if the infused CTL exhibited more consistent comparably high avidities and persisted *in vivo*.

# Lessons Learned

- **Protocol 2498:**

- Targeting WT1 with a characterized, **higher affinity TCR** (50% target lysis  $\sim 10^{-4}$  ng/ml) was **not toxic** at doses  $\leq 10^{10}$  cells/m<sup>2</sup> to tissues expressing physiological levels of WT1 (kidney, bone marrow) in the 3 patients treated to date.
- **Persistence** (>0.05% multimer<sup>+</sup> CD8<sup>+</sup> cells) observed in all treated patients **up to 28 days** after last infusion (range 0.051%-10.6%).
  - Maximum frequencies at 1-3 days infusions (range 1.42%-30.4%)
- Efficacy (inconclusive/data too preliminary).
  - 2 patients on Arm 2: 1 had a chloroma and progressed and one had MRD detected by flow (0.03%) that decreased to 0.006% after 4 infusions
  - One patient on Arm 1 (prophylactic: no detectable disease)

# Lessons Learned

- **Protocols 1655 and 2498:** No serious or unexpected toxicities
- **Toxicities observed (most common):**
  - Lymphopenia (transient)
  - Fever/chills within 24 hours of infusions compatible with a cytokine release syndrome. Spontaneous resolution observed in all cases.
  - Injection site reactions due to low-dose s.c IL-2.