

T Cell Immunotherapy- Optimizing Trial Design

Session I

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

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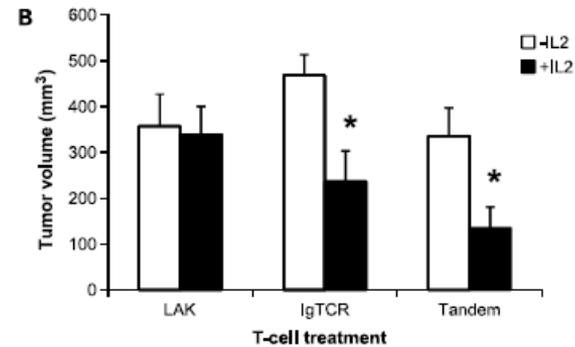
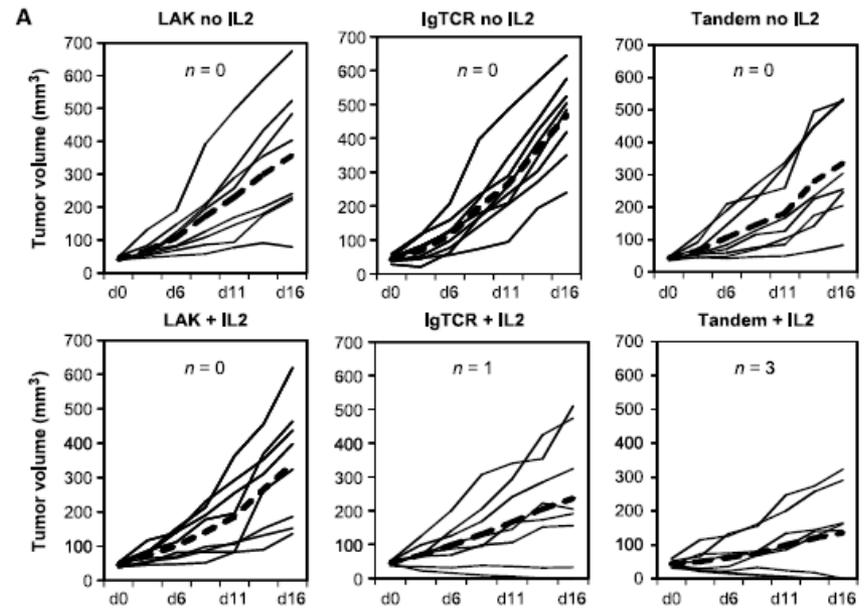
Overview of Trials

Protocol number/title	9804- 249/0301- 564: : Phase I Study of T Cells Modified with Chimeric Anti-CEA Immunoglobulin-T Cell Receptors (IgTCR) in Adenocarcinoma	0411-681: Phase Ia/Ib Trial of Anti-PSMA Designer T Cells in Advanced Prostate Cancer after Non-Myeloablative Conditioning
Disease indication/Research Participant population	Adenocarcinomas/Gastric ca	Prostate Cancer
TCR or CAR product (ex vivo cell/ vector/transgene) and Dose	<p>Vector: Retrovirus (non-lentivirus)/ CD3 zeta – 1st gen</p> <p>Dose: 1×10^9 – 1×10^{11} cells Simple Infusion; Escalation: Intra-patient</p> <p>–/+ IL2 (LDI: 75kiu/kg/d x 28d)</p>	<p>Vector: Retrovirus (non-lentivirus)/ CD3 zeta – 1st gen</p> <p>Dose: 1×10^9 – 1×10^{11} cells Lymphodepletion/Engraftment Escalation: Inter-patient</p> <p>+ IL2 (LDI: 75kiu/kg/d x 28d)</p>
Trial initiation date/status /enrollment	<p>Start date: April 1998</p> <p>Status: Closed</p> <p>Enrollment: 7</p>	<p>Start date: April 2008</p> <p>Status: Active</p> <p>Enrollment: 5</p>

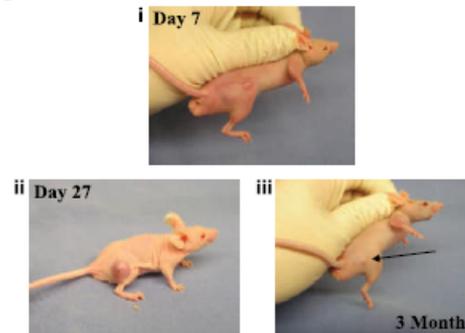
Overview of Trials (continued)

Protocol number/title	1207-1170/0301- 564: Phase II/Pilot Studies of 2nd Generation Anti-CEA Designer T Cells in Adenocarcinomas	1207- 1170: Phase I Trial of Intrahepatic Infusion of 2nd Generation Designer T Cells for CEA-Expressing Liver Metastases (S Katz)
Disease indication/Research Participant population	Adenocarcinomas / Gastric ca	Liver Metastases
TCR or CAR product (ex vivo cell/ vector/transgene) and Dose	<p>Vector: Retrovirus (non-lentivirus)/ CD3 zeta/CD28 – 2nd gen</p> <p>Dose: 1 x 10⁹ – 1 x 10¹¹ cells Simple Infusion (Systemic) Escalation: Inter-patient</p> <p>–/+ IL2 (LDI: 75kiu/kg/d x 28d)</p>	<p>Vector: Retrovirus (non-lentivirus)/ CD3 zeta/ CD28 – 2nd gen</p> <p>Dose: 1 x 10⁸ – 1 x 10¹⁰ cells Simple Infusion (Regional: Hep Artery) Escalation: Intra-patient</p> <p>–/+ IL2 (LDI: 75kiu/kg/d x 28d)</p>
Trial initiation date/status /enrollment	<p>Start date: July 2007</p> <p>Status: Open</p> <p>Enrollment: 11</p>	<p>Start date: June 2011</p> <p>Status: Closed</p> <p>Enrollment: 6</p>

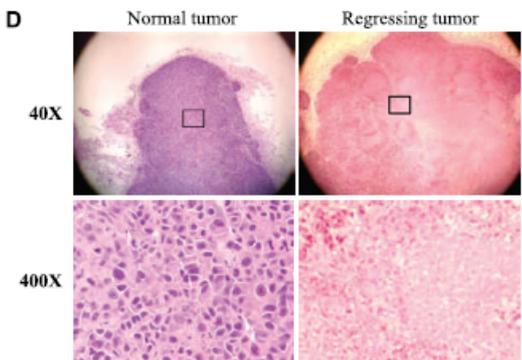
IL2 Critical for dTc to Control Established Solid Tumor



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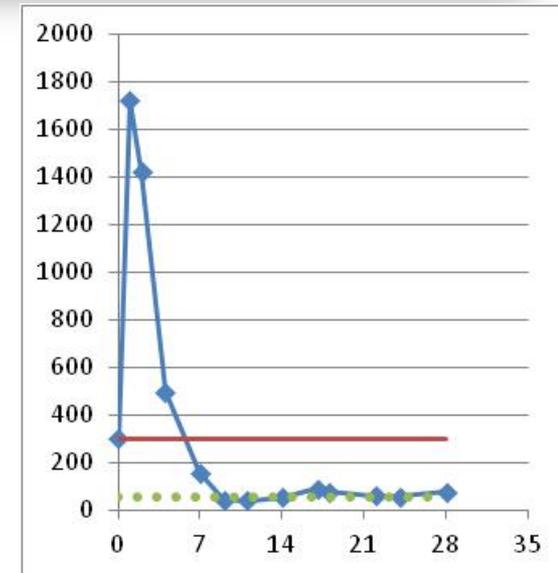
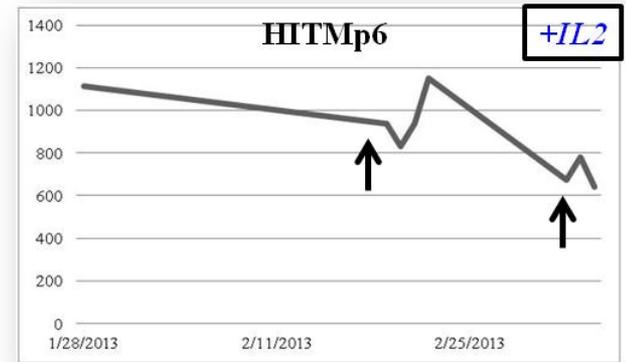
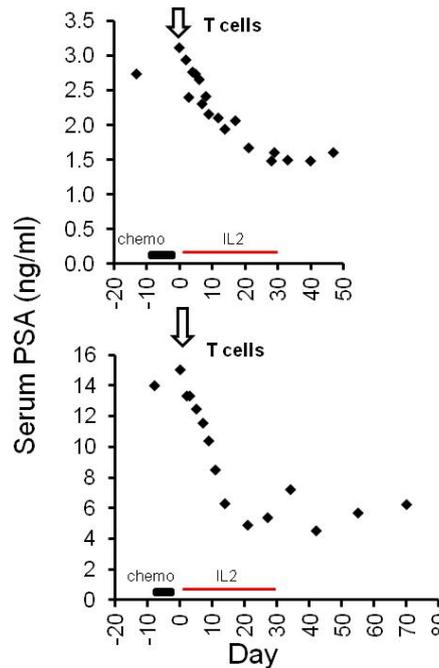
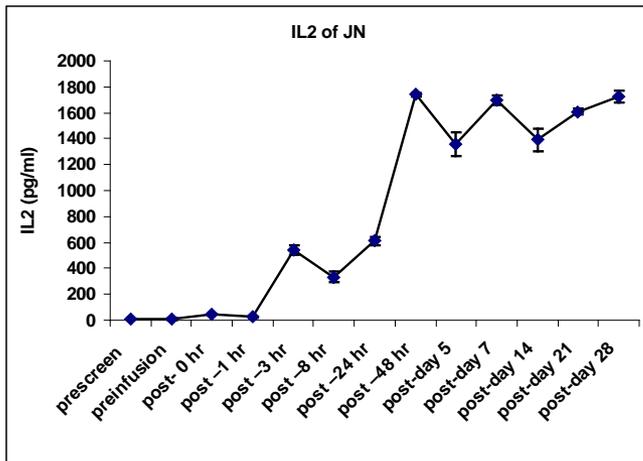


Condition	CR
LAK +IL2	0/15
dTc -IL2	0/16
dTc +IL2	8/16

$p=0.001$

Lessons Learned

IL2 important for solid tumor?



ANTIGEN	Gen	LD	IL2	Response	Toxicity
PSMA	1	+	low	-	-
			high	+	-
CEA	2	-	-	-	-
systemic			+	+	+
CEA			-	-	-
regional			+	+	+

Correlates with normal tissue toxicity

Lessons Learned

Summary of unexpected results (e.g., AEs)...

- **PSMA targeting**
 - No evident toxicity in brain or kidney
 - Because 1st gen less potent? perhaps 2nd gen more vigorous in tumor -- and toxic responses
- **CEA targeting**
 - Lung/dyspnea transient, self-limiting and reversing
 - Loss of dTc activity? Or loss of antigen?
 - Bowel/colitis, responds to steroid/5-ASA
 - Absorbed steroid, may limit tumor response?

Thoughts...

- **Normal tissue reactions may limit antigen targets**
 - Challenge for future is to find ways to protect normal tissues as potency of effectors increase
 - Protect (e.g., mesna w Cy) or remove normal target (e.g., diverting colostomy, colectomy???)
- **Inpatient escalation by infusion may be justified**
 - Safe, as toxicities evident before next dose at 2 wks
 - Effective, as patients get benefit of higher doses
 - Phase I's completed in fewer patients with less resources

Thoughts...

- **For new agents, infusion escalations may be safer for Phase I (safety) testing than LD/engraftment**
 - CEA safely tested that might have been lethal if engrafted
 - Save LD/Engraftment if dTc not effective but safe
 - “Strategy Escalation”
- **Future challenge: empower dTc to avoid need of LD**
 - GD2 neuroblastoma studies show sufficient immune activity can cure solid tumor without LD