

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	FHCRC 1503 – “1 st generation” anti-CD20 CAR	FHCRC 2154 – “3 rd generation” anti-CD20 CAR
Disease indication/Research Participant population	Relapsed/refractory indolent CD20+ lymphoma and mantle cell lymphoma	Relapsed/refractory indolent CD20+ lymphoma and mantle cell lymphoma
TCR or CAR product (ex vivo cell/ vector/transgene) and Dose	<ul style="list-style-type: none"> • αCD20-ζ • Naked DNA plasmid (electroporation with G418 selection) • 3 infusions 2-5 days apart at 10^8, 10^9, and 3.3×10^9 cells/m² • Low-dose IL-2 	<ul style="list-style-type: none"> • αCD20-CD28-41BB-ζ • Naked DNA plasmid (electroporation with G418 selection) • 3 infusions 2-5 days apart at 10^8, 10^9, and 3.3×10^9 cells/m² • 1 g/m² CY + low-dose IL-2
Trial initiation date/status /enrollment	Study closed in 2008 Accrued 10 patients, treated 7	Study closed in 2012 Accrued 4 patients, treated 3

Clinical Responses

Patient	Response	Duration (mo.)
A	NED	13
B	SD	3
D	SD	12
F	NED	3
G	SD (PET)	5
H	PR	3
I	SD	48

Summary of Trial #1

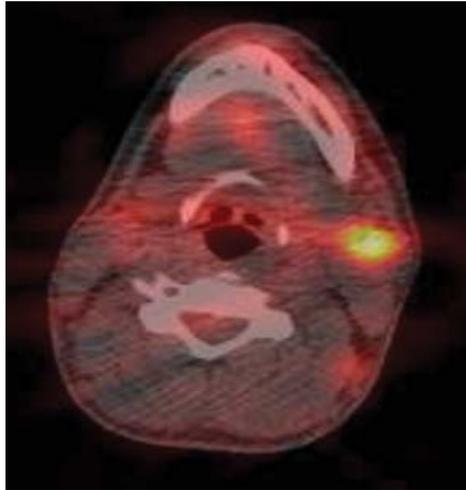
- No T cell-related AEs
- Bulk cultures more efficient than cloning
- *In vivo* persistence was modest but better with bulk culture cells + IL-2 (9 weeks)
- Modest clinical responses
- No cellular immune responses (but 2 pts HAMA+)

Clinical Responses

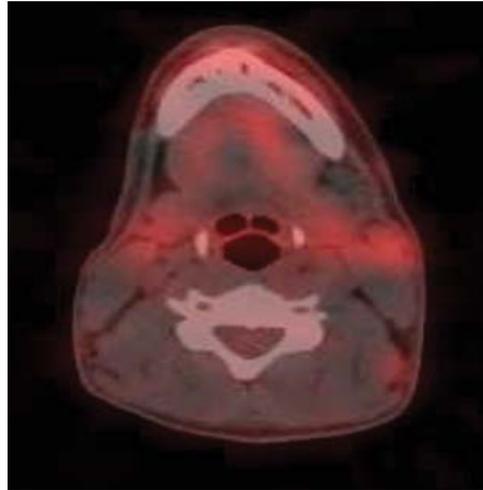
Patient	Response	Duration
UPN-02	NED	2 years
UPN-03	NED	1 year
UPN-04	PR	1 year

Partial Response (UPN-04)

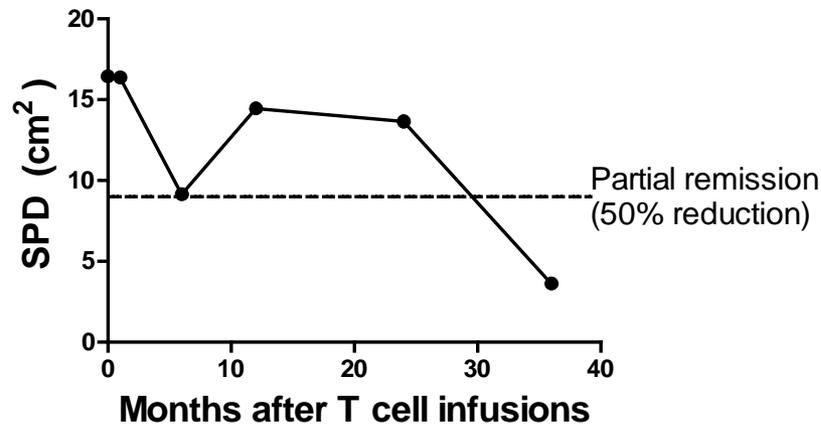
Baseline



3 months



Cumulative Tumor Area



Summary of Trial #2

- 1) 3 of 4 patients treated, generally tolerated well
- 2) Fever and hypoxemia after infusions in 1 pt
- 3) 1 partial remission, 2 pts NED for 1-2 years
- 4) T cells tracked to LN/BM, persisted 9-12 mo
- 5) CY 1 g/m² led to lymphodepletion
- 6) IL-2 led to increased Tregs
- 7) No evidence of immunogenicity

Lessons Learned

- Linearized plasmid vector was inefficient
- Only 1 of 10 pts with AEs: immediate and transient
- Longer *in vivo* persistence with IL-2 but increased Tregs
- T cells detectable to 1 year with 3rd generation CAR
- Intermediate dose CY well tolerated, led to effective lymphodepletion

Planned Trial

- Lentiviral vector encoding iCasp9 + α CD20-28-41BB- ζ CAR + truncated hCD19
- Use central memory T cells (CD14-/CD45RA-/CD62L+)
- Intermediate-dose CY (1 g/m²)
- Single T cell infusion in 4-pt dose-escalation cohorts
 - 2 x 10⁵, 2 x 10⁶, 2 x 10⁷ CAR+ cells/kg
- 12 patients with relapsed/refractory indolent CD20+ indolent NHL or mantle cell lymphoma