

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	MSKCC IRB# 06-138 A Phase I/IIa Trial For The Treatment of Relapsed or Chemotherapy Refractory Chronic Lymphocytic Leukemia or Indolent B Cell Lymphoma Using Autologous T Cells Genetically Targeted to the B Cell Specific Antigen CD19	MSKCC IRB #11-048 A Phase I Trial of Consolidation Therapy with Autologous T Cells Genetically Targeted to the B Cell Specific Antigen CD19 in Patients with Chronic Lymphocytic Leukemia Following Upfront Chemotherapy with Pentostatin, Cyclophosphamide and Rituximab
Disease indication/Research Participant population	Relapsed or refractory CD19+ leukemia or lymphoma, including CLL/SLL, follicular, Waldenstrom's, marginal zone, and mantle cell lymphoma	CLL patients who have achieved PR, nPR, or MRD+CR following frontline therapy with PCR
TCR or CAR product (ex vivo cell/ vector/transgene) and Dose	CAR Phase I: γ -retrovirus, 19-28z, $1 \times 10^7 - 3 \times 10^7$ CAR+ T cells/kg Phase IIa: 1:1 mixture of γ -retrovirus (19-28z) and lentivirus transduced (CART19:CD3z-4-1BB), 3×10^7 CAR+ T cells/kg	CAR γ -retrovirus 19-28z $3 \times 10^6 - 3 \times 10^7$ CAR+ T cells/kg
Trial initiation date/status /enrollment	March, 2007 Open to enrollment 13 patients treated (10 in phase I and 3 in phase IIa)	August, 2011 Open to enrollment 10 enrolled, 6 treated

Lessons Learned

- **Brief summary of important trial results...**
- **06-138:**
 - T cell collection and transduction feasible in these heavily pretreated patients
 - Results of 8 treated patients published (Blood 2011;118(18):4817-28)
 - Of the 5 remaining patients, 2 treated under phase I and 1 achieved MRD negative CR and remains in remission over one year; 3 patients treated under STRAP, and 1 patient achieved MRD negative CR (also had CRS).
- **11-048:**
 - T cell collection and transduction feasible after completion of PCR
 - Acceptable safety profile observed with no DLT
 - CRS observed in 2 patients with a positive correlation between the development of CRS and the modified T cell persistence
 - 2 patients who had PR following PCR achieved CR after the T cell infusion; 2 patients maintained PR; and 2 patients had progressive disease (one in LN only).

Lessons Learned

- **Summary of unexpected results (e.g., AE management)...**
 - Unlike in ALL, we have not observed mental status changes despite patients developing CRS, although to a lesser degree.
 - For patients treated under STRAP, two fever curves were observed, one immediately following the T cell infusion that lasts 2-7 days, and then a second wave of fever approximately 3 weeks thereafter.

Overview of Trials

Protocol number/title	NCT01044069 Precursor B Cell Acute Lymphoblastic Leukemia (B-ALL) Treated With Autologous T Cells Genetically Targeted to the B Cell Specific Antigen CD19
Disease indication/Research Participant population	Relapsed/Refractory B-ALL Adults \geq 18 years old
TCR or CAR product (ex vivo cell/ vector/transgene) and Dose	CAR: 1928z Vector: SFG Gene-Transfer: gammaretrovirus Cells: autologous bulk transduced T cells Dose: 3×10^6 CAR+ T cells
Trial initiation date/status /enrollment	Trial Initiation: 9/9/2009 Enrollment: 14 patients treated to date (12 have been treated in the last 14 months)

Lessons Learned

- **Impressive MRD- induction rate (11/14 patients had an optimal MRD- response). Compared to a 20% salvage CR rate in a similar population.**
- **Cytokine Release Syndromes (CRS) strongly correlate with leukemia burden at time of CAR T cell infusion.**
- **Neurologic adverse events are common as part of the CRS, but ultimately are reversible.**
- **CAR T cells migrate to the CNS but its unknown if the migration is related to disease status.**

Lessons Learned

- **CRS is manageable with steroids or IL6 blockade, but relapses have occurred after steroids.**
- **CAR T cell lifespan is limited and B cell aplasia is reversible so long-term immune system support is unnecessary**

Overview of Trials (continued)

Protocol number/title	MSKCC IRB# 12-117 A Phase I Trial of High Dose Therapy and Autologous Stem Cell Transplantation Followed by Infusion of Chimeric Antigen Receptor (CAR) Modified T-Cells Directed Against CD19+ B-Cells for Relapsed and Refractory Aggressive B Cell Non-Hodgkin Lymphoma
Disease indication/Research Participant population	relapsed and refractory aggressive B-cell non-Hodgkin's lymphoma
TCR or CAR product (ex vivo cell/ vector/transgene) and Dose	19-28z CAR Dose level #1: 5x10 ⁶ /kg Dose level #2: 1x10 ⁷ /kg Dose level #3: 2x10 ⁷ /kg
Trial initiation date/status /enrollment	4/23/13 2 patients enrolled and treated

Lessons Learned

- **Brief summary of important trial results**
- **Patient #1: fevers and MS changes during nadir. LP revealed lymphocytosis and protein >400 w/ evidence of 19-28z CAR-T on PCR. Symptoms abated with one dose of tocilizumab**
- **Patient #2: febrile neutropenia. No further complications.**
- **Both patients awaiting d100 restaging imaging.**
- **No DLT at current 5 x10e6/kg dose level**

Overview of Trials (continued)

Protocol number/title	<u>MSKCC IRB# 13-052</u> A Phase I Trial of Autologous T-Lymphocytes Genetically Targeted to the B-Cell Specific Antigen CD19 in Pediatric and Young Adult Patients with Relapsed B-Cell Acute Lymphoblastic Leukemia	<u>MSKCC IRB# 11-038</u> A Phase I Dose Escalation Trial Using In Vitro Expanded Allogeneic Epstein-Barr Virus Specific Cytotoxic T-Lymphocytes (EBV-CTLs) Genetically Targeted to B-Cell Specific Antigen CD19 Positive ALL
Disease indication/Research Participant population	B-ALL Pediatric Patients (0-26 years)	B-ALL (post-HSCT) Pediatric Patients (0-19 years)
TCR or CAR product (ex vivo cell/ vector/transgene) and Dose	CAR Autologous T cells γ -retrovirus 19-28z $3 \times 10^6 - 1 \times 10^7 - 3 \times 10^7$	CAR EBV-CTLs (donor) γ -retrovirus 19-28z $1 \times 10^6 - 3 \times 10^6 - 1 \times 10^7$ (Total T cells)
Trial initiation date/status /enrollment	May 2013 Open to Enrollment 2 patients treated	September 2011 Open to Enrollment 4 patients treated

Lessons Learned

- **Brief summary of important trial results... EBV CAR T cell trial**
- **EBV CAR T cells well tolerated (GVHD)**
- **Very limited persistence of T cells noted in these patients**
- **No objective responses**
- **No cytokine release syndrome noted**