

614. ACUTE LYMPHOBLASTIC LEUKEMIA: THERAPY, EXCLUDING TRANSPLANTATION | NOVEMBER 15, 2013

# T Cells Engineered With a Chimeric Antigen Receptor (CAR) Targeting CD19 (CTL019) Produce Significant In Vivo Proliferation, Complete Responses and Long-Term Persistence Without Gvhd In Children and Adults With Relapsed, Refractory ALL

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## Abstract



### Background

CARs combine a single chain variable fragment (scFv) of an antibody with intracellular signaling domains into a single chimeric protein. We previously reported on CTL019 cells expressing a CAR with intracellular activation plus costimulatory domains. Infusion of these cells results in 100 to 100,000x in vivo proliferation, durable anti-tumor activity, and prolonged persistence in pts with B cell tumors, including 1 sustained CR in a patient with ALL (Grupp, et al. NEJM 2013). We now report on outcomes and longer follow up from our pilot studies treating 20 pts (16 children and 4 adults) with relapsed, refractory ALL.

### Methods

T cells were lentivirally transduced with a CAR composed of anti-CD19 scFv/4-1BB/CD3 $\zeta$ , activated/expanded ex-vivo with anti-CD3/anti-CD28 beads, and then infused into pts with relapsed or refractory CD19+ ALL. 17/20 pts received lymphodepleting chemotherapy the week prior to CTL019 infusion. The targeted T cell dose range was  $10^7$  to  $10^8$  cells/kg with a transduction efficiency (TE) of 11-45%. On the adult protocol, the target dose was  $5 \times 10^9$  total cells split over 3 days with a TE of 6-31%. 11 pts had relapsed ALL after a prior allogeneic SCT. T cells were collected from the pt, regardless of prior SCT status, and not from allo donors. All pts s/p allo SCT had to be 6 mos s/p SCT with no GVHD or GVHD treatment.

### Results

16 children median age 9.5 y (5-22y) and 4 adults median age 50y (26-60y) with CD19+ ALL were treated. One child had T cell ALL aberrantly expressing CD19. 14/16 pediatric pts had active disease or +MRD after chemotherapy on the day prior to CTL019 cell infusion, while 2 were MRD(-). 3 of 4 adults had active disease prior to lymphodepleting chemotherapy, while 1 was in morphologic CR. Lymphodepleting chemotherapy varied with most receiving a Cytoxan-containing regimen the week prior to CTL019. A median of  $3.7 \times 10^6$  CTL019 cells/kg ( $0.7-18 \times 10^6$ /kg) were infused over 1-3 days.

There were no infusional toxicities >grade 2, although 5 pts developed fevers within 24 hrs of infusion and did not receive planned subsequent infusions of CTL019 cells. 14 patients (82%) achieved a CR, including the patient with CD19+ T ALL, 3 did not respond, and 3 are pending evaluation. 11/17 evaluable pts have ongoing BM CR with median follow up 2.6 mo (1.2-15 mo). Three patients with a CR at 1 month have subsequently relapsed, 1 with CD19(-) disease. Median follow-up as of August 1, 2013 was 2.6 mo (1-15 mo) for all pts.

All responding pts developed some degree of delayed cytokine release syndrome (CRS), concurrent with peak T cell expansion, manifested by fever, with variable degrees of myalgias, nausea, anorexia. Some experienced transient hypotension and hypoxia. Detailed cytokine analysis showed marked increases from baseline values of IL6 and IFN $\gamma$  (both up to 1000x), and IL2R, with mild or no significant elevation in systemic levels of TNF $\alpha$  or IL2. Treatment for CRS was required for hemodynamic or respiratory instability in 7/20 patients and was rapidly reversed in all cases with the IL6-receptor antagonist tocilizumab (7 pts), together with corticosteroids in 4 pts. Although T cells collected from the 11 pts who had relapsed after allo SCT were generally 100% of donor origin, no GVHD has been seen. Persistence of CTL019 cells detected by flow cytometry and/or QPCR in pts with ongoing responses continued for 1-15 months after infusion, resulting in complete B cell aplasia during the period of CTL019 persistence. Pts have been treated with IVIg without any unusual infectious complications. One child who entered a CR subsequently developed MDS with a new trisomy 8 in ALL remission and has gone to SCT, and 1 child developed a single leukemia cutis lesion at 6 mo, still BM MRD(-).

## Conclusions

CTL019 cells are T cells genetically engineered to express an anti-CD19 scFv coupled to CD3 $\zeta$  signaling and 4-1BB costimulatory domains. These cells can undergo robust in-vivo expansion and can persist for 15 mo or longer in pts with relapsed ALL. CTL019 therapy is associated with a significant CRS that responds rapidly to IL-6-targeted anti-cytokine treatment. This approach has promise as a salvage therapy for patients who relapse after allo-SCT, and collection of tolerized cells from the recipient appears to have a low risk of GVHD. CTL019 cells can induce potent and durable responses for patients with relapsed/refractory ALL. Multicenter trials are being developed to test this therapy for ALL in the phase 2 setting.


## Disclosures:

**Grupp:Novartis:** Research Funding. **Chew:Novartis:** Patents & Royalties. **Levine:Novartis:** cell and gene therapy IP, cell and gene therapy IP Patents & Royalties. **Litchman:Novartis Pharmaceuticals:** Employment, Equity Ownership. **Rheingold:Novartis:** Research Funding. **Shen:Novartis Pharmaceuticals:** Employment, Equity Ownership. **Wood:Novartis Pharmaceuticals:** Employment, Equity Ownership. **June:Novartis:** Patents & Royalties, Research Funding.

**Topics:** [cd19 antigens](#), [child](#), [chimeric antigen receptors](#), [graft-versus-host disease](#), [t-lymphocytes](#), [brachial plexus neuritis](#), [infusion procedures](#), [allopurinol](#), [chemotherapy regimen](#), [follow-up](#)

## Author notes

\* Asterisk with author names denotes non-ASH members.

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