

# RECOMBINANT HUMAN INTERLEUKIN-7 (CYT107) PROMOTES T CELL RECOVERY FOLLOWING T-CELL DEPLETED ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTION

M-A Perales<sup>1</sup>, JD Goldberg<sup>1</sup>, L Lechner<sup>1</sup>, G Koehne<sup>1</sup>, J Yuan<sup>1</sup>, EB Papadopoulos<sup>1</sup>, JW Young<sup>1</sup>, AA Jakubowski<sup>1</sup>, B Zaidi<sup>1</sup>, H Gallardo<sup>1</sup>, R Kendle<sup>1</sup>, C Liu<sup>1</sup>, T Rasalan<sup>1</sup>, Y Xu<sup>1</sup>, JD Wolchok<sup>1</sup>, T Croughs<sup>2</sup>, M Morre<sup>2</sup>, M Maloy<sup>1</sup>, G Heller<sup>1</sup>, MRM van den Brink<sup>1</sup>

<sup>1</sup>Memorial Sloan-Kettering Cancer Center (New York, US); <sup>2</sup>Cytheris, Inc (Issy Les Moulineaux, FR)

## Abstract

Delays in immune recovery after allogeneic hematopoietic stem cell transplantation (allo-HSCT) are associated with increased risks of infection and relapse. Strategies to enhance T cell reconstitution could therefore decrease morbidity and mortality. Interleukin-7 (IL-7) has a central role in T cell development and survival. Murine models of allo-HSCT have shown that IL-7 enhances thymopoiesis and peripheral T cell survival and expansion. Initial trials with recombinant human IL-7 (rhIL-7) have demonstrated a dose-dependent expansion of CD4+ and CD8+ T cells in patients with solid tumors or HIV infection. Hence we are conducting a phase I trial of rhIL-7 (CYT107; Cytheris Inc) in recipients of a T-cell depleted (TCD) allo-HSCT. To date, 12 patients (AML=6, MDS=2, CML=1; median age=60.4, range 27-67) have been treated with escalating doses of rhIL-7 (3 at 10mcg/kg, 6 at 20mcg/kg, 9 at 30mcg/kg administered SQ weekly for 3 weeks, starting at a median of 103 (range 60-244) days post HSCT). Toxicities included grade 2 hypersensitivity drug rash (n=3) and grade 2 fever (n=1). A patient with rash after the 1<sup>st</sup> injection (20 mcg/kg level) was removed from the study (feasible for toxicity only). No patients have developed GVHD, anti-IL-7 antibodies or neutralizing antibodies. Two patients with high-risk AML have relapsed (4 and 9 months post rhIL-7), an incidence consistent with published data in patients undergoing allo-HSCT for AML in CR. Ten patients remain alive with a median follow-up of 14 months. At baseline, the median T cell counts were 69mm<sup>3</sup> (0-272mm<sup>3</sup>), 32mm<sup>3</sup> (0-299mm<sup>3</sup>) and 0 (0-17/mm<sup>3</sup>) for CD4+, CD8+ and CD45RA+ T cells, respectively. Immune monitoring after rhIL-7 in 8 evaluable patients has demonstrated an increase in CD4+ T cells (naive or central memory, 69% median increase at day 21 – range 8%-35-fold increase) and CD8+ T cells (naive or effector memory, 94% median increase at day 28 – range 0-11-fold increase). There was no effect on CD4+CD25<sup>hi</sup>FoxP3<sup>+</sup> T cells, NK cells or B cells. Increased TOR exclusion circles (TREC) were noted in the 5/6 patients analyzed indicating enhanced T cell production. Finally, all 3 CMV-seropositive patients developed CD8+ T cell CMV-specific responses, including a patient with prior CMV viremia and low-level CMV-specific CD8+ T cells prior to rhIL-7 (5.3-fold increase to the A2021-restricted NLV peptide). Our pre-clinical data and early clinical results suggest that rhIL-7 enhances immune recovery in recipients of a TCD allo-HSCT without causing GVHD or other serious toxicity.

## Background

Interleukin 7 (IL-7) is required at various stages of T cell development from lymphoid precursor to memory T cell, and is a key regulator of peripheral T cell homeostasis.

Preclinical studies in mouse HSCT models have demonstrated that post-transplant administration of IL-7 enhances T cell reconstitution in recipients of a syngeneic or allogeneic HSCT through increased thymopoiesis, increased homeostatic proliferation of transferred and de novo generated mature T cells and decreased peripheral T cell apoptosis.

Initial clinical trials with rhIL-7 have shown dose-dependent expansion of CD4+ and CD8+ T cells with an acceptable toxicity profile in patients with solid tumors or HIV infection.

## Study Design

### Primary Objectives

- Safety and recommended dose of CYT107 (rh-IL-7) in recipients of TCD-BMT/PTBSC from HLA-MRD/MUD.
- MTD and DLT (if toxicities present).

### Secondary Objectives

- PK of CYT107
- Preliminary characterization of CYT107 on Engraftment and GVHD
- Recovery of T, NK and B cells.
- Risk of EBV-LPD.
- Risk of Relapse.

### Study Design

- Phase I dose escalation: 10 mcg/kg, 20 mcg/kg, 30 mcg/kg SQ weekly x 3
- CYT107 started from day +60 to day +210

### Inclusion Criteria

- Age > 15 years old.
- Non-lymphoid hematological malignancy, in remission.
- TCD-BMT/PTBSC from 8/8 HLA MRD/MUD after myeloablative conditioning, with >1x10<sup>7</sup> CD3+ T cells/kg.
- Documented engraftment, KPS ≥ 60%, adequate organ function.

### Exclusion Criteria

- Acute or chronic GVHD.
- Active uncontrolled infection.
- Lymphoid malignancy or acute biphenotypic leukemia.
- History of EBV-LPD, or peripheral lymphadenopathy.
- Patient or donor with live autologous disease.

## Patient Characteristics<sup>a</sup>

Age (median)	60 years (range 27-67 years)	
Gender	M=6	F=6
Disease	AML	n=9
	MDS	n=2
	CML	n=1
Regimen <sup>b</sup>	TBI	n=4
	Chemotherapy	n=8
Donor	MRD	n=7
	MUD	n=4
	MMUD	n=1
Median Day of rhIL-7 start post BMT	103 days (range 60-244 days)	
Baseline T cell counts (median) <sup>c</sup>		
	CD3+CD4+	69/mm <sup>3</sup> (range 0 – 272 /mm <sup>3</sup> )
	CD3+CD8+	32/mm <sup>3</sup> (range 0 – 299 /mm <sup>3</sup> )
	CD4+CD45RA+	0 (range 0 – 17 /mm <sup>3</sup> )

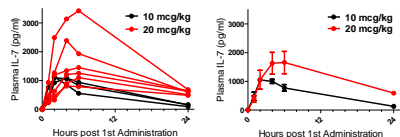
a: Pt 14-203 removed after single injection for biopsy-proven drug rash (evaluable for toxicity)  
b: Chemo=Busulfan/Melphalan/Flutamide; TBI=Total Body Irradiation; Cyto= Cyclophosphamide (n=3) or TBI/Thiotepa/Flutamide (n=1) - All patients received ATG  
c: Baseline T cell counts represent mean of two consecutive tests pre treatment

## Results

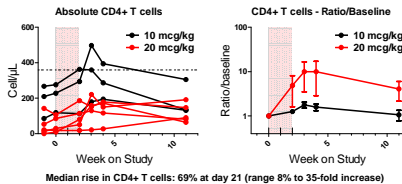
**Injection of rhIL-7 (CYT107) after TCD allo-HSCT was not associated with significant toxicities**

- Main toxicities possibly/probably related to CYT107:
  - Injection site reactions in 2/10 patients
  - Grade 2 skin biopsy-proven hypersensitivity rash in 3/10 patients; patient 14-203 with rash after 1<sup>st</sup> injection was removed from the study
  - Low-grade fever in 2/10 patients
  - Splenomegaly noted on CT in one patient
- No patients developed GVHD
- No patients developed anti-IL-7 antibodies or neutralizing antibodies
- 2 patients with high-risk AML, died of relapse, an incidence consistent with published data in patients undergoing allo-HSCT for AML in CR
- 1 patient developed an EBV-PTLD after treatment and responded to treatment with rituximab. The incidence is consistent with the risk of EBV-PTLD in allogeneic TCD-PTBSC
- 9/12 patients remain alive with median follow-up of 14 months

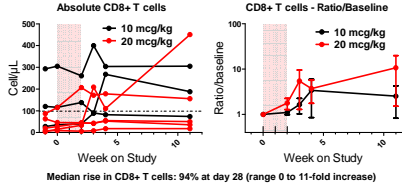
## PK studies demonstrate rapid plasma clearance of rhIL-7 (CYT107)



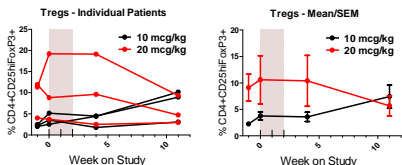
## rhIL-7 (CYT107) increases CD3+CD4+ T cell counts post TCD allo-HSCT



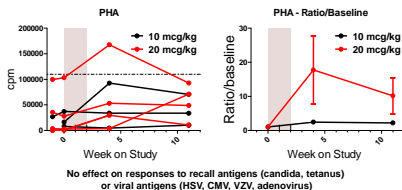
## rhIL-7 (CYT107) increases CD3+CD8+ T cell counts post TCD allo-HSCT



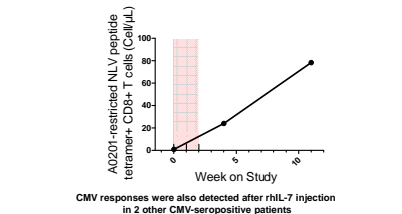
## rhIL-7 (CYT107) increases CD3+CD8+ T cell counts post TCD allo-HSCT



## rhIL-7 (CYT107) increases mitogen responses post TCD allo-HSCT



## CMV-specific responses increased in a patient with prior CMV viremia



## Conclusion

Administration of rhIL-7 (CYT107) after T-cell depleted allogeneic HSCT results in:
 

- No significant toxicities
- Increased CD4+ and CD8+ T cell counts
- No effect on NK, CD13+, or Tregs
- Expansion of naive + effector CD4+ T cells, and naive CD8+ T cells
- Increased CD4+ and CD8+ RTE in some patients
- Increased TREGs in 5/6 patients evaluated
- No effect on CD127 expression on CD4+CD8+ T cells
- No effect on Ki67 or Bcl2 expression on CD4+CD8+ T cells in most patients
- Increased mitogen responses
- Increased CMV-specific responses in CMV-seropositive patients