Phase I Study of Tagraxofusp With or Without Chemotherapy in Pediatric Patients with Relapsed or Refractory CD123-Expressing Hematologic Malignancies: A Therapeutic Advances in Childhood Leukemia and Lymphoma (TACL) Consortium Trial

Adam Lamble,[1] Yueh-Yun Chi,[2] Bill Chang,[3] Anupam Verma,[4] Kelly Faulk,[5] Alexandra Stevens,[6] Lauren Pommert,[7,8] Sarah Tucker,[1] Benjamin Brookhart,[2] Nirali N. Shah,[4] Chris Brooks,[9] Tariq Mughal,[9,10] Alan Wayne,[2] Soheil Meshinchi,[11] Todd Cooper[1]

[1]Division of Hematology/Oncology, University of Washington, Seattle Children's Hospital, Seattle, WA; [2]Division of Hematology/Oncology, Children's Hospital Los Angeles Cancer and Blood Disease Institute, Norris Comprehensive Cancer Center, Keck School of Medicine, University of Southern California, Los Angeles, CA; [3]Division of Hematology/Oncology, Oregon Health & Sciences University, Doernbecher Children's Hospital, Portland, OR; [4]Pediatric Oncology Branch, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD; [5]Center for Cancer and Blood Disorders, University of Colorado Anschutz Medical Campus, Children's Hospital Colorado, Aurora, CO; [6]Division of Hematology/Oncology, Baylor College of Medicine, Texas Children's Hospital, Houston, TX; [7]Division of Oncology, Cancer and Blood Diseases Institute, Cincinnati Children's Hospital Medical Center, Cincinnati, OH; [8]Department of Pediatrics, University of Cincinnati School of Medicine, Cincinnati, OH; [9]Stemline Therapeutics, New York, NY; [10]Tufts Medical Center, Boston, MA; [11]Fred Hutchinson Cancer Research Center, Seattle, WA

Background

- Tagraxofusp is a protein-drug conjugate consisting of a human interleukin-3 fused to a truncated diphtheria toxin payload
- First CD123 targeted agent FDA-approved as a single agent for the treatment of individuals age 2 years and above with blastic plasmacytoid dendritic cell neoplasm (BPDCN)
- CD123 is widely expressed on a variety of other hematologic malignancies, including the majority of patients with acute myeloid leukemia and some subtypes of B- and T-cell acute lymphoblastic leukemia
- The potent activity of tagraxofusp in BPDCN, coupled with the favorable toxicity profile, makes tagraxofusp a compelling agent for study in other CD123-expressing malignancies with high unmet needs

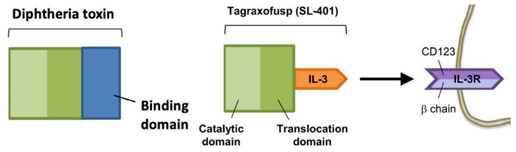

Figure 1: Tagraxofusp structure and mechanism of action

Objectives

- Primary objective: Assess safety and tolerability of tagraxofusp monotherapy (Part 1) and in combination with chemotherapy (Part 2) in pediatric and young adult patients with relapsed/refractory CD123-expressing hematologic malignancies.
- Secondary objectives: Pharmacokinetics and anti-tumor activity
- Correlative studies: Assess biomarkers of tagraxofusp response and explore potential mechanisms of resistance.

Methods

- Non-randomized, open-label, multicenter phase I dose-determination trial for children 1 to 21 years of age with relapsed and/or refractory CD123-expressing hematologic malignancies
- Two sequential parts with tagraxofusp administered intravenously once daily over 5 days
- Part 1: Tagraxofusp monotherapy at the FDA-approved dose of 12 mcg/kg with a single dose escalation and de-escalation.
- Part 2: Tagraxofusp at one dose level below the Part 1 recommended dose in combination with other agents in three cohorts with the option for a single dose escalation
  - Cohort A: myeloid-directed combination therapy (fludarabine, high-dose cytarabine)
  - Cohort B: lymphoid-directed combination therapy (vincristine, dexamethasone)
  - Cohort C: azacitidine
- Cohort allocation is determined by investigator preference but patients with 1% to < 5% blasts are only eligible for Cohort C.
- Depending on response, patients in both parts and all cohorts are eligible to receive subsequent cycles of tagraxofusp monotherapy (maximum of 5 additional cycles).

Study Design

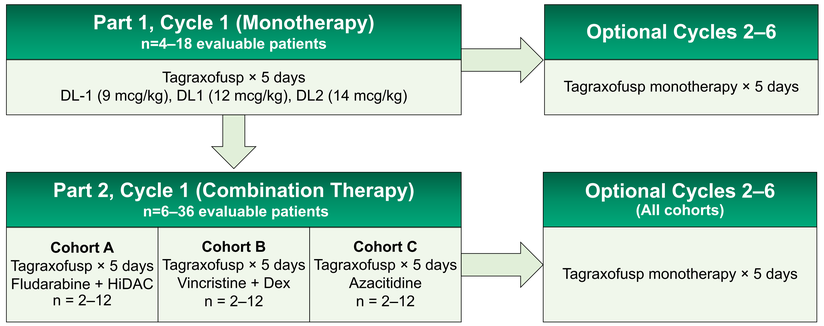

Figure 2: Experimental Schema.
Abbreviations: DL, dose level; HiDAC, high-dose cytarabine; Dex, dexamethasone.

Table 1: Key Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
• Age 1-21 years	• CNS disease (Part 1)
• CD123 expression by MFC or IHC	• Isolated CNS disease (Part 1 and 2)

• Disease status
  • 2nd or greater relapsed/refractory disease (Part 1)
  • 1st or greater relapsed/refractory disease (Part 2)
  • BPDCN in 1st or greater relapse/refractory (Part 1 and 2)
	• Prior treatment with tagraxofusp
	• Severe active infection
	• DNA fragility syndromes
	• Treatment for active GVHD
	• Standard organ function requirements
	• Standard therapy washout requirements

• Measurable disease
  • ≥5% disease in the bone marrow (Part 1 and Part 2, Cohorts A and B)
  • ≥1% disease in the bone marrow (Part 2, Cohort C)
  • Measurable disease by radiographic criteria	

• Patients with trisomy 21 permitted (Part 1)	

Abbreviations: BPDCN, blastic plasmacytoid dendritic cell neoplasm; MFC, multi-parameter flow cytometry; IHC, immunohistochemistry; CNS, central nervous system; GVHD, graft-versus-host-disease

Statistical Design

- Part 1: Standard 3+3 dose escalation/de-escalation design and, based on safety and tolerability, is planned to enroll between 4 and 18 patients with 3 dose levels.
- Part 2: Standard 3+3 design but with a single escalation and is planned to enroll between 6 and 36 patients.

Table 2: Dose level

Level	Dose
-2	7 mcg/kg/dose
-1	9 mcg/kg/dose
1	12 mcg/kg/dose
2	14 mcg/kg/dose

Treatment

Part 1

	1	2	3	4	5	6	7	8	9	10	11	15	22
Tagraxofusp	●	●	●	●	●								
IT Therapy	●												●

Part 2 Cohort A

	1	2	3	4	5	6	7	8	9	10	11	15	22	29
Fludarabine 30 mg/m^2	●	●	●	●	●									
Cytarabine 2000 mg/m^2	●	●	●	●	●									
Tagraxofusp				●	●	●	●	●						
CNS1 IT Therapy	●													●
CNS2/3 IT Therapy	●							●				●	●	●

Part 2 Cohort B

	1	2	3	4	5	8	9	10	11	12	15	16	17	18	19	22	29
Dex 10 mg/m^2 BID	●	●	●	●	●						●	●	●	●	●		
Vincristine 1.5 mg/m^2	●					●					●					●	
Tagraxofusp						●	●	●	●	●							
CNS1 IT Therapy	●																●
CNS2/3 IT Therapy	●					●					●					●	●

Part 2 Cohort C

	1	2	3	4	5	6	7	8	9	10	11	15	22	29
Tagraxofusp	●	●	●	●	●									
Azacitidine 75 mg/m^2	●	●	●	●	●									
CNS1 IT Therapy	●													●
CNS2/3 IT Therapy	●							●				●	●	●

Figure 3: Treatment program and combination dosing based on Part and Cohort.
Abbreviations: IT, intrathecal; Dex, dexamethasone.

Enrollment

- The study is conducted through the Therapeutic Advances in Childhood Leukemia and Lymphoma (TACL) Consortium. TACL website link: tacl.chla.usc.edu
- The study has been opened to accrual on 11NOV 2022 at select TACL sites and is currently recruiting participants.
- Additional information is available at ClinicalTrials.gov: https://clinicaltrials.gov/ct2/show/NCT05476770
- This study is conducted with financial support from Stemline Therapeutics.

TACL Therapeutic Advances in Childhood Leukemia & Lymphoma