A Phase I Multicenter Trial to Assess the Maximum Tolerated Dose, Safety, Pharmacokinetics, and Pharmacodynamics of CUDC-907 in Children with Relapsed/Refractory Solid Tumors and Lymphomas

David Shulman[1], W. Clay Gustafson[2], Kieuhoa Vo[2], Elizabeth Fox[3], Jodi Muscal[4], Jeffrey Supko[5], Andrew Place[1], Susan Chi[1], Suzanne Shusterman[1], Gina Hanna[1], Jane O'Brien[1], Suzanne Ezrre[1], Cecilia Carlowicz[1], Wendy B. London[1], Steven G. DuBois[1]

[1]Dana-Farber/Boston Children's Cancer and Blood Disorders Center [2]UCSF Benioff Children's Hospital
[3]Children's Hospital of Philadelphia [4]Texas Children's Hospital [5]Dana-Farber/Harvard Cancer Center

Abstract

BACKGROUND: CUDC-907 is an oral first-in-class small molecule that inhibits PI3K and HDAC, two enzymes commonly implicated in malignancies that affect children. Pre-clinical data from adult and pediatric solid tumors and lymphomas demonstrated that dual inhibition of these pathways decreases tumor growth. For example, in NHL, CUDC-907 was shown to inhibit tumor growth to a greater degree than PI3K or HDAC inhibitors alone or in combination.[1] Data from adult and pediatric pre-clinical models suggest that down-regulation of MYC signaling via inhibition of PI3K and HDAC may be key to the antineoplastic effects of CUDC-907. MYC signaling appears to drive a number of pediatric cancers, heralds a poor prognosis in many of these diseases and has proven difficult to target. In particular, pre-clinic data from pediatric neuroblastoma, medulloblastoma, glioma and lymphoma models has demonstrated decreased MYC signaling in response to CUDC-907. Phase I data from an adult study of patients with hematologic malignancies has demonstrated tolerability of CUDC-907 in a 5 days on/2 days off (5/2) dosing strategy. Diarrhea, fatigue, nausea and thrombocytopenia were the most commonly reported side effects.[2] Partial and completed responses were observed in MYC-driven lymphomas.

METHODS: This study is a phase I, open-label, multicenter trial of CUDC-907 in patients 1-21 years of age with relapsed/refractory solid tumors, brain tumors and lymphomas (NCT02909777). The primary objectives are to determine the recommended phase II dose, describe toxicities, and describe pharmacokinetic parameters of CUDC-907 in this population. Other objectives include evaluation of disease response and exploration of the pharmacodynamic effects of CUDC-907. Patients receive CUDC-907 orally on a 5/2 schedule in 28-day cycles, with a pediatric mini-tab formulation available for younger children. Part A consists of a standard 3+3 design evaluating up to three dose levels. Following dose escalation, Part B consists of two expansion cohorts for patients with MYCN/MYC-driven neuroblastoma or mature B-cell lymphoma. Up to 44 patients may be enrolled across Parts A and B. Detailed pharmacokinetic testing is required in the first two cycles. Optional pharmacodynamic testing will quantify histone acetylation, MYC protein, and phospho-S6 in serial blood samples. Enrollment began in October 2016 and is ongoing.

Objectives

Primary Objectives

•To determine the recommended pediatric phase 2 dose of CUDC-907 in children and young adults with relapsed or refractory solid tumors, CNS tumors, or lymphoma.

•To describe the toxicities of CUDC-907 in this population.

•To describe the pharmacokinetics of CUDC-907 in this population.

Secondary Objective

•To describe progression-free survival and objective response rate of CUDC-907, including in patients with *MYCN* amplified / MYC-positive neuroblastoma or in patients with mature B-cell lymphoma.

Exploratory Objectives

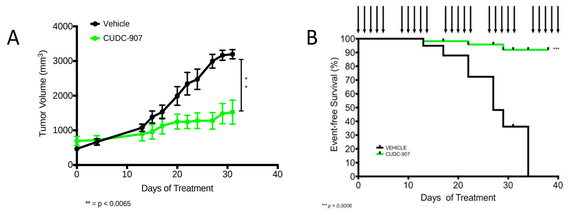
•To evaluate pharmacodynamic effects of CUDC-907 using peripheral blood as a surrogate tissue.

•To explore potential tissue markers predictive of clinical benefit and resistance to CUDC-907.

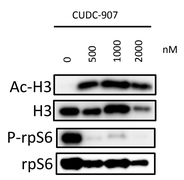
Background

•Oral, first-in-class, small molecule HDAC and PI3K inhibitor

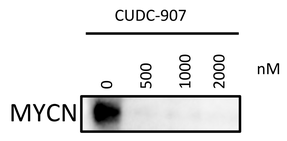
•Shown to decrease tumor growth in pediatric and adult solid tumor and lymphoma pre-clinical models



Growth (**A**) and survival (**B**) of *MYCN* amplified neuroblastoma patient-derived xenograft treated with CUDC-907 vs. vehicle. Arrows represent days of drug administration.

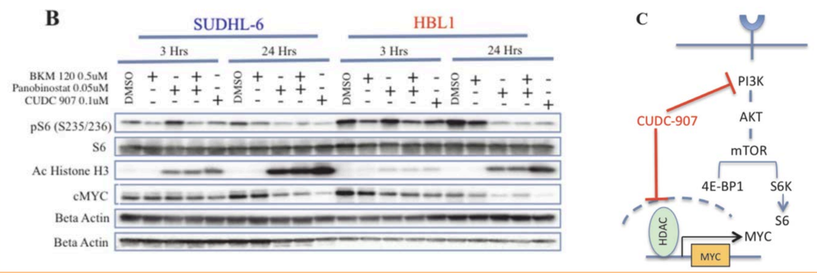


Increase in histone H3 acetylation and decrease in p-rpS6 in SNKBE2 neuroblastoma cell line after 24 hours of CUDC-907 exposure.



Reduction in MYCN protein levels in SNKBE2 neuroblastoma cell line after 24 hours of CUDC-907 exposure.

Dual inhibition of PI3K and HDAC leads to synergistic downregulation of MYC[3]



CUDC-907 Adult Clinical Experience

Overall well tolerated

- >50% - Diarrhea (reversible; generally low grade)
- 10-50% - Fatigue, nausea, neutropenia, thrombocytopenia, upper respiratory infection, cough, rash, constipation

Interrupted dosing schedule

- 5 days on / 2 days off
- Adult recommended phase 2 dose of 60 mg/dose on above schedule

Objective responses observed in lymphoma[2]

- 14% response rate in pooled lymphoma / multiple myeloma cohort
- 55% response rate in diffuse large B cell lymphoma

Study Design

Part A: Dose Escalation
Goal: Define dose of CUDC-907
Range of doses tested in 3+3 design
Range of pediatric histologies tested

Part B: Dose Expansion
Goal: Activity of CUDC-907
Recommended phase 2 dose
Neuroblastoma and Lymphoma

Part A + B
PK and PD effects of CUDC-907

Eligibility Criteria

- Age > 1 years and ≤ 21
- Karnofsky or Lansky performance status > 50%
- Part A: Dose escalation
  - Solid tumor
  - CNS tumor (DIPG may be radiologically diagnosed)
  - Lymphoma
- Part B: Dose expansion
  - Neuroblastoma – *MYCN* amplified, or > 1+ MYC or MYCN protein expression
  - DLBCL or Burkitt lymphoma
- Prior PI3K inhibitor or HDAC inhibitor allowed
- Ability to swallow tabs, or mini-tabs without chewing
- BSA > 0.5 m^2
- No hyperglycemia or known diabetes mellitus

Treatment

- Using adult 5 days on / 2 days off dosing schedule
- Evaluating new "mini-tab" formulation for children unable to swallow pills
- Dose escalation across three dose levels centered around equivalent of adult recommended phase 2 dose

Companion Studies

1. Required pharmacokinetic testing
2. Optional testing for pS6, pAKT, MYC, histone acetylation in PBMCs
3. Optional tumor testing MYCN/MYC biology

References

1. Qian C, Lai C-J, Bao R, et al. *Clin Cancer Res*. 2012;18(15):4104-4113.
2. Younes A, Berdeja JG, Patel MR, et al. *Lancet Oncol*. 2016;2045(15):1-10.
3. Mondello P, Derenzini E, Asgari Z, et al. *Oncotarget*. 2017;8(8):14017–28.

DANA-FARBER Boston Children's
CANCER AND BLOOD DISORDERS CENTER

HARVARD MEDICAL SCHOOL
TEACHING HOSPITAL