Poster # 4104

A Multi-Center Dose-Finding Study to Assess Safety, Tolerability, Pharmacokinetics and Preliminary Efficacy of Fimepinostat (CUDC-907) in Combination with Venetoclax in Patients with Relapsed/Refractory (R/R) Lymphoma

Anas Younes[1], Connie Lee Batlevi[1], Jonathon B. Cohen[2], Sven De Vos[3], Krish Patel[4], Jason Westin[5], Stefan K. Barta[6], Danial Landsburg[7], Sonali Smith[8], Dena Grayson[9], Reinhard von Roemeling[9], and Tycel Phillips[10]

[1]Memorial Sloan Kettering Cancer Center, New York, NY; [2]Winship Cancer Institute of Emory University, Atlanta, GA; [3]University of California, Los Angeles, CA; [4]Swedish Cancer Institute, Seattle, WA; [5]MD Anderson Cancer Center, Houston, TX; [6]University of Pennsylvania-Perelman, Philadelphia, PA; [7]University of Chicago, Chicago, IL; [8]Curis, Inc., Lexington, MA; [9]University of Michigan, Ann Arbor, MI

Introduction

High-grade B-cell lymphoma (HGBL) with *MYC* and *BCL2* and/or *BCL6* rearrangements (double- and triple-hit lymphoma), as well as diffuse large B-cell lymphoma (DLBCL), not otherwise specified (NOS) with increased expression of MYC and BCL2 (double-expressor lymphoma) are associated with a poor prognosis after front-line treatment with standard immunochemotherapy. Therapies for MYC- and BCL2-altered lymphomas are urgently needed. Currently, no approved therapies target MYC. Other than for a subset of patients who may benefit from chimeric antigen receptor T (CAR-T) cell therapy, no treatment has shown a significant durable benefit or impact on survival outcomes.

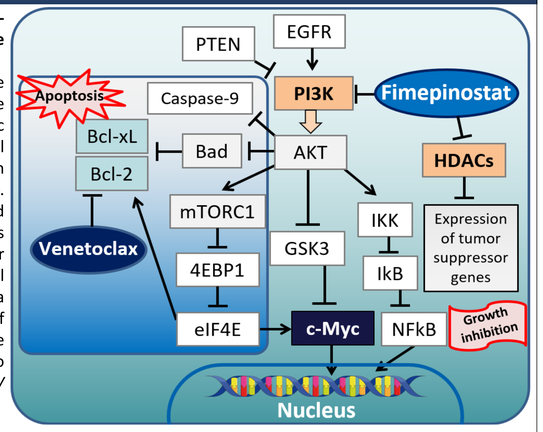
Fimepinostat is an investigational first-in-class small molecule dual inhibitor of HDAC (class I and II) and PI3K (α, β, and δ) enzymes which suppresses MYC through both of these pathways. In clinical studies, both single-agent fimepinostat, and fimepinostat with rituximab, were well tolerated with a favorable safety profile in patients with R/R lymphoma, and resulted in deep and durable responses in patients with R/R MYC-altered DLBCL with an overall response rate (ORR) of 23% and a median duration of response (DOR) of 13.6 months (*Landsburg 2018*).

This poster provides an overview of an ongoing and currently enrolling Phase 1/2 clinical trial of fimepinostat in combination with venetoclax in patients with DLBCL or HGBL with emphasis on patients with MYC-altered disease.

Scientific Rationale

Fimepinostat and venetoclax: novel-novel drug combination for the treatment of DLBCL

Venetoclax (ABT-199), a BCL2-selective inhibitor, is approved by FDA for the treatment of adult patients with chronic lymphocytic leukemia and small lymphocytic lymphoma and certain patients with acute myeloid leukemia. The combined inhibition of BCL2 and HDACs has shown synergy in cutaneous T-cell lymphoma and other malignancies, including mantle cell lymphoma (MCL) and glioblastoma *(Cyrenne BM et al., 2019).* Inhibition of PI3K has been shown to overcome acquired and intrinsic resistance to venetoclax in MCL and DLBCL *(Pham LV et al., 2018).*



The combined treatment with venetoclax and PI3K inhibitors exhibited robust and broad anti-AML activity both *in vitro* and *in vivo*, as well as against multiple forms of venetoclax resistance *(Rahmani M et al., 2018).* These results support a rationale to combine venetoclax therapy with PI3K and HDAC inhibitors for effective treatment of human cancer.

Study Design

CUDC-907-101 is a Phase 1/2, open-label, dose-escalation study of fimepinostat (CUDC-907) in combination with venetoclax in patients with R/R DLBCL or HGBL with or without MYC and BCL2 alterations.

The primary objectives are to determine MTD, RP2D, safety and tolerability, and to assess preliminary efficacy, as measured by ORR and DOR. Approximately 15 pts in the Phase 1 dose escalation (3+3 design) and 30 pts in the Phase 2 expansion will be enrolled to receive fimepinostat + venetoclax treatment. Patients will be treated until progression or unacceptable toxicity. The Ph 2 expansion will be an estimation study for detecting an efficacy signal. Patients who receive ≥1 dose and have ≥1 post-baseline response evaluation will be included in the efficacy analysis set. Investigator-assessed ORR based on Lugano criteria will be summarized as the proportion of pts who achieve a best response of CR/PR and the corresponding two-sided 95% confidence interval (CI, Clopper-Pearson) will be calculated. DOR will be summarized for pts who achieve response using the Kaplan-Meier (KM) product-limit method. The median DOR along with the two-sided 95% CI using the Brookmeyer and Crowley method will be calculated. PFS and OS will be estimated in pts using the KM product-limit method, along with the median and two-sided 95% CI.

The first patient in this study was treated in August 2019, and enrollment is ongoing. This new study represents the first clinical trial of the novel-novel combination of fimepinostat with venetoclax in pts with DLBCL or HGBL harboring alterations of both MYC and BCL2. Clinical trial: NCT01742988.

Phase 1/2 Trial Schema

Patient Population

Phase 1 Dose-Escalation [Fimepinostat + Venetoclax]: R/R DLBCL or HGBL

Phase 2 Dose-Expansion [Fimepinostat + Venetoclax]: R/R DHL, DEL or THL

ClinicalTrials.gov Identifier: NCT01742988

Phase 1b: Dose-Escalation

Fimepinostat + Venetoclax

N=15

RP2D determination

Phase 2: Dose-Expansion

Fimepinostat + Venetoclax

N=30

Objectives and Endpoints:

Primary -> MTD/RP2D, safety, tolerability, and preliminary efficacy (ORR/DOR by Lugano criteria)

Secondary -> PK, efficacy (PFS)

Exploratory-> Efficacy (OS, Response by RECIL, RECIST1.1)

Eligibility Criteria

Inclusion Criteria include the following:

- 18 years of age or older
- **For Dose-Escalation cohorts:** Histopathologically confirmed DLBCL or HGBL that is refractory to, or has relapsed after, treatment with at least 1 prior regimen
- **For Dose-Expansion cohorts:** R/R DLBCL or HGBL with both MYC and BCL2 alterations and/or overexpression (DHL, THL, or DEL) that is refractory to, or has relapsed after, 1 or more prior lines of therapy.
- Measurable disease by CT or PET/CT. MRI acceptable as per protocol.
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1.
- Recovery to Grade 1 or baseline of any toxicity due to prior systemic treatments (excluding alopecia).
- Absolute neutrophil count ≥ 1,000/μL; platelets ≥ 75,000/μL for patients with no bone marrow involvement by malignancy; platelets ≥ 50,000/μL for patients with bone marrow involvement by malignancy.
- Creatinine ≤ 1.5x upper limit of normal (ULN); total bilirubin ≤ 1.5x ULN; AST/ALT ≤ 2.5x ULN.
- Life expectancy of at least 3 months.

Exclusion Criteria include the following:

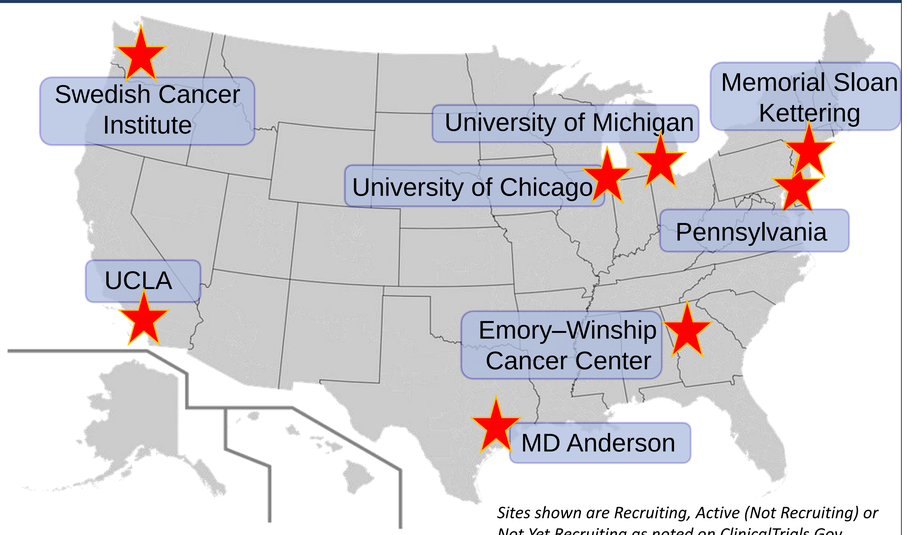
- Intention to undergo stem cell transplant or treatment with chimeric antigen receptor (CAR) T-cell therapy.
- Systemic anti-cancer therapy or investigational agent within 3 weeks of study entry, except for nitrosoureas or mitomycin C (6 weeks).
- Other non-cytotoxic anti-cancer therapy or investigational agent within 5 half-lives or 21 days prior to study treatment, whichever is shorter, as long as any drug related toxicities have resolved to Grade 1 or less. Dexamethasone up to 12 mg/d is allowed as supportive therapy and does not exclude participation.
- Graft vs. host disease following prior allogeneic transplant within 3 months prior to study treatment.
- Ongoing treatment with chronic immunosuppressants.
- Active CNS lymphoma.
- Known gastrointestinal condition that would interfere with swallowing or the oral absorption or tolerance of fimepinostat.
- Serious infection requiring systemic antibiotic therapy within 14 days prior to study treatment.
- Uncontrolled or severe cardiovascular disease
- Unstable or clinically significant concurrent medical condition.
- Second primary malignancy within 2 years of study entry other than what is specified in the protocol.
- Known HIV positive, hepatitis B surface antigen-positive status, or known or suspected active hepatitis C infection.
- Active CMV infection, presence of CMV antigenemia, or evidence of any invasive CMV end organ disease (e.g., CMV colitis).

Dose-Escalation Cohorts

Cohort	Fimepinostat**	Venetoclax	Cohort Status as of Nov 2019
Cohort 1	30 mg 5/2	400 mg QD	Evaluated; MTD not reached
Cohort 2	60 mg 5/2	400 mg QD	**Open**
Cohort 3	60 mg 5/2	800 mg QD	Not yet enrolling

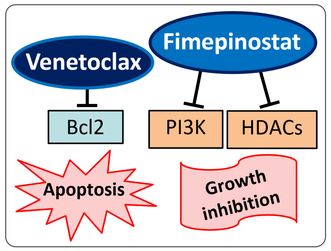
**Fimepinostat is administered on a 5-days-on/2-days-off schedule

Clinical Trial Sites



Sites shown are Recruiting, Active (Not Recruiting) or Not Yet Recruiting as noted on ClinicalTrials.Gov

Summary of Key Information



Nonclinical Studies

Nonclinical studies have shown that fimepinostat inhibits MYC transcription and a subset of MYC-associated genes (previously published results) and MYC protein levels are downregulated by fimepinostat, in part, through inhibition of PI3K-mediated ubiquitination. Treatment with fimepinostat in combination with venetoclax showed synergistic activity in preclinical tumor models of DHL and DEL. These data suggest that patients with MYC- and BCL2-altered tumors may benefit from combination therapy with fimepinostat and ventoclax.

Clinical Studies

CUDC-907-101 is a Phase 1/2 study evaluating fimepinostat (CUDC-907) in combination with venetoclax in adult patients with R/R DLBCL or HGBL and is currently enrolling patients in Cohort 2 (60 mg 5/2 fimepinostat and 400 mg QD venetoclax).

Contact and Acknowledgements

Curis Contacts:
Dena Grayson, MD, PhD
Clinical Lead
dgrayson@curis.com

P. Taylor Eves, PhD
Director, Clinical Science
teves@curis.com

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Curis, Inc.
4 Maguire Road
Lexington, MA 02421
www.curis.com