Durable Responses Achieved in Patients with MYC-altered Relapsed/Refractory Diffuse Large B-cell Lymphoma Treated with Fimepinostat (CUDC-907): Combined Results from a Phase 1 and Phase 2 Study

DJ Landsburg[1], R Ramchandren[2], Y Oki[3], JM Pagel[4], PJ Lugtenburg[5], RB Gharavi[6], A Ma[6], D Tuck, SK Barta[7]

[1] Abramson Cancer Center, Philadelphia, PA; [2]2Karmanos Cancer Institute, Wayne State University, Detroit, MI; [3]Department of Lymphoma/Myeloma, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX; [4]Swedish Cancer Institute, Seattle, WA; [5]Erasmus MC Cancer Institute, Department of Hematology, Rotterdam, Netherlands on behalf of the Lunenburg Lymphoma Phase I/II Consortium – HOVON /LLPC; [6]Curis, Lexington, MA; [7]Fox Chase Cancer Center, Philadelphia, PA

Introduction

- Herein we present the combined toxicities and outcomes of Fimepinostat in RR lymphoma as well as preclinical combination therapy data.
- The prognosis for patients with relapsed and/or refractory (RR) MYC-altered diffuse large B-cell lymphoma (DLBCL) is dismal as they are often ineligible for or progress following autologous stem cell transplantation and respond poorly to subsequent therapies (*Blood*. 2012 May 17;119(20):4619-24. and *Haematologica*. 2013 Oct;98(10):1554-62; *J Clin Oncol*. 2017 Jan;35(1):24-31; *Cancer*. 2017 Nov 15;123(22):4411-4418).
- Fimepinostat, a first-in-class oral dual inhibitor of HDAC (class I and II) and PI3K (class Iα, β, and δ) enzymes, has demonstrated downregulation of MYC mRNA and protein levels in MYC-altered DLBCL cell lines, as well as anti-tumor activity in multiple MYC-driven animal cancer models (*Mol Cancer Ther*. 2017 Feb;16(2):285-299).
- In a Phase 1 study, objective responses were reported in a number of patients with MYC-altered RR DLBCL treated with fimepinostat (*Haematologica*. 2017 Nov;102(11):1923-1930). The Phase 2 study was designed to further explore the efficacy of monotherapy fimepinostat in this population of high unmet need (NCT02674750).
- We have explored rational combinations with other agents to assess for synergy in murine xenograft models. Based on these findings, phase 1 trials exploring combination therapies with Fimepinostat in R/R lymphoma are planned.

Phase 1 & Phase 2 - Patients and Methods

- In the Phase 1 dose escalation and expansion study a total of 88 subjects with R/R lymphoma or MM (≥2 prior lines) received fimepinostat across all dose cohorts, including 37 subjects with R/R DLBCL. In the completed dose escalation phase, patients received fimepinostat daily (QD, doses: 30 or 60 mg), or intermittently on twice weekly (BIW) or thrice weekly (TIW) schedules (doses: 60, 90, 120 or 150 mg) or on a 5 days on, 2 days off (5/2) schedule (dose: 60 mg). Fimepinostat dosed at 60 mg on the 5/2 schedule was determined to be the RP2D.
- Expansion cohorts continued to assess the safety and tolerability of fimepinostat at the RP2D of 60 mg using 5/2 schedule with or without the standard dose of rituximab (R- fimepinostat) in patients with R/R DLBCL. The safety and efficacy results of all patients in dose escalation (Younes et al, 2016) and across all DLBCL patients in escalation and expansion (Oki et al, 2017) have been previously reported.
- In the Phase 2 study a total of 68 subjects were evaluated to determine the efficacy of monotherapy fimepinostat at the RP2D in R/R DLBCL patients with MYC-altered disease by central IHC determination.
- Key eligibility criteria include confirmed diagnosis of DLBCL (including high grade B-cell lymphoma with MYC and BCL2 and/or BCL6 rearrangements per 2016 WHO classifications), confirmed availability of viable biopsy tissue (fresh or archival) for central testing, ECOG score ≤1, 2-4 prior lines of therapy for DLBCL, and ineligible for/failed prior autologous stem cell transplantation.
- The primary endpoint was to assess the objective response rate (ORR) in MYC-altered patients by IHC. The response-evaluable population in this analysis was defined as any patient who received at least one dose of fimepinostat and had a post-baseline disease assessment.
- A summary of baseline parameters for the Phase 1 and 2 studies are shown below:

Baseline Parameters	Phase 1 (n = 37)	Phase 2 (n = 68)	Total (n = 105)
Male, n (%)	27 (73)	40 (59)	67 (64)
Caucasian, n (%)	30 (81)	59 (87)	89 (85)
Age, median (range)	61 (20-85)	64 (33-93)	64 (20-93)
De novo DLBCL, n (%)	24 (65)	54 (79)	78 (74)
t-FL, n (%)	13 (35)	14 (21)	27 (26)
Stage, n (%)			
I-II	2 (5)	10 (21)	12 (11)
III-IV	29 (78)	56 (82)	85 (81)
Unknown	6 (16)	2 (3)	8 (8)
No. prior treatments, median (range)	4 (2-10)	2 (2-4)	3 (2-10)
ECOG PS, n (%)			
0-1	35 (95)	62 (91)	97 (92)
2	2 (5)	6 (9)	8 (8)
IPI Risk Score, n (%)			
0-2	23 (62)	22 (32)	45 (43)
3-5	14 (38)	46 (68)	60 (57)
Elevated LDH, n (%)	20 (54)	46 (68)	66 (63)
Bulky disease (> 5 cm), n (%)	19 (51)	21 (31)	40 (38)
Elevated LDH and Bulky disease, n (%)	14 (38)	20 (29)	34 (32)
Prior SCT, n (%)	12 (32)	11 (16)	23 (22)
MYC-altered disease, n (%)	14 (38)	46 (68)	60 (57)

Phase 1 - Safety Results

- A summary of the most frequently reported treatment-emergent AEs (>10%) is provided below.

Event4	Overall (n = 37)			
	Grades 1-2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Total n (%)
Diarrhea	19 (51)	2 (5)	0	21 (57)
Thrombocytopenia	8 (22)	10 (27)	2 (5)	20 (54)
Fatigue	13 (35)	2 (5)	0	15 (41)
Nausea	14 (38)	0	0	14 (38)
Neutropenia	4 (11)	5 (14)	1 (3)	10 (22)
Constipation	9 (24)	0	0	9 (24)
Vomiting	8 (22)	1 (3)	0	9 (24)
Fever	6 (16)	1 (3)	0	7 (19)
Anemia	4 (11)	2 (5)	0	6 (16)
Cough	6 (16)	0	0	6 (16)
Hypokalemia	5 (14)	1 (3)	0	6 (16)
Abdominal pain	4 (11)	1 (3)	0	5 (14)
Edema	4 (11)	0	0	4 (11)
Hyperglycemia	3 (8)	1 (3)	0	4 (11)
Hypomagnesemia	4 (11)	0	0	4 (11)

Phase 2 - Safety Results

- A summary of the most frequently reported treatment-emergent AEs (>13%) is provided below.

AE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
	n (%)					
Diarrhea	22 (32)	13 (19)	12 (18)	0	0	47 (69)
Nausea	23 (34)	9 (13)	0	0	0	32 (47)
Thrombocytopenia	5 (7)	5 (7)	14 (21)	3 (4)	0	27 (40)
Hypokalemia	8 (12)	4 (6)	8 (12)	0	0	20 (29)
Fatigue	14 (21)	5 (7)	0	0	0	19 (28)
Anorexia	11 (16)	7 (10)	0	0	0	18 (27)
Vomiting	15 (22)	2 (3)	1 (2)	0	0	18 (27)
Hypomagnesemia	12 (18)	2 (3)	1 (2)	0	0	15 (22)
Neutropenia	1 (2)	0	9 (13)	3 (4)	0	13 (19)
Fever	11 (16)	1 (2)	0	0	0	12 (18)
Anemia	2 (3)	3 (4)	6 (9)	0	0	11 (16)
Constipation	7 (10)	4 (6)	0	0	0	11 (16)

Combined Phase 1 and 2 Analysis

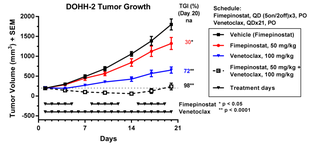
A combined analysis of MYC status per study definition of the 37 DLBCL (14 MYC-altered) patients from the Phase 1 (*Haematologica*. 2017 Nov;102(11):1923-1930) and Phase 2 studies are provided in the following table below.

Group	Total Responses	ORR		Median DOR (95% CI)	Median PFS (95% CI)	Median OS (95% CI)
		Evaluable Population	ITT Population			
MYC-altered	14 (8 CR, 6 PR)	29% (14/48)	23% (14/60)	13.6 (2.1, NC)	1.4 (1.2, 2.1)	7 (3.0, NC)
Non-MYC-altered	3 (1 CR, 2PR)	18% (3/17)	14% (3/22)	8.8 (3.3, 14.3)	1.4 (1.3, 2.7)	6.3 (3.3, NC)
MYC unknown	2 (2 PR)	13% (2/16)	9% (2/23)	10.8 (1.4, 20.2)	1.3 (1.0, 2.3)	5.7 (3.4, 14.4)
All	19 (9 CR, 10 PR)	24% (19/81)	18% (19/105)	13.6 (1.4, 20.2)	1.4 (1.3, 1.5)	6.3 (3.9, 14.2)

*DOR, PFS, and overall survival (OS) - all times in months

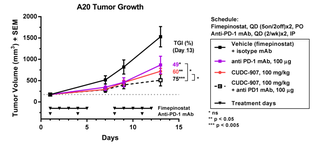
Preclinical Fimepinostat Drug Combination Data

A. Efficacy of fimepinostat ± venetoclax in the DOHH-2 DLBCL mouse xenograft tumor model



Drug	Dosage (mg/kg)	TGI % (Day 20)	# mice (Day 20)
Vehicle	-	na	9/9
Fimepinostat	50	30	9/9
Venetoclax	100	72	9/9
Fimepinostat + Venetoclax	50 + 100	98	7/9

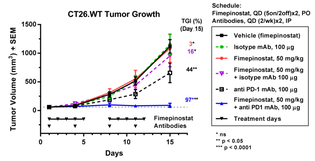
B. Efficacy of fimepinostat ± anti-PD-1 mAb in the A20 B-cell lymphoma tumor model



Drug	Dosage	TGI %* (Day 13)	# mice (Day 13)
Vehicle	-	na	8/8
anti–PD-1 mAb	100 µg	49	8/8
Fimepinostat	100 mpk	60	8/8
Fimepinostat + anti-PD-1 mAb	100 mg/kg + 100 µg	75	8/8

* Relative to Vehicle group

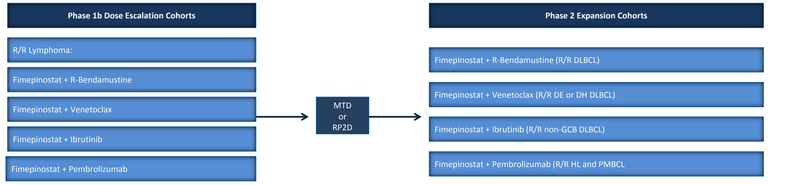
C. Efficacy of fimepinostat ± anti-PD-1 mAb in the CT26.WT colon carcinoma model



Drug	Dosage	TGI %* (Day 15)	# mice (Day 15)
Vehicle	-	na	7/8
Isotype mAb	100 µg	na	7/8
Fimepinostat	50 mpk	3	7/8
Fimepinostat + Isotype mAb	50 mg/kg + 100 µg	16	8/8
anti–PD-1 mAb	100 µg	44	8/8
Fimepinostat + anti-PD-1 mAb	50 mg/kg + 100 µg	97	8/8

* Relative to Vehicle group

Fimepinostat Phase 1/2 Combinations



Conclusions

- Fimepinostat treatment has demonstrated durable clinical activity in primarily MYC-altered patients, including DHL.
- The biologic rationale, tolerable safety profile, and evidence of anti-tumor activity in MYC-altered RR DLBCL support the continued development of fimepinostat in combination in this population of high unmet need.

NHL-145

SOHO Sept 12-15, 2018

Curis, Inc.
4 Maguire Road
Lexington, MA
02421