Poster # 4184

A Pooled Analysis of Relapsed/Refractory Diffuse Large B-Cell Lymphoma Patients Treated with the Dual PI3K and HDAC Inhibitor Fimepinostat (CUDC-907), Including Patients with MYC-Altered Disease

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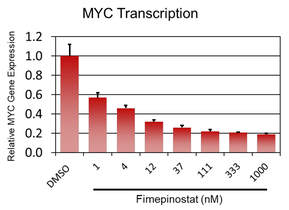
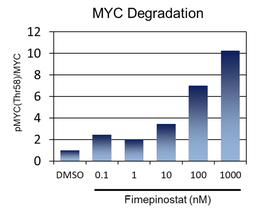
Introduction

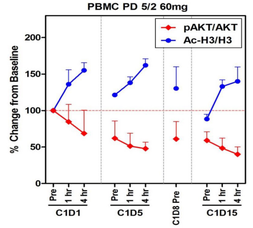
Patients with relapsed or refractory (R/R) MYC-altered DLBCL have poor outcomes, and other than for a subset of patients who may benefit from chimeric antigen receptor T (CAR-T) cell therapy, no treatment has shown a significant durable benefit or impact on survival outcomes. Fimepinostat is an oral first-in-class dual inhibitor of HDAC (class I and II) and PI3K (α, β, and δ) enzymes. Fimepinostat is well-tolerated, and pharmacodynamic inhibition of these targets has been demonstrated in human studies. Interestingly, nonclinical studies have shown that fimepinostat inhibits MYC transcription and a subset of MYC-associated genes. Additionally, MYC protein levels are downregulated by fimepinostat, in part, through inhibition of PI3K-mediated ubiquitination. These results suggest patients with MYC-altered/dependent tumors may benefit the most from fimepinostat therapy. Here, we report the outcomes of patients with R/R DBLCL treated with fimepinostat after a pooled analysis of two clinical trials, a Phase 1 and a Phase 2 study, with an emphasis on outcomes for patients with MYC-altered disease.

Single-Agent Fimepinostat Effects MYC Expression Levels in Nonclinical Cancer Models

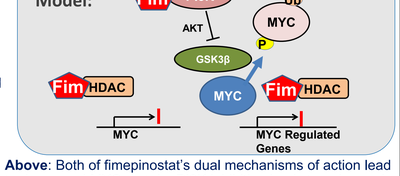




Left: Fimepinostat inhibits MYC transcription (left; red bars) and enhances MYC degradation (right; blue bars) in WSU DLCL2.



Left: Fimepinostat inhibits HDAC and PI3K in peripheral blood mononuclear cells (PBMCs) taken from patients on-treatment with fimepinostat.



Above: Both of fimepinostat's dual mechanisms of action lead to decreased MYC protein: PI3K inhibition leads to enhanced ubiquitin-mediated MYC protein degradation, and HDAC inhibition leads to repression of *MYC* gene expression.

Methods and Study Design

156 patients were enrolled and treated among both the Phase 1 study CUDC-907-101, which included R/R lymphomas or multiple myeloma, and the Phase 2 study CUDC-907-201, which included patients with DLBCL. Among both studies, a total of 105 patients had R/R DLBCL (Phase 1, n = 37; Phase 2 study, n = 68).

In CUDC-907-101, 14 patients were identified as having MYC-altered disease, defined as the presence of MYC rearrangement by either central or local testing by fluorescent in situ hybridization or MYC protein expression ≥40%) by immunohistochemistry (IHC). In CUDC-907-201, 46 patients had confirmed MYC-altered disease by central IHC testing. Across both studies, patients without available tissue or prior test results were deemed as having an unknown MYC status (n = 23).

Key eligibility criteria for patients with DLBCL for both studies include:

- ❑ histologically/cytologically-confirmed diagnosis (including high grade B-cell lymphoma with MYC and BCL2 and/or BCL6 rearrangements per 2016 WHO classifications)
- ❑ relapsed on or refractory to current standard-of-care treatment
- ❑ confirmed availability of viable biopsy tissue (fresh or archival) for central testing
- ❑ ECOG PS 0-2 (Ph1) or ECOG PS 0-1 (Ph2)
- ❑ 2-4 prior lines of therapy for DLBCL
- ❑ patients are ineligible for or failed prior stem cell transplantation

The primary endpoint was to assess the objective response rate (ORR) in patients with MYC-altered DLBCL. 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.

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Baseline Disease Characteristics of DLBCL Patients with Known MYC Status

Patients with unknown MYC alteration status were not included (23 patients)

	MYC-altered DLBCL	Non-MYC-altered DLBCL	Total DLBCL with known MYC status
Baseline Characteristics	(n=60)	(n=22)	(n=82)
Male, n (%)	36 (60%)	14 (64%)	50 (61%)
Caucasian, n (%)	54 (90%)	17 (77%)	71 (87%)
Age, median (range)	62 (34-93)	65 (20-85)	62 (20-93)
De novo DLBCL, n (%)	45 (75%)	17 (77%)	62 (76%)
t-FL, n (%)	15 (25%)	5 (23%)	20 (24%)
# prior treatments, median (range)	3 (1-8)	3 (2-6)	3 (1-8)
Stage, n (%)			
I-II	8 (13%)	3 (14%)	11 (13%)
III-IV	51 (85%)	17 (77%)	68 (83%)
Unknown	1 (2%)	2 (9%)	3 (4%)
ECOG PS, n (%)			
0-1	55 (92%)	21 (95%)	76 (93%)
2	5 (8%)	1 (5%)	6 (7%)
IPI Risk Score, n (%)			
0-2	24 (40%)	10 (45%)	34 (41%)
3-5	36 (60%)	12 (55%)	48 (59%)
Elevated LDH, n (%)	40 (67%)	11 (50%)	51 (62%)
Bulky disease (> 5 cm), n (%)	18 (30%)	9 (41%)	27 (33%)
Prior SCT, n (%)	11 (18%)	7 (32%)	18 (22%)

Results: Key Safety Summary

Most Frequent Related Treatment-Emergent AEs among Patients in CUDC-907-101 and CUDC-907-201:

- ❑ Fimepinostat was well-tolerated with diarrhea, nausea, and fatigue being the most commonly observed TEAEs.
- ❑ No related Grade 5 events were reported.
- ❑ The most frequent related Grade 3/4 adverse events were thrombocytopenia (Grade 3, 16%; Grade 4, 3%), neutropenia (Grade 3, 8%; Grade 4, 3%), diarrhea (Grade 3, 10%; no Grade 4), and anemia (Grade 3, 5%; no Grade 4).

	Grade 1/2	Grade 3	Grade 4	Total (Any grade)
Preferred term	n(%)	n(%)	n(%)	n(%)
Diarrhea	85(54)	15(10)	0(0)	100(64)
Nausea	55(35)	1(1)	0(0)	56(36)
Fatigue	49(31)	4(3)	0(0)	53(34)
Thrombocytopenia	9(6)	25(16)	5(3)	39(25)
Vomiting	25(16)	1(1)	0(0)	26(17)
Decreased appetite	22(14)	0(0)	0(0)	22(14)
Neutropenia	6(4)	12(8)	4(3)	22(14)
Anemia	10(6)	8(5)	0(0)	18(12)
Hypokalemia	11(7)	6(4)	1(1)	18(12)
Hypomagnesemia	16(10)	1(1)	0(0)	17(11)
Platelet count decreased	8(5)	4(3)	2(1)	14(9)
Constipation	10(6)	0(0)	0(0)	10(6)
Pyrexia	10(6)	0(0)	0(0)	10(6)
Weight decreased	10(6)	0(0)	0(0)	10(6)
Abdominal pain	9(6)	0(0)	0(0)	9(6)
Hyperglycemia	6(4)	2(1)	1(1)	9(6)
White blood cell count decreased	6(4)	3(2)	0(0)	9(6)

Results: Combined Phase 1 and Phase 2 Efficacy Outcomes

A combined analysis of the Phase 1 and Phase 2 studies of all patients with DLBCL, according to MYC status, is presented below. A total of 105 patients were treated with fimepinostat; of these, 81 patients were evaluable for response from both the Phase 1 (*Haematologica*. 2017 Nov;102(11):1923-1930) and Phase 2 studies.

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 (Duration of Response), PFS (Progression-Free Survival), and OS (Overall survival) - all times in months
^ORR = CRs (Complete Response) + PRs (Partial Response)

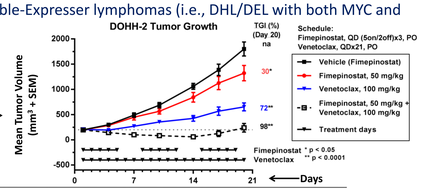
Nonclinical Anti-Tumor Activity of Combination Treatment

Efficacy of fimepinostat and venetoclax, administered as monotherapy or in combination, in the DOHH-2 DLBCL and SU-DHL-4 mouse xenograft tumor models.

- ❑ The combination of fimepinostat + venetoclax in both models strongly inhibited tumor growth and represents a mechanism-based treatment that targets key genetic aberrations present in Double-Hit/Double-Expresser lymphomas (i.e., DHL/DEL with both MYC and BCL2 alterations)

DOHH-2 Model:

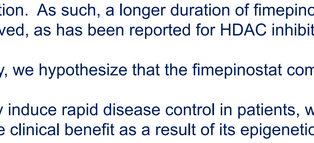
Drug	Dosage (mg/kg)	TGI % (Day 20)	# mice (Day 20)
Vehicle	-	na	9/9
Fimepinostat	50	30	9/9
Venetoclax	100	72	9/9
Fimepinostat + Venetoclax	50 + 100	98	7/9



SU-DHL-4 Model:

Drug	Dosage (mg/kg)	TGI % (Day 21)	# mice (Day 21)
Vehicle	-	na	8/8
Fimepinostat, PO, 5on/2off	75	60*	8/8
Venetoclax, PO, QD	50	60*	8/8
Fimepinostat + Venetoclax	75 + 50	97**	8/8

*p<0.05; **p<0.005



TGI= tumor growth inhibition

Phase 1/2 Amended Study Design

Study CUDC-907-101 was amended to assess additional combination treatments with fimepinostat in patients with R/R DLBCL

Patient population

Phase 1 Dose Escalation
[Fim+V]: R/R DLBCL
[Fim+R-Benda]: R/R lymphoma

Phase 2 Dose Expansion
[Fim+V]: R/R DHL, DEL or THL DLBCL
[Fim+R-Benda]: R/R DLBCL

Key eligibility criteria

- •Patients with R/R DLBCL may have either HGBL with MYC, BCL2 and/or BCL6 rearrangements, or DLBCL NOS
- •Patients with R/R DHL, DEL or THL DLBCL must have HGBL with MYC and BCL2 (± BCL6) rearrangements
- •≥ 1 prior treatment
- •≥ 18 years of age
- •Measurable disease
- •ECOG PS of 0-1
- •Life expectancy ≥ 3 months

ClinicalTrials.gov Identifier: NCT01742988

Phase 1b: Dose Escalation

Fimepinostat + Venetoclax
N=15

Fimepinostat + Rituximab/Bendamustine
N=15

Phase 2: Expansion

Fimepinostat + Venetoclax
N=30

Fimepinostat + Rituximab/Bendamustine
N=30

Objectives: Primary -> Safety, and preliminary efficacy
Exploratory-> Time to event outcome

Endpoints: Primary -> Ph1: MTD/RP2D in combination, ORR/DOR
Exploratory-> OS

Conclusions and Future Directions

- ❑ A combined analysis of patients with R/R DLBCL treated with fimepinostat (CUDC-907) in the Phase 1 and Phase 2 studies suggests that patients with MYC-altered disease had comparable, if not worse, baseline prognostic characteristics, yet had a higher response rate and improved outcomes, compared to patients with non-MYC-altered disease.
- ❑ Fimepinostat demonstrated efficacy and durable responses in patients with MYC-altered DLBCL, including Double-Hit/Double-Expresser lymphoma (DHL/DEL).
- ❑ Fimepinostat modulates epigenetics by inhibiting histone deacetylation. As such, a longer duration of fimepinostat treatment--several weeks to months—may be required for efficacy to be observed, as has been reported for HDAC inhibitors (Duvic M *et al*., (2015) *J Dermatol Clin*; Zain JM *et al.,* (2009) *J Clin Onc*).
- ❑ As R/R DLBCL patients have a poor prognosis and progress quickly, we hypothesize that the fimepinostat combination arms in this study will offer patients 2 distinct treatment options:
  1) Fimepinostat in combination with rituximab/bendamustine may induce rapid disease control in patients, while also providing a longer runway time for fimepinostat to demonstrate clinical benefit as a result of its epigenetic effects
  2) Fimepinostat in combination with venetoclax exhibits activity that is additive or synergistic in preclinical studies. For patients with DHL, DEL, or triple-hit lymphoma (THL) that harbor both MYC alterations and BCL2 aberrations, the combination of fimepinostat, which has shown enhanced efficacy in MYC-altered DLBCL patients, plus venetoclax (a BCL2 inhibitor), may provide synergistic clinical benefit

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