Fimepinostat (CUDC-907) in Relapsed/Refractory (R/R) Diffuse Large B-Cell Lymphoma (DLBCL), Including Patients with MYC-Altered Disease: Results from a Pooled Analysis

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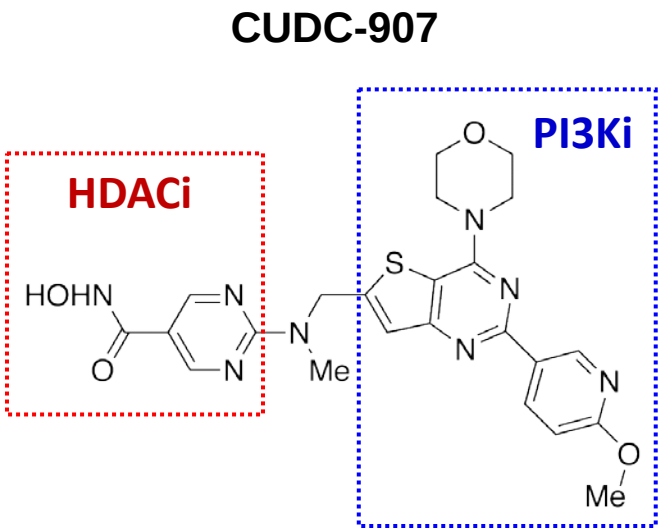
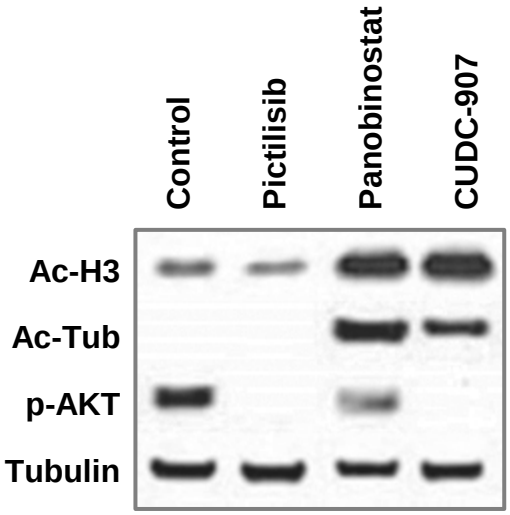
Consulting: Curis, Bayer, Merck, BMS, Roche, Xynomics, Epizyme, BPTH, ASANA

Honorarium: Takeda, Roche, Janssen, Abbvie

CUDC-907: Chemically Designed Oral, Dual Inhibitor of HDAC and PI3K

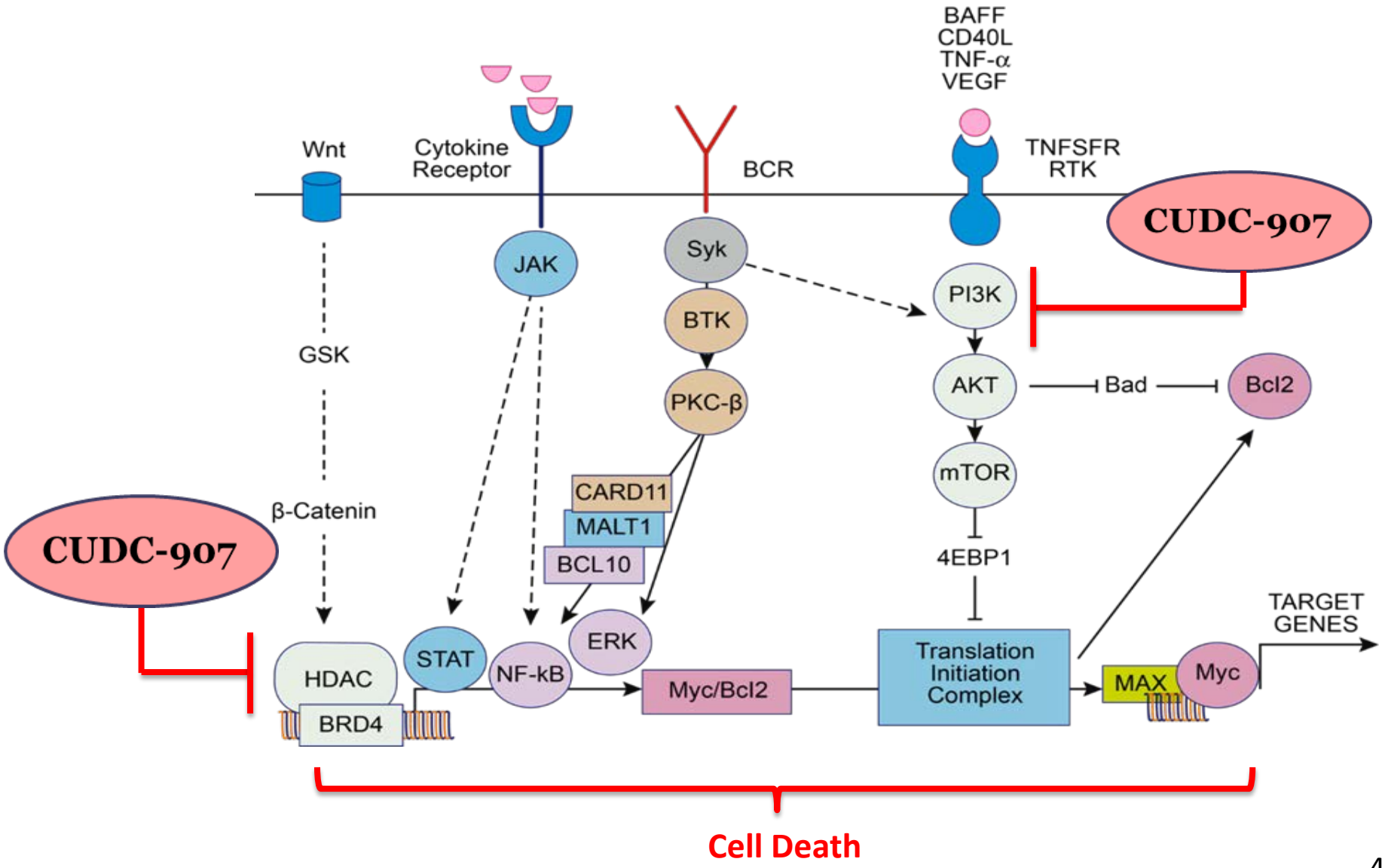
- First in class, rationally designed, dual inhibitor of HDAC (class I and II) and PI3K (class I α, β, and δ)
- Potential to overcome drug resistance by suppressing critical oncogenic networks





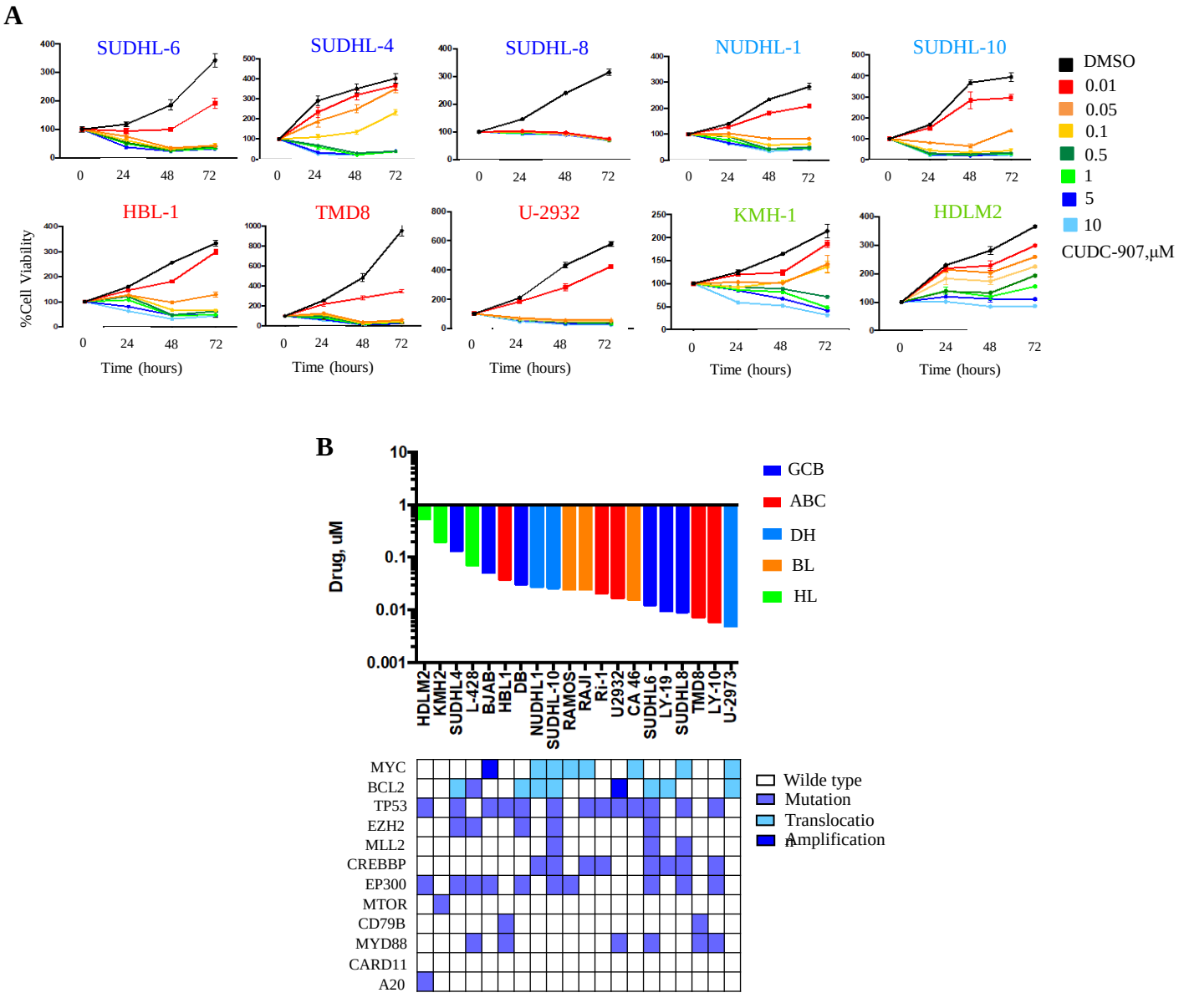
	HDAC					PI3K			
Isotype	1	2	3	6	10	Alpha	Delta	Beta	Gamma
IC50 (nM)	1.7	5	1.8	27	2.8	19	39	54	311

Proposed Mechanism of CUDC-907

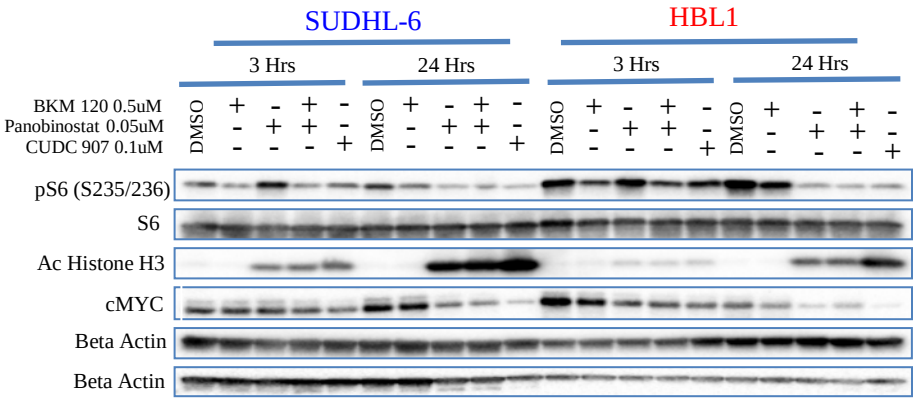


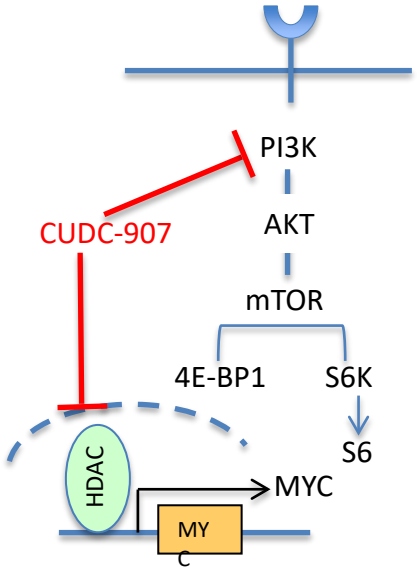
Mehta-Shah and Younes, Semin Hematol. 2015

In Vitro Activity of CUDC-907 in Lymphoma



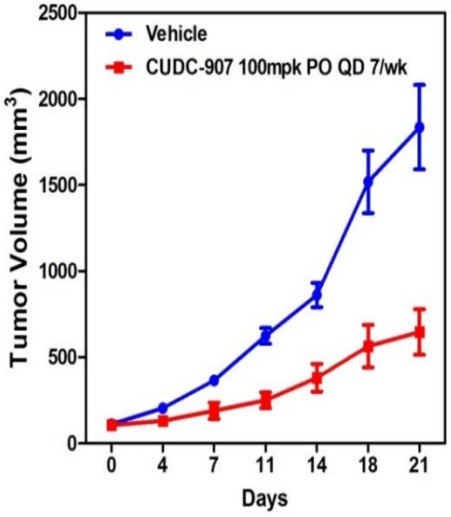
CUDC-907: Chemically Designed Oral, Dual Inhibitor of HDAC and PI3K





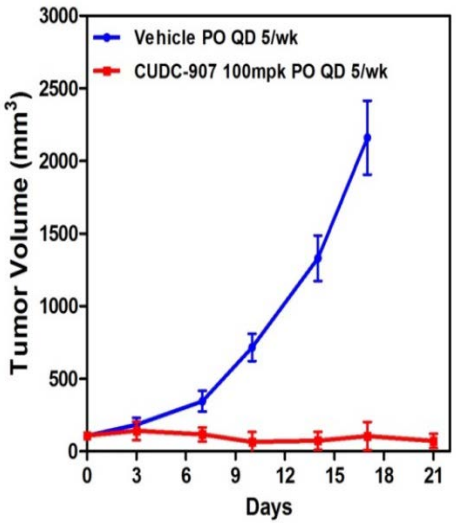
Efficacy in MYC-Altered Lymphoma Models

Mouse Xenograft & Transgenic Models



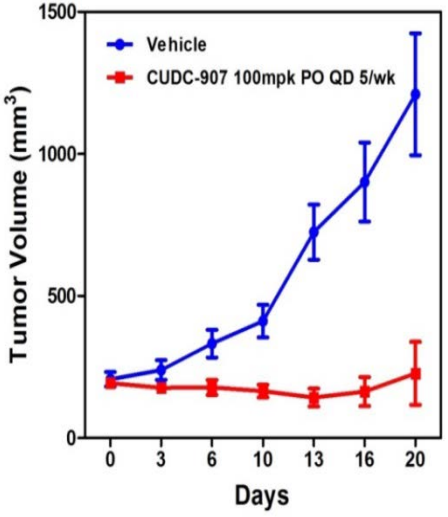
WSU-DLCL2
GCB DLBCL Xenograft

MYC & BCL2 translocations



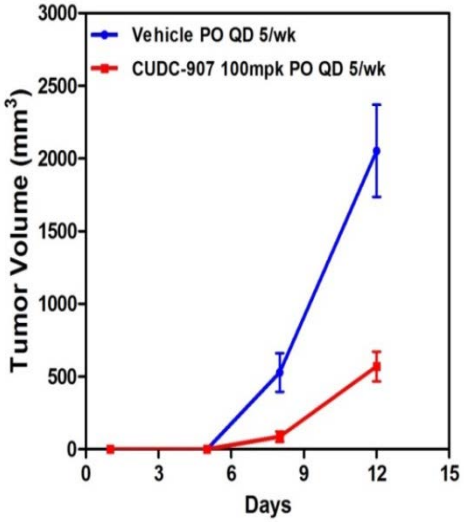
Daudi
Burkitt's Lymphoma Xenograft

MYC translocation



U2932
ABC DLBCL Xenograft

MYC over-expression
BCL2 amplification



Eμ-Myc Transgenic Model

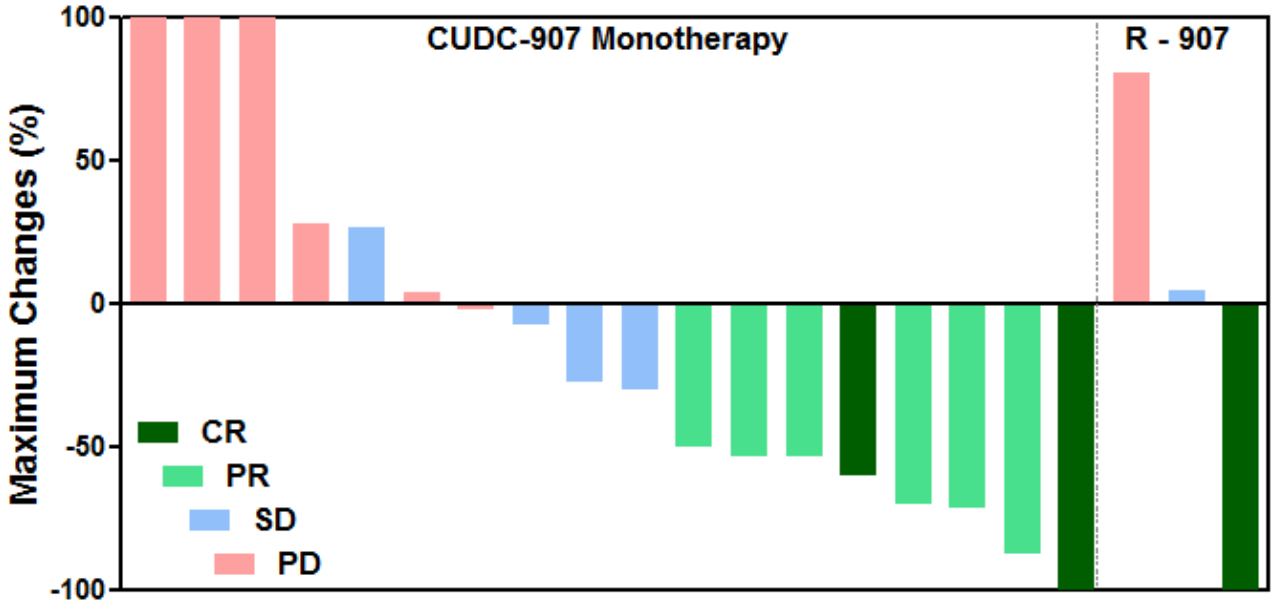
IgH-MYC translocation

WSU-DLCL2 (100mg/kg CUDC-907)

Elimination of MYC protein following
5QD oral dosing of CUDC-907

Sun et.al. Mol Cancer Ther. 2017. 6: 285

Responses in RR DLBCL:
5 MYC+ (3CR, 1PR, 1SD) and 3 DE (1CR, 1PR, 1SD)



***MYC* translocation**		N	N	N			N							N	N			N		N	N
***MYC* copy Number**		D	N				N							G	N			G		N	G
MYC IHC			30		10	30	0			40	25		45	1	20	15	25	60	0	25	
BCL2 translocation		N	T	T											N			T		N	T
BCL2 IHC		+		+	+	+	45	+	+	90	100		>70	98	20	>70	>76	96		95	
Disease Type	D	D	D	D	t	D	D	t	t	D	t	D	t	t	t	D	t	D	D	D	D
COO		NG	G	G		G	G				A				U			G		NG	G

- N **Normal**
- G ***MYC* Copy Number Gain**
- D ***MYC* partial deletion**
- **MYC IHC+ ≥40%**
- **MYC IHC+ <40%**
- T **Translocation**
- \+ **IHC+ or ≥70%**
- **IHC <70%**
- D **DLBCL**
- t **t-FL/DLBCL**
- G **GCB**
- NG **Non-GCB / ABC**
- U **Unclassified**
- **Unknown**

Younes A, et al: Lancet Oncology 2016

Pooled Analysis of DLBCL in Phase 1 and Phase 2: Baseline Characteristics

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)

Pooled Analysis of DLBCL in Phase 1 and 2 Studies

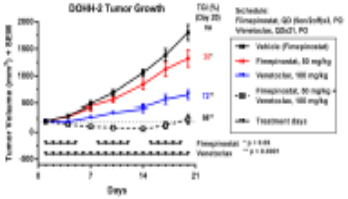
Population	Total Responses	ORR (ITT)	Median DOR (months)
MYC-altered (n = 60)	14 (8 CR, 6 PR)	23.3%	13.6*
Non-MYC-altered (n= 22)	3 (1 CR, 2 PR)	13.6%	14.1
MYC status unknown (n = 23)	2 (2 PR)	8.7%	10.8
Total (n = 105)	19 (9 CR, 10 PR)	18.1%	14.1*

*Two MYC-altered responders discontinued early to pursue SCT

Fimepinostat Combinations of Interest

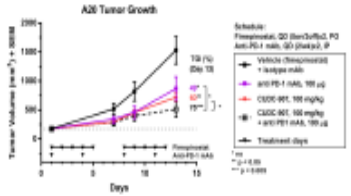
Preclinical Fimepinostat Drug Combination Data

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

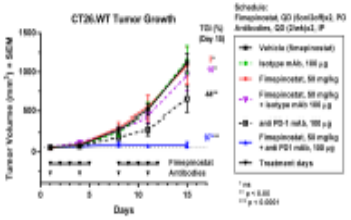
B. Efficacy of fimepinostat ± anti-PD-1 mAb in the A20 B-cell lymphoma tumor model



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 in combination with the following agents:
  - Venetoclax (DEL, DHL)
  - Bendamustine + rituximab (RR DLBCL)
  - Ibrutinib (Non-GCB DLBCL)
  - Pembrolizumab (HL, PMBCL)