The Combination of Venetoclax (ABT-199) and CUDC-907 Exhibits Synergistic Activity in Venetoclax-Refractory DLBCL

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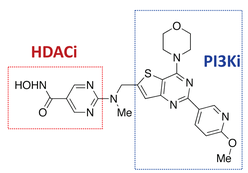
Introduction

CUDC-907 is a first-in-class, oral, dual inhibitor of Class I and II HDAC, as well as Class I PI3K enzymes. CUDC-907 is designed to inhibit HDACs 1, 2, 3, 6 and 10 and PI3K-alpha, delta and beta isoforms. Preclinical studies demonstrate that CUDC-907 has potent effects on acetylated histone-regulated genes and PI3K signaling. CUDC-907 showed potent antitumor activity in multiple preclinical tumor models as well as in patients with relapsed or refractory diffuse large B-cell lymphoma (RR DLBCL), with objective responses reported in multiple patients, including complete responses. Current clinical testing includes a Phase 2 study in patients with RR DLBCL, including those with MYC-alterations. Preclinical studies of CUDC-907 in combination with chemotherapeutic and targeted agents are in progress.

Venetoclax, a BH3 mimetic and selective BCL2 inhibitor, was recently approved for the treatment of patients with chronic lymphocytic leukemia (CLL) whose tumors had a 17p deletion. Results from a Phase 1 study of venetoclax monotherapy in patients with relapsed or refractory non-Hodgkin lymphoma showed that patients with DLBCL exhibited short-lived responses to venetoclax. Thus, combination approaches may be required to achieve durable responses to venetoclax in DLBCL.

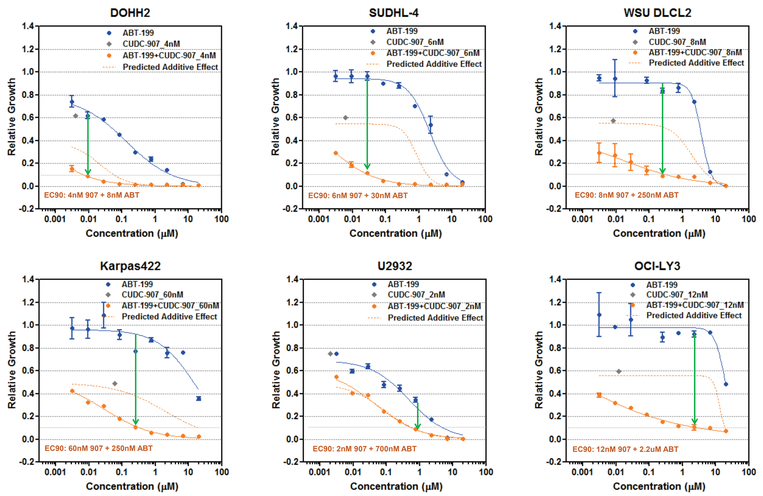
CUDC-907: a rationally designed dual HDAC/PI3K inhibitor

- **Potent HDAC and PI3K enzyme inhibition in one oral small molecule**
  - Distribution of both inhibitory activities within the same tissues and cells (advantage over combination of single agents)



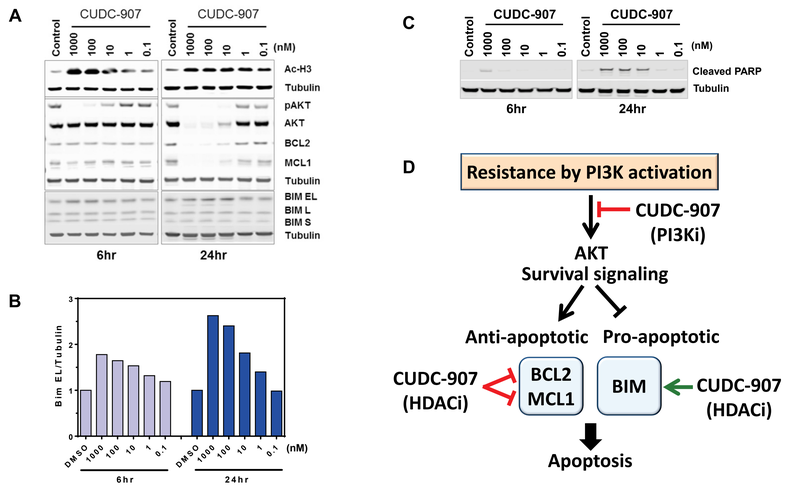
Enzyme	HDAC					PI3K			
Isotype	1	2	3	6	10	Alpha	Delta	Beta	Gamma
IC50 (nM)	1.7	5	1.8	27	2.8	19	39	54	311

CUDC-907 and venetoclax synergistically reduce cell viability in a panel of DLBCL cell lines



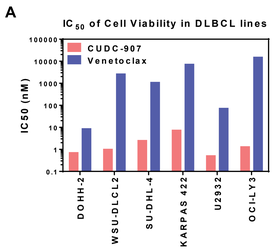
The Bliss independence method was used to determine combinatorial activity between a fixed concentration of CUDC-907 (~IC_{50} value of respective cell line, see graph legends) and increasing concentrations of venetoclax. The blue line is the effect of venetoclax alone. The dashed orange line represents the predicted additive effect calculated according to the Bliss independence method, whereas the solid orange line is the observed results of the CUDC-907 + venetoclax combination. All data points are the fractional cell viability remaining after 24 hrs

CUDC-907 induces upregulation of BIM and downregulation of BCL2 and MCL1 in WSU-DLCL2 cells

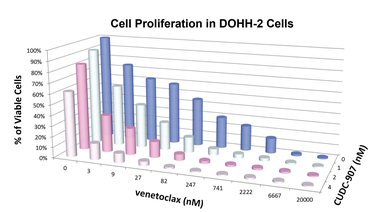


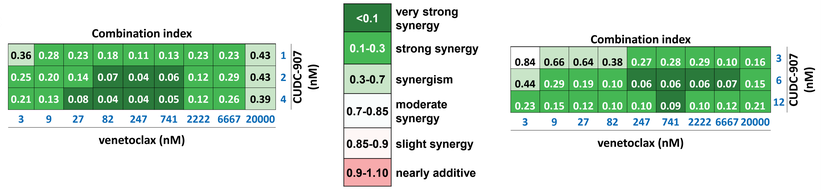
A. Immunoblots of lysates from 6 and 24 hr CUDC-907-treated WSU-DLCL2 cells. Tubulin was used as a loading control. Individual blots are boxed together
B. Intensity ratios of BIM EL to tubulin quantified from immunoblots in (A) and normalized to DMSO-treated cells
C. Immunoblots of lysates from 6 and 24 hr CUDC-907-treated WSU-DLCL2 showing evidence of apoptosis
D. Multiple mechanisms of apoptosis induction by dual HDAC/PI3K inhibitor activity of CUDC-907

CUDC-907 and venetoclax synergistically reduce cell viability in DOHH-2 and SU-DHL-4 cells

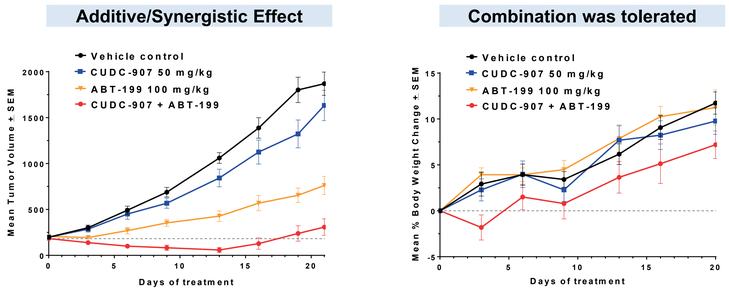


A. 48-hour cell viability IC_{50} values of CUDC-907 and venetoclax in a panel of DLBCL and FL cell lines
B. Synergistic cell killing with 24 hr CUDC-907 and venetoclax combination treatment in DOHH-2 and SU-DHL-4 cells. Data represent the viable cells from compound-treated cells normalized to DMSO-treated cells
C. Combination indexes (CI) from the data presented in B were calculated using Compusyn software. Criteria for synergy, additivity, and antagonism are shown





CUDC-907 plus venetoclax (ABT-199) combination exhibits enhanced efficacy in a DOHH-2 xenograft tumor model



Groups	%TGI
Vehicle (30% Captisol + 60% phosal 50PG, 30% PEG 400, 10% ethanol)	na (n=9)
CUDC-907, 50 mg/kg, po, qd, 5 days on/2 day off	14 (n=9)
ABT-199, 100 mg/kg, po, qd	67* (n=9)
CUDC-907 + ABT-199, as above	92* (n=7)
	*p<0.0001

Summary

- CUDC-907 + venetoclax combination synergistically reduced cell viability in a panel of DLBCL cell lines, including both ABC and GCB DLBCL subtypes
- CUDC-907 + venetoclax combination exhibited very strong synergism, as demonstrated with the combination index <0.1 at multiple dose combinations, in cell lines insensitive to venetoclax, such as SU-DHL-4 cells
- Additive/synergistic anti-tumor effect was observed for the CUDC-907 + venetoclax combination in mice bearing DOHH-2 xenograft tumors
- Western blot analysis showed that CUDC-907, at concentrations as low as 10 nM, simultaneously increased pro-apoptotic BIM protein and decreased anti-apoptotic BCL2 and MCL1 protein levels in WSU-DLCL2 cells
- In summary, the effect of CUDC-907 on multiple anti- and pro-apoptotic BCL2 family members may be the basis for the observed synergy with the BCL2-selective inhibitor venetoclax

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Disclosures: R. Booher*, K. Sun*, R. Atoyan*, M. Borek*, S. Dellarocca*, G. Rhyasen*, A. Fattaey*, D. Tuck*
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