The HDAC Inhibitor Entinostat (SNDX-275) Induces Clinical Responses in Patients with Relapsed or Refractory Hodgkin's Lymphoma: Results of ENGAGE 501 Multicenter Phase 2 Study

Anas Younes[1], Yvette Kasamon[2], R.Gregory Bociek[3], Peter Lee[4], Lia Gore[5], Amanda Copeland[1], and Francisco Hernandez-Ilizaliturri[6]

[1]M. D. Anderson Cancer Center, Houston, TX; [2]Johns Hopkins University, Baltimore, MD; [3]University of Nebraska Medical Center, Omaha, NE; [4]Tower Cancer Research Foundation, Beverly Hills, CA ; [5]University of Colorado Cancer Center, Aurora, CO; [6]Roswell Park Cancer Institute, Buffalo, NY

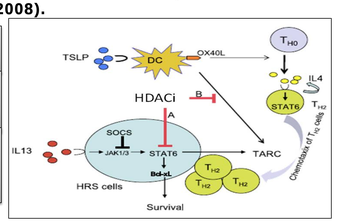
The authors wish to acknowledge the contributions of the ENCORE 501 research coordinators, study patients and study sponsor, Syndax Pharmaceuticals, Inc.

INTRODUCTION

Entinostat (ENT) has direct antiproliferative activity in HL cell lines involving several mechanisms: induction of apoptosis, regulation of cytokines and chemokines and alterations of cancer/testis antigens (Jóna, Exp Hematol 2011).

The prognosis of patients with relapsed Hodgkin's lymphoma is poor. HDACi are promising anticancer drugs. Preclinical studies identified at least three complementary mechanisms to explain how HDACi may be effective in the treatment of HL (Buglio, Blood 2008).

Induce cell death and growth arrest through ↓STAT and BCL-X in H-RS cells
Modulate epigenetic processes such as B-cell specific gene silencing and reactivation of antigen expression
Alter microenvironment through ↓STAT mediated cytokine and chemokine production and blockade of unfavorable TH2 cell growth and survival



ENTINOSTAT – CLASS 1 SELECTIVE HDACi

- **Oral, isoform-selective HDACi**
- **Long $T_{1/2}$ (80-100hrs) enables low dose, long exposure**
- **Targets cancer-relevant class 1 HDACs**
- **Combines safely with full-dose targeted therapies**
- **Well characterized safety profile: > 650 cancer patients treated**

STUDY DESIGN

To investigate the clinical activity of ENT dual targeting of cancer cell and tumor micro-environment in relapsed and refractory HL.

Population: Relapsed or refractory HL patients with >1 prior treatment who are ineligible for or progressed following stem cell transplant

Design: Phase II, multi-center, open label single arm study.
2 stage design: if >1/9 CR/PR → expand to 24 patients. Protocol amended from 10 mg biweekly to 15 mg biweekly based on the tolerability of 10 mg and an additional expansion phase (regimen 2) to evaluate 15 mg, 3 of 4 weeks

	N	ENT Regimen (28 day cycle)
Regimen 1	33	10 mg D1, 14 15 mg D1, 14 (D1 10mg C1 only)
Regimen 2	16	15 mg D1, 8, 14

Objectives: 1° Endpoint: ORR (CR+PR) *
2° Endpoints: DOR (CR/PR), safety, tolerability
Exploratory: OS and PFS, Biologic markers that may predict efficacy or toxicity of ENT, PK, PD based on immune modulation parameters

based on revised criteria for malignant lymphoma (Cheson 2007)

**efficacy (per protocol population) excluded patients who did not complete 2 cycles of Ent and/or end of Cycle 2 restaging*

KEY INCLUSION/EXCLUSION CRITERIA

Inclusion

- Pathologic confirmation of relapsed/refractory classical HL from last biopsy
- Progressed after or ineligible for stem cell transplantation
- Age 18 years or older
- ANC of ≥ 1,000/μL and platelets ≥ 50,000 (or 25,000/μL)

Exclusion

- Prior treatment with HDAC inhibitor
- Active immunosuppressive therapy within 3 months for allogeneic transplant or active GVHD requiring treatment

BASELINE CHARACTERISTICS (N=49)

	Regimen 1 (N=33)	Regimen 2 (N=16)
Median age (years)	33 (19-73)	33 (20-55)
Female **Male**	14 (42%) 19 (58%)	10 (63%) 6 (38%)
Median prior regimens* **≥4 prior regimens**	3 (1-10) 14 (42%)	3 (2-7) 8 (50%)
Prior autologous transplant **Prior allogeneic transplant** **Prior autologous & allogeneic transplant**	21 (64%) 4 (12%) 3 (9%)	9 (56%) -- 2 (13%)
Refractory to treatment—transplant ineligible	4 (12%)	4 (12%)
Response to last treatment **Refractory** <50% response to last treatment PD within 3 mo. of last dose of most recent therapy **Relapsed disease** PD following therapy(ies) with curative intent	 4 (12%) 9 (27%) 20 (61%)	 4 (25%) 4 (25%) 8 (50%)
Bulky disease (1 or more baseline lesions ≥ 5cm)	28 (85%)	11 (69%)
Prior radiotherapy	26 (79%)	12 (75%)

* *n=4 prior treatment with brentuximab vedotin*

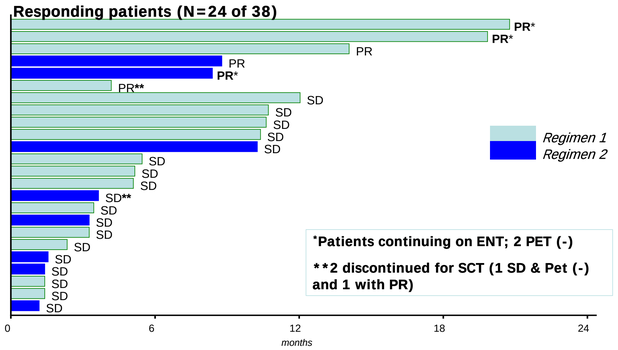
EFFICACY

	ENT Per Protocol Population*		
	Regimen 1 (N=27)	**Regimen 2** (N=11)	**Total** (N=38)
ORR	15%	18%	**16%**
CR	-	-	**-**
PR	4 (15%)	2 (18%)	**6 (16%)**
SD (≥6 mo)	4 (15%)	2 (18%)	**6 (16%)**
SD (<6 mo)	8 (30%)	4 (36%)	**12 (32%)****
Disease control ($CR+PR+SD_{\geq 6\ mo}$)	8 (30%)	4 (36%)	**12 (32%)****
PD	11 (41%)	3 (27%)	**14 (37%)**

*Efficacy population exclusions: *Regimen 1 n=6 PD and Regimen 2 n =1 PD, n=2 withdrew consent , n=1 unrelated SAE , n=1 protocol violation*

** 7 patients had SD per Cheson at end of treatment: 5 discontinued PI discretion, 1 SAE, and 1 patient decision

BEST OVERALL RESPONSE WITH TIME ON TREATMENT



*Patients continuing on ENT; 2 PET (-)

**2 discontinued for SCT (1 SD & Pet (-) and 1 with PR)

- **63% of patients had disease control within 2 months, both SD and PR achieved durable responses.**

GRADE 3/4 ADVERSE EVENTS[1]

	Regimen 1 N =33	Regimen 2 N =16	Total N=49
Thrombocytopenia	19 (58%)	12 (75%)	31 (63%)
Anemia	15 (45%)	8 (50%)	23 (47%)
Neutropenia	12 (36%)	8 (50%)	20 (41%)
Discontinuation due to toxicity	2 (6%)	3 (19%)	5 (10)%

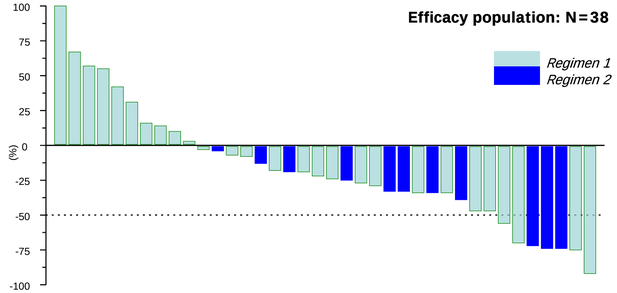
1 Occurring in >20%; Treatment-emergent Adverse Events, regardless of treatment attribution.

- **Gr 3/4 non-hematologic toxicities including fatigue and GI events were rare (<5%).**
- **There does not appear to be cumulative hematologic toxicity nor is there a higher incidence associated with the higher 15 mg dosing schedule. Delayed/dose reduced due to neutropenia or thrombocytopenia occurred in 31% of patients.**

PHARMACODYNAMIC ANALYSIS

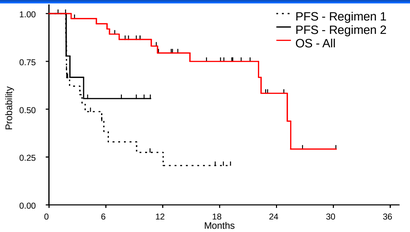
- **Blood samples from C1D1 (pre-treatment), C1D8, C1D15, and C3D15 were analyzed for changes in cytokines, chemokines and growth factor levels to provide support for the biological activity of ENT as an immunomodulatory agent**
- **Trends of increased Th1 cytokines such as IL12 and decreased Th2 cytokines such as IL13 in patients that had either objective tumor responses or prolonged stable disease were observed and are consistent with previously described *in vitro* effects of ENT**
- **TARC analysis is pending**

MAXIMUM DECREASE IN TUMOR BURDEN FROM BASELINE



- **~40% of patients with bulky disease demonstrated tumor decrease, however did not meet PR criteria**

PROGRESSION-FREE SURVIVAL/OVERALL SURVIVAL



PFS Regimen 1	15/27	2/7	1/4	0/2	
PFS Regimen 2	4/11	0/4	0/0	0/0	
OS	2/38	5/29	1/19	2/14	2/5	0/1

(#events/#at risk)

- **Median PFS 5.5 months (95% CI: 2.2, 12.0); Median OS 25.1 months (95% CI: 22.1, not reached). Median PFS and OS not yet reached for Regimen 2.**

SUMMARY

- **Disease control rate is consistent with activity demonstrated with other HDACi in HL. Antitumor activity observed in HL pts progressing after SCT with bulky disease in about a third of patients within 2 cycles of therapy.**
- **Regimens 1 and 2 exhibited similar toxicity with earlier control of bulky disease in Regimen 2.**
- **PFS: Durable responses in patients with bulky disease can be achieved with this single agent with tolerable toxicity.**
- **OS: The exploratory endpoint of OS is not mature at this time.**
- **ENT was well tolerated and the safety profile is consistent with previous studies, lowest rate of discontinuations due to toxicity.**
- **ENT provides a non-cross resistant mechanism of action with cytotoxic therapy and study in combination with other agents earlier in the disease course is warranted.**

Disclosures: A. Younes received research funding from Syndax Pharmaceuticals, Inc. F. Hernandez- Ilizaliturri, Y. Kasamon, R.G. Bociek, P. Lee, L. Gore, and A. Copeland have no relevant conflicts of interest to disclose.

American Society of Hematology 53nd Annual Meeting, San Diego, CA, 10-13Dec2011