Entinostat, a novel histone deacetylase inhibitor, added to exemestane improves PFS in advanced breast cancer in a randomized phase 2, double-blind study (ENCORE 301); with updated overall survival data

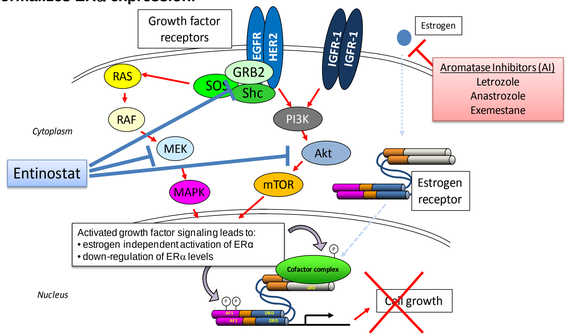
Yardley D[1], Ismail-Khan R[2], Klein P[3]

[1]Sarah Cannon Research Institute and Tennessee Oncology , PLLC, Nashville, TN; [2]H. Lee Moffitt Cancer Center, Tampa, FL; [3]PMK Consulting, San Francisco, CA

The authors wish to acknowledge the contributions of all of the ENCORE 301 investigators, research coordinators, study patients and study sponsor, Syndax Pharmaceuticals, Inc.

Entinostat Mechanism of Action

Overcoming resistance to AI therapy in advanced breast cancer represents an unmet need. Key events leading to AI resistance include ↓ ERα expression and ↑ growth factor signaling (ex. HER2), which result in estrogen-independent growth of breast cancer cells. Preclinical data demonstrates that entinostat, a histone deacetylase inhibitor (HDACi), inhibits growth factor signaling pathways and normalizes ERα expression.



Entinostat – Class 1 Selective HDAC inhibitor (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**
- **No evidence of cardiac toxicity**
- **No cytochrome p450 interaction**

ENCORE 301 Study Design

Population:
Post-menopausal ER+ locally advanced or metastatic breast cancer progressing on non-steroidal AI (NSAI) (letrozole or anastrozole)

RANDOMIZE

- Exemestane 25 mg PO QD + Entinostat 5 mg PO wkly (EE) N= 64
- Exemestane 25 mg PO QD + Placebo 5 mg PO wkly (EP) N= 66

Study Design*:
- 1° Endpoint: PFS
- 2° Endpoints: ORR, CBR
- 1-sided significance level p=0.10
- Disease assessments q8 wks
- Cycle 1 pre- and post-treatment blood samples for protein lysine acetylation

*Design assumptions based on the EFECT Study (Chia, 2008)

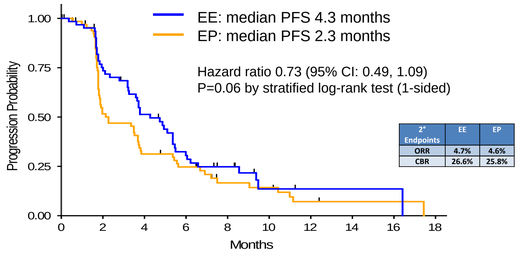
Selected Inclusion Criteria

- **Disease progression on non-steroidal Aromatase Inhibitor (NSAI) therapy**
  - **In the adjuvant setting, relapse after ≥ 12 mos. of therapy**
  - **In the metastatic or locally advanced setting, relapse after ≥ 3 mos. of therapy**
- **Evidence of metastatic disease based on radiographic imaging studies as follows:**
  - **≥ 1 measurable lesion ≥ 20 mm by conventional CT or ≥ 10 mm by spiral CT**
  - **Bone-only metastases with positive bone scan, confirmed with MRI, CT or PET**
- **0-1 prior chemotherapy permitted provided NSAI was last administered therapy**

Baseline Characteristics

	Exemestane + Placebo (N=66)	Exemestane + Entinostat (N=64)
Median Age (range)	62 (37-88)	63 (37-85)
ECOG Status, n (%) PS 0 / 1	50 (76%) / 16 (24%)	40 (63%) / 24 (38%)
Setting of NSAI Progression, n (%) Adjuvant / Metastatic	9 (14%) / 57 (86%)	10 (16%) / 54 (84%)
Sites of Metastases, n (%)		
Bone	47 (71%)	49 (77%)
Bone Only	11 (17%)	13 (20%)
Lymph Nodes	32 (48%)	30 (47%)
Visceral Involvement	44 (67%)	34 (53%)
Measurable Disease, n (%)	54 (82%)	52 (81%)
Prior Chemotherapy, n (%) Adjuvant / Metastatic	28 (42%) / 21 (32%)	22 (34%) / 22 (34%)

PFS (ITT) : Primary Endpoint



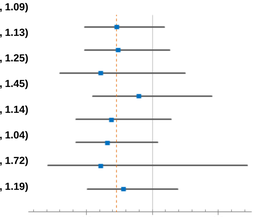
2° Endpoints	EE	EP
ORR	4.7%	4.6%
CBR	26.6%	25.8%

Placebo	31/66	13/33	4/20	4/15	1/7	3/6	0/2	0/1	1/1	
Entinostat	15/64	14/45	11/29	3/16	3/10	0/3	0/1	0/1	1/1	

(#events/#at risk)

PFS: Sub-group Analysis

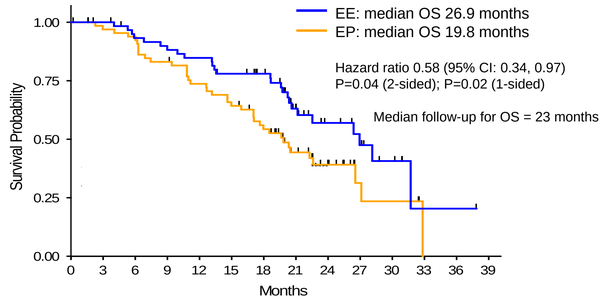
	Median (Months) EP	EE	Hazard Ratio	95% CI
All Subjects (n=130)	2.27	4.28	0.73	(0.49, 1.09)
Per-protocol set (n=116)	2.20	4.74	0.74	(0.49, 1.13)
NSAI resistant[1] (n=45)	1.78	3.72	0.61	(0.30, 1.25)
NSAI sensitive[1] (n=85)	3.36	4.87	0.90	(0.55, 1.45)
Visceral Involvement (n=78)	2.20	4.28	0.69	(0.42, 1.14)
PR positive (n=102)	1.97	4.28	0.66	(0.42, 1.04)
Last NSAI - Adjuvant (n=19)	1.78	3.49	0.61	(0.21, 1.72)
Last NSAI - Advanced (n=111)	2.27	4.87	0.78	(0.51, 1.19)



[1] NSAI sensitive defined as CR, PR or SD > 6 months during treatment with last NSAI. All other patients defined as NSAI resistant.

Positive PFS results were consistent across subgroups.

Overall Survival: Exploratory Endpoint



Placebo	2/66	2/63	7/61	6/54	6/47	6/41	5/32	2/20	1/12	1/4	1/3	0/0	0/0
Entinostat	0/64	4/61	3/55	2/52	4/50	0/45	7/41	2/24	2/14	1/10	1/5	0/1	0/1

(#events/#at risk)

Post study anticancer treatment therapies were generally well balanced between the treatment arms, both immediately following study therapy and throughout the post study survival period (with greater than 80% of patient data reported).

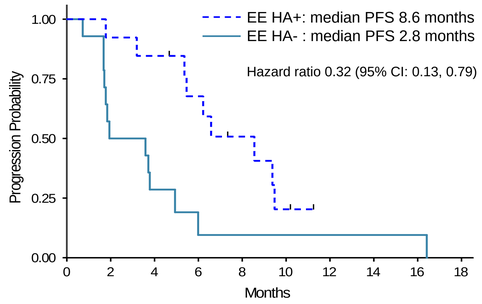
Adverse Events

Adverse Event[1]	Exemestane + Entinostat (N=63) Any Grade (G) n (%)	G3 n (%)	G4 n (%)	Exemestane + Placebo (N=66) Any Grade (G) n (%)	G3 n (%)	G4 n (%)
Fatigue	29 (46%)	7 (11%)	1 (2%)	17 (26%)	2 (3%)	-
Nausea	25 (40%)	3 (5%)	-	10 (15%)	1 (2%)	-
Weight Loss	11 (17%)	-	-	12 (18%)	-	-
Anemia[2]	12 (19%)	1 (2%)	-	8 (12%)	1 (2%)	1 (2%)
Back Pain	9 (14%)	-	-	11 (17%)	1 (2%)	-
Dyspnea	12 (19%)	2 (3%)	-	7 (11%)	-	-
Arthralgia	7 (11%)	1 (2%)	-	11 (17%)	-	-
Diarrhea	10 (16%)	-	-	8 (12%)	1 (2%)	-
Constipation	6 (10%)	-	-	10 (15%)	1 (2%)	-
Neutropenia[2]	16 (25%)	7 (11%)	1 (2%)	0 (0%)	-	-
Edema Peripheral	13 (21%)	-	-	3 (5%)	-	-
Vomiting	13 (21%)	3 (5%)	-	3 (5%)	-	-
Thrombocytopenia[2,3]	11 (17%)	-	-	4 (6%)	-	1 (2%)
Pain	10 (16%)	1 (2%)	-	4 (6%)	1 (2%)	-

[1] Safety Population, occurring in >15% in either group; Treatment-emergent AEs, regardless of treatment attribution
[2] Uncomplicated events
[3] Managed for most subjects with dose modifications, with only 1 case leading to study discontinuation.

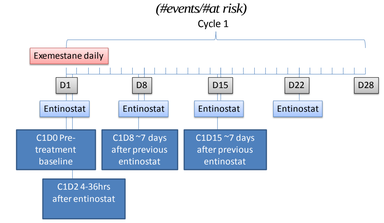
Eight SAEs occurred in each treatment group; no trends or imbalances seen. Discontinuations due to adverse events included 7 in the EE arm and 1 in the EP arm. No significant trends seen. Two subjects in the EE arm discontinued due to nausea and vomiting. No significant cardiac events were reported.

Pharmacodynamic Analysis - Acetylation: PFS



EE HA-	7/14	3/7	2/3	0/1	0/1	0/1	0/1	0/1	1/1	
EE HA+	1/13	1/12	2/11	2/8	3/5	0/2	0/0	0/0	0/0	

(#events/#at risk)



Protein lysine acetylation was measured in circulating B cells (shown), T cells and monocytes by multi-parameter flow cytometry from samples taken at pre-treatment, D1, D8, and D15 of cycle 1 from a subset of patients (n=49) treated with EE or EP. Percent change was calculated and related to PFS outcome data. Hyperacetylation (HA+) is defined as a % change increase above the calculated median % change.

Summary

This randomized, placebo controlled Phase 2 study of entinostat + exemestane:

- **Met the primary endpoint of improving PFS (EE 4.3 months vs EP 2.3 months)**
- **Showed an improvement in OS (EE 26.9 months vs EP 19.8 months), an exploratory endpoint with 23 months of follow-up**
- **Clinical benefit was seen across both NSAI resistant and NSAI sensitive subsets**
- **For the first time, an association was seen between protein lysine acetylation and improved clinical outcomes**
- **The combination was well tolerated and entinostat's toxicity profile was consistent with previous experience**

This combination warrants further investigation. Phase 3 study plans are underway.