

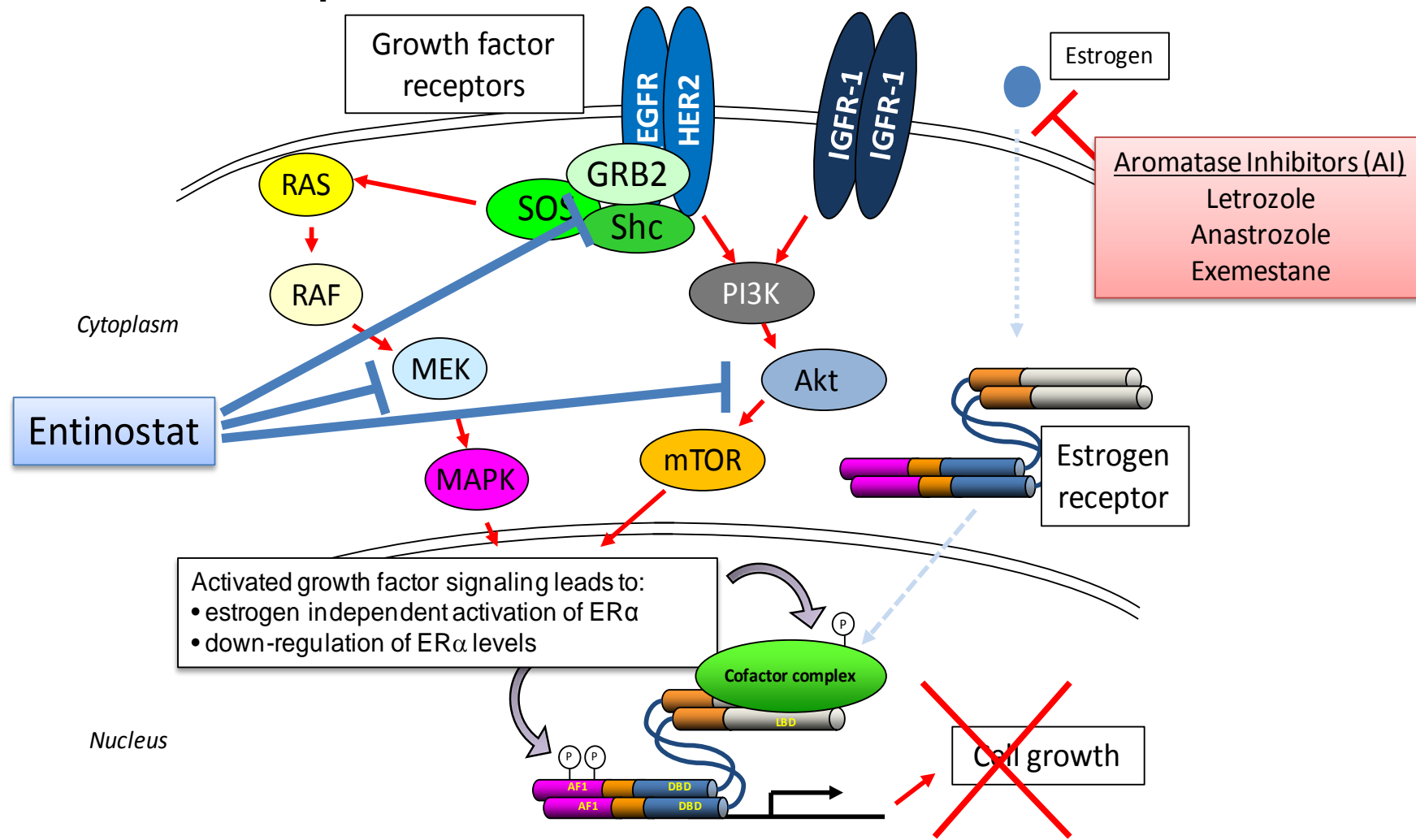
Entinostat, a novel histone deacetylase inhibitor, added to exemestane improves PFS in advanced breast cancer in a randomized phase 2, double-blind study (ENCORE 301); with updated overall survival data

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Entinostat Mechanism of Action

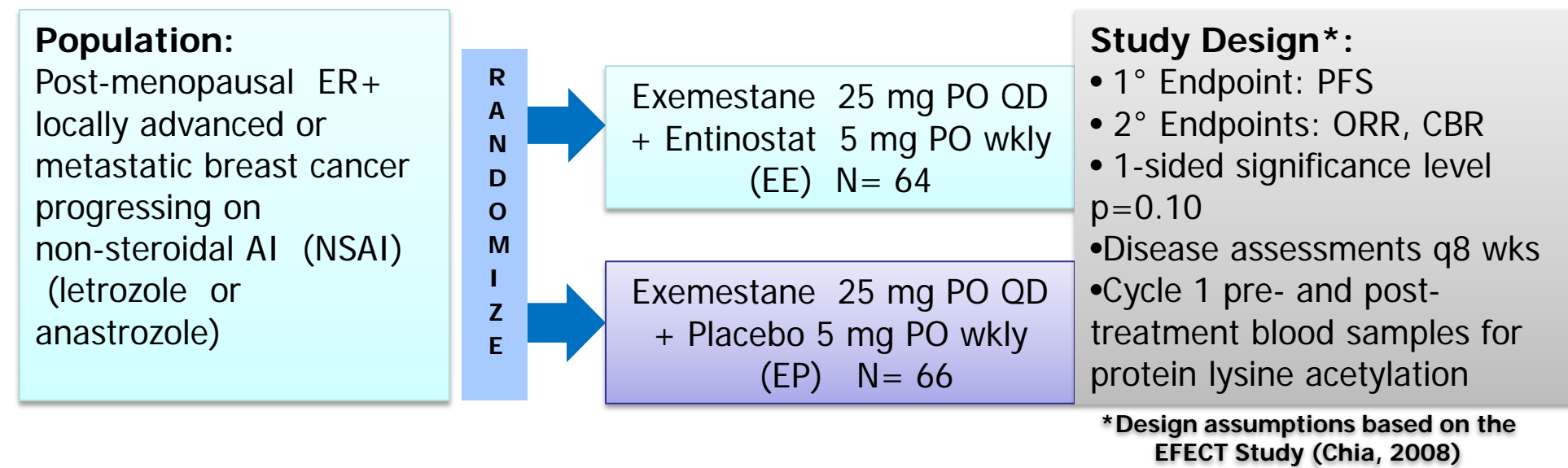
Overcoming resistance to AI therapy in advanced breast cancer represents an unmet need. Key events leading to AI resistance include ↓ ERα expression and ↑ growth factor signaling (ex. HER2), which result in estrogen-independent growth of breast cancer cells. Preclinical data demonstrates that entinostat,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



Entinostat – Class 1 Selective HDACi (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



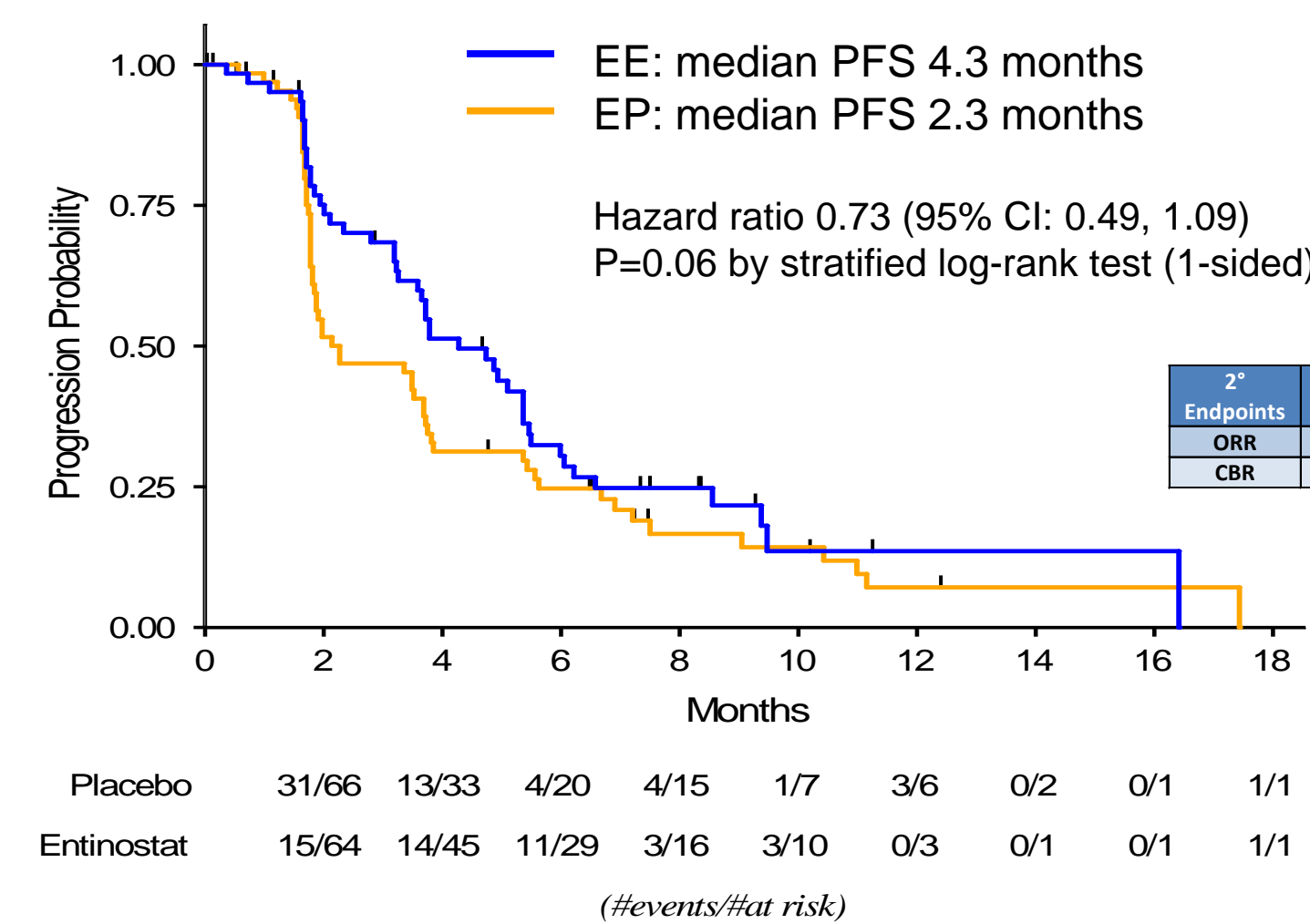
Selected Inclusion Criteria

- 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

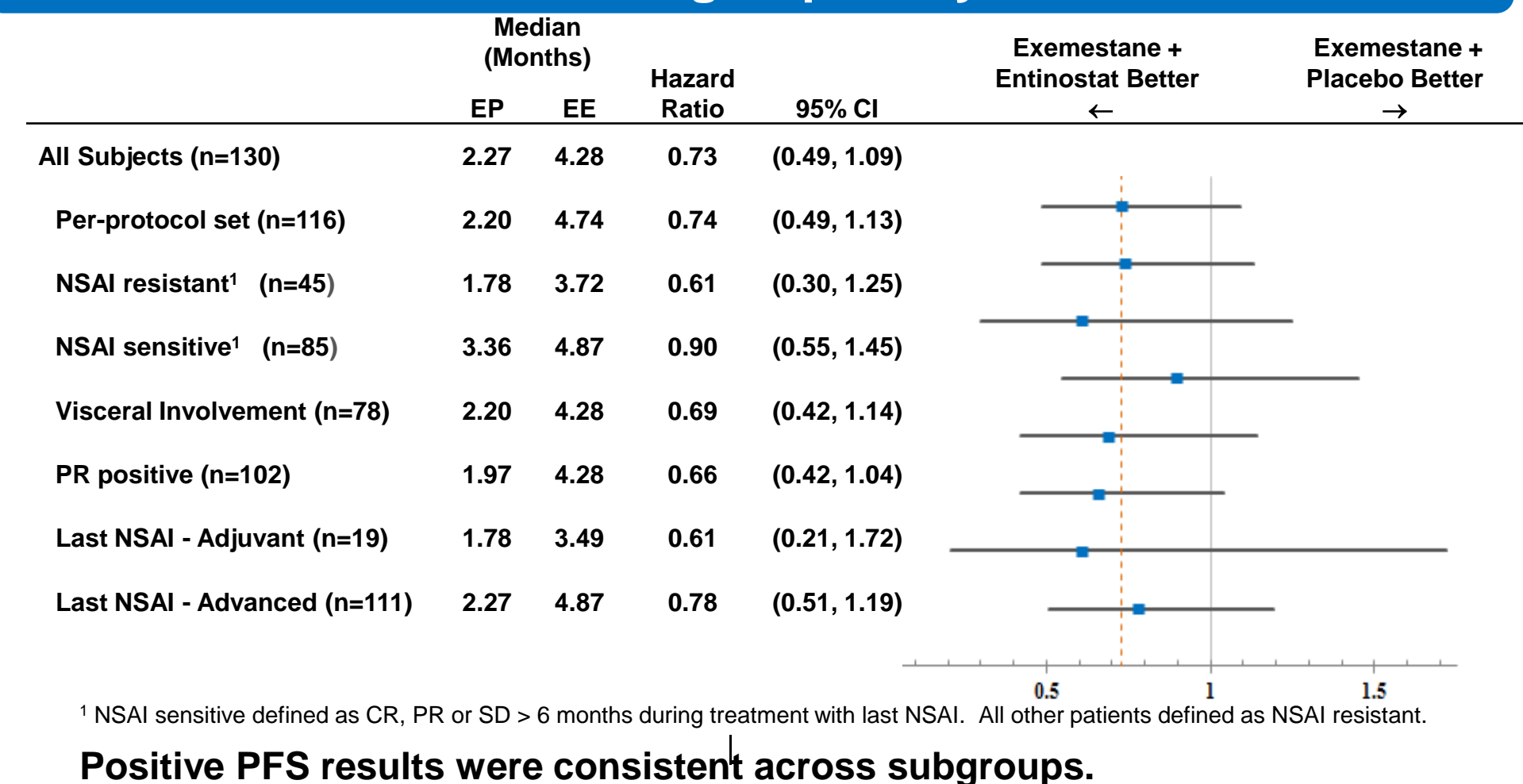
Baseline Characteristics

	Exemestane + Placebo (N=66)	Exemestane + Entinostat (N=64)
Median Age (range)	62 (37-88)	63 (37-85)
ECOG Status, n (%)	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%)

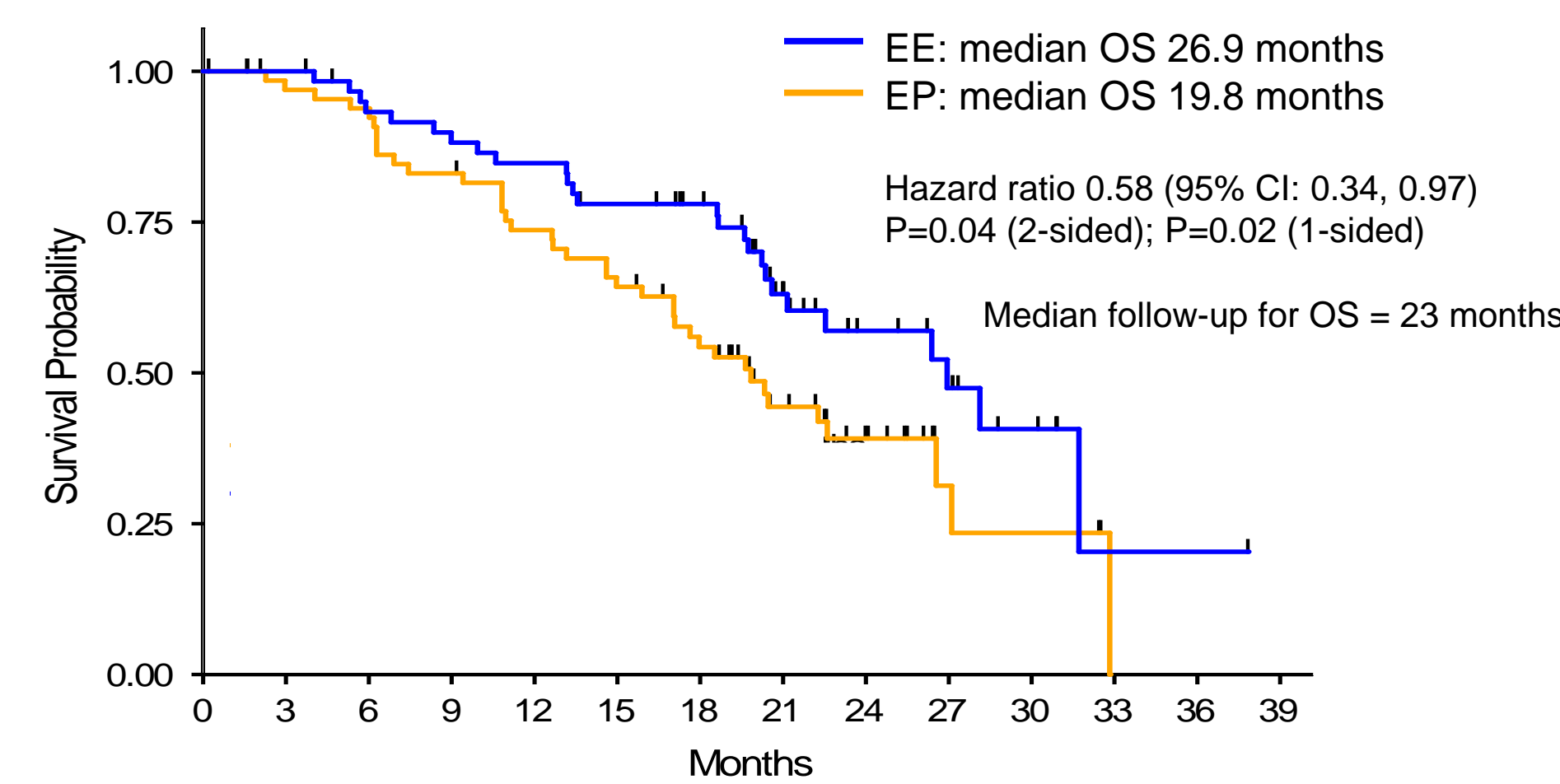
PFS (ITT) : Primary Endpoint



PFS: Sub-group Analysis



Overall Survival: Exploratory Endpoint



	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
Placebo													
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).

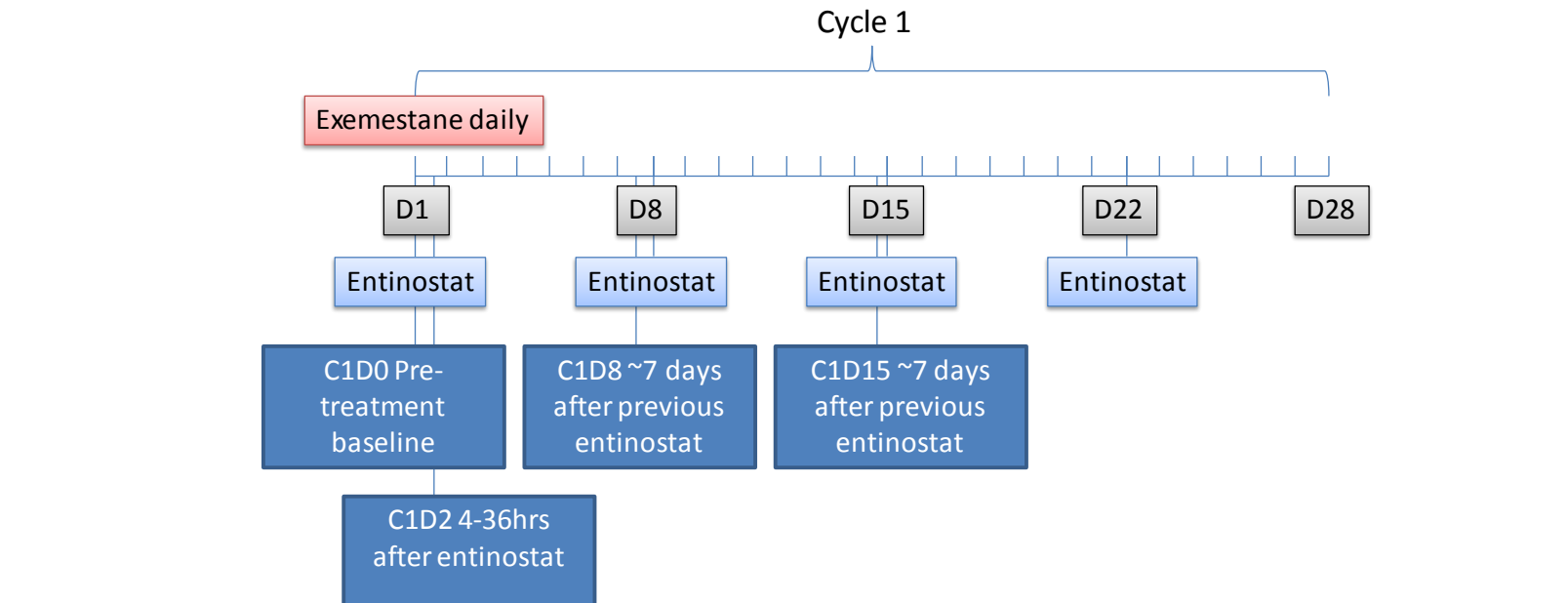
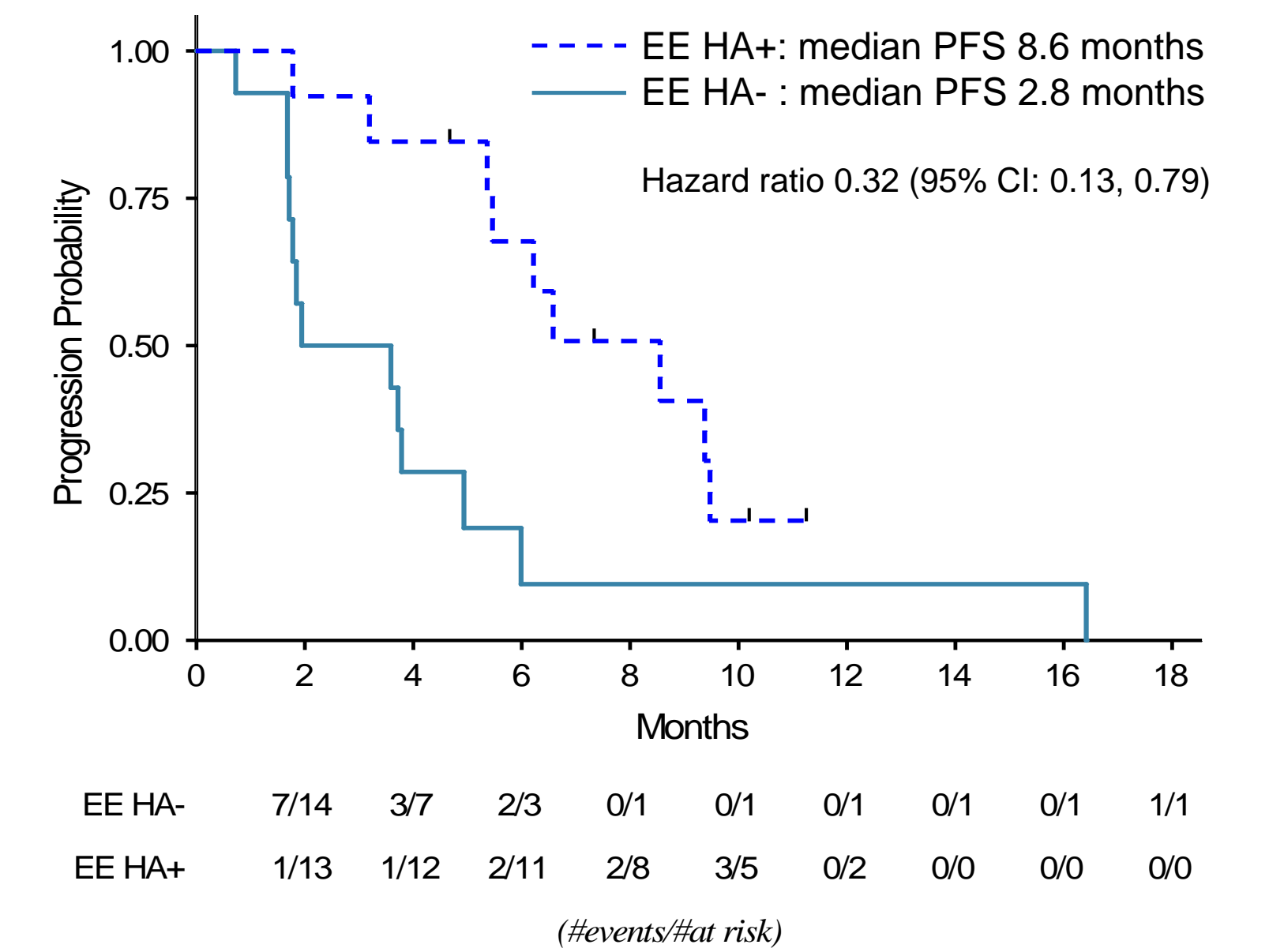
Adverse Events

Adverse Event ¹	Exemestane + Entinostat (N=63)			Exemestane + Placebo (N=66)		
	Any Grade (G) n (%)	G3 n (%)	G4 n (%)	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



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.