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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Overviewing resistance to AI therapy in advanced breast cancer represents an unmet need. Key events leading to AI resistance include: EFS expression and 1 growth factor signaling (ex. HER2), which result in estrogen-independent growth of breast cancer cells. Preclinical data demonstrating that entinostat, a histone deacetylase inhibitor (HDACi), inhibits growth factor signaling pathways and normalizes EFS expression.

**Entinostat Mechanism of Action**
- **Overcoming resistance to AI therapy in advanced breast cancer** represents an unmet need.
- **Key events** leading to AI resistance include: EFS expression and 1 growth factor signaling (ex. HER2), which result in estrogen-independent growth of breast cancer cells.
- **Preclinical data** demonstrating that entinostat, a histone deacetylase inhibitor (HDACi), inhibits growth factor signaling pathways and normalizes EFS expression.

**Selected Inclusion Criteria**
- Disease progression on non-steroidal AI (NSAI) therapy – in the adjacent setting, relapse after ≥ 12 mos. of therapy.
- In the metastatic or locally advanced setting, relapse after ≥ 2 mos. of therapy.
- Evidence of metastatic disease based on radiographic imaging studies as follows: ≥ 1 measurable lesion ≥ 2 cm by conventional CT or ≥ 2 cm by spiral CT.
- Bone-only metastases with positive bone scan, confirmed with MRI, CT or PET.
- 0-1 prior chemotherapy permitted (NSAI was last administered therapy).

**Overall Characteristics**
- **Population:** Adjuvant / Metastatic Visceral Involvement
- **NSAI sensitive1** (n=85) 3.36 4.87 0.90 (0.55, 1.45)
- **NSAI resistant1** (n=45) 1.78 3.72 0.61 (0.30, 1.25)
- **PR positive (n=102)** 1.97 4.28 0.66 (0.42, 1.04)
- **PR negative (n=37)** 0.86 2.07 0.43 (0.20, 0.93)

**Baseline Characteristics**

**Entinostat – Class 1 Selective HDAC inhibitor (HDACi)**
- **Combines safety with full-dose targeted therapies.**
- **No evidence of cardiac toxicity.**
- **No cytochrome p450 interaction.**

**ENCORE 301 Study Design**
- **Study Design:**
  - **Randomized, placebo controlled Phase 2 study of entinostat + exemestane.**
  - **Consistent with previous experience.**
- **The combination was well tolerated and entinostat’s toxicity profile was consistent with previous experience.**
- **For the first time, an association was seen between protein lysine acetylation and improved clinical outcomes.**
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**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, D5, and D7 of cycle 1.**
- **From a subset of patients (n=48) treated with EE or EE HA+.**
- **Percent change was calculated and reported as PFS outcome data.**
- **Hypersensitivity (HRP) is defined as a ≥ 5% increase above the calculated median % change.”

**Endorsed Study Statements**
- **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 85% of patient data reported).**

**Summary**
- **This randomized, placebo controlled Phase 2 study of entinostat + exemestane:**
  - Met the primary endpoint of improving PFS (EE 4.3 months vs EE 2.3 months)
  - Shown in improvement in OS (19.8 months vs 19.8 months), an exploratory endpoint with 23 months of follow-up
  - **Clinical benefit was seen across both NSAI resistant and NSAI sensitive subgroups.**
  - 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.”**

**Table:**

<table>
<thead>
<tr>
<th>Endpoints</th>
<th>EE</th>
<th>EE HA+</th>
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<tbody>
<tr>
<td>PFS Months</td>
<td>4.28</td>
<td>8.55</td>
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<tr>
<td>1-sided significance level</td>
<td>0.73</td>
<td>0.79</td>
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<td>Hazard ratio</td>
<td>0.32</td>
<td>0.30</td>
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<td>95% CI</td>
<td>(0.13, 1.14)</td>
<td>(0.05, 0.76)</td>
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**Figure:**

- **Cell growth and protein lysine acetylation:**
  - **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, D5, and D7 of cycle 1.**
  - **From a subset of patients (n=48) treated with EE or EE HA+.**
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