Overcoming Endocrine Therapy Resistance
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The Problem in ER+ Tumors is Endocrine Therapy Resistance

- About 50% of hormone receptor-positive breast cancers are de novo resistant to endocrine therapy
- Almost all patients with advanced disease will develop acquired resistance to endocrine therapies
- The mechanisms of de novo and acquired resistance are likely similar, but are not completely understood

Phase III Randomized Clinical Trial of Anastrozole vs Anastrozole + Fulvestrant as First-Line Therapy for MBC. SWOG S0226: Efficacy (Intent-to-Treat)

<table>
<thead>
<tr>
<th></th>
<th>Anastrozole (n = 345)</th>
<th>Anastrozole + fulvestrant (n = 349)</th>
<th>Hazard ratio</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS</td>
<td>13.5 mos</td>
<td>15.6 mos</td>
<td>0.8</td>
<td>0.007</td>
</tr>
<tr>
<td>Median OS</td>
<td>41.3 mos</td>
<td>47.7 mos</td>
<td>0.81</td>
<td>0.049</td>
</tr>
<tr>
<td>Grade ≥3 AE</td>
<td>12.2%</td>
<td>14.6%</td>
<td>—</td>
<td>NS</td>
</tr>
<tr>
<td>No prior adjuvant tamoxifen (n = 414)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median PFS</td>
<td>12.6 mos</td>
<td>17 mos</td>
<td>0.74</td>
<td>0.0055</td>
</tr>
<tr>
<td>Median OS</td>
<td>39.7 mos</td>
<td>47.7 mos</td>
<td>0.74</td>
<td>0.0362</td>
</tr>
</tbody>
</table>

The PI3K/AKT/mTOR Pathway

- mTOR (mammalian target of rapamycin) signaling plays a key role in
  - Cell growth
  - Cell proliferation
  - Regulation of
    - Apoptosis
    - Angiogenesis
    - Lymphocytes
    - Homeostasis
    - Metabolism

The mTOR Pathway Is Active in Breast Cancer

- Genetic alterations result in activation of the PI3K/AKT/mTOR pathway in breast cancer
  - Loss of PTEN protein (~30% - 48%), PTEN mutation (<5%)\(^1-3\)
  - PIK3CA mutation (~21% - 33%)\(^4-8\)
  - ~30% - 40% of breast cancer cells exhibit AKT activation\(^9,10\)
  - Overexpression/mutation of receptor tyrosine-kinases (eg, HER-2, EGFR, FGFR) also activates the PI3K/AKT/mTOR pathway\(^11\)


Crosstalk between ER and mTOR Signaling

- mTORC1 activates ER in a ligand-independent fashion\(^11\)
- Estradiol suppresses apoptosis induced by PI3K/mTOR blockade\(^2\)
- Hyperactivation of the PI3K/mTOR pathway occurs in endocrine-resistant BC cells\(^12\)

Signature of PI3K activation predicts poor response to adjuvant endocrine therapy

Phase III Study: Temsirolimus with Letrozole in Postmenopausal Women with Locally ABC/mBC

Key endpoints
- Primary: Progression free survival (PFS) (eg, time to emergence of endocrine resistance)
- Secondary: Overall survival, Safety, prognostic and pharmacogenomics analysis

- N = 992
  - Postmenopausal
  - No prior therapy

Trial was closed on the basis of data from a planned interim analysis that demonstrated a lack of benefit for the combination

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>LET+TEM (n = 493)</th>
<th>LET alone (n = 499)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS, months (95% CI)</td>
<td>9.2 mo (7.2 - 11.1)</td>
<td>9.2 mo (7.4 - 11.1)</td>
</tr>
<tr>
<td>Objective response rate*</td>
<td>24%</td>
<td>24%</td>
</tr>
<tr>
<td>Clinical benefit†</td>
<td>40%</td>
<td>43%</td>
</tr>
<tr>
<td>Progressive disease as best response</td>
<td>14%</td>
<td>18%</td>
</tr>
</tbody>
</table>

Potential reasons for lack of benefit include high frequency of dose reductions, incorrect dose or schedule, potency of agent, patient population
**Neoadjuvant Phase II**

**Letrozole ± Everolimus**

**Primary end point:** RR at 16 weeks (palpation)

**Secondary:** RR (ultrasound), biomarkers, safety, pharmacokinetics

- 270 Postmenopausal women with ER+ early BC, measurable disease
- Biopsy at baseline, 14 days, and surgical specimen

**Results:**
- Higher RR: Palpation: 68% vs 59% (P = 0.062), ultrasound: 58% vs 47% (P = 0.035)
- Greater antiproliferative response: KI67 by 57% vs 30% (P < 0.01)

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**TAMRAD: a Randomized Phase II trial of Everolimus with Tam vs Tam alone in HR+ MBC with Prior Exposure to AIs**

- Randomized Phase II, 111 PM women with MBC
- Prior exposure to AI, prior adj tam or chemo ok

**A:** Tamoxifen, 20 mg/d (TAM)

**B:** Tamoxifen 20 mg/d + RAD001 10 mg/d (TAM + RAD)

- Stratification: Primary or secondary hormone resistance
  - Primary: Relapse during adjuvant AI, progression within 6 months of starting AI treatment in metastatic setting
  - Secondary: Late relapse (≥6 months) or prior response and subsequent progression to metastatic AI treatment
- No crossover planned
- Median follow-up 22 months, median age 63-66

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**TAMRAD (Phase II): Tamoxifen ± Everolimus in Advanced BC**

- HR = 0.54
- Log-rank P = 0.002
- TAM = 4.5 mos
- TAM + EVE = 8.6 mos

**AI = aromatase inhibitor; BC = breast cancer; ER+ = estrogen receptor-positive; EVE = everolimus; TAM = tamoxifen**
Time to Progression As a Function of Intrinsic Hormone Resistance

- Primary hormone resistance (n = 54)
  - TAM: 3.9 mo.
  - TAM + RAD: 5.4 mo.
  - HR = 0.74 (0.42–1.3)

- Secondary hormone resistance (n = 56)
  - TAM: 5.0 mo.
  - TAM + RAD: 17.4 mo.
  - HR = 0.38 (0.21–0.71)

Phase III BOLERO-2 Trial: Exemestane +/- Everolimus in Advanced BC

- **Objective:**
  - Evaluate the efficacy of everolimus + exemestane vs. placebo + exemestane in postmenopausal ER+ un-resectable locally advanced or metastatic breast cancer.

- **Design:**
  - 2:1 randomization
  - 2 arms: Everolimus + Exemestane vs. Placebo + Exemestane
  - 724 patients

- **Endpoints:**
  - Primary: PFS (local assessment)
  - Secondary: OS, ORR, QOL, safety, bone markers, PK

- **Stratification:**
  - Sensitivity to prior hormone therapy and presence of visceral metastases

**BOLERO-2: Prior Therapy**

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Everolimus + Exemestane (N=485), %</th>
<th>Placebo + Exemestane (N=239), %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity to prior hormonal therapy</td>
<td>64 vs. 64</td>
<td></td>
</tr>
<tr>
<td>Last treatment: LET/ANA</td>
<td>74 vs. 75</td>
<td></td>
</tr>
<tr>
<td>Last treatment</td>
<td>Adjvant 21 vs. 15 Metastatic 79 vs. 85</td>
<td></td>
</tr>
<tr>
<td>Prior tamoxifen</td>
<td>47 vs. 50</td>
<td></td>
</tr>
<tr>
<td>Prior fulvestrant</td>
<td>17 vs. 16</td>
<td></td>
</tr>
<tr>
<td>Prior chemotherapy for metastatic BC</td>
<td>26 vs. 26</td>
<td></td>
</tr>
<tr>
<td>Number of prior therapies: 23</td>
<td>54 vs. 53</td>
<td></td>
</tr>
</tbody>
</table>

LET: letrozole, ANA: anastrozole
Hortobagyi G. et al, SABCS 2011 (Abstract #S3-7)
BOLERO-2 (12 mo f/up): PFS Local

HR = 0.44 (95% CI: 0.36-0.53) Log rank P value: <1 x 10^-16

EVE + EXE: 7.4 months PBO + EXE: 3.2 months

Hortobagyi G. et al, SABCS 2011 (Abstract #S3-7)

BOLERO-2 (12 mo f/up): PFS in Subgroups

Subgroups (N)
- Age <65 (449)
- ≥65 (275)
- YES (610)
- NO (114)
- YES (406)
- NO (318)
- YES (523)
- All (724)

BOLERO-2 (12 mo f/up): Response & Clinical Benefit

Response Clinical Benefit

P < 0.0001

Hortobagyi G. et al, SABCS 2011 (Abstract #S3-7)
**BOLERO-2 (12 mo f/up): Overall Survival**

- As of July 8, 2011: 137 deaths
  - 17.2% in everolimus arm
  - 22.7% in placebo arm
- OS final analysis at 392 events
  - 80% power to detect 26% reduction in risk

**BOLERO-2 (12 mo f/up): Most Common Adverse Events**

<table>
<thead>
<tr>
<th></th>
<th>Everolimus + Exemestane (n = 482), %</th>
<th>Placebo + Exemestane (n = 238), %</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>All Grades</td>
<td>Grade 3</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>59</td>
<td>8</td>
</tr>
<tr>
<td>Rash</td>
<td>39</td>
<td>1</td>
</tr>
<tr>
<td>Fatigue</td>
<td>36</td>
<td>4</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>33</td>
<td>2</td>
</tr>
<tr>
<td>Appetite decreased</td>
<td>30</td>
<td>1</td>
</tr>
<tr>
<td>Nausea</td>
<td>25</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Non-infectious</td>
<td>15</td>
<td>3</td>
</tr>
<tr>
<td>Pneumonitis*</td>
<td>14</td>
<td>5</td>
</tr>
<tr>
<td>Hyperglycemia*</td>
<td></td>
<td></td>
</tr>
</tbody>
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**Signal Transduction: PI3K/Akt Pathway**

- PI3K Inhibitors
  - XL147
  - PX866
  - GDC0941
  - CAL101
  - GSK1059615
  - BKM120
  - SF1126
- Akt Inhibitors
  - MK2207
  - SR13668
  - GSK560693
  - GSK21110183
  - Perifosine

- mTOR Inhibitors
  - Sirolimus
  - Temsirolimus
  - Everolimus
  - Ridaforolimus
  - Deforolimus
  - OSI-027

- PI3K + mTOR Inhibitors
  - XL765
  - PI103
  - BEZ235
  - BGT226

SWOG adjuvant AI +/- everolimus trial in high risk ER+ disease
Prostate Ca: Reciprocal Feedback regulation of PI3K and AR

Following benefit then progression on AI + mTOR inhibitor, ER blockade, PI3K blockade, or both?
Carver et al, Cancer Cell 2011

ERα and IGF Signaling

- ERα function is enhanced by IGF receptor activation
- In primary breast cancer, ERα and IGF1R are frequently co-expressed

Science-Driven Rationale for combined mTOR and IGFR1 Targeted Therapy

Feedback activation of AKT following mTOR inhibition by rapalog. Tumor sample of a patient on treatment with everolimus.
Evidence of anti-tumor activity in breast cancer

<table>
<thead>
<tr>
<th>Breast Cancer Subpopulation</th>
<th>N</th>
<th>FOQ-PET PR (EDITC)</th>
<th>PFS &gt; 6 months</th>
<th>Tumor Marker</th>
<th>RECIST PR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triple Negative</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>ER+</td>
<td>18</td>
<td>2</td>
<td>4</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>ER+ High proliferation</td>
<td>11</td>
<td>2</td>
<td>4</td>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td>ER+ Low proliferation</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>At breast cancer</td>
<td>23</td>
<td>5</td>
<td>21.7</td>
<td>17.3</td>
<td>8</td>
</tr>
</tbody>
</table>

- Overall, 10 of 23 (43%) breast cancer patients showed objective evidence of anti-tumor activity
  - 6 of 11 (54%) patients with ER+ high proliferation breast tumors
  - 0 of 5 patients with ER+ low proliferation breast tumors

Di Cesaro, et al ASCO 2010, abs #3008
**Lack of Benefit for Tam in ER+ Breast Cancer in Tumors with ↑ VEGFR2 (IHC)**


**CALGB 40503: First-line Endocrine Rx +/- Bevacizumab: Closed to Accrual**

Endocrine Therapy: Tamoxifen or Aromatase Inhibitor (letrozole)
Double-blind, placebo-controlled
Primary Endpoint: Progression-free Survival
Circulating tumor and endothelial cells measured during treatment
PI: Dickler

**Summary**

- Activation of PI3K pathway common in ER+ breast cancer
- mTOR inhibition with tamoxifen or AI of benefit in AI-pretreated pts – not in primary resistant disease??
- Does mTOR inhibition sensitize to subsequent endocrine therapy?
- Adjuvant everolimus + AI trial high risk ER+ breast cancer planned
- Anti-VEGF and anti-IGF1R agents under evaluation