Targeting the PI3K Pathway in the Therapy of Breast Cancer

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Physician-in-Chief
Estrogen receptor (ER) is the target of endocrine treatment and is expressed in ~70% of breast cancers

- Endocrine treatment, is an effective targeted therapy for ER+ patients
- However, a significant fraction of patients develop resistance
Targeting the PI3K/AKT/mTOR Pathway

- The PI3K/Akt pathway integrates signals arising from growth factor receptors, stress signals and nutrient availability
- Members of this pathway are often deregulated in human tumors
- mTOR is a major component of the PI3K pathway and a master regulator of translation initiation of proteins critical for proliferation and angiogenesis
- Rapalogs—mTOR signalling inhibitor
  - Anti-proliferative effects
  - Inhibitor of angiogenesis
  - Enhances effects of chemotherapy and other targeted agents
Everolimus Monotherapy

NCIC CTG TRIAL I163A

Progression-Free Survival - ER+HER2– Patients
(events include all deaths unless censored for other trt)

Out of 19 patients with ER+ HER2–, 1 CR and 2 PR (ORR: 16%).
Another patient with ER+ HER2 unknown had PR

Crosstalk between ER and mTOR Signaling

- mTORC1 activates ER in a ligand-independent fashion\(^1\)
- Estradiol suppresses apoptosis induced by PI3K/mTOR blockade\(^2\)
- Hyperactivation of the PI3K/mTOR pathway is observed in endocrine-resistant breast cancer cells\(^3\)
- mTOR is a rational target to enhance the efficacy of hormonal therapy

**Phase II neoadjuvant everolimus (RAD001) breast cancer study**

- Newly diagnosed, untreated patients with ER$^+$ localized breast cancer likely to benefit from hormonal therapy

- Palpable tumor: > 2 cm diameter

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**Diagram:**

- **Screening**
- **Randomization**
- **Treatment Groups:**
  - Letrozole 2.5 mg/d
  - RAD001 10 mg/d
  - Placebo
- **Surgery**

**Tumor Biopsy Schedule:**

- Pretreatment biopsies
- Day 15 biopsies
- Surgery samples

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*Baselga et al. J Clin Oncol. 2009*
Phase II neoadjuvant everolimus (RAD001) breast cancer study – Change in Ki67

- At day 15, a large difference in Ki67 values is seen between the everolimus + letrozole and the placebo + letrozole arms, which was not seen at baseline.
TAMRAD (Phase II): Tamoxifen +/- Everolimus in Advanced BC

Endpoints:
• **Primary**: Clinical benefit rate at 6 months
• **Secondary**: Time to progression, OS, biomarkers, safety

PMW = post-menopausal women
Bourgier C., et al. ECCOESMO 2011 (Abstract #5005)
TAMRAD: Clinical Benefit Rate and Time to Progression

Clinical Benefit Rate

\[ P = 0.045 \] (exploratory analysis)

<table>
<thead>
<tr>
<th>CBR, % of Patients (95% CI)</th>
<th>TAM</th>
<th>TAM + EVE</th>
</tr>
</thead>
<tbody>
<tr>
<td>42.1% (29.1-55.9)</td>
<td></td>
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</tr>
<tr>
<td>61.1% (46.9-74.1)</td>
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</tr>
</tbody>
</table>

Time to progression

\[ HR = 0.54 \] (CI: 0.36-0.81)

\[ P = 0.0021 \] (exploratory analysis)

TTP Probability

- TAM (4.5 months)
- TAM + EVE (8.6 months)

Bourgier C, et al. ECCO/ESMO 2011 (Abstract: 5005)
BOLERO-2: Trial Design

- Stratification:
  1. Sensitivity to prior hormonal therapy
  2. Presence of visceral disease
- No cross-over

ABC: advanced breast cancer, NSAIs: non steroidal aromatase inhibitors, HER2-: human epidermal growth factor receptor 2 – negative; PFS: progression-free survival; PK: pharmacokinetics

Primary end point: Progression-Free Survival
- 26% risk reduction (hazard ratio = 0.74)
- 528 events to achieve 90% power
  - O’Brien-Fleming boundary: $P < 0.0065$
- Assessment by investigator and independent central review

Cut-off date for this analysis was July 8, 2011
- 457 (86.6% of total 528 events) local PFS and 282 central PFS events
- Median duration of follow up 12.5 months

BOLERO-2 Primary Endpoint: PFS
Local Assessment

HR = 0.43 (95% CI: 0.35–0.54)
Log rank $P$ value = $1.4 \times 10^{-15}$

EVE + EXE: 6.9 months
PBO + EXE: 2.8 months
BOLERO-2 Primary Endpoint: PFS
Central Assessment

HR = 0.36 (95% CI: 0.27–0.47)
Log rank $P$ value = $3.3 \times 10^{-15}$

EVE + EXE: 10.6 Months
PBO + EXE: 4.1 Months

BOLERO-2 (18-mo follow-up): Response and Clinical Benefit Significantly Higher on Everolimus

Everolimus + Exemestane: 51.3% (P < 0.0001)
Placebo + Exemestane: 26.4%

Response: Everolimus + Exemestane, 12.6% (P < 0.0001)
Placebo + Exemestane, 1.7%

Exemestane Efficacy in BOLERO-2
*Similar to Published Data and Consistent With Study Assumptions*

<table>
<thead>
<tr>
<th></th>
<th>Lønning¹</th>
<th>Gennantas²</th>
<th>EFECT³,⁴</th>
<th>SoFEA⁵</th>
<th>BOLERO-2⁶</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Phase</strong></td>
<td>II</td>
<td>II</td>
<td>III</td>
<td>III</td>
<td>III</td>
</tr>
<tr>
<td><strong>N</strong></td>
<td>105</td>
<td>60</td>
<td>342</td>
<td>723</td>
<td>239</td>
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<tr>
<td>≥2 prior endocrine</td>
<td>98</td>
<td>100</td>
<td>58</td>
<td>&gt;67</td>
<td>62</td>
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<tr>
<td>therapies (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>ORR (%)</strong></td>
<td>6.6</td>
<td>20</td>
<td>6.7</td>
<td>3.6</td>
<td>1.7</td>
</tr>
<tr>
<td><strong>Clinical Benefit (%)</strong></td>
<td>24.3</td>
<td>38</td>
<td>31.5</td>
<td>26.9</td>
<td>26.4</td>
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<tr>
<td><strong>PFS (median, mo)</strong></td>
<td>2.9</td>
<td>3.2</td>
<td>3.7</td>
<td>3.4</td>
<td>3.2⁷, 4.1⁸</td>
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<tr>
<td><strong>OS (median, mo)</strong></td>
<td>Not reported</td>
<td>17.4</td>
<td>23.1</td>
<td>21.6</td>
<td>Not reached</td>
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</table>

BOLERO-2 (Longer Term Data): Reduction in Tumor Volume

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

-**Everolimus + Exemestane (n = 318)**
- **Best % change from Baseline**
- **Placebo + Exemestane (n = 155)**

<table>
<thead>
<tr>
<th>Change from Baseline</th>
<th>Everolimus + Exemestane</th>
<th>Placebo + Exemestane</th>
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</thead>
<tbody>
<tr>
<td>Decrease</td>
<td>70.75% (225)</td>
<td>29.68% (46)</td>
</tr>
<tr>
<td>Zero</td>
<td>9.12% (29)</td>
<td>12.90% (20)</td>
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<tr>
<td>Increase</td>
<td>12.26% (39)</td>
<td>36.77% (57)</td>
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<tr>
<td>% change in target lesion available but contradicted by Overall lesion response = PD</td>
<td>7.86% (25)</td>
<td>20.65% (32)</td>
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</tbody>
</table>

X - Best % change from baseline > 100%.
Hortobagyi G. et al, SABCS 2011 (Abstract #S3-7)
BOLERO-2 (18-mo follow-up): PFS in Subgroups

All N = 724

<table>
<thead>
<tr>
<th>Age group</th>
<th>N</th>
<th>Med PFS (months)</th>
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<tbody>
<tr>
<td>&lt; 65</td>
<td>449</td>
<td>7.82</td>
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<tr>
<td>≥ 65</td>
<td>275</td>
<td>3.19</td>
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<table>
<thead>
<tr>
<th>Region</th>
<th>N</th>
<th>Med PFS (months)</th>
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<tbody>
<tr>
<td>Asia</td>
<td>137</td>
<td>8.48</td>
</tr>
<tr>
<td>Europe</td>
<td>275</td>
<td>7.16</td>
</tr>
<tr>
<td>North America</td>
<td>274</td>
<td>8.31</td>
</tr>
<tr>
<td>Other</td>
<td>38</td>
<td>4.53</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Japanese patients</th>
<th>N</th>
<th>Med PFS (months)</th>
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<tbody>
<tr>
<td>Japan</td>
<td>106</td>
<td>8.54</td>
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<tr>
<td>Non-Japan</td>
<td>618</td>
<td>7.16</td>
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<table>
<thead>
<tr>
<th>Race</th>
<th>N</th>
<th>Med PFS (months)</th>
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<tr>
<td>Asian</td>
<td>143</td>
<td>8.48</td>
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<tr>
<td>Caucasian</td>
<td>547</td>
<td>7.36</td>
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<td>Other</td>
<td>34</td>
<td>6.93</td>
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<table>
<thead>
<tr>
<th>Baseline ECOG performance status</th>
<th>N</th>
<th>Med PFS (months)</th>
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<tr>
<td>0</td>
<td>435</td>
<td>8.25</td>
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<td>1, 2</td>
<td>274</td>
<td>6.93</td>
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<table>
<thead>
<tr>
<th>PgR status</th>
<th>N</th>
<th>Med PFS (months)</th>
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<tbody>
<tr>
<td>Negative</td>
<td>184</td>
<td>6.93</td>
</tr>
<tr>
<td>Positive</td>
<td>523</td>
<td>8.08</td>
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Hazard Ratio

Favors EVE + EXE

Favors PBO + EXE
BOLERO-2 (18-mo follow-up): PFS in Subgroups

### All

- **N** = 724

#### Number of organs involved

1. 1 organ: 219
2. 2 organs: 232
3. ≥ 3 organs: 271

#### Presence of visceral metastasis

- No: 318
- Yes: 406

#### Bone only lesions at baseline

- No: 573
- Yes: 151

#### Number of prior therapies

1. 1 therapy: 118
2. 2 therapies: 217
3. ≥ 3 therapies: 389

#### Prior chemotherapy

- No: 231
- Yes: 493

#### Prior use of hormonal therapy other than NSAIs

- No: 326
- Yes: 398

<table>
<thead>
<tr>
<th></th>
<th>EVE + EXE</th>
<th>PBO + EXE</th>
<th>HR</th>
<th>Median PFS, months</th>
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<tbody>
<tr>
<td>All</td>
<td>0.45</td>
<td>3.19</td>
<td></td>
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<tr>
<td>Number of organs</td>
<td>0.40</td>
<td>4.37</td>
<td></td>
<td></td>
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<tr>
<td>involved</td>
<td>0.52</td>
<td>3.45</td>
<td></td>
<td></td>
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<tr>
<td>≥ 3</td>
<td>0.41</td>
<td>2.56</td>
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<td></td>
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<tr>
<td>Presence of visceral</td>
<td>0.41</td>
<td>4.21</td>
<td></td>
<td></td>
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<tr>
<td>metastasis</td>
<td>0.47</td>
<td>2.76</td>
<td></td>
<td></td>
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<tr>
<td>Bone only lesions</td>
<td>0.48</td>
<td>2.83</td>
<td></td>
<td></td>
</tr>
<tr>
<td>at baseline</td>
<td>0.45</td>
<td>5.29</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 3 therapies</td>
<td>0.41</td>
<td>2.96</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior chemotherapy</td>
<td>0.53</td>
<td>3.45</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 3 therapies</td>
<td>0.41</td>
<td>3.19</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior use of hormonal</td>
<td>0.52</td>
<td>4.11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>therapy other than</td>
<td>0.39</td>
<td>2.76</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NSAIs</td>
<td></td>
<td></td>
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</tbody>
</table>

Favors EVE + EXE  

Favors PBO + EXE
BOLERO-2 (18-mo follow-up):

*PFS Benefit Comparable in Patients With and Without Visceral Metastases*

**Visceral Metastases**

**Median PFS**

- **EVE + EXE**: 6.83 months
- **PBO + EXE**: 2.76 months

*HR = 0.47 (95% CI = 0.37, 0.60)*

**No Visceral Metastases**

**Median PFS**

- **EVE + EXE**: 9.86 months
- **PBO + EXE**: 4.21 months

*HR = 0.41 (95% CI = 0.31, 0.55)*

**Abbreviations**: CI, confidence interval; EVE, everolimus; EXE, exemestane; HR, hazard ratio; PBO, placebo; PFS, progression-free survival.

Campone M, et al. 2012 ESMO Congress; Poster 324PD.
BOLERO-2 (18-mo follow-up):
*PFS in Patients With Bone-Only Metastases*

Patients with bone-only metastases

**Progression-Free Survival, %**

- **EVE + EXE**: 12.88 months
- **PBO + EXE**: 5.29 months

**HR = 0.33 (95% CI = 0.21, 0.53)**

Abbreviations: CI, confidence interval; EVE, everolimus; EXE, exemestane; HR, hazard ratio; PBO, placebo; PFS, progression-free survival.

Campone M, et al. 2012 ESMO Congress; Poster 324PD.
## Overall Survival

*Trend in Favor of Everolimus*

<table>
<thead>
<tr>
<th></th>
<th>PFS Interim&lt;sup&gt;1&lt;/sup&gt; (7-mo follow-up)</th>
<th>PFS Update (12-mo follow-up)</th>
<th>Second OS Interim</th>
<th>PFS Final (18-mo update)</th>
</tr>
</thead>
<tbody>
<tr>
<td>OS events (eve vs plb %)</td>
<td>83 (10.6 vs 13.0%)</td>
<td>137 (17.3 vs 22.7%)</td>
<td>182 (23.1 vs 29.3%)</td>
<td>200 (25.4 vs 32.2%)</td>
</tr>
<tr>
<td>Δ OS events</td>
<td>2.4%</td>
<td>5.4%</td>
<td>6.2%</td>
<td>6.8%</td>
</tr>
</tbody>
</table>

<sup>1</sup> Also OS 1<sup>st</sup> interim analysis

Note: 3<sup>rd</sup> OS interim analysis (275 deaths): available September 2012.
BOLERO-2 (18-mo follow-up):  
*Most Common Adverse Events*

<table>
<thead>
<tr>
<th></th>
<th>Everolimus + Exemestane (n = 482), %</th>
<th>Placebo + Exemestane (n = 238), %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 1</td>
<td>Grade 2</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>34</td>
<td>25</td>
</tr>
<tr>
<td>Rash</td>
<td>32</td>
<td>11</td>
</tr>
<tr>
<td>Fatigue</td>
<td>18</td>
<td>14</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>26</td>
<td>6</td>
</tr>
<tr>
<td>Appetite decreased</td>
<td>19</td>
<td>10</td>
</tr>
<tr>
<td>Nausea</td>
<td>21</td>
<td>9</td>
</tr>
<tr>
<td>Non-infectious Pneumonitis</td>
<td>9</td>
<td>7</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>5</td>
<td>6</td>
</tr>
</tbody>
</table>
Stomatitis: Clinical Presentation

- Mouth ulcers (canker sores) may occur in the oral cavity, inner surface of the lips, or tongue
- Ovoid, superficial, well-demarcated ulcerations with a grayish-white pseudo-membrane
- Distinct from chemotherapy-induced stomatitis
- Not contagious
- Ulcers typically develop acutely in the 4 weeks of therapy
- Severity usually peaks within the first 2 weeks of therapy
- All grades: 59%, grade 3: 8%, no grade 4

## Stomatitis

<table>
<thead>
<tr>
<th>Severity</th>
<th>Dose Adjustment and Management Recommendations</th>
</tr>
</thead>
</table>
| Grade 1: Minimal symptoms, normal diet                                  | • No dose adjustment required.  
• Manage with non-alcoholic or salt water (0.9%) mouth wash several times a day.                        |
| Grade 2: Symptomatic but can eat and swallow modified diet              | • Temporary dose interruption until recovery to grade ≤1.  
• Re-initiate everolimus at the same dose.  
• If stomatitis recurs at grade 2, interrupt dose until recovery to grade ≤1. Re-initiate everolimus at a lower dose.  
• Manage with topical analgesic mouth treatments (e.g. benzocaine, butyl aminobenzoate, tetracaine hydrochloride, menthol or phenol) with or without topical corticosteroids (i.e. triamcinolone oral paste). |
| Grade 3: Symptomatic and unable to adequately aliment or hydrate orally | • Temporary dose interruption until recovery to grade ≤1.  
• Re-initiate everolimus at a lower dose.  
• Manage with topical analgesic mouth treatments (i.e. benzocaine, butyl aminobenzoate, tetracaine hydrochloride, menthol or phenol) with or without topical corticosteroids (i.e. triamcinolone oral paste). |
| Grade 4: Symptoms associated with life-threatening consequences          | • Discontinue everolimus and treat with appropriate medical therapy.                                          |
Expand Into Adjuvant Therapy

SWOG—NSABP trial, USA, Start Q4 2012

Primary endpoint: invasive disease-free survival

Secondary endpoints:
OS, distant recurrence-free survival, safety, biomarkers

N = 3400
Pre & post-menopausal women
HR+ HER2–
>4 positive nodes or
0-3 nodes + RS >25
Prior standard chemotherapy

Stratification by risk level:
• Node negative (all RS >25)
• 1-3 positive lymph nodes (all RS >25)
• ≥4 positive lymph nodes and RS ≤25
• ≥4 positive lymph nodes and RS >25
• Neoadjuvant chemotherapy

Everolimus 10 mg/day for 1 year + endocrine therapy for 5 years

Placebo for 1 year + endocrine therapy for 5 years
HER2+: Everolimus + Weekly Trastuzumab and Paclitaxel

**Phase I**

Patients With Measurable Disease

Lesions cat. V V V V V NV V V NV V V V V V V NV NV NV V NV

% Change From Baseline

-100 -80 -60 -40 -20 0

0.0 0.0 -3.1 -3.4 -8.3 -11.1 -11.1 -18.5 -21.0 -25.5 -31.4 -32.7 -33.8 -35.1 -35.8 -37.9 -39.3 -49.4 -60.0 -60.3 -78.4

Patient resistant to trastuzumab and taxanes
Patient resistant to trastuzumab but NOT to taxanes

1) Patient not resistant to trastuzumab or taxanes.

Abbreviations: V, visceral; NV, non-visceral; SD, stable disease; PD, progressive disease; PR, partial response; CR, complete response.

Targeting mTOR in Breast Cancer

Summary

- Addition of everolimus to exemestane prolongs PFS in patients with ER+ HER2- breast cancer refractory to initial non-steroidal aromatase inhibitors. mTOR plus anti-estrogens in combination will be practice changing.

- Everolimus plus Tamoxifen has also similar improvement in clinical benefit.

- mTOR inhibitors in combination with anti-HER2 therapies result in robust anti-tumor activity in single arm studies. Randomized studies are underway.

- Toxicity is an issue. Mucositis occurs early in the course of therapy and should be monitored and mTOR inhibitors withheld and dose-reduced as recommended.

- To be studied in the Adjuvant Setting.

- Study of biomarkers of response currently underway.