TAMRAD: a GINECO randomized phase II trial of everolimus in combination with tamoxifen versus tamoxifen alone in patients with hormone receptor–positive, HER2-negative metastatic breast cancer with prior exposure to aromatase inhibitors

Thomas BACHELOT, Céline BOURGIER, Claire CROPET, Jean-Paul GUASTALLA, Jean-Marc FERRERO, Claire LEGER-FALANDRY, Patrick SOULIE, Jean-Christophe EYMARD, Marc DEBLED, Dominique SPAETH, Eric LEGOUFFE, Thierry DELOZIER, Claude EL KOURI and Jean CHIDIAC
Disclosures

- Novartis provided the study drug (everolimus) and research funding for this investigator-sponsored trial
- Thomas Bachelot is a member of an advisory board for Novartis
Strong Evidence Links Hormone Resistance to Cross-Talk Between Signal Transduction Pathways and ER Signalling

Everolimus (RAD001)

- Oral and potent inhibitor of mammalian target of rapamycin (mTOR)
  - Approved for renal cell carcinoma (multiple countries) and SEGA (US)
- Promising activity on \textit{in vitro} model of hormone resistance\textsuperscript{1}
- Promising activity in early clinical trials\textsuperscript{2,3}
- Significantly increases neoadjuvant letrozole antitumor activity\textsuperscript{4}

\textsuperscript{SEGA= subependymal giant cell astrocytoma}
ER and mTOR Inhibition

• Previously conducted randomized trials of first-line hormone therapy plus mTOR inhibition in metastatic breast cancer (mBC) have been disappointing\(^1\)

• Selection of aromatase inhibitor (AI)-pretreated mBC patients may enrich the study population with patients whose tumors are driven by activation of the PI3K/AKT/mTOR pathway

1. Chow et al. SABCS meeting 2006, Abstract 6091
TAMRAD PROTOCOL

Randomized Phase II
Metastatic patients with prior exposure to AI

• 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

A : Tamoxifen, 20 mg/d (TAM)

B : Tamoxifen 20 mg/d + RAD001 10 mg/d (TAM + RAD)
Key Inclusion Criteria

• Menopausal condition
• Hormone receptor positive and HER2 negative
• With or without measurable disease
• Treated with AI in adjuvant and/or metastatic setting
  – May have received tamoxifen in the adjuvant setting
  – May have received chemotherapy in the adjuvant/metastatic setting
Endpoints

- **Primary**: Clinical benefit rate (CBR) at 6 months \((CR + PR + SD \text{ at 6 months})\)
- **Secondary**:
  - Time to progression
  - Overall survival
  - Objective response rate
  - Toxicity
  - Translational studies

CR=complete response; PR=partial response; SD=stable disease
Statistical Considerations

- *Simon* two-stage *Minimax* design, with alpha = 5% and power = 90%
- Considering a gain in CBR of 20% as the minimum needed to warrant further study for the combination
- Assuming a CBR of 50% in the TAM arm, 53 evaluable patients were needed in both arms

Study Status

• 111 patients included from March 2008 to May 2009
  – First analysis: April 2010
  – Final analysis: October 2010
  – Translational research is ongoing
    • PI3K/mTOR pathway markers

<table>
<thead>
<tr>
<th>Follow-up</th>
<th>TAM n = 57</th>
<th>TAM + RAD n = 54</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median, months (range)</td>
<td>22.6 (0.9-29.7)</td>
<td>22.3 (2.6-29.3)</td>
</tr>
</tbody>
</table>
## Patient Characteristics

|                              | TAM  
n = 57 | TAM + RAD 
n = 54 |
<table>
<thead>
<tr>
<th></th>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Median age, years (range)</td>
<td>66 (42-86)</td>
<td>62.5 (41-81)</td>
</tr>
<tr>
<td>Median duration of metastatic disease (months)</td>
<td>14.4 (0-102)</td>
<td>13.2 (1.2-94.8)</td>
</tr>
<tr>
<td>Disease stage, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bone</td>
<td>45 (78.9)</td>
<td>41 (75.9)</td>
</tr>
<tr>
<td>Bone only</td>
<td>13 (22.8)</td>
<td>16 (29.6)</td>
</tr>
<tr>
<td>Visceral</td>
<td>30 (52.6)</td>
<td>31 (57.4)</td>
</tr>
<tr>
<td>3 or more</td>
<td>16 (28.1)</td>
<td>14 (25.9)</td>
</tr>
<tr>
<td>Previous anti-aromatase treatment, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjuvant only</td>
<td>19 (33.3)</td>
<td>15 (27.8)</td>
</tr>
<tr>
<td>Metastatic only</td>
<td>33 (57.9)</td>
<td>34 (63.0)</td>
</tr>
<tr>
<td>Adjuvant + metastatic</td>
<td>5 (8.8)</td>
<td>5 (9.2)</td>
</tr>
<tr>
<td>Previous adjuvant TAM treatment, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjuvant</td>
<td>32 (56.1)</td>
<td>25 (46.3)</td>
</tr>
<tr>
<td>Metastatic</td>
<td>15 (26.3)</td>
<td>13 (24.1)</td>
</tr>
<tr>
<td>Primary hormone resistance, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>28 (49.1)</td>
<td>26 (49.1)</td>
</tr>
<tr>
<td>Secondary hormone resistance, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>29 (50.9)</td>
<td>27 (50.9)</td>
</tr>
</tbody>
</table>
Primary Endpoint: Clinical Benefit Rate

P = 0.045 (exploratory analysis)

CBR, % of Patients

42.1% (29.1-55.9)

61.1% (46.9-74.1)

TAM

TAM + RAD
Time to Progression

Hazard Ratio (HR) = 0.53; 95% CI (0.35-0.81)
Exploratory log-rank: $P = 0.0026$

TAM: 4.5 mo.
TAM + RAD: 8.6 mo.

Patients at risk
TAM + RAD: n = 54 45 39 34 28 26 25 19 16 12 9 7 1 1 1 0
TAM : n = 57 44 30 24 22 16 13 11 7 6 2 1 0 0 0 0
Overall Survival (as of October 2010)

HR = 0.32; 95% CI (0.15-0.68)
Exploratory log-rank: $P = 0.0019$

Patients at risk

<table>
<thead>
<tr>
<th></th>
<th>TAM + RAD: n =</th>
<th>TAM : n =</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>54</td>
<td>57</td>
</tr>
<tr>
<td>3</td>
<td>53</td>
<td>55</td>
</tr>
<tr>
<td>6</td>
<td>51</td>
<td>53</td>
</tr>
<tr>
<td>9</td>
<td>49</td>
<td>50</td>
</tr>
<tr>
<td>12</td>
<td>49</td>
<td>44</td>
</tr>
<tr>
<td>15</td>
<td>45</td>
<td>38</td>
</tr>
<tr>
<td>18</td>
<td>38</td>
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<tr>
<td>30</td>
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<td>4</td>
<td>0</td>
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<tr>
<td>36</td>
<td>0</td>
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## Adverse Events

<table>
<thead>
<tr>
<th>Grade</th>
<th>TAM n = 57</th>
<th>TAM + RAD n = 54</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Any</td>
<td>3/4</td>
</tr>
</tbody>
</table>

### Most Common Adverse Events (AE)

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>TAM Any (n)</th>
<th>TAM 3/4 (n)</th>
<th>TAM + RAD Any (n)</th>
<th>TAM + RAD 3/4 (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>30 (52.6)</td>
<td>6 (10.5)</td>
<td>40 (74.1)</td>
<td>3 (5.6)</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>4 (7.0)</td>
<td>0</td>
<td>28 (51.9)</td>
<td>6 (11.1)</td>
</tr>
<tr>
<td>Rash</td>
<td>3 (5.3)</td>
<td>1 (1.8)</td>
<td>21 (38.9)</td>
<td>3 (5.6)</td>
</tr>
<tr>
<td>Anorexia</td>
<td>10 (17.5)</td>
<td>2 (3.5)</td>
<td>24 (44.4)</td>
<td>5 (9.3)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>5 (8.8)</td>
<td>0</td>
<td>21 (38.9)</td>
<td>1 (1.9)</td>
</tr>
<tr>
<td>Nausea</td>
<td>19 (33.3)</td>
<td>0</td>
<td>18 (33.3)</td>
<td>2 (3.7)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>7 (12.3)</td>
<td>2 (3.5)</td>
<td>9 (16.7)</td>
<td>0</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>2 (3.5)</td>
<td>2 (3.5)</td>
<td>9 (16.7)</td>
<td>1 (1.9)</td>
</tr>
<tr>
<td>Thromboembolic</td>
<td>4 (7.0)</td>
<td>4 (7.0)</td>
<td>7 (13.0)</td>
<td>3 (5.6)</td>
</tr>
<tr>
<td>Pain</td>
<td>48 (84.2)</td>
<td>11 (19.3)</td>
<td>42 (77.8)</td>
<td>5 (9.3)</td>
</tr>
</tbody>
</table>

### Dose reduction due to AE

- TAM: 0 (0)
- TAM + RAD: 15 (28)

### Treatment discontinuation due to AE

- TAM: 4 (7.0)
- TAM + RAD: 3 (5.6)
## Clinical Benefit in Selected Subgroup

<table>
<thead>
<tr>
<th></th>
<th>TAM</th>
<th>TAM + RAD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 57</td>
<td>n = 54</td>
</tr>
<tr>
<td><strong>ALL</strong></td>
<td>24/57 (42.1)</td>
<td>33/54 (61.1)</td>
</tr>
<tr>
<td>Visceral metastases</td>
<td>12/30 (40.0)</td>
<td>19/31 (61.3)</td>
</tr>
<tr>
<td>No visceral metastases</td>
<td>12/27 (44.4)</td>
<td>14/23 (60.9)</td>
</tr>
<tr>
<td>Previous adjuvant tamoxifen</td>
<td>9/23 (39.1)</td>
<td>11/17 (64.7)</td>
</tr>
<tr>
<td>No previous adjuvant tamoxifen</td>
<td>15/34 (44.1)</td>
<td>22/37 (59.5)</td>
</tr>
<tr>
<td>Previous metastatic chemotherapy</td>
<td>4/15 (26.7)</td>
<td>6/13 (46.2)</td>
</tr>
<tr>
<td>No previous metastatic chemotherapy</td>
<td>20/42 (47.6)</td>
<td>27/41 (65.9)</td>
</tr>
<tr>
<td>Primary hormone resistance</td>
<td>11/28 (39.3)</td>
<td>12/26 (46.2)</td>
</tr>
<tr>
<td>Secondary hormone resistance</td>
<td>13/29 (44.8)</td>
<td>21/27 (77.8)</td>
</tr>
</tbody>
</table>
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.
  - \( HR = 0.38 (0.21-0.71) \)
Conclusions

• In this randomized phase II trial of an mTOR inhibitor and anti-estrogen combination in AI-pretreated patients:

  – Everolimus combined with tamoxifen allowed for a 61% CBR, as compared with 42% for tamoxifen alone

  – Time to progression and survival increased with the addition of everolimus to tamoxifen compared with tamoxifen alone
    • TTP: HR = 0.53; 95% CI, 0.35-0.81
    • Survival: HR = 0.32; 95% CI, 0.15-0.68

  – Toxicity was manageable and consistent with previous studies

  – Clinical benefit may favor patients with secondary hormone resistance
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