Targeting mTOR pathway in ER+/Her2- breast cancers

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Gustave Roussy
Outline

• mTOR pathway

• Clinical development of rapalogs in breast cancer

• Moving beyond rapalogs
mTOR pathway

Adapted from Zoncu, Nat Rev Mol Cell Biol, 2011
Effects of TORC1 activation

- LKB1
- AKT
- PTEN
- PI3K
- mTOR
- TSC2/TSC1
- 4E-BP1
- S6K1
- eIF-4E
- mRNA translation
- Protein synthesis
- autophagy
- Glucose metabolism
- Lipid synthesis
- ER phosphorylation
- ERα
- Ser^{167}
- AMPK
- E
- P
- Ras-raf-MEK
Mechanisms of TORC1 activation in cancer cells

Gene-dependent and independent activation
PI3K dependent or independent activation
Drugs targeting PI3K / mTOR pathway

- **PI3K inhibitors**
- **PTEN**
- **AKT inhibitors**
- **AMPK**
- **LKB1**
- **Metformine**
- **Rapalogs**: Everolimus, Temsirolimus, ridaforolimus
- **Tyrosine kinase inhibitors**
- **TORC1**
- **TORC2**
- **mTORC1/2 inhibitors**

- **Ras-raf-MEK**
- **TSC2/TSC1**
- **PRAS40**
Outline

• mTOR pathway

• Clinical development of rapalogs in ER+/Her2-breast cancer

• Moving beyond rapalogs

• New concepts
Activation of AKT/mTOR pathway mediate resistance to endocrine therapy

Tamoxifen Efficacy

Does mTOR inhibitors reverse resistance to endocrine therapy?

deGraffenried, Clin Cancer Res, 2004
NCIC Randomized Phase II: Everolimus Monotherapy

Patients who had ≤1 prior chemotherapy for advanced/recurrent disease
N = 49

10 mg/day  n = 18
10 mg/day  n = 15
70 mg weekly  n = 16
70 mg weekly

4 OR (ER+)
15 SD
30 patients

The drug has single agent antitumor activity

### Overview of randomized trials testing everolimus in patients with Her2-/ER+ BC

<table>
<thead>
<tr>
<th>Treatment</th>
<th>setting</th>
<th>Pre treatment</th>
<th>phase</th>
<th>n</th>
<th>Effect on primary endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>Letrozole +/- everolimus</td>
<td>neoadjuvant</td>
<td>Endocrine naïve</td>
<td>Phase II randomized</td>
<td>270</td>
<td>Clinical response: 68% vs 59% (p=0.06, prespecified significance &lt;0.1)</td>
</tr>
<tr>
<td>(Baselga, J Clin Oncol, 2009)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tamoxifen +/- everolimus</td>
<td>metastatic</td>
<td>Resistant to AI</td>
<td>Phase II randomized</td>
<td>111</td>
<td>Clinical benefit rate: 61% (47-74) vs 42% (29-56)</td>
</tr>
<tr>
<td>(Bachelot, J Clin Oncol, 2012)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exemestane +/- everolimus</td>
<td>metastatic</td>
<td>Resistant to NSAI</td>
<td>Phase III registration</td>
<td>724</td>
<td>Primary endpoint: PFS</td>
</tr>
<tr>
<td>(BOLERO II) (Baselga, NEJM, 2012)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>HR: 0.43 (0.35-0.54) Median PFS: 6.9 vs 2.8 p&lt;0.001</td>
</tr>
</tbody>
</table>

Three randomized trials report CONSISTENT data about everolimus efficacy in ER+ BC Everolimus significantly improves PFS in patients with ER+/Her2- mBC resistant to NSAI The level of improvement is clinically meaningful (FDA/EMA approvals, NCCN guidelines)
Phase II Study: Neoadjuvant Letrozole ± Everolimus

<table>
<thead>
<tr>
<th>Assessment</th>
<th>Response Rates (CR + PR)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>Everolimus + letrozole</strong></td>
<td><strong>Placebo + letrozole</strong></td>
<td><em>P</em></td>
</tr>
<tr>
<td></td>
<td><em>n = 138</em></td>
<td><em>n = 132</em></td>
<td></td>
</tr>
<tr>
<td>Palpation</td>
<td>68.1%</td>
<td>59.1%</td>
<td>.062*</td>
</tr>
<tr>
<td>Ultrasound</td>
<td>58.0%</td>
<td>47.0%</td>
<td>.035*</td>
</tr>
<tr>
<td>Ki67 response</td>
<td>57.0%</td>
<td>30.0%</td>
<td>&lt; .01</td>
</tr>
</tbody>
</table>

*1-sided level of significance of 10%

BOLERO-2: Primary Endpoint, PFS (Local Assessment)

HR = 0.45 (95% CI = 0.38, 0.54)  
Log-rank P value: < .0001

Everolimus + Exemestane: 7.8 mo  
(E/N = 310/485)

Placebo + Exemestane: 3.2 mo  
(E/N = 200/239)

Number of patients still at risk

<table>
<thead>
<tr>
<th>Time, wk</th>
<th>Everolimus + Exemestane</th>
<th>Placebo + Exemestane</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>485</td>
<td>239</td>
</tr>
<tr>
<td>6</td>
<td>436</td>
<td>190</td>
</tr>
<tr>
<td>12</td>
<td>366</td>
<td>132</td>
</tr>
<tr>
<td>18</td>
<td>304</td>
<td>96</td>
</tr>
<tr>
<td>24</td>
<td>257</td>
<td>67</td>
</tr>
<tr>
<td>30</td>
<td>221</td>
<td>50</td>
</tr>
<tr>
<td>36</td>
<td>185</td>
<td>39</td>
</tr>
<tr>
<td>42</td>
<td>158</td>
<td>30</td>
</tr>
<tr>
<td>48</td>
<td>124</td>
<td>21</td>
</tr>
<tr>
<td>54</td>
<td>91</td>
<td>15</td>
</tr>
<tr>
<td>60</td>
<td>66</td>
<td>10</td>
</tr>
<tr>
<td>66</td>
<td>50</td>
<td>8</td>
</tr>
<tr>
<td>72</td>
<td>35</td>
<td>5</td>
</tr>
<tr>
<td>78</td>
<td>24</td>
<td>3</td>
</tr>
<tr>
<td>84</td>
<td>22</td>
<td>1</td>
</tr>
<tr>
<td>90</td>
<td>13</td>
<td>1</td>
</tr>
<tr>
<td>96</td>
<td>10</td>
<td>1</td>
</tr>
<tr>
<td>102</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>108</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>114</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>120</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; E/N, patients with events/total patients; HR, hazard ratio; PFS, progression-free survival.

BOLERO-2: Overall Response Rate and Clinical Benefit Rate (Local Assessment)

Abbreviations: CBR, clinical benefit rate; ORR, overall response rate.

**BOLERO-2 (39-mo): Final OS Analysis**

- **HR = 0.89 (95% CI, 0.73-1.10)**
  Log-rank $P = .14$

  Kaplan-Meier medians
  - EVE+EXE: 30.98 months
  - PBO+EXE: 26.55 months

  **Censoring times**
  - EVE+EXE (n/N = 267/485)
  - PBO+EXE (n/N = 143/239)

  **No. at risk**
  - PBO+EXE: 239, 232, 220, 211, 201, 194, 182, 170, 162, 153, 145, 130, 120, 113, 109, 102, 98, 77, 56, 41, 28, 18, 8, 5, 1, 0

- At 39 months’ median follow-up, 410 deaths had occurred (data cutoff date: 03 October 2013)
  - 55% deaths (n = 267) in the EVE+EXE arm vs 60% deaths (n = 143) in the PBO+EXE arm

One-sided $P$ value was obtained from the log-rank test stratified by sensitivity to prior hormonal therapy and presence of visceral metastasis from IXRS®.

Abbreviations: CI, confidence interval; EVE, everolimus; EXE, exemestane; HR, hazard ratio; IXRS®, Interactive Voice and Web Response System; PBO, placebo.
## Toxicities

<table>
<thead>
<tr>
<th></th>
<th>Everolimus + Exemestane (n = 482), %</th>
<th>Placebo + Exemestane (n = 238), %</th>
</tr>
</thead>
<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>29</td>
<td>&lt; 1</td>
</tr>
<tr>
<td><strong>Noninfectious</strong></td>
<td><strong>15</strong></td>
<td><strong>3</strong></td>
</tr>
<tr>
<td>pneumonitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>14</td>
<td>5</td>
</tr>
<tr>
<td>Infections and</td>
<td>50</td>
<td>4</td>
</tr>
<tr>
<td>infestations(^\text{a})</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Stomatitis: Clinical Presentation

- mTOR inhibitor-associated stomatitis\(^1,^2\)
  - Distinct from chemotherapy-induced stomatitis
  - Aphthous-like ulcers characterized by discrete, ovoid, superficial, well-demarcated ulcerations with a grayish-white pseudomembrane
  - Ulcers typically develop acutely in the first cycle of therapy
  - Severity usually peaks within the first 2 weeks of therapy

Abbreviation: mTOR, mammalian target of rapamycin.

Noninfectious Pneumonitis: Clinical Presentation

- Noninfectious pneumonitis should be considered in patients presenting with nonspecific respiratory symptoms and in whom infectious, neoplastic, and other etiologies have been excluded\(^1\)

- Noninfectious, nonmalignant infiltration of the lungs\(^2,3\)
  - Class effect associated with rapamycin derivatives\(^2,3\)

- Presents with no symptoms or with nonspecific signs and symptoms\(^2\)
  - Cough, shortness of breath/dyspnea, nonspecific radiologic changes, pleural effusion, or hypoxia

- Symptomatic cases are usually mild to moderate in severity and reversible; however, a small proportion may be severe\(^3,4\)

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Noninfectious Pneumonitis: Radiographic Appearance

- Obtain baseline radiographic image
- Radiographic appearance\(^1\)
  - Common appearances can include diffuse “ground-glass” or patchy opacification

During Everolimus Treatment\(^2\)

After AE Management\(^2\)

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Randomized trials testing everolimus in women with ER+ high risk early breast cancer

**SWOG-NSABP**
Phase 3 study; N = 3400
Pre and postmenopausal HR+ HER2− breast cancer
0-3N+ AND RS>25
>3 N+

- Everolimus 10 mg/d for 1 yr+
- Endocrine therapy for 5 yrs
- Placebo for 1 yr + endocrine therapy for 5 yrs

Primary endpoint: Invasive DFS

**UNICANCER**
Phase 3 study; N = 2010
Pre and postmenopausal HER2− breast cancer
(≥ 4+N or N+ post-neoadjuvant tt)

- Everolimus 10 mg/d for 2 yrs + Al or Tamoxifen
- Placebo for 2 yrs + Al or Tamoxifen

Primary endpoint: DFS at 2 yr

Relapse-free after 2-3 years of adjuvant endocrine therapy
Outline

• mTOR pathway

• Clinical development of rapalogs in ER+/Her2-breast cancer

• Moving beyond rapalogs:
  • Biomarkers
  • Resistance
Biomarkers: Four questions for further drug development

High sensitivity  Everolimus sensitivity  resistance
Biomarkers: Four questions for further drug development

Are mTOR « activated » tumors more sensitive to rapalogs?

1. Biomarker to define « average » sensitivity
   Define target population for further dvpt

How to measure mTOR activation?
Efficacy of everolimus according to level of mTOR activation (p4EBP1)

Efficacy of everolimus according to p4EBP1 in TAMRAD trial

<table>
<thead>
<tr>
<th>Biomarker subgroups</th>
<th>n</th>
<th>HR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low p4EBP1 expression</td>
<td>19</td>
<td>0.88 (0.34-2.30)</td>
</tr>
<tr>
<td>High p4EBP1 expression</td>
<td>27</td>
<td>0.37 (0.15-0.90)</td>
</tr>
</tbody>
</table>

Generate the hypothesis that mTOR activation is associated with sensitivity to everolimus

Consistent data in BOLERO 3 (Andre, Lancet Oncol, 2014)
Biomarkers: Four questions for further drug development

2. High sensitivity: Outlier responders

Are mTOR-addicted tumors highly sensitive to rapalogs?
Do these oncogenic mutations define a « highly sensitive » subset of patients ?
How to capture them ?
3. Is the everolimus efficacy driven by LKB1-AMPK or PI3K-AKT pathway?
Predictive value of PIK3CA mutations (BOLERO 2)

PIK3CA mutations is NOT predictive for the efficacy of everolimus
Consistent data in BOLERO 3 (Andre, Lancet Oncol, 2014)
Predictive value of coexisting oncogenic mutation?

Predictive value of K-Ras mutations?
(Alain, Cancer Res 2012)

Predictive value of 4EBP1/eIF4E expression?
(Alain, Cancer Res 2012)
## Multiple genomic alterations and resistance to everolimus

### Table

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>N</th>
<th>Events (%)</th>
<th>Median PFS (d)</th>
<th>HR* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EVE: WT</td>
<td>43</td>
<td>19 (44)</td>
<td>356</td>
<td>0.24 (0.11–0.54)</td>
</tr>
<tr>
<td>PBO: WT</td>
<td>18</td>
<td>14 (78)</td>
<td>203</td>
<td></td>
</tr>
<tr>
<td>EVE: Single</td>
<td>76</td>
<td>48 (63)</td>
<td>214</td>
<td>0.26 (0.16–0.43)</td>
</tr>
<tr>
<td>PBO: Single</td>
<td>35</td>
<td>31 (89)</td>
<td>77</td>
<td></td>
</tr>
<tr>
<td>EVE: Multiple</td>
<td>38</td>
<td>27 (71)</td>
<td>138</td>
<td>0.78 (0.39–1.54)</td>
</tr>
<tr>
<td>PBO: Multiple</td>
<td>17</td>
<td>14 (82)</td>
<td>128</td>
<td></td>
</tr>
</tbody>
</table>

Hortobagyi, ASCO, 2013
Biomarkers: Hypotheses

sensitivity  neutral  resistance

mTOR activation  PIK3CA mutations  Drivers outside mTOR pathway

Genomic instability

mTOR addiction

Very high sensitivity

sensitivity  resistance
Outline

• mTOR pathway

• Clinical development of rapalogs in ER+/Her2-breast cancer

• Moving beyond rapalogs:
  • Biomarkers
  • Resistance
Activating feedback loops
Activating feedback loops through IGF1R-PI3K and mTORC2 leading to AKT (O’Reilly, Cancer Res, 2006) and MAPK activation (Carracedo, JCI, 2008)
Early phase trials testing combination to overcome feedback loop

<table>
<thead>
<tr>
<th>drugs</th>
<th>phase</th>
<th>n</th>
<th>Efficacy data</th>
</tr>
</thead>
<tbody>
<tr>
<td>mTOR inh + IGF1R inh</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ridaforolimus + Dalotuzumab</td>
<td>I</td>
<td>23</td>
<td>13% OR (activity in 6/11 luminal B)</td>
</tr>
<tr>
<td><em>Di Cosimo, ASCO, 2010</em></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cixutumumab / temsirolimus</td>
<td>I</td>
<td>42</td>
<td>Breast cancers: 4 SD, 1&gt;5 months</td>
</tr>
<tr>
<td><em>Naing, Clin cancer Res, 2012</em></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mTOR + MEK inh</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PI3K + mTOR inhibitors</td>
<td></td>
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</tbody>
</table>

How to optimally develop these combinations? Is the feedback loop mediated by single pathway?
Partial bioactivity on 4EBP1

• How to overcome it?

Low impact on mRNA translation protein synthesis

Partial modulation of 4EBP1 (Choo, PNAS, 2008)

Rapalogs
Solution: mTORC1/C2 inhibitors

Inhibition of mTORC2-mediated activating feedback loop

ATP competitive inh: Strong inhibition on TORC1/C2

Inhibition of mRNA translation
Re-programming mRNA expression
(Hsieh, Nature, 2012)

Rapalogs

mTORC1

mTORC2

mTORC1/C2 inhibitors
Are mTORC1/2 inhibitors optimally bioactive on p4EBP1? Do they improve outcome over rapalogs?

Vilar, Mol Cancer Ther, 2011
Development according to «mTOR status»:
Future perspective (according to the speaker)

1. mTOR-activated tumors
- Optimize rapalogs
- Combination with IGF1R, PI3K inh, CDK4 inh

2. mTOR-addicted tumors
- ATP-competitive inhibitors
- Targeted therapies?

3. Magnitude of everolimus efficacy in LKB1-AMPK or PI3K-AKT activated pathway?

Intrinsic resistance
- Coexisting oncogenic mutation AND mTOR activation:
  - Combination therapy

1st line therapy
- K-Ras mutations AND mTOR activation:
  - Combination therapy

- 4EBP1/ eIF4E expression and mTOR activation
  - Combination with eIF4E inh