Hormone receptor positive metastatic breast cancer: Treatment sequence and endocrine resistance

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(Direktor: Univ.-Prof. Dr. Klaus Friese)
Endocrine therapy in mBC | Prof. Harbeck

ENDOCRINE THERAPY IS THE OLDEST TARGETED THERAPY IN BREAST CANCER

Estrogen receptor

DNA

Proliferation

Angiogenesis

Target tissues:
- Breast tissue
- Peripheral tissue
- Tumor tissue
Endocrine therapy in advanced breast cancer

- Standards
- Endocrine + targeted therapy: Overcoming endocrine resistance
- Patient management
- Open clinical questions
THERAPY STRATEGY IN METASTATIC BREAST CANCER

 Symptoms / Metastasis location*

 Slow disease progression

 Steroid hormone receptor status (ER, PR)

 ER / PR positive

 Endocrine therapy

 Exemestane + Everolimus

 Rapid therapy response required

 ER and PR negative

 HER2 status

 Chemotherapy (+ targeted)
  HER2 positive: + trastuzumab + pertuzumab / T-DM1 / lapatinib
  HER2 negative: ± bevacizumab

 Depending on clinical situation (response, disease progression)

 Bone metastases: + bisphosphonates / denosumab

 ER and PR negative

 HER2-Status

 Hormone receptor status

 modified after Bossung & Harbeck, Curr Opin Obs&Gyn '10

 Exemestane + Everolimus

 modified after Bossung & Harbeck, Curr Opin Obs&Gyn '10

 Exemestane + Everolimus
A biopsy (preferably providing histology) of a metastatic lesion should be performed, if easily accessible, to confirm diagnosis particularly when metastasis is diagnosed for the first time (LoE: 2 C).

Total number of votes: 28
1. YES: 96% (27)
2. NO: 4% (1)
3. ABSTAIN: 0%
Current ESMO Guidelines for the use of first-line endocrine therapy in postmenopausal ER+ ABC

ET, endocrine therapy; CT, chemotherapy; HER2, HER2-directed therapy; T, trastuzumab.
Points of transition from endocrine to chemotherapy

ET<sub>1</sub> → ET<sub>2</sub> → ET<sub>3</sub> → CT

No response

Endocrine therapy (ET) is the preferred option for hormone receptor positive disease, even in the presence of visceral disease, unless there is concern or proof of endocrine resistance, or there is disease needing a fast response (LoE: 1 A).

Total number of votes: 29
1. YES: 100% (29)
2. NO: 0%
3. ABSTAIN: 0%
Metastatic breast cancer – SABCS 2014
Visceral metastases from hormone receptor positive BC as sensitive to endocrine therapy as non visceral metastasis - P1-13-02

Robertson JFR et al. SABCS 2014 – P1-13-02
Real-world patterns of use of chemotherapy vs endocrine therapy \((n=355,\ 5\ European\ countries)\)

**Cohort**

- **A**
  - 62% of patients
  - \((n=218)\)

- **B**
  - 7% of patients
  - \((n=26)\)

- **C**
  - 31% of patients
  - \((n=111)\)

**First-line therapies**

- **ET ± TT**
  - \((n=218)\)
  - 39 weeks

- **ET ± TT**
  - \((n=26)\)
  - 46 weeks

- **CT ± HT ± TT**
  - \((n=111)\)
  - 28 weeks

**Second-line therapies**

- **CT ± HT ± TT**
  - \((n=218)\)
  - 24 weeks

- **ET ± TT**
  - \((n=26)\)
  - 31 weeks

- **Any therapy**
  - \((n=111)\)
  - 34 weeks

**Third-line therapies**

- Any (or none) \((n=69\ Tx,\ 149\ none)\)
- **CT ± HT ± TT**
  - \((n=26)\)
  - 23 weeks

- **CT ± HT ± TT**
  - \((n=26)\)
  - 28 weeks

- **Any (or none)**
  - \((n=38\ Tx,\ 73\ none)\)
  - 25 weeks

Majority (69%) of patients received HT in the first-line setting

Physician-reported reasons of choice for endocrine chemotherapy

“Absence of life-threatening metastasis” and “slow disease progression” are the major drivers of choice for first-line endocrine therapy.

Endocrine therapy* in advanced breast cancer

- **Adjuvant TAM** 5 years
- **Adjuvant AI** 5 years
- **Sequence** Tam 2-3y. \(\rightarrow\) AI
- **Extended adjuvant** TAM 5y. \(\rightarrow\) AI

**End of adjuvant therapy**

- **AI**
  - FUL
  - TAM
- **TAM**
  - FUL
  - AI
- **FUL**
  - TAM
  - AI
- **FUL**
  - TAM
  - AI

*premenopausal: + GnRH*
Metastatic breast cancer – SABCS 2014
First – Studie Robertson JFR et al. S06-04
**Metastatic breast cancer – SABCS 2014**

First – Studie Robertson JFR et al. S06-04

**FIRST: overall survival analysis**

- **Fulvestrant 500 mg**
  - n=102
  - Median OS (months): 54.1
  - 63 (51.8%) dead

- **Anastrozole 1 mg**
  - n=103
  - Median OS (months): 48.4
  - 74 (71.8%) dead

**HR=0.70**

95% CI (0.50, 0.98)

*p=0.041*
Metastatic breast cancer – SABCS 2014
First – Studie Robertson JFR et al. S06-04

Comparison of FIRST with Phase III studies of first-line endocrine monotherapy for ABC

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<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>Tam</td>
<td>7.0</td>
<td>6.0</td>
<td>5.8</td>
<td>Ana F500</td>
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<tr>
<td>Ana</td>
<td>8.5</td>
<td>9.4</td>
<td>9.9</td>
<td>13.1 23.4</td>
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<td>Median TTP (months)</td>
<td>40.1</td>
<td>30</td>
<td>43.3</td>
<td>48.4 54.1</td>
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<td>9.4</td>
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<td>37.2</td>
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<td>6.0</td>
<td>9.4</td>
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<td>Exe</td>
<td>9.9</td>
<td>9.9</td>
<td>9.9</td>
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<tr>
<td>Median OS (months)</td>
<td>39.2</td>
<td>30</td>
<td>43.3</td>
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</tbody>
</table>

Endocrine therapy in mBC | Prof. Harbeck
Main challenges in the treatment of hormone receptor positive breast cancer

Non-response and side effects

- About 50% of patients with ER+ breast cancer do not respond to the initial endocrine therapy\(^1,2,5\)
- The majority of patients who responded initially to an endocrine therapy develop resistance\(^2,5\)
- Patients may develop side effects / intolerance to medical therapies (Chemo- and endocrine therapy)\(^3\)

Development of resistance\(^3,4\)

- Often caused by activation of an alternative signaling pathway\(^3,4\)

Timeline of Approval of Agents for Hormone Receptor Positive Advanced Breast Cancer: No New Agents Approved in the Past Decade

- **Tamoxifen** (1977)
- **Anastrozole** (1995)
- **Letrozole** (1997)
- **Toremifene** (1997)
- **Fulvestrant** (2002)
- **Exemestane** (1999)
- **Everolimus** (2012)

Drugs@FDA. http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm Accessed May 24, 2012
mTOR-Inhibition in breast cancer

- Growth factor
- Estrogen

Plasma-membrane

Letrozole

Crosstalks

PTEN

PI3-K

Akt

mTOR

everolimus

EGFR / HER2

SOS

RAS

RAF

MEK

MAPK

PTEN

ER

mTOR

Proliferation ↓ Angiogenesis ↓ Metabolism ↓
BOLERO-2 (Ph 3): Everolimus in Advanced BC

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

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

N = 724
- Postmenopausal ER+
- Unresectable locally advanced or metastatic BC
- Recurrence or progression after letrozole or anastrozole

**EBE 10 mg daily + EXE 25 mg daily (n = 485)**

**Placebo + EXE 25 mg daily (n = 239)**

Abbreviations: BC, breast cancer; ER+, estrogen receptor-positive; EVE, everolimus; EXE, exemestane; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; Ph, phase; PK, pharmacokinetics; QOL, quality of life.

PFS Based on Central Review at 18-mo Follow-up in BOLERO-2 Confirms Earlier Reports and Local Assessment

HR = 0.38 (95% CI: 0.31-0.48)
Log-rank P value: < .0001

Kaplan-Meier medians
EVE 10 mg + EXE: 11.0 months
PBO + EXE: 4.1 months

Number of patients still at risk

<table>
<thead>
<tr>
<th></th>
<th>EVE 10 mg + EXE</th>
<th>PBO + EXE</th>
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<tr>
<td>108</td>
<td>485</td>
<td>239</td>
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<tr>
<td>102</td>
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<td>96</td>
<td>359</td>
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</table>

Abbreviations: CI, confidence interval; EVE, everolimus; EXE, exemestane; HR, hazard ratio; PBO, placebo; PFS, progression-free survival.
BOLERO-2 (18-mo f/up): Response Rates & Clinical Benefit Were Significantly Higher in the Everolimus Arm

Response: Everolimus + Exemestane 12.6% vs. Placebo + Exemestane 1.7%  
Clinical Benefit: Everolimus + Exemestane 51.3% vs. Placebo + Exemestane 26.4%  

BOLERO-2 (18-mo, Local Assessment): PFS Benefit Was Consistent in All Subgroups

Abbreviations: EVE, everolimus; EXE, exemestane; HR, hazard ratio; NSAI, nonsteroidal aromatase inhibitor; PBO, placebo; PFS, progression-free survival.

BOLERO-2: PFS in Patients Receiving First-Line Therapy for Metastatic BC

Local Assessment

Central Assessment

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

Metastatic breast cancer – SABCS 2014
BRAWO-NIS II°-Interims analysis – P5-19-12

Breast Cancer Treatment with Everolimus and Exemestane for ER+ Women - Results of the 2nd interim analysis of the non-interventional trial BRAWO

Christian Jackisch,1 Eva-Maria Grischke,2 Andreas Schneeweiss,3 Thomas Decke,4 Christoph Uleer,4 Frank Förster,5 Oliver Tomé,7 Pauline Wimberger,8 Christian Kurthacher,9 Bettina Mueller,10 Nadia Harbeck,11 Christoph Mündenke,12 Sherko Kümmel,13 Mathias Muth,14 Julia Kreuzeder,14 Wilhelm Bloch,15 Hans Tesch,16 Diana Lueftner,17 Florian Schütz,3 Peter Fasching18

Study Status
- 1,348 patients had entered study documentation by 19 August 2014
- This second interim analysis includes data of the first 500 patients (enrolled at 191 sites)
- The 500th patient had been included 12 months before the data cutoff on 11 July 2014

<table>
<thead>
<tr>
<th>Discontinuation of Therapy With EVE+EXE</th>
<th>Patients, n (%)</th>
<th>(N = 500)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progression</td>
<td>204 (40.8)</td>
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<tr>
<td>Adverse event</td>
<td>113 (22.6)</td>
<td></td>
</tr>
<tr>
<td>Poor compliance</td>
<td>4 (0.8)</td>
<td></td>
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<tr>
<td>Patient's wish</td>
<td>69 (13.8)</td>
<td></td>
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<tr>
<td>Missing (including ongoing patients)</td>
<td>110 (22.0)</td>
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</tbody>
</table>

*The data capture form asks for reason for discontinuation of documentation and reason for discontinuation of therapy as 2 separate questions. Therefore, various combinations of reasons are possible.*

Jackisch C. et al. SABCS 2014 – P5-19-12
Metastatic breast cancer – SABCS 2014
BRAWO-NIS II°- Interim analysis – P5-19-12

PFS for EVE+EXE by line of therapy (n = 497)

<table>
<thead>
<tr>
<th>Line of Therapy</th>
<th>Median PFS (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st line (n = 131)</td>
<td>10.1 (6.7-17.6)</td>
</tr>
<tr>
<td>2nd line (n = 144)</td>
<td>10.3 (8.2-12.2)</td>
</tr>
<tr>
<td>3rd line (n = 93)</td>
<td>7.2 (4.3-9.1)</td>
</tr>
<tr>
<td>4th line (n = 63)</td>
<td>6.1 (3.9-8.7)</td>
</tr>
<tr>
<td>5th line and later (n = 66)</td>
<td>4.2 (3.4-6.5)</td>
</tr>
</tbody>
</table>

PFS by prior therapy with Exemestane (n = 497)

<table>
<thead>
<tr>
<th>Prior Therapy</th>
<th>Median PFS (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No (n = 404)</td>
<td>8.0 (6.3, 9.3)</td>
</tr>
<tr>
<td>Yes (n = 93)</td>
<td>8.0 (5.3, 11.6)</td>
</tr>
</tbody>
</table>

Vertical lines represent censored data.

Jackisch C. et al. SABCS 2014 – P5-19-12
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

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.
**BOLERO-2 (39-mo): Longer Median Time From Randomization to First Chemotherapy or Death (Everolimus Plus Exemestane Arm)**

<table>
<thead>
<tr>
<th>Time From Randomization to First Chemotherapy or Death</th>
<th>Everolimus + Exemestane (n = 485)</th>
<th>Placebo + Exemestane (n = 239)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of events, n (%)</td>
<td>366 (75.5)</td>
<td>192 (80.3)</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>257 (53.0)</td>
<td>150 (62.8)</td>
</tr>
<tr>
<td>Death</td>
<td>109 (22.5)</td>
<td>42 (17.6)</td>
</tr>
<tr>
<td>Number censored, n (%)</td>
<td>119 (24.5)</td>
<td>47 (19.7)</td>
</tr>
<tr>
<td>Discontinued from study</td>
<td>105 (21.6)</td>
<td>45 (18.8)</td>
</tr>
<tr>
<td>Ongoing at data cutoff&lt;sup&gt;a&lt;/sup&gt;</td>
<td>14 (2.9)</td>
<td>2 (0.8)</td>
</tr>
</tbody>
</table>

**Time from randomization to first chemotherapy or death, months**

<table>
<thead>
<tr>
<th>Time from randomization to first chemotherapy or death, months</th>
<th>Everolimus + Exemestane</th>
<th>Placebo + Exemestane</th>
</tr>
</thead>
<tbody>
<tr>
<td>25th percentile (95% CI)</td>
<td>5.68 (5.03-6.57)</td>
<td>3.06 (2.53-3.48)</td>
</tr>
<tr>
<td>Median (95% CI)</td>
<td>11.86 (10.45-13.08)</td>
<td>5.98 (5.09-7.39)</td>
</tr>
<tr>
<td>75th percentile (95% CI)</td>
<td>25.10 (22.97-28.06)</td>
<td>14.16 (10.74-18.50)</td>
</tr>
</tbody>
</table>

<sup>a</sup> Ongoing without any chemotherapy by the cutoff date.

Piccart et al, EBCC 2014
Clinically Notable AEs Associated With mTOR Inhibition

- Stomatitis
- Noninfectious pneumonitis
- Infections
- Hyperglycemia and hyperlipidemia
- Skin rash

Abbreviations: AE, adverse event; mTOR, mammalian target of rapamycin.
## BOLERO-2 (18-mo f/up): Common Adverse Events Were Consistent With the Established Safety Profile of Everolimus

<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</td>
<td>Grade</td>
</tr>
<tr>
<td></td>
<td>All</td>
<td>1</td>
</tr>
<tr>
<td>Any AE</td>
<td>100</td>
<td>7</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>59</td>
<td>29</td>
</tr>
<tr>
<td>Rash</td>
<td>39</td>
<td>29</td>
</tr>
<tr>
<td>Fatigue</td>
<td>37</td>
<td>18</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>34</td>
<td>26</td>
</tr>
<tr>
<td>Nausea</td>
<td>31</td>
<td>21</td>
</tr>
<tr>
<td>Appetite decreased</td>
<td>31</td>
<td>19</td>
</tr>
<tr>
<td>Non-infectious pneumonitis</td>
<td>16</td>
<td>7</td>
</tr>
<tr>
<td>Hyperglycemiaa</td>
<td>14</td>
<td>4</td>
</tr>
</tbody>
</table>

* Adverse events of clinical interest.

BOLERO-2: Incidence and Distribution of Stomatitis and Related Events (Grade ≥2)

Number of Patients Still at Risk

<table>
<thead>
<tr>
<th>EVE</th>
<th>482</th>
<th>307</th>
<th>233</th>
<th>172</th>
<th>134</th>
<th>99</th>
<th>63</th>
<th>39</th>
<th>25</th>
<th>13</th>
<th>10</th>
<th>5</th>
<th>2</th>
<th>0</th>
</tr>
</thead>
<tbody>
<tr>
<td>PBO</td>
<td>238</td>
<td>168</td>
<td>115</td>
<td>70</td>
<td>47</td>
<td>33</td>
<td>20</td>
<td>11</td>
<td>7</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

Time, months

- EVE + EXE (n/N = 160/482)
- PBO + EXE (n/N = 7/238)

- Censoring Times

- No AEs (grade 0)
- Grade 1
- Grade 2
- Grade 3
- Grade 4

~88%

## mTOR Inhibitor-Related Stomatitis: Clinical Management Strategy

<table>
<thead>
<tr>
<th>Grade</th>
<th>Symptoms</th>
<th>Treatment</th>
<th>Dose Modification</th>
</tr>
</thead>
</table>
| 1 – Mild | Minimal (normal diet) | • Nonalcoholic mouthwash or 0.9% salt water  
• Avoid agents containing alcohol, hydrogen peroxide, iodine, and thyme derivatives  
• Cooling with ice, frozen pineapple chunks, or balls of frozen pineapple juice | • No change |
| 2 – Moderate | Symptomatic but can eat and follow modified diet | • Topical analgesic mouth treatments  
– Dobendan Strepsils® Dolo lozenges  
– Mouthwash with local anesthetic, +/- steroids  
– Ketamine oral rinse  
– Gelclair® oral gel  
– Supersaturated calcium phosphate solution | • Temporary dose interruption until recovery to grade ≤1, then restart at same dose  
• If stomatitis recurs at grade 2, interrupt dose until recovery to grade ≤1, then restart at lower dose |
| 3 – Severe | Symptomatic and unable to adequately aliment or hydrate orally | • Topical corticosteroid mouth treatments 0.5-mg/5-mL dexamethasone mouth rinse | • Temporary dose interruption until recovery to grade ≤1, then restart at reduced dose  
• Discontinue drug if no recovery to grade ≤1 within 4 weeks |
| 4 – Debilitating | Severe and may be associated with life-threatening consequences | • Topical antifungal therapy if needed  
• Systemic antifungal therapy for refractory or severe fungal infection  
• Avoid agents containing alcohol, hydrogen peroxide, iodine, and thyme derivatives  
• Antiviral therapy for confirmed herpes simplex virus infection | • Discontinue treatment |

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BOLERO-2: Cumulative Risk of Pneumonitis and Related Events (Grade ≥2)

Everolimus: Therapy Management Strategies

- **Patient:**
  - Patient awareness and early intervention are important
  - Advise patients to promptly report any new or worsening symptoms
  - **Stomatitis:** Consider evaluation for herpes virus or fungal infection; educate patients about good oral hygiene; advise patients to avoid foods that are spicy, acidic, salty

- **Physician:**
  - Monitoring of renal function, fasting serum glucose, lipid profile and complete blood count is recommended prior to use of everolimus
  - Possibility of dose modifications to manage occurrence and intensity of side effects
Managing AEs May Help Maintain HRQOL in Patients: Linear Mixed-Effects Model for EORTC QLQ-C30 QL2

- Early management of AEs may result in patients deriving full clinical benefit from EVE + EXE and ensure maintenance of long-term QOL

<table>
<thead>
<tr>
<th>Patients, n</th>
<th>EVE + EXE</th>
<th>PBO + EXE</th>
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</thead>
<tbody>
<tr>
<td>EVE + EXE</td>
<td>376</td>
<td>178</td>
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<tr>
<td></td>
<td>324</td>
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<tr>
<td></td>
<td>43</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>28</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>1</td>
</tr>
</tbody>
</table>

LSM, least squares mean; QL2, Global Health Status; SE, standard error.
## Latest major achievements in cancer treatment

<table>
<thead>
<tr>
<th>Targeted Agents</th>
<th>Indication</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gefitinib</td>
<td>EGFRmut NSCLC</td>
<td>0.30 (0.22 to 0.41)</td>
</tr>
<tr>
<td>(Maemondo, NEJM 2010)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trastuzumab</td>
<td>Her2+++ mBC</td>
<td>0.51 (0.41–0.63)</td>
</tr>
<tr>
<td>(Slamon, NEJM, 2001)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Imatinib</td>
<td>cKit+ GIST</td>
<td>0.35 (22-0.53)</td>
</tr>
<tr>
<td>(Ronald, Lancet, 2009)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sunitinib</td>
<td>kidney cancer (VHL-)</td>
<td>0.42 (0.32 to 0.54)</td>
</tr>
<tr>
<td>(Motzer, NEJM, 2007)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Everolimus</td>
<td>AI-resistant BC</td>
<td>0.36 (0.27 to 0.47)</td>
</tr>
</tbody>
</table>

**Efficacy of everolimus is in the range of the most important recent advances in medical oncology... although no molecular selection was applied**

F. Andre, Discussion of BOLERO 2 Trial, ESMO 2011
## Primary Endpoint TTP

### Product-Limit Survival Estimates

<table>
<thead>
<tr>
<th>Arm</th>
<th>N(%)</th>
<th>Median TTP</th>
<th>HR</th>
<th>95% CI</th>
<th>p-value Cox</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>18 (85.7)</td>
<td>2.9, 95% CI (1.6, 4.1)</td>
<td>.559</td>
<td>(.284, 1.10)</td>
<td>.092</td>
</tr>
<tr>
<td>RAD001</td>
<td>17 (94.4)</td>
<td>8.5, 95% CI (3.8, 9.2)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**stratified log rank:**

\[ p = 0.0556 \]

---

Harbeck et al, EBCC 2012
Forest Plot

Subgroups

- Age<65 years
- Age>=65 years
- KI<90%
- KI 90-100%
- ER and/or PgR positive
- no concomitant ET
- concomitant ET
- 1st line therapy
- 2nd line therapy
- no previous radiotherapy for metastatic disease
- previous radiotherapy for metastatic disease
- CA-15-3<28 U/ml
- CA-15-3>=28 U/ml
- AP<=120 U/l
- AP>120 U/l

RAD001 better <-> HR and 95% CI --> placebo b...
- **Primary resistance:** progression < 6 months

- **Secondary resistance:** progression > 6 months
mTOR inhibitor Temsirolimus in AI-naive patients

A

Progression-Free Survival (probability)

Stratified log-rank test $P = 25$
HR, 0.90; 95% CI, 0.78 to 1.07

- LET + TEMSR
- LET + placebo

Time (months)

B

Overall Survival (probability)

Stratified log-rank test $P = 50$
HR, 0.89; 95% CI, 0.65 to 1.23

- LET + TEMSR
- LET + placebo

Time (months)

Endocrine therapy in mBC | Prof. Harbeck

Randomized Phase III Placebo-Controlled Trial of Letrozole Plus Oral Temsirolimus As First-Line Endocrine Therapy in Postmenopausal Women With Locally Advanced or Metastatic Breast Cancer

Antonio C. Wolff, Amy A. Larson, Igor Bendelkoski, August H. Garin, Stephen Bricout, Louis Chen, Yao Sun, Zera Nadeem, Konstantinovic, Rodrigo C. Guimaraes, Pierre Fumoleau, Arlene Chen, Seid Funahashi, Andrew Strahl, Maria Cincotta, Anna Berkesblit, Mitte Krogdsv, Lif Lisa Kung, Lawrence Moore, and David F. Hayes

Improving Endocrine Therapy for Breast Cancer: It’s Not That Simple

E. Claire Bee and Lisa A. Carey, Lineberger Comprehensive Cancer Center, University of North Carolina at Chapel Hill, Chapel Hill, NC

The important take home message may be that ER-positive disease is more heterogeneous than appreciated. We know this to be true.
**Endocrine Therapy in Postmenopausal HER2 Negative Metastatic Breast Cancer Patients after Adjuvant Tamoxifen or no Prior Endocrine Treatment**

<table>
<thead>
<tr>
<th>Treatment sequence</th>
<th>Oxford / AGO LoE / GR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1st line:</strong> aromatase inhibitors (3rd gen)*</td>
<td>1a A ++</td>
</tr>
<tr>
<td>fulvestrant 250 mg + anastrozole</td>
<td>2b C +/-</td>
</tr>
<tr>
<td><strong>2nd line:</strong> fulvestrant</td>
<td>1b B</td>
</tr>
<tr>
<td>fulvestrant 500 mg</td>
<td>1b B ++</td>
</tr>
<tr>
<td>fulvestrant 250 mg</td>
<td>2b B +/-</td>
</tr>
<tr>
<td>exemestane + everolimus</td>
<td>1b A ++</td>
</tr>
<tr>
<td>tamoxifen</td>
<td>3b C +</td>
</tr>
<tr>
<td>aromatase inhibitor**</td>
<td>2b B +</td>
</tr>
<tr>
<td>tamoxifen + everolimus</td>
<td>2b B +</td>
</tr>
<tr>
<td>Further MPA/MA</td>
<td>4 D +/-</td>
</tr>
<tr>
<td>Lines: estradiol 6 mg daily</td>
<td>3b C +/-</td>
</tr>
<tr>
<td>repeat prior treatments</td>
<td>5 D +/-</td>
</tr>
</tbody>
</table>

* To date, there is no evidence for superiority of a single aromatase inhibitor.

** steroidal or non-steroidal depending on previous AI
Therapy Algorithm After Adjuvant Tamoxifen

Non-steroidal AI 3rd generation

Exemestane + everolimus

Fulvestrant 500mg

Tamoxifen

Fulvestrant 500mg

Exemestane + everolimus

Tamoxifen
The addition of everolimus to an AI is a valid option for some post-menopausal patients with disease progression after a non-steroidal AI, since it provides a significant benefit in PFS (about 5 months). However, data on OS are still awaited and the decision must take into account the increased toxicity. \( \text{LoE: 1 B} \)

At present, no predictive biomarker exists to identify those patients who will benefit from this approach.

Total number of votes: 40
1. YES: 90,0% (36)
2. NO: 2,5% (1)
3. ABSTAIN: 7,5% (3)

To include in manuscript: Refer to TAMRAD and Tamoxifen + everolimus as another potential option.
BOLERO-2 Biomarker Analyses: Greater PFS Benefit With EVE in Patients With Minimal Alterations in PIK3CA/PTEN/CCND1 or FGFR1/2

HR = 0.27; 95% CI = 0.18 - 0.41

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

Hortobagyi G, et al. ASCO 2013. abstract LBA509 (oral)
Endocrine and Targeted Therapies for HR+, HER2- Advanced Breast Cancer

PI3K/AKT/mTOR - signaling pathway. Function and activation

- Central regulatory role
- PI3K-signaling pathway activation\(^1,2\)
  - *De novo* in ~40% of HR+ breast cancers
  - Secondary during anti-cancer therapy, particularly due to endocrine agents (e.g. AI);
- Common changes
  - PIK3CA-gene mutation (in exon 1, 5, 7, 9 or 20)
  - PTEN-gene mutation (in exon 5, 6, 7 or 8) and/or loss of PTEN-expression

Targeting signal transduction by dual inhibition

Everolimus plus exemestane – BKM120 plus fulvestrant

**Aromatase Inhibitors**
- inhibit aromatase (converts androgen into estrogen)

**Everolimus (RAD001)**
- inhibits mTORC1

**BKM120**
- Pan - class I PI3K inhibitor

**Fulvestrant**
- Degrades ER-receptors; complete inhibition of ER-signaling pathway

Cell growth, -proliferation, -metabolism, -angiogenesis
Metastatic breast cancer – SABCS 2014

Krop I. et al.: FERGI Phase II Study of PI3K Inhibitor Pictilisib (GDC-0941) + Fulvestrant vs. Fulvestrant + Placebo in ER+, Aromatase Inhibitor (AI-) - Resistant Advanced or MBC
Metastatic breast cancer – SABCS 2014

Krop I. et al.: FERGI Phase II Study of PI3K Inhibitor Pictilisib (GDC-0941) + Fulvestrant vs. Fulvestrant + Placebo in ER+, Aromatase Inhibitor (AI-) Resistant Advanced or MBC

PR+ and PIK3CA mutation

PIK3CA-Mutant Population

PR+ and PIK3CA “Wild-Type” mutation

PIK3CA “Wild-Type” Population
Phase 2 TRIO-18: First-line PD0332991 + LET Significantly Increased PFS Versus LET Alone

- PD0332991 + LET showed statistically significant improvement in median PFS vs LET alone
- Selective biomarkers (cyclin D1 gain or p16 loss) did not identify patients who may benefit from PD0332991
- Most common adverse events were hematologic for combination therapy and fatigue, nausea, and hot flushes for LET alone
- Conclusions from this study are preliminary; data from phase 3 trials are needed

**Progression-Free Survival**

- **PD0332991 + LET**: HR = 0.37; 95% CI, 0.21-0.63; *P* < .001
- **LET**: Median PFS, mo
  - PD2991 + LET: 26.1
  - LET: 7.5

**Forest Plot of HRs**

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>HR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>0.37 (0.10-1.40)</td>
<td>.13</td>
</tr>
<tr>
<td>Negative</td>
<td>0.19 (0.05-0.67)</td>
<td>&lt; .01</td>
</tr>
<tr>
<td>Unknown</td>
<td>0.59 (0.11-3.08)</td>
<td>.53</td>
</tr>
</tbody>
</table>

Ongoing Phase 3 Trials for New First-line Agents in HR\(^+\), HER2\(^-\) ABC

**TRIO 22 (PALOMA 2): PD0332991 + LET versus LET alone\(^1\)**

- **Key endpoints**
  - **Primary:** PFS
  - **Secondary:** OS, OR, DOR, disease control, PK/PD, tolerability, QoL

- **Ongoing Phase 3 Trial**
  - **N ≈ 450**
  - **(Data expected in March 2015)**
  - PMW with ER\(^+\), HER2\(^-\) ABC
  - No prior systemic therapy for advanced disease

<table>
<thead>
<tr>
<th>R 2:1</th>
<th>PD0332991 (125 mg QD 21d on, 7d off) + LET (2.5 mg daily)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo (21d on, 7d off) + LET (2.5 mg daily)</td>
</tr>
</tbody>
</table>

**MONALEEESA-2: LEE-011 + LET versus LET alone\(^2\)**

- **Key endpoints**
  - **Primary:** PFS
  - **Secondary:** OS, OR, QoL, Safety, PK

- **Phase 3 Trial Initiating**
  - **N ≈ 500**
  - **(Data expected in December 2016)**
  - Postmenopausal HR\(^+\) HER2\(^-\) mBC
  - No prior therapy for advanced BC
  - De novo or >12 months post-adjuvant therapy

<table>
<thead>
<tr>
<th>R 1:1</th>
<th>LEE011 (600 mg/day) + LET</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo + LET</td>
</tr>
</tbody>
</table>

- **Stratification:** Visceral disease, no cross-over

---

Endocrine Therapy in Combination with Biological Agents in HER2 Neg. Metastatic Breast Cancer Pts.

- ET + everolimus: 1b B ++
- ET* + bevacizumab: 1b aB -
- letrozole + temsirolimus: 1b B --

*letrozole or fulvestrant
So, Where are we exactly?
Endocrine therapy for *advanced* breast cancer: Standards

- Endocrine therapy is the therapeutic backbone in early and advanced hormone receptor positive breast cancer
- Current guidelines support continuing endocrine-based therapeutic approaches after HR+ ABC progresses
- Options for post-progression ET
  - Switching to a different ET
  - Combining ET agents does not appear to add benefit; increasing dose intensity might provide benefit
  - Adding a targeted agent to ET is an emerging option
    - NCCN, Canadian Consensus, AGO, And ABC Guidelines include this approach
Endocrine therapy for advanced breast cancer: New options

✓ mTOR is a key signaling pathway involved in cell growth, proliferation, metabolism, and angiogenesis

✓ The oral mTOR inhibitor everolimus is active in early and metastatic breast cancer, particularly with endocrine therapy

   ✓ BOLERO 2 establishes everolimus and exemestane as a new standard after AI failure

✓ CDK 4/6 inhibition in combination with AI is currently explored in phase III as another promising therapeutic step after AI failure

✓ Close interaction and intensified communication between patient and physician necessary
Endocrine therapy for advanced breast cancer: Future directions

✓ Endocrine plus targeted agent is a promising approach for overcoming endocrine resistance

✓ New clinical challenges
   ✓ Proactive side effect management required
   ✓ Drug-drug interactions need to be considered

✓ Open clinical questions are:
   ✓ Premenopausal patients
   ✓ Predictive biomarkers
   ✓ Duration of therapy
   ✓ Optimal combination partners
   ✓ ...

Endocrine therapy in mBC | Prof. Harbeck
Annually updated, evidence-based Guidelines for diagnosis and therapy

AGO (DKG, DGGG)

www.ago-online.de
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