Endocrine Treatment in Advanced Breast Cancer

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Contents

• Overview

• Current options for ET in ER+ Advanced or Metastatic BC in postmenopausal women

• Proposed mechanisms of ET resistance

• Novel combinations with hormonal manipulation as a means of overcoming resistance.
Metastatic Breast Cancer: Overview

- Metastatic breast cancer (MBC) is an incurable disease.

- Treatment of metastatic breast cancer has the potential to provide:
  - Control and regression of disease
  - Palliation of symptoms
  - Improvement in quality of life
  - Prolongation of life

- Long-term survival is still a challenge despite new advances
Considerations in the treatment of MBC

- **Disease-related factors**
  - Tumor biology; ER, HER2, status, Ki-67 index
  - Previous therapy, response to prior treatment, DFI
  - Site and extent of disease, tumor burden; presence of life-threatening visceral metastases

- **Patient-related factors**
  - Age, menopausal status, performance status
  - Patient’s personal preferences
  - Co-morbidities
  - Convenience vs. compliance
  - Toxicity affecting normal life
Treatment Algorithms for MBC

Diagnosis of metastatic breast cancer

Determination of sites and extent of disease
Assessment of HER2, hormonal receptor status, disease-free interval, age, and menopausal status

No life-threatening disease or hormone-responsive

1st-line hormonal therapy

Response

Progression

2nd-line hormonal therapy

Response

Progression

3rd-line hormonal therapy

No Response

Hormone-unresponsive or life-threatening disease

1st-line chemotherapy

Progression

2nd-line chemotherapy

Progression

3rd-line chemotherapy

Supportive care
Historic Timeline of Therapies for HR+ Advanced Breast Cancer

<table>
<thead>
<tr>
<th>Year</th>
<th>Agent</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>1977</td>
<td>SERMs</td>
<td>Antagonizes estrogen receptor in breast tissue</td>
</tr>
<tr>
<td></td>
<td>Tamoxifen</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Toremifene</td>
<td></td>
</tr>
<tr>
<td>1990s</td>
<td>AIs</td>
<td>Inhibit estrogen production in postmenopausal women</td>
</tr>
<tr>
<td></td>
<td>Anastrozole</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Letrozole</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Exemestane</td>
<td></td>
</tr>
<tr>
<td>2000s</td>
<td>ERD</td>
<td>Impairs ER dimerization, increases ER degradation, and disrupts nuclear</td>
</tr>
<tr>
<td></td>
<td>Fulvestrant</td>
<td>localization of ER</td>
</tr>
<tr>
<td></td>
<td>(250 or 500 mg*)</td>
<td></td>
</tr>
</tbody>
</table>
Therapeutic Options for HR+ Advanced Breast Cancer in Postmenopausal Women
First-Line Endocrine Treatment

• Tamoxifen vs. 3rd generation A.I.’s

• First-line fulvestrant: “FIRST trial”
  - anastrozole vs. fulvestrant

• Combination better?
  - FACT trial: Ana vs. Ana+ Fulv.
  - SWOG 0226: Ana vs. Ana+ Fulv.
  - LEA trial: Let or Fuv vs. Let or Ful + Bev.
First-Line Endocrine Treatment

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**P025 Trial**

1

\textit{st} line Letrozole vs. Tamoxifen

Double-blind, randomized cross-over, multi-center, phase III study

- **Postmenopausal women** with ER-positive or unknown ABC (N = 916)
  - Letrozole 2.5 mg/d (n=458)
  - Tamoxifen 20 mg/d (n=458)
  - Letrozole 2.5 mg/d (n=458)
  - Tamoxifen 20 mg/d (n=458)

**Time to progression**

- Letrozole, n=453
  - median = 9.4 months
  - events = 68%

- Tamoxifen, n = 454
  - median = 6.0 months
  - events = 77%

**OS with cross-over**

- 1-y Survival
  - P=0.0038

- 2-y Survival
  - P=0.0246

- Overall log rank
  - P=0.53

## Al's vs Tamoxifen: First-line trials in postmenopausal women

<table>
<thead>
<tr>
<th></th>
<th>Phase III</th>
<th>Phase II</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anastrozole</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 mg</td>
<td>353</td>
<td>668</td>
</tr>
<tr>
<td><strong>ORR (%)</strong></td>
<td>21 vs 17</td>
<td>32.9 vs 32.6</td>
</tr>
<tr>
<td><strong>Clin benefit (%)</strong></td>
<td>59 vs 46</td>
<td>56.2 vs 55.5</td>
</tr>
<tr>
<td><strong>TTP (mo)</strong></td>
<td>11.1 vs 5.6</td>
<td>8.2 vs 8.3</td>
</tr>
<tr>
<td><strong>TTF (mo)</strong></td>
<td>7.6 vs 5.4</td>
<td>6.2 vs 6.0</td>
</tr>
</tbody>
</table>

| **Letrozole**    |           |
| 2.5 mg           | 907       |
| **ORR (%)**      | 30 vs 20  **<i>p=0.0001</i>** 44.6 vs 14.3 |
| **Clin benefit (%)** | 49 vs 38  **<i>p=0.001</i>** 55.3 vs 39.3 |
| **TTP (mo)**     | 9.4 vs 6.0  **<i>p=0.0001</i>** |
| **TTF (mo)**     | L > T     |

| **Exemestane**   |           |
| 25 mg            | 112       |
| **ORR (%)**      |           |
| **Clin benefit (%)** |           |
| **TTP (mo)**     |           |
| **TTF (mo)**     |           |

* p<0.01  ** p<0.001

First-Line Endocrine Treatment

• Tamoxifen vs. 3rd generation A.I.’s

• First-line fulvestrant: “FIRST trial”
  - anastrozole vs. fulvestrant

• Combination better?
  - FACT trial: Ana vs. Ana+ Fulv.
  - SWOG 0226: Ana vs. Ana+ Fulv.
  - LEA trial: Let or Fuv vs. Let or Ful + Bev.
Mode of Action of Fulvestrant

Estradiol

\[ E + ER \rightarrow AF1 \]

Receptor dimerisation

Tamoxifen

\[ T + ER \rightarrow AF1 \]

AF1 + AF2 ACTIVE

Fulvestrant

\[ F + ER \rightarrow AF1 \]

No dimerisation

AF1 + AF2 INACTIVE

No transcription (no tumour cell division)

AF1 + AF2 ACTIVE

FULLY ACTIVATED TRANSCRIPTION (tumour cell division)

AF1 ACTIVE AF2 INACTIVE

PARTIALLY INACTIVATED TRANSCRIPTION (reduced rate of tumour cell division)

ACCELERATED RECEPTOR DEGRADATION

Phase III CONFIRM trial:
Fulvestrant 500 mg versus 250 mg

a double-blind, parallel-group, multicenter, phase III study

Postmenopausal women with ER-positive advanced breast cancer (N = 736)

1:1 randomisation

Fulvestrant 250 mg (n = 374)
(250 mg D1, D15, and D 29 and then Q 28D)

Fulvestrant 500 mg (n = 362)
(500 mg D1, D15, and D 29 and then Q 28D)

Relapse on adjuvant ET or within 1 yr from completion of adjuvant ET

Primary endpoint: progression free survival (PFS)
Secondary endpoint: ORR, clinical benefit rate (CBR), duration of CB, OS, and QOL
CONFIRM trial: PFS & OS

Subsequent therapies were well balanced between arms, with approximately 60% of patients receiving subsequent chemotherapy and approximately one third receiving other hormonal therapy.

### CONFIRM: Adverse Events

<table>
<thead>
<tr>
<th>SAEs,* n (%)</th>
<th>Fulvestrant 500 mg (n = 361)</th>
<th>Fulvestrant 250 mg (n = 374)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any SAE</td>
<td>35 (9.7)</td>
<td>27 (7.2)</td>
</tr>
<tr>
<td>Any causally related SAE</td>
<td>8 (2.2)</td>
<td>4 (1.1)</td>
</tr>
<tr>
<td>SAEs with outcome of death during treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>· Acute myocardial infarction</td>
<td>0</td>
<td>2 (0.5)</td>
</tr>
<tr>
<td>· Acute renal failure</td>
<td>0</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>· Aspiration</td>
<td>0</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>· Cardiopulmonary failure</td>
<td>1 (0.3)</td>
<td>0</td>
</tr>
<tr>
<td>· Suicide</td>
<td>0</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>· Death (cause unknown)</td>
<td>1 (0.3)</td>
<td>0</td>
</tr>
<tr>
<td>· Dyspnea</td>
<td>2 (0.6)</td>
<td>0</td>
</tr>
<tr>
<td>· Hypertension</td>
<td>0</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>· Intestinal adenocarcinoma</td>
<td>1 (0.3)</td>
<td>0</td>
</tr>
<tr>
<td>· Meningitis</td>
<td>0</td>
<td>1 (0.3)</td>
</tr>
</tbody>
</table>

No clinically relevant differences between fulvestrant 500 mg and 250 mg.

The standard dosing schedule of fulvestrant should now be **500 mg** based on its increased efficacy and minimal toxicity.
Phase II ‘FIRST’ trial: Fulvestrant versus Anastrozole

A phase II, randomized, open-label, multicenter study

Postmenopausal women with ER+ MBC or LABC (N = 205)

No prior hormonal therapy for advanced disease

Primary endpoint: clinical benefit rate (CBR)
Secondary endpoint: ORR, TTP, duration of CB, duration of response

# FIRST: Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Fulvestrant 500 mg</th>
<th>Anastrozole 1 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number (%) of patients</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median age</td>
<td>66 years</td>
<td>68 years</td>
</tr>
<tr>
<td>Disease stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Locally advanced only</td>
<td>19 (18.6)</td>
<td>18 (17.5)</td>
</tr>
<tr>
<td>Metastatic</td>
<td>83 (81.4)</td>
<td>85 (82.5)</td>
</tr>
<tr>
<td>Measurable disease</td>
<td>89 (87.3)</td>
<td>93 (90.3)</td>
</tr>
<tr>
<td>Prior endocrine treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No prior endocrine treatment</td>
<td>73 (71.6)</td>
<td>80 (77.7)</td>
</tr>
<tr>
<td>Completed endocrine treatment for early disease</td>
<td>28 (27.5)</td>
<td>23 (22.3)</td>
</tr>
<tr>
<td>&gt;12 months prior to randomization</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior adjuvant chemotherapy received for early breast cancer</td>
<td>29 (28.4)</td>
<td>25 (24.3)</td>
</tr>
<tr>
<td>Previously received chemotherapy and endocrine treatment</td>
<td>19 (18.6)</td>
<td>13 (12.6)</td>
</tr>
</tbody>
</table>

*In addition, one patient in the fulvestrant group received prior adjuvant endocrine treatment within 12 months of randomization*
Fulvestrant 500 mg was at least as effective as anastrozole for the primary endpoint of clinical benefit rate.

Robertson JF. et al. SABCS 2014

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Fulvestrant 500 mg (n = 102)</th>
<th>Anastrozole 1 mg (n = 103)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical benefit rate, %</td>
<td>72.5</td>
<td>67.0</td>
<td>.386</td>
</tr>
<tr>
<td>Median time to progression, mos</td>
<td>23.4</td>
<td>13.1</td>
<td>.01</td>
</tr>
<tr>
<td>Median OS, mos</td>
<td>54.1</td>
<td>48.4</td>
<td>.041</td>
</tr>
</tbody>
</table>
TTP: updated analysis

**Timing of analysis**

<table>
<thead>
<tr>
<th>Timing of analysis</th>
<th>Fulvestrant 500 mg</th>
<th>Anastrozole 1 mg</th>
<th>HR(95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>JCO(2009)</td>
<td>Not reached</td>
<td>12.5 mo</td>
<td>0.63(0.39-1.00)</td>
<td>0.0496</td>
</tr>
<tr>
<td>BCRT(2012)</td>
<td>23.4 mo</td>
<td>13.1 mo</td>
<td>0.66(0.47-0.92)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

FIRST: Overall Survival

- OS analysis
  - Not a defined endpoint in original protocol
  - Median follow-up: fulvestrant (49.6 mos), anastrozole (42.5 mos)
  - Analysis conducted at 66.8% maturity (137 patients died)

Robertson JF. et al. SABCS 2014
Comparison with other studies

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

<table>
<thead>
<tr>
<th></th>
<th>Bonneterre et al.</th>
<th>Mouridsen et al.</th>
<th>Paridaens et al.</th>
<th>FIRST</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cancer 2001 (n=1021)</td>
<td>J Clin Oncol 2001 (n=916)</td>
<td>J Clin Oncol 2008 (n=371)</td>
<td>(n=205)</td>
</tr>
<tr>
<td>Tam</td>
<td>7.0</td>
<td>6.0</td>
<td>5.8</td>
<td>13.1</td>
</tr>
<tr>
<td>Ana</td>
<td>8.5</td>
<td>9.4</td>
<td>9.9</td>
<td>23.4</td>
</tr>
<tr>
<td>Median TTP (months)</td>
<td>13.1</td>
<td>23.4</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Robertson JF. et al. SABCS 2014
FALCON: Open-label Phase 3 Trial

Key Patient Criteria

- Postmenopausal women: ≥60 years, prior bilateral oophorectomy, or <60 years and amenorrheic under certain conditions
- ER-positive and/or PR-positive
- Locally advanced or metastatic disease
- ≥1 lesion accurately assessed at baseline and suitable for repeated assessment

Estimated enrollment 450 patients

Randomized (1:1)

- Fulvestrant 500 mg (2 x IM injections at day 1, 14, 28, and every 28 days thereafter) + anastrozole placebo (1 tablet daily)
- Anastrozole (1 mg tablet daily) + fulvestrant placebo (2 x IM injections at day 1, 14, 28, and every 28 days thereafter)

Endpoints

- Primary: PFS
- Secondary: OS, objective response rate, duration of response, clinical benefit rate

PFS = progression-free survival

First-Line Endocrine Treatment

• 3rd generation A.I.s vs. tamoxifen

• First-line fulvestrant: “FIRST trial”
  - anastrozole vs. fulvestrant

• Combination better?
  - FACT trial: Ana vs. Ana+ Fulv.
  - SWOG 0226: Ana vs. Ana+ Fulv.
  - LEA trial: Let or Fuv vs. Let or Ful + Bev.
Historically, combination regimens have failed to demonstrate a benefit over single endocrine agents. (ATAC trial)

In preclinical studies fulvestrant is active in a low estrogen environment and has demonstrated efficacy in combination with an AI.

Fulvestrant competes with estrogen for binding of the ER, and reducing estrogen levels might enhance efficacy by allowing increased fulvestrant-ER binding.
Phase III FACT trial: ANA vs. ANA + Fulv.

Primary endpoint: Time to Progression (TTP)
Secondary endpoint: OR, TTF, DoR, CBR, OS
## Adjuvant Endocrine Therapy

<table>
<thead>
<tr>
<th></th>
<th>Fulvestrant + Anastrozole (n=258)</th>
<th>Anastrozole (n=256)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No prior endocrine therapy</strong></td>
<td>78 (30.2%)</td>
<td>90 (35.2%)</td>
</tr>
<tr>
<td><strong>Anti-estrogen therapy</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relapse within 2 years of completion</td>
<td>Tamoxifen 30 (11.6%)</td>
<td>35 (13.7%)</td>
</tr>
<tr>
<td>Relapse after 2 years of completion</td>
<td>Tamoxifen 72 (27.9%)</td>
<td>65 (25.4%)</td>
</tr>
<tr>
<td></td>
<td>Toremifene 1</td>
<td>3</td>
</tr>
<tr>
<td>Relapse on treatment with</td>
<td>Tamoxifen 70 (27.1%)</td>
<td>61 (23.8%)</td>
</tr>
<tr>
<td></td>
<td>Raloxifien 1</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Toremifene 1</td>
<td>0</td>
</tr>
<tr>
<td>Aromatase inhibitory treatment</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>with washout period of at least one year before relapse</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>1†</td>
<td>1‡</td>
</tr>
</tbody>
</table>

† Farlutal; ‡ Protocol BIG1-98
The results from FACT show no suggestion of any TTP & OS benefit to adding fulvestrant to anastrozole in patients with HR+ MBC.

Phase III SWOG S0226 trial: ANA vs. ANA + Fulv.

Postmenopausal women with ER+ MBC (N = 707)

No prior chemotherapy, hormonal therapy, immunotherapy for metastatic disease

Anastrozole 1 mg/d (n = 352)

Women with PD encouraged to cross over to receive fulvestrant

Anastrozole 1 mg/day + Fulvestrant 500 mg (n = 355)

(Fulvestrant 500 mg on D1, 250 mg on D14, and D 28 and then 250 mg Q 28D)

Treatment until disease progression

Primary endpoint: progression free survival (PFS)
Secondary endpoint: (pre-specified) OS, safety
## Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Anastrozole</th>
<th>Anastrozole + Fulvestrant</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized</td>
<td>352</td>
<td>355</td>
<td>707</td>
</tr>
<tr>
<td>Ineligible or withdrew consent</td>
<td>7 (2.0%)</td>
<td>6 (1.7%)</td>
<td>13 (1.8%)</td>
</tr>
<tr>
<td>Analyzed</td>
<td>345</td>
<td>349</td>
<td>694</td>
</tr>
<tr>
<td>Age in years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>65 (36-91)</td>
<td>65 (27-92)</td>
<td>65 (27-92)</td>
</tr>
<tr>
<td>Prior adjuvant tamoxifen (stratification factor)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>206 (59.7%)</td>
<td>208 (59.6%)</td>
<td>414 (59.7%)</td>
</tr>
<tr>
<td>Yes</td>
<td>139 (40.3%)</td>
<td>141 (40.4%)</td>
<td>280 (40.3%)</td>
</tr>
<tr>
<td>Disease characteristics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Measurable</td>
<td>54.5%</td>
<td>53.9%</td>
<td>54.2%</td>
</tr>
<tr>
<td>Bone only</td>
<td>22.0%</td>
<td>21.5%</td>
<td>21.8%</td>
</tr>
<tr>
<td>De novo metastatic disease</td>
<td>41.8%</td>
<td>36.0%</td>
<td>38.9%</td>
</tr>
<tr>
<td>&gt; 10 years since previous dx</td>
<td>26.1%</td>
<td>30.7%</td>
<td>28.4%</td>
</tr>
<tr>
<td>HER2-positive</td>
<td>8.5%</td>
<td>10.4%</td>
<td>9.5%</td>
</tr>
</tbody>
</table>
The combination of anastrozole and fulvestrant was superior to anastrozole alone or sequential anastrozole and fulvestrant for the treatment of HR+ MBC, despite the use of a dose of fulvestrant that was below the current standard.

# S0226: PFS and OS by Previous Adjuvant Tamoxifen

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Anastrozole + Fulvestrant</th>
<th>Anastrozole</th>
<th>HR (95% CI)</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS (n = 694), mos</td>
<td>15.0</td>
<td>13.5</td>
<td>0.80</td>
<td>.007</td>
</tr>
<tr>
<td></td>
<td>(0.68-0.94)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>▪ No previous adjuvant tamoxifen (n = 414)</td>
<td>17.0</td>
<td>12.6</td>
<td>0.74</td>
<td>.0055</td>
</tr>
<tr>
<td></td>
<td>(0.59-0.92)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>▪ Previous adjuvant tamoxifen (n = 280)</td>
<td>13.5</td>
<td>14.1</td>
<td>0.89</td>
<td>.37</td>
</tr>
<tr>
<td></td>
<td>(0.69-1.15)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median OS (n = 694), mos</td>
<td>47.7</td>
<td>41.3</td>
<td>0.81</td>
<td>.049</td>
</tr>
<tr>
<td></td>
<td>(0.65-1.00)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>▪ No previous adjuvant tamoxifen (n = 414)</td>
<td>47.7</td>
<td>39.7</td>
<td>0.74</td>
<td>.0362</td>
</tr>
<tr>
<td></td>
<td>(0.56-0.98)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>▪ Previous adjuvant tamoxifen (n = 280)</td>
<td>49.6</td>
<td>44.5</td>
<td>0.91</td>
<td>.59</td>
</tr>
<tr>
<td></td>
<td>(0.65-1.28)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Why discordant results?
Fulv+ Ana vs. Ana

**SWOG S0226 trial**

- Median Progression-free Survival:
  - Combination, 15.0 mo (95% CI, 13.2–18.4)
  - Anastrozole, 13.5 mo (95% CI, 12.1–15.1)

- Hazard ratio, 0.80 (95% CI, 0.68–0.94)
- P = 0.007 by stratified log-rank test

<table>
<thead>
<tr>
<th>No. at Risk</th>
<th>Anastrozole + fulvestrant (n = 349)</th>
<th>Anastrozole (n = 345)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>199</td>
<td>193</td>
</tr>
<tr>
<td></td>
<td>114</td>
<td>92</td>
</tr>
<tr>
<td></td>
<td>53</td>
<td>39</td>
</tr>
<tr>
<td></td>
<td>21</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>3</td>
</tr>
</tbody>
</table>

- OS benefit demonstrated in SWOG 226
- > 70% had received prior antiestrogen treatment

**FACT trial**

- Progression-Free Survival (probability)
- No. at risk:
  - Anastrozole: 256
  - Anastrozole + fulvestrant: 258

- Hazard ratio: 0.99 (96% CI: 0.81 to 1.20)
- P = 0.91

- Median TTP in months:
  - Anastrozole: 10.8
  - Anastrozole + fulvestrant: 10.2

- Fulvestrant + anastrozole (n = 258)
- Anastrozole (n = 256)

- OS benefit demonstrated in SWOG 226 and the superior PFS in FIRST would support the use of HD fulvestrant as initial treatment in patients without prior exposure to ET, possibly in combination with a NSAI.
Fulvestrant summary

- HD Fulvestrant is a therapeutic option for women with locally advanced or MBC that has relapsed on or after adjuvant anti-estrogen therapy, or who developed disease progression on prior anti-estrogen therapy.

- In routine clinical practice, fulvestrant is normally utilised after aromtatase inhibition.

- However, the overall survival benefit demonstrated in SWOG 0226 and the superior PFS in FIRST would support the use of fulvestrant HD as initial treatment in patients without prior exposure to ET, possibly in combination with a NSAI.
Targeting Angiogenesis

• Preclinical and retrospective clinical data suggest that high VEGF level in tumor tissue from BC are associated with decreased response to endocrine therapy.

• The combination of endocrine therapy and bevacizumab has shown to be safe and active in phase II trials.

1. De la Haba J, AACR 2011;
2. Linderholm B, JCO 2000;
3. Ferrero-Torres, CBC 2010;
4. Traina TA, JCO 2010
LEA - Study Design and Treatment

Binational, multicentric, randomised, open label phase III study

N= 380 patients unresectable locally advanced or metastatic breast cancer HR+/HER2-

Stratification criteria:
- Adjuvant AI (yes/no)
- N° lesions (one/multiple)
- Measurable lesions (yes/no)
- Country (Spain/Germany)

R

ET

ET-B

Letrozole (2.5 mg/d) or Fulvestrant 250mg i.m. 1 q28

Till disease progression

Letrozole (2.5 mg/d) or Fulvestrant 250mg i.m. q28d + Bevacizumab (15 mg/kg q3w)

ET: Endocrine Therapy; B: Bevacizumab
LEA- Progression Free Survival

<table>
<thead>
<tr>
<th>Survival Outcome, Mos</th>
<th>Endocrine Therapy + Bevacizumab (n = 191)</th>
<th>Endocrine Therapy (n = 189)</th>
<th>HR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS</td>
<td>18.4</td>
<td>13.8</td>
<td>0.83 (0.65-1.06)</td>
<td>.14</td>
</tr>
<tr>
<td>Median OS</td>
<td>41</td>
<td>42</td>
<td>1.18 (0.77-1.81)</td>
<td>.469*</td>
</tr>
</tbody>
</table>
LEA: Safety

<table>
<thead>
<tr>
<th>Adverse Event, %</th>
<th>ET + Bev (n = 191)</th>
<th>ET (n = 189)</th>
<th>P Value</th>
<th>ET + Bev (n = 191)</th>
<th>ET (n = 189)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematologic</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>▪ Anemia</td>
<td>100</td>
<td>98.9</td>
<td>.143</td>
<td>1.1</td>
<td>0.6</td>
<td>NS</td>
</tr>
<tr>
<td>▪ Neutropenia</td>
<td>11.2</td>
<td>5.7</td>
<td>.061</td>
<td>0.5</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td>▪ Leukopenia</td>
<td>24.6</td>
<td>11.4</td>
<td>.001</td>
<td>2.1</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td>▪ Thrombocytopenia</td>
<td>19.3</td>
<td>9.1</td>
<td>.006</td>
<td>1.6</td>
<td>2.3</td>
<td>NS</td>
</tr>
<tr>
<td>Nonhematologic</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>▪ Fatigue</td>
<td>50.5</td>
<td>29.0</td>
<td>&lt; .001</td>
<td>2.1</td>
<td>0.6</td>
<td>.373</td>
</tr>
<tr>
<td>▪ Hypertension</td>
<td>59.0</td>
<td>15.9</td>
<td>&lt; .001</td>
<td>3.2</td>
<td>0</td>
<td>.030</td>
</tr>
<tr>
<td>▪ Hemorrhage</td>
<td>18.6</td>
<td>1.7</td>
<td>&lt; .001</td>
<td>0</td>
<td>0</td>
<td>NA</td>
</tr>
<tr>
<td>▪ Liver enzyme elevation</td>
<td>46.5</td>
<td>28.0</td>
<td>&lt; .001</td>
<td>1.6</td>
<td>0</td>
<td>.249</td>
</tr>
<tr>
<td>▪ Proteinuria</td>
<td>30.3</td>
<td>2.8</td>
<td>&lt; .001</td>
<td>1.1</td>
<td>0</td>
<td>.449</td>
</tr>
<tr>
<td>▪ Thromboembolic events</td>
<td>2.1</td>
<td>0.6</td>
<td>.373</td>
<td>2.1</td>
<td>0</td>
<td>.124</td>
</tr>
</tbody>
</table>

Several adverse events occurred at significantly higher frequency in bevacizumab-treated group

Endocrine Resistance
Endocrine Resistance in ER+ BC

- Approximately 50% of HR+ BC are *de novo* resistant to endocrine therapy

- Almost all patients with advanced disease will develop acquired resistance to endocrine therapies

- Delaying systemic chemotherapy is the preferred therapeutic strategy
ER expression is frequently retained upon acquisition of endocrine resistance

<table>
<thead>
<tr>
<th>Receptor status</th>
<th>n of changes, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ER or PR positive to negative</td>
<td>8 (5.0%)</td>
</tr>
<tr>
<td>ER or PR negative to positive</td>
<td>15 (9.4%)</td>
</tr>
<tr>
<td>HER-2 negative to positive</td>
<td>2 (1.2%)</td>
</tr>
<tr>
<td>HER-2 positive to negative</td>
<td>6 (3.8%)</td>
</tr>
</tbody>
</table>

Macfarlane et al. (2011) Oncologist 17: 172

<table>
<thead>
<tr>
<th>Marker</th>
<th>Decrease</th>
<th>Increase</th>
<th>% Change</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>primary → recurrence</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ER</td>
<td>+ → - : 8</td>
<td>→ + : 2</td>
<td>10/97 (10.3)</td>
</tr>
<tr>
<td>PgR</td>
<td>+ → - : 19</td>
<td>→ + : 6</td>
<td>25/97 (25.8)*</td>
</tr>
<tr>
<td>P53</td>
<td>+ → - : 5</td>
<td>→ + : 7</td>
<td>12/97 (12.4)</td>
</tr>
<tr>
<td>HER2</td>
<td>+ → - : 3</td>
<td>→ + : 11</td>
<td>14/97 (14.4)</td>
</tr>
</tbody>
</table>


Sequential hormonal therapy

First-line  Second-line  Third-line  Fourth-line
Definition of endocrine resistance

**PRIMARY ENDOCRINE RESISTANCE** is defined as:
Relapse while on the first 2 years of adjuvant ET, or PD within first 6 months of 1st line ET for MBC, while on ET

**SECONDARY (ACQUIRED) ENDOCRINE RESISTANCE** is defined as:
Relapse while on adjuvant ET but after the first 2 years, or Relapse within 12 months of completing adjuvant ET, or PD ≥6 months after initiating ET for MBC, while on ET

*(LoE: Expert opinion)*

Total number of votes: 33
1. YES: 66.6% (22)
2. NO: 12.1% (4)
3. ABSTAIN: 21.2% (7)
Mechanisms of Endocrine Resistance

- **Endocrine therapy**
  - AI
  - AE

- **RTK (EGFR, HER2, IGF-1R)**

- **Non-genomic pathway**
  - Crosstalk
  - Acquired resistance:
    1. Crosstalk between ER and RTKs or downstream effectors
    2. Expression ↑ of RTKs or downstream effectors

- **Genomic pathway**
  - De novo resistance:
    1. Lack of ER
  - Acquired resistance:
    3. ER expression ↓
    4. Altered expression of ER CoAs
    5. ESR1 mutations

- **Proliferation, survival**
To Overcome Endocrine Resistance

- Enhancing endocrine blockade
  - AIs + Fulvestrant
- Blockade of growth factor receptor pathways
  - PI3K inhibitors/mTOR inhibitors
  - EGFR/IGFR blockades
  - HER2 blockades
- CDK 4/6 inhibitors
- Targeting epigenetics (HDAC inhibitor)
- Others (FGFR inhibitor, Src inhibitors, )
To Overcome Endocrine Resistance

• Enhancing endocrine blockade
  – AIs + Fulvestrant

• Blockade of growth factor receptor pathways
  – PI3K inhibitors/mTOR inhibitors
  – EGFR/IGFR blockades
  – HER2 blockades

• CDK 4/6 inhibitors

• Targeting epigenetics (HDAC inhibitor)

• Others (FGFR inhibitor, Src inhibitors, )
EFECT: Fulvestrant vs. Exemestane

Prior nonsteroidal AI failure

Fulvestrant loading dose (500 mg D1, 250 mg D14 & 28, and monthly) + Placebo for exemestane (n=330)

Exemestane 25 mg orally daily + Placebo for fulvestrant (n=330)

Progression

Survival

Analysis after 580 events (progression or death)

EFFECT: Fulvestrant vs Exemestane After Progression of Nonsteroidal AI

SoFEA: Phase III Trial

Eligibility (N = 723)

- Postmenopausal
- Hormone receptor-positive BC
- Relapsed or progressed with locally advanced or metastatic disease on a non-steroidal AI

Primary endpoint: Progression-free survival

After loss of response to NSAIs, combination endocrine treatment with 250 mg fulvestrant combined with estrogen deprivation with AI is no better than either fulvestrant alone or exemestane.

*Johnston SR, Lancet Oncol 2013; 14: 989–98*
Combined Endocrine Therapy: What is the Answer?

- Two of three trials failed to show a benefit from combination endocrine therapy
  - Toxicity and cost are increased with this strategy
- **SWOG 0226** with unique patient population
  - 39% ‘de novo metastatic’
- It is likely that these patients with hormone therapy naïve disease influenced the positive results in the SWOG trial
- Should we use the combination?
  - Only in a SWOG like setting – hormone therapy naïve, de novo disease
To Overcome Endocrine Resistance

• Enhancing endocrine blockade
  – AIs + Fulvestrant

• Blockade of growth factor receptor pathways
  – PI3K inhibitors/mTOR inhibitors
  – EGFR/IGFR blockades
  – HER2 blockades

• CDK 4/6 inhibitors

• Targeting epigenetics (HDAC inhibitor)

• Others (FGFR inhibitor, Src inhibitors, )
Combining Targeted and Antiestrogen Therapies in HR-Positive Breast Cancer

**PI3K inhibitors**
- BMK120
- BYL790
- GDC0980

**mTOR Inhibitors**
- Everolimus
- Sirolimus
- Temsirolimus

**CDK 4/6 Inhibitor**
- PD 0332991

**HDAC Inhibitor**
- Entinostat

**Cell Cycle**
- Transcription Silencing

**Transcription Silencing**
- ER target gene transcription

**Aromatase Inhibitor**
- Nonsteroidal AIs
  - Anastrozole
  - Letrozole
- Steroidal AIs
  - Exemestane

**ER Downregulator**
- Fulvestrant

**Selective Estrogen Receptor Modulators**
- Tamoxifen
- Toremifene
Combining Targeted and Antiestrogen Therapies in HR-Positive Breast Cancer

**PI3K inhibitors**
- BMK120
- BYL790
- GDC0980

**mTOR Inhibitors**
- Everolimus
- Sirolimus
- Temsirolimus

**CDK 4/6 Inhibitor**
- PD 0332991

**HDAC Inhibitor**
- Entinostat

**Aromatase Inhibitor**
- Nonsteroidal AIs
  - Anastrozole
  - Letrozole
- Steroidal AIs
  - Exemestane

**ER Downregulator**
- Fulvestrant

**Selective Estrogen Receptor Modulators**
- Tamoxifen
- Toremifene

**Cell Cycle**

**Transcription Silencing**

**ER target gene transcription**
mTOR and ER Double Inhibition Establish New Therapeutic Milestone for HER2-/HR+ Patients

BOLERO-2: Phase III Study of Exemestane ± Everolimus in Patients with ABC Progressing After NSAIs

N = 724
PMW with HR+, HER2– ABC refractory to LET or ANA, defined as
• Recurrence during or within 12 months after end of adjuvant treatment, or
• Progression during or within 1 month after end of treatment for advanced disease

- Everolimus 10 mg/day + Exemestane 25 mg/day (n = 485)
- Placebo + Exemestane 25 mg/day (n = 239)

Primary endpoint:
PFS
Secondary endpoints:
OS, ORR, CBR, safety, QOL, bone markers

• Stratification
  1. Sensitivity to prior hormonal therapy
  2. Presence of visceral disease
• No crossover
# BOLERO-2: Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>EVE+EXE (n = 485), %</th>
<th>PBO+EXE (n = 239), %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, years (range)</td>
<td>62 (34 - 93)</td>
<td>61 (28 - 90)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>74</td>
<td>78</td>
</tr>
<tr>
<td>Asian</td>
<td>20</td>
<td>19</td>
</tr>
<tr>
<td>Black</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Other</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>ECOG performance status 0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visceral disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Measurable disease*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metastatic site</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td>29</td>
<td>33</td>
</tr>
<tr>
<td>Liver</td>
<td>33</td>
<td>30</td>
</tr>
<tr>
<td>Bone</td>
<td>76</td>
<td>77</td>
</tr>
<tr>
<td>Sensitivity to previous endocrine therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Purpose of most recent treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjuvant therapy</td>
<td>21</td>
<td>16</td>
</tr>
<tr>
<td>Therapy for advanced/metastatic disease</td>
<td>79</td>
<td>84</td>
</tr>
<tr>
<td>ANA or LET as most recent treatment</td>
<td>74</td>
<td>75</td>
</tr>
<tr>
<td>Previous tamoxifen</td>
<td>47</td>
<td>49</td>
</tr>
<tr>
<td>Previous fulvestrant</td>
<td>17</td>
<td>16</td>
</tr>
<tr>
<td>Any previous chemotherapy</td>
<td>69</td>
<td>65</td>
</tr>
<tr>
<td>Previous chemotherapy for metastatic BC</td>
<td>26</td>
<td>26</td>
</tr>
<tr>
<td>Previous radiotherapy</td>
<td>70</td>
<td>69</td>
</tr>
<tr>
<td>Number of prior therapies†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 or 2</td>
<td>46</td>
<td>48</td>
</tr>
<tr>
<td>≥3</td>
<td>54</td>
<td>53</td>
</tr>
</tbody>
</table>
The findings of the BOLERO-2 trial would indicate that the addition of everolimus to exemestane in postmenopausal patients who have developed endocrine resistance would be able to extend their chemotherapy-free period by a maximum of 10 months.
PFS - Subgroup Analyses

- The effect of EVE+EXE treatment was consistent among prospectively defined subgroups by local investigator and central review.

### Median PFS, mo

<table>
<thead>
<tr>
<th>Race</th>
<th>Median PFS, mo</th>
<th>HR</th>
<th>EVE+EXE</th>
<th>PBO+EXE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Race</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>724</td>
<td>0.45</td>
<td>7.8</td>
<td>3.2</td>
</tr>
<tr>
<td>Caucasian</td>
<td>547</td>
<td>0.42</td>
<td>13.88</td>
<td>4.14</td>
</tr>
<tr>
<td>Other</td>
<td>34</td>
<td>0.25</td>
<td>6.93</td>
<td>1.41</td>
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<tr>
<td><strong>Baseline ECOG performance status</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>435</td>
<td>0.48</td>
<td>8.25</td>
<td>4.11</td>
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<tr>
<td>1, 2</td>
<td>274</td>
<td>0.40</td>
<td>6.93</td>
<td>2.76</td>
</tr>
<tr>
<td><strong>PgR status</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>184</td>
<td>0.43</td>
<td>13.14</td>
<td>4.14</td>
</tr>
<tr>
<td>Positive</td>
<td>523</td>
<td>0.41</td>
<td>8.08</td>
<td>3.32</td>
</tr>
<tr>
<td><strong>Presence of visceral metastasis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>318</td>
<td>0.41</td>
<td>9.86</td>
<td>4.21</td>
</tr>
<tr>
<td>Yes</td>
<td>406</td>
<td>0.46</td>
<td>8.31</td>
<td>2.89</td>
</tr>
<tr>
<td><strong>Bone only lesions at baseline</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>573</td>
<td>0.48</td>
<td>6.90</td>
<td>2.83</td>
</tr>
<tr>
<td>Yes</td>
<td>151</td>
<td>0.33</td>
<td>12.88</td>
<td>5.29</td>
</tr>
</tbody>
</table>

**Favors EVE+EXE**

<table>
<thead>
<tr>
<th>Median PFS, mo</th>
<th>HR</th>
<th>EVE+EXE</th>
<th>PBO+EXE</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>724</td>
<td>0.45</td>
<td>7.8</td>
</tr>
<tr>
<td>Age group</td>
<td></td>
<td>0.45</td>
<td>11.00</td>
</tr>
<tr>
<td>&lt; 65</td>
<td>449</td>
<td>0.38</td>
<td>8.31</td>
</tr>
<tr>
<td>≥ 65</td>
<td>275</td>
<td>0.59</td>
<td>6.83</td>
</tr>
<tr>
<td>Region</td>
<td></td>
<td>0.50</td>
<td>10.84</td>
</tr>
<tr>
<td>Asia</td>
<td>137</td>
<td>0.60</td>
<td>8.48</td>
</tr>
<tr>
<td>Europe</td>
<td>275</td>
<td>0.45</td>
<td>7.16</td>
</tr>
<tr>
<td>North America</td>
<td>274</td>
<td>0.38</td>
<td>8.41</td>
</tr>
<tr>
<td>Other</td>
<td>38</td>
<td>0.40</td>
<td>4.53</td>
</tr>
<tr>
<td>Japanese patients</td>
<td></td>
<td>0.36</td>
<td>5.72</td>
</tr>
<tr>
<td>Japan</td>
<td>106</td>
<td>0.58</td>
<td>8.54</td>
</tr>
<tr>
<td>Non-Japan</td>
<td>618</td>
<td>0.42</td>
<td>7.16</td>
</tr>
</tbody>
</table>

**Median PFS, mo**

- **Favors EVE+EXE**
- **Favors PBO+EXE**

**Hazard Ratio and 95% CI**

- **Favors EVE+EXE**
- **Favors PBO+EXE**
## BOLERO-2: Adverse Events (18-Mo Follow-up)

<table>
<thead>
<tr>
<th>Adverse Event, %</th>
<th>Everolimus + Exemestane (n = 482)</th>
<th>Placebo + Exemestane (n = 238)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All</td>
<td>3</td>
</tr>
<tr>
<td>Total</td>
<td>100</td>
<td>44</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>37</td>
<td>4</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>34</td>
<td>2</td>
</tr>
<tr>
<td>Nausea</td>
<td>31</td>
<td>&lt; 1</td>
</tr>
<tr>
<td>Appetite decreased</td>
<td>31</td>
<td>1</td>
</tr>
<tr>
<td>Noninfectious pneumonitis</td>
<td>16</td>
<td>3</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>14</td>
<td>5</td>
</tr>
</tbody>
</table>

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

+ 4.4 months

Piccart M, et al. EBCC 2014
Longer median time from randomization to first chemotherapy or death

<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*</td>
<td>14 (2.9)</td>
<td>2 (0.8)</td>
</tr>
<tr>
<td>Time from randomization to first chemotherapy or death, months</td>
<td></td>
<td></td>
</tr>
<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><strong>Median (95% CI)</strong></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>

*aOngoing without any chemotherapy by the cutoff date.
BOLERO-2: Conclusions

- In patients with HR+ HER2– advanced BC progressing after initial NSAIs
  - The combination of EVE+EXE resulted in a clinically significant improvement of PFS compared to EXE alone
  - This effect was consistent among all prospectively defined subgroups
- There are fewer deaths in the EVE+EXE arm compared with PBO+EXE
- The adverse event profile was consistent with the known mTOR class safety events
- Careful monitoring from initiation of therapy and timely management of EVE associated adverse events including prevention strategies are important!
ENDOCRINE THERAPY FOR RECURRENT OR STAGE IV DISEASE

Postmenopausal Patients

- Non-steroidal aromatase inhibitor (anastrozole, letrozole)
- Steroidal aromatase inactivator (exemestane)
  - **Exemestane + everolimus**¹
- Palbociclib + letrozole²
- Fulvestrant
- Tamoxifen or toremifene
- Megestrol acetate
- Fluoxymesterone
- Ethinyl estradiol

---

¹A combination of exemestane with everolimus can be considered for patients who meet the eligibility criteria for BOLERO-2 (progressed within 12 mo or on non-steroidal AI, or any time on tamoxifen).
²Palbociclib in combination with letrozole may be considered as a treatment option for first-line therapy for postmenopausal patients with ER-positive, HER2-negative metastatic breast cancer.
HORIZON: 
letrozole + temsirolimus vs. letrozole

Phase 3 Placebo controlled study
N = 1,112
Postmenopausal women with ER\(^+\) advanced breast cancer
AI naïve

IDMC recommended to close the study for futility after the second planned interim analysis.

Exploratory analysis suggests benefit in patients younger than 65 (?)

Comparison of mTOR inhibitors + AIs

**BOLERO-2**

- Hazard ratio, 0.36 (95% CI, 0.27–0.47)
- P<0.001 by log-rank test
- Everolimus plus exemestane (median PFS, 10.6 mo)
- Placebo plus exemestane (median PFS, 4.1 mo)

**HORISON**

- Progression-Free Survival
- Stratified log-rank test P = .25
- HR, 0.50; 95% CI, 0.76 to 1.07

84% prior endocrine treatment
50% no prior endocrine treatment

TAMRAD: GINECO study

Open-label, randomized Phase II study

- Postmenopausal HER2-/ER+
- AI resistant MBC (N = 111)

1:1 randomisation

- Tamoxifen 20 mg/d (n=57)
- Tamoxifen 20 mg/d + RAD001 10 mg/d (n=54)

- Stratification: primary or secondary hormone resistance
  1. Primary: relapse during adjuvant AI; progression within 6 mo of starting AI treatment in MBC
  2. Secondary: late relapse(≥ 6 mo) or prior response & subsequent progression to metastatic AI treatment

- No cross-over planned
TAMRAD: TTP, OS & CBR

Conclusion:
Tamoxifen plus everolimus increased CBR, TTP, and overall survival compared with tamoxifen alone in postmenopausal women with AI-resistant mBC.

TAMRAD: TTP as a function of intrinsic Hormone Resistance

- **Primary resistance**
  - TAM: 3.8 months
  - TAM + RAD: 5.4 months
  - HR = 0.70 (0.40-1.21)
  - p = NS (exploratory analysis)

- **Secondary resistance**
  - TAM: 5.5 months
  - TAM + RAD: 14.8 months
  - HR = 0.46 (0.26-0.83)
  - p = 0.0087 (exploratory analysis)

Combining Targeted and Antiestrogen Therapies in HR-Positive Breast Cancer

Aromatase Inhibitor
Nonsteroidal AIs
Anastrozole
Letrozole
Steroidal AIs
Exemestane

ER Downregulator
Fulvestrant

Selective Estrogen Receptor Modulators
Tamoxifen
Toremifene

ER target gene transcription

PI3K inhibitors
BMK120
BYL790
GDC0980

mTOR Inhibitors
Everolimus
Sirolimus
Temsirolimus

CDK 4/6 Inhibitor
PD 0332991

HDAC Inhibitor
Entinostat

Cell Cycle
Transcription Silencing

PI3K
AKT
PTEN
mTOR
RAS
RAF
MEK
MAPK
EGFR
HER2
TKI

Transcription
Silencing
### PI3K/mTOR inhibitors in clinical development

<table>
<thead>
<tr>
<th>Drug</th>
<th>Pharma Source</th>
<th>Target(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BYL719</td>
<td>Novartis</td>
<td>PI3Kα</td>
</tr>
<tr>
<td>GDC-0032</td>
<td>Genentech</td>
<td>PI3Kα</td>
</tr>
<tr>
<td>MLN-1117</td>
<td>Millenium</td>
<td>PI3Kα</td>
</tr>
<tr>
<td>CAL-101</td>
<td>Calistoga</td>
<td>PI3Kδ</td>
</tr>
<tr>
<td>XL-147</td>
<td>Exelixis/Sanofi</td>
<td>Pan-PI3K</td>
</tr>
<tr>
<td>BKM120</td>
<td>Novartis</td>
<td>Pan-PI3K</td>
</tr>
<tr>
<td>GDC-0941</td>
<td>Genentech</td>
<td>Pan-PI3K</td>
</tr>
<tr>
<td>PKI-587</td>
<td>Pfizer</td>
<td>Pan-PI3K</td>
</tr>
<tr>
<td>XL-765</td>
<td>Exelixis/Sanofi</td>
<td>PI3K/mTOR</td>
</tr>
<tr>
<td>BEZ235</td>
<td>Novartis</td>
<td>PI3K/mTOR</td>
</tr>
<tr>
<td>GDC-0980</td>
<td>Genentech</td>
<td>PI3K/mTOR</td>
</tr>
<tr>
<td>PF-4691502</td>
<td>Pfizer</td>
<td>PI3K/mTOR</td>
</tr>
<tr>
<td>MLN-128</td>
<td>Millenium</td>
<td>TORC1/2</td>
</tr>
<tr>
<td>OSI-027</td>
<td>OSI Pharma</td>
<td>TORC1/2</td>
</tr>
<tr>
<td>AZD2014</td>
<td>AstraZeneca</td>
<td>TORC1/2</td>
</tr>
<tr>
<td>AZD5363</td>
<td>AstraZeneca</td>
<td>AKT (catalytic)</td>
</tr>
<tr>
<td>MK-2206</td>
<td>Merck</td>
<td>AKT (allosteric)</td>
</tr>
<tr>
<td>GDC-0068</td>
<td>Genentech</td>
<td>AKT (catalytic)</td>
</tr>
</tbody>
</table>
Phase II FERGI: Fulvestrant ± Pictilisib in ER+, AI-Resistant Adv or Metastatic BC

Stratified by PIK3CA mutation, PTEN loss, measurable disease, first- vs second-degree resistance

Postmenopausal women with ER+, HER2-, adv or metastatic breast cancer, prior AI (adjuvant or metastatic), 0-1 prior chemo regimens or ≤ 2 prior endocrine therapies (N = 168)

Fulvestrant 500 mg* + Pictilisib (GDC-0941) 340 mg QD (n = 89)

Fulvestrant 500 mg* + Placebo QD (n = 79)

*28-day cycles: Days 1, 15 in cycle 1, then Day 1 thereafter.

- Primary endpoints: PFS (ITT and with PIK3CA mutation), safety
- Secondary endpoints: ORR, DOR, pharmacokinetics

Fulvestrant ± Pictilisib in ER+, AI-Resistant Adv or Metastatic BC (FERGI): PFS (ITT)

Median PFS, mos
HR
Log-rank $P$ value

Placebo + Ful
5.1
0.738
0.0959

Pictilisib + Ful
6.6

Pts at Risk, n
Placebo + Ful 79 54 35 27 22 21 15 8 5 4 2 1 0
Pictilisib + Ful 89 63 45 37 30 26 25 18 9 8 3 2 2

Fulvestrant ± Pictilisib in ER+, AI-Resistant Adv or Met BC (FERGI): PFS (ER/PR+)

# Fulvestrant ± Pictilisib in ER+, AI-Resistant Adv or Metastatic BC (FERGI): Toxicity

<table>
<thead>
<tr>
<th>Adverse Event, %</th>
<th>Fulvestrant/Pictilisib (n = 89)</th>
<th>Fulvestrant/Placebo (n = 79)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 1-4</td>
<td>Grade 3/4</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>63</td>
<td>7</td>
</tr>
<tr>
<td>Nausea</td>
<td>48</td>
<td>3.4</td>
</tr>
<tr>
<td>Rash</td>
<td>43</td>
<td>17</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>35</td>
<td>--</td>
</tr>
<tr>
<td>Fatigue</td>
<td>27</td>
<td>6</td>
</tr>
<tr>
<td>Vomiting</td>
<td>20</td>
<td>3</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>19</td>
<td>1</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>17</td>
<td>5</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>16</td>
<td>2</td>
</tr>
<tr>
<td>Hot flash</td>
<td>11</td>
<td>--</td>
</tr>
<tr>
<td>AST increase</td>
<td>11</td>
<td>3</td>
</tr>
</tbody>
</table>

- Dose reduction due to AE, %: 24 (Fulvestrant/Pictilisib) vs. 1 (Fulvestrant/Placebo)
- Discontinued pictilisib/placebo, %: 90 (Fulvestrant/Pictilisib) vs. 87 (Fulvestrant/Placebo)

# Ongoing Clinical Trials of PI3K inhibitors with Endocrine Therapy

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Disease conditions</th>
<th>Trial status</th>
<th>Trial number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase I</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BYL719 + letrozole</td>
<td>Postmenopausal women hormone receptor-positive stage IV breast cancer</td>
<td>Ongoing</td>
<td>NCT01791478</td>
</tr>
<tr>
<td>BKM120 + fulvestrant</td>
<td>Postmenopausal women estrogen receptor-positive stage IV breast cancer</td>
<td>Ongoing</td>
<td>NCT01339442</td>
</tr>
<tr>
<td>BKM120 or BEZ235 + letrozole</td>
<td>Postmenopausal women hormone receptor-positive stage IV breast cancer</td>
<td>Ongoing, not recruiting</td>
<td>NCT01248494</td>
</tr>
<tr>
<td>XL147 or XL765 + letrozole</td>
<td>Postmenopausal women hormone receptor-positive stage IV breast cancer</td>
<td>Completed</td>
<td>NCT01082068</td>
</tr>
<tr>
<td>Phase II</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PF-04691502 + exemestane vs</td>
<td>Estrogen receptor-positive stage IV breast cancer</td>
<td>Withdrawn prior to enrolment</td>
<td>NCT01658176</td>
</tr>
<tr>
<td>exemestane alone</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PF-4691502 + letrozole vs letrozole alone</td>
<td>Postmenopausal women estrogen receptor-positive early (phase II) and advanced (phase I b) breast cancer</td>
<td>Terminated</td>
<td>NCT01430585</td>
</tr>
<tr>
<td>GDC-0941 or GDC-0980/placebo + fulvestrant</td>
<td>Postmenopausal women estrogen receptor-positive, AI treated, stage III B-IV breast cancer</td>
<td>Ongoing</td>
<td>NCT01437566</td>
</tr>
<tr>
<td>Phase III</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BKM120/placebo + fulvestrant</td>
<td>Postmenopausal women hormone receptor-positive, AI treated, stage III B-IV breast cancer progressed on or after mTOR inhibitor-based treatment</td>
<td>Ongoing</td>
<td>NCT01633060</td>
</tr>
<tr>
<td>BKM120/placebo + fulvestrant</td>
<td>Postmenopausal women hormone receptor-positive, stage III B-IV breast cancer refractory to AIs</td>
<td>Ongoing</td>
<td>NCT01610284</td>
</tr>
</tbody>
</table>
To Overcome Endocrine Resistance

- Enhancing endocrine blockade
  - AIs + Fulvestrant

- Blockade of growth factor receptor pathways
  - PI3K inhibitors/mTOR inhibitors
  - EGFR/IGFR blockades
  - HER2 blockades

- CDK 4/6 inhibitors

- Targeting epigenetics (HDAC inhibitor)

- Others (FGFR inhibitor, Src inhibitors, )
Targeting HER2 to prevent acquired endocrine resistance

**Effect of trastuzumab alone or in combination with letrozole on MCF7Ca xenografts**

- Control (ΔA 100μg/day)
- Trastuzumab (5mg/kg/week)
- Letrozole (10μg/day)
- Trastuzumab plus Letrozole
- Letrozole Switched to Trastuzumab
- Letrozole Switched to Trastuzumab plus Letrozole

**Mean Tumor Volume (mm³)**

- **Control**
- Trastuzumab
- Letrozole
- Trastuzumab plus Letrozole
- Letrozole Switched to Trastuzumab
- Letrozole Switched to Trastuzumab plus Letrozole

**Weeks**

Source: Macedo et al, Cancer 2008 112; (suppl 3) 679-88
TAnDEM
(Trastuzumab + Anastrozole vs. Anastrozole)

Eligibility:
HER2-positive, HR-positive MBC

Randomization (N=208)

Anastrozole 1mg daily +
Trastuzumab 4 mg/kg
loading dose → 2 mg/kg qw

Anastrozole 1mg daily

Treatment continued until disease progression
TAnDEM: Progression Free Survival

<table>
<thead>
<tr>
<th>Events</th>
<th>Median PFS</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>87</td>
<td>4.8 months</td>
<td>3.7, 7.0</td>
<td>0.0016</td>
</tr>
<tr>
<td>99</td>
<td>2.4 months</td>
<td>2.0, 4.6</td>
<td></td>
</tr>
</tbody>
</table>

No. at risk:

- **A + H**: 103, 48, 31, 17, 14, 13, 11, 9, 4, 1, 1, 1, 0, 0, 0
- **A**: 104, 36, 22, 9, 5, 4, 2, 1, 0, 0, 0, 0, 0, 0

Months:

0 5 10 15 20 25 30 35 40 45 50 55 60
EGF 30008 Trial: PFS
(Letrozole + lapatinib vs. letrozole alone)
To Overcome Endocrine Resistance

• Enhancing endocrine blockade
  – AIs + Fulvestrant

• Blockade of growth factor receptor pathways
  – PI3K inhibitors/mTOR inhibitors
  – EGFR/IGFR blockades
  – HER2 blockades

• CDK 4/6 inhibitors

• Targeting epigenetics (HDAC inhibitor)

• Others (FGFR inhibitor, Src inhibitors, )
Combining Targeted and Antiestrogen Therapies in HR-Positive Breast Cancer

- **PI3K inhibitors**
  - BMK120
  - BYL790
  - GDC0980

- **mTOR Inhibitors**
  - Everolimus
  - Sirolimus
  - Temsirolimus

- **CDK 4/6 Inhibitor**
  - PD 0332991

- **HDAC Inhibitor**
  - Entinostat

- **Aromatase Inhibitor**
  - Nonsteroidal AIs
    - Anastrozole
    - Letrozole
  - Steroidal AIs
    - Exemestane

- **ER Downregulator**
  - Fulvestrant

- **Selective Estrogen Receptor Modulators**
  - Tamoxifen
  - Toremifene

- **ER target gene transcription**

**Cell Cycle**

**Transcription Silencing**
Luminal type breast cancer is driven by CDK4/6

Cyclin D1 is downstream of oncogenic events in ER positive breast cancer
ER+ BC cells are sensitive to CDK4/6 inhibition

Light blue: luminal
Dark blue bars or stripes: HER2 amplified
Yellow: nonluminal/undergone EMT
Red; nonluminal
Turquoise; immotolized

Finn RA et al. Breast Cancer Res. 2009;11(5):R77
Cyclin D/CDK4/6 Inhibitors

Several novel compounds in clinical trials

CDK4/6 Inhibitors
Phase 2 Study Design
ER+, HER2−, Locally Recurrent or Metastatic Breast Cancer

**Part 1**
- **Randomization**
  - Post-menopausal
  - ER+, HER2−, BC status
  - No prior treatment for advanced disease

  Palbociclib 125 mg QD\(^a\) + Letrozole 2.5 mg QD

  Letrozole 2.5 mg QD

  N=66

**Part 2**
- **Randomization**
  - Post-menopausal
  - ER+, HER2− BC with CCND1 amplification and/or loss of p16
  - No prior treatment for advanced disease

  Palbociclib 125 mg QD\(^a\) + Letrozole 2.5 mg QD

  Letrozole 2.5 mg QD

  N=99

---

**Key Eligibility Criteria**
- Measurable disease (RECIST 1.0) or bone-only disease
- ECOG PS of 0 or 1
- Adequate blood counts and organ function
- No prior/current brain metastases

**Stratification Factors**
- Disease Site (Visceral vs Bone only vs Other)
- Disease-Free Interval (>12 vs ≤12 mo from end of adjuvant to recurrence or de novo advanced disease)

\(^a\) Schedule 3/1
Study Design: Phase II Trial (2 parts)

PD 0332991 125 mg QD × 3 wk, 1 week off; plus letrozole 2.5 mg QD × 4 wk
4-week treatment cycle

Letrozole 2.5 mg QD × 4 wk

Study population
- Postmenopausal women with ER* HER2- breast cancer
- Patients with CCND1 amplification and/or loss of p16 (Part 2)

Stratification factors
- Disease site (visceral vs bone only vs other)
- Disease-free interval (> 12 vs ≤ 12 mo from end of adjuvant to recurrence or de novo advanced disease)

N = 165
(66 part 1 and 99 part 2)

Response Efficacy (ORR, CBR, PFS)

<table>
<thead>
<tr>
<th></th>
<th>Letrozole + PD 991 (n=84)</th>
<th>Letrozole (n=81)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR n (%)</td>
<td>29 (34%)</td>
<td>21 (26%)</td>
</tr>
<tr>
<td>CBR n (%)</td>
<td>59 (70%)</td>
<td>56 (44%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>PD 991 + LET (n = 84)</th>
<th>LET (n = 81)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS, mo (95% CI)</td>
<td>26.1 (12.7, 26.1)</td>
<td>7.5 (5.6, 12.6)</td>
</tr>
<tr>
<td>Hazard Ratio (95% CI)</td>
<td>0.37 (0.21, 0.63)</td>
<td></td>
</tr>
<tr>
<td>P value</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

Finn RS et al. SABCS 2012; # S1-6.
Overall Survival (ITT) At Time of Final PFS Analysis

- **Number of Events (%)**:
  - **PAL + LET (N=84)**: 30 (36)
  - **LET (N=81)**: 31 (38)

- **Median OS, months**:
  - **PAL + LET (95% CI)**: 37.5 (28.4, NR)
  - **LET (95% CI)**: 33.3 (26.4, NR)

- **Hazard Ratio (95% CI)**:
  - **PAL + LET** vs **LET**: 0.813 (0.492, 1.345)

- **p-value**: 0.2105

**Number of patients at risk**:

<table>
<thead>
<tr>
<th></th>
<th>PAL + LET (N=84)</th>
<th>LET (N=81)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>84</td>
<td>81</td>
</tr>
<tr>
<td>4</td>
<td>80</td>
<td>76</td>
</tr>
<tr>
<td>8</td>
<td>78</td>
<td>74</td>
</tr>
<tr>
<td>12</td>
<td>78</td>
<td>67</td>
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<td>16</td>
<td>73</td>
<td>67</td>
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<td>20</td>
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<td>24</td>
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<td>28</td>
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<td>32</td>
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<td>36</td>
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<td>14</td>
</tr>
<tr>
<td>40</td>
<td>17</td>
<td>12</td>
</tr>
<tr>
<td>44</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>48</td>
<td>7</td>
<td>1</td>
</tr>
</tbody>
</table>

AACR 2014
## Letrozole ± Palbociclib in ER+, HER2-MBC: Grade 3/4 AEs

<table>
<thead>
<tr>
<th>Grade 3/4 AE, %</th>
<th>Palbociclib + LET (n = 83)</th>
<th>LET (n = 77)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>51</td>
<td>1</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Anemia</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Nausea</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Hot flush</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Alopecia</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>4</td>
<td>0</td>
</tr>
</tbody>
</table>

To Overcome Endocrine Resistance

• Enhancing endocrine blockade
  – AIs + Fulvestrant

• Blockade of growth factor receptor pathways
  – PI3K inhibitors/mTOR inhibitors
  – EGFR/IGFR blockades
  – HER2 blockades

• CDK 4/6 inhibitors

• Targeting epigenetics (HDAC inhibitor)

• Others (FGFR inhibitor, Src inhibitors, )
HDAC Inhibitors: Mechanism of Action

- HDAC inhibitors relax the structure of DNA making it more accessible to RNA polymerases

ENCORE 301 - Phase II RCT of Exemestane +/- Entinostat in ER+ MBC progressing after NSAI

Hypothesis: Entinostat re-sensitizes tumors to aromatase inhibitors (AI)

- Post-menopausal women with metastatic or locally advanced ER+ breast cancer progressing on a non-steroidal AI (anastrozole or letrozole)

Randomized, **double-blind**, placebo-controlled
Endpoints include: 1st PFS, 2nd ORR and CBR; Exploratory Endpoint - OS

- Exemestane + Entinostat (ENT)
  5 mg po weekly
  N ~ 57

- Exemestane + Placebo (PLA)
  5 mg po weekly
  N ~ 57
ENCORE 301: PFS, OS

PFS - ITT population

- EE: median PFS 4.3 months
- EP: median PFS 2.3 months

Hazard ratio 0.73 (95% CI: 0.50, 1.07)

P = 0.055 (1-sided)

OS - ITT population

- EE: median OS 28.1 months
- EP: median OS 19.8 months

Hazard Ratio 0.59 (95% CI: 0.36, 0.97)

P = 0.04 (2-sided); P = 0.02 (1-sided)

Endocrine Therapy; Summary

- Continue endocrine therapies until resistance.
- AI or fulvestrant are most effective first-line single agents; fulvestrant ± AI reasonable choice for endocrine therapy–naive patients with MBC.
- mTOR inhibition with everolimus + exemestane is best second-line therapy after progression on nonsteroidal AI.
- After everolimus, back to anti-ER therapy alone or enhanced blockade of PI3K pathway
- Addition of CDK4/6 inhibitor to first-line letrozole may become a new SOC; phase III trial under way.
Estrogen Receptor Mutations in ER+ Breast Cancer

- Estrogen receptor: key driver in breast cancer oncogenesis; target of current endocrine therapy
  - Endocrine therapy resistance remains clinical challenge for patients with ER+ breast cancer
Genetic events are acquired in metastatic breast cancer

ESR1 ligand-binding domain mutations in hormone-resistant breast cancer

ESR mutations occur in 15-20% of endocrine-resistant ER+ BCs.

Point Mutation in ESR1 in Patient-Derived Xenograft Models

- Point mutation: patient with stage 3 ER+/HER2- disease resistant to multiple lines of endocrine therapy
  - Analysis revealed **point mutation in ligand binding domain of ESR1 (Y537S)**

![Graph showing tumor volume over days with and without estradiol](Image)

- Without estradiol
- With estradiol

N = 10
$P = 0.7$

Translocations in ESR1 in Patient-Derived Xenograft Models

- Gene Translocation: patient with stage 4 ER+/HER2- disease resistant to multiple lines of endocrine therapy
  - Analysis revealed activating ESR1/YAP1 fusion

![Graphs showing tumor volume changes with and without estradiol and fulvestrant treatments.](image)

Shao J, et al. SABCS 2013. Abstract S3-05..
Gene amplifications in ESR1 in Patient-Derived Xenograft Models

- Gene amplification: patient with stage 3A ER+/HER2- disease resistant to multiple lines of endocrine therapy with paradoxical response to estradiol treatment
  - Analysis revealed **ESR1 gene amplification** resulting in high protein expression

Effects of ER Mutational Status

- In matched pairs for sequential biopsies, 2 LBD mutations detected in MBC but not in primary tumor

ER Mutations in Breast Cancer: Main Conclusions

- Mutation of ESR1 found in tumors in patients with ER+ MBC
  - Mutations led to resistance to endocrine therapy
  - 3 Type of mutation leads to differential treatment resistance
    1) Ligand-binding domain mutations: resistance to AIs; potentially treatable with high-dose fulvestrant or antiestrogens
    2) Gene translocations: resistance to classic endocrine treatment
    3) Gene amplifications: resistance to AIs; potentially treatable with estradiol or antiestrogens

- Mutations mostly absent in primary tumors, and correlates with increasing number of endocrine therapies
  - Mutations potential driver of endocrine resistance

Thank you for your attentions!!