Optimizing therapy selection in ER[+] HER2[-] Advanced Breast Cancer

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Evolution of Breast Cancer Treatment

Early-stage breast cancer

- Neoadjuvant therapy: Reduce tumour size prior to surgery + reduce risk of recurrence
- Adjuvant therapy: Reduce risk of recurrence after surgery

Locally inoperable or initially metastatic breast cancer

- 30% will progress to advanced disease

Advanced breast cancer

- Palliative therapy: Prolong survival and control disease symptoms

First Line is a mixed scenario of “naive” and “pretreated” patients

Goal: curative treatment

5 to >30% of patients are Stage IV at diagnosis

Goals in the Treatment of MBC
ESMO/NCCN Guidelines

• Metastatic breast cancer is incurable yet treatable
• Treatment aims:
  – Maintain or improve quality of life
  – Delay disease progression
  – Control disease symptoms
• Treatment decision guided by tumour phenotype
• A large number of active agents – combinations, but standard management still debatable
• Appropriate management supports goal of improving survival

In 2015 Molecular Phenotypes Drive Treatment Algorithms for ABC

**HER2+**
- Anti-HER2 agents extremely effective

**TNBC**
- Cytotoxic therapy as the only option

**ER/PR+ HER2−**
- Endocrine and cytotoxic therapies are effective

- Great OS Expectations linked to new agents
- Limited benefits with chemotherapy and dismal prognosis
- Wide range of options with (apparent) low impact on OS

*Physician’s concern*
- Grant access to new targeted agents
- Promote translational research
- Individualize strategies based on scenarios
### ASCO recommendations

*Endocrine therapy, rather than chemotherapy, should be offered as the standard first-line treatment for patients with hormone receptor–positive advanced/metastatic breast cancer*, except for immediately life threatening disease or if there is concern regarding endocrine resistance.

- **The main benefit is less toxicity and better quality of life** for the patient associated with endocrine therapy compared with chemotherapy (potential benefit: high). The harm is that metastatic disease could progress rapidly and prove fatal if there is no response, but the risk of this is low (potential harm: low).

### ESMO/ABC2 recommendations

ESMO guidelines reinforce the preferential use of endocrine therapy, even in the presence of visceral metastases, for ER-positive, HER2-negative advanced breast cancer. Chemotherapy should be reserved for cases of rapidly progressive disease or proven endocrine resistance.

### NCCN recommendations

Women with recurrent or metastatic disease characterized by tumors that are ER- and/or PR-positive are appropriate candidates for initial endocrine therapy.

- Less toxic
- Better QoL

---

Chemotherapy vs Endocrine Therapy Trials: Objective Response Rate

Receptor status was mostly unknown in all studies

Chemotherapy vs Endocrine Therapy Trials: Overall Survival

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Endocrine therapy</th>
<th>Chemotherapy</th>
<th>Hazard Ratio Exp[(O-E)/V], Fixed, 95% CI</th>
<th>Weight</th>
<th>Hazard Ratio Exp[(O-E)/V], Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dixon 1992</td>
<td>18/30</td>
<td>14/30</td>
<td></td>
<td>5.8 %</td>
<td>0.76 [ 0.34, 1.66 ]</td>
</tr>
<tr>
<td>Tashiro 1990</td>
<td>23/30</td>
<td>24/26</td>
<td></td>
<td>10.5 %</td>
<td>0.76 [ 0.42, 1.36 ]</td>
</tr>
<tr>
<td>ANZBCTG 1986</td>
<td>95/113</td>
<td>100/113</td>
<td></td>
<td>47.1 %</td>
<td>0.85 [ 0.65, 1.12 ]</td>
</tr>
<tr>
<td>Taylor 1986</td>
<td>68/99</td>
<td>69/95</td>
<td></td>
<td>32.3 %</td>
<td>0.80 [ 0.58, 1.12 ]</td>
</tr>
<tr>
<td>Clavel 1982</td>
<td>17/34</td>
<td>16/30</td>
<td></td>
<td>4.3 %</td>
<td>1.61 [ 0.65, 4.00 ]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td></td>
<td></td>
<td></td>
<td>100.0 %</td>
<td>0.84 [ 0.70, 1.02 ]</td>
</tr>
</tbody>
</table>

Heterogeneity: Chi² = 2.25, df = 4 (P = 0.69); I² = 0.0%
Test for overall effect: Z = 1.77 (P = 0.076)
Test for subgroup differences: Not applicable

Receptor status was mostly unknown in all studies
Treatment of “Rapidly Progressive Disease”
ABC Recommendations

ER POSITIVE MBC

- 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).

VISCERAL CRISIS

- is defined as severe organ dysfunction as assessed by signs and symptoms, laboratory studies, and rapid progression of disease.

Visceral crisis is not the mere presence of visceral metastases but implies important visceral compromise leading to a clinical indication for a more rapidly efficacious therapy, particularly since another treatment option at progression will probably not be possible. (LoE: Expert opinion).

Visceral Metastases from HR+ MBC are not a Criteria for Endocrine Resistance

Combined analysis of four, Phase III, randomised controlled trials of 1st-line ET for ABC in postmenopausal women with available data on visceral vs. non-visceral metastases*

*Similar results were observed from studies using tamoxifen only. Robertson JFR, et al. SABCS 2014 (Abstract P1-13-02).

“ET for advanced/metastatic BC is as effective in responsive patients with visceral metastases as in those with non-visceral metastases.”

DoCB, duration of clinical benefit
*Median DoCB

Patients with visceral metastases: 14.0 months
Patients with non-visceral metastases: 14.4 months

HR (95% CI): 0.92 (0.78, 1.09); p=0.35

95% CI, 95% confidence interval; DoCB, duration of clinical benefit; HR, hazard ratio
First Line Therapy
HR[+] Metastatic Breast Cancer

Endocrine Sensitive
“De Novo” MBC
Naïve MBC
MBC > 1 year from the end of ET for EBC
EORTC Premenopausal: Survival Benefit for Ovarian Suppression and TAM

Overall Survival

Overall Logrank test: p=0.0114

<table>
<thead>
<tr>
<th></th>
<th>O</th>
<th>N</th>
<th>Number of patients at risk</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>43</td>
<td>54</td>
<td>29  11  2  1</td>
</tr>
<tr>
<td></td>
<td>35</td>
<td>53</td>
<td>39  23  11  4</td>
</tr>
<tr>
<td></td>
<td>44</td>
<td>54</td>
<td>34  16  6  0</td>
</tr>
</tbody>
</table>

Treatment
- LHRH-A
- LHRH-A+TAM
- TAM

First-Line Therapy: Aromatase Inhibitors Showed Consistent Superiority over Tamoxifen (Postmenop)

<table>
<thead>
<tr>
<th>TTP (months)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Letrozole</td>
<td>9.4</td>
</tr>
<tr>
<td>Tamoxifen</td>
<td>6.0</td>
</tr>
<tr>
<td>Anastrozole</td>
<td>10.7</td>
</tr>
<tr>
<td>Tamoxifen</td>
<td>6.4</td>
</tr>
<tr>
<td>Exemestane</td>
<td>10.5</td>
</tr>
<tr>
<td>Tamoxifen</td>
<td>5.5</td>
</tr>
</tbody>
</table>

AI, aromatase inhibitor; TAM, tamoxifen.

HER2 Overexpression is a Strong Predictor of Endocrine Resistance Among ER+ ABC Patients

30008 Study: Letrozole arm efficacy by HER2 status

- Comparison of control arms (LET) in both groups of treatment (by HER2 status)
- Median TTP for LET alone
  - 14.2 mos (HER2−)
  - 3.0 mos (HER2+)

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>PFS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HER2[−]</td>
<td>644</td>
<td>14.2</td>
</tr>
<tr>
<td>HER2[+]</td>
<td>108</td>
<td>3.0</td>
</tr>
</tbody>
</table>

HER2, human epidermal growth factor receptor 2; LET, letrozole; mos, months; TTP, time-to-progression. Adapted from Johnston S, et al. J Clin Oncol 2009;27:5538–5546.
## Front-Line Aromatase Inhibitors Improving Efficacy Over the Last Decade

<table>
<thead>
<tr>
<th>Letrozole single agent first-line trials</th>
<th>Year</th>
<th>Criteria</th>
<th>CBR (%)</th>
<th>TTP median (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mouridsen</td>
<td>2004</td>
<td>ER+</td>
<td>50</td>
<td>9.4</td>
</tr>
<tr>
<td>Wolf</td>
<td>2012</td>
<td>ER+</td>
<td>–</td>
<td>9.0</td>
</tr>
<tr>
<td>Johnston</td>
<td>2009</td>
<td>ER+/HER2−</td>
<td>64</td>
<td>15.0</td>
</tr>
<tr>
<td>Martin</td>
<td>2015</td>
<td>ER+/HER2−</td>
<td>67</td>
<td>14.4</td>
</tr>
<tr>
<td>Dickler</td>
<td>2015</td>
<td>ER+/HER2−</td>
<td>62</td>
<td>16.0</td>
</tr>
</tbody>
</table>

CBR, clinical benefit rate

New Approaches: LET + Bevacizumab  
CALGB-40503 and GEICAM-LEA

Statistically significant ($P = 0.016$), but clinically nonrelevant  
Predefined benefit: HR<0.67  
Median TTP increase >6 months

Nonsignificant ($P = 0.126$);  
8 toxicity deaths on bevacizumab

ASO 2015  
Combination treatment: mTOR Inhibitors: Temsirolimus

Progression-Free Survival (probability)

Stratified log-rank test $P = .25$
HR, 0.90; 95% CI, 0.76 to 1.07

- **LET + TEMSR**
- **LET + placebo**

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>LET + TEMSR</th>
<th>LET + placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>387/79</td>
<td>365/110</td>
</tr>
<tr>
<td>4</td>
<td>278/63</td>
<td>276/58</td>
</tr>
<tr>
<td>6</td>
<td>193/43</td>
<td>211/35</td>
</tr>
<tr>
<td>8</td>
<td>149/19</td>
<td>154/18</td>
</tr>
<tr>
<td>10</td>
<td>102/21</td>
<td>110/21</td>
</tr>
<tr>
<td>12</td>
<td>61/19</td>
<td>65/21</td>
</tr>
<tr>
<td>14</td>
<td>40/10</td>
<td>37/9</td>
</tr>
<tr>
<td>16</td>
<td>22/2</td>
<td>18/6</td>
</tr>
<tr>
<td>18</td>
<td>5/4</td>
<td>6/2</td>
</tr>
<tr>
<td>20</td>
<td>0/3</td>
<td>2/0</td>
</tr>
<tr>
<td>22</td>
<td>0/0</td>
<td>0/0</td>
</tr>
</tbody>
</table>
Fulvestrant: The dual Mechanism of action may explain the delay (PFS gains) on resistance mechanisms

1. Fulvestrant competitively binds ER, creating a conformational change, blocking oestrogen binding$^{1-6}$

2. Fulvestrant accelerates degradation of ER, inhibiting both receptor dimerisation and translocation to the nucleus, resulting in inhibition of oestrogen-stimulated cell division$^{1-4}$

Combination treatment: SWOG S0226
Fulvestrant (250) and Anastrozole

- Phase III SWOG S0226 study
- Postmenopausal with inoperable IIIB or IV breast cancer ER/P+
- Measurable evaluable disease
- Primary objective: Progression-free survival (PFS)

Fulvestrant is not approved in this setting. Please refer to the Summary of Product of Characteristics (SmPC) for all licensed indications. The SmPC is available from your local representative.
New Approaches: Phase II - FIRST Study
Fulvestrant HD vs. Anastrozole

Postmenopausal patients with Stage IIIB or IV, ER/PR+ HER2–
Primary Objective: CB (no differences)

Fulvestrant 500 mg (n=102) 23.4 mo
Anastrozole 1 mg (n=103) 13.1 mo
HR=0.66
95% CI 0.47, 0.92
p=0.01

Fulvestrant 500 mg (n=102) 54.1 mo
Anastrozole 1 mg (n=103) 48.4 mo
HR=0.70
95% CI 0.50, 0.98
p=0.041

Fulvestrant is not approved in Korea

CB, clinical benefit; HD, high dose.
Postmenopausal women with ER+ and/or PgR+ locally advanced or metastatic breast cancer not previously treated with any hormonal therapy

Randomisation 1:1

Final analysis precluded for ESMO-2016

+ placebo to anastrozole (1 mg/day p.o.)

Progression

Survival

PFS analysis at 306 progression events

OS analysis at 50%

Progression

Survival
Cyclin D – Retinoblastoma cascade regulates the G1/S Checkpoint in Breast Cancer

D-type cyclins regulated in response to mitogenic stimuli, including activation of RTKs and steroid hormone receptors\(^1\)

- Cyclin D1 is amplified in 15–20% of breast cancers\(^2,3\)
- Human ER+ breast cancer cell lines (including those with HER2 amplification) sensitive to G0/G1 arrest\(^4\)

CDK4/6 inhibitors currently in Phase III First Line

<table>
<thead>
<tr>
<th>Agent</th>
<th>Company</th>
<th>Development Status</th>
<th>Trials Brand Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Palbociclib (PD0332991)</td>
<td>Pfizer</td>
<td>Phase III</td>
<td>PALOMA-2</td>
</tr>
<tr>
<td>Ribociclib (LEE011)</td>
<td>Novartis</td>
<td>Phase III</td>
<td>MONALEESA-2</td>
</tr>
<tr>
<td>Abemaciclib (LY28335219)</td>
<td>Lilly</td>
<td>Phase III</td>
<td>MONARCH-3</td>
</tr>
</tbody>
</table>
New approaches: Phase II – PALOMA-1
Palbociclib Front-Line: PFS (ITT Population)

**Phase III PALOMA-2 reported positive**

**Data presentation at ASCO-2016**

Palbociclib is not approved in Korea


<table>
<thead>
<tr>
<th></th>
<th>PAL + LET (n=84)</th>
<th>LET (n=81)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Events (%)</td>
<td>41 (49)</td>
<td>59 (73)</td>
</tr>
<tr>
<td>Median PFS, months</td>
<td>20.2 (13.8, 27.5)</td>
<td>10.2 (5.7, 12.6)</td>
</tr>
<tr>
<td>Hazard Ratio</td>
<td>0.488 (0.319, 0.748)</td>
<td></td>
</tr>
</tbody>
</table>
N=304 (152 per treatment arm)

Fulvestrant HD (500 mg) + palbociclib (3w/4)

Letrozole + palbociclib (3w/4)

Stratification factors:
- Visceral disease
- Adjuvant AI

Primary Objective:
- 1-year PFS Rates
- Odds Ratio: 70% vs. 85%

PD, progressive disease; R, randomisation.

Aromatase inhibitors are first-line endocrine therapy for postmenopausal patients.

- Approximately 50% of ER+ patients do NOT respond to initial treatment.
- Even those who do respond to initial treatment will eventually progress.

“Optimal post-aromatase inhibitor treatment is uncertain.”

ER+, estrogen receptor positive.

Second Line Therapy – Progression to AI
HR[+] Metastatic Breast Cancer

Endocrine Resistant
“De Novo” MBC
Naïve MBC
MBC > 1 year from the end of ET for EBC
When to Switch from Endocrine to Chemotherapy

“Chemotherapy should be reserved for cases of rapidly progressive disease or proven endocrine-resistance.” – ESMO/ABC2 guidelines

“Endocrine therapy, rather than chemotherapy… except for immediately life threatening disease or if there is concern regarding endocrine resistance.” – ASCO guidelines


LTD, life threatening disease; PD, progressive disease.
HER2, human epidermal growth factor receptor 2.

*Consider the addition of everolimus to exemestane in women who fulfill the entry criteria for BOLERO-2.

Primary Endocrine Resistance is defined as:  
• Relapse while on the first 2 years of adjuvant ET, or  
• PD within first 6 mos of initiating 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

ET resistance is a “progressive, step-wise process, and the underlying mechanism remains unclear.”

Clinical Benefit Criteria: Prognostic Marker for Endocrine Treatment

Overall survival by response to ET

<table>
<thead>
<tr>
<th>ORR (PR + CR)</th>
<th>SD &gt; 24 weeks</th>
<th>Disease Progression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anastrozole</td>
<td>33</td>
<td>85%</td>
</tr>
<tr>
<td>Megestrol Ac.</td>
<td>31</td>
<td>70%</td>
</tr>
</tbody>
</table>

Clinical Benefit to the previous line of endocrine therapy seems the best predictor for new benefits on subsequent endocrine lines.

<table>
<thead>
<tr>
<th>Clinical Benefit on Prior Line</th>
<th>2nd Line</th>
<th>3rd Line</th>
<th>4th Line</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>CB (%)</td>
<td>N</td>
</tr>
<tr>
<td>YES</td>
<td>68</td>
<td>69%</td>
<td>23</td>
</tr>
<tr>
<td>NO</td>
<td>17</td>
<td>29%</td>
<td>9</td>
</tr>
</tbody>
</table>

The absence of Clinical Benefit does not formally contraindicate new endocrine therapies, but closer follow-up seems reasonable.

Misinterpretation:
If median TTP is 3.7 months whatever the Endocrine option $\Rightarrow$ Chemotherapy may be more effective

- Fulvestrant: 250 mg – no lowering dose
- 60% >2 prior endocrine lines

NSAI, non-steroidal aromatase inhibitor

**Historic Second Line Endocrine Therapy**

**Phase III Results**

Postmenopausal Patients Progressing on tamoxifen, letrozole or anastrozole

<table>
<thead>
<tr>
<th></th>
<th>LET</th>
<th>EXE</th>
<th>FULV 250</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Control</strong></td>
<td>MEG. AC</td>
<td>MEG. AC</td>
<td>EXE</td>
</tr>
<tr>
<td>HR PFS</td>
<td>1.04</td>
<td>0.82</td>
<td>0.96</td>
</tr>
<tr>
<td><strong>p</strong></td>
<td>NS</td>
<td>0.037</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Median PFS</strong></td>
<td>3.8</td>
<td>4.8</td>
<td>3.7</td>
</tr>
</tbody>
</table>

LET, letrozole; EXE, exemestane; FULV 250, fulvestrant 250 mg; MEG AC, megestrol acetate

Efficacy of First-Line Chemotherapy in ER+/HER2−: Capecitabine (RIBBON I study)

<table>
<thead>
<tr>
<th>Capecitabine + PBO (n=206)</th>
<th>Capecitabine + PBO (n=206)</th>
<th>Capecitabine + beva (n=409)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median age</strong></td>
<td>57.0 (23–88)</td>
<td></td>
</tr>
<tr>
<td><strong>Sites of dis, %</strong></td>
<td>Visceral 71.4</td>
<td></td>
</tr>
<tr>
<td><strong>HR status, %</strong></td>
<td>Positive 73.7</td>
<td></td>
</tr>
</tbody>
</table>

**ORR, %**
- Capecitabine + PBO: 23.6
- Capecitabine + beva: 35.4
- p value: 0.0097

**CR, %**
- Capecitabine + PBO: 0.6
- Capecitabine + beva: 2.2

**PR, %**
- Capecitabine + PBO: 23
- Capecitabine + beva: 33.2

**CBR, %**
- Not assessed
- Not assessed

**Baseline risk factor**

<table>
<thead>
<tr>
<th><strong>Hormone receptor status</strong></th>
<th><strong>Capecitabine + PBO, median</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>458</td>
</tr>
<tr>
<td>Negative</td>
<td>143</td>
</tr>
<tr>
<td></td>
<td><strong>6.2</strong></td>
</tr>
<tr>
<td></td>
<td><strong>4.2</strong></td>
</tr>
</tbody>
</table>

Beva, bevacizumab; PBO, placebo.

# How Are Physicians Treating ER+/HER2–?

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Nº ER+/HER2–</th>
<th>First-Line Treatment for ABC</th>
<th>Number of ET Lines Before First CT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>CT</td>
<td>ET</td>
</tr>
<tr>
<td>US¹</td>
<td>19,120</td>
<td>40%</td>
<td>60%</td>
</tr>
<tr>
<td>Europe²</td>
<td>355</td>
<td>31%</td>
<td>69%</td>
</tr>
</tbody>
</table>

- Front-line endocrine therapy is chosen for 60%–70% of ER+ ABC patients.
- Fewer than 1 out of 4 (25%) treated with front-line ET continue on a second endocrine option.
- Chemotherapy is the preferred option on progression to a first-line endocrine treatment.

CT, chemotherapy; HT, hormonal therapy.

Second Line (AI Resistant): CONFIRM
Fulvestrant HD (500) vs LD (250) – TTP (ITT)

- Similar toxicity profile

Second Line (AI Resistant): CONFIRM

PFS by Predefined Covariates

- **Receptor status**
  - ER+ and PgR+
  - ER+ and PgR-
or unknown

- **Visceral involvement**
  - No
  - Yes

- **Response to last endocrine therapy prior to fulvestrant**
  - Responsive
  - Poorly responsive or unknown

- **Measurable disease**
  - No
  - Yes

- **Age, years**
  - < 65
  - ≥ 65

- **Last endocrine therapy prior to fulvestrant**
  - Aromatase inhibitor
  - Anti-estrogen

All patients

Hazard ratio (fulvestrant 500 mg v fulvestrant 250 mg) and 95% CI

Second Line (AI Resistant): CONFIRM Long-term Benefits in OS (ITT)

- **Fulvestrant 500 mg**
  - Median time to death (months): 26.4
- **Fulvestrant 250 mg**
  - Median time to death (months): 22.3

HR (95% CI): 0.81 (0.69-0.96)

p-value: 0.016

*aNominal value, cannot be claimed as statistically significant*
ER Signaling Pathways: Most Prevalent Mechanisms of Resistance to AI

Endocrine and Targeted Therapies for HR+/HER2– Advanced Breast Cancer

BOLERO-2: Phase III 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 endocrine therapy
  2. Presence of visceral disease
• No crossover

NSAI, nonsteroidal aromatase inhibitor; LET, letrozole; ANA, anastrozole; QOL, quality of life.
EVE + EXE More Than Doubled Median PFS - Final Analysis by Local Assessment

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

Kaplan-Meier medians
EVE+EXE: 7.8 months
PBO+EXE: 3.2 months

EVE + EXE Demonstrated a 4.4-month Not Statistically Significant Improvement in OS at 39-month Final Analysis

- At 39 months’ median follow-up, 410 deaths had occurred (data cutoff date: October 3, 2013)
- 55% of patients (n = 267) in the EVE + EXE arm
- 60% of patients (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®.

IXRS, Interactive Voice and Web Response System.
### BOLERO-2: Longer Median Time from Randomization to First Chemotherapy or Death for EVE + EXE vs PBO + EXE

<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(^a)</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></th>
<th>Everolimus + Exemestane (n = 485)</th>
<th>Placebo + Exemestane (n = 239)</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>

\(^a\)Ongoing without any chemotherapy by the cutoff date.

PALOMA-3: Phase III Trial of FUL ± PAL in Women with HR+/HER2– MBC Progressing on Prior ET

Objectives

• To determine efficacy and safety of palbociclib (PAL) plus fulvestrant (FUL) in pts with HR+/HER2– mBC progressing on prior ET

Methodology

N = 521
• HR+/HER2– ABC progressing on prior ET in advanced setting
• Pre/peri or postmenopausal

PAL + FUL (n = 347)

PBO + FUL (n = 174)

Evaluation

• Primary: PFS
• Secondary: OS, ORR, DOR, CBR, safety, HRQoL, biomarkers

ABC, advanced breast cancer; CBR, clinical benefit rate; DOR, duration of response; ET, endocrine therapy; FUL, fulvestrant; HRQoL, health related quality of life; MBC, metastatic breast cancer; ORR, objective response rate; OS, overall survival; PAL, palbociclib; PFS, progression free survival.

Paloma 3: PALBO-FULV vs. FLV 500
PFS población global (ITT)

- Palbociclib + Fulvestrant (n=347)
  - Median PFS: 9.5 months
  - 95% CI (9.2–11.0)
  - Hazard Ratio: 0.46
  - 95% CI (0.36–0.59)
  - P < 0.0001

- Placebo + Fulvestrant (n=174)
  - Median PFS: 4.6 months
  - 95% CI (3.5–5.6)

Number of Patients at Risk:
- PAL+FUL: 347, 333, 281, 273, 247, 244, 202, 197, 91, 86, 32, 23, 7, 7, 1, 0
- PCB+FUL: 174, 165, 112, 105, 83, 80, 59, 58, 22, 22, 13, 7, 2, 1, 0

FUL = fulvestrant; PAL = palbociclib; PCB = placebo; PFS = progression-free survival.
*Investigator-assessed.

Palbociclib is not approved in Korea

M Cristofanili; SABCS 2015
## Second Line Endocrine Therapy
### Phase III Results

Postmenopausal Patients Progressing on tamoxifen, letrozole or anastrozole

<table>
<thead>
<tr>
<th></th>
<th>LET</th>
<th>EXE</th>
<th>FV LD</th>
<th>FV HD</th>
<th>EXE + RAD</th>
<th>FVHD + PALBO</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Control</strong></td>
<td>MEG. AC</td>
<td>MEG. AC</td>
<td>EXE</td>
<td>FV LD</td>
<td>EXE</td>
<td>FV HD</td>
</tr>
<tr>
<td>HR PFS</td>
<td>1.04</td>
<td>0.82</td>
<td>0.96</td>
<td>0.80</td>
<td>0.43</td>
<td>0.42</td>
</tr>
<tr>
<td><em>p</em></td>
<td>NS</td>
<td>0.037</td>
<td>NS</td>
<td>0.006</td>
<td>&lt;0.00001</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td><strong>Median PFS</strong></td>
<td>3,8</td>
<td>4,8</td>
<td>3,7</td>
<td>6,5</td>
<td>7,8</td>
<td>9,2</td>
</tr>
</tbody>
</table>

LET, letrozole; EXE, exemestane; FVLD, fulvestrant 250 mg; FVHD, fulvestrant 500 mg; RAD, everolimus; PALBO, palbociclib; MEG AC, megestrol acetate

All studies had the same indication, but not the same population

<table>
<thead>
<tr>
<th>Percentage</th>
<th>CONFIRM</th>
<th>PALOMA-3</th>
<th>BOLERO-2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progression on AI</td>
<td>65</td>
<td>85</td>
<td>100</td>
</tr>
<tr>
<td>Benefit to prior line of ET</td>
<td>NK</td>
<td>79</td>
<td>85</td>
</tr>
<tr>
<td>Prior chemotherapy for ABC</td>
<td>NK</td>
<td>31</td>
<td>24</td>
</tr>
<tr>
<td>1st – 2nd ABC line of therapy</td>
<td>100</td>
<td>62</td>
<td>61</td>
</tr>
<tr>
<td>Dose intensity</td>
<td>98</td>
<td>91</td>
<td>78</td>
</tr>
<tr>
<td>Discontinuations</td>
<td>2,3</td>
<td>2,5</td>
<td>6.5 + 6.7*</td>
</tr>
<tr>
<td>PFS HR</td>
<td>0.80</td>
<td>0.42</td>
<td>0.45</td>
</tr>
</tbody>
</table>

*Includes treatment discontinuations and consent withdrawal.
## CONFIRM / Fulvestrant Toxicity profile

<table>
<thead>
<tr>
<th>Outcome</th>
<th>N (%) patients</th>
<th>N (%) patients</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fulvestrant 500mg</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N=361</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endometrial dysplasia</td>
<td>0 (0.3)</td>
<td>0 (0.3)</td>
<td>1.000</td>
</tr>
<tr>
<td>GI disturbances</td>
<td>73 (20.2)</td>
<td>76 (20.3)</td>
<td>1.000</td>
</tr>
<tr>
<td>Hot flushes</td>
<td>30 (8.3)</td>
<td>23 (6.1)</td>
<td>0.318</td>
</tr>
<tr>
<td>Injection site reactions</td>
<td>49 (13.6)</td>
<td>50 (13.4)</td>
<td>1.000</td>
</tr>
<tr>
<td>Joint disorders</td>
<td>68 (18.8)</td>
<td>70 (18.7)</td>
<td>1.000</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>1 (0.3)</td>
<td>0 (0.3)</td>
<td>0.492</td>
</tr>
<tr>
<td>Thromboembolic events</td>
<td>3 (0.8)</td>
<td>6 (1.6)</td>
<td>0.506</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>8 (2.2)</td>
<td>8 (2.1)</td>
<td>1.000</td>
</tr>
<tr>
<td>Vaginitis</td>
<td>3 (0.8)</td>
<td>1 (0.3)</td>
<td>0.366</td>
</tr>
<tr>
<td>Weight gain</td>
<td>1 (0.3)</td>
<td>1 (0.3)</td>
<td>1.000</td>
</tr>
<tr>
<td><strong>Fulvestrant 250mg</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N=374</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endometrial dysplasia</td>
<td>0 (0.3)</td>
<td>0 (0.3)</td>
<td>1.000</td>
</tr>
<tr>
<td>GI disturbances</td>
<td>1 (0.3)</td>
<td>1 (0.3)</td>
<td>1.000</td>
</tr>
<tr>
<td>Hot flushes</td>
<td>3 (0.8)</td>
<td>1 (0.3)</td>
<td>0.366</td>
</tr>
<tr>
<td>Injection site reactions</td>
<td>70 (18.7)</td>
<td>70 (18.7)</td>
<td>1.000</td>
</tr>
<tr>
<td>Joint disorders</td>
<td>70 (18.7)</td>
<td>70 (18.7)</td>
<td>1.000</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>68 (18.8)</td>
<td>68 (18.8)</td>
<td>1.000</td>
</tr>
<tr>
<td>Thromboembolic events</td>
<td>50 (13.4)</td>
<td>50 (13.4)</td>
<td>1.000</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>76 (20.3)</td>
<td>76 (20.3)</td>
<td>1.000</td>
</tr>
<tr>
<td>Vaginitis</td>
<td>73 (18.7)</td>
<td>73 (18.7)</td>
<td>1.000</td>
</tr>
<tr>
<td>Weight gain</td>
<td>68 (18.8)</td>
<td>68 (18.8)</td>
<td>1.000</td>
</tr>
</tbody>
</table>
## BOLERO-2 / Everolimus

### Toxicity profile

<table>
<thead>
<tr>
<th>AE (Preferred Term)</th>
<th>EVE + EXE (n = 482), %</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All</td>
<td>1</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>Diarrhoea</td>
<td>34</td>
<td>26</td>
</tr>
<tr>
<td>Nausea</td>
<td>31</td>
<td>21</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>31</td>
<td>19</td>
</tr>
<tr>
<td>Weight decreased</td>
<td>28</td>
<td>10</td>
</tr>
<tr>
<td>Cough</td>
<td>26</td>
<td>21</td>
</tr>
<tr>
<td>Pneumonitis*</td>
<td>16</td>
<td>7</td>
</tr>
<tr>
<td>Hyperglycaemia*</td>
<td>14</td>
<td>4</td>
</tr>
</tbody>
</table>

*Incidence <25%, but AE of special interest.

# PALOMA-3 / Palbociclib

## Adverse Events—All Cause

<table>
<thead>
<tr>
<th>AE, %</th>
<th>Palbociclib + Fulvestrant (n=345)</th>
<th>Placebo + Fulvestrant (n=172)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any Grade</td>
<td>Grade 3</td>
</tr>
<tr>
<td>Any AE</td>
<td>98</td>
<td>59</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>79</td>
<td>53</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>46</td>
<td>25</td>
</tr>
<tr>
<td>Anemia</td>
<td>26</td>
<td>3</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>19</td>
<td>2</td>
</tr>
<tr>
<td>Fatigue</td>
<td>38</td>
<td>2</td>
</tr>
<tr>
<td>Nausea</td>
<td>29</td>
<td>0</td>
</tr>
<tr>
<td>Headache</td>
<td>21</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Upper respiratory infection&lt;sup&gt;a&lt;/sup&gt;</td>
<td>19</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>19</td>
<td>0</td>
</tr>
<tr>
<td>Constipation</td>
<td>17</td>
<td>0</td>
</tr>
<tr>
<td>Alopecia</td>
<td>15</td>
<td>0</td>
</tr>
</tbody>
</table>

AE=adverse event. AEs with ≥15% incidence in the palbociclib + fulvestrant group reported.


Palbociclib is not approved in India
Other Options After NSAI: Phase II–III Trials
Face-to-Face – Endocrine Therapy vs Capecitabine

**Phase II, BOLERO-6**
- Postmenopausal women with HR+ ABC following progression on NSAI
  - N = 300
  - 1:1:1
  - Exemestane 25 mg QD + Everolimus 10 mg QD
  - Everolimus 10 mg QD
  - Capecitabine (1250 mg/m² BID 2/1 schedule)

**Phase III, PEARL**
- Postmenopausal women HR+/HER2– MBC resistant to NSAI
  - N = 348
  - 1:1
  - Palbociclib (125 mg QD, 3/1 schedule) + exemestane (25 mg QD)
  - Capecitabine (1250 mg/m² BID, 2/1 schedule)

1. Clinicaltrials.gov NCT01783444;
2. Clinicaltrials.gov NCT02028507.
ER Signaling Pathways: Most Prevalent Mechanisms of Resistance to AI

Acquired Resistance

$PI3KCA$ mutations

Sustaining proliferative signaling
BELLE-2 Met the Primary Endpoint for PFS Improvement in the Full Population

- A similar PFS improvement was observed in the main population (HR 0.80 [95% CI, 0.68–0.94]; one-sided P value = .003)
- Follow-up for OS analysis is ongoing, with a prespecified target of 588 deaths in the full population
  - At the time of primary PFS analysis, OS data were immature (281 deaths in the full population), with a trend in favor of the buparlisib arm

**Table:**

<table>
<thead>
<tr>
<th></th>
<th>Full Population (N = 1147)</th>
<th>Buparlisib + Fulvestrant n = 576</th>
<th>Placebo + Fulvestrant n = 571</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS, months (95% CI)</td>
<td>6.9 (6.8–7.8)</td>
<td>5.0 (4.0–5.2)</td>
<td></td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.78 (0.67–0.89)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>One-sided P value</td>
<td>&lt;.001</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CI, confidence interval; HR, hazard ratio; OS, overall survival; PFS, progression-free survival.

### Buparlisib + Fulvestrant: Clinically Meaningful PFS Improvement in Patients with ctDNA PIK3CA Mutations

<table>
<thead>
<tr>
<th>ctDNA PIK3CA Mutant</th>
<th>Buparlisib + Fulvestrant (n = 87)</th>
<th>Placebo + Fulvestrant (n = 113)</th>
<th>Median PFS, months (95% CI)</th>
<th>HR (95% CI)</th>
<th>One-sided nominal P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ctDNA PIK3CA Mutant</td>
<td>7.0 (5.0–10.0)</td>
<td>3.2 (2.0–5.1)</td>
<td>0.56 (0.39–0.80)</td>
<td>&lt;.001</td>
<td></td>
</tr>
</tbody>
</table>

### ctDNA PIK3CA Nonmutant

<table>
<thead>
<tr>
<th>ctDNA PIK3CA Nonmutant</th>
<th>Buparlisib + Fulvestrant (n = 199)</th>
<th>Placebo + Fulvestrant (n = 188)</th>
<th>Median PFS, months (95% CI)</th>
<th>HR (95% CI)</th>
<th>One-sided nominal P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ctDNA PIK3CA Nonmutant</td>
<td>6.8 (4.7–8.5)</td>
<td>6.8 (4.7–8.6)</td>
<td>1.05 (0.82–1.34)</td>
<td>.642</td>
<td></td>
</tr>
</tbody>
</table>

---

CI, confidence interval; HR, hazard ratio; OS, overall survival; PFS, progression-free survival.

Alpelisib + Fulvestrant Activity in Patients with ABC Harboring Mutant or Wildtype PIK3CA

- Alpelisib + Fulvestrant 500 mg demonstrated encouraging clinical activity across dose levels
- Patients with PIK3CA-altered tumors had better response vs WT
  - Increased ORR (not shown)
  - Longer PFS benefit

<table>
<thead>
<tr>
<th>Treatment group (QD)</th>
<th>Median PFS (months)</th>
<th>95% CI (months)</th>
<th>Total number, n</th>
<th>Number censored, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PIK3CA-altered</td>
<td>8.3</td>
<td>6.1–12.4</td>
<td>50</td>
<td>27 (54.0)</td>
</tr>
<tr>
<td>PIK3CA WT</td>
<td>4.7</td>
<td>1.8–5.5</td>
<td>31</td>
<td>13 (41.9)</td>
</tr>
</tbody>
</table>

ABC, advanced breast cancer; CI, confidence interval; ORR, overall response rate; PFS, progression-free survival; PIK3CA, phosphoinositide 3-kinase, catalytic, alpha; QD, once daily; WT, wildtype. Reprinted from Janku F, et al. SABCS 2014. Abstract PD5-5 (poster presentation); www.clinicaltrials.gov (NCT01219699).
SOLAR-1: Alpelisib + Fulvestrant Treatment in ABC Following AI Therapy

SOLAR-1 (NCT02437318)\(^1\): Phase III randomized, double-blind, placebo-controlled study

**Endpoints**
- Primary
  - PFS
- Secondary
  - OS
  - ORR
  - Safety
  - CBR
  - QOL

**Target N = 820**
- HR+, HER2- ABC/MBC
- Men or postmenopausal women
- Known PIK3CA status
- PD/recurrence with AI therapy

**Alpelisib + Fulvestrant**

**Placebo + Fulvestrant**

Enrollment began July 2015; study is currently enrolling

ABC, advanced breast cancer; AI, aromatase inhibitor; CBR, clinical benefit rate; HER2, human epidermal growth factor receptor-2; HR, hormone receptor; IM, intramuscular; MBC, metastatic breast cancer; ORR, overall response rate; PD, progressive disease; PFS, progression-free survival; PIK3CA, phosphoinositide 3-kinase, catalytic, alpha; PO, oral; QOL, quality of life.

*Alpelisib or placebo (300 mg; PO; once daily); fulvestrant (500 mg; IM; Day 1 and Day 15 of Cycle 1, then Day 1 of each subsequent 28-day cycle).

Acquired Resistance

ESR1 mutations

Signaling independent of estrogen stimulation-inhibition
ESR1 Mutations in Metastatic Breast Cancer

Mutations of the ER gene (ESR1 mutations) have recently been identified as a causative factor for the development of endocrine resistance

ESR1 mutations are only rarely found in primary breast cancer and are only found at an appreciable frequency after the development of hormone resistance

Most of the ESR1 mutations occur in a hotspot within the ligand binding domain (LBD), and constitutively activate the ER in a ligand independent manner

![Graph](image)

**Fig. 4. Validation and independent series confirm the importance of timing of previous AI exposure for ESR1 mutation selection.** (A) ESR1 mutation rate assessed only in patients with detection of a mutation other than ESR1 in plasma DNA. $P = 0.061$, $\chi^2$ test overall; $P = 0.035$, adjuvant AI only versus metastatic AI only. (B) Assessment of ESR1 mutation rate in an independent series of 49 breast tumor biopsies that had recurred after previous AI therapy. No ESR1 mutations were identified in breast tumor biopsies relapsing after adjuvant AI (0%; 95% CI, 0 to 10.9). (C) Reassessment of a second independent series of ESR1 mutant-positive cancers, with timing of previous AI therapy (9).
ctDNA *ESR1* Mutations: Potential Mechanism of Resistance to Aromatase Inhibitors

PFS on AI therapy after ctDNA analysis for patients with *ESR1* mutant and WT ctDNA (HR, 3.1; 95% CI, 1.9 to 23.1; *P* = 0.0041, log-rank test).

ctDNA *ESR1* Mutations: Not a Resistant Mechanism for Fulvestrant (FERGI Trial)

BOLERO-2: *ESR1* Mutations and Overall Survival

- Cell free DNA samples analysed from 541 of the 724 women in BOLERO-2
- Almost 30% tested positive for *ESR1* mutations (D538G and Y537S)

![Bar chart showing median overall survival (OS) by ESR1 mutation status.](chart.png)

Phase I Study of ARN-810 (GDC-0810), a Novel and Potent Oral Selective Estrogen Receptor Degrader, in Postmenopausal Women with Metastatic Estrogen Receptor Positive (ER+), HER2- Breast Cancer

Aditya Bardia,1 Maura N Dickler,2 Ingrid A Mayer,3 Eric Winer,4 Umar Mahmood,1 Gary Ulane,2 H Charles Manning,3 Peter Rix,5 Jeffrey H Hager,5 Debasish Roychowdhury,5 Edna Chow Maneval,5 Carlos L Arteaga,3 and Jose Baselga2

1Massachusetts General Hospital Cancer Center, Boston, MA; 2Memorial Sloan-Kettering Cancer Center, New York, NY; 3Vanderbilt-Ingram Cancer Center, Vanderbilt University, Nashville, TN; 4Dana Farber Cancer Institute, Boston, MA; 5Seragen Pharmaceuticals, a wholly owned subsidiary of Genentech, Inc., San Diego, CA

Waterfall plot showing FES-PET response rates across 6 different dose regimens

- 200 mg QD F
- 400 mg QD F
- 600 mg QD F
- 800 mg QD F
- 600 mg QD NF
- 800 mg QD NF
- 300 mg BID NF

Note: Only 1 patient at 800 mg QD F had pre- and post-treatment images. No images were collected for the 100 mg QD dose cohort and post-treatment scans had not yet been performed for the 800 mg QD NF and 400 mg BID NF cohorts at the time of data cutoff. All patients treated at 600 and 800 mg QD had FES-PET scans performed between 18 and 24 hours post-dose.

Baseline (ESR1 mutation patient)

Cycle 2 (treated at 600 mg QD F)

Baseline

Post-Treatment

ERα

Ki67
Conclusions

Progression on endocrine therapy in adjuvant/advanced setting

Alternate endocrine options
- Exemestane - everolimus
- Fulvestrant
- Endocrine + CDK4/6 inhibitors
- Tamoxifen

Resistance to ER-directed therapy

Chemotherapy
- Taxanes
- Anthracyclines
- Other

NCCN\(^1\)
- Recommend 3 consecutive endocrine therapy regimens before switching to chemotherapy

ABC\(^1\)\(^2\)
- No consensus following initial AI therapy; options include
  - Tamoxifen
  - Another AI
  - Fulvestrant
  - Megestrol acetate

Als, aromatase inhibitors; ER, estrogen receptor; HR, hormone receptor; NCCN, National Comprehensive Cancer Center. Guidelines refer to postmenopausal HR+ advanced breast cancer, and recommend endocrine therapy for patients who are not in visceral crisis.

Endocrine-Resistant ER+/HER2− ABC: Treatment Decision Guided by Patient Scenario

PROFILE A
Good response, nonvisceral disease
- Long DFI post-adjuvant Rx (eg, >12 mo) or long response to 1L ET Rx (eg, >12 mo)
- Predominantly bone-only mets
- Possible low-risk soft tissue mets (eg, skin/lymph)
- Asymptomatic

PROFILE B
Moderate response, nonvisceral disease
- Short DFI (eg, <12 mo) or recurrence while on adjuvant Rx or moderate response to 1L ET Rx (eg, ~6 mo)
- Predominantly bone-only mets
- Possible low-risk soft tissue mets (eg, skin/lymph)
- No or minimal symptoms

PROFILE C
Low visceral burden
- Good or moderate response to prior endocrine therapy*
- Lower risk due to lower tumor burden (eg, discrete 1–2 mets)
- No or minimal symptoms

PROFILE D
Moderate visceral burden
- Moderate response to prior endocrine therapy*
- Increased risk due to greater disease burden
- More extensive visceral met(s)
- Minimal/moderate symptoms

PROFILE E
Medical crisis stage
- Fast-progressing, life-threatening, aggressive disease
- Resistant to endocrine therapy
- Mets in high-risk sites requiring immediate medical intervention
- Highly symptomatic, requiring systemic treatment

Patient Factors

Fulvestrant
EVE (Palbo?)
Chemotherapy
Sequential ET

EVE (Palbo?)
Fulv
CT