Hormonal therapy of metastatic breast cancer: what is new?

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Topics

- Poly-endocrine therapy: ready for prime time?

- 1\textsuperscript{st} line treatment options: Fulvestrant and Everolimus. How should we sequence?

- Forthcoming options/strategies
Poly- versus Single-agent endocrine therapy for menopausal patients with advanced breast cancer
Two phase III trials (1° line treatment)

FACT*  No. 514 pts.  → Anastrozole
   → Anastrozole + Fulvestrant

SWOG** No. 694 pts.  → Anastrozole
   → Anastrozole + Fulvestrant

<table>
<thead>
<tr>
<th></th>
<th>FACT*</th>
<th></th>
<th>SWOG**</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A</td>
<td>A+F</td>
<td>A</td>
<td>A+F</td>
</tr>
<tr>
<td>% ORR</td>
<td>34</td>
<td>32</td>
<td>22</td>
<td>27</td>
</tr>
<tr>
<td>Median TTP- mos.</td>
<td>10.2</td>
<td>10.8</td>
<td>13.5</td>
<td>15.0</td>
</tr>
<tr>
<td></td>
<td>HR=0.80</td>
<td></td>
<td>HR=0.80</td>
<td></td>
</tr>
<tr>
<td></td>
<td>p=.007</td>
<td></td>
<td>p=.05</td>
<td></td>
</tr>
<tr>
<td>Median OS – mos.</td>
<td>38.2</td>
<td>37.8</td>
<td>41.3</td>
<td>47.7</td>
</tr>
</tbody>
</table>

Subgroup analyses

The SWOG trial suggests that most of the benefit is seen in patients previously untreated with endocrine therapy (tamoxifen).

- No prior exposure
  \[ HR = 0.74 \text{ (95\% CI: 0.59-0.92)} \]
  \[ p = .006 \]

- Prior exposure
  \[ HR = 0.89 \text{ (95\% CI: 0.69-1.15)} \]
  \[ p = .37 \]

<table>
<thead>
<tr>
<th></th>
<th>FACT</th>
<th>SWOG</th>
</tr>
</thead>
<tbody>
<tr>
<td>% pts. unexposed to TAMOXIFEN (no.)</td>
<td>33</td>
<td>60</td>
</tr>
<tr>
<td></td>
<td>(171)</td>
<td>(414)</td>
</tr>
</tbody>
</table>
SoFEA: Patients Derive Clinical Benefit With Additional Endocrine Therapy After Progressing After a Nonsteroidal Aromatase Inhibitor

**Phase 3 study; N = 750**
- Postmenopausal women with HR+ advanced breast cancer
- Progressed after nonsteroidal AI therapy in adjuvant or first-line metastatic setting

**Table**

<table>
<thead>
<tr>
<th></th>
<th>Fulvestrant + Anastrozole (n = 250)</th>
<th>Fulvestrant (n = 250)</th>
<th>Exemestane (n = 250)</th>
<th>P value&lt;sup&gt;a&lt;/sup&gt;</th>
<th>P value&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS (mo)</td>
<td>4.4</td>
<td>4.8</td>
<td>3.4</td>
<td>.98</td>
<td>.56</td>
</tr>
<tr>
<td>OS (mo)</td>
<td>20.2</td>
<td>19.4</td>
<td>21.6</td>
<td>.61</td>
<td>.68</td>
</tr>
<tr>
<td>ORR (%)</td>
<td>7.4</td>
<td>6.9</td>
<td>3.6</td>
<td>.82</td>
<td>.10</td>
</tr>
</tbody>
</table>

AI, aromatase inhibitor; HR, hormone receptor; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.

<sup>a</sup> Fulvestrant + anastrozole versus fulvestrant alone.  
<sup>b</sup> Fulvestrant alone versus exemestane alone.

Interpretation

Luminal A tumors
(i.e. no primary endocrine-resistance)

No prior exposure to endocrine therapy
(i.e. no acquired endocrine-resistance)

Might support the use of Poly-endocrine therapy

However confirmation in the context of prospective studies is required
Fulvestrant at full doses: The CONFIRM trial
Trial design and main eligibility criteria

- Post-menopausal
- Advanced disease
- ER+

Relapsing pts.

- 1st line HT
- "de novo" advanced pts.

Allowed prior hormonotherapy (HT)

- Post-menopausal
- Advanced disease
- ER+

- Fulvestrant 250 mg (1 injection i.m.) + placebo (1 injection i.m.) days 0, 14 (2 placebo injections), 28, and every 28 days thereafter
- Fulvestrant 500 mg (2 injections 250 mg i.m.) days 0, 14, 28, and every 28 days thereafter

Start adjuvant HT

5 yrs.

12 mos. gap

1st line HT
Primary endpoint: progression-free survival

Proportion of patients progression-free

Time (months)

Fulvestrant 500 mg
Fulvestrant 250 mg

HR = 0.80; 95% CI: 0.68, 0.94; p=0.006

Median PFS (months)
Fulvestrant 500 mg  6.5
Fulvestrant 250 mg  5.5

Patients at risk:
500 mg  362  216  163  113  90  54  37  19  12  7  3  2  0
250 mg  374  199  144  85  60  35  25  12  4  3  1  1  0

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

Overall survival: first (50% events) and final (75% events) analyses

50% events

75% events

**50% events**

Proportion of patients alive

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>Fulvestrant 500 mg</th>
<th>Fulvestrant 250 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>4</td>
<td>0.9</td>
<td>0.9</td>
</tr>
<tr>
<td>8</td>
<td>0.8</td>
<td>0.8</td>
</tr>
<tr>
<td>12</td>
<td>0.7</td>
<td>0.7</td>
</tr>
<tr>
<td>16</td>
<td>0.6</td>
<td>0.6</td>
</tr>
<tr>
<td>20</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>24</td>
<td>0.4</td>
<td>0.4</td>
</tr>
<tr>
<td>28</td>
<td>0.3</td>
<td>0.3</td>
</tr>
<tr>
<td>32</td>
<td>0.2</td>
<td>0.2</td>
</tr>
<tr>
<td>36</td>
<td>0.1</td>
<td>0.1</td>
</tr>
<tr>
<td>40</td>
<td>0.1</td>
<td>0.1</td>
</tr>
<tr>
<td>44</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>48</td>
<td>0.0</td>
<td>0.0</td>
</tr>
</tbody>
</table>

Median time to death (months)

- Fulvestrant 500 mg: 25.1
- Fulvestrant 250 mg: 22.8

Patients at risk:

- Fulvestrant 500 mg:
  - 500 mg: 362
  - 250 mg: 374

- Fulvestrant 250 mg:
  - 500 mg: 330
  - 250 mg: 338

**75% events**

Proportion of patients alive

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<th>Time (months)</th>
<th>Fulvestrant 500 mg</th>
<th>Fulvestrant 250 mg</th>
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<tbody>
<tr>
<td>0</td>
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<tr>
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<td>0.9</td>
<td>0.9</td>
</tr>
<tr>
<td>8</td>
<td>0.8</td>
<td>0.8</td>
</tr>
<tr>
<td>12</td>
<td>0.7</td>
<td>0.7</td>
</tr>
<tr>
<td>16</td>
<td>0.6</td>
<td>0.6</td>
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<td>0.5</td>
<td>0.5</td>
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<td>0.4</td>
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<td>0.3</td>
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</tr>
<tr>
<td>32</td>
<td>0.2</td>
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</tr>
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<td>36</td>
<td>0.1</td>
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</tr>
<tr>
<td>40</td>
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</tr>
<tr>
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<td>0.0</td>
<td>0.0</td>
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<tr>
<td>48</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>52</td>
<td>0.0</td>
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</tr>
<tr>
<td>56</td>
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<td>0.0</td>
</tr>
<tr>
<td>60</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>64</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>68</td>
<td>0.0</td>
<td>0.0</td>
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<tr>
<td>72</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>76</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>80</td>
<td>0.0</td>
<td>0.0</td>
</tr>
</tbody>
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Median time to death (months)

- Fulvestrant 500 mg: 26.4
- Fulvestrant 250 mg: 22.3

Patients at risk:

- Fulvestrant 500 mg:
  - 500 mg: 362
  - 250 mg: 374

- Fulvestrant 250 mg:
  - 500 mg: 333
  - 250 mg: 338

**HR = 0.84; 95% CI: 0.69, 1.03; p=0.091**

**IR (95% CI): 0.81 (0.69, 0.96)**

**p-value: 0.016**

*Nominal value, cannot be claimed as statistically significant*
Targeting the PI3K-MTOR pathway
Rationale

Reciprocal crosstalk between estrogen receptor (ER) $\alpha$ and PI3K signaling
PI3K pathway alterations in breast cancer by molecular phenotype

Table 1. Phosphatidylinositol 3-kinase pathway alterations in human breast cancers by molecular subtype

<table>
<thead>
<tr>
<th>Gene (protein)</th>
<th>Alteration</th>
<th>Effect on signaling</th>
<th>Luminal (ER+)</th>
<th>HER2+</th>
<th>Basal (TN)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ErbB2 (HER2)</td>
<td>Gene amplification or overexpression</td>
<td>Hyperactivation of ErbB2 signaling (PI3K, MEK)</td>
<td>10%</td>
<td>~100%</td>
<td>0%</td>
</tr>
<tr>
<td>PTEN</td>
<td>Loss-of-function mutation or reduced expression</td>
<td>Hyperactivation of PI3K signaling</td>
<td>29-44%</td>
<td>22%</td>
<td>67%</td>
</tr>
<tr>
<td>PIK3CA (p110α/PI3K)</td>
<td>Activating mutation</td>
<td>Hyperactivation of PI3K signaling</td>
<td>28-47%</td>
<td>23-33%</td>
<td>8-25%</td>
</tr>
<tr>
<td>PIK3CB (p110β/PI3K)</td>
<td>Amplification</td>
<td>Unknown</td>
<td></td>
<td>5%</td>
<td>5%</td>
</tr>
<tr>
<td>IGF1R and INSR (IGF-1R, InsR)</td>
<td>Receptor activation, IGF1R amplification</td>
<td>Activates IGF-IR/InsR signaling (PI3K, MEK)</td>
<td>41-48%</td>
<td>18-64%</td>
<td>42%</td>
</tr>
<tr>
<td>FGFR1</td>
<td>Amplification, activating mutation</td>
<td>Hyperactivation of FGFR signaling (PI3K, MEK)</td>
<td>8.6-11.6%</td>
<td>5.4%</td>
<td>5.6%</td>
</tr>
<tr>
<td>RPS6K1 (p70S6K)</td>
<td>Amplification</td>
<td>Unknown</td>
<td></td>
<td>3.8-12.5%</td>
<td>3.8-12.5%</td>
</tr>
<tr>
<td>INPP4B</td>
<td>Reduced expression or genomic loss</td>
<td>Hyperactivation of PI3K signaling</td>
<td></td>
<td>10-33%</td>
<td>54%</td>
</tr>
<tr>
<td>PIK3R1 (p85α/PI3K)</td>
<td>Inactivating mutation</td>
<td>Derepression of catalytic activity of p110α</td>
<td></td>
<td>2%</td>
<td>53%</td>
</tr>
<tr>
<td>AKT1</td>
<td>Activating mutation</td>
<td>Hyperactivation of AKT</td>
<td>3.6-3.8%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>AKT2</td>
<td>Amplification</td>
<td>Hyperactivation of AKT</td>
<td></td>
<td>2.8%</td>
<td>0.8%</td>
</tr>
<tr>
<td>EGFR</td>
<td>Amplification</td>
<td>Hyperactivation of EGFR signaling (PI3K, MEK)</td>
<td></td>
<td>0.8%</td>
<td>2.8%</td>
</tr>
<tr>
<td>PDK1</td>
<td>Amplification or overexpression</td>
<td>Hyperactivation of PDK1 (AKT, TORC1)</td>
<td>22%</td>
<td>22%</td>
<td>38%</td>
</tr>
<tr>
<td>KRAS</td>
<td>Activating mutation</td>
<td>Hyperactivation of PI3K and MEK</td>
<td></td>
<td>4-6%</td>
<td>4-6%</td>
</tr>
</tbody>
</table>

Miller T W et al BCR 2011
Progression-free survival advantage when everolimus is combined with exemestane versus exemestane alone

ER+ menopausal pts. progressing to nsAI

No. = 724

- Exemestane + everolimus
- Exemestane + placebo

The use of everolimus in combination with endocrine therapy may increase toxicity…

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Everolimus N = 482</th>
<th>Placebo N = 238</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% G3-G4 (%G1-G4)</td>
<td>% G3-G4 (%G1-G4)</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>8 (56)</td>
<td>1 (11)</td>
</tr>
<tr>
<td>Anemia</td>
<td>6 (16)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>4 (18)</td>
<td>1 (9)</td>
</tr>
<tr>
<td>Hyperglicemia</td>
<td>4 (13)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>4 (33)</td>
<td>1 (26)</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>3 (12)</td>
<td>- (-)</td>
</tr>
</tbody>
</table>

A possible treatment algorithm

HR+ menopausal patient recurring on/after adjuvant therapy with aromatase inhibitors

**Endocrine therapy***

Fulvestrant 500 mg

or

Tamoxifen or AIs

* decision based on clinical criteria such as: symptoms, tumor burden, disease-free interval, patient’s wishes

**Chemotherapy***

Everolimus + Exemestane

PD

PD
Forthcoming options/strategies:

• PI3K/AKT/MTOR inhibitors

• CDK 4-6 inhibitors
The PI3K/AKT/mTOR Pathway in Breast Cancer: Common Molecular Alterations

- The PI3K/AKT/mTOR pathway is frequently activated in breast cancers due to:  
  - Increased HER2-mediated signaling
  - Mutational inactivation or loss of PTEN
  - Activating mutation or amplification of PIK3CA
- Inhibitors of the PI3K/AKT/mTOR pathway are currently in clinical trials

Incidence of PI3K and PTEN mutations in 547 human breast cancer samples

## PI3K Pathway Inhibitors in Clinical Development in Breast Cancer

<table>
<thead>
<tr>
<th>Drug</th>
<th>Source</th>
<th>Target(s)</th>
</tr>
</thead>
<tbody>
<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>BYL719</td>
<td>Novartis</td>
<td>PI3Kα</td>
</tr>
<tr>
<td>GS-1101</td>
<td>Gilead</td>
<td>PI3Kδ</td>
</tr>
<tr>
<td>XL-147/SA245408</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>PF-05212384/PKI-587</td>
<td>Pfizer</td>
<td>Pan-PI3K</td>
</tr>
<tr>
<td>GDC-0941</td>
<td>Genentech</td>
<td>Pan-PI3K</td>
</tr>
<tr>
<td>XL-765/SAR245409</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>MLN-128/MLN0128</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>MK2206</td>
<td>Merck</td>
<td>AKT (allosteric)</td>
</tr>
<tr>
<td>GDC-0068</td>
<td>Genentech</td>
<td>AKT (catalytic)</td>
</tr>
</tbody>
</table>
Pre-clinical and early clinical data on timing of PI3K pathway activation in breast cancer cells

- Breast cancer cells exposed to long-term estrogen deprivation may have PIK3CA gene mutations and activation of the PI3K/MTOR pathway (Yue W et al 2003; Miller TW et al 2010)

- Tumors carrying PIK3CA gene mutations seem to be initially more sensitive to endocrine therapy (Sanchez CG et al 2011; Loi S et al PNAS 2010)
PIK3CA mutations may confer increased sensitivity to endocrine therapies

ER + PIK3CA mutated tumors tend to have a longer time to relapse than ER+ PIK3CA wild type tumors (Sanchez CG et al, Breast Cancer Res 2011)

ER+ PIK3CA mutated tumors seem to be as sensitive to tamoxifen as ER+ PIK3CA wild type low proliferative tumors (Loi S et al, Proc Natl Acad Sci 2010)

PIK3CA mutated tumors may have decreased expression of downstream PI3K/AKT/MTOR proteins (Loi S et al, Proc Natl Acad Sci 2010)
A unifying hypothesis: PIK3CA mutations can predict either sensitivity or resistance to endocrine therapies.

**ER+ tumor untreated with endocrine therapy**

- **PIK3CA mutation**: Negative
- **feed-back**: OFF

**PI3K/AKT/MTOR pathway is down-regulated**

- The tumor is sensitive to endocrine therapy

**ER+ tumor with “secondary resistance” to endocrine therapy**

- **PIK3CA mutation**: Negative
- **feed-back**: OFF

**PI3K/AKT/MTOR pathway is activated**

- The tumor is resistant to endocrine therapy
DNA extraction from circulating tumor cells and gene sequencing is feasible

MBC patients untreated for at least 3 weeks

Whole blood

CellSearch
CTCs enrichment
EpCAM
EpCAM + CD146

Analyser
CTCs count

Cut off CTC ≥ 5

900 µl

14 µl

DEPArray™ system:
CTCs count and sorting: single CTCs or a poll of pure CTCs, putative CTCs and WBC

Whole genome amplification
Ampli1 WGA Kit

Whole genome
amplification

Ion Torrent
(Ion AmpliSeq technology) to detect mutations in a panel of 50 target genes and/or in other genes (customised probes)
A pilot study from our group testing the feasibility of detecting PIK3CA gene mutations from CTC of advanced breast cancer patients

- 21 ER+ pts. with \( \geq 5 \) CTC/7.5 ml blood sample (by CellSearch®)

  - 15 pts.
  - No PIK3CA mutations
  - 6 pts. with PIK3CA mutations
    - 4 pts. with mutations at exons 9 or 20 (confirmed in all recovered CTC, range 1-4)
    - 1 pt. with LOH (8 CTC)
    - 1 pt. with heterogeneity between CTC (19 CTC)

Pestrin M et al, Ann Oncol 24 (Suppl 3): iii29-iii38, 2013 (abstr. no. 71P)
Targeting the Cyclin D1 – CDK 4-6 pathway. Rationale

The CDK4/6- CyclinD1- E2F pathway

Evidence suggests that:
- in AI resistance models ER drives a CDK4/E2F dependent transcriptional program
- CDK4-6 inhibition reduces cell proliferation in both ER dependent and ER independent, AI res breast cancer models

(Miller T.W. et al, Cancer Discovery 2011)

Lange C A, Yee D Endocr Relat Cancer 2011;18:C19-C24
PD 0332991 has shown activity preferentially on ER+, luminal breast cancer cell lines with or without HER2 amplification.

- RB1, cyclin D1, and CDKN2A (p16) were differentially expressed - with higher levels of RB1 and cyclin D1, and lower levels of p16, in the sensitive group.
- Resistance to PD in many of the nonluminal breast cancer cell lines may be explained by the absence of pRb. Recent publications highlighted the lack of pRb in basal-like breast cancer tissue and observed that pRb depletion can result in the characteristic epithelial-to-mesenchymal transition changes.
- The lack of activity of a CDK4/6 inhibitor in cell lines and tumors that lack pRb can be explained by the fact that cyclin D1 does not offer G1 control in the absence of pRb.

Finn et al, BCR 2011
Study Design: Phase 2 Part 2

Primary Endpoint: PFS
Designed to detect a 50% improvement in median PFS from 9 to 13.5 months (80% power, 1-sided $\alpha = 10\%$

Study population
- Postmenopausal women with ER+ HER2- breast cancer
- Patients with CCND1 amplification and/or loss of p16

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

N = 150

4-week treatment cycle
- PD 0332991 125 mg QD x 3 weeks, 1 week off; plus letrozole 2.5 mg QD x 4 weeks
- Letrozole 2.5 mg QD x 4 weeks

Finn R et al, proc. SABCS, December 2012
Progression-Free Survival

- PD 0332991 + LET (N = 34), Median PFS = 18.2 mo (CI, 12.6-)
- LET (N = 32), Median PFS = 5.7 mo (CI, 2.8-12.9)

Hazard ratio = 0.35
95% CI, 0.17-0.72
P = 0.006

Finn R et al, proc. SABCS December 2012
Design of palbociclib phase III first-line trial

- ~450 patients
  - Postmenopausal women aged ≥18 years
  - Locoregionally recurrent or metastatic, ER(+)/HER2(−) advanced BrCa
  - No prior systemic treatment for advanced disease

2:1 Randomization
- Stratification: Disease site (visceral vs not)
- Disease-free Interval (de novo metastatic, ≤12 mo, >12 mo)
- Prior anticancer therapy (hormonal vs not)

Palbociclib (125 mg QD 21 d on, 7 d off) + Letrozole (2.5 mg daily)

Placebo (21 d on, 7 d off) + Letrozole (2.5 mg daily)

Disease assessments every 12 wk ± 7 d from randomization date
Repeat bone scans every 24 wk ± 7 d from randomization date

Finn RS et al. Poster (Abstract TPS652), ASCO 2013
Trend: A phase II randomised trial assessing PD 0332991 (CDK 4-6 inhibitor) to revert resistance to endocrine therapy

- Advanced BC pts.
- N=100 pts.
- HR+
- Progressing on AI or Fulvestrant

CDK 4-6 inh. alone

CDK 4-6 inh. + last line of endocrine therapy

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