Ongoing Clinical Trials
Combining CDK 4/6 Inhibitors
and Related Biomarkers

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• Predictive biomarkers
• Resistance mechanisms
• Future perspectives: Ongoing clinical trials
Predictive biomarkers

• HR-positivity
• Recurrent genomic alterations
• Molecular alterations on the CDK4/6/Rb pathway
Predictive biomarkers

• **HR-positivity**

• Recurrent genomic alterations
  – PIK3CA mutations
  – ESR1 mutations

• Molecular alterations on the CDK4/6/Rb pathway
  – Cyclin D1, p16, and RB inactivation
  – CDK2 activation, Cyclin E, RB1 subclonal alteration
CDK4/6 inhibitors don’t work in **HR- BC**

Patnaik A et al, Cancer Discovery 2016 Jul;6(7):740-53
Level of ER expression is not predictive in HR+ BC

Predictive biomarkers

- HR-positivity

- **Recurrent genomic alterations**
  - PIK3CA mutations
  - ESR1 mutations

- Molecular alterations on the CDK4/6/Rb pathway
  - Cyclin D1, p16, and RB inactivation
  - CDK2 activation, Cyclin E, RB1 subclonal alteration
PIK3CA mutations do not predict resistance to CDK4/6 inhibitors

**PIK3CA-WT patients (n=266)**

<table>
<thead>
<tr>
<th></th>
<th>PAL + FUL (n=180)</th>
<th>PBO + FUL (n=86)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS, months (95% CI)</td>
<td>9.9 (9.2–13.9)</td>
<td>4.6 (3.4–7.3)</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.45 (0.31–0.64)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

**Patients with PIK3CA mutations (n=129)**

<table>
<thead>
<tr>
<th></th>
<th>PAL + FUL (n=85)</th>
<th>PBO + FUL (n=44)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS, months (95% CI)</td>
<td>9.5 (5.7–11.2)</td>
<td>3.6 (1.9–5.6)</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.48 (0.30–0.78)</td>
<td>0.002</td>
</tr>
</tbody>
</table>

ESR1 mutations (ctDNA) do not predict resistance to CDK4/6 inhibitors

• PIK3CA and ESR1 mutant BC are sensitive to CDK4/6 inhibitors.
• It’s unlikely that drugs targeting these alterations will substitute CDK4/6 inhibitors in 1st line setting.
• BRCA, AKT1 and HER2 mutations are missing.
Predictive biomarkers

• HR-positivity
• Recurrent genomic alterations
  – PIK3CA mutations
  – ESR1 mutations
• Molecular alterations on the CDK4/6/Rb pathway
  – Cyclin D1, p16, and RB inactivation
  – CDK2 activation, Cyclin E, RB1 subclonal alteration
**P16INK4A and Rb Status Are Associated with Response to Palbociclib in Surgical Specimens and Explants**

<table>
<thead>
<tr>
<th>Specimen</th>
<th>Responsive</th>
<th>Non-Responsive</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RB</td>
<td>RB</td>
</tr>
<tr>
<td></td>
<td>p16</td>
<td>p16</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Explant</th>
<th>Responsive</th>
<th>Non-Responsive</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RB</td>
<td>RB</td>
</tr>
<tr>
<td></td>
<td>p16</td>
<td>p16</td>
</tr>
</tbody>
</table>

**Rb Inactivation** Is Associated with Palbociclib Resistance in ER+ Breast Cancer Cell Lines

Analysis of palbociclib-resistant T47D cells revealed reduced abundance of Rb1 RNA transcripts and loss of Rb1 protein, suggesting that Rb1 gene deletion is the likely resistance mechanism in these cells.

Lee NV, et al. Presented at SABCS 2015; San Antonio, Texas, USA (Poster 3-06-01)
CCND1 amplification and/or p16 loss and efficacy of CDK4/6 inhibitors


### Cohort 1

<table>
<thead>
<tr>
<th></th>
<th>PAL + LET (N=34)</th>
<th>LET (N=32)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of events (%)</td>
<td>15 (44)</td>
<td>25 (78)</td>
</tr>
<tr>
<td>Median PFS, months (95% CI)</td>
<td>26.1 (11.2–NE)</td>
<td>5.7 (2.6–10.5)</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.299 (0.156–0.572)</td>
<td></td>
</tr>
<tr>
<td>P value</td>
<td>&lt;0.001</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

### Cohort 2

<table>
<thead>
<tr>
<th></th>
<th>PAL + LET (N=50)</th>
<th>LET (N=49)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of events (%)</td>
<td>26 (52)</td>
<td>34 (69)</td>
</tr>
<tr>
<td>Median PFS, months (95% CI)</td>
<td>18.1 (13.1–27.5)</td>
<td>11.1 (7.1–16.4)</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.508 (0.303–0.853)</td>
<td></td>
</tr>
<tr>
<td>P value</td>
<td>0.0046</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

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## Cyclin D1 and p16 expression in PALOMA-2

### Qualitative Analysis

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>666</td>
<td>0.58 (0.46–0.72)</td>
</tr>
<tr>
<td>ER+</td>
<td>504</td>
<td>0.57 (0.44–0.74)</td>
</tr>
<tr>
<td>ER–</td>
<td>62</td>
<td>0.41 (0.22–0.75)</td>
</tr>
<tr>
<td>Rb+</td>
<td>512</td>
<td>0.53 (0.42–0.68)</td>
</tr>
<tr>
<td>Rb–</td>
<td>51</td>
<td>0.68 (0.31–1.48)</td>
</tr>
<tr>
<td>Cyclin D1+</td>
<td>549</td>
<td>0.56 (0.44–0.71)</td>
</tr>
<tr>
<td>Cyclin D1–</td>
<td>15</td>
<td>1.0 (0.29–3.46)</td>
</tr>
<tr>
<td>p16+</td>
<td>466</td>
<td>0.52 (0.40–0.67)</td>
</tr>
<tr>
<td>p16–</td>
<td>84</td>
<td>0.73 (0.39–1.36)</td>
</tr>
<tr>
<td>Ki-67 ≤20%</td>
<td>318</td>
<td>0.53 (0.38–0.74)</td>
</tr>
<tr>
<td>Ki-67 &gt;20%</td>
<td>235</td>
<td>0.57 (0.41–0.79)</td>
</tr>
</tbody>
</table>

### Quantitative Analysis

<table>
<thead>
<tr>
<th>Percentile</th>
<th>n</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>666</td>
<td>0.58 (0.46–0.72)</td>
</tr>
<tr>
<td>ER status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤25th</td>
<td>142</td>
<td>0.50 (0.32–0.78)</td>
</tr>
<tr>
<td>&gt;25th to &lt;75th</td>
<td>282</td>
<td>0.53 (0.37–0.74)</td>
</tr>
<tr>
<td>≥75th</td>
<td>142</td>
<td>0.65 (0.41–1.05)</td>
</tr>
<tr>
<td>Rb status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤25th</td>
<td>154</td>
<td>0.57 (0.36–0.88)</td>
</tr>
<tr>
<td>&gt;25th to &lt;75th</td>
<td>249</td>
<td>0.46 (0.32–0.67)</td>
</tr>
<tr>
<td>≥75th</td>
<td>160</td>
<td>0.63 (0.42–0.95)</td>
</tr>
<tr>
<td>Cyclin D1 status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤25th</td>
<td>141</td>
<td>0.41 (0.26–0.65)</td>
</tr>
<tr>
<td>&gt;25th to &lt;75th</td>
<td>247</td>
<td>0.69 (0.48–1.00)</td>
</tr>
<tr>
<td>≥75th</td>
<td>176</td>
<td>0.52 (0.34–0.78)</td>
</tr>
<tr>
<td>p16 status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤25th</td>
<td>140</td>
<td>0.74 (0.46–1.20)</td>
</tr>
<tr>
<td>&gt;25th to &lt;75th</td>
<td>258</td>
<td>0.62 (0.44–0.89)</td>
</tr>
<tr>
<td>≥75th</td>
<td>152</td>
<td>0.33 (0.21–0.52)</td>
</tr>
</tbody>
</table>

Finn RS, et al. ESMO 2016
Rb expression in PALOMA-2

PAL+LET (n=72) PCB+LET (n=31)

\[
\text{Median (95% CI)} \quad \text{PFS, mo} \\
19.6 \quad (14.0–24.9) \quad 12.9 \quad (5.3–16.5)
\]

HR (95% CI); \( P \) value
0.47 \((0.27–0.82); 0.0060\)

>25% to <75%

PAL+LET (n=172) PCB+LET (n=77)

\[
\text{Median (95% CI)} \quad \text{PFS, mo} \\
25.7 \quad (25.1–NE) \quad 13.9 \quad (11.3–22.0)
\]

HR (95% CI); \( P \) value
0.46 \((0.32–0.67); <0.0001\)

≥75%

PAL+LET (n=101) PCB+LET (n=59)

\[
\text{Median (95% CI)} \quad \text{PFS, mo} \\
19.5 \quad (14.1–23.7) \quad 11.2 \quad (6.4–17.0)
\]

HR (95% CI); \( P \) value
0.63 \((0.42–0.95); 0.0267\)

Finn RS, et al. ESMO 2016
Patients without RB changes might present primary resistance.
Gene expression analyses to identify predictive markers (Pre-op palbo trial)

- No evidence that a recurrent targetable genomic alteration is associated with resistance.
- Common alterations on Cyclin D/CDK4/Rb pathway have not yet been reported to be predictive.
- Maintenance of Rb phosphorylation under treatment is associated with primary resistance: alternative pathway that activates Rb
CDK2 maintains RB phosphorylation under palbociclib

Herrera-Abreu MT et al, Cancer Res 2016 April;76(8):2301-13
Combination Treatment with Palbociclib and a CDK2 Inhibitor Can Overcome Resistance

Increased killing of palbociclib-resistant MCF7 clones was observed with combination treatment with palbociclib and the CDK2 inhibitor PF7741, compared with control or either agent alone.

Lee NV, et al. Presented at SABCS 2015; San Antonio, Texas, USA (Poster 3-06-01)
Other Factors Driving Palbociclib Resistance

*In Vivo* Include **Cyclin E Dysregulation**

Palbociclib-resistant MCF7 cells demonstrate intact Rb function, but a range of other aberrations including upregulation of Cyclin E1 and Myc are present.

Engineered overexpression of Cyclin E1 confers a 10-fold increase in palbociclib resistance to ER + breast cancer cell lines.

Knock-down of Cyclin E1 restores palbociclib sensitivity to resistant clones.

Cyclin E1 dysregulation is also implicated in resistance to hormonal therapy:
- Cyclin E1 knock-down resensitizes palbociclib-resistant MCF7 cells to fulvestrant treatment.

Lee NV, et al. Presented at SABCS 2015; San Antonio, Texas, USA (Poster 3-06-01)
RB1 mutations and secondary resistance

Relevant patients? Frequency of this event? Predictive value of RB1 subclonal alterations at baseline?

Herrera-Abreu MT et al, Cancer Res 2016 April;76(8):2301-13
Summary on predictive biomarkers

• Recurrent and common alterations at baseline do not predict primary resistance.
  – Primary resistance is rare
  – The maintenance of Rb phosphorylation may be associate with primary resistance.
• CDK2 emerges as a targetable mechanism of adaptation and resistance.
• RB1 mutations have been described in resistant xenograft models
Ongoing clinical trials:
Neoadjuvant/adjuvant setting
Short-term, Single-agent, Preoperative Palbociclib vs. No Treatment in Early Breast Cancer: POP Study

**Aim:** to identify if short-term preoperative single-agent palbociclib is associated with decreased cell proliferation and/or early biomarker changes in patients with early breast cancer

- **N=100**
  - Untreated HR+/HER2−, HER2+ or triple negative early breast cancer
  - Candidate for upfront surgery
  - Pre- or postmenopausal women

**RANDOMIZATION**

**Primary endpoint:**
- Antiproliferative response (lnKi67)

**Secondary endpoints:**
- Ki67 change from baseline
- Safety

**Exploratory analyses:**
- Association of pretreatment tumor molecular characteristics with proliferation changes
- Evaluation of pretreatment tumor molecular characteristics and their early changes with palbociclib

**Single-agent palbociclib 125 mg/day (days 1–14)**

**No treatment**

**Surgery (day 15)**

**FFPE and frozen samples were collected at baseline and surgery**

**Immunostaining (Ki67, Rb, pRb, P16, pAkt, pER), FISH (CCND1) and gene expression arrays were performed pre- and post-treatment**

**PIK3CA and Akt1 mutations were assessed pretreatment**

Overall, 100 patients were enrolled; the mean patient age was 54 years, 55% were postmenopausal, and the majority had HR+/HER2– disease (84%).

An antiproliferative response (lnKi67<1) was observed in significantly more patients treated with palbociclib vs. patients who received no preoperative treatment (43 [58%] vs. 3 [12%], P<0.001).

Palbociclib decreased Ki67 from baseline in 70% of patients with HR+/HER2– disease.

No antiproliferative response was observed in patients with HR+/HER2+ disease or TNBC, although only 15 patients were evaluated from these subgroups combined.

Interaction test P=0.002*

Molecular subtype, % (n)

<table>
<thead>
<tr>
<th>Molecular subtype</th>
<th>Palbociclib (n=73)</th>
<th>No treatment (n=26)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR+/HER2–</td>
<td></td>
<td></td>
</tr>
<tr>
<td>InKi67&lt;1</td>
<td>70 (43)</td>
<td>9 (2)</td>
</tr>
<tr>
<td>InKi67&gt;1</td>
<td>30 (18)</td>
<td>91 (21)</td>
</tr>
<tr>
<td>HER2+ or TNBC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>InKi67&lt;1</td>
<td>0</td>
<td>33 (1)</td>
</tr>
<tr>
<td>InKi67&gt;1</td>
<td>100 (12)</td>
<td>67 (2)</td>
</tr>
</tbody>
</table>

*Logistic model with Firth’s correlation
HR, hormone receptor

Across all patients, palbociclib significantly decreased pRb vs. no treatment (P=0.001)*
- no significant interaction was observed between HR+ status and decrease in pRb (interaction test P=0.872)
However in a subset of patients with HR+/HER2– disease, palbociclib did not decrease pRb
In addition, a significant correlation was observed between lack of Ki67 response at surgery and lack of pRb decrease across all patients (P<0.001)

Lack of pRb decrease may define a subset of patients with HR+/HER2– disease who have primary resistance to palbociclib treatment

*ANCOVA after log transformation
HR, hormone receptor; pRb, phosphorylated retinoblastoma protein

POP Study: Further Analysis of Molecular and Genetic Biomarkers

No baseline biomarkers predictive of palbociclib efficacy were identified

- No significant association was found between evaluated baseline biomarkers and antiproliferative response (lnKi67<1) at surgery

<table>
<thead>
<tr>
<th>Group</th>
<th>Biomarker</th>
<th>P_interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>All tumors</td>
<td>Rb</td>
<td>0.641</td>
</tr>
<tr>
<td></td>
<td>pRb</td>
<td>0.856</td>
</tr>
<tr>
<td></td>
<td>P16</td>
<td>0.218</td>
</tr>
<tr>
<td></td>
<td>pAkt (Ser473)</td>
<td>0.484</td>
</tr>
<tr>
<td></td>
<td>pER</td>
<td>0.856</td>
</tr>
<tr>
<td></td>
<td>CCND1 amplification</td>
<td>0.388</td>
</tr>
</tbody>
</table>

HR+/HER2–

- Gene expression array analysis identified CDK1 and CDC25C as weak predictors of antiproliferative response (lnKi67<1) at surgery following palbociclib for patients with HR+/HER2– tumors

- Short-term palbociclib did not appear to activate alternative pathways driving proliferation in HR+/HER2– tumors

  - Across all tumor subtypes, no paradoxical activation of Akt or ER was observed following short-term palbociclib treatment (P=0.925 and P=0.644, respectively*)

  - Genes involved in the cell cycle, including PLK1, BUB1 and FOXM1, were observed to decrease following palbociclib in patients with HR+/HER2– tumors

  - Palbociclib therapy did not appear to increase the expression of any genes evaluated in the panel for patients with HR+/HER2– tumors

*Non-parametric ANCOVA

Akt, protein kinase B; BUB1, budding uninhibited by benzimidazoles 1; CCND1, cyclin D1; CDC25C, cell division cycle 25C; FOXM1, forkhead box protein M1; HR, hormone receptor; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha; PLK1, polo-like kinase 1; pRb, phosphorylated retinoblastoma

Neoadjuvant Palbociclib + Anastrozole: NeoPalAna

- Single-arm phase II study
- Primary endpoint: Complete cell cycle arrest (CCCA, defined as Ki67 ≤ 2.7%) on C1D15 biopsy following 2 weeks of palbociclib + anastrozole
- Secondary endpoints: Clinical, radiographic and pathologic responses, safety, CCCA rate and changes in Ki67 by intrinsic subtype and PIK3CA mutation status, molecular effect of palbociclib and NGS of an 83-gene panel to explore resistance mechanisms

C, cycle; D, day; NGS, next-generation sequencing; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha

Additive proliferation suppression by palbociclib + anastrozole vs anastrozole alone was observed in patients with **PIK3CA Mutant** and **PIK3CA Wild Type**
Additive proliferation suppression by palbociclib + anastrozole vs anastrozole alone was observed for both Luminal A and Luminal B.

Somatic mutation, intrinsic subtype and clinicopathological characteristics of individual tumors in relation to Ki67 response.

Fig. 2 shows the somatic mutations in 41 patients with:

- **Anastrozole-sensitive** (C1D1 Ki67<2.7%; n=9)

- **Palbociclib-sensitive** (C1D1 Ki67>2.7% but C1D15 Ki67≤2.7%; n=24)

- **Resistant** (C1D15 Ki67>2.7%, n=5) tumors (C1D1/C1D15 Ki67 missing, n=3)

In addition to **PIK3CA**, the most common mutations were:

- **CDH1, PTEN, TP53, TBX3** and **MAP3K1**

Preoperative Abemaciclib + Anastrozole: neoMONARCH

Rationale:
♦ Change in Ki67 at 2 weeks in neoadjuvant studies may be predictive of improved disease-free survival in adjuvant studies.\(^1,2\)

Secondary and exploratory objectives:
♦ Safety, clinical, radiologic and pathological response, cell cycle associated gene expression.

Statistical design:
♦ 220 randomized patients required to achieve 50 evaluable patients in each arm
♦ 80% power at one-sided alpha of 0.1, assuming:
  • Assumed mean reduction of 82% for anastrozole alone and 91% for combination

♦ 2 mg loperamide was administered prophylactically with each abemaciclib dose for the first 28 days then at discretion of investigator.


Hurvit, SABCS, 2016
**Ki67 Expression and Response at Week 2**

**Geometric Mean Change**  
(Primary Endpoint of Study)

- **Anastrozole 1 mg**
- **Abemaciclib 150 mg**
- **Abemaciclib 150 mg + Anastrozole 1 mg**

**Complete Cell Cycle Arrest**

- **OR =** 8.2 (3.4, 20.2)  
  p < 0.001

- **Responders:** 8, 37, 30  
  (Ki67 index < 2.7% at 2 weeks)

**Geometric Mean Ratio (GMR), 2-sided 90% confidence interval (CI), p-value.**

<table>
<thead>
<tr>
<th>GMR</th>
<th>0.20 (0.13, 0.30)</th>
<th>p &lt; 0.001</th>
</tr>
</thead>
</table>

**Change from Baseline (%):**

- **n = 54**
  - 0 to 50
  - -50 to -100

- **n = 56**
  - 0 to 50
  - -50 to -100

- **n = 51**
  - 0 to 50
  - -50 to -100

**OR =** 11.2 (4.7, 27.4)  
p < 0.001

**Responders:** 14.8, 66.1, 58.8

*Patient had received dose intensity of 19% for abemaciclib prior to Week 2 biopsy.*

---

**a** Geometric Mean Ratio (GMR), 2-sided 90% confidence interval (CI), p-value. p-values are based on a one-sided hypothesis test from a linear model with treatment.

**b** A responder is identified as a patient with a ln(Ki67) value of less than 1. Odds ratio (OR), 2-sided 90% CI, p value. p value is calculated by Fisher's Exact test of a one-sided hypothesis. * Patient had received dose intensity of 19% for abemaciclib prior to Week 2 biopsy.

Hurvit, SABCS, 2016
# Tumor Differentiation & Immune Infiltrates Over Time

<table>
<thead>
<tr>
<th>Time</th>
<th>H&amp;E</th>
<th>Total T cells (CD3)</th>
<th>Suppressor/ Cytotoxic T cells (CD8)</th>
<th>T Regulatory cells (FOXP3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td><img src="image" alt="H&amp;E Baseline" /></td>
<td><img src="image" alt="CD3 Baseline" /></td>
<td><img src="image" alt="CD8 Baseline" /></td>
<td><img src="image" alt="FOXP3 Baseline" /></td>
</tr>
<tr>
<td>C1D15</td>
<td><img src="image" alt="H&amp;E C1D15" /></td>
<td><img src="image" alt="CD3 C1D15" /></td>
<td><img src="image" alt="CD8 C1D15" /></td>
<td><img src="image" alt="FOXP3 C1D15" /></td>
</tr>
<tr>
<td>(Abemaciclib monotherapy)</td>
<td>Moderately Differentiated</td>
<td>Ki67: 20%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C5D28</td>
<td><img src="image" alt="H&amp;E C5D28" /></td>
<td><img src="image" alt="CD3 C5D28" /></td>
<td><img src="image" alt="CD8 C5D28" /></td>
<td><img src="image" alt="FOXP3 C5D28" /></td>
</tr>
<tr>
<td>(Abemaciclib &amp; Anastrozole)</td>
<td>Well Differentiated</td>
<td>Ki67: 3.4%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Ki67: 0.2%</td>
</tr>
</tbody>
</table>

Hurvit, SABCS, 2016
Phase II Randomized Study of Palbociclib + Letrozole as Neoadjuvant Therapy in Postmenopausal Women with ER+/HER2– Primary Breast Cancer: PALLET

NCT02296801

N=300

Primary endpoints:
- Change in the proliferation marker Ki67 at week 14
- Clinical CR at week 14

Secondary endpoints:
- Pathological CR,
- Preoperative Endocrine Prognostic Index Score,
- Safety, molecular and genetic profiles of samples

Operable ER+/HER− invasive early breast cancer
Suitable for neoadjuvant therapy with letrozole
Postmenopausal

- Letrozole (2.5 mg QD) for 14 weeks
- Letrozole (2.5 mg QD) for 2 weeks
- Palbociclib (125 mg QD) for 2 weeks
- Palbociclib (125 mg QD, 3/1 schedule) + letrozole (2.5 mg QD) for 12 weeks

CR, complete response
Phase III Study of Palbociclib in High-risk Early Breast Cancer: PENELOPE-B

N=800

Primary endpoint:
IDFS

Secondary endpoints: OS, iDFS excluding second non-breast cancer, DDFS, LRFS, iDFS by commercially available multigene assay subtyping, safety, PROs, biomarkers

Stratification factors: lymph node status, age, biomarkers (Ki67, pRb, Cyclin D), and region

N=800

RANDOMIZATION

1:1

Palbociclib
(125 mg QD, 3/1 schedule) + SOC

Placebo
(3/1 schedule) + SOC

Non-study adjuvant endocrine therapies being taken for 5–10 years after surgery were permitted during the study:
- tamoxifen (pre- and postmenopausal women)
- goserelin agonists (premenopausal)
- AIs: anastrozole, letrozole (postmenopausal)

PENELOPEa,1,2

Early ER+ breast cancer “high risk” (CPS-EG ≥3)
Premenopausal/postmenopausal
Completed taxane-based neoadjuvant therapy, surgery, radiotherapy

1. ClinicalTrials.gov NCT01864746
2. Data on file, Pfizer

In collaboration with GBG (Germany)

DDFS, distant disease-free survival; IDFS, invasive disease-free survival; LRFS, local recurrence-free survival; pRb, phosphorylated retinoblastoma protein
**Randomized, Open-label Phase III Study of Palbociclib + Adjuvant Endocrine Therapy vs. Adjuvant Endocrine Therapy Alone in HR+/HER2– Early Breast Cancer: PALLAS**

**Sponsor:** Alliance for Clinical Trials in Oncology Foundation, ABCSG

*Stage IIA limited to maximum 1000 patients*

DRFS, distant recurrence-free survival; iDFS, invasive disease-free survival; LRRFS, locoregional recurrence-free survival

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**N=4600**

- Histologically confirmed HR+/HER2– early invasive breast cancer
- Stage IIA or III
- Pre- or postmenopausal women
- Men are eligible
- ≤12 months since initial pathologic diagnosis
- Prior chemotherapy allowed

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**Randomization**

**Primary endpoint:** iDFS

**Secondary endpoints:**
- iDFS excluding second primary cancers of non-breast origin; DRFS; LRRFS; OS; PROs; safety

**Stratification factors:**
- Pathologic stage (IIA vs. IIIB/III) or clinical stage (if preoperative therapy was given with the higher stage determining eligibility); neo/adjuvant chemotherapy (yes vs. no); age (<50 vs. ≥50 years); geographic region (North America vs. Europe vs. Asia)

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**Arm A**
- Palbociclib (2 years) + Endocrine therapy (5–10 years)

**Arm B**
- Endocrine therapy (5–10 years)

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2. Meyer E, et al. Presented at SABCS 2015; San Antonio, Texas, USA (Oral presentation OT1-03-21)
Ongoing Clinical Trials :
Metastatic setting
PEARL<sup>1</sup>

Phase III, international, multicenter, open-label, controlled study  NCT02028507

Part 1

Eligibility criteria
- HR+/HER2– MBC
- Prior AI therapy

Stratification
- Visceral metastases
- Prior sensitivity to hormonal treatment
- Prior chemotherapy for MBC

1:1 Randomization

Arm A: Palbociclib + exemestane
Arm B: Capecitabine

N=300

Part 2

Eligibility criteria
- Visceral metastases
- Prior sensitivity to hormonal treatment
- Prior chemotherapy for MBC

1:1 Randomization

Arm A: Palbociclib + fulvestrant
Arm B: Capecitabine

N=300

Primary endpoint: PFS
- In all Part 2 patients regardless of ESR1 mutational status
- In all patients with WT ESR1 at study entry

Sponsored by GEICAM (Spanish Breast Cancer Research Group) with participation from CECOG
GEICAM, Grupo Español de Investigación en Cáncer de Mama; CECOG, Central European
Cooperative Oncology Group; HR, hormone receptor

N=122, 1:1 Randomization
Primary end point: Progression free survival (PFS)

Secondary end point:
Overall survival (OS) / Toxicity / Object response rate (ORR) /
Disease control rate (CR+PR+SD, DCR) / Biomarker / QoL

Experimental arm vs. Control arm: 8m vs. 5m (HR: 0.625)
Duration: enrollment: 32m, F/U: 18m – 50 months
Palbociclib + Exemestane + Gosereline

Capecitabine 1250mg/m² bid D1-14 q3w

Screening Randomization

Tissue (M.N)*: mandatory

Disease evaluation: every 6 weeks till first 12 weeks, then follow-up evaluation at every 3 cycles (9-12 weeks till progression)
CT and Bone scan

At PD, tissue biopsy is optional/mandatory

CBC, Chemistry, ECG

*M: Metastatic (biopsy)
N: New biopsy
Or Archival breast tissue
PARSIFAL

Phase II, international, randomized, open-label, controlled, multicenter study

NCT02491983

N=304

Stratification
- Visceral vs. non-visceral disease
- De-novo vs. non-de-novo disease

Randomization
1:1

Palbociclib (125 mg/day, 3/1 schedule) + letrozole (2.5 mg QD, continuous)

Palbociclib (125 mg/day, 3/1 schedule) + fulvestrant (500 mg IM q4w)

• ER+, HER2– locally advanced or MBC
• Postmenopausal, or premenopausal and receiving an LHRH agonist
• No prior chemotherapy in the metastatic setting

Primary endpoint: 1-year PFS
Secondary endpoints: Safety, TTP, OS, CBR, ORR

Prospective translational studies aim to identify:
- Potential predictive biomarkers for palbociclib benefit
- Mechanisms of resistance to palbociclib + endocrine therapy

PALESTRA

- Phase II, randomized, open-label study being conducted at 16 centers in Canada

- Histologically confirmed ER+/HER2− advanced/MBC
- Pre- or postmenopausal women
- Progressed on or ≤12 months after completion of adjuvant endocrine therapy or progressed during endocrine therapy for advanced/MBC
- ≤1 prior line of chemotherapy for advanced/MBC allowed in addition to endocrine therapy

Primary endpoint:
PFS

Secondary endpoints:
RR; DOR; CBR; OS; safety

Arm A
Palbociclib (125 mg/day; 3/1 schedule) + endocrine therapy

Arm B
Palbociclib (100 mg/day; 3/1 schedule) + endocrine therapy

Sponsor: Canadian Cancer Trials Group

Progression on or within 1 month of completing endocrine therapy

Fulvestrant, tamoxifen or AI at standard doses/schedules

CBR, clinical benefit rate; RR, response rate

Conclusions

• ER-positive phenotype is in essence the only biomarker.
• It is unknown whether
  – ESR1 mutated tumors respond further to palbociclib.
  – Exposure to palbociclib favors emergence of ESR1 mutations.
• Markers of ER-independent proliferation are possible predictors of a response to palbociclib.
• Ongoing studies are investigating the combination of CDK4 and CDK6 inhibitors and inhibitors of signaling pathways such as those interfering with PI3K/Akt/mTOR and HER2 pathways.
• Other therapies: AI + HDAC before or after exposure to palbociclib or another CDK4/6 inhibitor (ECOG-ACRIN 2112, NCT02115282).