Clinical Spotlight in Breast Cancer

Reference Slide Deck

Abstract #1815
Impact of Palbociclib Plus Fulvestrant on Global QOL, Functioning, and Symptoms Compared to Placebo Plus Fulvestrant in Postmenopausal Women With Hormone Receptor–Positive, HER2-Negative, Endocrine-Resistant Metastatic Breast Cancer (PALOMA-3)

Abstract #1815

Background

- Palbociclib is an orally bioavailable small-molecule inhibitor of CDK4 and CDK6, with a high level of selectivity for CDK4 and CDK6 over other cyclin-dependent kinases.
- Palbociclib in combination with fulvestrant has shown significant efficacy improvement (median progression-free survival [PFS] 9.2 vs 3.8 months) compared with fulvestrant alone in hormone receptor (HR)-positive, HER2-negative, endocrine-resistant metastatic breast cancer in the PALOMA-3 study (NCT01942135).


The main objective of the current analysis was to compare patient-reported global quality of life (QOL), functioning, and symptoms between palbociclib plus fulvestrant and placebo plus fulvestrant in HR-positive, HER2-negative advanced/metastatic breast cancer.
Materials and Methods
Patients, Study Design, and Dosing Regimen

• PALOMA-3 is a double-blind, randomized phase III study in patients with HR-positive, HER2-negative advanced/metastatic breast cancer whose cancer had relapsed or progressed during prior endocrine therapy.

• Patients in the study were randomized 2:1 to receive palbociclib 125 mg/d orally for 3 weeks followed by 1 week off (n = 347) and fulvestrant (500 mg intramuscularly every 14 days for first 3 injections and then every 28 days) or placebo and fulvestrant (n = 174). Two (0.6%) patients in the palbociclib plus fulvestrant arm and 2 (1.1%) patients in the placebo plus fulvestrant arm were randomized but not treated.

• Additional details on study design and patient eligibility criteria have been reported previously\(^1\)


The primary endpoint was PFS in the intent-to-treat (ITT) population (all patients randomized to study treatment) as assessed by investigator using RECIST version 1.1.

Secondary endpoints included overall response; clinical benefit response; overall survival; safety outcomes; and patient-reported outcomes (PROs) including time to deterioration in pain scores.
Patient-reported outcomes (PROs) were assessed at baseline; on day 1 of cycles 2, 3, and 4; and on day 1 of every other cycle starting with C6, using European Organization for the Research and Treatment of Cancer (EORTC) QLQ-C30 and breast cancer module QLQ-BR23\(^1,2\).

Both EORTC QLQ-C30 and BR-23 include single-item and/or multi-item subscales assessing functioning, breast cancer-specific functioning and symptoms, and global QOL.

The EORTC QLQ-BR23 functional scales consist of the 4 scales that assess body image, sexual functioning, sexual enjoyment, and future perspective.

The EORTC QLQ-BR23 symptom scales consist of the 4 scales that assess systemic therapy side effects, breast symptoms, arm symptoms, and upset by hair loss.


Materials and Methods
PRO Questionnaires and Scoring (cont)

• The average of the items contributing to a multi-item subscale was calculated to compute the raw score of the scale

• Raw scores were transformed to a standardized scale of 0–100 using the linear transformation formula provided in the scoring manual¹

• Higher scores within the possible range (0–100) indicated better functioning/QOL or higher symptom severity


Materials and Methods
Data Analyses

- At each timepoint, the number and percentage of patients who completed the questionnaire were summarized by treatment group.

- The PRO-evaluable population was defined as patients who completed ≥1 question both at baseline and at ≥1 timepoint post-baseline.

- Repeated measures mixed-effects analyses were performed to compare on-treatment overall global QOL scores and change from baseline scores for functioning and symptoms between treatments with no adjustment for multiple comparisons.

- Time to deterioration (TTD), defined as time to ≥10-point increase from baseline for pain, was estimated using Kaplan-Meier methods and compared between groups using an unstratified log-rank test and Cox proportional hazards model.
Results
Baseline Characteristics

• Between September 2013 and August 2014, a total of 521 patients were randomized: 347 patients to the palbociclib plus fulvestrant arm and 174 patients to the placebo plus fulvestrant arm

• Demographic characteristics were comparable between the treatment groups

Results

Questionnaire Completion Rates

- Questionnaire completion rates at baseline and across treatment cycles were ≥95% in each group.

- Baseline mean scores for global QOL were similar for palbociclib plus fulvestrant and placebo plus fulvestrant (65.9 [95% CI, 63.5–68.2] vs 65.3 [95% CI, 61.9–68.6]; \( P = .768 \)).

- Baseline mean scores for the symptoms of the EORTC QLQ-C30 were similar in both treatment arms for all symptoms except insomnia (26.3 in the palbociclib plus fulvestrant arm vs 32.9 in the placebo plus fulvestrant arm).

- Baseline mean scores for the symptoms indicate low symptom severity in both treatment arms.

<table>
<thead>
<tr>
<th>Domain/Scale</th>
<th>Palbociclib + Fulvestrant Mean (95% CI)</th>
<th>Placebo + Fulvestrant Mean (95% CI)</th>
<th>P Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Global QoL</td>
<td>65.9 (63.5, 68.2)</td>
<td>65.3 (61.9, 68.6)</td>
<td>.768</td>
</tr>
<tr>
<td>Physical Functioning</td>
<td>79.4 (77.3, 81.5)</td>
<td>78.9 (76.1, 81.7)</td>
<td>.761</td>
</tr>
<tr>
<td>Role Functioning</td>
<td>78.5 (75.7, 81.2)</td>
<td>77.6 (73.8, 81.5)</td>
<td>.717</td>
</tr>
<tr>
<td>Emotional Functioning</td>
<td>74.6 (72.4, 76.8)</td>
<td>72.8 (69.7, 76.0)</td>
<td>.370</td>
</tr>
<tr>
<td>Cognitive Functioning</td>
<td>84.8 (82.8, 86.8)</td>
<td>82.1 (79.2, 85.1)</td>
<td>.131</td>
</tr>
<tr>
<td>Social Functioning</td>
<td>81.3 (78.7, 83.9)</td>
<td>78.5 (74.7, 82.4)</td>
<td>.232</td>
</tr>
<tr>
<td>Fatigue</td>
<td>32.1 (29.7, 34.5)</td>
<td>32.2 (28.9, 35.5)</td>
<td>.964</td>
</tr>
<tr>
<td>Nausea/Vomiting</td>
<td>7.4 (5.6, 9.1)</td>
<td>5.2 (3.4, 7.0)</td>
<td>.092</td>
</tr>
<tr>
<td>Pain</td>
<td>26.6 (23.9, 29.3)</td>
<td>27.5 (23.7, 31.3)</td>
<td>.706</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>15.7 (13.3, 18.1)</td>
<td>16.5 (13.0, 19.9)</td>
<td>.709</td>
</tr>
<tr>
<td>Insomnia</td>
<td>26.3 (23.4, 29.1)</td>
<td>32.9 (28.4, 37.5)</td>
<td>.011</td>
</tr>
<tr>
<td>Appetite Loss</td>
<td>16.8 (14.1, 19.5)</td>
<td>12.9 (9.4, 16.3)</td>
<td>.083</td>
</tr>
<tr>
<td>Constipation</td>
<td>13.6 (11.1, 16.2)</td>
<td>13.7 (10.5, 16.8)</td>
<td>.984</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>5.4 (3.9, 6.9)</td>
<td>6.2 (4.1, 8.4)</td>
<td>.548</td>
</tr>
</tbody>
</table>

The between-treatment comparison of palbociclib plus fulvestrant vs placebo plus fulvestrant showed a statistically significant difference (66.1 [95% CI, 64.5–67.7] vs 63.0 [95% CI, 60.6–65.3]; \( P = .0313 \)) favoring palbociclib plus fulvestrant.
A significantly greater improvement from baseline was observed in the palbociclib plus fulvestrant arm for emotional functioning (2.7 [95% CI, 1.1–4.3] vs −1.9 [95% CI, −4.2 to 0.5]; \( P = .0016 \))

No statistically significant difference was found in physical, role, cognitive, and social functioning between the 2 treatment arms

EORTC QLQ-C30 Symptom Scales

• A significantly greater improvement from baseline was observed in the palbociclib plus fulvestrant arm for pain (-3.3 [95% CI, -5.1 to -1.5] vs 2.0 [95% CI, -0.6 to 4.6]; \( P = .0011 \))

• Statistically significantly less deterioration was observed for nausea and vomiting in overall change from baseline scores in the palbociclib plus fulvestrant arm compared with placebo plus fulvestrant arm (1.7 [95% CI, 0.4–3.0] vs 4.2 [95% CI, 2.3–6.1]; \( P = .0369 \))

• No significant differences between treatment arms were observed in any other EORTC QLQ-C30 symptoms

Difference Between Treatment Arms in Change From Baseline Scores for EORTC QLQ-C30 Symptoms

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Estimate (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>-1.5 (-4.5, 1.5)</td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td>-2.5 (-4.8, -0.2)</td>
</tr>
<tr>
<td>Pain</td>
<td>-5.3 (-8.5, -2.1)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>-0.5 (-3.7, 2.8)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>-2.0 (-5.5, 1.6)</td>
</tr>
<tr>
<td>Appetite loss</td>
<td>-0.6 (-4.1, 2.9)</td>
</tr>
<tr>
<td>Constipation</td>
<td>0.7 (-2.5, 3.9)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>-0.6 (-2.8, 1.7)</td>
</tr>
<tr>
<td>Financial difficulties</td>
<td>0.3 (-3.1, 3.6)</td>
</tr>
</tbody>
</table>

No significant differences were observed for breast cancer-specific functional scales of body image, sexual functioning, sexual enjoyment, and future perspective.

Estimates (95% CI):
- Body image: 2.3 (-0.7, 5.2)
- Sexual functioning: -0.8 (-3.1, 1.6)
- Sexual enjoyment: 1.4 (-4.4, 7.3)
- Future perspective: 3.6 (-0.5, 7.6)

Difference Between Treatment Arms in Change From Baseline for EORTC QLQ-BR23 Symptoms

• No significant differences were observed between the treatment groups in breast and arm symptoms.

• Among patients reporting hair loss in each treatment arm, a significantly greater deterioration from baseline was observed for upset by hair loss (2.9 [95% CI, –1.7 to 7.4] vs -6.0 [95% CI, -12.3 to 0.3]; \( P = .0255 \)) in the palbociclib plus fulvestrant arm compared with the placebo plus fulvestrant arm.

• Previously reported analyses have shown that alopecia (hair loss) reported as an adverse event (AE) were mostly grade 1 using the Common Terminology Criteria (CTCAE 4.0); grade 1 (12.4%) and grade 2 (1.2%).


Difference Between Treatment Arms in Change From Baseline for EORTC QLQ-BR23 Symptoms

- **Systemic therapy side effects**: Estimate (95% CI) 0.4 (-1.6, 2.3)
- **Breast symptoms**: Estimate (95% CI) -0.9 (-2.6, 0.7)
- **Arm symptoms**: Estimate (95% CI) -0.2 (-2.6, 2.2)
- **Upset by hair loss**: Estimate (95% CI) 8.9 (1.1, 16.6)

Time to Deterioration (TTD) Analysis for Pain

- The median TTD in pain was 8 months (95% CI, 5.6–not estimable) in the palbociclib plus fulvestrant arm compared with 2.8 months (95% CI, 2.3–5.4) in the placebo plus fulvestrant arm.

- Treatment with palbociclib plus fulvestrant significantly delayed deterioration in pain compared with placebo plus fulvestrant (hazard ratio, 0.642 [95% CI, 0.487–0.846]; \( P < .001 \)).
Time to Deterioration in Pain

Survival Distribution Function

QLQ-C30 Time to Deterioration (TTD)*, Months

*Symptom scale of pain increase of ≥10 points – patient-reported outcome analysis set.
QLQ, quality of life questionnaire.

Conclusions

- Addition of palbociclib to fulvestrant in previously endocrine-treated HR-positive, HER2-negative advanced/metastatic breast cancer patients was associated with:
  - Significantly higher on treatment global QOL scores
  - A significant improvement in emotional functioning and pain scores
  - A significant delay in deterioration of pain