Breast Cancer

ESMO 2016 Breast Cancer CDK4/6 Headlines

Our Experience
#ESMO16 #BreastCancer: #Palbociclib, #Ribociclib and #Abemaciclib Data #Ibrance #Pfizer #Novartis #Lilly
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#Pfizer #Novartis #Lilly
ESMO Breast Cancer Track: Palbociclib, Ribociclib and Abemaciclib

Cyclin-dependent Kinase 4 and 6 (CDK4/6) inhibitors have shown clinical activity in patients with endocrine-resistant metastatic breast cancer. During the European Society for Medical Oncology (ESMO) Annual Meeting 2016, significant updates on studies with CDK4/6 inhibitors ribociclib, palbociclib and abemaciclib were presented.

Up to 75% of breast cancers express the oestrogen receptor or progesterone receptor. Endocrine therapy is the standard of care for postmenopausal women with advanced breast cancer that is hormone receptor-positive and human epidermal growth factor receptor 2-negative, with
aromatase inhibitors being the preferred first-line treatment option.

**ESMO 2016 Ribociclib**

Dr Hortobagyi discussed the results of the first-line MonaLEEsa-2 study in 668 patients with hormone-receptor positive (HR+) and human epidermal receptor 2 (HER2) negative advanced breast cancer (ABC) (abstract LBA 1_PR). Subjects were randomised 1:1 to either ribociclib (600 mg/day for 21 days in 28-day cycles) plus letrozole (2.5 mg/day, continuous) or ribociclib-matching placebo plus letrozole.

The study met its primary endpoint, investigator-assessed progression-free survival (PFS), at the first preplanned interim analysis, when 243 PFS events had occurred (Figure 1). The addition of ribociclib to letrozole reduced the relative risk of progression disease by 44%. Median PFS for letrozole plus placebo was 14.7 months, median PFS in the ribociclib plus letrozole group was not yet reached (HR = 0.56; 95% CI: 0.43–0.72; P < 0.0001).

Most common grade 3/4 adverse event in the ribociclib plus letrozole group were neutropenia, which occurred in 59% of patients, and leukopenia (21%). In the letrozole plus placebo arm, neutropenia and leukopenia occurred in 1% of patients each.

Other grade 3/4 adverse events in the ribociclib plus letrozole arm included elevated alanine aminotransferase (9%), hypertension (10%), lymphopenia (7%), and elevated aspartate aminotransferase (6%). In the placebo plus letrozole group, these adverse events accounted for 1%, 11%, 1%, and 1% respectively. OS data were not mature at the time of presentation.

*Figure 1. Kaplan–Meier Analysis of progression-free survival in MonaLEEsa-2 study at median 18 months follow-up. Courtesy of G.N. Hortobagyi et al., NEJM 2016*
Ribociclib group

Placebo group

Hazard ratio, 0.56 (95% CI, 0.43–0.72)
P=3.29×10^{-6} for superiority

No. at Risk
Ribociclib 334 294 277 257 240 226 164 119 68 20 6 1 0
Placebo 334 279 264 237 217 192 143 88 44 23 5 0 0

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Should all Women with Endocrine-Sensitive and Operable Breast Cancer Receive Adjuvant Hormonal Therapy?
ESMO 2016 Palbociclib

The results of the first-in-class CDK4/6 inhibitor palbociclib included a biomarker analysis in the phase III PALOMA-2 trial and a poster discussion on the health-related quality of life (HRQoL) in the same study.

About the PALOMA-2

The phase III PALOMA-2 study randomised 666 women with HR+ and HER2-negative ABC in a 2:1 fashion to either receive palbociclib (125 mg/day for 21 days in 28-day cycles) plus letrozole (2.5 mg/day, continuously) or palbociclib-matching placebo plus letrozole as a first-line treatment.

During the American Society of Clinical Oncology (ASCO) annual conference, held in June 2016, the efficacy results of the PALOMA-2 study were presented. At that time, the results showed a significant 42% relative risk reduction for
PFS in women receiving palbociclib plus letrozole when compared to placebo plus letrozole. Median PFS was 24.8 months vs. 14.5 months respectively (HR = 0.58; 95% CI: 0.46-0.72; P < 0.0001).

Also read:

**Luminal Breast Cancer: Can CDK4/6 Inhibition by Palbociclib Improve on Chemotherapy?** (May 2017)

**Biomarkers**

This ESMO 2016 conference, Dr Finn presented a biomarker analysis on tissue samples of 568 subjects who participated in the PALOMA-2 study (Abstract LBA15). Analysis of oestrogen receptor (ER) expression, cyclin D1 (CCND1), retinoblastoma (RB) and P16 (CDKN2A) status, as well as Ki67 expression, did not result in the identification of sub-populations who did not derive benefit from the addition of palbociclib to letrozole. By H-score, some variation between subgroups was observed, but the addition of palbociclib to letrozole improved PFS across all
Quality of Life

Dr Rugo discussed the analysis of the HRQoL in the PALOMA-2 study (Abstract 225PD). Participants were asked to complete the Functional Assessment of Cancer Therapy – Breast (FACT-B) questionnaire, which included the FACT-general (FACT-G) and breast cancer-specific subscale (BCS). The results did not show a significant difference in HRQoL outcome between the palbociclib plus letrozole group when compared to placebo plus letrozole (Table 1).

Table 1: HRQoL outcome in the phase III Palome-2 study: No significant difference was observed between palbociclib plus letrozole and placebo plus letrozole. Higher scores indicate better quality of life. FACT-B produces five subscale scores: physical well-being (PWB), social/family well-being (SWB), emotional well-being (EWB), functional well-being (FWB), and a BC subscale (BCS).

<table>
<thead>
<tr>
<th></th>
<th>PAL + LET</th>
<th>PBO + LET</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TOI</td>
<td>-0.1</td>
<td>0.71</td>
<td>0.325</td>
</tr>
<tr>
<td>Fact-G</td>
<td>-0.39</td>
<td>-0.53</td>
<td>0.882</td>
</tr>
<tr>
<td>FACT-B</td>
<td>-0.11</td>
<td>0.22</td>
<td>0.782</td>
</tr>
<tr>
<td>PWB</td>
<td>-0.5</td>
<td>-0.3</td>
<td>0.414</td>
</tr>
<tr>
<td>SWB</td>
<td>-0.6</td>
<td>-0.7</td>
<td>0.762</td>
</tr>
<tr>
<td>EWB</td>
<td>0.7</td>
<td>0.5</td>
<td>0.538</td>
</tr>
<tr>
<td>FWB</td>
<td>0.2</td>
<td>0.3</td>
<td>0.707</td>
</tr>
<tr>
<td>BCS</td>
<td>0.19</td>
<td>0.83</td>
<td>0.055</td>
</tr>
</tbody>
</table>

“Endocrine therapy is an established first-line treatment for ABC. However, endocrine therapy resistance and disease progression eventually occur in most patients. Cyclin-dependent kinase 4/6 inhibition is a valid treatment strategy for hormone receptor positive advanced breast cancer and may help overcome or delay endocrine therapy resistance.”

ESMO 2016 Abemaciclib

ESMO abemaciclib data included two oral presentations.

Dr Hurvitz presented results of the phase II neoadjuvant neoMONARCH study in women with untreated early-stage invasive HR+ and HER2-negative breast cancer (Abstract LBA13).

The study compared in a 1:1:1 fashion abemaciclib (150 mg BID) plus anastrozole (1 mg QD), abemaciclib monotherapy, and anastrozole monotherapy and investigated drop in Ki67 after two weeks of treatment. Upon completion of initial two-week treatment, all patients continued to receive abemaciclib plus anastrozole for an additional 14 weeks, to complete 16 weeks of neoadjuvant treatment. Patients received prophylactic loperamide concomitantly with abemaciclib.
Abemaciclib neoMONARCH Ki67 Effect

The data represented a first pre-specified interim analysis at nine months. Ki67 data was available for 64 patients (Table 2). Reduction in Ki67 geometric mean percent change from baseline was significantly higher in the abemaciclib plus anastrozole combination and abemaciclib monotherapy arms than in patients receiving anastrozole monotherapy (P = 0.001). Moreover, the number of Ki67 responders (patients achieving a Ki67 < 2.7% at week 2) was higher in the combination and the abemaciclib monotherapy arms.

Table 2: Reduction in Ki67 geometric mean percent (Mean ΔKi67) change from baseline. ABE = abemaciclib; ANZ = anastrozole.

<table>
<thead>
<tr>
<th></th>
<th>ABE Mono</th>
<th>ABE+ANZ</th>
<th>ANZ Mono</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>19</td>
<td>23</td>
<td>22</td>
</tr>
<tr>
<td>Mean ΔKi67</td>
<td>-93.5%</td>
<td>-93.1%</td>
<td>-71.0%</td>
</tr>
</tbody>
</table>

Table 3: Efficacy data in evaluable patients (HER2-negative group: n = 75; HER2-positive group: n = 12). ABE = abemaciclib; ANZ = anastrozole; EXE = exemestane; LET = Letrozole; RAD001 = everolimus; TAM = tamoxifen; TMAB = trastuzumab.

<table>
<thead>
<tr>
<th></th>
<th>ORR</th>
<th>CBR</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABE + TAM (n = 15)</td>
<td>20%</td>
<td>80%</td>
</tr>
<tr>
<td>ABE + ANZ (n = 15)</td>
<td>20%</td>
<td>87%</td>
</tr>
<tr>
<td>ABE + LET (n = 14)</td>
<td>14%</td>
<td>57%</td>
</tr>
<tr>
<td>ABE + EXE (n = 13)</td>
<td>46%</td>
<td>69%</td>
</tr>
<tr>
<td>ABE + EXE + RAD001 (n = 15)</td>
<td>33%</td>
<td>73%</td>
</tr>
<tr>
<td>ABE + TMAB (n = 12)</td>
<td>17%</td>
<td>42%</td>
</tr>
</tbody>
</table>

neoMONARCH Toxicities

Common grade 3/4 side effects in 173 subjects were neutropenia (7.4%), diarrhoea (2.9%), constipation (1%), and creatinine increase (1%).

This data shows abemaciclib, either in combination with anastrozole or as monotherapy, reduces Ki67 more than anastrozole. Diarrhoea is less severe and frequent when prophylactic loperamide is given concomitantly.

Abemaciclib: Endocrine and Trastuzumab combinations

Finally, Dr Beeram presented the results of a phase Ib study combining abemaciclib (BID) with either trastuzumab (HER2-positive group, n = 24) or hormonal therapies (HER2-negative group, n = 86) in patients with metastatic breast cancer (LBA18).

Treatment-related adverse events were mostly fatigue, gastrointestinal and haematological toxicities. However, the abemaciclib combination with exemestane and everolimus was less well tolerated and was associated with stomatitis, leukopenia, thrombocytopenia, and rash.
75 patients in the HER2-negative group and 12 patients in the HER2-positive group were evaluable for efficacy (Table 3). Dr Beeram concluded that combination of abemaciclib with endocrine treatment or trastuzumab was associated with clinical activity and acceptable safety.

References


Hortobagyi, G. N. (2016, October). LBA1 PR - First-line ribociclib + letrozole for postmenopausal women with hormone receptor-positive (HR+), HER2-negative (HER2−), advanced breast cancer (ABC). Presidential Symposium session presented at the 41st Annual Congress of the European Society of Medical Oncology (ESMO), Copenhagen, Denmark.

Finn, R. (2016, October). LBA15 - Biomarker analyses from the phase 3 PALOMA-2 trial of palbociclib (P) with letrozole (L) compared with placebo (PLB) plus L in postmenopausal women with ER + /HER2-advanced breast cancer (ABC). Proffered Poster session presented at the 41st Annual Congress of the European Society of Medical Oncology (ESMO), Copenhagen, Denmark.

Rugo, H. (2016, October). 225PD - Impact of palbociclib plus letrozole on health related quality of life (HRQOL) compared with letrozole alone in treatment naïve postmenopausal patients with ER+ HER2-metastatic breast cancer (MBC): results from PALOMA-2. Poster Discussion session presented at the 41st Annual Congress of the European Society of Medical Oncology (ESMO), Copenhagen, Denmark.


Beeram, M. (2016, October). LBA18 - A phase 1b study of abemaciclib, an inhibitor of CDK4 and CDK6, in combination with endocrine and HER2-targeted therapies for patients with metastatic breast cancer. Poster Discussion session presented at the 41st Annual Congress of the European Society of Medical Oncology (ESMO), Copenhagen, Denmark.

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Novel Biomarker for #Ipilimumab Treatment may aid Future #Patient Selection in Several #Malignancies #CISC
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