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Fulvestrant plus palbociclib versus fulvestrant plus placebo for treatment of hormone-receptor-positive, HER2-negative metastatic breast cancer that progressed on previous endocrine therapy (PALOMA-3): final analysis of the multicentre, double-blind, phase 3 randomised controlled trial.

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Abstract

BACKGROUND:

In the PALOMA-3 study, the combination of the CDK4 and CDK6 inhibitor palbociclib and fulvestrant was associated with significant improvements in progression-free survival compared with fulvestrant plus placebo in patients with metastatic breast cancer. Identification of patients most suitable for the addition of palbociclib to endocrine therapy after tumour recurrence is crucial for treatment optimisation in metastatic breast cancer. We aimed to confirm our earlier findings with this extended follow-up and show our results for subgroup and biomarker analyses.

METHODS:

In this multicentre, double-blind, randomised phase 3 study, women aged 18 years or older with hormone-receptor-positive, HER2-negative metastatic breast cancer that had progressed on previous endocrine therapy were stratified by sensitivity to previous hormonal therapy, menopausal status, and presence of visceral metastasis at 144 centres in 17 countries. Eligible patients-ie, any menopausal status, Eastern Cooperative Oncology Group performance status 0-1, measurable disease or bone disease only, and

disease relapse or progression after previous endocrine therapy for advanced disease during treatment or within 12 months of completion of adjuvant therapy-were randomly assigned (2:1) via a centralised interactive web-based and voice-based randomisation system to receive oral palbociclib (125 mg daily for 3 weeks followed by a week off over 28-day cycles) plus 500 mg fulvestrant (intramuscular injection on days 1 and 15 of cycle 1; then on day 1 of subsequent 28-day cycles) or placebo plus fulvestrant. The primary endpoint was investigator-assessed progression-free survival. Analysis was by intention to treat. We also assessed endocrine therapy resistance by clinical parameters, quantitative hormone-receptor expression, and tumour PIK3CA mutational status in circulating DNA at baseline. This study is registered with ClinicalTrials.gov, NCT01942135.

FINDINGS:

Between Oct 7, 2013, and Aug 26, 2014, 521 patients were randomly assigned, 347 to fulvestrant plus palbociclib and 174 to fulvestrant plus placebo. Study enrolment is closed and overall survival follow-up is in progress. By March 16, 2015, 259 progression-free-survival events had occurred (145 in the fulvestrant plus palbociclib group and 114 in the fulvestrant plus placebo group); median follow-up was 8·9 months (IQR 8·7-9·2). Median progression-free survival was 9·5 months (95% CI 9·2-11·0) in the fulvestrant plus palbociclib group and 4·6 months (3·5-5·6) in the fulvestrant plus placebo group (hazard ratio 0·46, 95% CI 0·36-0·59, p<0·0001). Grade 3 or 4 adverse events occurred in 251 (73%) of 345 patients in the fulvestrant plus palbociclib group and 38 (22%) of 172 patients in the fulvestrant plus placebo group. The most common grade 3 or 4 adverse events were neutropenia (223 [65%] in the fulvestrant plus palbociclib group and one [1%] in the fulvestrant plus placebo group), anaemia (ten [3%] and three [2%]), and leucopenia (95 [28%] and two [1%]). Serious adverse events (all causalities) occurred in 44 patients (13%) of 345 in the fulvestrant plus palbociclib group and 30 (17%) of 172 patients in the fulvestrant plus placebo group. PIK3CA mutation was detected in the plasma DNA of 129 (33%) of 395 patients for whom these data were available. Neither PIK3CA status nor hormone-receptor expression level significantly affected treatment response.

INTERPRETATION:

Fulvestrant plus palbociclib was associated with significant and consistent improvement in progression-free survival compared with fulvestrant plus placebo, irrespective of the degree of endocrine resistance, hormone-receptor expression level, and PIK3CA mutational status. The combination could be considered as a therapeutic option for patients with recurrent hormone-receptor-positive, HER2-negative metastatic breast cancer that has progressed on previous endocrine therapy.