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Optimal regimen for treatment-naïve hormone receptor-positive HER-2 negative metastatic breast cancer

Burak Bilgin¹, Mehmet AN Şendur^{*,1}, Mutlu Hızal¹, Muhammed Bülent Akıncı¹, Didem Şener Dede¹ & Bülent Yalçın¹

¹Department of Medical Oncology, Yıldırım Beyazıt University, Ankara, Turkey

*Author for correspondence: Tel.: +90 312 291 2525; Fax: +90 312 291 2726; masendur@yahoo.com.tr

“Results of the OS analyses and final analyses of the trials can be help us to determine optimal treatment strategy in MBC with hormone receptor positive, HER-2 negative.”

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Breast cancer is the most common type of cancer and one of the leading causes of cancer-related deaths among women. Approximately 10% of patients presented with *de novo* metastatic breast cancer (MBC) [1]. Estrogen receptor (ER), progesterone receptor (PR) and HER2 status are important predictive and prognostic markers for both early-stage breast cancer and MBC. More than 70% of patients with breast cancer are hormone-receptor (ER/PR) positive, and 20–25% of patients are HER2-positive. Endocrine therapy is the mainstay therapeutic option for MBC, especially in the absence of the visceral crisis and rapid tumor progression. In premenopausal patients with MBC, tamoxifen and aromatase inhibitor (AI) plus luteinizing hormone-releasing hormone (LHRH) agonists are suggested treatment options as first-line treatment. In postmenopausal patients, steroidal or nonsteroidal AIs are the first-line treatment options for patients without visceral crisis or rapid tumor progression. However, resistance to endocrine therapy can occur within 1 year after beginning treatment due to various mechanisms including loss of the ER/PR expression and activation of estrogen-independent growth signaling pathways [2]. In the past years, many new drugs were developed to overcome the endocrine resistance. Efficacy of CDK4/6 inhibitors, everolimus, a mammalian target of rapamycin (mTOR) inhibitor, and fulvestrant, a selective ER degrader have been determined for patients who progressed after first-line endocrine therapy [3–5]. Nowadays, the efficacy of CDK4/6 inhibitors (palbociclib, ribociclib and abemaciclib) in combination with AIs and fulvestrant monotherapy have also been showed as a first-line treatment for postmenopausal patients with hormone receptor positive, HER-2 negative MBC according to recently published four trials.

In Phase III, randomized, double-blind, FALCON trial; 462 patients with endocrine therapy-naïve (defined as the patient who was not received any endocrine treatment and also received up to one chemotherapy) ER-positive or PR-positive, or both, locally advanced or MBC were randomly assigned (1:1) to fulvestrant (500 mg intramuscular injection; on days 0, 14, 28, then every 28 days thereafter) or anastrozole (1 mg orally daily) as a first-line treatment [6]. The primary end point of the study was progression-free survival (PFS) and secondary end points included objective response rate, duration of response, clinical benefit rate and overall survival (OS). Median PFS was found significantly better in fulvestrant arms; 16.6 months with fulvestrant and 13.8 months with anastrozole. There was 20% risk reduction for disease progression (hazard ratio [HR]: 0.797, 95% CI: 0.637–0.999; $p = 0.0486$). The objective response rate was similar between two groups; 46% with fulvestrant and 45% with anastrozole (OR: 1.07, 95% CI: 0.72–1.61; $p = 0.7290$). Clinical benefit rate was not also significantly different. Median OS was not reached. In nonvisceral disease subgroup, risk reduction for progression was about 40% and median progression-free survival (mPFS) was 22.3 months in the fulvestrant group versus 13.8 months in the anastrozole group (HR: 0.59, 95% CI: 0.41–0.83). On the other hand, in the visceral disease subgroup, the HR was 0.99 (0.74–1.33), with median PFS of 13.8 months in the fulvestrant group versus 15.9 months in the anastrozole group. p -value for consistency of the treatment effects across the visceral and nonvisceral subgroups was

0.0092 according to post hoc interaction test. Adverse events were similar with AIs and mean FACT-B and Trial Outcome Index scores were also maintained and similar in both treatment groups.

PALOMA-2, a randomized, double-blind, Phase III trial was published in 2017 [7]. In this trial, postmenopausal patients with untreated, HR-positive, HER2-negative, MBC were enrolled and were randomized in a 2:1 ratio to receive palbociclib (125 mg, 3 weeks on/1 week off) plus letrozole (2.5 mg) versus letrozole (2.5 mg) plus placebo. The primary end point was investigator-assessed PFS. Median PFS was significantly better in combination arm with 24.8 months in the palbociclib–letrozole group and 14.5 months in the placebo–letrozole group (HR: 0.58, 95% CI: 0.46–0.72; $p < 0.001$). In the subgroup analyses of PFS, there was a consistent benefit of palbociclib–letrozole across all subgroups including visceral or nonvisceral disease. HR for disease progression or death in nonvisceral subgroup was 0.50 (95% CI: 0.36–0.70) and 0.63 (95% CI: 0.47–0.85) in visceral disease subgroup. Objective response rate (ORR) was also found better in letrozole plus palbociclib arm compared to letrozole plus placebo arm (42.1 vs 34.7%, $p = 0.06$). Among patients who had measurable disease according to RECIST, the rate of ORR was significantly higher in palbociclib plus letrozole arms compared to letrozole arm alone (55.3 vs 44.4%, $p = 0.03$). The most common grade 3 or 4 hematologic adverse events were neutropenia, leukopenia, anemia and thrombocytopenia. Grade 3 or 4 febrile neutropenia also occurred 1.8% of patients in the palbociclib–letrozole group and in no patients in the placebo–letrozole group.

A recently published analyses including PALOMA-2 was evaluated to efficacy of palbociclib in treatment-naïve and pretreated patient with HR-positive and HER2-negative MBC according to metastasis pattern (visceral or nonvisceral) [8]. In patients with visceral metastasis, median PFS is significantly better in palbociclib and letrozole arm compared with letrozole and placebo in (19.3 vs 12.9 months, respectively; HR: 0.63, 95% CI: 0.47–0.85). ORR was also significant better in palbociclib plus letrozole arm, 55.1 versus 40.0%, respectively. In addition, mPFS was also significantly longer in patients treated with palbociclib plus letrozole than placebo plus letrozole with the mPFS not yet reached for patients in the palbociclib plus letrozole arm in patients without visceral metastases (not reached [NR] vs 16.8, respectively; HR: 0.50, 95% CI: 0.36–0.70). However, ORR was not statistically different between two arms with 30% for palbociclib plus letrozole arm and 29.5% for placebo plus letrozole arm.

In a recently published randomized, double-blind, placebo-controlled, Phase III MONALEESA-2 trial, postmenopausal women with locally HR-positive, HER2-negative recurrent or MBC who had not received previous systemic therapy for advanced disease were enrolled and were randomly assigned to receive either oral ribociclib plus letrozole or placebo plus letrozole [9]. The primary end point was PFS. A total of 668 patients were randomized, with 334 assigned to receive ribociclib plus letrozole and 334 assigned to receive placebo plus letrozole. Median PFS was not reached in the ribociclib group versus 14.7 months in the placebo group (HR: 0.56, 95% CI: 0.43–0.72; $p = 3.29 \times 10^{-6}$ for superiority). At 18 months, the PFS rate was 63.0 and 42.2%, respectively. The PFS benefit in the ribociclib group was observed across all predefined subgroups. Patients with visceral metastasis, HR for progression or death was 0.57 and in nonvisceral metastasis subgroup, HR was also 0.55. The overall response rates were 40.7% in the ribociclib plus letrozole group and 27.5% in the placebo plus letrozole. OS results were not mature at the time of the interim analysis. The most common grade 3 or 4 adverse events were neutropenia, leukopenia, hypertension, increased alanine aminotransferase level, lymphopenia and increased aspartate aminotransferase level. Febrile neutropenia occurred in five patients (1.5%) in the ribociclib plus letrozole group and none in the placebo plus letrozole group. Serious adverse events also occurred in 21.3% in the ribociclib plus letrozole group and in 11.8% in the placebo plus letrozole group.

Abemaciclib is another selective small-molecule inhibitor of CDK4 and CDK6. In a Phase III placebo-controlled MONARCH 3 trial; the efficacy and safety of abemaciclib in combination with letrozole as initial treatment in women with HR-positive, HER2-negative advanced breast cancer was evaluated [10]. After median 17.8-month follow-up, median PFS was significantly longer in abemaciclib arm and not reached whereas 14.7 months for placebo and 46% risk reduction for progression was also detected (HR: 0.54, 95% CI: 0.41–0.72; $p = 0.00002$). ORR was 48.2% for abemaciclib and 34.5% for placebo. In patients with measurable disease, the objective response rate was 59% in the abemaciclib arm whereas only 44% in the placebo arm ($p = 0.004$). A PFS benefit was also demonstrated across all prespecified subgroups. In visceral metastatic and bone-only metastatic subgroups, HR for progression or death was 0.61 and 0.58, respectively. Diarrhea was the most frequent adverse event (81.3%) but mostly grade 1 (44.6%). Comparing the previous trials, the grade 3 or 4 neutropenia were observed only 21.1% of patients treated with abemaciclib arm.

BOLERO-4, a Phase II trial that investigated everolimus and letrozole in previously untreated hormone receptor positive and HER2-negative breast cancer was announced in ESMO 2016 [11]. The estimated PFS rates were 83.6

and 71.4% (64.0–77.5%) at 6 and 12 months, respectively. ORR and clinically benefit rate (CBR) were also found as 42.6 and 74.3%, respectively. The most common adverse events were stomatitis, weight loss and diarrhea.

Depending on the above-mentioned recent developments in breast cancer, first-line treatment of patients without visceral crisis or rapid tumor progression in HER-2 negative, hormone-receptor positive postmenopausal MBC was changed within 1 year. However, there was a new confusion that which drug should be used in which patient or situation. As mentioned above, CDK4/6 inhibitors were active in all subgroups of trials including visceral and nonvisceral metastatic patients. On the other hand, fulvestrant was not superior than AI in patient with visceral metastasis. Thus, CDK4/6 inhibitor may be considered that optimal first-line treatment in patients with visceral metastasis. In addition, there was no head-to-head comparison trial between ribociclib, abemaciclib and palbociclib, so both of these drugs can be used combined with letrozole in the first-line settings. In our opinion, there was a big challenge for treatment choice in nonvisceral metastatic patient. In FALCON trial, mPFS was statistical better in fulvestrant arm compared with AI in nonvisceral metastatic subgroup. Risk reduction for progression and death was about 40%. In addition, PALOMA-2, MONALEESA -2 and MONARCH-3 trials were showed that risk reduction for progression and death palbociclib, ribociclib and abemaciclib were 42, 44 and 46%, respectively [12]. ORR of these drugs was also similar. Due to lack of head-to-head comparison trial between fulvestrant and CDK4/6 inhibitors, a definitive conclusion cannot be reached about which agent is optimal in this condition. When consider to cost effectively and adverse event profile of these treatments, fulvestrant may be a good option according to low cost and better adverse event profile than CDK4/6 inhibitors. In addition, fulvestrant can be used as a first-line treatment of patient with nonvisceral metastasis in the country which cannot access to CDK4/6 inhibitors. Results of the OS analyses and final analyses of the trials can be help us to determine optimal treatment strategy in MBC with hormone receptor positive, HER-2 negative.

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