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Commentary

to *Effect of ribociclib plus fulvestrant on overall survival in the treatment of advanced breast cancer — updated MONALEESA-3 results*

Inhibitors of cyclin-dependent kinases 4/6 (CDK 4/6) are currently widely used in the treatment of patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative (HR+/HER2−) advanced breast cancer. The biological rationale for the benefit of this treatment has been supported by the results of several randomized controlled trials that have consistently shown an improvement in progression-free survival (PFS) for the three approved CDK 4/6 inhibitors (ribociclib, abemaciclib, and palbociclib). A benefit has been noticed in first-line and second-line treatment, in hormone-sensitive and hormone-refractory patients, in combination with an aromatase inhibitor (IA) or fulvestrant, and regardless of the patients' menopausal status. Obviously, the evaluation of the effect of these drugs on overall survival (OS) required a longer follow-up. The results of the MONALEESA-2 and MONALEESA-7 studies have recently been presented, which confirmed the improving OS by using ribociclib in combination with IA.

The design of these studies and the results to date supported using CDK 4/6 inhibitors in combination with IA in the first-line treatment and with fulvestrant in the second-line treatment. It should be noted, however, that the linearity of treatment was not always clearly defined in the studies; in MONARCH-2, the definition of treatment context was associated with sensitivity to hormone therapy, and the combination of fulvestrant with a CDK 4/6 inhibitor (abemaciclib in this case) was also administered in patients with relapse during (neo) adjuvant treatment or within 12 months of completing adjuvant treatment.

The MONALEESA-3 study is the first to investigate the combination of the CDK4/6 inhibitor ribociclib in combination with fulvestrant in first-line treatment [newly diagnosed advanced breast cancer or relapse more than 12 months after completion of (neo)adjuvant hormone therapy], and in this context, the treatment was used in almost half of the study population. It is important that the results of the phase-III FALCON study, which compared anastrozole with fulvestrant in first-line treatment, showed benefits of fulvestrant in terms of PFS (median PFS — 16.6 *vs.* 13.8 months, risk reduction by 20%, p = 0.049). This was especially true for patients without parenchymal metastases (median PFS — 22.3 *vs.* 13.8 months, risk reduction by 41%) [1].

The optimal timing for fulvestrant use in the therapeutic algorithm of patients with advanced HR+/HER2– breast cancer has not yet been clearly defined. Monotherapy with fulvestrant indicates its advantage over IA in patients who have not previously received hormone therapy due to advanced disease, while the combination of fulvestrant with a CDK4/6 inhibitor has so far been the preferred treatment option in patients after prior IA treatment. This approach is changed by the results of the MONALEESA-3 study, which was described in detail by Dubiański [2]. After a median follow-up of 56.3 months, the previously observed benefit of fulvestrant with ribociclib was confirmed with a statistically significant extension of the median OS

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from 41.5 months in the placebo/fulvestrant group to 53.7 months in the ribociclib group in the general patient population (risk reduction by 27%) [3].

Subgroup analysis showed that the benefit of fulvestrant in combination with ribociclib was the highest in first-line patients. In this subgroup, median OS in the experimental arm was still not reached and median OS in the control arm was 51.8 months. In the subgroup of patients treated in the second line, the benefit of fulvestrant in combination with ribociclib is also numerically significant, but statistically insignificant (median — 39.7 *vs.* 33.7, respectively; risk reduction by 22% with a 95% confidence interval of 0.59–1.04).

The combination of fulvestrant with ribociclib is, therefore, becoming a valuable treatment option for patients not receiving prior hormone therapy due to advanced disease. It is also well-tolerated, safe, and maintains a good quality of life. However, it is not clear whether the use of fulvestrant as a hormonal partner for the CDK 4/6 inhibitor is the best option for all patients.

It is worth emphasizing that in recent years, oral preparations have been developed that belong to the group of selective estrogen receptor degraders (SERDs), which includes also fulvestrant. Study results indicate that they are more active than fulvestrant and show activity in patients with hormone resistance and the ESR1 mutation [4]. They are currently being intensively evaluated in clinical trials in combination with CDK4/6 inhibitors and phosphoinositide 3-kinase (PI3K) inhibitors. The next steps will be to identify non-estrogen receptor biomarkers that determine treatment response.

The introduction of CDK 4/6 inhibitors permanently changed the paradigm of treatment of patients with advanced HR+/HER2- breast cancer. These drugs are well-tolerated, and most side effects are generally manageable and resolve after dose reduction.

Real-word evidence observational studies can also provide valuable data, which will increase the knowledge regarding the implementation of these drugs in everyday practice.

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