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REVIEW ARTICLE

Roman Dubiański

Department of Breast Cancer and Reconstructive Surgery, Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw

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

Address for correspondence:
Roman Dubiański, MD PhD
Department of Breast Cancer
and Reconstructive Surgery,
Maria Sklodowska-Curie National Research
Institute of Oncology, Warsaw
W. K. Roentgena 5 St., 02–781 Warsaw,
Poland
e-mail: r.dubianski@hotmail.com

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ABSTRACT

The results of the treatment of ER-positive/HER2-negative advanced breast cancer have been improved in the last few years due to the use of CDK4/6 inhibitors combined with endocrine therapy. Ribociclib with fulvestrant significantly prolonged progression-free survival and overall survival in the phase-III MONALEESA-3 trial. The newest update of the trial (after 56.3 months of observation) showed significant improvement in overall survival in the experimental arm for more than a year: mOS was 53.7 months in the ribociclib plus fulvestrant arm and 41.5 months in the placebo plus fulvestrant arm (risk reduction of 27%). Subgroup analysis confirmed the efficacy of the treatment in both the first and second lines of treatment. The study also showed that adding ribociclib to the endocrine treatment prolongs the median time to chemotherapy. No new toxicities were observed in longer observation.

Key words: breast cancer, ribociclib, fulvestrant, CDK4/6 inhibitor

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Introduction

There are many molecular pathways in breast cancer cells that could be blocked by targeted drugs, for example, cyclin-dependent kinases 4/6 (CDK 4/6) inhibitors. The complex interactions between cyclins and CDKs control the cell life cycle because these enzymes play a regulatory role at all stages of cell division. The initiation of division depends primarily on kinases 4 and 6 (CDK 4 and 6), which are structurally related and have similar biological and biochemical properties [1]. Changes in the cell cycle are typical of malignant neoplasms, including its disruption leading to uncontrolled growth. Numerous changes in regulatory proteins and disturbances in the regulation of the cyclin D1:CDK4/6 axis have been described in breast cancer cells [2–4]. Activation of this axis is characteristic of luminal breast cancer, in which cells contain more cyclin D than in other types of breast cancer [5]. There is evidence concerning conduction between ER and cyclin D1 (CCND1) pathways in ER-positive breast cancer cells [6]. Inhibition of CDKs has become an important target of new treatments for breast cancer patients. Initially, non-specific CDK inhibitors were used; however, their value assessed in clinical trials was unsatisfactory [7, 8]. Only the use of specific second-generation inhibitors targeting CDK4/6 showed very promising results. CDK4/6 inhibitors currently available for the

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treatment of patients with ER+/HER2- breast cancer include abemaciclib, palbociclib, and ribociclib.

Ribociclib is a highly selective CDK4/6 inhibitor, which in preclinical studies showed high activity in solid tumors (including ER+/HER2- advanced breast cancer) [9]. *In vitro* and *in vivo* studies in humans have shown that it is metabolized in the liver (mainly via CYP3A4). Ribociclib and its metabolites are mainly excreted in the feces and, to a small extent, via the kidneys.

Three phase-III studies were conducted, which aimed at confirming the effectiveness of ribociclib in the treatment of patients with advanced breast cancer. The first was the phase-III MONALEESA-2 study, which involved patients with hormone-dependent and HER2-negative advanced breast cancer, who did not previously receive systemic treatment due to the disease progression [10]. The study enrolled 668 patients randomly assigned to treatment with ribociclib in combination with letrozole or with letrozole as monotherapy. The primary endpoint was progression-free survival, which was significantly longer in the ribociclib arm; the 18-month PFS rate was 63% [95% CI (confidence interval) 54.6–70.3] versus 42.2% with a 95% CI of 34.8–49.5 in the placebo group, and the median PFS was 14.7 months (95% CI 13.0–16.5) in the placebo group (in experimental group median OS was not reached). In the updated analysis, after a median follow-up of 26.4 months, the median PFS was 25.3 months in the experimental arm and 16 months in the control arm, which corresponded to a hazard ratio (HR) of 0.568; 95% CI 0.457–0.704; $p = 9.63 \times 10^{-8}$ [11]. The study showed an improvement in overall survival (OS) which was a secondary endpoint. During the ESMO (European Society for Medical Oncology) Congress 2021, the updated results of the study were presented, which showed an extension of OS in the group receiving combination treatment; the median was 63.9 months *vs.* 51.4 months (HR 0.76; 95% CI 0.63–0.93; p = 0.004) [12]. It was an outstanding observation, showing that patients with advanced breast cancer could survive for more than 5 years.

On the other hand, the MONALEESA-7 study was the first phase-III study with a CDK4/6 inhibitor, recruiting only premenopausal or perimenopausal patients [13]. The study included 672 patients who could receive hormone therapy or chemotherapy as neo- or adjuvant treatment, and one line of chemotherapy for advanced disease. Patients received either ribociclib in combination with tamoxifen or an aromatase inhibitor (letrozole or anastrozole) and goserelin, or hormone therapy alone in the control arm. The primary endpoint was PFS, whose median in the ribociclib arm was 23.8 months vs. 13 months for placebo (HR 0.55; 95% CI 0.44–0.69; p < 0.0001). The first data on the addition of ribociclib to hormone therapy in the MONALEESA-7 study showed a significant increase in OS compared to hormone therapy and placebo. The OS rate at 42 months of follow-up was 70.2% in the ribociclib group (95% CI 63.5–76.0) and 46% (95% CI 32.0–58.9) for placebo (HR 0.71; 95% CI 0.54–0.95; p = 0.00973) [14]. The median OS was not reached in the ribociclib arm at this time point. Further updated results of the MONALEESA-7 study were presented at the San Antonio Breast Cancer Symposium (SABCS) in December 2020 [15]. After an additional mean follow-up of 53.5 months, the median OS in the experimental arm was 58.7 months and was more than 10 months longer than in the placebo arm (48 months; HR, 0.76; 95% CI 0.61–0.96).

The MONALEESA-3 study was the third trial in which ribociclib was used in the treatment of advanced ER+/HER2– breast cancer. This article aims to present an overview of this study and its updated results.

MONALEESA-3 study

MONALEESA-3 is a phase-III clinical study investigating the efficacy of ribociclib in combination with fulvestrant and including 726 postmenopausal patients. The included patients had histopathologically-confirmed, generalized, or locally advanced ER+/HER2- breast cancer, ineligible for local treatment. The study included patients with newly diagnosed advanced ER+/HER2- breast cancer, with relapse during or at least 12 months after the completion of neoadjuvant or adjuvant hormone therapy, and patients previously treated with one line of hormone therapy for advanced breast cancer[16]. A summary of indications for prior treatment is presented in Table 1.

Other inclusion criteria included the presence of measurable lesion according to the Response Evaluation Criteria In Solid Tumors (RECIST 1.1) or at least one lytic bone lesion, performance status according to Eastern Cooperative Oncology Group scoring sys-

Table 1. Distribution of patients participating in MONALEESA-3 according to prior treatment for breast cancer

First-line treatment	*De novo* diagnosed advanced breast cancer
	Relapse more than 12 months after completion of neoadjuvant or adjuvant hormone therapy
Second-line treatment	Relapse during neoadjuvant or adjuvant hormone therapy or less than 12 months after completion
	Progression after a single line of hormone therapy for advanced breast cancer without prior neoadjuvant or adjuvant hormone therapy
	Progression after a single line of hormone therapy for advanced breast cancer in patients with relapse more than 12 months after completion of neoadjuvant or adjuvant hormone therapy

tem (ECOG PS) 0 or 1. Patients previously receiving chemotherapy for advanced breast cancer, before the fulvestrant or CDK4/6 inhibitor, as well as with clinically significant arrhythmias and uncontrolled cardiovascular diseases, were excluded from the study.

Patients were randomly assigned (2:1) either to the experimental arm with ribociclib and fulvestrant (484 patients) or the control arm with fulvestrant and placebo (242 patients). Patients received 500 mg of fulvestrant intramuscularly (day 1 of the 28-day cycle and additionally on day 15 of cycle 1) and either placebo or ribociclib at a dose of 600 mg/day according to a 3-weeks-on/1-week-off schedule. The primary endpoint of the study was PFS. The median PFS was significantly greater in the ribociclib group compared to the placebo group: 20.5 months *vs.* 12.8 months (HR 0.593; 95% CI 0.480-0.732; P=0.00000041) [16]. The obtained results led to very fast approval of ribociclib in combination with fulvestrant as the first- and second-line treatment of patients with advanced breast cancer. The secondary much-awaited endpoint of the study was OS because it is not always possible to achieve OS prolongation in oncology even with a significant extension of PFS. Additionally, the MONALEESA-3 study also assessed: PFS2 (time from the randomization to the first documented disease progression during the next line of treatment or death from any cause), time to chemotherapy use (measured from the randomization to receiving the first chemotherapy after completing the study treatment), and chemotherapy-free survival (time to the first chemotherapy or death). The assumptions of the study also included OS subgroups analysis (patients receiving first-line and second-line treatment, patients with hormone sensitivity and hormone resistance, and patients with or without lung and/or liver metastases). Median OS and OS duration were estimated using the Kaplan-Meier method.

The first results of the MONALEESA-3 study for OS were presented at the ESMO Congress 2019 and published in full in the New England Journal of Medicine [17]. OS was significantly improved in patients receiving ribociclib in combination with fulvestrant. After 42 months of follow-up, an improvement in OS rate was evident in patients receiving combination therapy, 57,8% in the experimental arm compared to 45.9% in the control arm (HR 0.72; 95% CI 0.57–0.92; p = 0.00455). At the time of the first survival analysis, the median OS in the ribociclib arm was not reached, while it was 40 months in the placebo arm. The benefit of using ribociclib in combination with fulvestrant was demonstrated in both the first- (median OS for the ribociclib arm not reached, 45.1 months in the placebo arm; HR 0.70; 95% CI 0.479–1.021) and the second-line treatment (40.2 months for ribociclib with fulvestrant *vs.* 32.5 months for fulvestrant alone; HR 0.730; 95% CI 0.530–1.004).

The latest update of OS data was made after a median follow-up of 56.3 months (data cut-off: 30 October 2020) [18]. More than a year after the previous analysis, study treatment was still received by 14% of patients in the ribociclib arm and 8.7% of patients in the placebo arm, and death occurred in 45.9% and 58.7% of patients, respectively. There was a significant increase in median OS from 41.5 months in patients receiving placebo plus fulvestrant to 53.7 months in the group with ribociclib and fulvestrant (HR 0.73; 95% CI 0.59–0.90) (Fig. 1). Kaplan-Meier estimates of the 5-year survival rate were

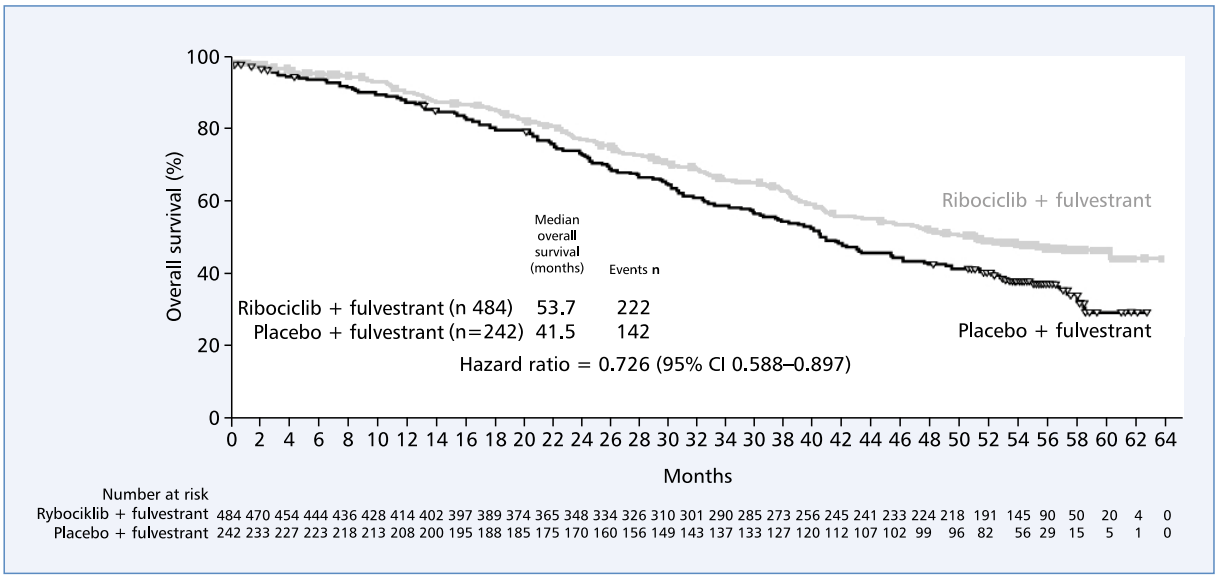

Figure 1. Overall survival in general population; CI — confidence interval

Table 2. Overall survival in individual groups of patients in the MONALEESA-3 study

	Median overall survival	
	ribociclib + fulvestrant (months)	**placebo + fulvestrant (months)**
First-line treatment	Not reached	51.8
Second-line treatment	39.7	33.7
Patients with lung/liver metastases	46.9	39.4
Patients with hormone resistance	35.6	31.7
Patients with hormone sensitivity	49	41.8
Hormone-naïve patients	59.9	50.9

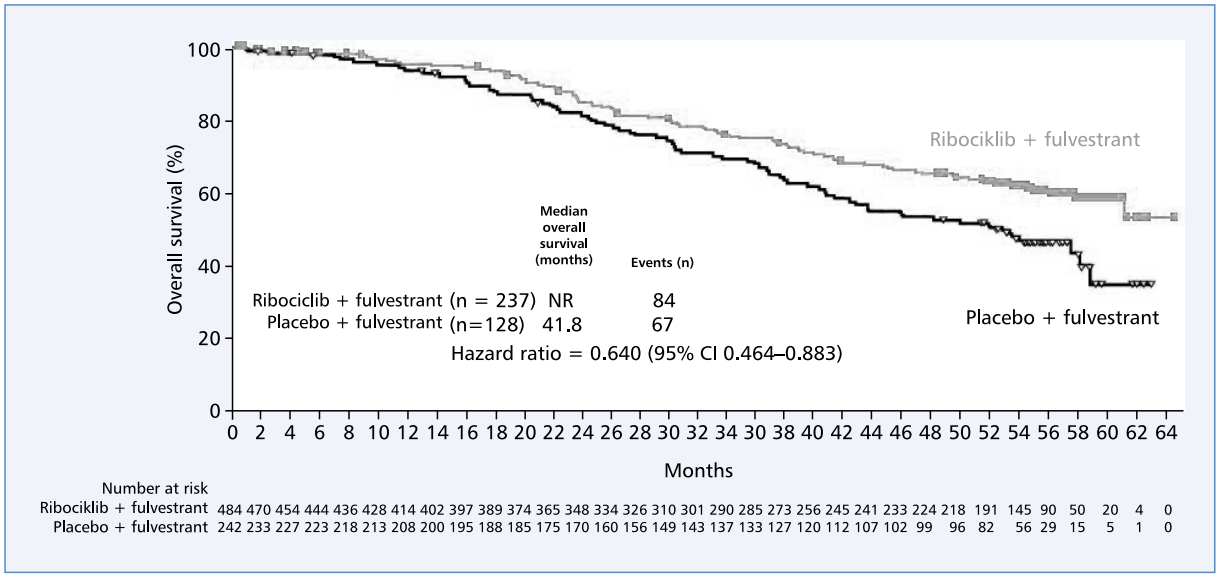

Figure 2. Overall survival in patients receiving ribociclib in combination with fulvestrant in first-line treatment; CI — confidence interval; NR — not reached

46% (95% CI 49–58%) in the experimental arm versus 31% (95% CI 23–40%) in the control arm.

Overall survival outcomes in individual patient subgroups from the most recent analysis are presented in Table 2 and Figures 2 and 3.

Combination therapy with ribociclib and fulvestrant turned out to be more effective than fulvestrant as monotherapy, regardless of treatment line, previous hormone therapy, no use of hormonal drugs, as well as hormone resistance or hormone sensitivity. Factors that did not affect the efficacy of ribociclib were, among others, patient age and the number of metastases (OS prolongation was stratified according to under and over 65 years of age and fewer and more than three metastases).

In both arms, as many as 80% of patients after treatment completion received one or more subsequent treatment lines, with the most commonly used hormone therapy alone (28% in the ribociclib arm and 21% in the placebo arm), and chemotherapy as the second most common option (23 and 20%, respectively), followed by hormone therapy in combination with a molecularly targeted drug. Patients from both groups received the CDK4/6 inhibitor after study completion, more than twice as often in the control arm (30% *vs.* 14% in the ribociclib arm). Importantly, the time to chemotherapy was significantly longer (by almost 20 months) in the ribociclib arm (48.1 months) than in the placebo arm (28.8 months; HR 0.70; 95% CI 0.57–0.88). Chemotherapy-free survival (time to first chemotherapy or death) was 32.3 months in the experimental arm *vs.* 22.4 months in the placebo arm (HR 0.70; 95% CI 0.57–0.88) (Fig. 4). Regarding PFS2, another endpoint of the MONALEESA-3 study, the use of fulvestrant with ribociclib was also superior, with significant prolongation in the experimental arm (37.4 months compared to 28.1 months in the placebo group, HR 0.7069; 95% CI 0.57–0.84), which is another argument supporting the use of combination therapy.

The latest update of the MONALEESA-3 study does not provide a detailed discussion of treatment toxicity,

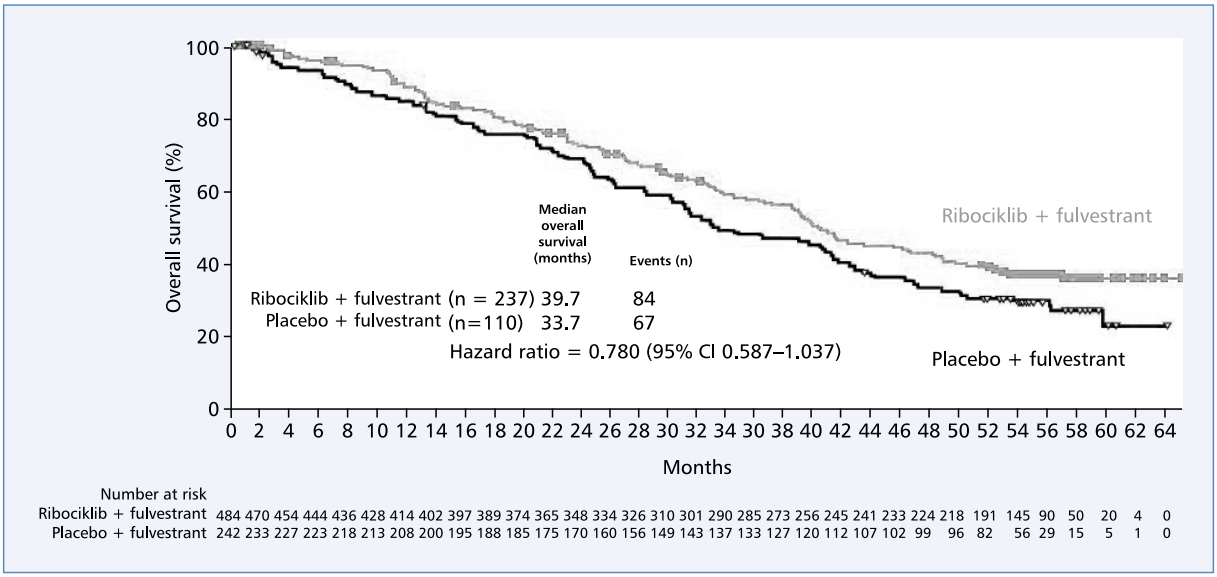

Figure 3. Overall survival in patients receiving ribociclib in combination with fulvestrant in second-line treatment; CI — confidence interval; NR — not reached

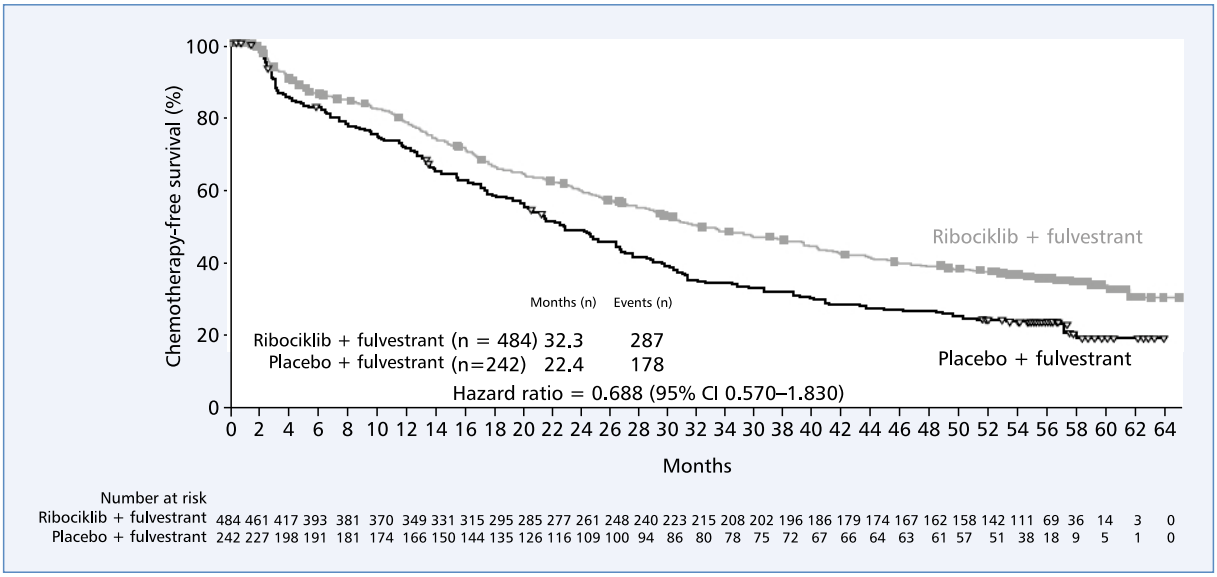

Figure 4. Chemotherapy-free survival; CI — confidence interval

as the extended follow-up did not reveal any additional or significant data in terms of side effects. The authors only confirm the toxicity profile of ribociclib, with neutropenia as the most common side effect, which occurred in grade 3 or 4 in 58.2% of patients (0.8% of patients in the placebo arm).

Discussion

The latest update of the MONALEESA-3 study, after an exceptionally long follow-up period (median 56.3 months) confirms the effectiveness of ribociclib with fulvestrant, already presented in the previous reports [16, 17], in patients with advanced ER-positive and HER2-negative breast cancer [18]. OS prolongation was achieved in patients receiving ribociclib in the first- and second-line treatment. The advantage of the combination treatment with ribociclib and fulvestrant was confirmed in all subgroups (including patients with metastases in parenchymal organs, for whom chemotherapy is still too often used in clinical practice). Other subgroups with prolonged OS included patients with hormone resistance and hormone sensitivity, as well as elderly patients, who unfortunately commonly receive less intensive treatment. It has also been shown that the

addition of ribociclib to hormone therapy with fulvestrant significantly prolongs the time to chemotherapy and in practice extends the time to treatment initiation, much more often associated with the occurrence of side effects and deterioration of the quality of life. In conclusion, the most recent data on treatment with ribociclib in combination with fulvestrant, indicating the prolongation of OS by more than one year, may support using this treatment regimen in clinical practice in patients with advanced ER-positive and HER2-negative breast cancer. According to the latest guidelines, a combination of CDK4/6 inhibitor with hormone therapy is the standard of care in the first-line treatment in patients with advanced breast cancer and should be used in all patients who do not require chemotherapy due to the presence of a visceral crisis [19–21].

Conflict of interest

Advisory boards, lectures, conferences: Novartis, Accord, Eli Lilly, Pfizer, Roche, Amgen, Egis, Pierre Fabre.

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