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Phase III Randomized Study of Ribociclib and Fulvestrant in Hormone Receptor–Positive, Human Epidermal Growth Factor Receptor 2–Negative Advanced Breast Cancer: MONALEESA-3

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ABSTRACT

Purpose
This phase III study evaluated ribociclib plus fulvestrant in patients with hormone receptor–positive/human epidermal growth factor receptor 2–negative advanced breast cancer who were treatment naïve or had received up to one line of prior endocrine therapy in the advanced setting.

Patients and Methods
Patients were randomly assigned at a two-to-one ratio to ribociclib plus fulvestrant or placebo plus fulvestrant. The primary end point was locally assessed progression-free survival. Secondary end points included overall survival, overall response rate, and safety.

Results
A total of 484 postmenopausal women were randomly assigned to ribociclib plus fulvestrant, and 242 were assigned to placebo plus fulvestrant. Median progression-free survival was significantly improved with ribociclib plus fulvestrant versus placebo plus fulvestrant: 20.5 months (95% CI, 18.5 to 23.5 months) versus 12.8 months (95% CI, 10.9 to 16.3 months), respectively (hazard ratio, 0.593; 95% CI, 0.480 to 0.732; $P < .001$). Consistent treatment effects were observed in patients who were treatment naïve in the advanced setting (hazard ratio, 0.577; 95% CI, 0.415 to 0.802), as well as in patients who had received up to one line of prior endocrine therapy for advanced disease (hazard ratio, 0.565; 95% CI, 0.428 to 0.744). Among patients with measurable disease, the overall response rate was 40.9% for the ribociclib plus fulvestrant arm and 28.7% for placebo plus fulvestrant. Grade 3 adverse events reported in ≥ 10% of patients in either arm (ribociclib plus fulvestrant *v* placebo plus fulvestrant) were neutropenia (46.6% *v* 0%) and leukopenia (13.5% *v* 0%); the only grade 4 event reported in ≥ 5% of patients was neutropenia (6.8% *v* 0%).

Conclusion
Ribociclib plus fulvestrant might represent a new first- or second-line treatment option in hormone receptor–positive/human epidermal growth factor receptor 2–negative advanced breast cancer.

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INTRODUCTION

The cyclin D–cyclin-dependent kinase (CDK) 4/6–retinoblastoma pathway is frequently dysregulated in hormone receptor (HR) –positive breast cancer[1] and is implicated in resistance to endocrine monotherapy.[2] Preclinical data indicate that CDK4/6-targeted agents inhibit HR-positive breast cancer cell-line growth and may act synergistically with hormonal blockade in this molecular subtype of the disease.[3]

Ribociclib is an orally bioavailable, highly selective small-molecule inhibitor of CDK4/6, with antitumor activity as a single agent and in combination with letrozole and fulvestrant in xenograft models of estrogen receptor–positive breast cancer.[4,5] In the phase III MONALEESA-2

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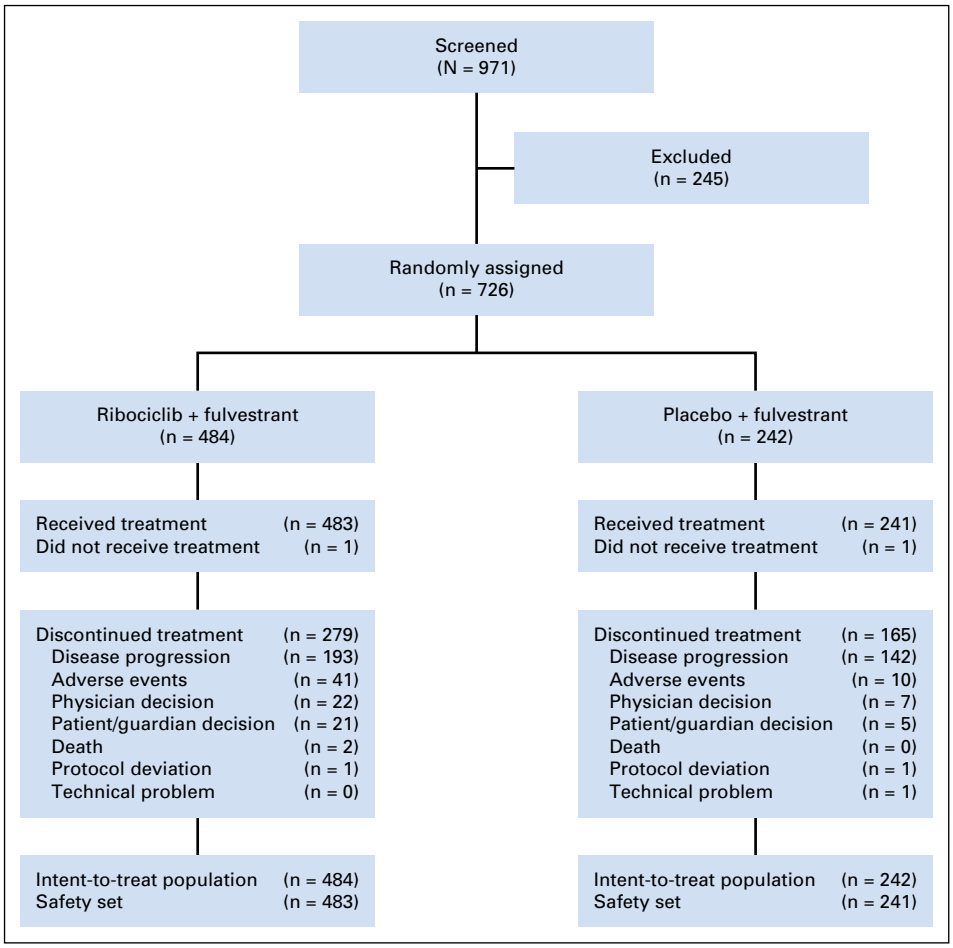

Fig 1. CONSORT diagram.

(Mammary ONcology Assessment of LEE011 [ribociclib] Efficacy and SAfety) study, ribociclib plus letrozole significantly prolonged progression-free survival (PFS) versus placebo plus letrozole in postmenopausal women with HR-positive/human epidermal growth factor receptor 2 (HER2)–negative advanced breast cancer who had received no prior therapy for advanced disease.[6] Ribociclib and endocrine therapy combinations (tamoxifen or a nonsteroidal aromatase inhibitor and goserelin) also significantly improved PFS versus placebo plus endocrine therapy in premenopausal women with HR-positive/HER2-negative advanced breast cancer in the phase III MONALEESA-7 study.[7]

CDK4/6 inhibitors combined with fulvestrant have demonstrated efficacy in patients with HR-positive breast cancer who experienced progression during prior endocrine therapy.[8-10] However, no study has evaluated ribociclib in combination with fulvestrant in HR-positive/HER2-negative advanced breast cancer or CDK4/6 inhibitor and fulvestrant combinations in patients with HR-positive/HER2-negative de novo advanced breast cancer or those who experienced relapse > 12 months after prior endocrine therapy.

Here, we present results from the MONALEESA-3 trial, which evaluated ribociclib plus fulvestrant in patients with HR-positive/HER2-negative advanced breast cancer who were treatment naïve in the advanced setting or had received up to one line of prior endocrine therapy for advanced disease.

PATIENTS AND METHODS

Study Design

In this phase III, double-blind, placebo-controlled international study, patients were randomly assigned at a two-to-one ratio to receive ribociclib (600 mg orally per day; 3 weeks on, 1 week off) plus fulvestrant (500 mg intramuscularly on day 1 of each 28-day cycle, with an additional dose on day 15 of cycle 1) or placebo plus fulvestrant. Random assignment was stratified by the presence or absence of lung or liver metastases (yes *v* no) and prior endocrine therapy (treatment naïve in the advanced setting *v* received up to one line of endocrine therapy for advanced disease, as described in Patients). Treatment continued until disease progression, unacceptable toxicity, death, or discontinuation for any other reason. Ribociclib dose modifications, including interruption and up to two dose reductions, were permitted to manage adverse events (AEs). Fulvestrant dose modifications were not allowed.

Written informed consent was obtained from all patients. The trial was conducted in accordance with the Good Clinical Practice guidelines and Declaration of Helsinki. The study protocol and any modifications were approved by an independent ethics committee or institutional review board at each site. A steering committee comprising participating international investigators and Novartis representatives oversaw the study conduct. An independent data monitoring committee assessed the safety data.

Patients

Postmenopausal women and men with histologically and/or cytologically confirmed HR-positive/HER2-negative advanced breast cancer were eligible. Patients were required to have advanced (metastatic or

locoregionally recurrent disease not amenable to curative treatment) breast cancer. Additional eligibility criteria were as follows: (1) newly diagnosed (de novo), advanced breast cancer, (2) relapse > 12 months from completion of (neo)adjuvant endocrine therapy with no treatment for advanced or metastatic disease (criteria 1 and 2 referred to as treatment naïve in the advanced setting hereafter), (3) relapse on or within 12 months from completion of (neo)adjuvant endocrine therapy with no treatment for advanced or metastatic disease (early relapse), (4) relapse > 12 months from completion of (neo)adjuvant therapy with subsequent progression after one line of endocrine therapy for advanced or metastatic disease, and (5) advanced or metastatic breast cancer at diagnosis that progressed after one line of endocrine therapy for advanced disease with no prior (neo)adjuvant treatment for early disease (criteria 3 to 5 referred to as received up to one line of endocrine therapy for advanced disease hereafter). Criteria 1 and 2 includes patients receiving treatment in the first-line setting; criteria 3 to 5 includes patients receiving treatment in the second-line setting or with an early relapse.

Patients had at least one measurable lesion per Response Evaluation Criteria In Solid Tumors (RECIST; version 1.1)[11] or one predominantly lytic bone lesion, with adequate organ and bone marrow function and an Eastern Cooperative Oncology Group performance status of 0 or 1.

Patients were ineligible if they had received prior treatment with chemotherapy for advanced disease, fulvestrant, or a CDK4/6 inhibitor; if they had inflammatory breast cancer, symptomatic visceral disease, or any disease burden that made the patient ineligible for endocrine therapy per investigator judgment; or if they had clinically significant cardiac arrhythmias and/or uncontrolled heart disease, including a QT interval corrected for heart rate according to Fridericia's formula (QTcF) > 450 ms.

Procedures

Tumor response was assessed locally per RECIST (version 1.1) at screening, every 8 weeks after random assignment for 18 months, and every 12 weeks thereafter until disease progression, death, withdrawal of consent, or loss to follow-up; for patients who discontinued for any other reason, assessments continued per protocol. Imaging data from approximately 40% of randomly selected patients were reviewed centrally by a blinded independent review committee (BIRC).

AEs were monitored and graded according to the Common Terminology Criteria for Adverse Events (version 4.03).[12] Safety follow-up was conducted for at least 30 days after patients' last study treatment dose. ECG assessments were performed at screening, on day 15 of cycle 1, on days 1 and 15 of cycle 2, on day 1 of all subsequent cycles up to cycle 6, at end of treatment, and as clinically indicated. In patients with a QTcF ≥ 481 ms at any time before cycle 7, additional ECGs were performed predose on day 1 of subsequent cycles and postdose every third cycle.

Primary and Secondary End Points

The primary end point was locally assessed PFS. To support the primary end point, a BIRC performed a central assessment of PFS in a randomly selected subgroup of patients. Secondary end points included overall survival (OS), overall response rate (ORR), clinical benefit rate, and safety and tolerability.

Statistical Analysis

The primary analysis compared PFS between the treatment arms using a stratified log-rank test. The treatment effect was estimated using a Cox proportional hazards model overall and in relevant subgroups. The central PFS assessment used in support of the primary efficacy end point was analyzed using a Cox proportional hazards model. The primary PFS analysis was to be performed after observing approximately 364 local PFS events to detect a hazard ratio of 0.67 with 95% power and a one-sided 2.5% level of significance.

OS was compared between the treatment groups using a stratified log-rank test at a one-sided 2.5% level if the primary PFS end point was significant. A three-look design was used, with up to two OS interim analyses (the first was performed at the time of the PFS analysis) and a final OS analysis planned. The Lan-DeMets α-spending function with

Table 1. Demographics and Baseline Characteristics

Characteristic	Ribociclib + Fulvestrant (n = 484), No. (%)	Placebo + Fulvestrant (n = 242), No. (%)
Gender		
Female	484 (100)	242 (100)
Age, year		
Median	63.0	63.0
Range	31–89	34–86
Race		
White	406 (83.9)	213 (88.0)
Asian	45 (9.3)	18 (7.4)
Native American	5 (1.0)	1 (0.4)
Black	3 (0.6)	2 (0.8)
Unknown	15 (3.1)	5 (2.1)
Other	10 (2.1)	3 (1.2)
ECOG PS		
0	310 (64.0)	158 (65.3)
1	173 (35.7)	83 (34.3)
Missing	1 (0.2)	1 (0.4)
Disease stage at study entry		
II	2 (0.4)	0 (0.0)
III	4 (0.8)	2 (0.8)
IV	478 (98.8)	239 (98.8)
Missing	0 (0.0)	1 (0.4)
Hormone receptor status		
ER positive	481 (99.4)	241 (99.6)
PR positive	353 (72.9)	167 (69.0)
Disease-free interval, months*		
De novo	97 (20.0)	42 (17.4)
Non-de novo	387 (80.0)	199 (82.2)
≤12	22 (4.5)	9 (3.7)
>12	365 (75.4)	190 (78.5)
Missing	0 (0.0)	1 (0.4)
Prior endocrine therapy status†		
Treatment naïve	238 (49.2)	129 (53.3)
Up to one line of endocrine therapy	236 (48.8)	109 (45.0)
Prior endocrine therapy setting		
(Neo)adjuvant	289 (59.7)	142 (58.7)
Advanced	110 (22.7)	40 (16.5)
Prior chemotherapy		
Adjuvant	209 (43.2)	101 (41.7)
Neoadjuvant	65 (13.4)	30 (12.4)
Metastatic sites		
0	2 (0.4)	0 (0.0)
1	151 (31.2)	73 (30.2)
2	156 (32.2)	76 (31.4)
3	114 (23.6)	48 (19.8)
4	38 (7.9)	34 (14.0)
≥5	23 (4.8)	10 (4.1)
Missing	0 (0.0)	1 (0.4)
Sites of metastases		
Bone	367 (75.8)	180 (74.4)
Bone only	103 (21.3)	51 (21.1)
Visceral	293 (60.5)	146 (60.3)
Lung	146 (30.2)	72 (29.8)
Liver	134 (27.7)	63 (26.0)
Lung or liver	242 (50.0)	121 (50.0)
Central nervous system	6 (1.2)	2 (0.8)
Other‡	102 (21.1)	51 (21.1)
Lymph nodes	199 (41.1)	115 (47.5)
Soft tissue	23 (4.8)	14 (5.8)
Skin	20 (4.1)	8 (3.3)
Breast	4 (0.8)	1 (0.4)
None	2 (0.4)	0 (0.0)
Missing	0 (0.0)	1 (0.4)

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; ER, estrogen receptor; PR, progesterone receptor.

*De novo includes patients with no first recurrence/progression or with a first recurrence/progression within 90 days of diagnosis with no prior medication. For non-de novo disease, disease-free interval is defined as the time from initial diagnosis to first recurrence/progression.

†Fourteen patients not included because of missing data or criteria not being met.

‡Other visceral sites include metastatic site other than soft tissue, breast, bone, lung, liver, central nervous system, skin, and lymph nodes.

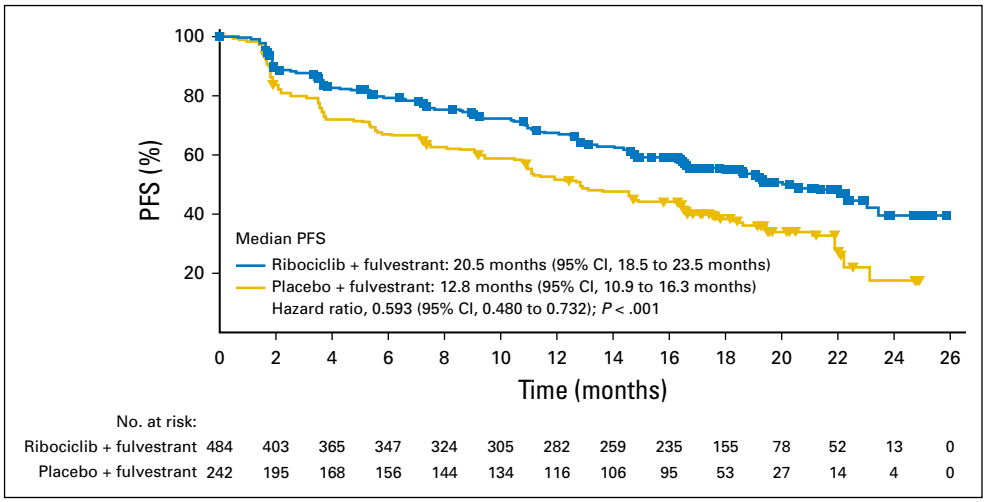

Fig 2. Kaplan-Meier analysis of locally assessed progression-free survival (PFS).

O'Brien-Fleming boundary was used to control for multiplicity. ORR and clinical benefit rate were compared between treatment arms using the Cochran-Mantel-Haenszel χ^2 test at a one-sided 2.5% level.

All efficacy analyses were performed in the full analysis set, comprising all randomly assigned patients. Safety analyses were performed in patients who received at least one dose of any study treatment and had at least one postbaseline safety assessment.

RESULTS

Study Population and Disposition

Between June 2015 and June 2016, 726 patients from 177 study sites in 27 countries were randomly assigned at a two-to-one ratio to ribociclib plus fulvestrant (n = 484) or placebo plus fulvestrant (n = 242; Fig 1). Baseline demographics and disease characteristics were well balanced between arms (Table 1). Although male patients were eligible for enrollment after a protocol amendment, because of rapid recruitment, no male patients were enrolled. Median time from random assignment to data cutoff was 20.4 months. A total of 354 patients were treatment naïve for advanced disease, and 372 patients had received up to one line of prior endocrine therapy for advanced disease.

As of November 3, 2017, 42.1% of patients in the ribociclib plus fulvestrant arm versus 31.4% of patients in the placebo plus fulvestrant arm were still receiving treatment. The most common reasons for treatment discontinuation (ribociclib plus fulvestrant *v* placebo plus fulvestrant) were disease progression (39.9% *v* 58.7%) and AEs (8.5% *v* 4.1%).

Median duration of exposure to study treatment was 15.8 months (range, 0.9 to 27.4 months) for the ribociclib plus fulvestrant arm versus 12.0 months (range, 0.9 to 25.9 months) for the placebo plus fulvestrant arm. Median relative dose-intensity was 92.1% for ribociclib and 100% for placebo.

Primary End Point

At data cutoff, 210 PFS events had occurred in the ribociclib plus fulvestrant arm versus 151 in the placebo plus fulvestrant arm. PFS was significantly improved in the ribociclib plus fulvestrant arm versus the placebo plus fulvestrant arm, with a median PFS of 20.5 months (95% CI, 18.5 to 23.5 months) versus 12.8 months (95% CI, 10.9 to 16.3 months), respectively, and a hazard ratio of 0.593 (95% CI, 0.480 to 0.732; $P < .001$; Fig 2).

PFS analyses based on the BIRC were supportive of the primary efficacy results. In the 40% of randomly assigned patients (n = 290) included in the BIRC review, the PFS hazard ratio was 0.492 (95% CI, 0.345 to 0.703).

Exploratory analyses demonstrated consistent treatment effects across prespecified subgroups (Fig 3). The PFS hazard ratio was 0.577 (95% CI, 0.415 to 0.802) in patients who were treatment naïve in the advanced setting and 0.565 (95% CI, 0.428 to 0.744) in patients who had received up to one line of endocrine therapy for advanced disease. Due to a small sample size and limited number of events, the treatment effect hazard ratio in the Asian subgroup of patients should be interpreted with caution.

Secondary End Points

At this first planned interim OS analysis, data were immature (34% information fraction). A total of 70 deaths (14.5%) were observed in the ribociclib plus fulvestrant arm versus 50 (20.7%) in the placebo plus fulvestrant arm, with results not crossing the prespecified O'Brien-Fleming stopping boundary.

ORR was 32.4% (95% CI, 28.3% to 36.6%) versus 21.5% (95% CI, 16.3% to 26.7%) for the ribociclib plus fulvestrant versus placebo plus fulvestrant arms, respectively, in all patients ($P < .001$; Table 2) and 40.9% (95% CI, 35.9% to 45.8%) versus 28.7% (95% CI, 22.1% to 35.3%), respectively, among patients with measurable disease at baseline ($P = .003$).

The safety population included 724 patients. The most common all-grade AEs reported in ≥ 30% of patients in either arm were neutropenia, nausea, and fatigue (Table 3). The most common grade 3 AEs occurring in ≥ 10% of patients were neutropenia and leukopenia. The only grade 4 event reported in ≥ 5% of patients was neutropenia. Febrile neutropenia occurred in 1.0% of patients in the ribociclib plus fulvestrant arm versus 0% of patients in the placebo plus fulvestrant arm.

AEs of ECG QT prolonged (any grade) occurred in 6.2% of patients receiving ribociclib plus fulvestrant and 0.8% of patients receiving placebo plus fulvestrant. Based on ECG assessments, a postbaseline QTcF > 480 ms occurred in 5.6% of patients in the ribociclib plus fulvestrant arm and 2.5% of patients in the placebo plus fulvestrant arm; of these, 1.7% and 0.4%, respectively, experienced a postbaseline QTcF interval > 500 ms. An increase of

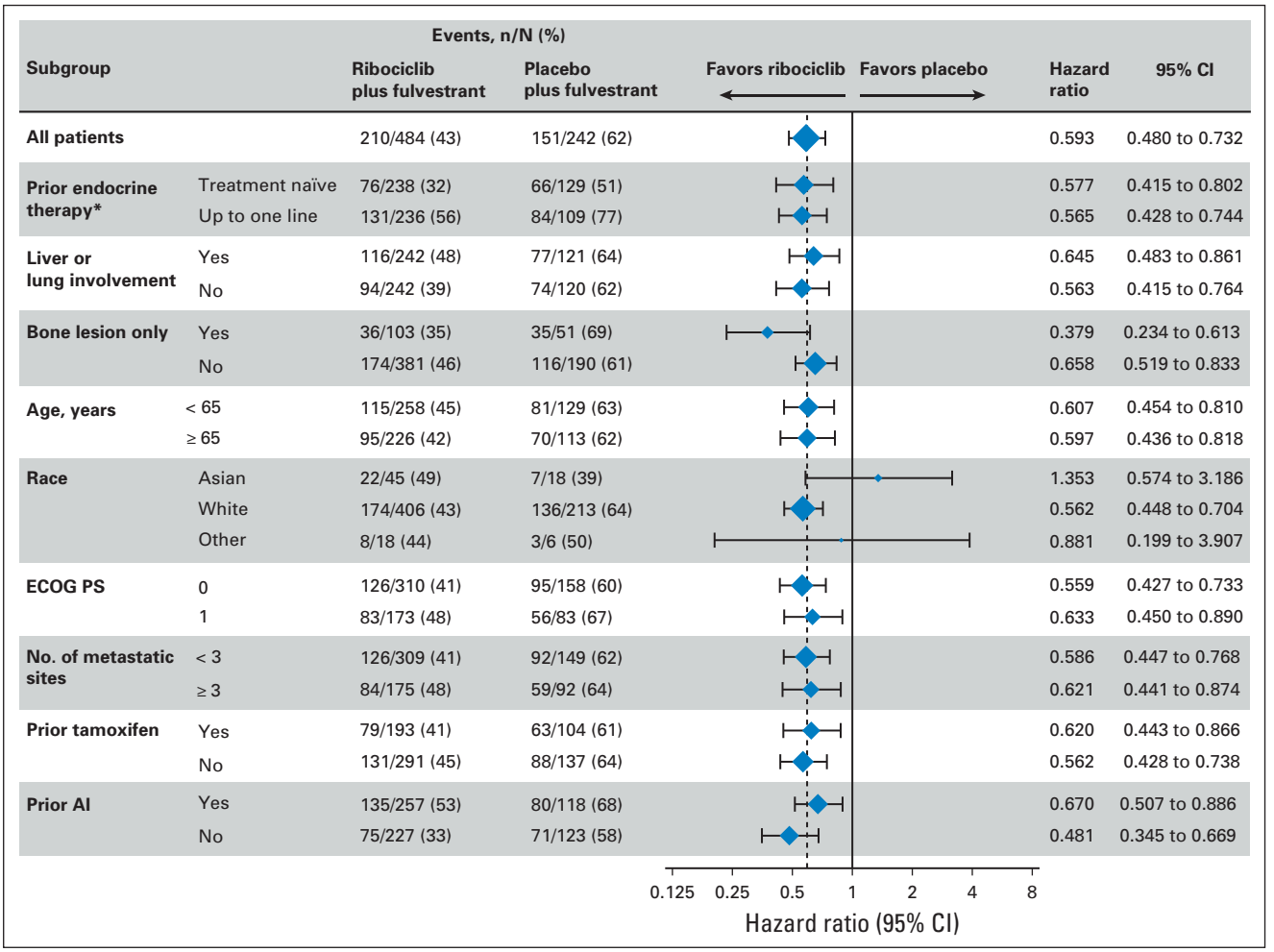

Fig 3. Progression-free survival outcomes in patient subgroups. Hazard ratios were estimated on the basis of stratified Cox proportional hazards model, except in subgroups related to stratification factors (presence or absence of lung or liver metastases and prior endocrine therapy), where an unstratified analysis was used. AI, aromatase inhibitor; ECOG PS, Eastern Cooperative Oncology Group performance status. (*) Prior endocrine therapy for advanced disease; 14 patients were not included in the prior endocrine therapy subgroup analysis because of missing data or criteria not being met.

> 60 ms from baseline in the QTcF interval occurred in 6.5% and 0.4% of patients randomly assigned to ribociclib plus fulvestrant and placebo plus fulvestrant, respectively. Three patients (0.6%) in the ribociclib plus fulvestrant arm and no patient in the placebo plus fulvestrant arm discontinued study treatment because of a prolonged QTcF interval. There were no cases of torsades de pointes.

In the ribociclib plus fulvestrant arm, grade 3 or 4 elevated ALT occurred in 32 (6.6%) and nine patients (1.9%), respectively, and elevated AST in 23 (4.8%) and six patients (1.2%), respectively. In the placebo plus fulvestrant arm, grade 3 ALT and AST events occurred in one (0.4%) and two patients (0.8%), respectively, and there were no grade 4 elevated ALT or AST events. Two patients receiving ribociclib plus fulvestrant were confirmed cases of Hy's law; their liver enzymes returned to normal after discontinuation of ribociclib.

Serious AEs occurred in 138 (28.6%) and 40 patients (16.6%) in the ribociclib plus fulvestrant and placebo plus fulvestrant arms, respectively; of these, 54 (11.2%) and six (2.5%) were attributed to the study medication. The most common all-grade all-causality serious AEs reported in ≥ 1% of patients (ribociclib plus fulvestrant *v* placebo plus fulvestrant) were pneumonia (1.9% *v* 0%) and dyspnea (1.2% *v* 2.1%).

Ribociclib or placebo dose reductions were reported in 183 (37.9%) and 10 patients (4.1%) in the ribociclib plus fulvestrant and placebo plus fulvestrant arms, respectively; 148 (30.6%) and nine (3.7%) had a single dose reduction. AEs were the most common reason for dose reduction; 160 patients (33.1%) in the ribociclib plus fulvestrant arm had at least one dose reduction because of an AE versus eight (3.3%) in the placebo plus fulvestrant arm.

There were 13 deaths (2.7%) in the ribociclib plus fulvestrant arm and eight (3.3%) in the placebo plus fulvestrant arm during or within 30 days after treatment discontinuation; most resulted from disease progression (seven [1.4%] in the ribociclib plus fulvestrant arm *v* seven [2.9%] in the placebo plus fulvestrant arm). In the ribociclib plus fulvestrant arm, there was one death resulting from acute respiratory distress syndrome in a patient with baseline lung metastases, which was suspected to be related to study treatment. The remaining five deaths were unrelated to treatment and included cardiac failure, pneumonia, pulmonary embolism, hemorrhagic shock, and ventricular arrhythmia (one patient each). The patient with a ventricular arrhythmia had normal QTcF values while receiving treatment. After disease progression and treatment discontinuation, docetaxel plus capecitabine was initiated. The

Table 2. Best Overall Response per Local Assessment in All Patients and in Patients With Measurable Disease

Best Overall Response	No. (%)	
	Ribociclib + Fulvestrant	Placebo + Fulvestrant
All patients	n = 484	n = 242
CR	8 (1.7)	0 (0.0)
PR	149 (30.8)	52 (21.5)
SD	161 (33.3)	83 (34.3)
Non-CR/non-PD	88 (18.2)	54 (22.3)
PD	48 (9.9)	40 (16.5)
Unknown	30 (6.2)	13 (5.4)
ORR*	157 (32.4)	52 (21.5)
95% CI	28.3 to 36.6	16.3 to 26.7
CBR†	340 (70.2)	152 (62.8)
95% CI	66.2 to 74.3	56.7 to 68.9
Patients with measurable disease	n = 379	n = 181
CR	6 (1.6)	0 (0.0)
PR	149 (39.3)	52 (28.7)
SD	161 (42.5)	83 (45.9)
PD	40 (10.6)	35 (19.3)
Unknown	23 (6.1)	11 (6.1)
ORR*	155 (40.9)	52 (28.7)
95% CI	35.9 to 45.8	22.1 to 35.3
CBR‡	263 (69.4)	108 (59.7)
95% CI	64.8 to 74.0	52.5 to 66.8

Abbreviations: CBR, clinical benefit rate; CR, complete response; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease.
*Overall response included CR or PR ($P < .001$ for all patients and $P = .003$ for patients with measurable disease for comparison with placebo).
†Clinical benefit was defined as CR or PR, SD ≥ 24 weeks, or neither CR nor PD ≥ 24 weeks ($P = .020$ for comparison with placebo).
‡Clinical benefit among patients with measurable disease at baseline was defined as CR or PR or SD ≥ 24 weeks ($P = .015$ for comparison with placebo).

patient then developed a ventricular arrhythmia 17 days (more than five ribociclib half-lives; five half-lives is equivalent to 7 days) after the last ribociclib dose. The remaining death in the placebo plus fulvestrant arm resulted from a pulmonary embolism.

DISCUSSION

The MONALEESA-3 study demonstrated that ribociclib plus fulvestrant significantly improves PFS compared with fulvestrant alone in postmenopausal women with HR-positive/HER2-negative advanced breast cancer, resulting in a 41% reduction in the risk of progression. To our knowledge, MONALEESA-3 is the first study to evaluate a CDK4/6 inhibitor–based combination with fulvestrant in patients who are treatment naïve in the advanced setting (ie, patients with de novo disease and those who experienced relapse > 12 months from completion of [neo]adjuvant endocrine therapy with no treatment for advanced disease). Median PFS for this subgroup was not reached for patients receiving ribociclib plus fulvestrant and was 18.3 months for those in the fulvestrant plus placebo arm, corresponding to a 42% reduction in the risk of progression. Ribociclib plus letrozole also demonstrated improved outcomes in patients who had received no prior therapy in the advanced setting, with a PFS hazard ratio of 0.568, compared with single-agent letrozole.[13] These data provide additional confirmation of the use of ribociclib and endocrine therapy combinations, including fulvestrant, as effective first-line treatment for postmenopausal women with HR-positive/HER2-negative advanced breast cancer.

Patients who had received up to one line of prior endocrine therapy for advanced disease also derived benefit from ribociclib plus fulvestrant versus fulvestrant monotherapy, with a median PFS of 14.6 versus 9.1 months, respectively, and a 43% reduction in the risk of progression. In previous phase III studies, CDK4/6 inhibitor and fulvestrant combinations also prolonged PFS versus fulvestrant alone,[8,10] confirming the clinical utility of these combinations in patients whose disease progressed during prior endocrine therapy.

OS results from MONALEESA-3 were not mature at the time of this analysis. They have yet to be reported for other CDK4/6 inhibitors in HR-positive/HER2-negative advanced breast cancer.

Similar to results from other ribociclib studies, ribociclib treatment effect was consistent across most prespecified subgroups, further supporting use of ribociclib-based therapy for a broad range of patients with HR-positive/HER2-negative advanced breast cancer.[6,7] Although men were eligible for enrollment after a protocol amendment, no male patients were enrolled. Nevertheless, it remains conceivable that ribociclib plus fulvestrant may also provide benefit in male patients with HR-positive/HER2-negative advanced breast cancer.

The safety profile of ribociclib plus fulvestrant was consistent with that observed in other studies of ribociclib.[6,7] Most AEs observed in the ribociclib plus fulvestrant arm were of mild or moderate severity, with no new safety signals observed. Although neutropenia was the most common all-grade and grade 3 or 4 AE, events were generally uncomplicated. AE-related treatment discontinuations were rare, further supporting the manageable safety profile of ribociclib-based combinations. The incidence of QTcF prolongation observed with ribociclib plus fulvestrant was similar to that previously reported with ribociclib,[6,7] and there were no incidences of torsades de pointes. The frequency of elevated transaminases was higher in the ribociclib plus fulvestrant arm versus the placebo plus fulvestrant arm. However, the overall incidence of events was comparable to that observed in other studies of ribociclib.[6,7] There were two patients in the ribociclib plus fulvestrant arm with cases of Hy's law, and in both patients, liver enzymes returned to normal after ribociclib discontinuation. Increased liver enzymes have also been observed in patients receiving fulvestrant monotherapy.[14,15]

Multiple studies have evaluated CDK4/6 inhibitor regimens in HR-positive/HER2-negative advanced breast cancer, and data from MONALEESA-3 provide additional confirmation of the efficacy and safety of ribociclib in this patient population. To the best of our knowledge, this is the first study to demonstrate that CDK4/6 inhibitor and fulvestrant combinations are efficacious in patients with de novo advanced breast cancer and in those who experienced relapse > 12 months after prior endocrine therapy. Additional analyses from the study may help further elucidate mechanisms of resistance to endocrine therapy and CDK4/6 inhibitors.

In conclusion, the MONALEESA-3 study demonstrates significantly improved PFS with ribociclib plus fulvestrant, with treatment benefit observed irrespective of prior endocrine therapy for advanced disease. Ribociclib and fulvestrant may represent a new therapeutic option in this subtype of advanced breast cancer, both for patients receiving treatment in the first-line setting (ie, treatment naïve for advanced breast cancer; including patients whose disease relapsed >12 months after completion of [neo]adjuvant therapy or patients with de novo advanced/metastatic disease [no prior

Table 3. AEs Occurring in at Least 15% of Patients in Either Arm (safety population)

	No. (%)					
	Ribociclib + Fulvestrant (n = 483)			Placebo + Fulvestrant (n = 241)		
AE	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
Neutropenia*	336 (69.6)	225 (46.6)	33 (6.8)	5 (2.1)	0 (0.0)	0 (0.0)
Nausea	219 (45.3)	7 (1.4)	0 (0.0)	68 (28.2)	2 (0.8)	0 (0.0)
Fatigue	152 (31.5)	8 (1.7)	0 (0.0)	80 (33.2)	1 (0.4)	0 (0.0)
Diarrhea	140 (29.0)	3 (0.6)	0 (0.0)	49 (20.3)	2 (0.8)	0 (0.0)
Leukopenia†	137 (28.4)	65 (13.5)	3 (0.6)	4 (1.7)	0 (0.0)	0 (0.0)
Vomiting	129 (26.7)	7 (1.4)	0 (0.0)	31 (12.9)	0 (0.0)	0 (0.0)
Constipation	120 (24.8)	4 (0.8)	0 (0.0)	28 (11.6)	0 (0.0)	0 (0.0)
Arthralgia	116 (24.0)	3 (0.6)	0 (0.0)	64 (26.6)	1 (0.4)	0 (0.0)
Cough	105 (21.7)	0 (0.0)	0 (0.0)	37 (15.4)	0 (0.0)	0 (0.0)
Headache	104 (21.5)	4 (0.8)	0 (0.0)	49 (20.3)	1 (0.4)	0 (0.0)
Pruritus	96 (19.9)	1 (0.2)	0 (0.0)	16 (6.6)	0 (0.0)	0 (0.0)
Alopecia	90 (18.6)	0 (0.0)	0 (0.0)	11 (4.6)	0 (0.0)	0 (0.0)
Rash	89 (18.4)	2 (0.4)	0 (0.0)	14 (5.8)	0 (0.0)	0 (0.0)
Back pain	85 (17.6)	8 (1.7)	0 (0.0)	42 (17.4)	2 (0.8)	0 (0.0)
Anemia‡	83 (17.2)	15 (3.1)	0 (0.0)	13 (5.4)	5 (2.1)	0 (0.0)
Decreased appetite	78 (16.1)	1 (0.2)	0 (0.0)	31 (12.9)	0 (0.0)	0 (0.0)
Pain in extremity	66 (13.7)	3 (0.6)	0 (0.0)	39 (16.2)	2 (0.8)	0 (0.0)
Hot flush	64 (13.3)	0 (0.0)	0 (0.0)	41 (17.0)	0 (0.0)	0 (0.0)

Abbreviation: AE, adverse event.
*Neutropenia includes neutropenia, decreased neutrophil count, febrile neutropenia, and neutropenic sepsis.
†Leukopenia includes leukopenia, decreased white blood cell count, lymphopenia, and decreased lymphocyte count.
‡Anemia includes anemia, decreased hemoglobin level, and decreased red blood cell count.

exposure to endocrine therapy]) and for those receiving treatment in the second-line setting or who had an early relapse (ie, received up to one line of prior endocrine therapy in the advanced setting [early relapse defined as disease relapse on or ≤12 months since the completion of (neo)adjuvant endocrine therapy]). The efficacy results seen here for treatment-naïve advanced disease as well as those from other studies of CDK4/6 inhibitors in HR-positive/HER2-negative breast cancer support the study of ribociclib in early HR-positive/HER2-negative disease.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at jco.org.

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Phase III Randomized Study of Ribociclib and Fulvestrant in Hormone Receptor–Positive, Human Epidermal Growth Factor Receptor 2–Negative Advanced Breast Cancer: MONALEESA-3

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