Key aims: To compare progression free survival and overall survival between CDK4/6 inhibitor + letrozole versus placebo + letrozole in post menopausal women with homone receptor +ve, HER 2-ve recurrent or metastatic breast cancer

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Results: Median progression free survival was 25 months in treatment arm and 16 months in placebo arm. Ribociclib was effective regardless of tumour genetics and mutation type.

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ORIGINAL ARTICLE

Discussion: Ribociclib now licensed as first line treatment for post menopausal HR +ve HER2 -ve advanced breast cancer patients. Main AE are neutropenia and pneumonia. MONALEESA - 3 adds fulvestrant to ribociclib and MONALEESA - 7 expands to pre/peri-menopausal patients.

Updated results from MONALEESA-2, a phase III trial of first-line ribociclib plus letrozole versus placebo plus letrozole in hormone receptor-positive, HER2-negative advanced breast cancer

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Background: The phase III MONALEESA-2 study demonstrated significantly prolonged progression-free survival (PFS) and a manageable toxicity profile for first-line ribociclib plus letrozole versus placebo plus letrozole in patients with hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2–) advanced breast cancer. Here, we report updated efficacy and safety data, together with exploratory biomarker analyses, from the MONALEESA-2 study.

Patients and methods: A total of 668 postmenopausal women with HR+, HER2– recurrent/metastatic breast cancer were randomized (1 : 1; stratified by presence/absence of liver and/or lung metastases) to ribociclib (600 mg/day; 3-weeks-on/1-week-off; 28-day treatment cycles) plus letrozole (2.5 mg/day; continuous) or placebo plus letrozole. The primary end point was locally assessed PFS. The key secondary end point was overall survival (OS). Other secondary end points included overall response rate (ORR) and safety. Biomarker analysis was an exploratory end point.

Results: At the time of the second interim analysis, the median duration of follow-up was 26.4 months. Median PFS was 25.3 months [95% confidence interval (CI) 23.0–30.3] for ribociclib plus letrozole and 16.0 months (95% CI 13.4–18.2) for placebo plus letrozole (hazard ratio 0.568; 95% CI 0.457–0.704; log-rank $P = 9.63 \times 10^{-8}$). Ribociclib treatment benefit was maintained irrespective of *PIK3CA* or *TP53* mutation status, total Rb, Ki67, or p16 protein expression, and *CDKN2A*, *CCND1*, or *ESR1* mRNA levels. Ribociclib benefit was more pronounced in patients with wild-type versus altered receptor tyrosine kinase genes. OS data remain immature, with 116 deaths observed; 50 in the ribociclib arm and 66 in the placebo arm (hazard ratio 0.746; 95% CI 0.517–1.078). The ORR was 42.5% versus 28.7% for all patients treated with ribociclib plus letrozole versus placebo plus letrozole, respectively, and 54.5% versus 38.8%, respectively, for patients with measurable disease. Safety results, after a further 11.1 months of follow-up, were comparable with those reported at the first analysis, with no new or unexpected toxicities observed, and no evidence of cumulative toxicity.

Conclusions: The improved efficacy outcomes and manageable tolerability observed with first-line ribociclib plus letrozole are maintained with longer follow-up, relative to letrozole monotherapy.

Clinical trials number: NCT01958021

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

Introduction

At the first preplanned interim analysis of the phase III MONALEESA-2 study (NCT01958021; median follow-up: 15.3 months; data cut-off 29 January 2016), ribociclib plus letrozole significantly prolonged progression-free survival (PFS) versus placebo plus letrozole in patients with hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2–) advanced breast cancer (ABC) who had received no prior treatment of advanced disease [1]. At this first interim analysis (data cut-off 29 January 2016), median PFS in the ribociclib plus letrozole arm was not reached [95% confidence interval (CI) 19.3 to not reached] versus 14.7 months (95% CI 13.0–16.5) for placebo plus letrozole (hazard ratio 0.556; 95% CI 0.429–0.720; $P = 3.29 \times 10^{-6}$) [2]. Overall survival (OS) data were immature, with 23 deaths in the ribociclib plus letrozole arm and 20 deaths in the placebo plus letrozole arm [1]. The prespecified O'Brien–Fleming stopping boundary for OS was not crossed (hazard ratio 1.128; 95% CI 0.619–2.055; $P = 0.653$). Ribociclib plus letrozole was generally well tolerated, with neutropenia and leukopenia the most common grade 3/4 adverse events (AEs) (National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03) [1].

Here, we report updated efficacy and safety data from the MONALEESA-2 trial, with a median duration of follow-up of 26.4 months. Exploratory biomarker analyses are also described.

Methods

Study design and patients

Full details of the study design have been reported previously [1]. Briefly, MONALEESA-2 is a phase III, randomized, double-blind, placebo-controlled, multicenter study of first-line ribociclib plus letrozole versus placebo plus letrozole. Eligible patients were postmenopausal women with HR+, HER2– recurrent/metastatic breast cancer who had not received previous systemic therapy for advanced disease. Previous (neo)adjuvant therapy was permitted; time since the last dose of nonsteroidal aromatase inhibitors must have been greater than 12 months. Patients were required to have ≥1 measurable lesion per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 [3] or ≥1 predominantly lytic bone lesion, and an Eastern Cooperative Oncology Group performance status ≤1. Patients with inflammatory breast cancer, active cardiac disease, or history of cardiac dysfunction, including QT interval corrected using Fridericia's formula (QTcF) >450 msec, were excluded.

The study was conducted in accordance with Good Clinical Practice, all applicable regulatory requirements, and the guiding principles of the Declaration of Helsinki. The institutional review board at each participating center reviewed the protocol and subsequent amendments, and all patients provided written informed consent before enrollment.

Randomization and masking

Patients were randomized (1 : 1) to oral ribociclib (600 mg/day; 3-weeks-on/1-week-off in 28-day treatment cycles) plus letrozole (2.5 mg/day on a continuous schedule) or placebo plus letrozole until disease progression, unacceptable toxicity, death, or discontinuation for any other reason. Randomization was stratified according to the presence or absence of liver and/or lung metastases. Treatment crossover was not permitted. Following the first (data cut-off 29 January 2016) and second (data cut-off 4 January 2017) analyses, the trial continued in a double-blinded manner to maintain integrity of OS and PFS analyses. Emergency investigator unblinding was allowed for safety reasons essential for effective treatment.

Procedures

Tumor assessments were conducted at screening, every 8 weeks during the first 18 months, then every 12 weeks thereafter until disease progression, and at end of treatment.

Pretreatment plasma and tumor tissue samples were collected for exploratory biomarker analyses. Additional details for the biomarker analyses are provided in the supplementary material, available at *Annals of Oncology* online.

AEs were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03 [4]. Ribociclib dose interruptions and/or reductions (600 to 400 to 200 mg/day) were permitted to manage AEs; letrozole dose reductions were not allowed. Electrocardiogram (ECG) assessments were conducted at screening, on day 15 of cycle 1, and day 1 of cycles 2 and 3. After a protocol amendment, additional ECG assessments were carried out on day 1 of cycles 4–9 in all patients and on day 1 of subsequent cycles in patients with a mean QTcF of ≥481 msec at any time before cycle 10. ECGs were reviewed by an independent central committee blinded to treatment allocation.

Outcomes

The primary end point was locally assessed PFS, per RECIST v1.1. The key secondary end point was OS. Other secondary end points included overall response rate (ORR), clinical benefit rate, and safety. Biomarker analyses were an exploratory end point.

Statistical analyses

The primary efficacy analysis compared the distribution of PFS between the two treatment groups using a one-sided stratified log-rank test with a 2.5% level of significance. An updated analysis of locally assessed PFS was carried out at the time of the second analysis for OS. OS was statistically evaluated using a log-rank test only if the primary end point of PFS was significantly different between the two arms. If a patient was not known to have died, OS was censored at the last known date the patient was alive. A maximum of four OS analyses are planned, with the first occurring at the time of the interim analysis for PFS. The second interim analysis for OS was planned after approximately 100 deaths; the third and fourth analyses are planned after approximately 300 and 400 deaths, respectively. The type I error probability was controlled using a separate Lan–DeMets (O'Brien–Fleming) α-spending function for the OS analysis to guarantee protection of the overall α-level (2.5%) across repeated testing of the OS hypotheses. Kaplan–Meier estimates were used to estimate the distribution of PFS and OS; hazard ratios and 95% CIs were estimated using a Cox proportional hazards model. Significance for OS in this updated analysis was determined using stringent O'Brien–Fleming stopping boundary criteria (one-sided $P = 3.15 \times 10^{-5}$). For biomarker analyses, median PFS (time to event) and the corresponding 95% CI were generated by the Kaplan–Meier survival method. All biomarker data were generated blinded to treatment arm and clinical outcome.

Efficacy analyses were based on data from the full analysis set, which included all randomized patients on an intent-to-treat basis. Safety

analyses were carried out in patients who received at least one dose of the study regimens and had at least one postbaseline safety assessment ('as-treated' patient population).

Results

Patient characteristics and disposition

A total of 668 patients were randomized to ribociclib plus letrozole ($n = 334$) and placebo plus letrozole ($n = 334$) between 24 January 2014 and 24 March 2015 [1]. Prior (neo)adjuvant hormonal therapy had been received by 175 (52.4%) and 171 (51.2%) patients in the ribociclib plus letrozole and placebo plus letrozole arms, respectively.

As of 2 January 2017, 219 (32.8%) patients remained on-study; 131 (39.2%) patients receiving ribociclib plus letrozole and 88 (26.3%) patients receiving placebo plus letrozole (Figure 1). A total of 203 (60.8%) and 246 (73.7%) patients in the ribociclib plus letrozole and placebo plus letrozole arms, respectively, had permanently discontinued study treatment. The most common reasons for treatment discontinuation (ribociclib plus letrozole versus placebo plus letrozole) were disease progression (39.8% versus 60.8%) and AEs (8.1% versus 2.4%), consistent with the first interim analysis results.

Efficacy

Median duration of follow-up for this updated analysis was 26.4 months. Updated PFS analyses demonstrated continued treatment benefit for ribociclib plus letrozole versus placebo plus letrozole (hazard ratio 0.568; 95% CI 0.457–0.704; $P = 9.63 \times 10^{-8}$; Figure 2). Median PFS was prolonged by 9.3 months, from 16.0 months (95% CI 13.4–18.2) for patients receiving placebo plus letrozole to 25.3 months (95% CI 23.0–30.3) for those receiving ribociclib plus letrozole. Treatment benefit was consistent across patient subgroups, with estimated PFS hazard ratios favoring ribociclib plus letrozole (Figure 3). In patients from the EU region, median PFS was 27.6 months for the ribociclib plus letrozole arm ($n = 150$) versus 16.5 months for the placebo plus letrozole arm ($n = 146$; hazard ratio 0.56; 95% CI 0.41–0.78), and in patients from the US was 27.6 months ($n = 100$) versus 15.0 months ($n = 113$; hazard ratio 0.527; 95% CI 0.351–0.793), respectively. The mean relative ribociclib/placebo dose intensity was 476.8 mg/day for the ribociclib plus letrozole arm and 591.4 mg/day for the placebo plus letrozole arm.

OS data remain immature, with 50 deaths in the ribociclib arm and 66 in the placebo arm (Figure 4), and results of the stratified log-rank test not exceeding the O'Brien–Fleming stopping boundary.

The ORR (ribociclib plus letrozole versus placebo plus letrozole) was 42.5% versus 28.7% ($P = 9.18 \times 10^{-5}$; supplementary Table S1, available at *Annals of Oncology* online) and among patients with measurable disease at baseline, the ORR was 54.5% versus 38.8% ($P = 2.54 \times 10^{-4}$). At the first tumor evaluation (week 8), decreased tumor size was observed in 76% (180/238) of patients in the ribociclib plus letrozole arm versus 67% (152/227) in the placebo plus letrozole arm, with the difference between treatment arms sustained to the second interim analysis cut-off date.

Biomarkers

Baseline circulating tumor (ct) DNA samples were successfully sequenced in 494 of 668 randomized patients. No genetic

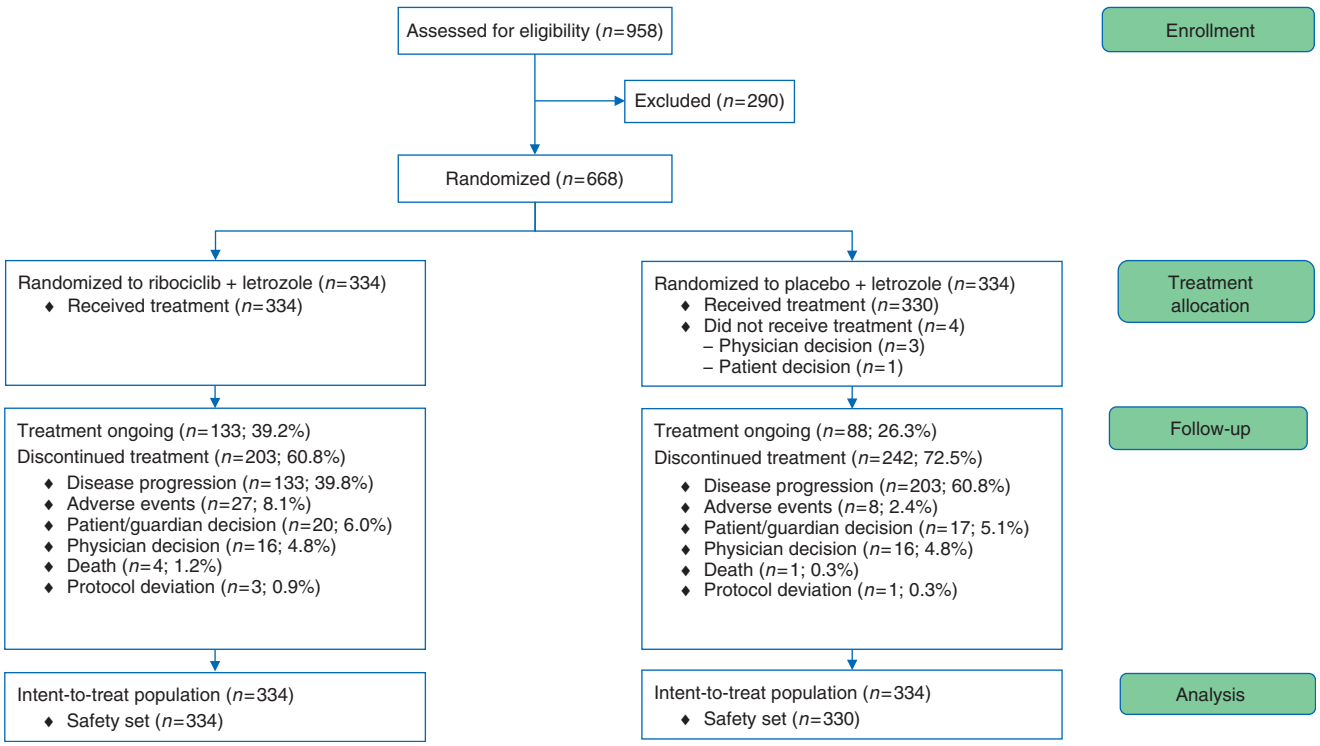

Figure 1. CONSORT diagram of patient flow in MONALEESA-2.

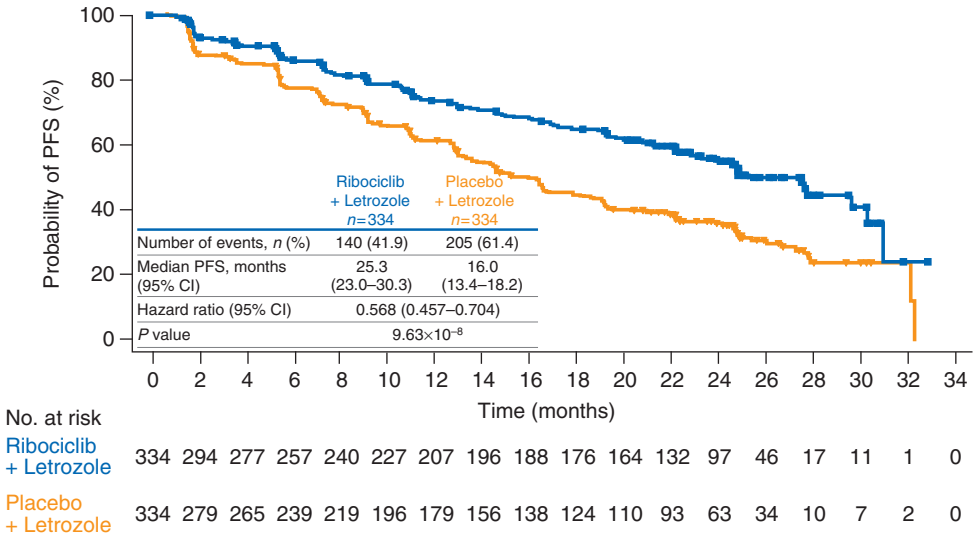

Figure 2. Kaplan–Meier graph of investigator-assessed PFS for ribociclib plus letrozole versus placebo plus letrozole. CI, confidence interval; PFS, progression-free survival. Data cut-off: 2 January 2017.

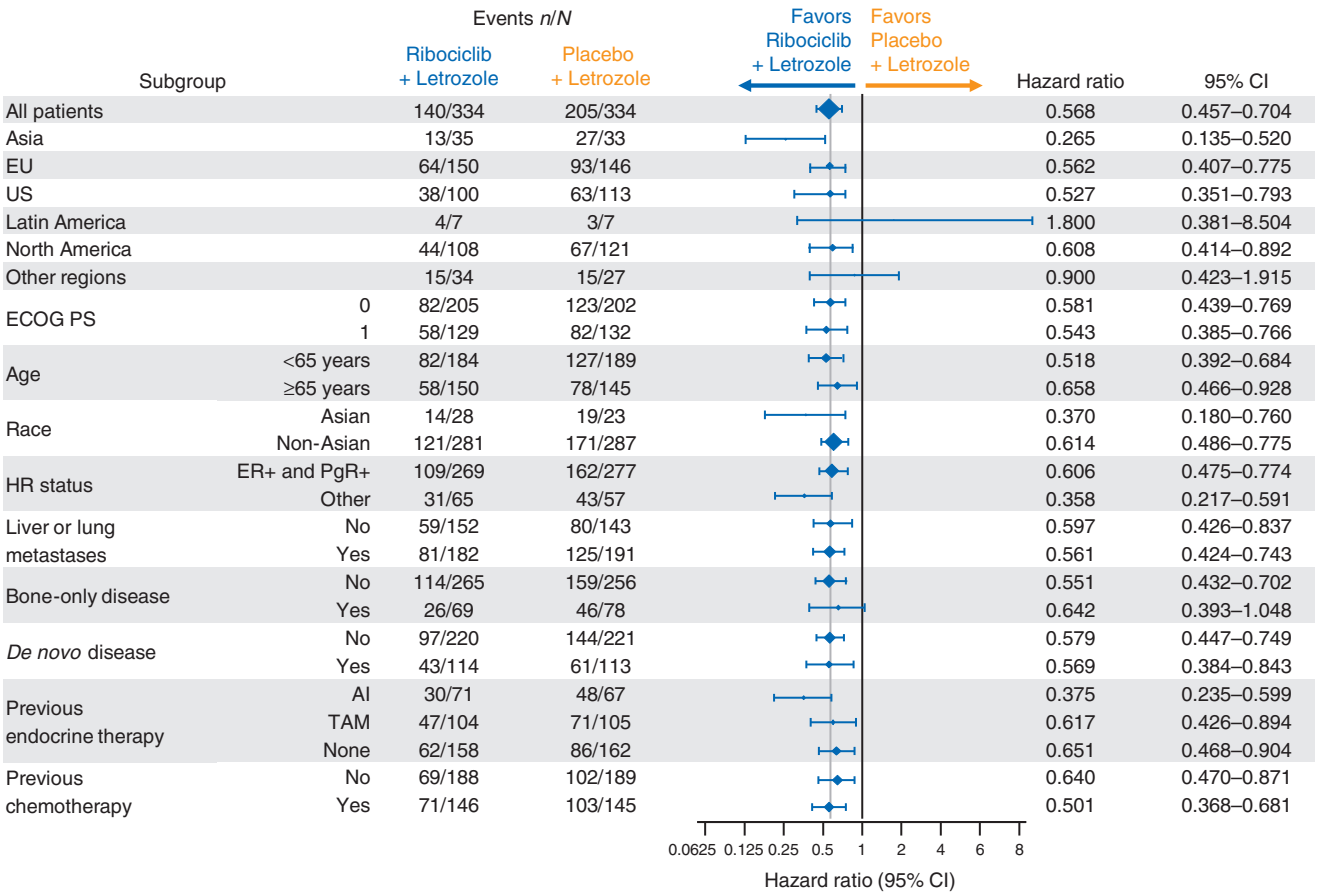

Figure 3. Subgroup analysis of PFS for ribociclib plus letrozole versus placebo plus letrozole. AI, aromatase inhibitor; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; ER+, estrogen receptor-positive; HR, hormone receptor; PFS, progression-free survival; PgR+, progesterone receptor-positive; TAM, tamoxifen. Data cut-off: 2 January 2017.

alterations were detected in 67 of these patients due to too few genetic alterations in the tumor or low plasma ctDNA levels. As such, baseline ctDNA data were correlated with PFS data in 427 patients (cut-off of 2 January 2017). *PIK3CA* short variants (mutations and short insertions/indels) were detected in 142 (33%) patients, *TP53* short variants in 53 (12%) patients, and alterations in genes involved in receptor tyrosine kinase (RTK) signaling (amplifications and short variants) in 51 of 427 (12%) patients.

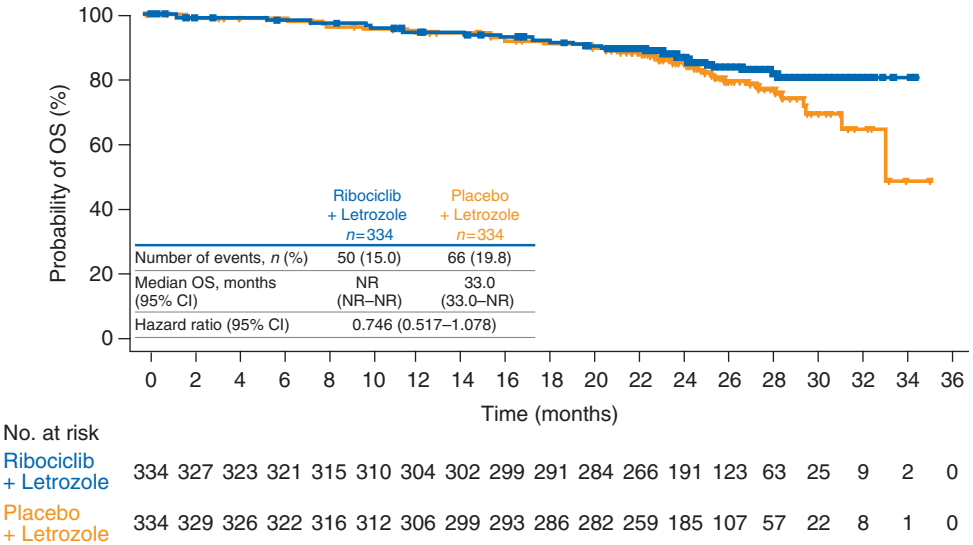

Figure 4. Kaplan–Meier graph of investigator-assessed OS for ribociclib plus letrozole versus placebo plus letrozole. CI, confidence interval; NR, not reached; OS, overall survival. Data cut-off: 2 January 2017.

Ribociclib treatment prolonged PFS irrespective of *PIK3CA* or *TP53* mutation status; patients with wild-type *PIK3CA* and *TP53* had a numerically longer PFS versus those harboring altered *PIK3CA* or *TP53*, irrespective of treatment (supplementary Figure S1, available at *Annals of Oncology* online). Ribociclib plus letrozole was also associated with a greater PFS benefit versus placebo plus letrozole in patients with wild-type versus altered RTK genes. At the earlier data cut-off of 29 January 2016, treatment benefit with ribociclib was maintained irrespective of total Rb, Ki67, or p16 protein expression, or *CDKN2A*, *CCND1*, or *ESR1* mRNA levels (supplementary Figure S2, available at *Annals of Oncology* online).

Safety

In general, safety results at the updated analysis (data cut-off 4 January 2017, unless stated otherwise) were similar to those reported at the first analysis [1].

Median duration of exposure to study treatment was 20.2 (range 0–34) months in the ribociclib plus letrozole arm and 14.1 (range 0–32) months in the placebo plus letrozole arm.

The most common all-cause, all-grade, and grade 3/4 AEs are shown in Table 1. The most frequent all-cause grade 3/4 AEs (≥15% in either arm; ribociclib plus letrozole versus placebo plus letrozole) were neutropenia and leukopenia.

As of 2 January 2017, a >60 msec prolongation from baseline in QTcF interval occurred in 10 patients (3.0%) in the ribociclib plus letrozole arm and one patient (0.3%) in the placebo plus letrozole arm. A total of 12 patients (3.6%) receiving ribociclib plus letrozole had at least one postbaseline QTcF of >480 msec versus two patients (0.6%) in the placebo plus letrozole arm; in the ribociclib plus letrozole arm, 11 of these patients had been reported at the time of the first analysis [1]. Two (0.6%) of the 12 patients in the ribociclib plus letrozole arm experienced a postbaseline QTcF of greater than 500 msec; one of these patients received a concomitant prohibited medication with a known risk to prolong QT, as described previously [1]. ECG changes were mostly asymptomatic; events were managed effectively using ribociclib dose modifications.

All-grade, all-causality serious AEs were reported in 85 (25.4%) versus 51 (15.5%) patients in the ribociclib plus letrozole versus placebo plus letrozole arms, respectively; the most common (≥1.5%) were pneumonia (1.8% versus 0.9%), abdominal pain (1.5% versus 0%), dyspnea (1.5% versus 0.6%), and vomiting (1.5% versus 0.6%).

Overall, 192 patients (57.5%) in the ribociclib plus letrozole arm had at least one ribociclib/placebo dose reduction versus 26 (7.9%) in the placebo plus letrozole arm; most patients required a single dose reduction [115 (34.4%) versus 20 (6.1%), respectively]. At least one dose reduction due to an AE occurred in 182 patients (54.5%) and 14 patients (4.2%) in the ribociclib plus letrozole and placebo plus letrozole arms, respectively; the most common all-grade AE leading to ribociclib dose reduction (≥10%) was neutropenia (24.9%). Median time to first ribociclib dose reduction was 2.9 (range 0.0–29.4) months.

At least one dose interruption due to an AE was reported in 239 patients (71.6%) in the ribociclib plus letrozole arm versus 54 patients (16.4%) in the placebo plus letrozole arm. The most frequent all-grade AE leading to ribociclib dose interruption (≥15%) was neutropenia (41.9%).

As of 2 January 2017, 10 on-treatment deaths (≤30 days after last study dose) were reported; seven (2.1%) in the ribociclib plus letrozole arm and three (0.9%) in the placebo plus letrozole arm. Causes of death in the ribociclib plus letrozole arm were underlying breast cancer ($n=2$; one of which was reported previously [1]), acute respiratory failure ($n=2$), pneumonia ($n=1$), sudden death ($n=1$, as reported previously [1]), and death due to unknown cause ($n=1$; as reported previously [1]). Of the three additional deaths reported at the time of the updated analysis, only one was considered to be related to study treatment (acute respiratory failure). Deaths in the placebo plus letrozole arm were due to underlying breast cancer ($n=2$) and subdural hematoma ($n=1$).

Table 1. Most common AEs, irrespective of causality (≥20% in either treatment arm)

AE, *n* (%)	Ribociclib (600 mg) plus letrozole (2.5 mg) *n* = 334			Placebo plus letrozole (2.5 mg) *n* = 330		
	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 4
Neutropenia[a]	257 (76.9)	175 (52.4)	32 (9.6)	19 (5.8)	4 (1.2)	0
Nausea	178 (53.3)	8 (2.4)	0	101 (30.6)	2 (0.6)	0
Fatigue	138 (41.3)	9 (2.7)	1 (0.3)	107 (32.4)	3 (0.9)	0
Diarrhea	128 (38.3)	8 (2.4)	0	81 (24.5)	3 (0.9)	0
Alopecia	115 (34.4)	0	0	53 (16.1)	0	0
Vomiting	112 (33.5)	12 (3.6)	0	55 (16.7)	3 (0.9)	0
Arthralgia	111 (33.2)	2 (0.6)	1 (0.3)	108 (32.7)	4 (1.2)	0
Leukopenia[b]	110 (32.9)	67 (20.1)	4 (1.2)	15 (4.5)	3 (0.9)	0
Constipation	93 (27.8)	4 (1.2)	0	71 (21.5)	0	0
Headache	90 (26.9)	1 (0.3)	0	69 (20.9)	2 (0.6)	0
Hot flash	82 (24.6)	1 (0.3)	0	84 (25.5)	0	0
Back pain	81 (24.3)	10 (3.0)	0	67 (20.3)	1 (0.3)	0
Cough	77 (23.1)	0	0	70 (21.2)	0	0
Rash[c]	74 (22.2)	5 (1.5)	0	29 (8.8)	0	0
Anemia[d]	71 (21.3)	6 (1.8)	2 (0.6)	19 (5.8)	4 (1.2)	0
Decreased appetite	69 (20.7)	5 (1.5)	0	52 (15.8)	1 (0.3)	0
Abnormal LFTs[e]	67 (20.1)	28 (8.4)	6 (1.8)	21 (6.4)	8 (2.4)	0

Data cut-off: 4 January 2017.

[a]Neutropenia includes 'neutropenia', 'decreased neutrophil count', and 'granulocytopenia'.

[b]Leukopenia includes 'decreased white blood cell count' and 'leukopenia'.

[c]Rash includes 'rash' and 'maculopapular rash'.

[d]Anemia includes 'anemia', 'decreased hemoglobin', and 'macrocytic anemia'.

[e]Abnormal LFTs includes 'increased alanine aminotransferase', 'increased aspartate aminotransferase', and 'increased blood bilirubin'.

AE, adverse event; LFT, liver function test.

Discussion

After 26.4 months of follow-up in the MONALEESA-2 study, treatment benefit with first-line ribociclib plus letrozole is maintained in postmenopausal women with HR+, HER2– ABC.

Updated PFS results are consistent with those reported at the first analysis [1], with the magnitude of treatment benefit for ribociclib plus letrozole versus placebo plus letrozole remaining unchanged in this updated analysis. After an additional 11 months of follow-up, a 9.3-month improvement in median PFS was observed with the addition of ribociclib to letrozole versus placebo plus letrozole. At the first analysis (data cut-off 29 January 2016), PFS improvement with ribociclib plus letrozole was observed in all patient subgroups, including elderly patients (aged ≥65 years) and those with *de novo* disease [5, 6]. Ribociclib treatment benefit continues to be demonstrated across subgroups, indicating that ribociclib-based therapy can be used in a broad range of patient populations.

Analysis of baseline ctDNA samples demonstrated that ribociclib treatment benefit was similar regardless of *PIK3CA* or *TP53* alteration status. Patients with wild-type *TP53* had a longer PFS versus those with altered *TP53*, irrespective of treatment, confirming *TP53* as a prognostic factor in breast cancer [7]. Ribociclib benefit was more pronounced in patients with wild-type genes involved in RTK signaling. *ESR1* alterations were observed in 18 of 427 (4%) patients, similar to the prevalence previously observed in this patient population [8], and too few patients to draw firm conclusions regarding ribociclib benefit. Treatment benefit with ribociclib was also maintained irrespective of baseline Rb, Ki67, or p16 protein expression; or *CDKN2A*, *CCND1*, or *ESR1* mRNA levels. Further biomarker analyses from the study are ongoing.

At the time of this updated analysis, the study remains immature for OS, with results not crossing the stringent prespecified O'Brien–Fleming stopping boundary for significance.

Updated safety results for ribociclib plus letrozole are consistent with those reported at the first analysis, with no new or unexpected toxicities observed, further supporting the manageable tolerability profile of the combination regimen [1]. AEs generally occurred early and were effectively managed by patient monitoring and ribociclib dose interruptions or reductions. Few patients required more than a single ribociclib dose reduction, with most patients requiring no, or only one, ribociclib dose reduction. Permanent study discontinuation due to AEs remained infrequent in the ribociclib plus letrozole arm and a larger proportion of patients receiving ribociclib plus letrozole versus placebo plus letrozole remained on-treatment at this later data cut-off. Hematologic AEs continue to represent the most common grade 3/4 AEs in the ribociclib plus letrozole arm, consistent with other CDK4/6 inhibitors [9, 10]. Neutropenia was the most common all-causality, all-grade, and grade 3/4 AE, and the most frequent AE leading to study drug interruption or reduction observed in patients receiving ribociclib plus letrozole. No new cases of febrile neutropenia were observed in this updated analysis and there is no evidence of cumulative bone marrow toxicity

with long-term treatment. The incidence of ECG changes was similar to that observed at the first analysis. QT prolongation observations in the MONALEESA-2 study support the cardiac monitoring requirements as described in the prescribing information, which includes careful selection of patients with QTcF values <450 msec. Patients scheduled to receive ribociclib should undergo ECG monitoring before treatment initiation, then on day 14 of the first cycle and at the beginning of the second cycle, and as clinically indicated. Monitoring of serum electrolytes (before treatment initiation and at the beginning of each cycle for six cycles), with correction of abnormalities as required, is also recommended. Concomitant use of medications known to prolong the QT interval may lead to clinically meaningful prolongation of the QTcF interval and should therefore be avoided with ribociclib.

Previous analyses have demonstrated that health-related quality of life was maintained in patients treated with ribociclib plus letrozole, similar to results seen with placebo plus letrozole, thus addition of ribociclib does not negatively impact patient-reported outcomes [11].

In summary, these updated results provide further confirmation that addition of ribociclib to letrozole significantly improves efficacy outcomes relative to letrozole monotherapy in patients with HR+, HER2– ABC who received no prior treatment of advanced disease, with treatment benefit observed in all subgroups. The tolerability profile remains manageable, with no evidence of cumulative toxicity. Most AEs occur early and are effectively managed through patient monitoring and ribociclib dose adjustments.

Ribociclib and endocrine therapy combinations are being further investigated in ongoing phase III studies in HR+, HER2– ABC.

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Disclosure

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