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ORIGINAL ARTICLE

Ribociclib plus fulvestrant for postmenopausal women with hormone receptor-positive, human epidermal growth factor receptor 2-negative advanced breast cancer in the phase III randomized MONALEESA-3 trial: updated overall survival

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Background: Ribociclib plus fulvestrant demonstrated significant progression-free survival (PFS) and overall survival (OS) benefits in patients with hormone receptor-positive, human epidermal growth factor receptor 2-negative (HR+/HER2−) advanced breast cancer (ABC). Here we present a new landmark in survival follow-up for a phase III cyclin-dependent kinases 4 and 6 inhibitor clinical trial in patients with ABC (median, 56.3 months).

Patients and methods: This phase III, randomized, double-blind, placebo-controlled trial was conducted at 174 sites (30 countries). Patients were men and postmenopausal women (age ≥18 years) with histologically/cytologically confirmed HR+/HER2− ABC. Patients could have received ≤1 line of endocrine therapy (ET) but no chemotherapy for ABC. Patients, assigned 2:1, were stratified by the presence/absence of liver/lung metastases and previous ET. Patients received intramuscular fulvestrant (500 mg, day 1 of each 28-day cycle plus day 15 of cycle 1) with oral ribociclib (600 mg/day, 3 weeks on, 1 week off) or placebo. Efficacy analyses were by intention to treat. Safety was assessed in patients receiving ≥1 dose study treatment. OS was a secondary endpoint. MONALEESA-3 is registered with ClinicalTrials.gov (NCT02422615; no longer enrolling).

Results: Between 18 June 2015 and 10 June 2016, 726 patients were randomly assigned (484, ribociclib; 242, placebo). At data cut-off (30 October 2020), median OS (mOS) was 53.7 months (ribociclib) versus 41.5 months (placebo) [hazard ratio (HR), 0.73; 95% confidence interval (CI) 0.59-0.90]. Subgroup analyses were consistent with overall population. In the first-line setting, most patients in the ribociclib arm (∼60%) lived longer than median follow-up; mOS was 51.8 months in the placebo arm (HR, 0.64; 95% CI 0.46-0.88). In the second-line setting, mOS was 39.7 months (ribociclib) versus 33.7 months (placebo) (HR, 0.78; 95% CI 0.59-1.04). No apparent drug—drug interaction between ribociclib and fulvestrant or new safety signals were observed.

Conclusions: This analysis reported extended OS follow-up in MONALEESA-3. mOS was ∼12 months longer in patients with HR+/HER2− ABC treated with ribociclib plus fulvestrant compared with fulvestrant monotherapy.

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

INTRODUCTION

Cyclin-dependent kinases 4 and 6 (CDK4/6) are crucial to cell cycle progression and have become an effective target in the treatment of advanced breast cancer (ABC).[1-3] Ribociclib is a selective small-molecule inhibitor of CDK4/6, and is approved in combination with fulvestrant for the

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treatment of postmenopausal patients with hormone receptor-positive/human epidermal growth factor receptor 2-negative (HR+/HER2−) ABC as first- or second-line therapy following progression on endocrine therapy (ET).[4] Ribociclib plus fulvestrant showed a significant benefit in progression-free survival (PFS) versus placebo plus fulvestrant with a median PFS (mPFS) of 20.5 versus 12.8 months [hazard ratio (HR), 0.59; 95% confidence interval (CI) 0.48-0.73, $P < 0.001$], which was reported as the primary endpoint for the MONALEESA-3 trial.[4]

Overall survival (OS) is a secondary endpoint in phase III clinical trials of CDK4/6 inhibitors,[5-10] and improving OS while maintaining quality of life is the ultimate goal of any new therapy in ABC. Three trials have previously reported OS results of CDK4/6 inhibitors in combination with fulvestrant.[6,8,10] The PALOMA-3 trial showed a median OS (mOS) of 34.9 versus 28.0 months for palbociclib plus fulvestrant versus placebo plus fulvestrant (HR, 0.81; 95% CI 0.64-1.03); however, this difference did not reach statistical significance ($P = 0.09$).[10] A significant OS benefit was demonstrated in the MONARCH-2 trial, with an mOS of 46.7 months for abemaciclib plus fulvestrant versus 37.3 months for placebo plus fulvestrant (HR, 0.76; 95% CI 0.61-0.95; $P = 0.01$).[8] The MONALEESA-3 trial also reported a significant OS benefit for ribociclib plus fulvestrant versus placebo plus fulvestrant, with an mOS of not reached (NR) versus 40.0 months (HR, 0.72; 95% CI 0.57-0.92; $P = 0.00455$).[6]

The MONALEESA-7 trial of ribociclib plus ET in pre-/perimenopausal women with HR+/HER2− ABC recently reported an exploratory OS analysis with a median follow-up of 53.5 months.[11] In this exploratory OS update, ribociclib plus ET showed a clinically relevant and significant mOS benefit of 58.7 months compared with 48.0 months in the placebo group (HR, 0.76; 95% CI 0.61-0.96).[11] Similar to MONALEESA-7, we undertook an exploratory OS update for MONALEESA-3 with an extended follow-up (median, 56.3 months) in order to analyze the long-term OS benefit of ribociclib plus fulvestrant versus placebo plus fulvestrant.

PATIENTS AND METHODS

Study design and participants

As previously reported, MONALEESA-3 was a randomized, double-blind, placebo-controlled, phase III trial in which patients were randomized 2:1 to receive fulvestrant with either oral ribociclib or matching placebo.[4] MONALEESA-3 allowed enrollment of men and postmenopausal women of at least 18 years of age, with histologically and/or cytologically confirmed HR+/HER2− ABC that was locoregionally recurrent or metastatic and not amenable to curative therapy. Patients were required to have an Eastern Cooperative Oncology Group performance score of 0 or 1 and measurable disease according to RECIST version 1.1 or at least one predominantly lytic bone lesion.

Patients included those who had received no prior ET for advanced disease, up to one line of ET for advanced disease, or had relapsed during or within 12 months of completion of (neo)adjuvant ET. Patients who received prior chemotherapy in the advanced setting, any previous treatment with fulvestrant, or any prior CDK4/6 inhibitor were not enrolled. Patients who received first-line treatment included those who were newly diagnosed (*de novo*) with ABC, or who had relapsed >12 months from completion of (neo)adjuvant ET with no treatment for advanced or metastatic disease. Patients who received treatment in the second line or early relapse included those who experienced relapse on or within 12 months from completion of (neo)adjuvant ET with no treatment for advanced or metastatic disease (early relapse), relapse >12 months from completion of (neo)adjuvant ET with subsequent progression after one line of ET for advanced or metastatic disease, and finally those with advanced or metastatic breast cancer at diagnosis who progressed after one line of ET for advanced disease with no prior (neo) adjuvant treatment for early disease. Patients were not eligible if they could not receive ET as per investigator judgment or if they had clinically significant cardiac arrhythmias and/or uncontrolled heart disease.

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 investigators and Novartis representatives, supervised the study conduct. An independent data monitoring committee assessed the safety data.

Randomization and masking

Randomized numbers were generated by the interactive response technology provider using a validated system that automated random assignment of patients into treatment arms, which were in turn linked to medication numbers. A separate medication randomization list was produced using a validated system that automated the random assignment of numbers to medication packs. All patients—as well as investigators who administered treatment, assessed endpoints, and analyzed data—were blinded to the trial group assignments until the final OS analysis. Randomization was stratified according to the presence or absence of liver or lung metastases and previous ET in the advanced setting. Unblinding only occurred during the trial for safety reasons, for regulatory reporting purposes, and at the conclusion of the study. Crossover was not permitted until the final OS analysis was completed. Patients and investigators were unblinded after the final OS analysis, following which, patients still receiving study treatment in the placebo arm were given the option to switch to ribociclib.

Procedures

Patients received either oral ribociclib (600 mg/day on a 3-week-on, 1-week-off schedule) or matching placebo. Both groups received intramuscular fulvestrant (500 mg, day 1 of every 28-day cycle, with an additional dose on day 15 of cycle 1). Tumor response was assessed locally as per RECIST 1.1 at screening, every 8 weeks after randomization for 18 months, every 12 weeks until month 36, and then as clinically indicated until disease progression, death, withdrawal of consent, loss to follow-up, or subject/guardian decision; for patients who discontinued for any other reason, assessments continued as per protocol. Survival follow-up continued for patients who discontinued study treatment.

Adverse events 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.

Outcomes

The primary endpoint of investigator-assessed PFS and the secondary endpoint of OS were previously reported.[4,6] OS was a protocol-specified secondary endpoint and defined as the time from randomization to death from any cause.[6] PFS2, time to chemotherapy, and chemotherapy-free survival were additional exploratory endpoints that have been previously reported.[6] PFS2 was defined as the time from randomization to the first documented disease progression following discontinuation from study treatment while the patient was receiving next-line therapy (as reported by the investigator) or death from any cause, whichever occurred first. Time to chemotherapy was defined as the time from randomization to the beginning of the first subsequent chemotherapy following discontinuation of study treatment, and chemotherapy-free survival was defined as time to first chemotherapy or death.

To evaluate ribociclib pharmacokinetics (PK), plasma samples were collected at predose; 2, 4, and 6 h postdose at cycle 1 day 15 and cycle 2 day 15; and predose on cycle 2 day 1.

Statistical analysis

Statistical methods for the protocol-prespecified final analysis of PFS and OS were previously reported.[4,6] For the original analysis, an estimated total of 660 patients were needed for 95% power to detect an HR of 0.67 for the primary endpoint. The primary analysis of investigator-assessed PFS has been previously reported with the data cut-off date of 3 November 2017.[4] At the time of the final OS analysis (data cut-off date 3 June 2019), 153 patients were still receiving study treatment (121 of 484 in the ribociclib group and 32 of 242 in the placebo group).[6] The mOS was NR for the ribociclib arm at the time of the final OS analysis. In the current follow-up (data cut-off date 30 October 2020), sufficient events were reported in the ribociclib arm to provide a stable estimate of mOS.

In this exploratory analysis, mOS and OS rates were estimated using the Kaplan—Meier method. The HR for OS was estimated with the use of a stratified Cox proportional hazards model. Patients were censored at the date the patient was last known to be alive. Analyses were carried out on data from the following subgroups: patients receiving first-line therapy, patients receiving second-line therapy, including patients with early relapse [within 12 months after completion of (neo)adjuvant ET]. Additional subgroups of interest included the presence/absence of liver or lung metastases and response to prior ET. Endocrine resistance was defined as a relapse while on the first 2 years of (neo)adjuvant ET or progressive disease within the first 6 months of first-line ET for ABC while receiving ET. Endocrine naïve was defined as patients who did not receive any prior ET in any setting. Patients not described as ET resistant or ET naïve were deemed to be ET sensitive. In addition to the updates of OS results, exploratory analyses for PFS2, time to chemotherapy, chemotherapy-free survival, and PK were also carried out.

The rank-preserving structural-failure time (RPSFT) model was used as a sensitivity analysis on OS to assess the effects of crossover and administration of subsequent CDK4/6 inhibitors in the placebo group.[13]

Role of the funding source

The funder of the study, in conjunction with the authors and the study steering committee members, designed this study. Representatives of the trial sponsor carried out data collection and analysis. All authors reviewed and approved the data, contributed to the development and approval of the manuscript, and accepted the decision to submit the manuscript for publication.

RESULTS

Overall survival

From 18 June 2015 to 10 June 2016, a total of 726 patients were randomly assigned: 484 to the ribociclib group and 242 to the placebo group (Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2021.05.353). Previously published efficacy analyses included the baseline characteristics.[4] At the cut-off date for this exploratory OS analysis (30 October 2020), 68 (14.0%) of 484 patients in the ribociclib group and 21 (8.7%) of 242 patients in the placebo group were still receiving study treatment. Following the final OS analysis, two patients crossed over from placebo to ribociclib. At a median 56.3-month follow-up (minimum, 52.7 months), 222 (45.9%) of 484 patients receiving ribociclib and 142 (58.7%) of 242 patients receiving placebo had died. A significant OS benefit, with an mOS of 53.7 months (95% CI 46.9-NR months) in the ribociclib arm versus 41.5 months (95% CI 37.4-49.0 months) in the placebo arm (HR, 0.73; 95% CI 0.59-0.90), was observed (Figure 1A). Kaplan—Meier-estimated 4-year survival rates were 54% (95% CI 49% to 58%) and 45% (95% CI 38% to 51%) for ribociclib and placebo, respectively, while the 5-year survival rates were estimated to be 46%

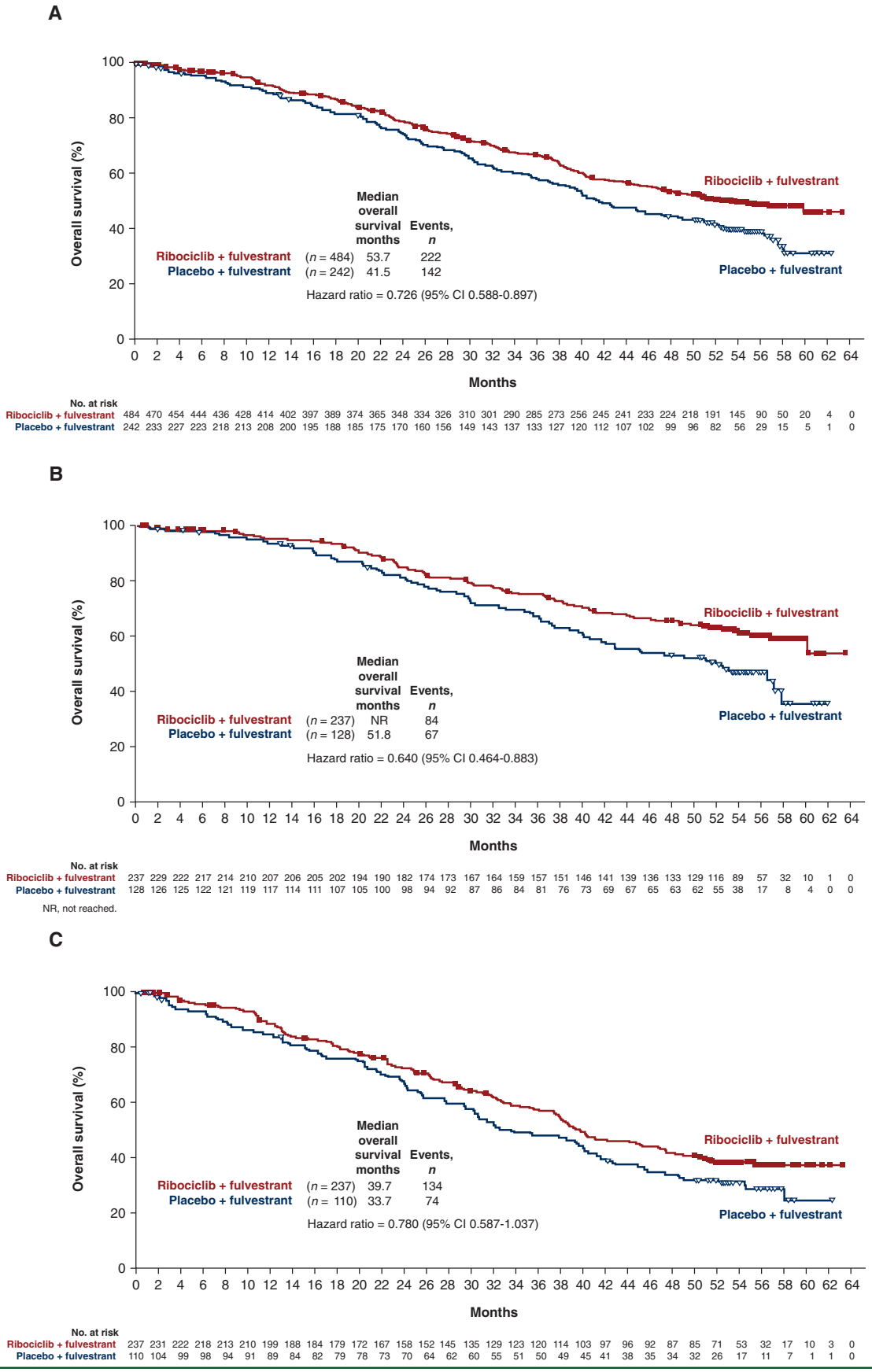

Figure 1. Overall survival.
(A) Overall survival in all patients. (B) Overall survival in patients receiving ribociclib plus fulvestrant as first-line therapy. (C) Overall survival in patients receiving ribociclib plus fulvestrant as second-line therapy.
CI, confidence interval; NR, not reached.

(95% CI 40% to 52%) and 31% (95% CI 23% to 40%), respectively.

Analysis of subgroups according to prior lines of ET was also carried out. Of the 365 patients who received study treatment as a first-line therapy, 84 (35.4%) of 237 patients in the ribociclib group and 67 (52.3%) of 128 patients in the placebo group died (Figure 1B). Patients in the first-line subgroup had an mOS of NR (95% CI 59.9-NR months) in the ribociclib group and 51.8 months (95% CI 40.4-57.6 months) in the placebo group (HR, 0.64; 95% CI 0.46-0.88). At 56 months (approximately the median follow-up time), the OS rate in the ribociclib group was 60.5%. In the first-line subgroup, the 4-year OS rates were estimated to be 66% (95% CI 59% to 72%) and 53% (95% CI 44% to 62%) in the ribociclib and placebo groups, respectively. The 5-year OS rates were estimated to be 54% (95% CI 41% to 65%) and 36% (95% CI 23% to 49%) in the ribociclib and placebo groups, respectively. Of the 347 patients who received study treatment as a second-line therapy, 134 (56.5%) of 237 patients in the ribociclib group and 74 (67.3%) of 110 patients in the placebo group died (Figure 1C). Patients in the second-line subgroup had an mOS of 39.7 months (95% CI 37.4-46.9 months) in the ribociclib group and 33.7 months (95% CI 27.8-41.3 months) in the placebo group (HR, 0.78; 95% CI 0.59-1.04). In the second-line subgroup, the 4-year OS rates were estimated to be 42% (95% CI 35% to 48%) and 34% (95% CI 25% to 43%) in the ribociclib and placebo groups, respectively, while the 5-year OS rates were estimated to be 37% (95% CI 31% to 44%) and 24% (95% CI 15% to 36%) in the ribociclib and placebo groups, respectively.

Of 364 patients with lung or liver metastases, 118 (48.8%) of 242 patients in the ribociclib group and 77 (63.1%) of 122 patients in the placebo group died (Figure 2). Patients with lung or liver metastases had an mOS of 46.9 months (95% CI 38.1-NR months) with ribociclib versus 39.4

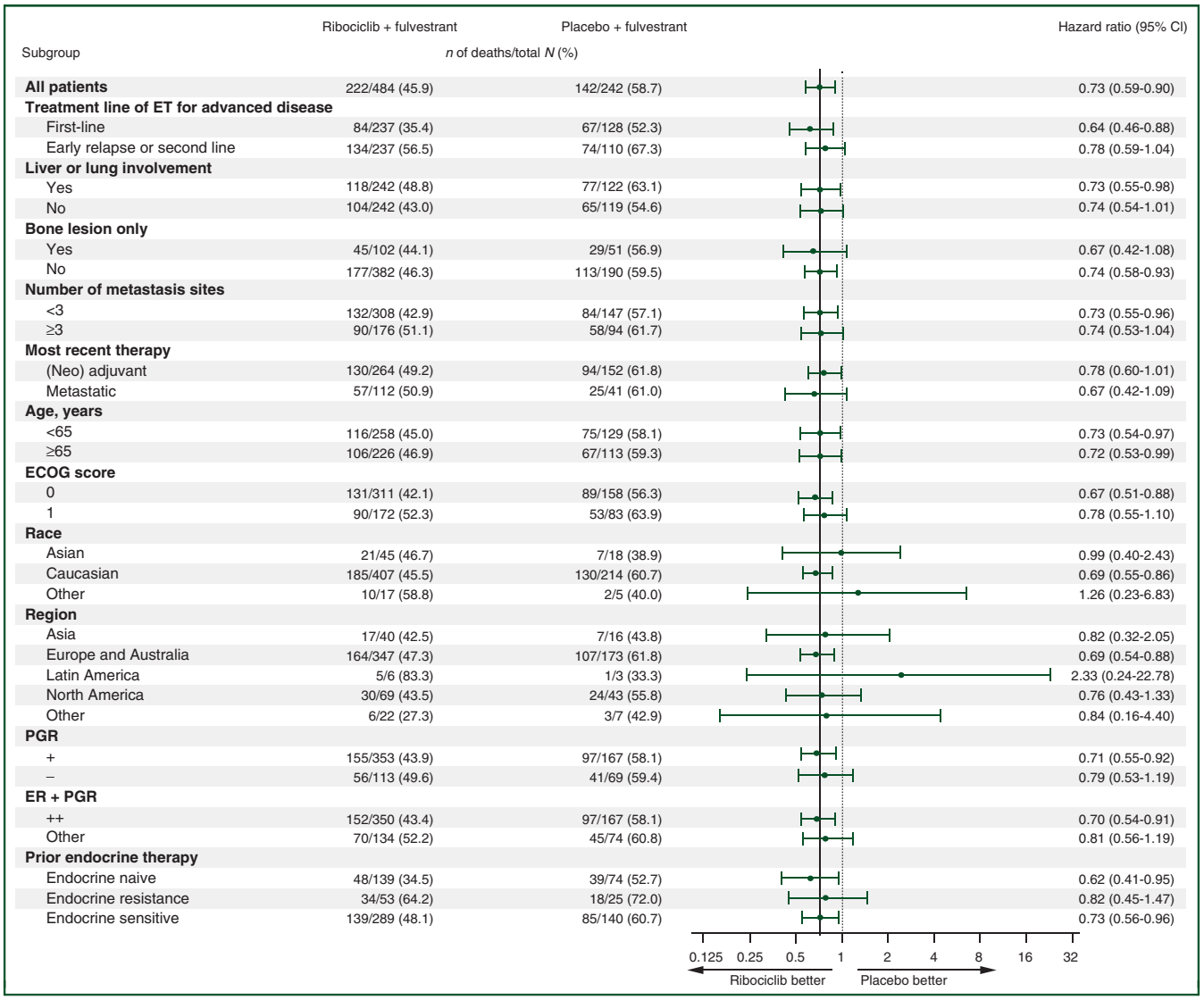

Figure 2. Exploratory analyses of overall survival in subgroups.
ER and PGR status ++ means that patients were positive for both ER and PGR.
CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; ER, estrogen receptor; ET, endocrine therapy; PGR, progesterone receptor.

months (95% CI 29.9-44.9 months) with placebo (HR, 0.73; 95% CI 0.55-0.98). Overall, 507 study patients had received prior ET (342 in the ribociclib group and 165 in the placebo group); 53 (15.5%) and 25 (15.2%) patients were endocrine resistant in the ribociclib and placebo groups, respectively, while 289 (84.5%) and 140 (84.8%) were endocrine sensitive. In the endocrine-resistant subgroup, the mOS was 35.6 months (95% CI 28.6-42.2 months) with ribociclib compared with 31.7 months (95% CI 13.0-41.5 months) with placebo. In the endocrine-sensitive subgroup, the mOS was 49.0 months (95% CI 40.7-NR months) with ribociclib and 41.8 months (95% CI 33.0-48.6 months) with placebo. Of the 213 patients who were ET naïve, 48 (34.5%) of 139 in the ribociclib group and 39 (52.7%) of 74 in the placebo group died (Supplementary Figure S1, available at https://doi.org/10.1016/j.annonc.2021.05.353). Patients in the ET naïve subgroup had an mOS of 59.9 months (95% CI 59.9-NR months) in the ribociclib group and 50.9 months (95% CI 37.4-NR months) in the placebo group (HR, 0.62; 95% CI 0.41-0.95). Results for OS analyses in other subgroups were generally consistent with the overall population.

Subsequent therapy

The percentage of patients reporting subsequent therapies after discontinuation of study treatment was comparable between study arms: 340 patients (81.9%) in the ribociclib group and 190 (86.4%) in the placebo group (Table 1). As reported in the final OS analysis, the most common first subsequent therapies were hormonal therapy alone (28% and 21%), chemotherapy alone (23% and 20%), and hormonal therapy plus targeted therapy/other (21% and 31%) for ribociclib and placebo, respectively. The use of CDK4/6 inhibitors any time after discontinuation of study treatment was lower in the ribociclib (14%) than in the placebo (30%) group.

Table 1. Subsequent antineoplastic therapies among patients who discontinued the trial regimen

Variable	Ribociclib + fulvestrant $n = 484$	Placebo + fulvestrant $n = 242$
Patients who discontinued the trial regimen, *n*	415	220
Patients who received any subsequent therapy, *n* (%)	340 (81.9)	190 (86.4)
First subsequent antineoplastic therapy		
Chemotherapy alone	96 (23.1)	44 (20.0)
Chemotherapy plus hormone therapy or other therapy[a]	36 (8.7)	29 (13.2)
Hormone therapy alone	115 (27.7)	47 (21.4)
Hormone therapy plus other therapy[b]	88 (21.2)	55 (18.0)
Targeted therapy alone	5 (1.2)	1 (0.5)
Patients who received any subsequent CDK4/6 inhibitor, *n* (%)	58 (14.0)	66 (30.0)
Palbociclib	36 (8.7)	52 (23.6)
Ribociclib	14 (3.4)	11 (5.0)
Abemaciclib	10 (2.4)	5 (2.3)

CDK4/6, cyclin-dependent kinases 4 and 6.
[a] This category includes patients who received chemotherapy in combination with any non-chemotherapy.
[b] This category includes patients who received hormone therapy plus another medication without chemotherapy.

Subsequent chemotherapy, alone or in combination, at any time after study treatment was received by 215 (44.4%) patients in the ribociclib group and 131 (54.1%) patients in the placebo group. The median time to chemotherapy (time from randomization to the beginning of the first subsequent chemotherapy following discontinuation of study treatment) was 48.1 months (95% CI 38.2-NR months) versus 28.8 months (95% CI 24.3-37.5 months) with ribociclib versus placebo (HR, 0.70; 95% CI 0.57-0.88), respectively (Figure 3A). The median chemotherapy-free survival (time to first chemotherapy or death) was 32.3 months (95% CI 28.1-38.5 months) in patients receiving ribociclib versus 22.4 months (95% CI 19.4-26.1 months) in patients receiving placebo (HR, 0.69; 95% CI 0.57-0.83) (Figure 3B).

Progression-free survival 2

Overall, 265 (54.8%) and 163 (67.4%) patients treated with ribociclib and placebo, respectively, had disease progression while receiving subsequent therapy or died of any cause (Figure 4A). The mPFS2 was 37.4 months (95% CI 31.1-42.6 months) in the ribociclib group and 28.1 months (95% CI 24.0-31.6 months) in the placebo group (HR, 0.7069; 95% CI 0.57-0.84). In the subgroup of patients who received study treatment as first-line therapy, 107 (45.1%) patients in the ribociclib group and 82 (64.1%) patients in the placebo group had disease progression while receiving subsequent therapy or died of any cause (Figure 4B). The mPFS2 was 53.7 versus 35.5 months with ribociclib and placebo, respectively (HR, 0.63; 95% CI 0.47-0.84). For patients who received study treatment in the second line, 153 (64.6%) patients treated with ribociclib and 80 (72.7%) patients treated with placebo had progression while receiving subsequent therapy or died of any cause. The mPFS2 in the ribociclib group was 26.0 months compared with 20.5 months in the placebo group (HR, 0.73; 95% CI 0.56-0.96) (Figure 4C).

Sixty-eight patients in the placebo group went on to receive ribociclib or another CDK4/6 inhibitor as a subsequent therapy after discontinuation, including 66 patients after discontinuing study treatment and 2 patients who crossed over from placebo to ribociclib (Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2021.05.353). A RPSFT model-based sensitivity analysis was used to account for this. After adjusting for the subsequent CDK4/6 inhibitor treatment, the mOS in the placebo group was estimated to be 40.4 months (95% CI 35.4-47.2 months) (HR, 0.70; 95% CI 0.55-0.88) compared with 41.5 months (95% CI 37.4-49.0 months) in the main analysis (HR, 0.73; 95% CI 0.59-0.90).

Safety

Adverse events were consistent with those previously reported in the primary PFS and final OS analyses[4,6] and were generally more common in patients treated with ribociclib (Supplementary Table S2, available at https://doi.org/10.

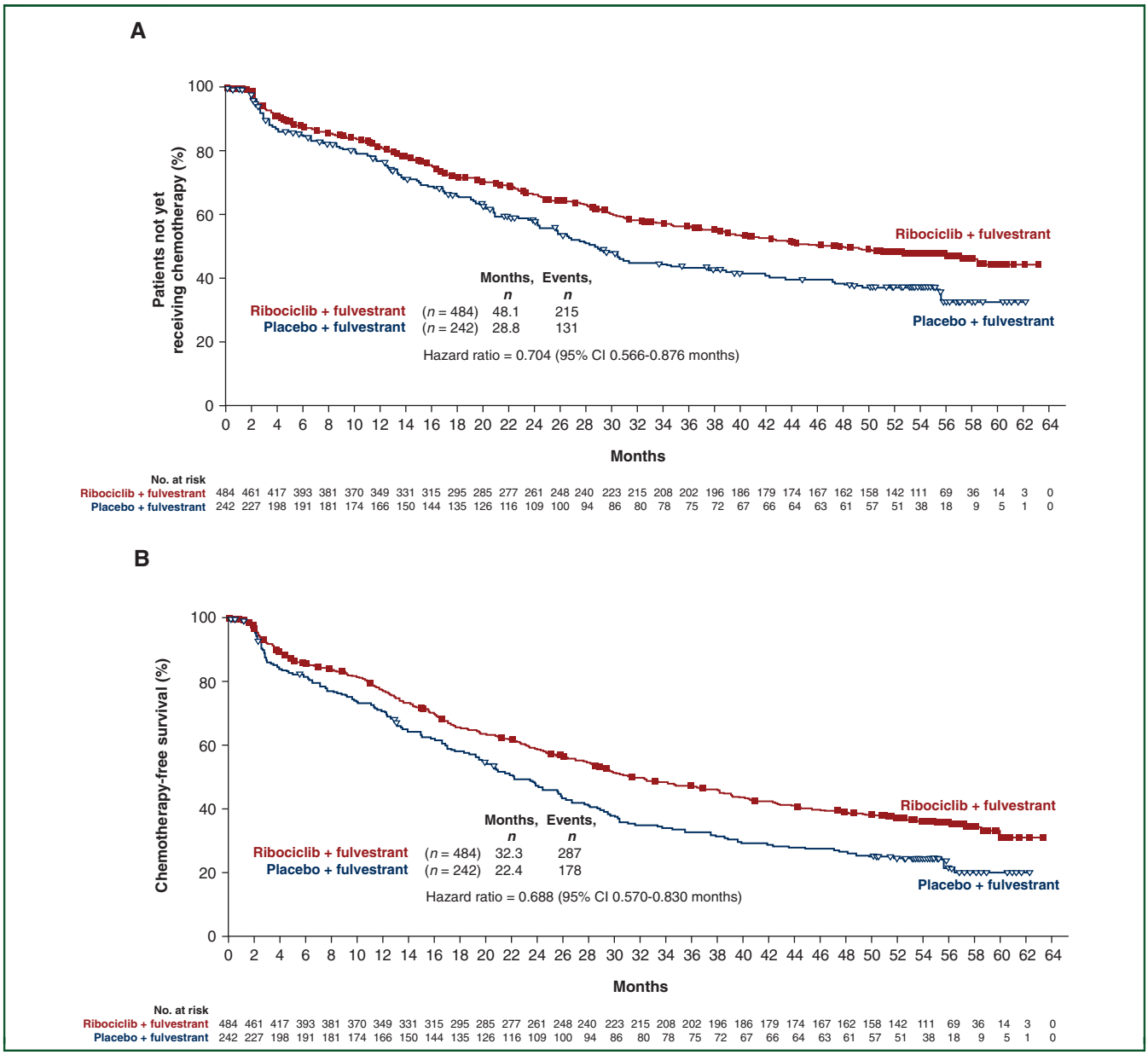

Figure 3. Time to first subsequent chemotherapy and chemotherapy-free survival.
(A) Time to first chemotherapy. (B) Chemotherapy-free survival.
CI, confidence interval.

1016/j.annonc.2021.05.353). Neutropenia (58.2%, ribociclib; 0.8%, placebo) was the most frequent grade 3 or 4 adverse event. Grade 3 or 4 adverse events of special interest included hepatobiliary toxicity (13.9%, ribociclib; 6.2%, placebo) and prolonged QT interval (3.1%, ribociclib; 1.2%, placebo).

Pharmacokinetics

In this study, the geometric mean trough plasma concentrations of ribociclib when combined with fulvestrant were largely consistent with the exposure of ribociclib as a single agent,[14] suggesting that fulvestrant had no effect on the PK of ribociclib (Supplementary Table S3, available at https://doi.org/10.1016/j.annonc.2021.05.353). There is no known drug–drug interaction (DDI) with fulvestrant or *in vivo* interaction with cytochrome *P*-450 3A4 (CYP3A4) substrates or modulators.[15] Ribociclib is unlikely to impact fulvestrant PK based on its metabolism and DDI data (a substrate and moderate-to-strong inhibitor of CYP3A4).[16,17]

DISCUSSION

This extended follow-up (median, 56.3 months) analysis of MONALEESA-3 is the longest reported follow-up for any CDK4/6 inhibitor clinical trial in a purely postmenopausal patient population and demonstrates a lasting benefit of OS with ribociclib plus fulvestrant versus fulvestrant alone in patients with HR+/HER2− ABC. This benefit was maintained when ribociclib was given in both the first and second lines and was maintained across most subgroups. In patients who received ribociclib either as a first-line therapy

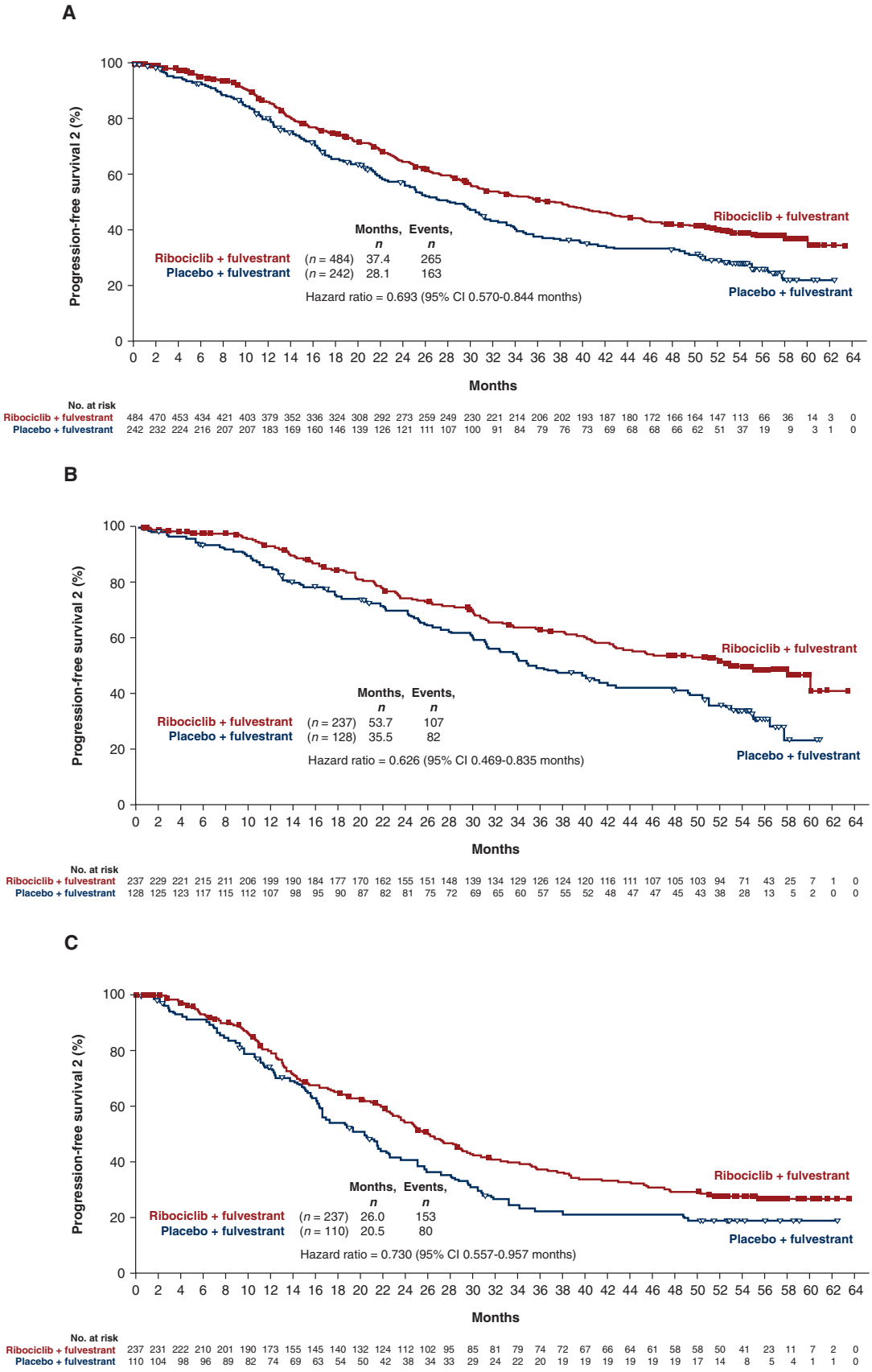

Figure 4. Progression-free survival 2.
(A) Progression-free survival 2 in all patients. (B) Progression-free survival 2 in patients receiving ribociclib plus fulvestrant as first-line therapy. (C) Progression-free survival 2 in patients receiving ribociclib plus fulvestrant as second-line therapy.
CI, confidence interval.

or as a second-line therapy, the OS benefit remained consistently strong from the final OS analysis throughout the duration of this follow-up.[6] Moreover, treatment with ribociclib had a positive effect on subsequent chemotherapy use, and the benefit of ribociclib during study treatment was maintained over subsequent lines of therapy. Furthermore, ribociclib treatment delayed the time until chemotherapy was required regardless of censoring for death, prolonging the time these patients were chemotherapy-free. Safety signals were consistent with those previously reported for MONALEESA-3,[4,6] and PK analyses indicated no apparent DDI between ribociclib and fulvestrant. These results strengthen the previously published final OS analysis of MONALEESA-3 and support a lasting effect of ribociclib treatment, including beyond study treatment.

Currently, almost all patients with ABC will receive a CDK4/6 inhibitor during the course of their disease. In MONALEESA-3, investigators and patients were unblinded following the final OS analysis, after which two patients in the placebo group crossed over to receive ribociclib by the data cut-off date (30 October 2020). Additionally, a greater percentage of patients in the placebo group (30.0%) compared with the ribociclib group (14.0%) went on to receive a CDK4/6 inhibitor as a subsequent therapy. Despite more patients in the placebo arm going on to receive a subsequent CDK4/6 inhibitor, the mOS in the ribociclib arm remained significantly longer than in the placebo arm. When adjusted for subsequent CDK4/6 inhibitor use, the OS benefit was maintained.

This OS analysis is an extended follow-up analysis (median, 56.3-month follow-up) for the MONALEESA-3 trial of ribociclib in combination with fulvestrant for treatment of HR+/HER2− ABC. The PALOMA-3 and MONARCH-2 trials for CDK4/6 inhibitors in combination with fulvestrant also reported OS benefits. PALOMA-3 described an mOS of 34.9 months in the palbociclib group versus 28.0 months in the placebo group at the 44.8-month follow-up point.[10] At a follow-up of 47.7 months, MONARCH-2 reported an mOS of 46.7 versus 37.3 months with abemaciclib and placebo, respectively.[8] With a median follow-up of 56.3 months, the current analysis of MONALEESA-3 reports the longest mOS in a clinical trial of a CDK4/6 inhibitor in combination with fulvestrant. However, cross-trial comparisons should be interpreted with caution due to differences in patient population characteristics, including prior treatment.[6,8,10]

These results complement the extended follow-up results of the MONALEESA-7 trial, which reported a 58.7-month mOS for pre-/perimenopausal women treated with ribociclib in combination with ET (nonsteroidal aromatase inhibitor or tamoxifen) in the first-line setting.[11] Similarly, MONALEESA-3 has continued to demonstrate a larger OS benefit with ribociclib versus placebo over this period of extended follow-up, in the first-line and also in the second-line subgroups. These results confirm the prolonged and consistent benefit of ribociclib for the treatment of HR+/HER2− ABC, regardless of the ET partner used in combination with ribociclib or the patient's menopausal status, and further strengthen the use of ribociclib in first-line as well as in second-line therapy.

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DATA SHARING

Novartis made the study protocols available for MONALEESA-3 at the time of primary publications. Individual participant data will not be made available.

REFERENCES

1. Hamilton E, Infante JR. Targeting CDK4/6 in patients with cancer. *Cancer Treat Rev*. 2016;45:129-138.
2. Fry DW, Harvey PJ, Keller PR, et al. Specific inhibition of cyclin-dependent kinase 4/6 by PD 0332991 and associated antitumor activity in human tumor xenografts. *Mol Cancer Ther*. 2004;3(11):1427-1438.
3. Finn RS, Dering J, Conklin D, et al. PD 0332991, a selective cyclin D kinase 4/6 inhibitor, preferentially inhibits proliferation of luminal estrogen receptor-positive human breast cancer cell lines in vitro. *Breast Cancer Res*. 2009;11(5):R77.
4. Slamon DJ, Neven P, Chia S, et al. Phase III randomized study of ribociclib and fulvestrant in hormone receptor-positive, human epidermal growth factor receptor 2-negative advanced breast cancer: MONALEESA-3. *J Clin Oncol*. 2018;36(24):2465-2472.
5. Hortobagyi GN, Stemmer SM, Burris HA, et al. Ribociclib as first-line therapy for HR-positive, advanced breast cancer. *N Engl J Med*. 2016;375(18):1738-1748.
6. Slamon DJ, Neven P, Chia S, et al. Overall survival with ribociclib plus fulvestrant in advanced breast cancer. *N Engl J Med*. 2020;382(6):514-524.
7. Im SA, Lu YS, Bardia A, et al. Overall survival with ribociclib plus endocrine therapy in breast cancer. *N Engl J Med*. 2019;381(4):307-316.
8. Sledge GW Jr, Toi M, Neven P, et al. The effect of abemaciclib plus fulvestrant on overall survival in hormone receptor-positive, ERBB2-negative breast cancer that progressed on endocrine therapy-MONARCH 2: a randomized clinical trial. *JAMA Oncol*. 2019;6(1):116-124.
9. Goetz MP, Toi M, Campone M, et al. MONARCH 3: abemaciclib as initial therapy for advanced breast cancer. *J Clin Oncol*. 2017;35(32):3638-3646.
10. Turner NC, Slamon DJ, Ro J, et al. Overall survival with palbociclib and fulvestrant in advanced breast cancer. *N Engl J Med*. 2018;379(20):1926-1936.
11. Tripathy D, Im S-A, Colleoni M, et al. Updated overall survival (OS) results from the phase III MONALEESA-7 trial of pre-or perimenopausal patients with HR+/HER2− advanced breast cancer (ABC) treated with endocrine therapy (ET) ± ribociclib. *SABCS*. 2020. Poster PD2-04.
12. National Cancer Institute Cancer Therapy Evaluation Program. Common Terminology Criteria for Adverse Events (CTCAE) v4.0. Available at http://Ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. Accessed June 1, 2021.
13. Robins JM, Tsiatis AA. Correcting for non-compliance in randomized trials using rank preserving structural failure time models. *Commun Stat Theory Methods*. 1991;20(8):2609-2631.
14. Infante JR, Cassier PA, Gerecitano JF, et al. A phase I study of the cyclin-dependent kinase 4/6 inhibitor ribociclib (LEE011) in patients with advanced solid tumors and lymphomas. *Clin Cancer Res*. 2016;22(23):5696-5705.
15. AstraZeneca. Faslodex (fulvestrant) prescribing information. Available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/021344s015lbl.pdf. Accessed June 1, 2021.
16. James AD, Schiller H, Marvalin C, et al. An integrated assessment of the ADME properties of the CDK4/6 inhibitor ribociclib utilizing preclinical in vitro, in vivo, and human ADME data. *Pharmacol Res Perspect*. 2020;8(3):e00599.
17. Samant TS, Huth F, Umehara K, et al. Ribociclib drug-drug interactions: clinical evaluations and physiologically-based pharmacokinetic modeling to guide drug labeling. *Clin Pharmacol Ther*. 2020;108(3):575-585.