Updated Overall Survival of Ribociclib plus Endocrine Therapy versus Endocrine Therapy Alone in Pre- and Perimenopausal Patients with HR$^+$/HER2$^-$ Advanced Breast Cancer in MONALEESA-7: A Phase III Randomized Clinical Trial

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ABSTRACT

Purpose: Ribociclib plus endocrine therapy (ET) demonstrated a statistically significant progression-free survival and overall survival (OS) benefit in the phase III MONALEESA-7 trial of pre-/perimenopausal patients with hormone receptor (HR)-positive (HR$^+$), HER2-negative (HER2$^-$) advanced breast cancer (ABC). The median OS was not reached in the ribociclib arm in the protocol-specified final analysis; we hence performed an exploratory OS and additional outcomes analysis with an extended follow-up (median, 53.5 months).

Patients and Methods: Patients were randomized to receive ET [goserelin plus nonsteroidal aromatase inhibitor (NSAI) or tamoxifen] with ribociclib or placebo. OS was evaluated with a stratified Cox proportional hazard model and summarized with Kaplan–Meier methods.

Results: The intent-to-treat population included 672 patients. Median OS was 58.7 months with ribociclib versus 48.0 months with placebo [hazard ratio = 0.76; 95% confidence interval (CI), 0.61–0.96]. Kaplan–Meier estimated OS at 48 months was 60% and 50% with ribociclib and placebo, respectively. Subgroup analyses were generally consistent with the OS benefit, including patients who received NSAI and patients aged less than 40 years. Subsequent antineoplastic therapies following discontinuation were balanced between the ribociclib (77%) and placebo (78%) groups. Use of cyclin-dependent kinase 4/6 inhibitors after discontinuation was higher with placebo (26%) versus ribociclib (13%). Time to first chemotherapy was significantly delayed with ribociclib versus placebo. No drug–drug interactions were observed between ribociclib and either NSAI.

Conclusions: Ribociclib plus ET continued to show significantly longer OS than ET alone in pre-/perimenopausal patients, including patients aged less than 40 years, with HR$^+$/HER2$^-$ ABC with 53.5 months of median follow-up (ClinicalTrials.gov, NCT02278120).

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Translational Relevance

Pre-/perimenopausal patients with hormone receptor–positive (HR^+)/HER2-negative ($HER2^-$) advanced breast cancer (ABC) typically have a poorer prognosis and are underrepresented in clinical trials. MONALEESA-7 is a phase III trial that studied ribociclib plus endocrine therapy (ET) versus placebo plus ET and was dedicated specifically to pre-/perimenopausal patients with $HR^+/HER2^-$ ABC. The final protocol-specified overall survival (OS) analysis of MONALEESA-7 demonstrated a statistically significant OS benefit with ribociclib; however, outcomes can change over time, requiring prolonged observation to account for this disease's long natural history. An exploratory OS analysis of MONALEESA-7 with an extended follow-up (median, 53.5 months) was conducted revealing a median OS of 58.7 months in the ribociclib group versus 48.0 months in the placebo group [hazard ratio = 0.76; 95% confidence interval (CI), 0.61–0.96] with no new safety signals observed. These results show that ribociclib plus ET continued to demonstrate OS benefit in pre-/perimenopausal patients for long term.

Introduction

The phase III MONALEESA-7 trial was the only trial to date of a cyclin-dependent kinase 4/6 (CDK4/6) inhibitor dedicated solely to pre- or perimenopausal women with hormone receptor–positive (HR^+), HER2-negative ($HER2^-$) advanced disease (1). MONALEESA-7 randomized patients who were naive to endocrine therapy (ET) in the advanced setting to ribociclib or placebo, both in combination with goserelin and a nonsteroidal aromatase inhibitor (NSAI) or tamoxifen. Ribociclib was associated with a significant improvement in progression-free survival (PFS; primary endpoint), with a median of 23.8 versus 13.0 months with placebo [hazard ratio = 0.55; 95% confidence interval (CI), 0.44–0.69; $P < 0.001$]. The safety profile was consistent with that reported for other ribociclib combinations in phase III trials (2–4).

Despite prior lack of success in achieving a significant improvement in overall survival (OS) in a first-line setting in $HR^+/HER2^-$ advanced breast cancer (ABC), results of the prespecified second interim analysis of the MONALEESA-7 trial demonstrated a significant improvement in OS for ribociclib plus ET versus placebo plus ET, with a median OS that was not reached versus 40.9 months (hazard ratio = 0.71; 95% CI, 0.54–0.95; ref. 5). The protocol-specified boundary was crossed, supporting superiority in OS of ribociclib over placebo, and per the statistical plan was considered to be final. The median duration of follow-up for that analysis was 34.6 months. Patients with $HR^+/HER2^-$ ABC have a long natural history and their outcomes may change over time; therefore, it is important to report long-term follow-up in this patient group.

Although ribociclib achieved the milestone of significantly improving OS in premenopausal patients, the Kaplan–Meier curves showed a late separation. Therefore, we undertook an exploratory analysis in the MONALEESA-7 trial of what we believe is the longest follow-up reported to date (median, 53.5 months) with a CDK4/6 inhibitor clinical trial focused exclusively on premenopausal patients with ABC. Clinically relevant subgroups were also evaluated, including patients less than 40 years of age; these patients tend to have a more aggressive disease course than patients aged ≥40 years (6). Additional new analyses were performed to evaluate intrinsic subtype distribution in patients less than 40 or ≥40 years of age, plasma estradiol concentration on cycle 3 day 15, and pharmacokinetics.

Patients and Methods

Study design and treatment

As reported previously (1), MONALEESA-7 was a randomized, double-blind, placebo-controlled, phase III trial that was conducted in 188 centers in 30 countries, and patients were randomized 1:1 to ribociclib (orally, 600 mg/day on 3-weeks-on, 1-week-off schedule) or matching placebo. Both groups received goserelin (subcutaneously 3.6 mg on day 1 of each 28-day cycle) and simultaneously also received either an NSAI (letrozole 2.5 mg or anastrozole 1 mg, both orally, daily) or tamoxifen (20 mg daily). Crossover was not permitted until the final OS analysis was completed. All patients and investigators who administered treatment, assessed outcomes, and analyzed data were unaware of the group assignments until unblinding occurred at the final analysis (5). Once unblinded, patients still receiving study treatment in the placebo arm were given an option to switch to ribociclib. Crossover treatment was optional and only done with the consent of the patient. Stratification factors for randomization included the presence or absence of liver or lung metastases, prior chemotherapy for advanced disease (yes or no), and ET partner (NSAI or tamoxifen; ref. 5).

Patients

MONALEESA-7 enrolled pre- or perimenopausal women 18 to 59 years of age with histologically or cytologically confirmed $HR^+/HER2^-$ ABC that was locoregionally recurrent and not amenable to curative therapy, or was metastatic; pre- or perimenopausal status was defined by the presence of menstrual cycles or premenopausal serum estradiol/follicle-stimulating hormone levels. Patients must have had an Eastern Cooperative Oncology Group performance status of 0 or 1 and measurable disease (according to RECIST version 1.1) or ≥1 predominantly lytic bone lesion (7). Patients may have received prior adjuvant or neoadjuvant ET, but no prior ET for advanced disease, with some exceptions for tamoxifen or aromatase inhibitors for ABC within 14 days prior to randomization. This includes patients who relapsed on or within 12 months after the end of adjuvant or neoadjuvant ET. Patients may have received up to one prior line of chemotherapy for advanced disease, but previous treatment with a CDK4/6 inhibitor was not allowed. Additional enrollment criteria were previously published (1). The CONSORT diagram is outlined in Supplementary Fig. S1.

MONALEESA-7 was conducted in accordance with provisions of the Declaration of Helsinki and Good Clinical Practice guidelines. The trial protocol and amendments were approved by an independent ethics committee or institutional review board at each site. The trial conduct was overseen by a steering committee of participating international investigators and representatives of the sponsor. An independent data monitoring committee assessed the safety data. All patients provided written informed consent prior to enrollment. The sponsor's representatives designed the trial, compiled the data, and vouch for the accuracy of the analyses.

Sample size, randomization, stratification, and blinding

Methods relating to sample size, randomization, stratification, and blinding were previously reported (1, 5). As previously described, sample sizes were calculated using East 6.3 software (1, 5). As outlined in prior reports, randomization numbers were generated to ensure that treatment assignment was unbiased and concealed from patients and

investigator staff (1, 5). A patient randomization list was produced by the Interactive Response Technology (IRT) provider using a validated system that automated the random assignment of patient numbers to random arms, which were in turn linked to medication numbers (1, 5). As previously described, a separate medication randomization list was produced by or under the responsibility of Novartis Drug Supply Management using a validated system that automated the random assignment of medication numbers to medication packs containing each of the study treatments (1, 5).

As previously described, prior to dosing, patients fulfilling the enrollment criteria were randomized via IRT (1, 5). The investigator or his/her delegate would call or log on to the IRT and confirm that the patient fulfilled all criteria. The IRT assigned a randomization number to the patient, which was used to link the patient to the treatment arm and specified a unique medication number for the first package of the study treatment to be dispensed. The randomization number was not communicated to the caller.

Study allocation, losses, and exclusions

Six hundred and seventy-two patients were enrolled in MONALEESA-7 and randomized 1:1, with 335 patients assigned to the ribociclib group and 337 patients assigned to the placebo group. Of those, 87 patients in the ribociclib arm and 90 patients in the placebo arm received tamoxifen plus goserelin, and 248 patients in the ribociclib arm and 247 patients in the placebo arm received NSAI plus goserelin. All patients in MONALEESA-7 received at least one component of study treatment.

Important protocol amendments

The MONALEESA-7 protocol for ECG assessments was amended first to include assessments on cycle 3 day 1; then, a second amendment included triplicate 12-lead ECGs for all assessments to maintain consistency across clinical trials of ribociclib.

Endpoints

The primary endpoint, investigator-assessed PFS, and key secondary endpoint, OS, were previously reported (1, 5). OS was defined as time from randomization to death from any cause. The time to first subsequent chemotherapy was defined as time from randomization to the beginning of the first chemotherapy after discontinuation of the trial regimen, censoring for death. Chemotherapy-free survival was analyzed from randomization to initiation of first chemotherapy or death. PFS2 was defined as time from randomization to first documented disease progression (physician reported) while the patient was receiving second-line antineoplastic therapy or death from any cause, whichever occurred first. Adverse events were graded according to the NCI Common Terminology Criteria for Adverse Events, version 4.03 (CTCAE; RRID:SCR_010296). Estradiol concentration was measured at baseline and cycle 3 day 15 in patients who received an NSAI with a minimum detectable limit of 0.5 pg/mL. Pharmacokinetic data in plasma evaluated maximal concentration (C_{max}), time to reach C_{max} (T_{max}), area under the concentration curve (AUC), and trough concentration before the next dose (C_{trough}).

Statistical analyses

The statistical methods for the primary and protocol-specified final analysis of OS were previously reported (1, 5). At the time of the final analysis of OS, 173 patients were still receiving trial treatment (116 of 335 in the ribociclib group and 57 of 337 in the placebo group), and the median duration of follow-up was 34.6 months (1, 5). The prespecified Lan-DeMets (O'Brien–Fleming) efficacy stopping boundary of $P = 0.01018$ to claim superior efficacy of ribociclib was crossed at the interim analysis ($P = 0.00973$), and the results were considered final per the protocol.

In this exploratory analysis, median OS was estimated using Kaplan–Meier methods, and hazard ratios were estimated using both stratified and unstratified Cox proportional hazards models. Patients were censored at the date the patient was last known to be alive.

The rank-preserving structural-failure time (RPSFT) model was used as a sensitivity analysis to assess the effect of crossover and subsequent administration of CDK4/6 inhibitors in the placebo arm (8).

Data availability statement

The data generated in this study are available within the article and its supplementary data files.

Results

Patients

In total, 335 and 337 patients were randomly assigned to ribociclib and placebo, respectively, between December 17, 2014, and August 1, 2016 (Supplementary Table S1). Details regarding patient screening and the population included in prior efficacy analyses were previously published (1). At the data cut-off (June 29, 2020) for this exploratory analysis, 102 patients were still receiving study treatment, 71 (21%) with ribociclib and 31 (9%) with placebo. The median duration of follow-up was 53.5 months (minimum, 46.9 months). Following the final protocol-specified OS analysis, 15 patients crossed over from placebo to ribociclib.

OS

At the time of data cut-off, 141 patients (42%) receiving ribociclib and 167 patients (50%) receiving placebo had died. The median OS was 58.7 versus 48.0 months in the ribociclib versus placebo arm (hazard ratio = 0.76; 95% CI, 0.61–0.96; **Fig. 1A**). Survival rates at 4 years were 60% versus 50% and at 54 months were 53% versus 44%.

Similar to the final OS analysis, subgroups defined by the ET partner were also assessed. Of the patients receiving an NSAI, 107 of 248 (43%) in the ribociclib arm and 120 of 247 (49%) in the placebo arm died. Median OS was 58.7 versus 47.7 months in the ribociclib versus placebo arms (hazard ratio = 0.80; 95% CI, 0.62–1.04; **Fig. 1B**). Of the patients receiving tamoxifen, 34 of 87 (39%) in the ribociclib group and 47 of 90 (52%) of the placebo group died. Median OS was not estimable versus 49.3 months for ribociclib versus placebo (hazard ratio = 0.71; 95% CI, 0.45–1.10; **Fig. 1C**).

Exploratory subgroups similar to those previously presented were also assessed for OS (**Fig. 2**). In patients with *de novo* disease [no prior (neo)adjuvant ET and no prior ET for ABC except the short period permitted by the protocol; includes patients with/without prior (neo) adjuvant chemotherapy or chemotherapy for ABC], the median OS was not reached versus 49.6 months with ribociclib versus placebo (hazard ratio = 0.53; 95% CI, 0.36–0.79). In patients less than 40 years of age, the median OS was 51.3 versus 40.5 months for ribociclib versus placebo (hazard ratio = 0.65; 95% CI, 0.43–0.98). In patients ≥40 years of age, the median OS was 58.8 versus 51.7 months for ribociclib versus placebo (hazard ratio = 0.81; 95% CI, 0.62–1.07; Supplementary Fig. S2). The intrinsic subtype distribution in patients less than 40 years of age was: luminal A, 34.6%; luminal B, 33.3%; HER2-enriched (HER2E), 24.4%; and basal-like, 7.7%. In patients ≥40 years of age, subtype distribution was: luminal A, 52.4%; luminal B, 28.1%; HER2E, 15.1%; and basal-like, 4.3%. Patients who received prior chemotherapy in the advanced setting (each arm, 14%) had a median OS of 47.2

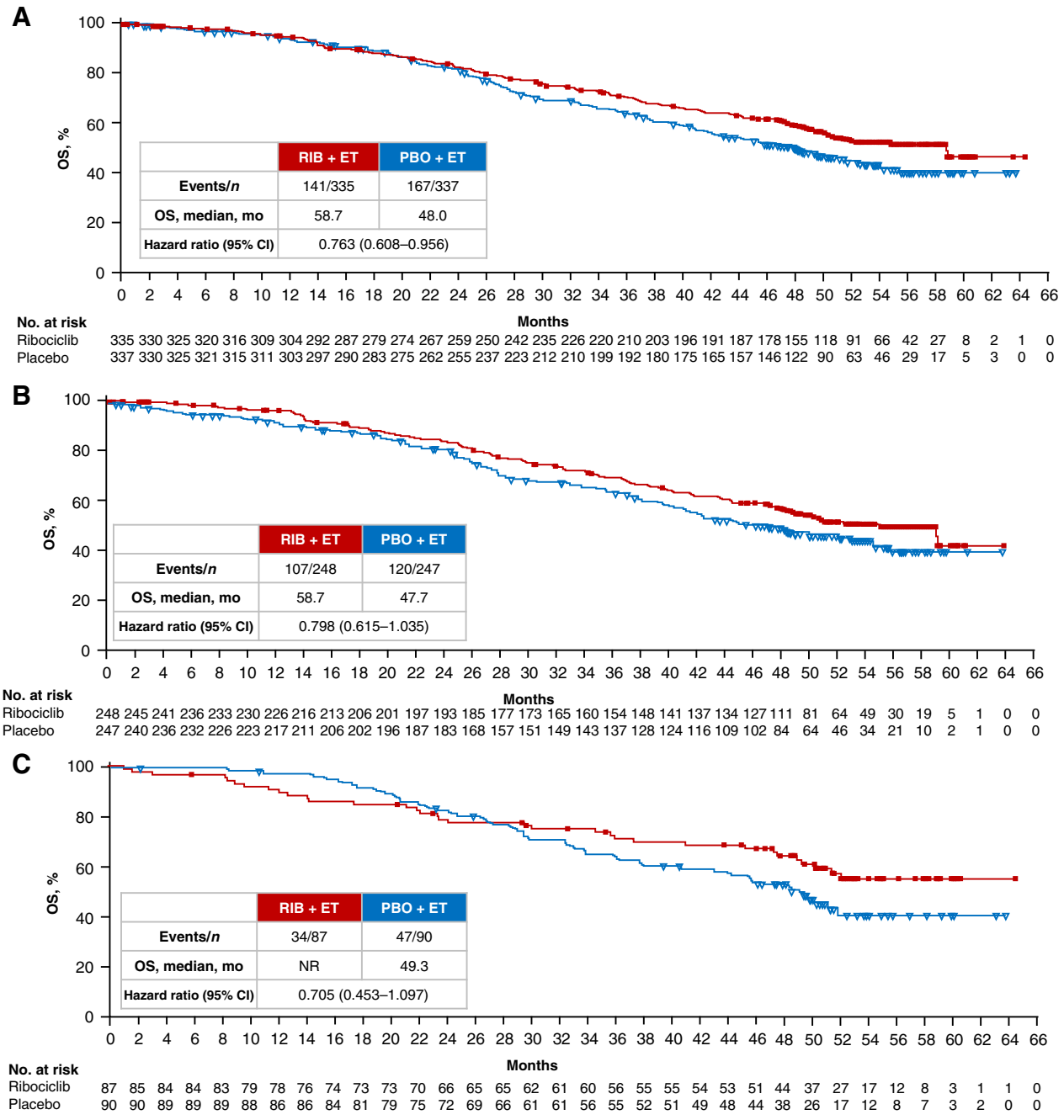

Figure 1.

OS. **A,** All patients. **B,** Patients who received an NSAI. **C,** Patients who received tamoxifen. mo, months; PBO, placebo; RIB, ribociclib.

versus 39.0 months (hazard ratio = 0.75; 95% CI, 0.44–1.27). These subgroups have a generally consistent OS benefit compared with the overall population; however, these data should be interpreted with caution due to the small sample size and related wide confidence intervals.

Overall, 95 patients receiving placebo switched over to other CDK4/6 inhibitors via cross-over or as subsequent therapies post discontinuation (including 15 patients who crossed over and 80 who received subsequent CDK4/6 inhibitors at any line after discontinuing study treatment). The sensitivity analysis using the RPSFT model to account for this gives a median OS in the placebo arm of 46.1 months (hazard ratio = 0.74; 95% CI, 0.57–0.95) compared with 48.0 months in the main analysis.

Subsequent therapy

Discontinuations of ribociclib and placebo occurred in 264 (79%) and 306 (91%) patients, respectively. Reasons for discontinuation are outlined in Supplementary Table S1. Similar percentages of patients

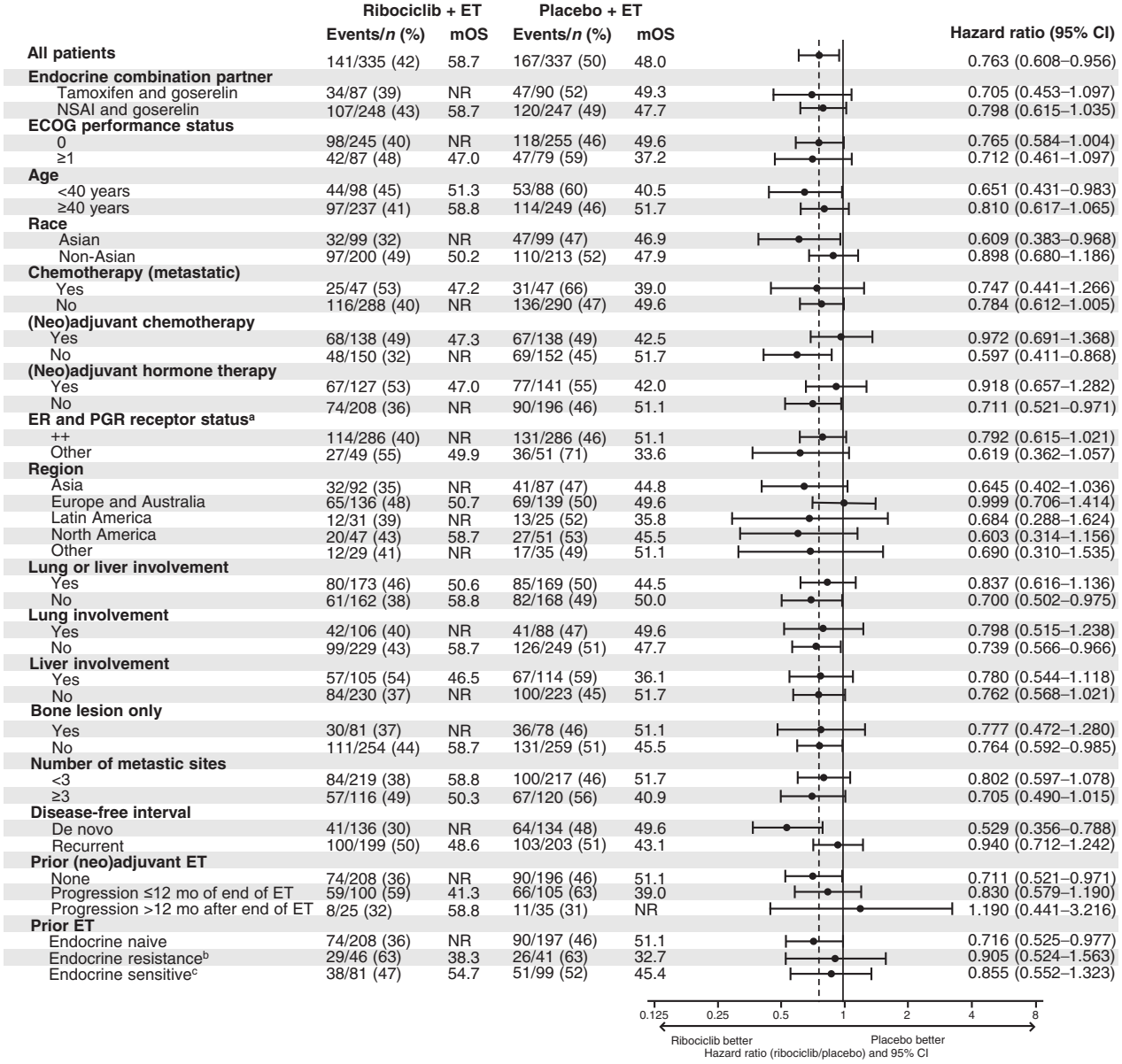

Figure 2.

Exploratory analyses of OS in subgroups. ECOG, Eastern Cooperative Oncology Group; ER, estrogen receptor; mOS, median overall survival; NR, not reached; PGR, progesterone receptor; mo, months. [a]ER and PGR receptor status $^{++}$ means that patients were positive for both estrogen and progesterone receptors. [b]Patients who relapsed within the first 2 years of (neo)adjuvant ET. [c]Patients who received prior ET and did not experience relapse within the first 2 years of (neo)adjuvant ET.

received a subsequent antineoplastic therapy: 204 patients (77%) in the ribociclib group and 239 patients (78%) in the placebo group (**Table 1**). Similar to the final OS analysis, the most common first subsequent therapies were chemotherapy alone (ribociclib, 22%; placebo, 28%) and hormonal therapy alone (ribociclib, 28%; placebo, 18%). The most common first subsequent chemotherapies following progression were capecitabine (ribociclib, 40%; placebo, 41%) and paclitaxel (28% in each arm). The use of CDK4/6 inhibitors following discontinuation of study treatment was lower with ribociclib (13%) versus placebo (26%; **Table 1**).

Chemotherapy was received as a subsequent therapy at any time after the trial regimen was completed in 144 patients (43%) in the ribociclib group and 173 patients (51%) in the placebo group. The median time to first chemotherapy was 50.9 versus 36.8 months for ribociclib versus placebo (hazard ratio = 0.69; 95% CI, 0.56–0.87; **Fig. 3A**). Receipt of chemotherapy or death occurred in 190 (57%) and 236 (70%) patients in the ribociclib and placebo groups, respectively. The median chemotherapy-free survival was 42.4 versus 26.4 months for ribociclib versus placebo (hazard ratio = 0.67; 95% CI, 0.55–0.81; **Fig. 3B**).

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

Variable	Ribociclib group *n* = 335	Placebo group *n* = 337
No. of patients who discontinued the trial regimen	264	306
Patients who received any subsequent therapy, *n* (%)	204 (77.3)	239 (78.1)
First subsequent antineoplastic therapy		
Chemotherapy alone	59 (22.3)	87 (28.4)
Chemotherapy plus hormone therapy or other therapy[a]	27 (10.2)	31 (10.1)
Hormone therapy alone	73 (27.7)	56 (18.3)
Hormone therapy plus other therapy[b]	40 (15.2)	55 (18.0)
Other	5 (1.9)	10 (3.3)
Patients who received any subsequent CDK4/6 inhibitor, *n* (%)[c]	34 (12.9)	80 (26.1)
Palbociclib	25 (9.5)	67 (21.9)
Ribociclib	6 (2.3)	12 (3.9)
Abemaciclib	4 (1.5)	2 (0.7)

[a]This category includes patients who received chemotherapy in combination with any nonchemotherapy.
[b]This category includes patients who received hormone therapy plus another medication without chemotherapy; for example, this includes patients who received a subsequent PI3K inhibitor in combination with fulvestrant (one in the ribociclib arm).
[c]One patient from the ribociclib arm and one patient from the placebo arm received more than one of the CDK4/6 inhibitor therapies.

The duration of the first subsequent antineoplastic therapy following discontinuation of study treatment was similar overall in the ribociclib and placebo arms (7.5 vs. 9.0 months; Supplementary Fig. S3). Differences in duration of first subsequent therapy according to the subgroup of treatment types should be interpreted with caution because they are limited by potentially unbalanced patient characteristics and small sample size, especially in the CDK4/6 inhibitors and everolimus subgroups.

PFS2

Overall, 177 (53%) and 221 (66%) patients treated with ribociclib and placebo, respectively, had disease progression while receiving a subsequent therapy or died from any cause. The median PFS2 was 44.2 months versus 31.0 months in the ribociclib versus placebo arms (hazard ratio = 0.68; 95% CI, 0.56–0.83; **Fig. 4**). The PFS2 benefit was generally consistent within subgroup analyses (Supplementary Table S2).

Safety

Adverse events in both arms were consistent with those reported in the primary and final OS analyses, suggesting that there is no added toxicity associated with longer exposure (Supplementary Table S3). Similar to the final OS analysis, grade 3 or 4 adverse events of special interest were neutropenia (ribociclib, 65%; placebo, 6%), hepatobiliary toxicity (ribociclib, 12%; placebo, 7%), and prolonged QT interval (ribociclib, 2%; placebo, 1%).

Estradiol plasma concentration

At cycle 3 day 15, the mean percentage decrease in plasma estradiol concentration compared with baseline was similar in both groups (ribociclib, 89%; placebo, 85%). At this time point, 86 of 90 (96%) patients receiving ribociclib and 72 of 78 (92%) receiving placebo had estradiol below the minimum detectable limit (0.5 pg/mL), indicating a high degree of estradiol suppression.

Pharmacokinetics

There was similar exposure for letrozole and anastrozole among the treatment groups, suggesting no effect of ribociclib on the exposure of NSAIs (Supplementary Table S4). Steady-state exposure of ribociclib at 600 mg in combination with an NSAI was largely consistent with its exposure as a single agent (600 mg; ref. 9), suggesting no apparent effect of NSAIs on ribociclib pharmacokinetics (Supplementary Table S4). Tamoxifen exposure was approximately 2 times greater with ribociclib versus placebo; ribociclib exposure in combination with tamoxifen was lower than in combination with an NSAI or as a single agent (9).

Discussion

In this analysis of MONALEESA-7 with extended follow-up (53.5 months), ribociclib plus ET showed a persistent, significantly longer OS than ET alone (58.7 vs. 48.0 months), with an improvement in OS of 10.7 months in patients with $HR^+/HER2^-$ ABC. These results show a 24% reduction in the relative risk of death and were consistent with the final OS analysis (5). In most patient subgroups, this benefit was similarly maintained. Additionally, treatment with ribociclib delayed the time to chemotherapy and PFS2. These results indicate that the benefit of ribociclib extends beyond the first-line period in this patient population. No new safety signals were reported, and pharmacokinetic results showed no apparent drug–drug interaction between ribociclib and an NSAI partner.

Following the final OS analysis, patients and investigators were unblinded to the treatment assignment, and 15 patients in the placebo arm crossed over to the ribociclib arm. Additionally, 26% versus 13% of patients in the placebo versus ribociclib group received a subsequent CDK4/6 inhibitor following discontinuation of the study, a difference that could confound interpretation of OS results. Despite these two considerations, the OS benefit of first-line ribociclib was still significant. Additionally, in the sensitivity analysis using an RPSFT model taking into account placebo patients receiving a subsequent CDK4/6 inhibitor, the hazard ratio was 0.74 (95% CI, 0.57–0.95), indicating a 26% reduction in the relative risk of death, an increase to the 24% in the intent-to-treat population.

At the time of the final OS analysis, MONALEESA-7 was the first trial of a CDK4/6 inhibitor to demonstrate a statistically significant OS benefit (5). Since then, the MONALEESA-3 and MONARCH 2 trials have also demonstrated a statistically significant improvement in OS (10, 11). MONALEESA-3 evaluated ribociclib plus fulvestrant versus fulvestrant alone in the first- and second-line setting in postmenopausal women, while MONARCH 2 evaluated abemaciclib plus fulvestrant or fulvestrant alone in the second-line setting in pre- and postmenopausal women. The key differences between MONALEESA-7 and these two trials include endocrine partner, menopausal status (only 17% of patients enrolled in MONARCH 2 were premenopausal), allowing for prior chemotherapy in the advanced setting (14% of patients in each arm of MONALEESA-7 had prior chemotherapy in the advanced setting; the other two trials did not enroll such patients), and line of therapy (MONALEESA-3 enrolled 50% of patients in the first-line setting). In MONALEESA-3, the first-line subgroup included patients with *de novo* disease and patients with late relapse [relapse more than 12 months from completion of (neo)adjuvant ET with no treatment for ABC) whereas

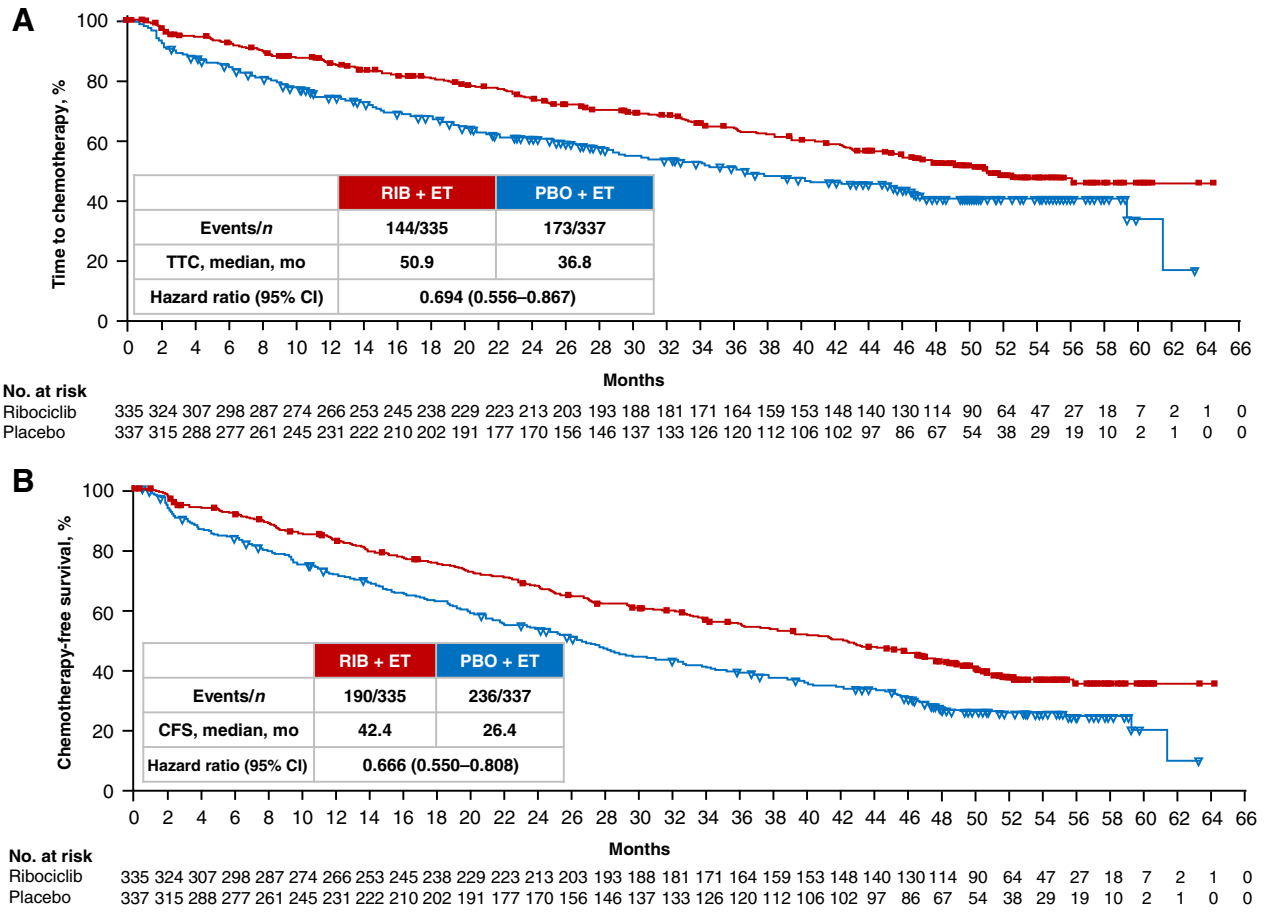

Figure 3.

Time to first subsequent chemotherapy and chemotherapy-free survival. **A,** Time to first subsequent chemotherapy. **B,** Chemotherapy-free survival. CFS, chemotherapy-free survival; mo, months; PBO, placebo; RIB, ribociclib; TTC, time to chemotherapy.

MONARCH 2 did not include either of these patient populations. MONARCH 2 did not include patients with late relapse in the study and patients in the *de novo* cohort have thus far not been included in OS analyses. Of note, OS benefit was observed for ribociclib plus ET versus ET alone in patients that had received prior chemotherapy in the advanced setting in MONALEESA-7 (hazard ratio = 0.75; 95% CI, 0.44–1.27). Although ribociclib and abemaciclib have both demonstrated a significant OS benefit in different patient populations, integrating pharmacokinetic data and *in vitro* selectivity for CDK4 versus CDK6 inhibition has revealed differences among the CDK4/6 inhibitors,

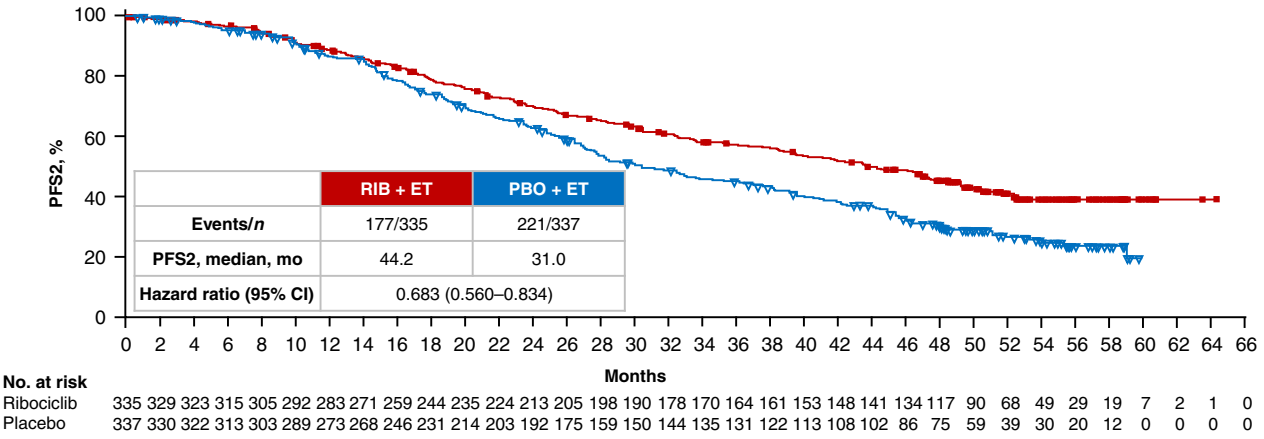

Figure 4.

PFS2, progression-free survival following receipt of subsequent therapy. mo, months; PBO, placebo.

suggesting that ribociclib may show preferential inhibition of CDK4 versus CDK6 *in vivo* at clinically relevant concentrations (11, 12).

Younger women with HR^+ ABC have a worse prognosis than older women and tend to be underrepresented in clinical trials. Specifically, women aged less than 40 years are more likely to have poorer clinical outcomes, including increased risk of recurrence and decreased survival rates (11). In the subgroup analysis of OS, patients less than 40 years in the placebo arm had one of the shortest median OSs reported in this study. However, the relative OS benefit for ribociclib over placebo was greater in patients less than 40 years of age than those ≥40 years of age; the addition of ribociclib in patients less than 40 years of age demonstrated a significant OS benefit, with a 51.3-month median OS in these patients versus 40.5 months in the placebo arm (hazard ratio = 0.65). This represents a 35% reduction in the risk of death in this patient population, which has a significant unmet need. Similar benefits for younger patients were also observed with respect to PFS, as shown in an updated analysis of previously reported results (13). In the ribociclib versus placebo arms, the median PFS was 29.7 versus 10.8 months in patients less than 40 years of age (hazard ratio = 0.47; 95% CI, 0.33–0.68) and 26.4 versus 15.6 months in patients ≥40 years of age (hazard ratio = 0.66; 95% CI, 0.53–0.82; Supplementary Fig. S4). Compared with patients ≥40 years of age, patients less than 40 years of age had an increased frequency of the luminal B subtype and the HER2E subtype, which has been associated with resistance to ET and is reported to be a biomarker of poor prognosis (14, 15). A prior pooled analysis of the MONALEESA-2, -3, and -7 trials showed that treatment with ribociclib had a consistent PFS benefit in all intrinsic subtypes except for basal-like (although the sample size in the basal-like subgroup was small). A particularly pronounced benefit was observed in patients with the HER2E subtype (16). Therefore, even though this study has shown that patient subtypes may differ in patients ≥40 or less than 40 years of age, treatment with ribociclib demonstrates a survival benefit regardless of age or subtype.

In addition to survival, reducing impact on quality of life is important when making clinical decisions. This includes delaying chemotherapy as long as is feasible in patients with $HR^+/HER2^-$ ABC. Longer follow-up of patients receiving ribociclib continues to demonstrate a significant delay in the time to first chemotherapy. This analysis showed a significant delay in chemotherapy with ribociclib, with a 14.1-month difference when censoring for death and a 16.0-month difference without censoring. It was also previously reported that the premenopausal patients in MONALEESA-7 in the ribociclib arm had improved quality of life compared with the patients in the placebo arm (17).

At a median follow-up of 53.5 months for OS, the longest reported for any CDK4/6 inhibitor trial focused exclusively on premenopausal patients with ABC, ribociclib continued to demonstrate a clinically significant OS benefit of 10.7 months over ET alone with a hazard ratio of 0.76 that was consistent with the prior OS analyses. Given a median OS of approximately 3 years for patients with ABC estimated from registry data, the almost 1-year (10.7 months—corresponding to a 22% increase in survival over the MONALEESA-7 placebo arm) improvement in OS observed here is meaningful (18, 19). The 58.7-month median OS in the ribociclib arm reported in $HR^+/HER2^-$ ABC is the longest of any ABC phase III trial for premenopausal disease, regardless of subtype. These data confirm the benefit and continued use of ribociclib in the first-line setting for pre- and perimenopausal patients with $HR^+/HER2^-$ ABC.

Authors' Disclosures

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