

ORIGINAL ARTICLE



Overall Survival with Ribociclib plus Letrozole in Advanced Breast Cancer

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Abstract

BACKGROUND

In a previous analysis of this phase 3 trial, first-line ribociclib plus letrozole resulted in significantly longer progression-free survival than letrozole alone among postmenopausal patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced breast cancer. Whether overall survival would also be longer with ribociclib was not known.

METHODS

Here we report the results of the protocol-specified final analysis of overall survival, a key secondary end point. Patients were randomly assigned in a 1:1 ratio to receive either ribociclib or placebo in combination with letrozole. Overall survival was assessed with the use of a stratified log-rank test and summarized with the use of Kaplan–Meier methods after 400 deaths had occurred. A hierarchical testing strategy was used for the analysis of progression-free survival and overall survival to ensure the validity of the findings.

RESEARCH SUMMARY

Overall Survival with Ribociclib plus Letrozole in Advanced Breast Cancer



RESULTS

After a median follow-up of 6.6 years, 181 deaths had occurred among 334 patients (54.2%) in the ribociclib group and 219 among 334 (65.6%) in the placebo group. Ribociclib plus letrozole showed a significant overall survival benefit as compared with placebo plus letrozole. Median overall survival was 63.9 months (95% confidence interval [CI], 52.4 to 71.0) with ribociclib plus letrozole and 51.4 months (95% CI, 47.2 to 59.7) with placebo plus letrozole (hazard ratio for death, 0.76; 95% CI, 0.63 to 0.93; two-sided P=0.008). No new safety signals were observed.

CONCLUSIONS

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First-line therapy with ribociclib plus letrozole showed a significant overall survival benefit as compared with placebo plus letrozole in patients with HR-positive, HER2-negative advanced breast cancer. Median overall survival was more

than 12 months longer with ribociclib than with placebo. (Funded by Novartis; MONALEESA-2 ClinicalTrials.gov number, [NCT01958021](#).)



QUICK TAKE

Ribociclib plus Letrozole for Advanced Breast Cancer

1m 35s

Hormone receptor (HR)–positive, human epidermal growth factor receptor 2 (HER2)–negative disease is the most common subtype of metastatic breast cancer and remains incurable.^{1,2} Cyclin-dependent kinases 4 and 6 (CDK4/6) play a key function in regulating cell-cycle progression and have a known role in promoting growth in cancer.³ Increased expression of CDK4 has been shown to drive resistance to endocrine therapy in patients with HR-positive breast cancer.⁴⁻⁷ Preclinically, ribociclib has been shown to inhibit CDK4 preferentially and has also shown high drug concentrations at clinically relevant doses.⁸ The use of CDK4/6 inhibitors (ribociclib, abemaciclib, and palbociclib) improved progression-free survival in this patient population, leading to regulatory approvals.⁹⁻¹³

Significant improvement in overall survival is one of the primary goals in the treatment of advanced breast cancer, in addition to maintaining or improving quality of life. However, evaluating overall survival among patients receiving first-line therapy is challenging owing to increasing survival after progression in this patient population. To date, two trials evaluating ribociclib that included some patients receiving first-line therapy showed a significant overall survival benefit.¹⁴⁻¹⁶ Among premenopausal patients who had not received previous endocrine therapy for advanced disease but may have received up to one line of chemotherapy for advanced disease in the MONALEESA-7 (Mammary Oncology Assessment of LEE011's [Ribociclib's] Efficacy and Safety-7) trial, overall survival was significantly longer with ribociclib plus endocrine therapy than with endocrine therapy alone.¹⁴ In addition, the MONALEESA-3 trial showed significantly longer overall survival among postmenopausal patients with first- and second-line ribociclib plus fulvestrant than with fulvestrant alone.¹⁵ The MONARCH 3 trial investigating first-line abemaciclib and the PALOMA-2 (Palbociclib: Ongoing Trials in the Management of Breast Cancer-2) trial investigating first-line palbociclib, both involving postmenopausal patients with HR-positive, HER2-negative advanced breast cancer, have yet to report final data on overall survival.

The MONALEESA-2 trial is a phase 3 trial evaluating the efficacy and safety of ribociclib in combination with letrozole as the first line of any treatment in postmenopausal patients with HR-positive, HER2-negative advanced breast cancer. In the primary and updated analyses of MONALEESA-2, progression-free survival was significantly longer with ribociclib plus letrozole than with placebo plus letrozole (median in updated analysis, 25.3 months vs. 16.0 months; hazard ratio for disease progression or death, 0.57; 95% confidence interval [CI], 0.46 to 0.70; $P < 0.001$).^{10,17} Data for overall survival were immature at the time of the primary and updated analyses. Here we report findings from the protocol-specified final analysis of overall survival, a key secondary end point.

Methods

TRIAL DESIGN AND PATIENTS

We have described the design of the MONALEESA-2 trial in previous publications.^{10,17} Patients were randomly assigned in a 1:1 ratio to receive either ribociclib (600 mg per day, administered orally once daily for 21 consecutive days, followed by 7 days off, for a complete cycle of 28 days) or a matching placebo. Patients in both groups received letrozole (2.5 mg per day on a continuous schedule). Crossover between the two groups was not allowed until the final analysis of overall survival was completed.

Eligible patients included postmenopausal women with locally confirmed, HR-positive, HER2-negative recurrent or metastatic breast cancer who had not received previous systemic therapy for advanced disease. Patients were required to have an Eastern Cooperative Oncology Group performance-status score of 0 or 1 (on a 5-point scale in which higher scores indicate greater disability) and adequate bone marrow and organ function, along with measurable disease (according to Response Evaluation Criteria in Solid Tumors, version 1.1) or at least one predominantly lytic bone lesion.

Patients who had received previous systemic endocrine therapy or chemotherapy for advanced disease; neoadjuvant or adjuvant endocrine therapy were eligible. Endocrine therapy with a nonsteroidal aromatase inhibitor was not permitted unless the interval between the completion of treatment and randomization was greater than 12 months.

Randomization was stratified according to the presence or absence of liver or lung metastases. All the investigators who administered ribociclib or placebo, analyzed data, and assessed outcomes, as well as all the patients, were unaware of the trial-group assignments.

END POINTS

The results for the primary end point, investigator-assessed progression-free survival, were reported previously.^{10,17} Overall survival, defined as the time from randomization to death from any cause, was the protocol-specified key secondary end point. The time to first subsequent chemotherapy was defined as the time from randomization to the start of the first chemotherapy after discontinuation of the trial regimen, with censoring for death. Chemotherapy-free survival (time to first subsequent chemotherapy or death) was defined as the time from randomization to the beginning of the first chemotherapy after discontinuation of the trial regimen or death from any cause, whichever occurred first. Subsequent antineoplastic therapies after discontinuation of the trial regimen were also evaluated and summarized.

TRIAL OVERSIGHT

This trial was conducted in accordance with the provisions of the Declaration of Helsinki and Good Clinical Practice guidelines and was funded by Novartis. The trial [protocol](#) and all amendments (available with the full text of this article at NEJM.org) were approved by the institutional review board at each site or by an independent ethics committee. The conduct of the trial was overseen by a trial steering committee made up of participating international investigators as well as representatives of the sponsor. An independent data monitoring committee assessed safety data. Before enrollment, all the patients provided written informed consent. Representatives of the sponsor were responsible for the trial design, data compilation, and confirmation of the accuracy of analyses. All the authors had access to the data and vouch for the completeness and accuracy of the data and for the fidelity of the trial to the protocol. All the authors participated in the writing and review of all manuscript drafts and contributed to the interpretation of the data. Two professional medical writers provided editorial support and were paid by the sponsor.

STATISTICAL ANALYSIS

The number of patients required for this trial was determined on the basis of the primary end point of investigator-assessed progression-free survival. Overall survival was to be tested under a five-look group sequential design only if progression-free survival results reached statistical significance according to the prespecified conditions in the protocol. The progression-free survival analysis was conducted at a data cutoff date of January 29, 2016, after 243 patients had disease progression or had died, and the results reached statistical significance. A hierarchical testing strategy between progression-free survival and overall survival was used to control the familywise type I error rate at 2.5% and supported the validity of the findings. We calculated that 400 deaths would be required for the trial to have 90.2% power to reject the null hypothesis of no difference in overall survival between the trial groups in favor of superior efficacy of ribociclib plus letrozole as compared with placebo plus letrozole (if the true hazard ratio was 0.72, under an alternative hypothesis), at a one-sided overall significance level of 2.5% with a one-sided stratified log-rank test with a Lan–DeMets (O’Brien–Fleming) boundary for the P value. A two-sided version of the P value is reported.

The Kaplan–Meier method was used to estimate median overall survival, and a stratified Cox proportional-hazards model was used to estimate the hazard ratio and 95% confidence interval for death in the analysis of overall survival. Data for patients not known to have died by the date of analysis cutoff were censored on the date that the patient was last known to be alive for the overall survival analysis. In addition to the overall survival analysis, exploratory analyses of the time to first chemotherapy and chemotherapy-free survival were also performed. The rank-preserving structural failure time (RPSFT) model was used in a sensitivity analysis of overall survival to assess the effects of subsequent administration of CDK4/6 inhibitors in the placebo group after discontinuation of the trial regimen.¹⁸

Results

PATIENTS AND TREATMENT

From January 24, 2014, to March 24, 2015, a total of 668 patients were randomly assigned to the ribociclib group (334 patients) or the placebo group (334 patients) (Table S1 and Fig. S1 in the [Supplementary Appendix](#), available at NEJM.org). Four patients assigned to the placebo group did not receive placebo plus letrozole as assigned.

Epidemiologic data explicitly for patients with HR-positive, HER2-negative metastatic breast cancer are quite limited; however, the patients in this trial were representative of patients with breast cancer overall with respect to sex and age (Table S2). Owing to high enrollment rates, 95.5% of patients were White. Unfortunately, only 2.5% of women in the trial were Black, and 1.5% were Hispanic or Latino. The trial did not represent in our trial. At the data cutoff date for this final analysis of overall survival, 30 of 334 patients (9.0%) in the ribociclib group and 17 of 334 patients (5.1%) in the placebo group were still receiving ribociclib plus letrozole or placebo plus letrozole as assigned.

Among all patients, the median duration of follow-up (randomization to data cutoff) was 80 months (minimum, 75 months). The median duration of exposure to trial treatment in the ribociclib group was 20.2 months (interquartile range, 7.4 to 45.1), which is 7 months longer than it was at the time of the primary analysis of progression-free survival.¹⁰ The median duration of exposure to placebo was 14.1 months (interquartile range, 7.1 to 28.9).

OVERALL SURVIVAL

The data cutoff date for overall survival was June 10, 2021. The final analysis of overall survival was performed after 400 deaths had occurred: 181 among 334 patients (54.2%) in the ribociclib group and 219 among 334 patients (65.6%) in the placebo group. Death during the treatment period occurred in 8 of 334 patients in the ribociclib group (in 2 from breast cancer, in 2 from respiratory failure, in 1 from pneumonia, and in 3 from other causes) and in 3 of 330 patients in the placebo group (in 2 from breast cancer and in 1 from subdural hematoma).

A significant overall survival benefit was observed, with a median overall survival of 63.9 months (95% CI, 52.4 to 71.0) in the ribociclib group and 51.4 months (95% CI, 47.2 to 59.7) in the placebo group (hazard ratio for death, 0.76; 95% CI, 0.63 to 0.93; two-sided $P=0.008$) (Figure 1). The Kaplan–Meier estimate of overall survival at 60 months was 52.3% (95% CI, 46.5 to 57.7) in the ribociclib group and 43.9% (95% CI, 38.3 to 49.4) in the placebo group and at 72 months was 44.2% (95% CI, 38.5 to 49.8) and 32.0% (95% CI, 26.8 to 37.3), respectively (Table 1).

An analysis of overall survival was also performed in exploratory patient subgroups defined by patient and disease characteristics, geographic region, previous therapies, and metastatic sites (Figure 2). The overall survival benefit with ribociclib in these subgroups was consistent with the results in the overall population; however, the small number of patients in some subgroups resulted in wide confidence intervals.

SUBSEQUENT THERAPY

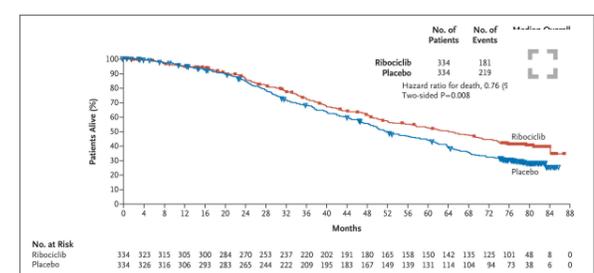
Among the patients who discontinued the trial regimen, subsequent antineoplastic therapies were received by 267 of 304 patients (87.8%) in the ribociclib group and 286 of 317 patients (90.2%) in the placebo group (Table 2 and S3). Endocrine therapy alone was the most common subsequent antineoplastic therapy and was received by 32.9% of the patients in the ribociclib group and by 29.0% of those in the placebo group. Subsequent use of CDK4/6 inhibitors, including palbociclib, abemaciclib, and ribociclib, in any line of therapy occurred in fewer patients in the ribociclib group (66 of 304 patients [21.7%]) than in the placebo group (109 of 317 patients [34.4%]) (Table 2). An RPSFT sensitivity analysis was used to account for this. After adjustment for the subsequent treatment with a CDK4/6 inhibitor, the median overall survival in the placebo group was estimated to be 50.5 months (95% CI, 45.0 to 55.4), as compared with 51.4 months (95% CI, 47.2 to 59.7) in the main analysis (hazard ratio for death, 0.73; 95% CI, 0.58 to 0.92).

In the intention-to-treat population, chemotherapy alone or in combination was received as the first subsequent therapy by 179 of 621 patients (28.8%) who discontinued the trial regimen (85 of 304 patients [28.0%] in the ribociclib group and 94 of 317 patients [29.7%] in the placebo group). The median time to first subsequent chemotherapy was 50.6 months in the ribociclib group and 38.9 months in the placebo group (hazard ratio for receipt of first chemotherapy, 0.74; 95% CI, 0.61 to 0.91) (Fig. S3). Chemotherapy use or death before chemotherapy was reported in 229 of 334 patients (68.6%) in the ribociclib group and 258 of 334 patients (77.2%) in the placebo group. The median chemotherapy-free survival was 39.9 months in the ribociclib group and 30.1 months in the placebo group (hazard ratio for receipt of first subsequent chemotherapy or death, 0.74; 95% CI, 0.62 to 0.89) (Fig. S2).

SAFETY

Adverse-event profiles in both groups were consistent with those previously reported results (Table S1). The most common grade 3 or 4 adverse event of special interest was neutropenia, occurring in 63.8% of patients who received ribociclib and in 1.2% of those who received

FIGURE 1



Overall Survival.

TABLE 1

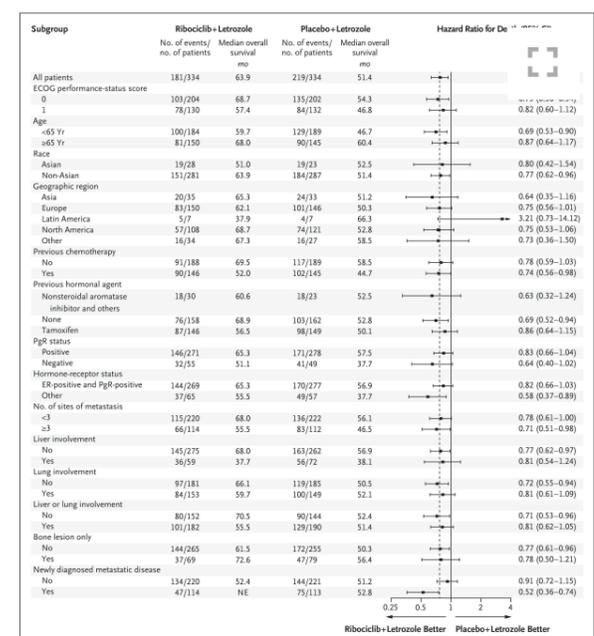
Table 1. Overall Survival and Kaplan–Meier Estimates.			
Variable	Ribociclib + Letrozole (N=334)	Placebo (N=334)	
Death—no. (%) ^a	181 (54.2)	219 (65.6)	
Data censored [†]	153 (45.8)	115 (34.4)	
Median overall survival (95% CI)—mo	63.9 (52.4–71.0)	51.4 (47.2–59.7)	
Kaplan–Meier estimated overall survival (95% CI)—%			
At 48 mo	60.9 (55.2–66.1)	55.2 (49.5–60.5)	
At 60 mo	52.3 (46.5–57.7)	43.9 (38.3–49.4)	
At 72 mo	44.2 (38.5–49.8)	32.0 (26.8–37.3)	

^a The hazard ratio for death was 0.76 (95% CI, 0.63 to 0.93), as calculated with the use of a stratified Cox proportional-hazards model. A two-sided P value of 0.008 was calculated with a stratified log-rank test.

[†] Data for patients were censored on the date that the patient was last known to be alive.

Overall Survival and Kaplan–Meier Estimates.

FIGURE 2



Exploratory Analysis of Overall Survival in

TABLE 2

placebo. Additional key grade 3 or 4 adverse events of special interest in the ribociclib and placebo groups were hepatobiliary toxic effects (14.4% and 4.8%, respectively) and prolonged QT interval (4.5% and 2.1%, respectively). Grade 3 interstitial lung disease or pneumonitis occurred in 2 patients (0.6%) in the ribociclib group and 0 patients in the placebo group. No grade 4 adverse events or deaths related to interstitial lung disease or pneumonitis occurred in the ribociclib group.

Variable	Ribociclib + Letrozole (N=334)	Placebo (N=317)
Discontinuation of the trial regimen — no. (%)	304 (91.0)	317 (94.9)
Receipt of first subsequent antineoplastic therapy — no./total no. (%)†	267/304 (87.8)	286/317 (90.2)
Endocrine therapy alone	100/304 (32.9)	92/317 (29.0)
Endocrine therapy plus other therapy‡	74/304 (24.3)	94/317 (29.7)
Chemotherapy alone	53/304 (17.4)	61/317 (19.2)
Chemotherapy plus endocrine therapy or other therapy§	32/304 (10.5)	33/317 (10.4)
Targeted therapy alone	6/304 (2.0)	2/317 (0.6)
Targeted therapy plus other therapy	1/304 (0.3)	0/317
Immunotherapy alone	1/304 (0.3)	1/317 (0.3)
Other	0/304	3/317 (0.9)
Receipt of any subsequent CDK4/6 inhibitor — no./total no. (%)†	66/304 (21.7)	109/317 (34.4)
Palbociclib	49/304 (16.1)	100/317 (31.5)
Ribociclib	14/304 (4.6)	6/317 (1.9)
Abemaciclib	8/304 (2.6)	12/317 (3.8)

* CDK4/6 denotes cyclin-dependent kinases 4 and 6.
† The percentages reported are based on the number of patients who discontinued the trial regimen. A patient with multiple occurrences is counted only once in the total row.
‡ Included are patients who received endocrine therapy in combination with another medication without chemotherapy.
§ Included are patients who received chemotherapy in combination with any nonchemotherapy agents.

Subsequent Antineoplastic Therapies.

Discussion

In our trial, the addition of ribociclib significantly prolonged overall survival as compared with letrozole alone when given to postmenopausal patients with HR-positive, HER2-negative advanced breast cancer exclusively as first-line therapy, with a risk of death that was 24% lower than that with placebo. The Kaplan–Meier analysis shows that the overall survival benefit of ribociclib began to emerge at approximately 20 months and continued to increase with longer follow-up, as indicated by survival at 5 years and 6 years. The overall survival benefit of ribociclib was generally consistent across patient subgroups. After a median of 20.2 months of treatment exposure in the ribociclib group, no new safety signals were revealed. This trial has a long follow-up (median, 80 months).^{19–23}

Post-treatment observations provide additional insights into these results, particularly in a trial with such extended follow-up (>6.5 years). Subsequent CDK4/6 inhibitor use is especially important in understanding survival results. Although subsequent use of CDK4/6 inhibitors in any line of therapy was more frequent in the placebo group than in the ribociclib group (34.4% vs. 21.7%), the ribociclib group had a significant overall survival benefit. In addition, the overall survival benefit was further increased on adjustment for subsequent use of CDK4/6 inhibitors. These findings underscore the substantial benefit of ribociclib as up-front therapy in patients with advanced breast cancer.

Other trials also investigating CDK4/6 inhibitors as first-line therapy in postmenopausal patients (PALOMA-2 and MONARCH 3) have yet to report final overall survival. The MONALEESA-2 trial provides evidence of a significant improvement in overall survival with a nonsteroidal aromatase inhibitor plus a CDK4/6 inhibitor in postmenopausal women, as well as impressive median survival to date (63.9 months) among women with HR-positive, HER2-negative advanced breast cancer.^{16,20,22–29} This survival of more than 5 years in the ribociclib group supports the introduction of ribociclib as first-line therapy for postmenopausal patients with HR-positive, HER2-negative advanced breast cancer.

Previously, the MONALEESA-7, MONALEESA-3, and MONARCH 2 trials have shown a significant overall survival benefit with the addition of a CDK4/6 inhibitor (either ribociclib or abemaciclib) in broad groups of patients with HR-positive, HER2-negative advanced breast cancer.^{14–16} These trials showed a 29%, 28%, and 24% lower risk of death, respectively. The PALOMA-3 trial showed a 19% lower risk of death, which was not considered to be significant.³⁰

This analysis of the MONALEESA-2 trial showed a significant and clinically meaningful difference in overall survival of 12.5 months with first-line ribociclib plus letrozole as compared with placebo plus letrozole in postmenopausal patients with advanced HR-positive, HER2-negative breast cancer, with a 24% relative reduction in the risk of death. Taken together, the MONALEESA trials of ribociclib have shown a consistent overall survival benefit regardless of accompanying endocrine therapy, line of therapy, or menopausal status.

NOTES

A [data sharing statement](#) provided by the authors is available with the full text of this article at NEJM.org.

Supported by Novartis.

[Disclosure forms](#) provided by the authors are available with the full text of this article at NEJM.org.

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SUPPLEMENTARY MATERIAL

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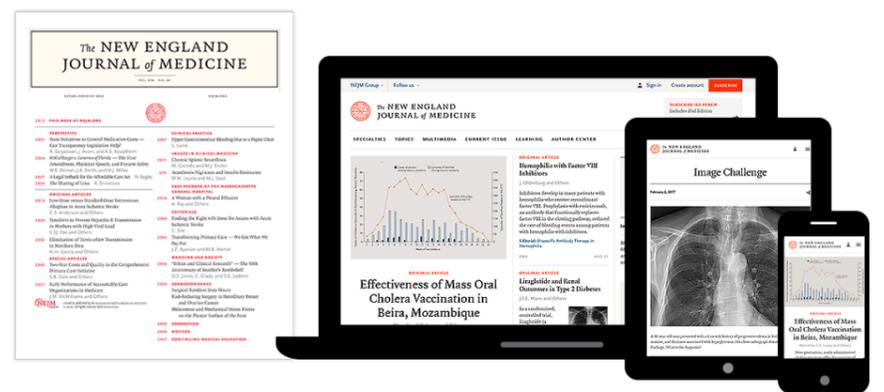
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