ORIGINAL ARTICLE

Ribociclib as First-Line Therapy for HR-Positive, Advanced Breast Cancer

G.N. Hortobagyi, S.M. Stemmer, H.A. Burris, Y.-S. Yap, G.S. Sonke, S. Paluch-Shimon, M. Campone, K.L. Blackwell, F. André, E.P. Winer, W. Janni, S. Verma, P. Conte, C.L. Arteaga, D.A. Cameron, K. Petrakova, L.L. Hart, C. Villanueva, A. Chan, E. Jakobsen, A. Nusch, O. Burdaeva, E.-M. Grischke, E. Alba, E. Wist, N. Marschner, A.M. Favret, D. Yardley, T. Bachelot, L.-M. Tseng, S. Blau, F. Xuan, F. Souami, M. Miller, C. Germa, S. Hirawat, and J. O'Shaughnessy

ABSTRACT

BACKGROUND

The inhibition of cyclin-dependent kinases 4 and 6 (CDK4/6) could potentially overcome or delay resistance to endocrine therapy in advanced breast cancer that is positive for hormone receptor (HR) and negative for human epidermal growth factor receptor 2 (HER2).

METHODS

In this randomized, placebo-controlled, phase 3 trial, we evaluated the efficacy and safety of the selective CDK4/6 inhibitor ribociclib combined with letrozole for first-line treatment in 668 postmenopausal women with HR-positive, HER2-negative recurrent or metastatic breast cancer who had not received previous systemic therapy for advanced disease. We randomly assigned the patients to receive either ribociclib (600 mg per day on a 3-weeks-on, 1-week-off schedule) plus letrozole (2.5 mg per day) or placebo plus letrozole. The primary end point was investigator-assessed progression-free survival. Secondary end points included overall survival, overall response rate, and safety. A preplanned interim analysis was performed on January 29, 2016, after 243 patients had disease progression or died. Prespecified criteria for superiority required a hazard ratio of 0.56 or less with $P<1.29\times10^{-5}$.

RESULTS

The duration of progression-free survival was significantly longer in the ribociclib group than in the placebo group (hazard ratio, 0.56; 95% CI, 0.43 to 0.72; $P=3.29\times10^{-6}$ for superiority). The median duration of follow-up was 15.3 months. After 18 months, the progression-free survival rate was 63.0% (95% confidence interval [CI], 54.6 to 70.3) in the ribociclib group and 42.2% (95% CI, 34.8 to 49.5) in the placebo group. In patients with measurable disease at baseline, the overall response rate was 52.7% and 37.1%, respectively (P<0.001). Common grade 3 or 4 adverse events that were reported in more than 10% of the patients in either group were neutropenia (59.3% in the ribociclib group vs. 0.9% in the placebo group) and leukopenia (21.0% vs. 0.6%); the rates of discontinuation because of adverse events were 7.5% and 2.1%, respectively.

CONCLUSIONS

Among patients receiving initial systemic treatment for HR-positive, HER2-negative advanced breast cancer, the duration of progression-free survival was significantly longer among those receiving ribociclib plus letrozole than among those receiving placebo plus letrozole, with a higher rate of myelosuppression in the ribociclib group. (Funded by Novartis Pharmaceuticals; ClinicalTrials.gov number, NCT01958021.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Hortobagyi at the Department of Breast Medical Oncology, Division of Cancer Medicine, University of Texas M.D. Anderson Cancer Center, 1515 Holcombe Blvd., Houston, TX 77030, or at ghortoba@mdanderson.org.

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Up to 75% of breast cancers express the estrogen receptor or progesterone receptor (hormone-receptor [HR]–positive).[1,2] Endocrine therapy is the standard of care for postmenopausal women with advanced breast cancer that is HR-positive and human epidermal growth factor receptor 2 (HER2)–negative, with aromatase inhibitors being the preferred first-line treatment option.[3,4] However, in the majority of patients, resistance to currently available options eventually develops, which requires the administration of sequential therapy with alternative endocrine regimens.[4-8] Thus, the identification of effective treatment options that prolong or restore sensitivity to endocrine therapies is important.

Cyclin-dependent kinases 4 and 6 (CDK4/6) in conjunction with their protein regulator, cyclin D1 (encoded by *CCND1*), a direct transcriptional target of estrogen-receptor signaling, regulate cell-cycle progression.[9] CDK4/6 overexpression and *CCND1* amplification are frequently encountered in HR-positive breast cancers[10] and are key mediators of endocrine resistance.[11] The inhibition of the pathway consisting of cyclin D, CDK4/6, inhibitor of CDK4 (INK4), and retinoblastoma protein is an effective therapeutic strategy for HR-positive advanced breast cancer, both as a first-line option[12,13] and in patients in whom disease has progressed while they were receiving endocrine therapy.[14,15]

Ribociclib (LEE011) is an orally bioavailable, selective, small-molecule inhibitor of CDK4/6 that blocks the phosphorylation of retinoblastoma protein, thereby preventing cell-cycle progression and inducing G1 phase arrest.[16] Ribociclib has previously been shown to have antitumor activity in xenograft models of estrogen-receptor–positive breast cancer as a single agent and in combination with letrozole and phosphatidylinositol 3-kinase (PI3K) inhibitors.[17] In a phase 1b study involving postmenopausal women with estrogen-receptor–positive, HER2-negative advanced breast cancer, ribociclib had an acceptable safety profile and showed signs of clinical activity in combination with letrozole, particularly in patients who had received no previous systemic treatment for advanced disease, with an overall response rate of 46% and a clinical benefit rate of 79% among patients with measurable disease.[18]

Here, we present the results of the preplanned interim analysis of the Mammary Oncology Assessment of LEE011's (Ribociclib's) Efficacy and Safety (MONALEESA-2) trial, which evaluated the efficacy and safety of the combination of ribociclib and letrozole as initial therapy in patients with HR-positive, HER2-negative advanced breast cancer.

METHODS

STUDY DESIGN

In this randomized, double-blind, placebo-controlled, phase 3 trial conducted in 29 countries, patients at 223 trial centers were randomly assigned to receive either oral ribociclib (600 mg per day on a 3-weeks-on, 1-week-off schedule in 28-day treatment cycles) plus letrozole (2.5 mg per day on a continuous schedule) or placebo plus letrozole. We selected the ribociclib dose of 600 mg per day on the basis of the results of a phase 1 study involving patients with advanced cancer.[19] Ribociclib was administered with or without food.[20] Randomization was stratified according to the presence or absence of liver or lung metastases. Patients received treatment until disease progression, unacceptable toxicity, death, or discontinuation of ribociclib or letrozole for any other reason. Dose reductions for ribociclib (from 600 mg to 400 mg to 200 mg per day) were permitted to manage treatment-related adverse events; no dose reductions were allowed for letrozole. Patients who discontinued either ribociclib or placebo were permitted to continue receiving letrozole. No treatment crossover was allowed.

PATIENTS

Postmenopausal women with locally confirmed, HR-positive, HER2-negative recurrent or metastatic breast cancer who had not received previous systemic therapy for advanced disease were eligible. Patients had either measurable disease (according to Response Evaluation Criteria in Solid Tumors [RECIST], version 1.1)[21] or at least one predominantly lytic bone lesion, along with an Eastern Cooperative Oncology Group performance status[22] of 0 or 1 (on a 5-point scale on which a higher score indicates greater disability) and adequate bone marrow and organ function.

Patients were excluded if they had received a previous CDK4/6 inhibitor or any previous systemic chemotherapy or endocrine therapy for advanced disease. Previous neoadjuvant or adjuvant therapy with a nonsteroidal aromatase inhibitor was not allowed, unless the disease-free interval

was more than 12 months. Also excluded were patients with inflammatory breast cancer, central nervous system metastases, a history of cardiac disease or dysfunction (including a QT interval corrected for heart rate according to Fridericia's formula [QTcF] of >450 msec at screening), or impaired gastrointestinal function that altered drug absorption. The use of concomitant medications with a known risk of prolonging the QT interval or inducing torsades de pointes was not permitted.

END POINTS

The primary end point was locally assessed progression-free survival, according to RECIST, version 1.1. The key secondary end point was overall survival. Other secondary end points included the overall response rate (complete or partial response), the clinical benefit rate (overall response plus stable disease lasting 24 weeks or more), safety, and quality-of-life assessments. Exploratory end points included pharmacokinetics and biomarkers of response or resistance. The results of quality-of-life assessments and exploratory analyses are not reported here.

ASSESSMENTS

Tumor assessments (computed tomography or magnetic resonance imaging) were performed at screening, every 8 weeks during the first 18 months, every 12 weeks thereafter until disease progression (including in patients who discontinued treatment for reasons other than progressive disease), and at the end of treatment. An independent review committee whose members were unaware of treatment assignments prospectively reviewed all imaging data.

Adverse events were characterized and graded throughout the study according to National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03.[23] Biochemical and hematologic laboratory tests were performed at screening, on day 15 of cycle 1, and on day 1 of subsequent cycles until the end of treatment. Electrocardiographic assessments were performed at screening, on day 15 of cycle 1, and on day 1 of cycles 2 and 3 in all patients; after a protocol amendment, additional electrocardiographic assessments were performed on day 1 of cycles 4 through 9 in all patients and on day 1 of subsequent cycles in patients with a mean QTcF interval of 481 msec or more at any time before cycle 10. On-study electrocardiograms were reviewed by a central panel in a blinded fashion.

Representative tumor samples (obtained on fresh biopsy or from archival tissue) were obtained for biomarker analyses when available at screening, with an optional tumor sample collected at the time of disease progression. Blood samples were collected for analysis of estradiol levels and molecular alterations in circulating tumor DNA.

STUDY OVERSIGHT

The trial protocol and statistical analysis plan are available with the full text of this article at NEJM.org. Any modifications were approved by an independent ethics committee and institutional review board at each site. A steering committee oversaw the conduct of the trial in conformation with the approved protocol. Written informed consent was obtained from all the patients.

The trial was conducted in accordance with the Good Clinical Practice guidelines and the provisions of the Declaration of Helsinki. An independent data and safety monitoring committee reviewed the efficacy and safety data. Representatives of the trial sponsor, Novartis Pharmaceuticals, collected and analyzed the data. All the authors had full access to the data, were involved in the development and approval of the manuscript, and had final responsibility for the decision to submit the manuscript for publication. The manuscript was prepared by the authors with assistance from a medical writer funded by the sponsor. The authors assume responsibility for the accuracy and completeness of the data and vouch for the fidelity of the trial to the protocol.

STATISTICAL ANALYSIS

For the primary efficacy analysis, we compared progression-free survival in the two groups using a log-rank test stratified according to the presence or absence of liver or lung metastases. A determination that 302 patients had disease progression or died was required to detect a hazard ratio of 0.67 with a power of 93.5% at a one-sided alpha level of 0.025 with the use of a two-look Haybittle–Peto efficacy stopping boundary.[24,25] A stratified Cox regression analysis was performed to estimate the hazard ratio and 95% confidence intervals of progression-free survival.

A prespecified interim analysis was planned after disease progression or death was reported

in 211 of 302 patients (70%). The superiority of ribociclib plus letrozole versus placebo plus letrozole would be defined as a hazard ratio of 0.56 or less with $P<1.29\times10^{-5}$.

Efficacy analyses were performed in the intention-to-treat population. Safety analyses were performed in patients who received at least one dose of a study regimen and had at least one safety assessment after baseline.

RESULTS

PATIENT CHARACTERISTICS

From January 24, 2014, to March 24, 2015, a total of 668 patients underwent randomization, with 334 assigned to receive ribociclib plus letrozole and 334 assigned to receive placebo plus letrozole (Fig. S1 in the Supplementary Appendix, available at NEJM.org). The characteristics of the patients at baseline were well balanced between the two groups (Table 1). The median age was 62 years; all the patients had HR-positive disease, and all but 1 patient in each group had HER2-negative disease. A total of 227 patients (34.0%) had newly diagnosed advanced or metastatic disease (34.1% in the ribociclib group and 33.8% in the placebo group). The disease-free interval at baseline was more than 24 months in 397 patients (59.4%). Visceral disease (including liver, lung, and other visceral metastases) was present in 393 patients (58.8%), and 147 (22.0%) had bone-only disease.

TREATMENT

At the cutoff date (January 29, 2016), treatment was still being administered in 195 patients in the ribociclib group and in 154 in the placebo group. The median duration of exposure to treatment (i.e., from the first dose to the last dose of either ribociclib or placebo) was 13.0 months and 12.4 months, respectively. The most common reasons for discontinuation were progressive disease in 87 patients (26.0%) in the ribociclib group and in 146 (43.7%) in the placebo group; a decision by the patient or physician in 22 (6.6%) and in 26 (7.8%), respectively; and adverse events in 25 (7.5%) and 7 (2.1%), respectively. The median duration of follow-up from randomization to data cutoff was 15.3 months. The median relative dose intensity was 100% for letrozole in the two groups, 100% for placebo, and 87.5% for ribociclib. Interruptions in the dose of ribociclib occurred in 257 patients (76.9%), and letrozole was interrupted in 132 patients (39.5%) in the ribociclib group. Among the 330 patients in the placebo safety population, placebo was interrupted in 134 (40.6%), and letrozole was interrupted in 107 (32.4%). Dose reductions occurred in 53.9% of the patients in the ribociclib group and in 7.0% of those in the placebo group, most commonly for adverse events (in 169 patients [50.6%] and 14 [4.2%], respectively). The most frequent adverse event leading to dose reduction was neutropenia (in 104 patients receiving ribociclib and in no patients receiving placebo).

EFFICACY OF RIBOCICLIB PLUS LETROZOLE

The interim analysis was triggered after at least 211 patients had disease progression or died. Because of a delay in reporting from local trial centers, at the time of the data cutoff, 243 patients had disease progression or died and were included in the interim analysis. The trial met its primary end point: the median duration of progression-free survival was not reached in the ribociclib group (95% CI, 19.3 to not reached) versus 14.7 months (95% CI, 13.0 to 16.5) in the placebo group (hazard ratio, 0.56; 95% CI, 0.43 to 0.72; $P = 3.29\times10^{-6}$ for superiority) (Fig. 1). The rate of locally assessed progression-free survival was significantly higher in the ribociclib group than in the placebo group. After 12 months, the progression-free survival rate was 72.8% (95% confidence interval [CI], 67.3 to 77.6) in the ribociclib group and 60.9% (95% CI, 55.1 to 66.2) in the placebo group; after 18 months, the progression-free survival rate was 63.0% (95% CI, 54.6 to 70.3) and 42.2% (95% CI, 34.8 to 49.5), respectively.

The blinded central analysis of progression-free survival by an independent review committee supported the results of the primary efficacy analysis, with a hazard ratio of 0.59 (95% CI, 0.41 to 0.85; P=0.002). The progression-free survival benefit in the ribociclib group (as assessed by investigators) was observed across all predefined subgroups (Fig. 2). The overall response rates were 40.7% in the ribociclib group and 27.5% in the placebo group in the intention-to-treat population and 52.7% and 37.1%, respectively, among patients with measurable disease (P<0.001 for both comparisons) (Table 2). The clinical benefit rates were 79.6% in the ribociclib group and 72.8% in the placebo group in the

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Ribociclib Group (N=334)	Placebo Group (N=334)
Median age (range) — yr	62 (23–91)	63 (29–88)
Race — no. (%)†		
White	269 (80.5)	280 (83.8)
Asian	28 (8.4)	23 (6.9)
Black	10 (3.0)	7 (2.1)
Other or unknown	27 (8.1)	24 (7.2)
ECOG performance status — no. (%)		
0	205 (61.4)	202 (60.5)
1	129 (38.6)	132 (39.5)
Disease stage — no. (%)		
III	1 (0.3)	3 (0.9)
IV	333 (99.7)	331 (99.1)
Hormone-receptor status — no. (%)		
Estrogen-receptor positive	332 (99.4)	333 (99.7)
Progesterone-receptor positive	271 (81.1)	278 (83.2)
Disease-free interval — no. (%)		
Newly diagnosed disease	114 (34.1)	113 (33.8)
Existing disease	220 (65.9)	221 (66.2)
≤12 mo	4 (1.2)	10 (3.0)
>12 to ≤24 mo	14 (4.2)	15 (4.5)
>24 mo	202 (60.5)	195 (58.4)
Unknown	0	1 (0.3)
Previous treatment — no. (%)‡		
Neoadjuvant or adjuvant chemotherapy	146 (43.7)	145 (43.4)
Neoadjuvant or adjuvant endocrine therapy	175 (52.4)	171 (51.2)
Anastrozole	47 (14.1)	42 (12.6)
Exemestane	19 (5.7)	25 (7.5)
Goserelin	6 (1.8)	3 (0.9)
Letrozole	34 (10.2)	25 (7.5)
Tamoxifen	140 (41.9)	145 (43.4)
Other	2 (0.6)	4 (1.2)
Metastatic sites — no. (%)		
0	2 (0.6)	1 (0.3)
1	100 (29.9)	117 (35.0)
2	118 (35.3)	103 (30.8)
≥3	114 (34.1)	113 (33.8)
Site of metastases — no. (%)		
Breast	8 (2.4)	11 (3.3)
Bone		
Any	246 (73.7)	244 (73.1)
Only	69 (20.7)	78 (23.4)
Visceral§	197 (59.0)	196 (58.7)
Lymph nodes	133 (39.8)	123 (36.8)
Other	35 (10.5)	22 (6.6)

* There were no significant differences between the groups. ECOG denotes Eastern Cooperative Oncology Group.
† Race was self-reported.
‡ Some patients received both chemotherapy and endocrine therapy as neoadjuvant or adjuvant treatment.
§ Visceral involvement included liver, lung, and other visceral metastases.

intention-to-treat population and 80.1% and 71.8%, respectively, among patients with measurable disease (P=0.02 for both comparisons).

Overall survival results were not mature at the time of the interim analysis, with 43 deaths (23 in the ribociclib group and 20 in the placebo group) at the time of data cutoff. The study remains blinded for follow-up of overall survival.

SAFETY

In the safety population (334 patients in the ribociclib group and 330 in the placebo group), adverse events of any grade that occurred in at least 35% of the patients in either group were neutropenia (74.3% in the ribociclib group and 5.2% in the placebo group), nausea (51.5% and 28.5%, respectively), infections (50.3% and 42.4%), fatigue (36.5% and 30.0%), and diarrhea (35.0% and 22.1%) (Table 3). Nausea, infections, fatigue, and diarrhea were mostly grade 1 or 2. The most common grade 3 or 4 adverse events (≥5% of the patients in either group) were neutropenia (59.3% in the ribociclib group and 0.9% in the placebo group), leukopenia (21.0% and 0.6%, respectively), hypertension (9.9% and 10.9%), increased alanine aminotransferase level (9.3% and 1.2%), lymphopenia (6.9% and 0.9%), and increased aspartate aminotransferase level (5.7% and 1.2%). Febrile neutropenia occurred in 5 patients (1.5%) in the ribociclib group and in none in the placebo group.

Four patients (1.2%) in the ribociclib group were confirmed as having met the biochemical definition of Hy's law (concomitant increases in aminotransferase and bilirubin levels in the absence of cholestasis). Three of the four cases in the ribociclib group were suspected by the investigator to be related to the study treatment. None of these cases resulted in death, and aminotransferase and bilirubin levels returned to normal in all four patients after the discontinuation of ribociclib.

Infections were reported in 168 patients (50.3%) in the ribociclib group and in 140 (42.4%) in the placebo group; of these infections, the most common were urinary tract infections (10.8% and 8.2%, respectively) and upper respiratory tract infections (10.5% and 10.6%), predominantly of grade 1 or 2. The only grade 3 infections were reported in the ribociclib group, with grade 3 urinary tract infection in 2 patients (0.6%); there were no grade 4 infections in either group.

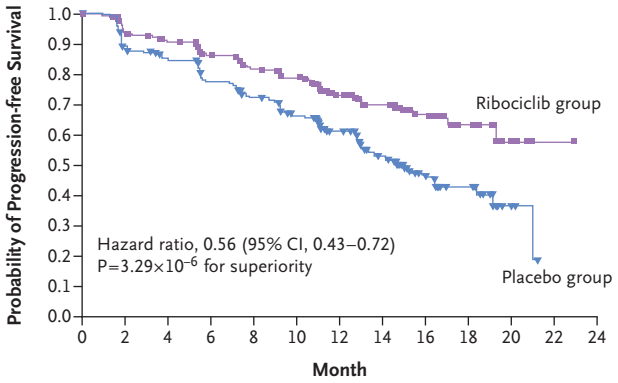

Figure 1. Kaplan–Meier Analysis of Progression-free Survival.
After 18 months, the progression-free survival rate was 63.0% (95% CI, 54.6 to 70.3) in the ribociclib group and 42.2% (95% CI, 34.8 to 49.5) in the placebo group. The median duration of progression-free survival was not reached in the ribociclib group and was 14.7 months in the placebo group.

An increase of more than 60 msec from baseline in the QTcF interval occurred in 9 patients (2.7%) in the ribociclib group and in no patients in the placebo group. In the ribociclib group, 11 patients (3.3%) had at least one average QTcF interval of more than 480 msec after baseline, including 1 patient who presented with cardiac abnormalities at baseline and 6 who had an increase of more than 60 msec from baseline. Of these patients, most were able to continue treatment at the 600-mg dose of ribociclib without interruption. One patient (0.3%) in the placebo group had an average post-baseline QTcF interval of more than 480 msec.

Serious adverse events occurred in 71 patients (21.3%) in the ribociclib group and in 39 (11.8%) in the placebo group (Table S1 in the Supplementary Appendix). Of these events, 25 (7.5%) in the ribociclib group and 5 (1.5%) in the placebo group were deemed to be related to the study regimen. There were 4 deaths (3 [0.9%] in the ribociclib group and 1 (0.3%) in the placebo group) during treatment. One patient in each group died from the progression of underlying breast cancer. The remaining 2 deaths in the ribociclib group were due to sudden death and death from an unknown cause. The case of sudden death was considered to be related to ribociclib and occurred on day 11 in cycle 2 in association with grade 3 hypokalemia (treated with oral potassium supplements) and a grade 2

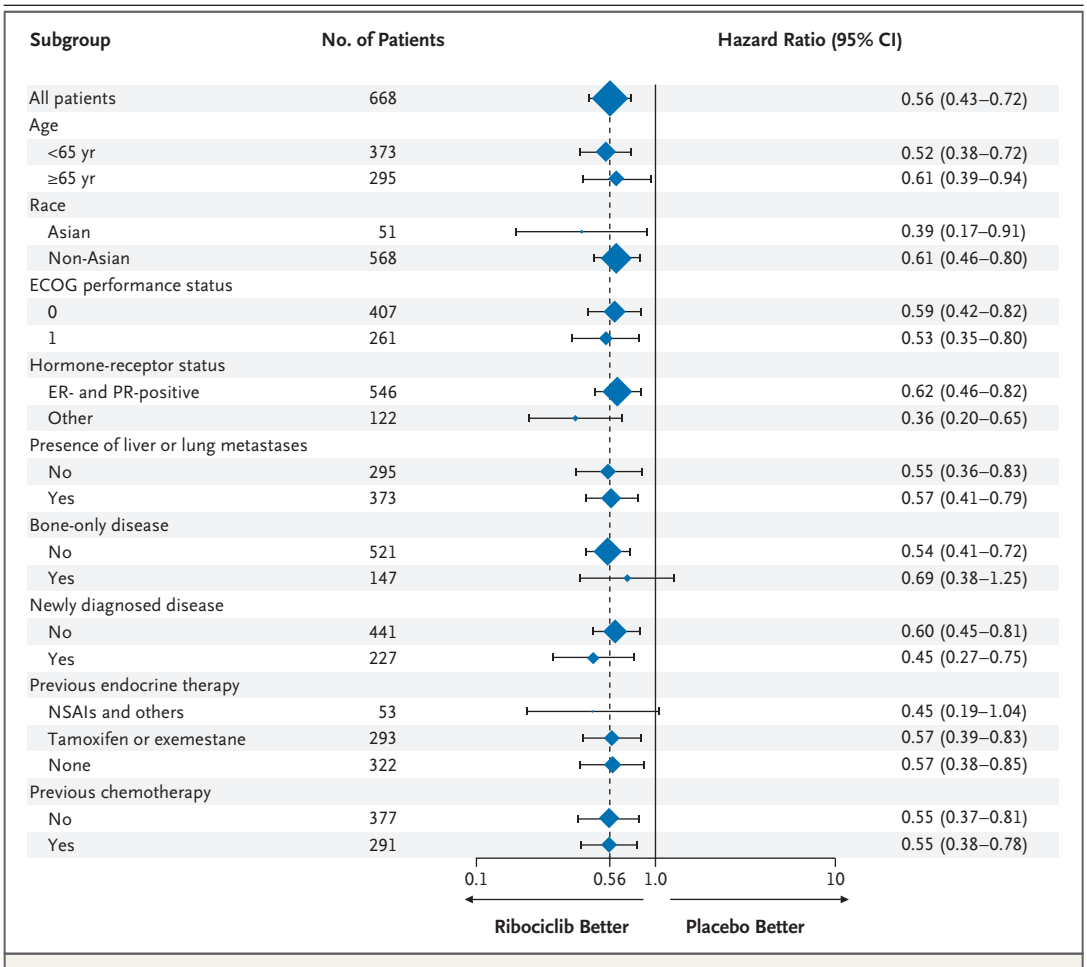

Figure 2. Subgroup Analysis of Progression-free Survival.

The progression-free survival benefit in the ribociclib group (as assessed by investigators) was observed across all predefined subgroups (overall hazard ratio, 0.56; 95% CI, 0.43 to 0.72; $P<3.29\times10^{-6}$ for superiority) (dashed line). Among the patients who had received previous endocrine therapy, those taking nonsteroidal aromatase inhibitors (NSAIs) or other therapies not listed here had not received tamoxifen. Previous endocrine therapy and chemotherapy include neoadjuvant and adjuvant treatment. The size of the data points is proportional to the number of patients included in the subgroup analysis. ECOG denotes Eastern Cooperative Oncology Group.

prolongation in the QTcF interval on day 1 of cycle 2; the patient had taken a prohibited concomitant medication with a known risk for QT prolongation (methadone) during cycle 1. The patient who died from an unknown cause received ribociclib for 4 days before withdrawing consent and discontinuing the study treatment; her death was reported 19 days later and was not considered to be related to ribociclib by the investigator.

DISCUSSION

At the prospectively planned interim analysis, we found that postmenopausal women with HR-positive, HER2-negative advanced breast cancer who were receiving first-line treatment with ribociclib plus letrozole had a significantly longer duration of progression-free survival than did those receiving placebo plus letrozole, with a 44% lower relative risk of progression. The trial population included a high proportion of patients who had disease that was expected to be sensitive to endocrine therapy (i.e., those with newly diagnosed advanced breast cancer or with a disease-free interval of >24 months). However, the duration of progression-free survival was longer in all preplanned patient subgroups receiving ribociclib, including those with newly diagnosed or pretreated metastatic disease and those with

Table 2. Best Overall Response, According to Local Assessment.

Response	Ribociclib Group	Placebo Group
All patients — no.	334	334
Confirmed best overall response — no. (%)		
Complete response	9 (2.7)	7 (2.1)
Partial response	127 (38.0)	85 (25.4)
Stable disease	95 (28.4)	111 (33.2)
Neither complete response nor progressive disease*	66 (19.8)	75 (22.5)
Progressive disease	19 (5.7)	40 (12.0)
Unknown	18 (5.4)	16 (4.8)
Overall response†		
No. of patients	136	92
Percentage of patients (95% CI)	40.7 (35.4–46.0)	27.5 (22.8–32.3)
Clinical benefit‡		
No. of patients	266	243
Percentage of patients (95% CI)	79.6 (75.3–84.0)	72.8 (68.0–77.5)
Patients with measurable disease at baseline — no.	256	245
Confirmed best overall response — no. (%)		
Complete response	8 (3.1)	6 (2.4)
Partial response	127 (49.6)	85 (34.7)
Stable disease	95 (37.1)	111 (45.3)
Progressive disease	13 (5.1)	31 (12.7)
Unknown	13 (5.1)	11 (4.5)
Overall response†		
No. of patients	135	91
Percentage of patients (95% CI)	52.7 (46.6–58.9)	37.1 (31.1–43.2)
Clinical benefit§		
No. of patients	205	176
Percentage of patients (95% CI)	80.1 (75.2–85.0)	71.8 (66.2–77.5)

* In this category, the best overall response was evaluated only among patients who had no measurable disease at baseline, according to the Response Evaluation Criteria in Solid Tumors, version 1.1. One patient with measurable disease in the placebo group was misclassified as having a best overall response of neither complete response nor progressive disease.

† Overall response included a complete or partial response ($P<0.001$ for the comparison with placebo).

‡ Clinical benefit in the overall population was defined as a complete or partial response, stable disease lasting 24 weeks or more, or neither a complete response nor progressive disease lasting 24 weeks or more ($P=0.02$ for the comparison with placebo).

§ Clinical benefit among patients with measurable disease at baseline was defined as a complete or partial response or stable disease lasting 24 weeks or more ($P=0.02$ for the comparison with placebo).

or without liver or lung metastases. Further analyses of these subgroups are ongoing. Ribociclib plus letrozole was also associated with significantly higher rates of overall response and clinical benefit than was placebo plus letrozole, a finding that was consistent with observations from an earlier phase 1 trial.[18]

Most patients had an acceptable adverse-event profile with long-term administration of ribociclib plus letrozole, with 7.5% of patients requiring permanent discontinuation of both ribociclib and letrozole because of adverse events and similar percentages because of decisions made by either patients or physicians in the two groups. The majority of nonhematologic adverse events in the ribociclib group were of grade 1 or 2, and grade 3 or 4 events were reversible by dose interruptions and reductions, which allowed most

Table 3. Adverse Events.*

Adverse Event	Ribociclib Group (N=334)			Placebo Group (N=330)†		
	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
	number of patients (percent)					
Any adverse event	329 (98.5)	221 (66.2)	50 (15.0)	320 (97.0)	105 (31.8)	3 (0.9)
Neutropenia‡	248 (74.3)	166 (49.7)	32 (9.6)	17 (5.2)	3 (0.9)	0
Nausea	172 (51.5)	8 (2.4)	0	94 (28.5)	2 (0.6)	0
Infections	168 (50.3)	12 (3.6)	2 (0.6)	140 (42.4)	7 (2.1)	1 (0.3)
Fatigue	122 (36.5)	7 (2.1)	1 (0.3)	99 (30.0)	3 (0.9)	0
Diarrhea	117 (35.0)	4 (1.2)	0	73 (22.1)	3 (0.9)	0
Alopecia	111 (33.2)	NA	NA	51 (15.5)	NA	NA
Leukopenia	110 (32.9)	66 (19.8)	4 (1.2)	13 (3.9)	2 (0.6)	0
Vomiting	98 (29.3)	12 (3.6)	0	51 (15.5)	3 (0.9)	0
Arthralgia	91 (27.2)	2 (0.6)	1 (0.3)	95 (28.8)	3 (0.9)	0
Constipation	83 (24.9)	4 (1.2)	0	63 (19.1)	0	0
Headache	74 (22.2)	1 (0.3)	0	63 (19.1)	1 (0.3)	0
Hot flush	70 (21.0)	1 (0.3)	0	78 (23.6)	0	0
Back pain	66 (19.8)	7 (2.1)	0	58 (17.6)	1 (0.3)	0
Cough	65 (19.5)	0	NA	59 (17.9)	0	NA
Anemia§	62 (18.6)	3 (0.9)	1 (0.3)	15 (4.5)	4 (1.2)	0
Decreased appetite	62 (18.6)	5 (1.5)	0	50 (15.2)	1 (0.3)	0
Rash	57 (17.1)	2 (0.6)	0	26 (7.9)	0	0
Increased alanine aminotransferase	52 (15.6)	25 (7.5)	6 (1.8)	13 (3.9)	4 (1.2)	0
Increased aspartate aminotransferase	50 (15.0)	16 (4.8)	3 (0.9)	12 (3.6)	4 (1.2)	0

* Listed are events that were reported in at least 15% of the patients in any group. One event of interest (hypertension) fell below the reporting threshold listed here. NA denotes not applicable, since grade 4 cough and grade 3 and 4 alopecia are not included in the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03.
† Four patients who were randomly assigned to the placebo group did not receive either placebo or letrozole.
‡ Neutropenia includes a decreased neutrophil count and granulocytopenia.
§ This category includes both anemia and a decreased hemoglobin level.

patients to remain on treatment. Hematologic adverse events in the ribociclib group reflected on-target CDK4/6 inhibition, which resulted in reversible bone marrow stem-cell quiescence.[26] Neutropenia occurred mainly within the first 4 weeks of treatment and resulted in five cases (1.5%) of febrile neutropenia in the ribociclib group. Grade 3 or 4 elevations in alanine and aspartate aminotransferase levels were reported in 9.3% and 5.7%, respectively, of patients receiving ribociclib in this study and have also been observed with other CDK4/6 inhibitors in combination with aromatase inhibitors.[27-29] The majority of cases of liver-enzyme elevation were isolated and asymptomatic and were reversible with dose adjustment. Prolongation of the QTcF interval to more than 480 msec occurred in 3.3% of patients treated at the 600-mg dose of ribociclib, with changes mostly occurring within the first 4 weeks of treatment. Our protocol excluded patients who were deemed to be at high risk for prolongation of the QTc interval; during treatment, such prolongation was limited by proactive dose interruption or reduction, since this side effect is dose-dependent. In routine practice, careful monitoring should be implemented to limit the incidence of these events to the levels observed during this study.

In conclusion, this phase 3 trial showed significant prolongation of progression-free survival and higher rates of overall response with the addition of ribociclib to letrozole than with the addition of placebo to letrozole for first-line treatment in postmenopausal women with HR-positive, HER2-negative advanced breast cancer. The improvement in the duration of progression-free survival was associated with a higher rate of myelosuppression among patients in the ribociclib group.

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APPENDIX

The authors' full names and academic degrees are as follows: Gabriel N. Hortobagyi, M.D., Salomon M. Stemmer, M.D., Howard A. Burris, M.D., Yoon-Sim Yap, M.D., Gabe S. Sonke, M.D., Ph.D., Shani Paluch-Shimon, M.D., Mario Campone, M.D., Ph.D., Kimberly L. Blackwell, M.D., Fabrice André, M.D., Ph.D., Eric P. Winer, M.D., Wolfgang Janni, M.D., Ph.D., Sunil Verma, M.D., Pierfranco Conte, M.D., Ph.D., Carlos L. Arteaga, M.D., David A. Cameron, M.D., Katarina Petrakova, M.D., Ph.D., Lowell L. Hart, M.D., Cristian Villanueva, M.D., Arlene Chan, M.D., Erik Jakobsen, M.D., M.P.H., Arnd Nusch, M.D., Olga Burdaeva, M.D., Eva-Maria Grischke, M.D., Emilio Alba, M.D., Ph.D., Erik Wist, M.D., Ph.D., Norbert Marschner, M.D., Anne M. Favret, M.D., Denise Yardley, M.D., Thomas Bachelot, M.D., Ph.D., Ling-Ming Tseng, M.D., Sibel Blau, M.D., Fengjuan Xuan, Ph.D., Farida Souami, M.Sc., Michelle Miller, M.D., Caroline Germa, M.D., Samit Hirawat, M.D., and Joyce O'Shaughnessy, M.D.

The authors' affiliations are as follows: the University of Texas M.D. Anderson Cancer Center, Houston (G.N.H.), and Texas Oncology–Baylor Charles A. Sammons Cancer Center and the U.S. Oncology Network, Dallas (J.O.) — all in Texas; Davidoff Center, Rabin Medical Center, Tel Aviv University, Tel Aviv (S.M.S.), and Sheba Medical Center, Ramat Gan (S.P.-S.) — both in Israel; the Sarah Cannon Research Institute (H.A.B., D.Y.), Vanderbilt–Ingram Cancer Center (C.L.A.), and Tennessee Oncology (D.Y.) — all in Nashville; National Cancer Center Singapore, Singapore (Y.-S.Y.); Netherlands Cancer Institute and BOOG Study Center, Amsterdam (G.S.S.); Institut de Cancérologie de l'Ouest/René Gauducheau, Saint-Herblain (M.C.), Institut Gustave Roussy, Université Paris Sud, Villejuif (F.A.), University Hospital of Besançon, Besançon (C.V.), and Centre Léon Bérard, Lyon (T.B.) — all in France; Duke University Medical Center, Durham, NC (K.L.B.); Dana–Farber Cancer Institute, Boston (E.P.W.); University of Ulm, Ulm (W.J.), Onkologische Praxis, Velbert (A.N.), University of Tübingen, Tübingen (E.-M.G.), and Joint Practice for Interdisciplinary Oncology and Hematology, Freiburg (N.M.) — all in Germany; Tom Baker Cancer Centre, Calgary, AB, Canada (S.V.); University of Padua and Istituto Oncologico Veneto, Istituto di Ricovero e Cura a Carattere Scientifico, Padua, Italy (P.C.); Edinburgh Cancer Research Centre, University of Edinburgh, Edinburgh (D.A.C.); Masaryk Memorial Cancer Institute, Brno, Czech Republic (K.P.); Florida Cancer Specialists–Sarah Cannon Research Institute, Fort Myers (L.L.H.); Breast Cancer Research Centre–Western Australia and Curtin University, Perth, Australia (A.C.); Department of Oncology, Vejle Hospital, Vejle, Denmark (E.J.); Arkhangelsk Clinical Oncology Dispensary, Arkhangelsk, Russia (O.B.); Hospital Universitario Virgen de la Victoria, Institute of Biomedical Research in Málaga, Málaga, Spain (E.A.); Oslo University Hospital, Oslo (E.W.); Virginia Cancer Specialists, Arlington (A.M.F.); Taipei Veterans General Hospital, National Yang-Ming University, Taipei, Taiwan (L.-M.T.); Rainier Hematology–Oncology, Northwest Medical Specialties, Puyallup, WA (S.B.); Novartis Pharmaceuticals, East Hanover, NJ (F.X., M.M., C.G., S.H.); and Novartis Pharma, Basel, Switzerland (F.S.).

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