ORIGINAL ARTICLE

Ribociclib plus Endocrine Therapy in Early Breast Cancer

D. Slamon, O. Lipatov, Z. Nowecki, N. McAndrew, B. Kukielka-Budny, D. Stroyakovskiy, D.A. Yardley, C.-S. Huang, P.A. Fasching, J. Crown, A. Bardia, S. Chia, S.-A. Im, M. Ruiz-Borrego, S. Loi, B. Xu, S. Hurvitz, C. Barrios, M. Untch, R. Moroose, F. Visco, K. Afenjar, R. Fresco, I. Severin, Y. Ji, F. Ghaznawi, Z. Li, J.P. Zarate, A. Chakravartty, T. Taran, and G. Hortobagyi

ABSTRACT

BACKGROUND

Ribociclib has been shown to have a significant overall survival benefit in patients with hormone receptor (HR)–positive, human epidermal growth factor receptor 2 (HER2)–negative advanced breast cancer. Whether this benefit in advanced breast cancer extends to early breast cancer is unclear.

METHODS

In this international, open-label, randomized, phase 3 trial, we randomly assigned patients with HR-positive, HER2-negative early breast cancer in a 1:1 ratio to receive ribociclib (at a dose of 400 mg per day for 3 weeks, followed by 1 week off, for 3 years) plus a nonsteroidal aromatase inhibitor (NSAI; letrozole at a dose of 2.5 mg per day or anastrozole at a dose of 1 mg per day for ≥5 years) or an NSAI alone. Premenopausal women and men also received goserelin every 28 days. Eligible patients had anatomical stage II or III breast cancer. Here we report the results of a prespecified interim analysis of invasive disease–free survival, the primary end point; other efficacy and safety results are also reported. Invasive disease–free survival was evaluated with the use of the Kaplan–Meier method. The statistical comparison was made with the use of a stratified log-rank test, with a protocol-specified stopping boundary of a one-sided P-value threshold of 0.0128 for superior efficacy.

RESULTS

As of the data-cutoff date for this prespecified interim analysis (January 11, 2023), a total of 426 patients had had invasive disease, recurrence, or death. A significant invasive disease–free survival benefit was seen with ribociclib plus an NSAI as compared with an NSAI alone. At 3 years, invasive disease–free survival was 90.4% with ribociclib plus an NSAI and 87.1% with an NSAI alone (hazard ratio for invasive disease, recurrence, or death, 0.75; 95% confidence interval, 0.62 to 0.91; P=0.003). Secondary end points — distant disease–free survival and recurrence-free survival — also favored ribociclib plus an NSAI. The 3-year regimen of ribociclib at a 400-mg starting dose plus an NSAI was not associated with any new safety signals.

CONCLUSIONS

Ribociclib plus an NSAI significantly improved invasive disease–free survival among patients with HR-positive, HER2-negative stage II or III early breast cancer. (Funded by Novartis; NATALEE ClinicalTrials.gov number, NCT03701334.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Dr. Slamon can be contacted at dslamon@mednet.ucla.edu or at the David Geffen School of Medicine at the University of California, Los Angeles, 885 Tiverton Dr., Los Angeles, CA 90095.

A list of the investigators in this trial is provided in the Supplementary Appendix, available at NEJM.org.

N Engl J Med 2024;390:1080-91.
DOI: 10.1056/NEJMoa2305488

Hormone receptor (HR)–positive, human epidermal growth factor receptor 2 (HER2)–negative breast cancer is the most common subtype of breast cancer, accounting for 70 to 75% of cases.[1] The majority of cases with this subtype are diagnosed early (at stage I to III).[2] Early breast cancer is treated with curative intent; HR-positive, HER2-negative early breast cancer is treated with surgery with or without radiotherapy or chemotherapy, followed by adjuvant endocrine therapy for 5 to 10 years.[3] Adjuvant endocrine therapy improves outcomes in these patients; however, recurrence occurs in 27 to 37% of patients with stage II disease and in 46 to 57% of patients with stage III disease and can occur up to 20 years after diagnosis.[4]

The results of trials in which the cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitors ribociclib, palbociclib, and abemaciclib were evaluated have shown significant improvements in progression-free survival among patients with HR-positive, HER2-negative advanced breast cancer.[5-10] Ribociclib and abemaciclib have also been shown to have a significant overall survival benefit in the same patient population.[11-14] In early breast cancer, the use of CDK4/6 inhibitors has had varying results. In the PENELOPE-B and PALLAS trials, palbociclib plus endocrine therapy did not show a significant invasive disease–free survival benefit.[15,16] Conversely, a significant invasive disease–free survival benefit was seen in the monarchE trial after 2 years of adjuvant therapy with abemaciclib; these results led to the approval of abemaciclib by international health authorities for the treatment of HR-positive, HER2-negative early breast cancer in patients with node-positive disease at high risk for recurrence.[17-19]

The established benefit that was observed with ribociclib in advanced breast cancer prompted its investigation in early breast cancer. The NATALEE trial is a phase 3 trial comparing ribociclib plus endocrine therapy with endocrine therapy alone that was designed to test CDK4/6 inhibition in a broad population of patients with stage II or III HR-positive, HER2-negative early breast cancer. We report results from a protocol-specified interim efficacy analysis.

METHODS

TRIAL DESIGN AND PATIENTS

We conducted an international, open-label, randomized, phase 3 trial involving patients with HR-positive, HER2-negative early breast cancer. We planned to enroll 5000 patients, with approximately 2000 (approximately 40%) having stage II disease.

The design and rationale of the trial have been reported previously.[20] Patients were randomly assigned in a 1:1 ratio to receive ribociclib (at a dose of 400 mg, administered orally once daily for 21 consecutive days, followed by 7 days off, for a complete cycle of 28 days, administered for 36 months) plus a nonsteroidal aromatase inhibitor (NSAI; letrozole at a dose of 2.5 mg, administered orally once daily, or anastrozole at a dose of 1 mg, administered orally once daily, on a continuous schedule for 60 months) or an NSAI alone. Patients in the ribociclib–NSAI group were expected to continue to receive the NSAI after completing the 36 months of treatment with ribociclib and were considered to be receiving trial treatment during this time. Additional treatment with the NSAI beyond 60 months was at the discretion of the treating physician and was not considered to be part of the trial treatment. Men and premenopausal women in both groups also received goserelin for gonadal suppression (at a dose of 3.6 mg, administered subcutaneously once every 28 days).

Eligible patients were men or premenopausal or postmenopausal women who were 18 years of age or older and had histologically confirmed HR-positive, HER2-negative early breast cancer according to local assessment. Patients were required to have stage II or III disease on the basis of anatomical stage according to the *American Joint Committee on Cancer Staging Manual, Eighth Edition*.[21] The anatomical stage was derived with the use of tumor–node–metastasis (TNM) staging that was determined at the time of surgery for patients who had not received adjuvant or neoadjuvant treatment; for patients who had received adjuvant or neoadjuvant treatment, the "worst stage" was derived with the use of TNM staging at diagnosis and at the time of surgery. All patients with stage III or IIB disease were allowed to participate in the trial irrespective of nodal status. Patients with stage IIA disease were eligible if they had at least one lymph node involved; patients who had no nodal involvement and a grade 2 tumor with a Ki-67 proliferation index of at least 20% (according to findings on local pathological assessment) or who were considered to be in a high genomic risk group were eligible. Patients with stage IIA disease with no

A Quick Take is available at NEJM.org

nodal involvement and grade 3 tumors were also eligible (Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). For trial-related staging purposes at baseline, the nodal status used reflected the greatest number of involved nodes observed on the basis of radiologic or surgical findings, regardless of the timing of staging. High genomic risk was defined as either an Oncotype DX Breast Recurrence Score of 26 or higher or as a result that was categorized as high risk on the Prosigna PAM50, MammaPrint, or EndoPredict assay.

Patients could have received any adjuvant or neoadjuvant endocrine therapy for up to 12 months before randomization. Patients were ineligible if they had received a previous CDK4/6 inhibitor or if they had had clinically significant, uncontrolled heart disease, cardiac repolarization abnormalities, or both. Randomization was stratified according to anatomical stage (II or III), menopausal status (premenopausal women and men or postmenopausal women) (Table S2), previous adjuvant or neoadjuvant chemotherapy (yes or no), and geographic location (North America, Western Europe, Oceania, or rest of the world).

END POINTS

The primary end point was invasive disease–free survival, which was defined according to standardized definitions for efficacy end points (STEEP) criteria, version 1.0, as assessed by the investigator (Table S3).[22] Distant disease–free survival, recurrence-free survival, overall survival, safety, quality of life, and pharmacokinetics were secondary end points. Distant recurrence–free survival was an exploratory end point. Adverse events were monitored for 36 months beginning at the time of randomization, and serious adverse events were monitored throughout the trial. Events were graded according to the Common Terminology Criteria for Adverse Events, version 4.03.

TRIAL OVERSIGHT

The trial was funded by Novartis and was overseen in collaboration with Translational Research in Oncology (also known as TRIO). The trial was conducted in accordance with the provisions of the Declaration of Helsinki and Good Clinical Practice guidelines. The trial protocol and all amendments (available at NEJM.org) were approved by an institutional review board or independent ethics committee at each site. The conduct of the trial was overseen by a steering committee, which included the participating international investigators as well as representatives of the sponsor and a patient advocate. An independent data monitoring committee assessed efficacy and safety data in accordance with the trial protocol. All the patients provided written informed consent. Representatives of the sponsor designed the trial and confirmed the accuracy of the data, and the authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol. All the authors contributed to the writing and review of the manuscript. Two professional medical writers, funded by the sponsor, provided editorial assistance.

STATISTICAL ANALYSIS

Invasive disease–free survival (the primary end point) was compared between the groups with the use of a stratified log-rank test; the same stratification factors that were used for randomization were applied to the analysis. We estimated that 500 events (invasive disease, recurrence, or death[22]) would need to occur to provide the trial with approximately 85% power to detect a hazard ratio for invasive disease, recurrence, or death of 0.76 at a one-sided alpha level of 0.025. This report is based on all data collected up to the time of the protocol-specified second interim efficacy analysis (January 11, 2023), which was performed after 426 events had occurred. At the time of this analysis, a prespecified Lan–DeMets (O'Brien–Fleming) stopping boundary of a one-sided P-value threshold of 0.0128 was used by the independent data monitoring committee to conclude that treatment with ribociclib plus an NSAI was significantly superior to an NSAI alone with respect to efficacy; the two-sided stopping boundary (P-value threshold, 0.0256) is reported. All end points were evaluated with the use of the Kaplan–Meier method. Hazard ratios were estimated by means of a stratified Cox proportional-hazards model. All reported 95% confidence intervals are two-sided. The widths of the confidence intervals have not been adjusted for multiplicity and thus may not be used in place of hypothesis testing. The secondary end points were compared between the groups with the use of a stratified log-rank test.

The efficacy analyses were performed in the intention-to-treat population, which included all

the patients who had undergone randomization. The safety analyses were performed in the safety population, which included all the patients who had undergone randomization and had received at least one dose of the trial treatment.

RESULTS

PATIENTS AND TREATMENT

From January 10, 2019, to April 20, 2021, a total of 5101 patients were randomly assigned to receive either ribociclib plus an NSAI (2549 patients) or an NSAI alone (2552 patients) (Fig. S2). Demographic and baseline clinical characteristics were well balanced in the two groups (Table 1). A majority of the patients (73.4%) were White, 13.2% were Asian, and 1.7% were Black. At the time of data cutoff, 1984 patients (77.8%) in the ribociclib–NSAI group were either still receiving ribociclib plus an NSAI or were continuing to receive an NSAI, and 1826 (71.6%) in the NSAI group were still receiving an NSAI (Fig. S3). Overall, 515 patients (20.2%) completed the planned 3 years of treatment with ribociclib. In the ribociclib–NSAI group, 1147 patients (45.0%) were continuing to receive ribociclib, and 1449 (56.8%) had completed at least 2 years of treatment with ribociclib plus an NSAI. The median duration of follow-up (from randomization to the data cutoff) was 34 months (minimum, 21 months). The median duration of exposure to the trial treatment was 30 months in the ribociclib–NSAI group and 30 months in the NSAI group. In the ribociclib–NSAI group, the median duration of exposure to ribociclib alone was 27 months.

EFFICACY

The second interim efficacy analysis for invasive disease–free survival (data-cutoff date, January 11, 2023) was performed after 426 patients had had invasive disease, recurrence, or death: 189 patients (7.4%) in the ribociclib–NSAI group and 237 patients (9.3%) in the NSAI group. The median duration of follow-up (from randomization to the last completed recurrence assessment) was 28 months. The risk of invasive disease, recurrence, or death was significantly lower (by 25.2%) with the addition of ribociclib to NSAI than with NSAI alone. Kaplan–Meier estimates of invasive disease–free survival at 3 years were 90.4% with ribociclib plus an NSAI and 87.1% with an NSAI alone (hazard ratio for invasive disease, recurrence, or death, 0.75; 95% confidence interval [CI], 0.62 to 0.91) (Fig. 1). Ribociclib plus an NSAI showed statistically significant and clinically superior efficacy. The two-sided P value was 0.003, which crossed the prespecified stopping boundary (P-value threshold of 0.0256). Distant recurrences were the most commonly reported type of event in the analysis of invasive disease–free survival, occurring in 120 patients (4.7%) in the ribociclib–NSAI group and in 170 patients (6.7%) in the NSAI group; the most frequent sites of disease recurrence were bone and liver in each group (Table S5).

An analysis of invasive disease–free survival across prespecified subgroups was performed (Fig. S4). At 3 years, the absolute invasive disease–free survival benefit with ribociclib and NSAI was 3.0 percentage points among patients with stage II disease and 3.2 percentage points among those with stage III disease.

Several secondary efficacy end points also showed a consistent benefit with ribociclib. At 3 years, distant disease–free survival was 90.8% with ribociclib plus an NSAI and 88.6% with an NSAI alone (hazard ratio for distant disease or death, 0.74; 95% CI, 0.60 to 0.91) (Fig. 2A). At 3 years, recurrence-free survival was 91.7% with ribociclib plus an NSAI and 88.6% with an NSAI alone (hazard ratio for disease recurrence or death, 0.72; 95% CI, 0.58 to 0.88) (Fig. 2B). The median duration of follow-up for overall survival was 30 months. At the time of the data cutoff, 61 of the 2549 patients (2.4%) in the ribociclib–NSAI group and 73 of the 2552 patients (2.9%) in the NSAI group had died (hazard ratio for death, 0.76; 95% CI, 0.54 to 1.07) (Fig. 2C).

The exploratory end point, distant recurrence–free survival, was also improved with ribociclib plus an NSAI as compared with an NSAI alone. The hazard ratio for distant recurrence or death was 0.72 (95% CI, 0.58 to 0.89) (Fig. S5).

SAFETY

The safety analyses included 2524 patients in the ribociclib–NSAI group and 2444 patients in the NSAI group (Table 2). At least one adverse event occurred in 2470 patients (97.9%) in the ribociclib–NSAI group and in 2128 patients (87.1%) in the NSAI group. Serious adverse events were reported in 336 patients (13.3%) in the ribociclib–NSAI group and in 242 patients (9.9%) in the NSAI group. Adverse events that led to early discontinu-

Table 1. Demographic and Baseline Clinical Characteristics.*

Characteristic	Ribociclib + NSAI (N = 2549)	NSAI Alone (N = 2552)	All Patients (N = 5101)
Median age (range) — yr	52 (24–90)	52 (24–89)	52 (24–90)
Menopausal status — no. (%)			
Premenopausal women	1115 (43.7)	1123 (44.0)	2238 (43.9)
Postmenopausal women	1423 (55.8)	1420 (55.6)	2843 (55.7)
Men	11 (0.4)	9 (0.4)	20 (0.4)
Anatomical stage — no. (%)†			
I	9 (0.4)	5 (0.2)	14 (0.3)
IIA	479 (18.8)	521 (20.4)	1000 (19.6)
IIB	532 (20.9)	513 (20.1)	1045 (20.5)
III	1528 (59.9)	1512 (59.2)	3040 (59.6)
Data missing	1 (<0.1)	1 (<0.1)	2 (<0.1)
Nodal status at diagnosis — no. (%)‡			
NX	272 (10.7)	264 (10.3)	536 (10.5)
N0	694 (27.2)	737 (28.9)	1431 (28.1)
N1	1050 (41.2)	1049 (41.1)	2099 (41.1)
N2 or N3	483 (18.9)	467 (18.3)	950 (18.6)
Data missing	50 (2.0)	35 (1.4)	85 (1.7)
Nodal status at surgery — no. (%)‡			
NX	2 (0.1)	5 (0.2)	7 (0.1)
N0	378 (14.8)	418 (16.4)	796 (15.6)
N1	1062 (41.7)	1039 (40.7)	2101 (41.2)
N2 or N3	1105 (43.4)	1089 (42.7)	2194 (43.0)
Data missing	2 (0.1)	1 (<0.1)	3 (0.1)
Histologic grade at diagnosis — no. (%)			
X§	30 (1.2)	32 (1.3)	62 (1.2)
1	218 (8.6)	240 (9.4)	458 (9.0)
2	1458 (57.2)	1451 (56.9)	2909 (57.0)
3	521 (20.4)	549 (21.5)	1070 (21.0)
Not assessed	292 (11.5)	258 (10.1)	550 (10.8)
Data missing	30 (1.2)	22 (0.9)	52 (1.0)
Previous endocrine therapy — no. (%)	1824 (71.6)	1801 (70.6)	3625 (71.1)
Ovarian function–suppression therapy	670 (26.3)	620 (24.3)	1290 (25.3)
Aromatase inhibitor	1601 (62.8)	1592 (62.4)	3193 (62.6)
Antiestrogen	344 (13.5)	341 (13.4)	685 (13.4)
Other	4 (0.2)	13 (0.5)	17 (0.3)
Previous neoadjuvant or adjuvant chemotherapy — no. (%)			
Any	2249 (88.2)	2245 (88.0)	4494 (88.1)
Neoadjuvant	1085 (42.6)	1095 (42.9)	2180 (42.7)
Adjuvant	1223 (48.0)	1220 (47.8)	2443 (47.9)

Table 1. (Continued.)

Characteristic	Ribociclib + NSAI (N = 2549)	NSAI Alone (N = 2552)	All Patients (N = 5101)
ECOG performance-status score — no. (%)¶			
0	2106 (82.6)	2132 (83.5)	4238 (83.1)
1	440 (17.3)	418 (16.4)	858 (16.8)
Data missing	3 (0.1)	2 (0.1)	5 (0.1)
Geographic region — no. (%)			
Asia	281 (11.0)	290 (11.4)	571 (11.2)
Europe	1505 (59.0)	1506 (59.0)	3011 (59.0)
North America or Australia	624 (24.5)	612 (24.0)	1236 (24.2)
Latin America	139 (5.5)	144 (5.6)	283 (5.5)
Histologic type — no. (%)			
Invasive ductal not otherwise specified	1857 (72.9)	1881 (73.7)	3738 (73.3)
Invasive lobular	455 (17.9)	450 (17.6)	905 (17.7)
Medullary	1 (<0.1)	1 (<0.1)	2 (<0.1)
Mucinous	17 (0.7)	16 (0.6)	33 (0.6)
Papillary	18 (0.7)	12 (0.5)	30 (0.6)
Tubular	5 (0.2)	3 (0.1)	8 (0.2)
Ductal in situ‖	1 (<0.1)	0	1 (<0.1)
Lobular in situ	0	0	0
Other	194 (7.6)	189 (7.4)	383 (7.5)
Data missing	1 (<0.1)	0	1 (<0.1)

* Percentages may not total 100 because of rounding. NSAI denotes nonsteroidal aromatase inhibitor.
† The stage was derived with the use of tumor–node–metastasis (TNM) staging that was determined at the time of surgery for patients who had not received adjuvant or neoadjuvant treatment; for patients who had received adjuvant or neoadjuvant treatment, the "worst stage" was derived with the use of TNM staging at diagnosis and at the time of surgery.
‡ N0 indicates no nodal involvement, N1 indicates 1 to 3 axillary lymph nodes, N2 indicates 4 to 9 axillary lymph nodes, N3 indicates 10 or more axillary lymph nodes or infraclavicular or supraclavicular lymph nodes, and NX indicates that regional lymph nodes were not assessed. Nodal status was evaluated at diagnosis (radiologic evaluation) and after surgery (pathological evaluation), and the worse of the two findings was used in staging according to the *American Joint Committee on Cancer Staging Manual, Eighth Edition*. Additional details are provided in Table S1.
§ X indicates that the grade could not be determined.
¶ The Eastern Cooperative Oncology Group (ECOG) performance-status scores range from 0 to 5, with higher scores indicating greater disability.
‖ One patient with ductal carcinoma in situ was included in the ribociclib–NSAI group; however, the predominant histologic type was invasive ductal carcinoma.

ation of ribociclib were reported in 477 patients (18.9%). Adverse events that led to early discontinuation of both ribociclib and the NSAI occurred in 83 patients (3.3%). The percentages of patients who discontinued the NSAI for any cause or because of adverse events were similar in the two groups.

The most common adverse events of any grade were neutropenia (in 62.1% of the patients in the ribociclib–NSAI group and in 4.5% of those in the NSAI group), arthralgia (in 36.5% and 42.5%, respectively), and liver-related events (in 25.4% and 10.6%). These events were also the most common events of grade 3 or higher; the most frequent event of grade 3 or higher was neutropenia, occurring in 43.8% of the patients in the ribociclib–NSAI group and in 0.8% of those in the NSAI group.

The most common adverse events of any grade that led to discontinuation of any trial treatment were liver-related events (in 8.9% of the patients in the ribociclib–NSAI group and in 0.1% of

those in the NSAI group) and arthralgia (in 1.3% and 1.9%, respectively). Most discontinuations of ribociclib occurred early during treatment, with a median time to ribociclib discontinuation of 4 months. The incidence of NSAI-related events leading to discontinuation of treatment was similar in the two treatment groups. Dose reductions of ribociclib occurred in 554 patients (21.9%).

Liver-related adverse events of grade 3 or 4 were reported in 209 patients (8.3%) in the ribociclib–NSAI group and in 37 (1.5%) of those in the NSAI group. Cases that met Hy's law criteria (jaundice associated with drug-induced liver injury without biliary obstruction) were reported in 8 patients (0.3%) in the ribociclib–NSAI group and in 1 patient (<0.1%) in the NSAI group.

QT-interval prolongation of any grade was observed in 5.2% of the patients in the ribociclib–NSAI group and in 1.2% of those in the NSAI group. A new QT interval corrected for heart rate of greater than 500 msec occurred in 3 of 2505 patients (0.1%) in the ribociclib–NSAI group and in 1 of 2380 patients (<0.1%) in the NSAI group. An increase from baseline of greater than 60 msec in the QT interval corrected for heart rate occurred in 19 of 2505 patients (0.8%) in the ribociclib–NSAI group and in 2 of 2380 patients (0.1%) in the NSAI group.

Deaths from any cause were reported in 60 patients (2.4%) in the ribociclib–NSAI group and in 74 patients (3.0%) in the NSAI group (Table S6). No deaths were considered to be related to the trial treatment. Deaths without disease progression or recurrence occurred in 19 patients in the ribociclib–NSAI group and in 13 patients in the NSAI group. Deaths during treatment or within 30 days after the last dose of the trial treatment occurred in 17 patients (0.7%) in the ribociclib–NSAI group and in 9 patients (0.4%) in the NSAI group; among these deaths, 10 (0.4%) occurred within 30 days after the last dose of ribociclib (Table S7).

PHARMACOKINETICS

The geometric mean trough plasma concentration of ribociclib at a steady state was 289.5 ng per milliliter at cycle 1, day 15 (Table S8). On the basis of this finding and previous reports, approximately 80% inhibition of CDK4/6 is estimated at the mean steady-state trough concentration, which suggests greater than 80% target inhibition during ribociclib treatment at a steady state.[23,24]

DISCUSSION

After our initial report described the growth inhibitory effects of CDK4/6 inhibitors in HR-positive, HER2-negative breast cancer cells,[25] multiple clinical studies were undertaken to assess the efficacy and safety of these therapies in both advanced breast cancer and early breast cancer.[5-19] In the NATALEE trial, we examined CDK4/6 inhibition in HR-positive, HER2-negative disease by evaluating the addition of 3 years of ribociclib

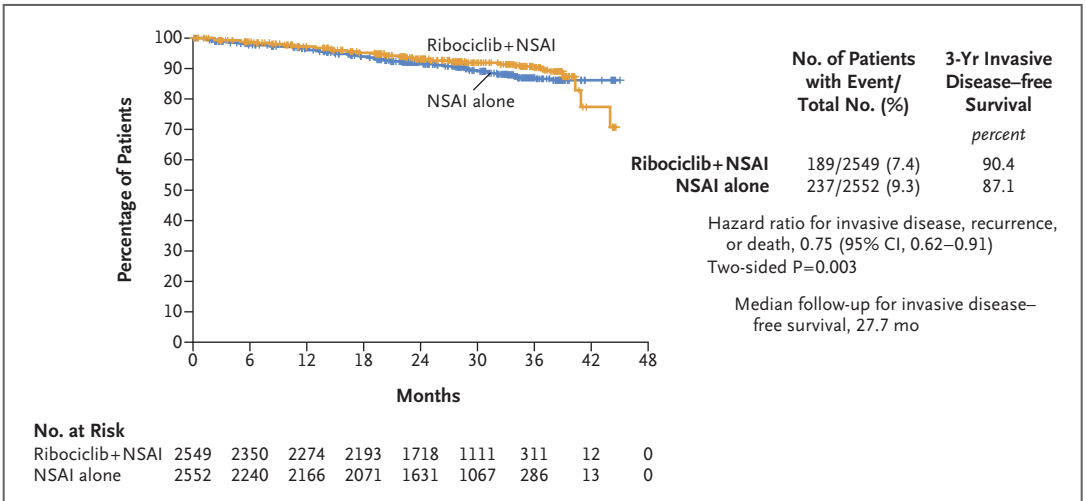
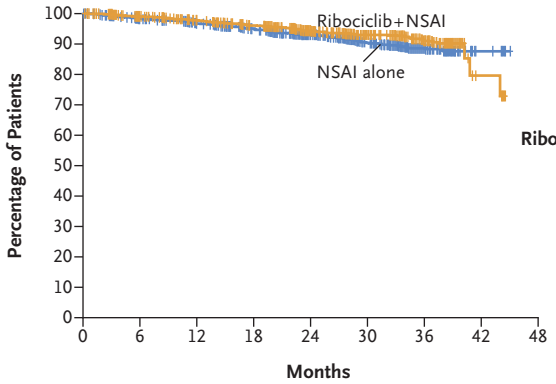


Figure 1. Kaplan–Meier Estimates of Invasive Disease–free Survival.
Tick marks indicate censored data. NSAI denotes nonsteroidal aromatase inhibitor.

A Distant Disease–free Survival



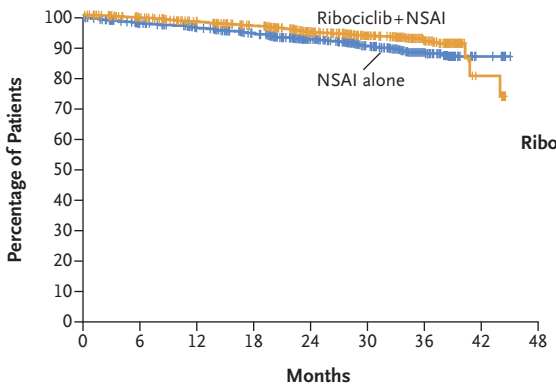
	No. of Patients with Event/ Total No. (%)	3-Yr Distant Disease–free Survival
		percent
Ribociclib+NSAI	167/2549 (6.6)	90.8
NSAI alone	212/2552 (8.3)	88.6

Hazard ratio for distant disease or death, 0.74 (95% CI, 0.60–0.91)

No. at Risk

Ribociclib+NSAI	2549	2352	2280	2199	1729	1119	311	12	0
NSAI alone	2552	2244	2168	2080	1643	1076	288	13	0

B Recurrence-free Survival



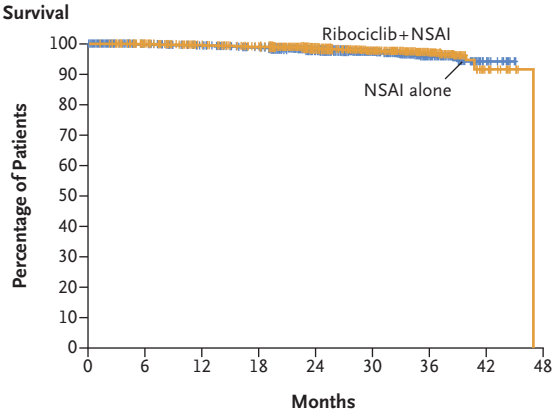
	No. of Patients with Event/ Total No. (%)	3-Yr Recurrence-free Survival
		percent
Ribociclib+NSAI	159/2549 (6.2)	91.7
NSAI alone	207/2552 (8.1)	88.6

Hazard ratio for recurrence or death, 0.72 (95% CI, 0.58–0.88)

No. at Risk

Ribociclib+NSAI	2549	2358	2283	2210	1733	1124	314	12	0
NSAI alone	2552	2247	2174	2086	1646	1080	290	13	0

C Overall Survival



	No. of Patients with Event/ Total No. (%)
Ribociclib+NSAI	61/2549 (2.4)
NSAI alone	73/2552 (2.9)

Hazard ratio for death, 0.76 (95% CI, 0.54–1.07)

No. at Risk

Ribociclib+NSAI	2549	2405	2337	2303	1905	1338	451	21	0
NSAI alone	2552	2303	2256	2209	1823	1273	385	22	0

Figure 2. Kaplan–Meier Estimates of Secondary Efficacy End Points.
Tick marks indicate censored data.

Table 2. Adverse Events.*

Event	Ribociclib + NSAI (N = 2524)				NSAI Alone (N = 2444)			
	All Grades	Grade 3	Grade 4	Grade 5	All Grades	Grade 3	Grade 4	Grade 5
	number of patients (percent)							
Any adverse event	2470 (97.9)	1437 (56.9)	130 (5.2)	12 (0.5)	2128 (87.1)	394 (16.1)	38 (1.6)	4 (0.2)
Adverse events that occurred in ≥15% of patients in either group								
Neutropenia†	1568 (62.1)	1054 (41.8)	52 (2.1)	0	110 (4.5)	17 (0.7)	3 (0.1)	0
Arthralgia	921 (36.5)	24 (1.0)	0	0	1038 (42.5)	31 (1.3)	0	0
Nausea	580 (23.0)	6 (0.2)	0	0	184 (7.5)	1 (<0.1)	0	0
Headache	556 (22.0)	10 (0.4)	0	0	403 (16.5)	4 (0.2)	0	0
Fatigue	554 (21.9)	18 (0.7)	0	0	311 (12.7)	4 (0.2)	0	0
SARS-CoV-2 test positive	487 (19.3)	0	0	0	310 (12.7)	0	0	0
Covid-19	477 (18.9)	18 (0.7)	0	3 (0.1)	314 (12.8)	11 (0.5)	0	1 (<0.1)
Alanine aminotransferase increased	478 (18.9)	154 (6.1)	31 (1.2)	0	128 (5.2)	15 (0.6)	1 (<0.1)	0
Hot flush	473 (18.7)	6 (0.2)	0	0	482 (19.7)	3 (0.1)	0	0
Asthenia	417 (16.5)	15 (0.6)	0	0	273 (11.2)	3 (0.1)	0	0
Aspartate aminotransferase increased	408 (16.2)	96 (3.8)	16 (0.6)	0	131 (5.4)	12 (0.5)	0	0

* Covid-19 denotes coronavirus disease 2019, and SARS-CoV-2 severe acute respiratory syndrome coronavirus 2.
† Neutropenia is a grouped term that combines the preferred terms neutropenia and neutrophil count decreased.

treatment to a standard NSAI as adjuvant therapy in a broad population of patients with early breast cancer. The results of this trial showed a significant invasive disease–free survival benefit over NSAI alone as adjuvant therapy in stage II or III HR-positive, HER2-negative early breast cancer; a 25.2% lower risk of invasive disease, recurrence, or death; and an absolute invasive disease–free survival benefit of 3.3 percentage points at 3 years. Overall survival data are currently immature. No new safety signals were observed for either ribociclib or the NSAIs.[5-7] Treatment with ribociclib at a dose of 400 mg per day was associated with a lower incidence of dose-dependent toxic effects than the 600-mg starting dose that is used in patients with advanced breast cancer and did not adversely affect the side-effect profile of NSAI in combination. At the time of this analysis, follow-up was ongoing, and 20% of the patients had completed 3 years of ribociclib–NSAI treatment; thus, additional analyses with longer follow-up are continuing in order to fully assess the larger clinical effect of 3 years of CDK4/6 inhibition in this patient population.

The NATALEE trial showed that ribociclib treatment benefits a broad population of patients with early breast cancer who are at increased risk for recurrence. Abemaciclib treatment also showed a significant invasive disease–free survival benefit in patients with node-positive early breast cancer in the monarchE trial, which was conducted in a population that was enriched for high-risk patients. The monarchE trial also required additional high-risk features in patients with one to three lymph nodes, as part of the inclusion criteria.[19] By contrast, the NATALEE trial included patients with node-negative or node-positive disease as well as those with stage II or stage III disease. The difference in the risk profiles of the NATALEE and monarchE trial populations is evident when the Kaplan–Meier 3-year invasive-disease estimates in the groups that received endocrine therapy alone in the these two trials are compared. At 28 months of follow-up, the 3-year estimate of invasive disease–free survival was 87.1% with NSAI alone in the NATALEE trial; in the monarchE trial, at 27 months of follow-up, the estimate was 83.4% with endocrine therapy alone, a result that was consistent with the higher-risk population of that trial.[18]

The endocrine therapy used in these two trials differed. In the monarchE trial, both NSAIs and tamoxifen were allowed (with approximately 30% of the patients receiving tamoxifen), whereas only NSAIs were allowed in the NATALEE trial.[17] Aromatase inhibitors have shown superior efficacy in patients at increased risk for recurrence in early breast cancer. The results of the SOFT (Suppression of Ovarian Function Trial), TEXT (Tamoxifen and Exemestane Trial), and BIG (Breast International Group) 1-98 trials have all shown that aromatase inhibitors have advantages over tamoxifen.[26,27] All the premenopausal women in the NATALEE trial received ovarian function–suppression therapy in addition to an NSAI, unlike the monarchE trial, in which only 48% received such therapy.[28] In the monarchE trial, the incidence of venous thromboembolic events was higher among the premenopausal patients who were receiving tamoxifen than among those who were receiving an aromatase inhibitor.[28] Ribociclib is not indicated for patients who are also receiving treatment with tamoxifen.

In advanced breast cancer, most adverse events that are associated with ribociclib treatment, such as neutropenia and transaminitis, are asymptomatic laboratory findings that can be monitored and managed. In a pooled analysis of the MONALEESA-2, MONALEESA-3, and MONALEESA-7 trials, the most common adverse events that led to discontinuation of ribociclib at the 600-mg dose level were increased levels of alanine aminotransferase (in 4.0% of the patients who received ribociclib plus endocrine therapy vs. 0.4% of those who received placebo plus endocrine therapy) or increased levels of aspartate aminotransferase (in 2.4% vs. 0.6%).[29] A key feature of the NATALEE trial design was the use of a reduced dose of ribociclib (400 mg per day) to improve safety and adherence over a 3-year period while maintaining efficacy. In addition, a 3-year duration of ribociclib treatment was implemented with the goal of preventing recurrences by prolonging the duration of cell-cycle arrest and potentially driving more tumor cells into irreversible senescence. Although caution is advised when comparing dose levels between early and advanced breast cancer, the 400-mg dose was associated with a lower incidence of known dose-dependent toxic effects — namely, neutropenia and QT prolongation — than that seen with the 600-mg dose, a finding that was also observed in the AMALEE trial.[30]

Our trial has limitations. This report repre-

sents 28 months of follow-up. The Kaplan–Meier curves for invasive disease–free survival crossed at the end of the curves, particularly after approximately 40 months, owing to three events occurring in the ribociclib group among a low number of patients at risk at that time point. Additional follow-up will be needed to further characterize the long-term efficacy of ribociclib in this population. Although our trial included a large number of patients with HR-positive, HER2-negative early breast cancer, Black patients were underrepresented, and patients in the trial were younger than the median age at diagnosis in the United States (Table S4).[1,31] The invasive disease–free survival benefit that was observed in this trial did not appear to be driven by any age subgroup.

This prespecified interim analysis showed a significantly lower risk of invasive disease, recurrence, or death with adjuvant ribociclib plus an NSAI than with an NSAI alone in patients with stage II or III HR-positive, HER2-negative early breast cancer. The absolute benefit with ribociclib plus an NSAI at 3 years was 3.3 percentage points. These results support the use of ribociclib in the treatment of HR-positive, HER2-negative early breast cancer.

Supported by Novartis.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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

We thank the patients who participated in the trial and their families and caregivers, the members of the independent data monitoring committee, the members of the trial steering committee, the staff members who assisted with the trial at each site, and Tara Wabbersen, Ph.D., and Casey Nielsen, Ph.D., of Nucleus Global for medical editorial assistance with earlier versions of the manuscript. Ribociclib was discovered by Novartis Institutes for BioMedical Research in collaboration with Astex Pharmaceuticals.

APPENDIX

The authors' full names and academic degrees are as follows: Dennis Slamon, M.D., Ph.D., Oleg Lipatov, M.D., Zbigniew Nowecki, M.D., Nicholas McAndrew, M.D., Bozena Kukielka-Budny, M.D., Daniil Stroyakovskiy, M.D., Ph.D., Denise A. Yardley, M.D., Chiun-Sheng Huang, M.D., Ph.D., Peter A. Fasching, M.D., John Crown, M.D., Aditya Bardia, M.D., Stephen Chia, M.D., Seock-Ah Im, M.D., Ph.D., Manuel Ruiz-Borrego, M.D., Sherene Loi, M.D., Ph.D., Binghe Xu, M.D., Ph.D., Sara Hurvitz, M.D., Carlos Barrios, M.D., Michael Untch, M.D., Ph.D., Rebecca Moroose, M.D., Frances Visco, J.D., Karen Afenjar, M.S., Rodrigo Fresco, M.D., Irene Severin, B.Sc., Yan Ji, Ph.D., Farhat Ghaznawi, M.D., Zheng Li, Ph.D., Juan P. Zarate, M.D., Arunava Chakravartty, Ph.D., Tetiana Taran, M.D., and Gabriel Hortobagyi, M.D.

The authors' affiliations are as follows: the David Geffen School of Medicine at the University of California, Los Angeles (D. Slamon, N.M.); Republican Clinical Oncology Dispensary, Ufa (O.L.), and Moscow City Oncology Hospital No. 62, Moscow (D. Stroyakovskiy) — both in Russia; Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw (Z.N.), and Centrum Onkologii Ziemi Lubelskiej im. św. Jana z Dukli, Lublin (B.K.-B.) — both in Poland; the Sarah Cannon Research Institute at Tennessee Oncology, Nashville (D.A.Y.); the National Taiwan University Hospital, National Taiwan University College of Medicine, Taipei City (C.-S.H.); University Hospital Erlangen, the Comprehensive Cancer Center Erlangen–European Metropolitan Region of Nuremberg, Friedrich-Alexander University Erlangen–Nuremberg, Erlangen (P.A.F.), and the Interdisciplinary Breast Cancer Center, Helios Klinikum Berlin–Buch, Berlin (M.U.) — both in Germany; St. Vincent's Hospital, Dublin (J.C.); Massachusetts General Hospital Cancer Center, Harvard Medical School, Boston (A.B.); the British Columbia Cancer Agency, Vancouver (S.C.), and Translational Research in Oncology (TRIO), Edmonton, AB (I.S.) — both in Canada; the Cancer Research Institute, Seoul National University Hospital, Seoul National University College of Medicine, Seoul, South Korea (S.-A.I.); Hospital Virgen del Rocío, Seville, and Grupo Español de Investigación en Cáncer de Mama, Spanish Breast Cancer Group, Madrid — both in Spain (M.R.-B.); the Peter MacCallum Cancer Centre, Melbourne, VIC, Australia (S.L.); the Department of Medical Oncology Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing (B.X.); the Fred Hutchinson Cancer Center, University of Washington, Seattle (S.H.); the Latin American Cooperative Oncology Group, Porto Alegre, Brazil (C.B.); the Orlando Health Cancer Institute, Orlando, FL (R.M.); the National Breast Cancer Coalition, Washington, DC (F.V.); TRIO, Paris (K.A.); TRIO, Montevideo, Uruguay (R.F.); Novartis Pharmaceuticals, East Hanover, NJ (Y.J., F.G., Z.L., J.P.Z., A.C.); Novartis Pharma, Basel, Switzerland (T.T.); and the Department of Breast Medical Oncology, University of Texas M.D. Anderson Cancer Center, Houston (G.H.).

REFERENCES

1. Howlader N, Altekruse SF, Li CI, et al. US incidence of breast cancer subtypes defined by joint hormone receptor and HER2 status. J Natl Cancer Inst 2014;106(5):dju055.
2. Iqbal J, Ginsburg O, Rochon PA, Sun P, Narod SA. Differences in breast cancer stage at diagnosis and cancer-specific survival by race and ethnicity in the United States. JAMA 2015;313:165-73.
3. Pistilli B, Lohrisch C, Sheade J, Fleming GF. Personalizing adjuvant endocrine therapy for early-stage hormone receptor-positive breast cancer. Am Soc Clin Oncol Educ Book 2022;42:1-13.
4. Pan H, Gray R, Braybrooke J, et al. 20-Year risks of breast-cancer recurrence after stopping endocrine therapy at 5 years. N Engl J Med 2017;377:1836-46.
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;375:1738-48.
6. 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;36:2465-72.
7. Tripathy D, Im S-A, Colleoni M, et al. Ribociclib plus endocrine therapy for premenopausal women with hormone-receptor-positive, advanced breast cancer (MONALEESA-7): a randomised phase 3 trial. Lancet Oncol 2018;19:904-15.
8. Sledge GW Jr, Toi M, Neven P, et al. MONARCH 2: abemaciclib in combination with fulvestrant in women with

HR+/HER2- advanced breast cancer who had progressed while receiving endocrine therapy. J Clin Oncol 2017;35:2875-84.
9. Goetz MP, Toi M, Campone M, et al. MONARCH 3: abemaciclib as initial therapy for advanced breast cancer. J Clin Oncol 2017;35:3638-46.
10. Turner NC, Ro J, André F, et al. Palbociclib in hormone-receptor–positive advanced breast cancer. N Engl J Med 2015; 373:209-19.
11. Hortobagyi GN, Stemmer SM, Burris HA, et al. Overall survival with ribociclib plus letrozole in advanced breast cancer. N Engl J Med 2022;386:942-50.
12. Slamon DJ, Neven P, Chia S, et al. Overall survival with ribociclib plus fulvestrant in advanced breast cancer. N Engl J Med 2020;382:514-24.
13. Im S-A, Lu Y-S, Bardia A, et al. Overall survival with ribociclib plus endocrine therapy in breast cancer. N Engl J Med 2019;381:307-16.
14. 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 2020;6:116-24.
15. Loibl S, Marmé F, Martin M, et al. Palbociclib for residual high-risk invasive HR-positive and HER2-negative early breast cancer — the Penelope-B Trial. J Clin Oncol 2021;39:1518-30.
16. Gnant M, Dueck AC, Frantal S, et al. Adjuvant palbociclib for early breast cancer: the PALLAS trial results (ABCSG-42/AFT-05/BIG-14-03). J Clin Oncol 2022;40: 282-93.
17. Johnston SRD, Harbeck N, Hegg R, et al. Abemaciclib combined with endocrine therapy for the adjuvant treatment of HR+, HER2-, node-positive, high-risk, early breast cancer (monarchE). J Clin Oncol 2020;38:3987-98.
18. Harbeck N, Rastogi P, Martin M, et al. Adjuvant abemaciclib combined with endocrine therapy for high-risk early breast cancer: updated efficacy and Ki-67 analysis from the monarchE study. Ann Oncol 2021;32:1571-81.
19. Johnston SRD, Toi M, O'Shaughnessy J, et al. Abemaciclib plus endocrine therapy for hormone receptor-positive, HER2-negative, node-positive, high-risk early breast cancer (monarchE): results from a preplanned interim analysis of a randomised, open-label, phase 3 trial. Lancet Oncol 2023;24:77-90.
20. Slamon DJ, Fasching PA, Hurvitz S, et al. Rationale and trial design of NATALEE: a phase III trial of adjuvant ribociclib + endocrine therapy *versus* endocrine therapy alone in patients with HR+/HER2- early breast cancer. Ther Adv Med Oncol 2023;15:17588359231178125.
21. Amin MB, Edge SB, Greene FL, et al., eds. AJCC cancer staging manual. 8th ed. New York: Springer, 2017.
22. Hudis CA, Barlow WE, Costantino JP, et al. Proposal for standardized definitions for efficacy end points in adjuvant breast cancer trials: the STEEP system. J Clin Oncol 2007;25:2127-32.
23. 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.
24. Chen P, Lee NV, Hu W, et al. Spectrum and degree of CDK drug interactions predicts clinical performance. Mol Cancer Ther 2016;15:2273-81.
25. 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.
26. Francis PA, Pagani O, Fleming GF, et al. Tailoring adjuvant endocrine therapy for premenopausal breast cancer. N Engl J Med 2018;379:122-37.
27. Regan MM, Neven P, Giobbie-Hurder A, et al. Assessment of letrozole and tamoxifen alone and in sequence for postmenopausal women with steroid hormone receptor-positive breast cancer: the BIG 1-98 randomised clinical trial at 8·1 years median follow-up. Lancet Oncol 2011;12:1101-8.
28. Paluch-Shimon S, Neven P, Huober J, et al. Efficacy and safety results by menopausal status in monarchE: adjuvant abemaciclib combined with endocrine therapy in patients with HR+, HER2-, node-positive, high-risk early breast cancer. Ther Adv Med Oncol 2023;15: 17588359231151840.
29. Burris HA, Chan A, Bardia A, et al. Safety and impact of dose reductions on efficacy in the randomised MONALEESA-2, -3 and -7 trials in hormone receptor-positive, HER2-negative advanced breast cancer. Br J Cancer 2021;125:679-86.
30. Cardoso F, Jacot W, Kummel S, et al. Primary efficacy and safety results from the AMALEE trial evaluating 600 mg vs 400 mg starting doses of first-line ribociclib in patients with HR+/HER2– advanced breast cancer. Cancer Res 2023; 83(5):Suppl:PD17-12. abstract (https://doi.org/10.1158/1538-7445.SABCS22-PD17-12).
31. American Cancer Society. Breast cancer facts & figures 2019-2020. 2019 (https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/breast-cancer-facts-and-figures/breast-cancer-facts-and-figures-2019-2020.pdf).