ORIGINAL ARTICLE

Overall Survival with Ribociclib plus Fulvestrant in Advanced Breast Cancer

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ABSTRACT

BACKGROUND

In an earlier analysis of this phase 3 trial, ribociclib plus fulvestrant showed a greater benefit with regard to progression-free survival than fulvestrant alone in postmenopausal patients with hormone-receptor–positive, human epidermal growth factor receptor 2 (HER2)–negative advanced breast cancer. Here we report the results of a protocol-specified second interim analysis of overall survival.

METHODS

Patients were randomly assigned in a 2:1 ratio to receive either ribociclib or placebo in addition to fulvestrant as first-line or second-line treatment. Survival was evaluated by means of a stratified log-rank test and summarized with the use of Kaplan–Meier methods.

RESULTS

This analysis was based on 275 deaths: 167 among 484 patients (34.5%) receiving ribociclib and 108 among 242 (44.6%) receiving placebo. Ribociclib plus fulvestrant showed a significant overall survival benefit over placebo plus fulvestrant. The estimated overall survival at 42 months was 57.8% (95% confidence interval [CI], 52.0 to 63.2) in the ribociclib group and 45.9% (95% CI, 36.9 to 54.5) in the placebo group, for a 28% difference in the relative risk of death (hazard ratio, 0.72; 95% CI, 0.57 to 0.92; P=0.00455). The benefit was consistent across most subgroups. In a descriptive update, median progression-free survival among patients receiving first-line treatment was 33.6 months (95% CI, 27.1 to 41.3) in the ribociclib group and 19.2 months (95% CI, 14.9 to 23.6) in the placebo group. No new safety signals were observed.

CONCLUSIONS

Ribociclib plus fulvestrant showed a significant overall survival benefit over placebo plus fulvestrant in patients with hormone-receptor–positive, HER2-negative advanced breast cancer. (Funded by Novartis; MONALEESA-3 ClinicalTrials.gov number, NCT02422615.)

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Cyclin-dependent kinases 4 and 6 (CDK4/6) have emerged as important targets in the treatment of breast cancer, given their role in cell-cycle progression and the successes that inhibitors of these kinases have had in improving outcomes in patients with advanced breast cancer.[1-10] Ribociclib is one of three selective small-molecule inhibitors of CDK4/6 currently approved for the treatment of advanced hormone-receptor–positive, human epidermal growth factor receptor 2 (HER2)–negative breast cancer after showing significantly better progression-free survival outcomes as compared with standard therapy.[7,8,10]

Significantly longer overall survival with the best possible quality of life is the ultimate goal for treatment of advanced cancer; however, until recently, no CDK4/6 inhibitor combination had shown a significant overall survival benefit in patients with advanced breast cancer. In the PALOMA-3 (Palbociclib: Ongoing Trials in the Management of Breast Cancer–3) trial, overall survival was longer with palbociclib plus endocrine therapy than with endocrine therapy alone, but the difference was not significant.[11] Recent results of the MONALEESA-7 (Mammary Oncology Assessment of LEE011's [Ribociclib's] Efficacy and Safety–7) trial, however, showed significantly longer overall survival with ribociclib plus endocrine therapy than with endocrine therapy alone among premenopausal or perimenopausal patients with hormone-receptor–positive, HER2-negative advanced breast cancer (hazard ratio for death, 0.71; 95% confidence interval [CI], 0.54 to 0.95; P=0.00973 by log-rank test).[12] A recent report showed a significant improvement in overall survival with the addition of abemaciclib to fulvestrant in the MONARCH 2 trial (hazard ratio for death, 0.76; 95% CI, 0.61 to 0.95; P=0.01).[13]

The MONALEESA-3 trial is an international, randomized, placebo-controlled, phase 3 trial comparing ribociclib with placebo, in combination with fulvestrant, in postmenopausal patients with hormone-receptor–positive, HER2-negative advanced breast cancer. In the primary analysis of the trial, ribociclib plus fulvestrant resulted in significantly longer progression-free survival than placebo plus fulvestrant (median, 20.5 vs. 12.8 months; hazard ratio for disease progression or death, 0.59; 95% CI, 0.48 to 0.73; P<0.001).[8] Results for overall survival were not yet mature at the time of the primary analysis. The trial included patients receiving first-line or second-line treatment. We report the results from the second protocol-specified interim analysis of overall survival and an updated analysis of progression-free survival.

Methods

Trial Design and Patients

Details of the MONALEESA-3 trial were described previously.[8] Patients were randomly assigned in a 2:1 ratio to receive ribociclib (at a dose of 600 mg, 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 fulvestrant (at a dose of 500 mg, administered intramuscularly on day 1 of each 28-day cycle, with an additional dose on day 15 of cycle 1).

Eligible patients included men and postmenopausal women who were at least 18 years of age at trial entry, with histologically or cytologically confirmed hormone-receptor–positive, HER2-negative advanced breast cancer (metastatic or locoregionally recurrent disease not amenable to curative treatment). Patients must have had an Eastern Cooperative Oncology Group performance-status score of 0 or 1 (on a 5-point scale in which higher scores reflect greater disability) and measurable disease according to Response Evaluation Criteria in Solid Tumors, version 1.1, or at least one predominantly lytic bone lesion. Crossover between the two groups was not permitted.

The trial population included patients who had not previously received treatment in the context of advanced disease, those who had received up to one line of therapy for advanced disease, and those who had had a relapse during or within 12 months after completion of adjuvant or neoadjuvant endocrine therapy (Table S2 in the Supplemental Appendix, available with the full text of this article at NEJM.org).[8] Patients who had received previous chemotherapy for advanced disease or any previous treatment with fulvestrant or a CDK4/6 inhibitor were not enrolled.

Randomization was stratified according to the presence or absence of liver or lung metastases

and previous endocrine therapy (previously untreated in the context of advanced disease vs. having received up to one line of endocrine therapy for advanced disease). All the patients as well as all investigators who administered treatment, assessed outcomes, and analyzed data were unaware of the trial-group assignments.[8] The protocol, along with the statistical analysis plan, is available at NEJM.org.

END POINTS

The results regarding the primary end point, investigator-assessed progression-free survival, were reported previously[8]; progression-free survival results in this analysis are descriptive only. Overall survival, a protocol-specified secondary end point, was defined as the time from randomization to death from any cause. Progression-free survival 2, defined as the time from randomization to the first documented disease progression while the patient was receiving next-line therapy (as reported by the investigator) or death from any cause, whichever occurred first, was a prespecified exploratory end point. The time to first subsequent chemotherapy was defined as the time from randomization to the beginning of the first chemotherapy after discontinuation of the trial regimen. Adverse events were continuously monitored throughout the trial and were graded according to the Common Terminology Criteria for Adverse Events, version 4.03.

TRIAL OVERSIGHT

The trial was funded by Novartis and conducted in accordance with the provisions of the Declaration of Helsinki and Good Clinical Practice guidelines. The trial protocol and all amendments were approved by an independent ethics committee or the institutional review board at each site. Trial conduct was supervised by a trial steering committee composed of participating international investigators and representatives of the sponsor. Safety data were assessed by an independent data monitoring committee. Written informed consent was provided by all the patients. Representatives of the sponsor designed the trial and confirmed the accuracy of and compiled the data for analysis. 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 contributed to the writing and review of all manuscript drafts and were involved in the interpretation of the data. Two professional medical writers provided editorial support and were paid by the sponsor.

STATISTICAL ANALYSIS

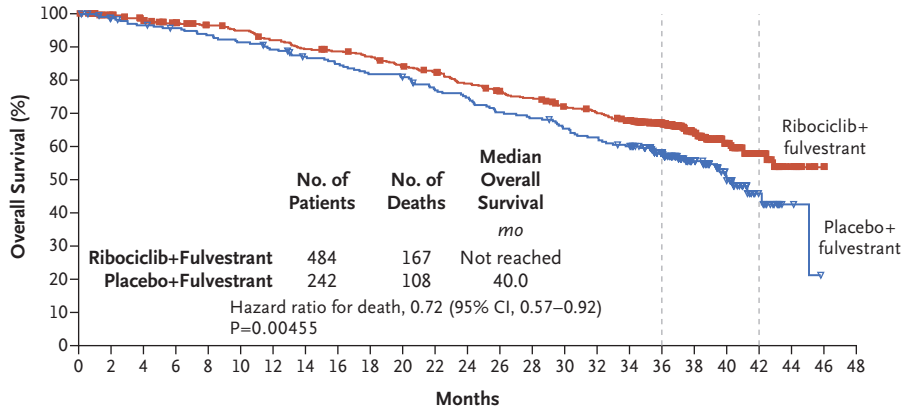
The number of patients required for this trial was calculated on the basis of the primary end point of progression-free survival. The primary analysis of investigator-assessed progression-free survival was conducted after 361 patients had had disease progression or had died at the data-cutoff date of November 3, 2017. A hierarchical testing strategy between progression-free survival and overall survival was used to control the one-sided type I error at 2.5%, and overall survival was to be tested only if the results for progression-free survival were positive.

It was determined that 351 deaths would be required for the trial to have 85% power to reject the null hypothesis of no difference in overall survival between the trial groups in favor of superior efficacy of ribociclib plus fulvestrant as compared with placebo plus fulvestrant, at a one-sided overall significance level of 2.5%, with the use of a three-look group sequential design and a stratified log-rank test. Median overall survival was estimated with the use of the Kaplan–Meier method, and hypothesis testing was carried out with the use of a stratified log-rank test. The one-sided test, which assumes that the treatment effect can go in only one direction, was chosen to test only for the superiority of riboci-

Figure 1 (facing page). Overall Survival in the Overall Population and According to Line of Treatment for Advanced Disease.

Patients with hormone-receptor–positive, human epidermal growth factor receptor 2 (HER2)–negative breast cancer were assigned to receive either ribociclib or placebo in addition to fulvestrant. Panel A shows the overall population, Panel B patients who received trial treatment as first-line therapy, and Panel C patients who received trial treatment as second-line therapy or who had early relapse (within 12 months after completion of adjuvant or neoadjuvant endocrine therapy). In Panel A, the dashed lines represent the estimated overall survival at 36 months and 42 months. In Panel B, the median progression-free survival among patients receiving placebo plus fulvestrant may not be estimated reliably because the last patient died during follow-up at 45.1 months. The squares and triangles in all panels indicate censored data.

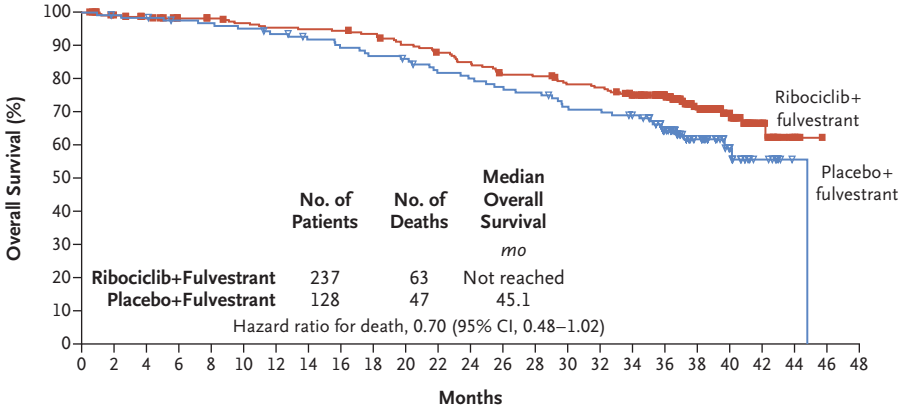
A Overall Population



No. at Risk

Ribociclib+fulvestrant	484	470	454	444	436	428	414	402	397	389	374	365	348	334	326	309	300	287	237	159	92	41	14	2	0
Placebo+fulvestrant	242	233	227	223	218	213	207	199	194	187	184	174	169	159	155	147	141	134	107	64	37	14	3	0	0

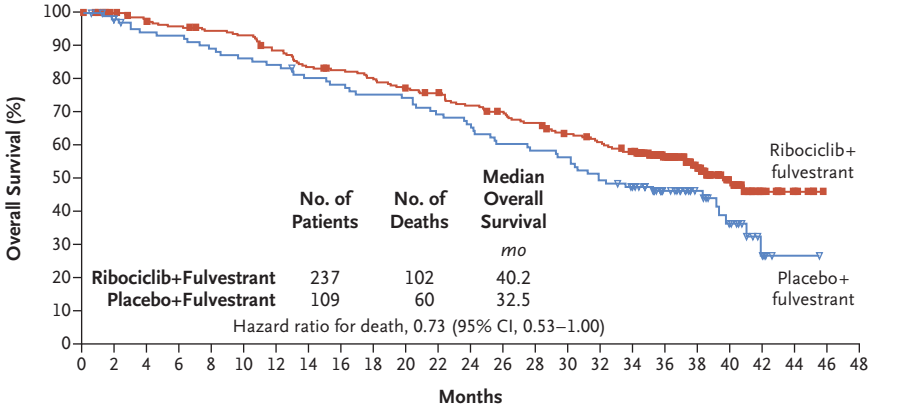
B Patients Receiving First-Line Treatment



No. at Risk

Ribociclib+fulvestrant	237	229	222	217	214	210	207	206	205	202	194	190	182	174	173	166	163	157	138	92	54	22	6	1	0
Placebo+fulvestrant	128	126	125	122	121	119	116	113	110	106	104	99	97	93	91	85	84	82	70	40	21	8	2	0	0

C Patients with Early Relapse or Receiving Second-Line Treatment



No. at Risk

Ribociclib+fulvestrant	237	231	222	218	213	210	199	188	184	179	172	167	158	152	145	135	129	122	94	63	36	17	7	1	0
Placebo+fulvestrant	109	103	98	97	93	90	88	83	81	78	77	72	69	63	61	59	54	49	35	23	15	6	1	0	0

Table 1. Overall Survival and Kaplan–Meier Estimates.*

Variable	Ribociclib Group (N=484)	Placebo Group (N=242)
Deaths — no. (%)	167 (34.5)	108 (44.6)
Data censored†	317 (65.5)	134 (55.4)
Median overall survival (95% CI) — mo	NE (42.5–NE)	40.0 (37.0–NE)
Kaplan–Meier estimated overall survival (95% CI)		
36 mo	67.0 (62.4–71.2)	58.2 (51.5–64.3)
42 mo	57.8 (52.0–63.2)	45.9 (36.9–54.5)

* NE indicates that the value could not be estimated.
† Data for patients were censored at the date that the patient was last known to be alive.

clib plus fulvestrant over placebo plus fulvestrant. The hazard ratio for death in the analysis of overall survival was estimated with the use of a stratified Cox proportional-hazards model. On the basis of the significant difference in progression-free survival between the two groups, the first planned interim analysis of overall survival was performed concurrently and was based on 120 deaths (approximately 34% of the total 351 deaths). Those results did not cross the prespecified Lan–DeMets (O'Brien–Fleming) stopping boundary of a P value threshold of 0.00013. The second interim analysis of overall survival was planned after approximately 263 deaths had occurred (75% of the total 351 deaths). On the basis of the observed number of deaths at the time of this second interim analysis, the P value threshold was 0.01129.

Analyses were performed in the following subgroups: patients receiving first-line therapy and patients receiving second-line therapy plus those with early relapse (within 12 months after completion of adjuvant or neoadjuvant endocrine therapy). An additional exploratory analysis was carried out to assess the consistency of survival benefit in subgroups based on previous response to endocrine therapy. Although not prespecified, this exploratory analysis was performed because of the recent scientific interest in this prognostic factor. During follow-up for survival, descriptive analyses that were defined according to line of therapy for progression-free survival and exploratory analyses of progression-free survival 2 and time to first subsequent chemotherapy were performed. Data on overall survival were censored at the last date that a patient was known to be alive.

RESULTS

PATIENTS AND TREATMENT

From June 2015 through June 2016, a total of 726 patients were randomly assigned in a 2:1 ratio to the ribociclib group (484 patients) or the placebo group (242 patients) (Table S3 and Fig. S1). At the cutoff date for this analysis of overall survival, 121 of 484 patients (25.0%) in the ribociclib group and 32 of 242 patients (13.2%) in the placebo group were still receiving trial treatment. The median duration of follow-up for all patients was 39.4 months (minimum, 35.8 months), and the median duration of treatment was 15.8 months in the ribociclib group and 12.0 months in the placebo group. (A descriptive analysis of time to discontinuation of trial treatment is shown in Fig. S2.)

OVERALL SURVIVAL

At the data cutoff date for the second prespecified interim analysis of overall survival (June 3, 2019), 275 deaths had occurred: 167 among 484 patients (34.5%) in the ribociclib group and 108 among 242 patients (44.6%) in the placebo group. Kaplan–Meier estimated overall survival at 42 months was 57.8% (95% CI, 52.0 to 63.2) in the ribociclib group and 45.9% (95% CI, 36.9 to 54.5) in the placebo group. A significant overall survival benefit was noted in the ribociclib group as compared with the placebo group, with a 28% difference in the relative risk of death (hazard ratio for death, 0.72; 95% CI, 0.57 to 0.92) (Fig. 1A). The one-sided stratified log-rank test P value, 0.00455, crossed the prespecified O'Brien–Fleming stopping boundary to claim superior efficacy (Fig. 1A and Table 1). At the time of this

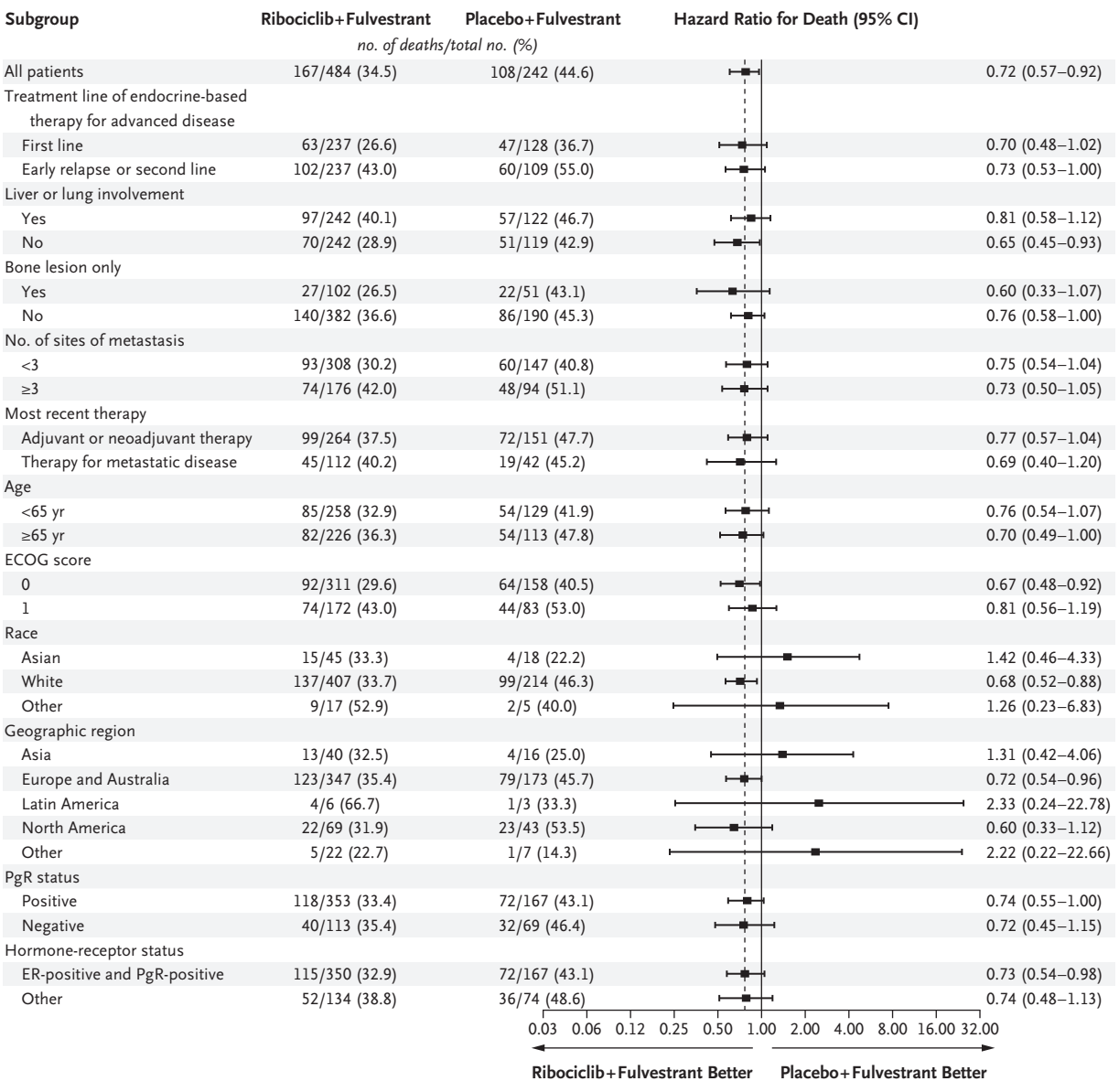
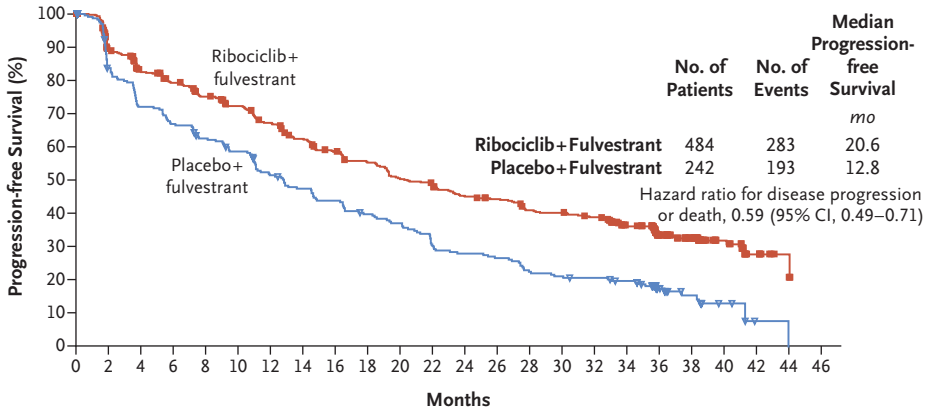


Figure 2. Exploratory Analyses of Overall Survival in Subgroups.

Percentages may not add up to 100 because of rounding. Eastern Cooperative Oncology Group (ECOG) performance-status scores range from 0 to 5, with higher scores indicating greater disability. Race was reported by the patient. The solid vertical line shows the no-effect point, and the dashed vertical line indicates the hazard ratio of 0.72 for the overall population. Hazard ratios were estimated on the basis of a stratified Cox proportional-hazards model, except in subgroups related to stratification factors (presence or absence of lung or liver metastases and previous endocrine therapy), for which an unstratified analysis was used. Subgroup data are based on case-report forms. The hazard ratios for some subgroups had wide confidence intervals owing to the small number of patients. A total of 15 patients were not included in the subgroup analysis with respect to previous endocrine therapy because of missing data or criteria not being met. ER denotes estrogen receptor, and PgR progesterone receptor.

analysis, the median overall survival in the ribociclib group was not reached; the median overall survival in the placebo group was 40.0 months (95% CI, 37.0 to could not be estimated) (Fig. 1A). These results for overall survival are considered final according to the protocol because they

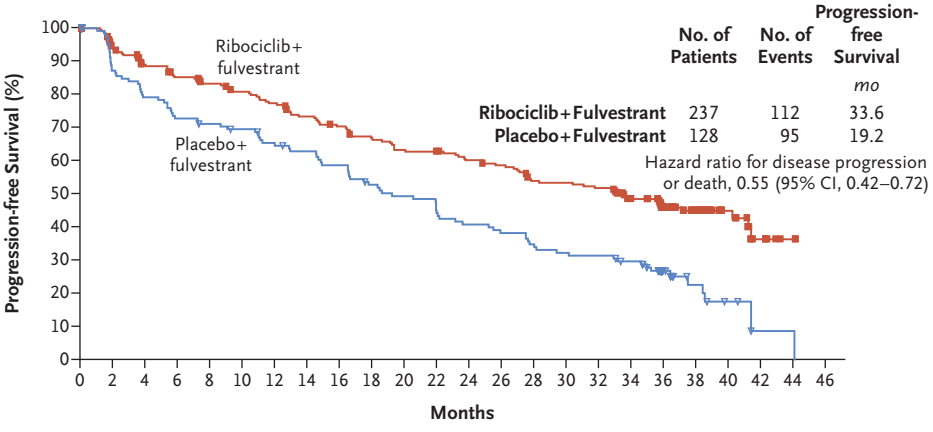
A Overall Population



No. at Risk

Ribociclib+fulvestrant	484	403	364	346	323	305	282	258	239	225	205	198	181	174	159	156	149	127	92	65	29	11	4	0
Placebo+fulvestrant	242	195	168	156	144	134	116	106	98	88	82	68	62	59	51	47	45	41	21	13	6	2	1	0

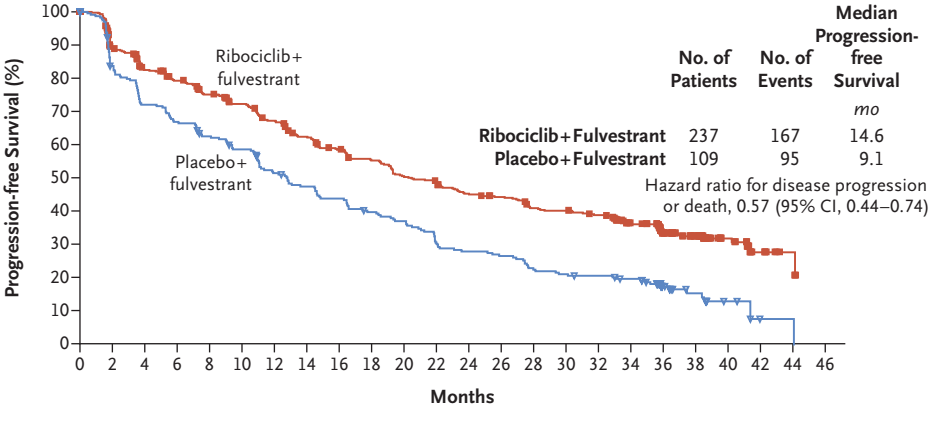
B Patients Receiving First-Line Treatment



No. at Risk

Ribociclib+fulvestrant	237	204	187	178	171	164	157	147	140	132	125	123	117	113	102	101	98	84	63	44	20	7	2	0
Placebo+fulvestrant	128	109	99	91	88	85	78	75	70	62	58	52	48	45	41	38	37	33	17	9	5	1	1	0

C Patients with Early Relapse or Receiving Second-Line Treatment



No. at Risk

Ribociclib+fulvestrant	237	189	168	160	144	134	119	105	93	87	74	69	58	56	52	50	47	41	27	19	9	4	2	0
Placebo+fulvestrant	109	82	66	62	53	46	35	28	25	23	21	14	12	12	8	8	7	7	3	3	1	1	0	0

Figure 3 (facing page). Descriptive Analyses of Progression-free Survival in the Overall Population and According to Line of Treatment for Advanced Disease.

These data are based on a descriptive analysis of progression-free survival. Panel A shows the overall population, Panel B patients who received trial treatment as first-line therapy, and Panel C patients who received trial treatment as second-line therapy or who had early relapse (within 12 months after completion of adjuvant or neoadjuvant endocrine therapy). The squares and triangles in all panels indicate censored data.

crossed the efficacy stopping boundary with a significant superiority of ribociclib over placebo.

Subgroup analyses that were defined according to line of therapy were also performed. Of the 365 patients who received trial treatment as first-line therapy, 63 of 237 patients (26.6%) in the ribociclib group and 47 of 128 patients (36.7%) in the placebo group died. The estimated overall survival at 42 months among the patients who received trial treatment as first-line therapy was 66.9% (95% CI, 58.7 to 73.9) in the ribociclib group and 56.3% (95% CI, 44.2 to 66.8) in the placebo group (hazard ratio for death, 0.70; 95% CI, 0.48 to 1.02) (Fig. 1B). Of the 346 patients who received trial treatment as second-line therapy or who had early relapse, 102 of 237 (43.0%) in the ribociclib group and 60 of 109 (55.0%) in the placebo group died. The median overall survival in this subgroup was 40.2 months in the ribociclib group and 32.5 months in the placebo group (hazard ratio for death, 0.73; 95% CI, 0.53 to 1.00) (Fig. 1C). Results for overall survival in other exploratory subgroups were generally consistent with those in the overall population (Fig. 2), including a post hoc analysis based on previous response to endocrine therapy (Table S4); however, some subgroups (e.g., Asian patients) showed greater variability, possibly because of the small sample size.

PROGRESSION-FREE SURVIVAL

A descriptive update indicated that results for progression-free survival were consistent with those of the primary analysis (Fig. 3).[8] The median progression-free survival in the subgroup of patients who received trial treatment as first-line therapy, which had not been reached in the primary report,[8] was 33.6 months (95% CI, 27.1 to 41.3) in the ribociclib group and 19.2 months (95% CI, 14.9 to 23.6) in the placebo group (hazard ratio for disease progression or death, 0.55; 95% CI, 0.42 to 0.72) (Fig. 3B). (Results for progression-free survival 2 are shown in Fig. S3.)

SUBSEQUENT THERAPY

In total, 362 patients (74.8%) in the ribociclib group and 209 patients (86.4%) in the placebo group discontinued trial treatment. Subsequent antineoplastic therapies were received by 295 of 362 patients (81.5%) in the ribociclib group and 177 of 209 patients (84.7%) in the placebo group (Table S5). Subsequent CDK4/6 inhibitors, including palbociclib, abemaciclib, and ribociclib, were received by 40 of 362 patients (11.0%) in the ribociclib group and 53 of 209 patients (25.4%) in the placebo group (Table S6).

Chemotherapy, alone or in combination, was received as the first subsequent therapy by 205 of the 571 patients who discontinued trial treatment (130 of 362 patients [35.9%] in the ribociclib group and 75 of 209 patients [35.9%] in the placebo group). Estimates for the percentage of patients who had not yet received chemotherapy at 42 months were 56.4% (95% CI, 51.3 to 61.1) in the ribociclib group and 43.7% (95% CI, 36.3 to 50.8) in the placebo group (Fig. 4).

ADVERSE EVENTS

Adverse events were consistent with those in the primary report, and no new safety signals were observed (Table S7).[8] Adverse events were generally more frequent in the ribociclib group, and the most common grade 3 or 4 adverse events were neutropenia (57.1% in the ribociclib group and 0.8% in the placebo group) and leukopenia (15.5% in the ribociclib group and 0% in the placebo group). Other key grade 3 or 4 adverse events of special interest were hepatobiliary toxic effects (13.7% and 5.8%, respectively) and prolonged QT interval (3.1% and 1.2%, respectively). Grade 3 or 4 interstitial lung disease was observed in 1 patient (0.2%) in the ribociclib group and no patients in the placebo group.

DISCUSSION

In this second preplanned interim analysis of overall survival, the addition of ribociclib to fulvestrant was associated with a significant benefit with respect to overall survival, with a 28% relative difference in the risk of death as com-

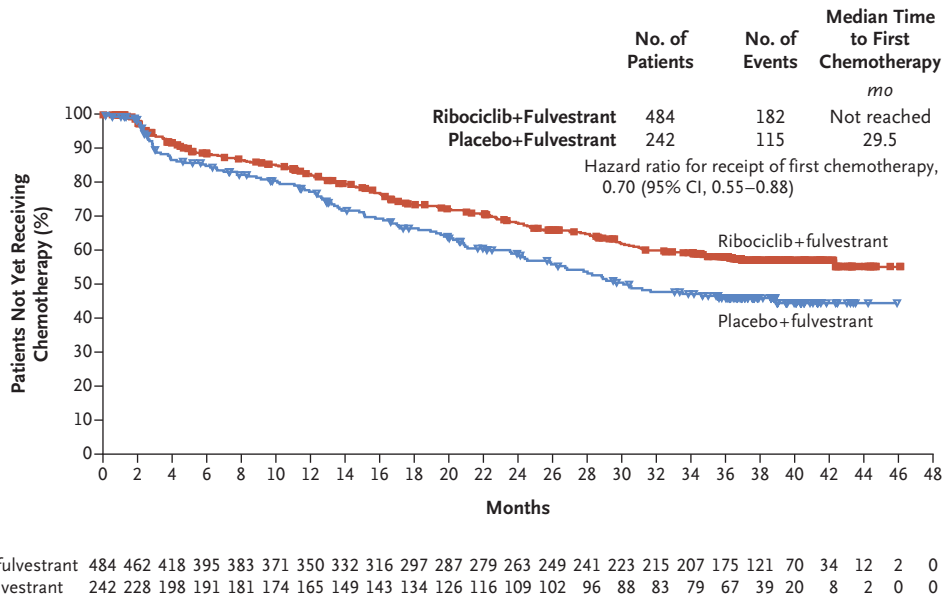


Figure 4. Time to First Subsequent Chemotherapy after Discontinuation.

Time to first subsequent chemotherapy was defined as the time from randomization to the beginning of the first chemotherapy after discontinuation of the trial regimen. The squares and triangles indicate censored data.

pared with placebo. These results crossed the prespecified Lan–DeMets (O'Brien–Fleming) stopping criteria in this second interim analysis and are therefore considered final according to the protocol. At the time of this analysis, 25.0% of the patients in the ribociclib group and 13.2% of those in the placebo group were still receiving trial treatment. The Kaplan–Meier curve for overall survival showed separation between the two groups beginning at approximately 6 months, and the separation widened over time. This overall survival benefit was generally consistent across patient subgroups, including those who received first-line treatment and those who received second-line treatment or who had early relapse after adjuvant or neoadjuvant endocrine therapy. The small subgroup of Asian patients seemed to be an exception. In addition, the longer follow-up at this analysis did not reveal any new safety signals.

The MONALEESA-3 trial is the second large phase 3 trial evaluating a ribociclib combination treatment to show a significant overall survival benefit in patients with advanced hormone-receptor–positive, HER2-negative breast cancer.[12] In the MONALEESA-7 trial, ribociclib combined with endocrine therapy showed a significant overall survival benefit over endocrine therapy alone, with a 29% relative difference in the risk of death among premenopausal or perimenopausal patients. Before the overall survival benefit shown in the MONALEESA-7 trial, it had been considered challenging for targeted therapies to show a significant improvement in overall survival among patients with hormone-receptor–positive, HER2-negative advanced breast cancer, probably because of trial-group crossover and subsequent receipt of active treatments.[11,14] Although cross-trial comparisons must be made with caution, data on overall survival have been reported in two other phase 3 trials with CDK4/6 inhibitor combinations.[11,13] The PALOMA-3 trial showed a longer overall survival with the addition of palbociclib to fulvestrant that did not achieve significance (hazard ratio for death, 0.81; 95% CI, 0.64 to 1.03), and the MONARCH 2 trial showed a significant difference for the addition of abemaciclib to fulvestrant, with a hazard ratio for death of 0.76 (95% CI, 0.61 to 0.95).[11,13] Results for overall survival with ribociclib in combination with endocrine therapy reached significance in two phase 3 trials, with hazard ratios for death of 0.71 (95% CI, 0.54 to 0.95) in the MONALEESA-7 trial and 0.72

(95% CI, 0.57 to 0.92) in the MONALEESA-3 trial.[12] Possible explanations for these differences in treatment effects with regard to overall survival may include differences in patient populations and unique pharmacologic properties of the individual CDK4/6 inhibitors, such as pharmacokinetics and the degree of selectivity for CDK4 as compared with CDK6 (e.g., ribociclib is more selective for CDK4 than for CDK6).[15-17]

Previously, the longest median progression-free survival for first-line treatment with CDK4/6 inhibitors plus endocrine therapy in postmenopausal patients had been 28 months.[5,7,18-20] In the descriptive update of progression-free survival performed during this interim analysis, the median progression-free survival among patients receiving first-line therapy was 33.6 months (95% CI, 27.1 to 41.3) in the ribociclib group. This finding, together with data on overall survival, may support consideration of ribociclib plus fulvestrant as initial therapy in patients with advanced disease. Progression-free and overall survival among patients receiving second-line therapy or who had early relapse also suggested benefit with ribociclib and were consistent with the findings in the overall population. Investigation into the appropriate treatment sequence for CDK4/6 inhibitors in patients with hormone-receptor–positive, HER2-negative advanced breast cancer is ongoing.

Most patients received a subsequent therapy after discontinuation of trial treatment, a finding consistent with those of other trials investigating a CDK4/6 inhibitor. Both time to subsequent chemotherapy and progression-free survival 2 were longer in the ribociclib group than in the placebo group, despite the percentage of patients with subsequent CDK4/6 inhibitor use being higher in the placebo group (25.4%) than in the ribociclib group (11.0%).[11,12]

The benefits of ribociclib with respect to overall survival in the MONALEESA program are noteworthy in the context of CDK4/6 inhibitors in advanced breast cancer. The combinations of ribociclib with fulvestrant in the MONALEESA-3 trial and with endocrine therapy, particularly nonsteroidal aromatase inhibitors, in the MONALEESA-7 trial have shown a consistent and meaningful prolongation of survival over placebo. Indeed, both trials showed an approximate 30% difference in the relative risk of death with ribociclib as compared with placebo in combination with different endocrine-therapy partners, regardless of menopausal status in patients with hormone-receptor–positive, HER2-negative advanced breast cancer. These data support the further study of ribociclib, including in the treatment of early breast cancer.

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APPENDIX

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