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ORIGINAL ARTICLE

Overall Survival with Palbociclib and Fulvestrant in Advanced Breast Cancer

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ABSTRACT

BACKGROUND

The cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitor palbociclib, in combination with fulvestrant therapy, prolongs progression-free survival among patients with hormone-receptor–positive, human epidermal growth factor receptor 2 (HER2)–negative advanced breast cancer. We report the results of a prespecified analysis of overall survival.

METHODS

We randomly assigned patients with hormone-receptor–positive, HER2-negative advanced breast cancer who had progression or relapse during previous endocrine therapy to receive palbociclib plus fulvestrant or placebo plus fulvestrant. We analyzed overall survival; the effect of palbociclib according to the prespecified stratification factors of presence or absence of sensitivity to endocrine therapy, presence or absence of visceral metastatic disease, and menopausal status; the efficacy of subsequent therapies after disease progression; and safety.

RESULTS

Among 521 patients who underwent randomization, the median overall survival was 34.9 months (95% confidence interval [CI], 28.8 to 40.0) in the palbociclib–fulvestrant group and 28.0 months (95% CI, 23.6 to 34.6) in the placebo–fulvestrant group (hazard ratio for death, 0.81; 95% CI, 0.64 to 1.03; P=0.09; absolute difference, 6.9 months). CDK4/6 inhibitor treatment after the completion of the trial regimen occurred in 16% of the patients in the placebo–fulvestrant group. Among 410 patients with sensitivity to previous endocrine therapy, the median overall survival was 39.7 months (95% CI, 34.8 to 45.7) in the palbociclib–fulvestrant group and 29.7 months (95% CI, 23.8 to 37.9) in the placebo–fulvestrant group (hazard ratio, 0.72; 95% CI, 0.55 to 0.94; absolute difference, 10.0 months). The median duration of subsequent therapy was similar in the two groups, and the median time to the receipt of chemotherapy was 17.6 months in the palbociclib–fulvestrant group, as compared with 8.8 months in the placebo–fulvestrant group (hazard ratio, 0.58; 95% CI, 0.47 to 0.73; P<0.001). No new safety signals were observed with 44.8 months of follow-up.

CONCLUSIONS

Among patients with hormone-receptor–positive, HER2-negative advanced breast cancer who had sensitivity to previous endocrine therapy, treatment with palbociclib–fulvestrant resulted in longer overall survival than treatment with placebo–fulvestrant. The differences in overall survival in the entire trial group were not significant. (Funded by Pfizer; PALOMA-3 ClinicalTrials.gov number, NCT01942135.)

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In 2018, approximately 266,000 new cases of breast cancer are estimated to occur in women in the United States, with 41,000 deaths.[1] Of these, hormone-receptor–positive breast cancer is the most common disease subtype.[2] The cyclin-dependent kinases 4 and 6 (CDK4/6) are key promoters of tumor growth in hormone-receptor–positive breast cancer, cooperating with estrogen-receptor pathway activation.[3,4] Preclinical models of hormone-receptor–positive breast cancer were highly sensitive to the CDK4/6 inhibitor palbociclib (Ibrance, Pfizer),[4] and in a subsequent phase 2 study (Palbociclib: Ongoing Trials in the Management of Breast Cancer [PALOMA]–1), palbociclib resulted in a progression-free survival benefit in patients with previously untreated, estrogen-receptor–positive, human epidermal growth factor receptor 2 (HER2)–negative advanced breast cancer.[5] Subsequently, the randomized, phase 3 trial PALOMA-2 confirmed that palbociclib substantially prolonged progression-free survival, in combination with letrozole, as first-line therapy for estrogen-receptor–positive, HER2-negative advanced breast cancer (hazard ratio for disease progression or death, 0.58; 95% confidence interval [CI], 0.46 to 0.72).[6]

In the phase 3 trial PALOMA-3, we assessed whether treatment with palbociclib, in combination with fulvestrant, prolonged progression-free survival among patients with hormone-receptor–positive, HER2-negative advanced breast cancer who had disease progression after previous endocrine therapy. The primary aim of the trial was met, with the trial showing significantly longer progression-free survival with combination palbociclib–fulvestrant therapy than with placebo–fulvestrant (median, 11.2 months [95% CI, 9.5 to 12.9] vs. 4.6 months [95% CI, 3.5 to 5.6]; hazard ratio for disease progression or death, 0.50; 95% CI, 0.40 to 0.62; absolute difference, 6.6 months).[7-9]

Palbociclib and other CDK4/6 inhibitors in combination with endocrine therapy have become a standard of care on the basis of prolonged progression-free survival.[5,10,11] However, long-term data regarding the effect of palbociclib on overall survival and the efficacy of subsequent therapy have been limited. Here, we report the results of a prespecified analysis of the PALOMA-3 trial in which we assessed the effect of palbociclib on overall survival and the efficacy of therapies administered after disease progression.

Methods

Trial Design and Patients

We conducted this prospective, international, randomized, double-blind, placebo-controlled, phase 3 trial to compare treatment with palbociclib–fulvestrant with placebo–fulvestrant in women with hormone-receptor–positive, HER2-negative advanced breast cancer who had disease progression after previous endocrine therapy. Patients were randomly assigned, in a 2:1 ratio, to receive either palbociclib (at a dose of 125 mg, administered orally, once daily for 21 consecutive days, followed by 7 days off, to comprise a complete cycle of 28 days) plus fulvestrant (at a dose of 500 mg, administered as an intramuscular injection according to standard of care, every 14 days for the first three injections and then every 28 days) or placebo plus fulvestrant. Crossover between the two groups was not permitted.

Women were enrolled regardless of menopausal status; postmenopausal women were at least 60 years of age, had undergone bilateral oophorectomy, or were younger than 60 years of age and had had a cessation of regular menses for at least 12 consecutive months. Premenopausal or perimenopausal patients were required to receive concurrent goserelin for at least 4 weeks before the start of the trial intervention and to continue receiving it every 28 days for the duration of the trial intervention.

Randomization was stratified according to the presence or absence of documented sensitivity to previous endocrine therapy, the presence or absence of visceral metastatic disease, and menopausal status at trial entry. Sensitivity to previous endocrine therapy was defined as either a documented clinical benefit (complete response, partial response, or stable disease for ≥24 weeks) from at least one previous endocrine therapy regimen in the context of metastatic disease or the receipt of at least 24 months of adjuvant endocrine therapy before recurrence. Detailed methods of this trial have been reported previously.[7,8] The protocol, with the statistical analysis plan, is available with the full text of this article at NEJM.org.

End Points

The primary end point, investigator-assessed progression-free survival, was reported previously.[7,8] Overall survival, a prespecified key secondary

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end point, was defined as the time from randomization to death from any cause. Exploratory analyses included the investigator-assessed time receiving subsequent therapy (i.e., the time from randomization to the end of the immediate subsequent line of therapy after disease progression) and time from randomization to the receipt of chemotherapy. Safety data were updated with additional follow-up time.

OVERSIGHT

The trial was designed by an academic steering committee that included representatives of the sponsor (Pfizer). Data were gathered by representatives of the sponsor. All the authors confirm that the trial conformed to the protocol and attest to the accuracy and completeness of the data. All the authors and participating institutions have agreements with the sponsor regarding confidentiality of the data. The first author wrote the first draft of the manuscript. All the authors had full access to the data and were involved in interpreting the data, in writing and reviewing subsequent drafts of the manuscript, and in making the decision to submit the manuscript for publication. A professional medical writer provided editorial assistance and was paid by the sponsor. AstraZeneca provided fulvestrant and had no involvement with the data collection or analysis or with any aspect of the manuscript preparation.

The trial was approved by the institutional review board at each site, and all the patients provided written informed consent before enrollment. The trial was conducted according to the principles of Good Clinical Practice and the Declaration of Helsinki. The conduct of the trial was monitored by an academic steering committee.

STATISTICAL ANALYSIS

The median overall survival among women with advanced or metastatic breast cancer who are treated with fulvestrant monotherapy was assumed to be 24 months. The trial was powered for its primary end point, progression-free survival. The planned final analysis of overall survival was performed after approximately 60% data maturity (i.e., when death had occurred in 60% of the 521 patients who had undergone randomization), with one interim analysis of overall survival conducted at the time of the interim analysis of progression-free survival, when 28 deaths had occurred, and one interim analysis conducted when 112 deaths had occurred. The family-wise error rate was protected at the one-sided 0.025 level, with a hierarchical testing strategy between progression-free survival and overall survival.[12,13] The median overall survival was estimated with the use of the Kaplan–Meier method, and the significance was determined with the use of a one-sided log-rank test with stratification according to presence or absence of sensitivity to previous endocrine therapy and the presence or absence of visceral metastases at randomization in the intention-to-treat population. All the P values reported herein are two-sided. The prespecified significance threshold was a two-sided P value of 0.047, which was adjusted for the planned interim analyses. The rank-preserving structural-failure time method was used as a sensitivity analysis to evaluate the effect of crossover to receive a CDK4/6 inhibitor in the placebo–fulvestrant group after the completion of the trial intervention. The rank-preserving structural-failure time analysis is based on the intention-to-treat population and can provide a more accurate estimation of the treatment effect by correcting for crossover between groups.[14,15]

RESULTS

PATIENTS

A total of 521 patients were enrolled between October 7, 2013, and August 26, 2014 (Fig. S1 in the Supplementary Appendix, available at NEJM .org). A total of 347 patients were randomly assigned to the palbociclib–fulvestrant group and 174 to the placebo–fulvestrant group (intention-to-treat population). A total of 345 patients in the palbociclib–fulvestrant group and 172 in the placebo–fulvestrant group received at least one dose of the assigned intervention (safety population).

Double-blinding was maintained after both the primary analysis and the interim analysis. After a request from the investigator, unblinding occurred in 12 patients (3%) who received palbociclib and in 18 (10%) who received placebo. Most of these unblinding events (in 7 patients in the palbociclib–fulvestrant group and in 17 in the placebo–fulvestrant group) occurred after disease progression.

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OVERALL SURVIVAL

The data regarding overall survival were analyzed at a cutoff date of April 13, 2018, with a median follow-up of 44.8 months and 60% data maturity (310 deaths among 521 patients). A total of 201 deaths occurred in the palbociclib–fulvestrant group, and 109 deaths in the placebo–fulvestrant group. The median overall survival was 34.9 months (95% CI, 28.8 to 40.0) in the palbociclib–fulvestrant group and 28.0 months (95% CI, 23.6 to 34.6) in the placebo–fulvestrant group. The stratified hazard ratio for death was 0.81 (95% CI, 0.64 to 1.03; P=0.09) (Fig. 1A). The unstratified hazard ratio was 0.79 (95% CI, 0.63 to 1.00). The estimated rate of overall survival at 3 years in the Kaplan–Meier analysis was 50% (95% CI, 44 to 55) in the palbociclib–fulvestrant group and 41% (95% CI, 33 to 48) in the placebo–fulvestrant group.

Subgroup analyses of overall survival were performed in prespecified subgroups (Fig. 1B). The three prespecified stratification factors were the presence or absence of sensitivity to previous endocrine therapy, the presence or absence of visceral metastatic disease, and menopausal status. Among 410 patients with documented sensitivity to previous endocrine therapy, the median overall survival was 39.7 months (95% CI, 34.8 to 45.7) in the palbociclib–fulvestrant group and 29.7 months (95% CI, 23.8 to 37.9) in the placebo–fulvestrant group (hazard ratio for death, 0.72; 95% CI, 0.55 to 0.94) (Figs. 1B and 2A). Among 111 patients without documented sensitivity to previous endocrine therapy (also referred to as intrinsic endocrine resistance), the median overall survival was 20.2 months (95% CI, 17.2 to 26.4) in the palbociclib–fulvestrant group and 26.2 months (95% CI, 17.5 to 31.8) in the placebo–fulvestrant group (hazard ratio, 1.14; 95% CI, 0.71 to 1.84; P=0.12 for interaction) (Figs. 1B and 2B). In the updated analysis of PALOMA-3, which was conducted at a data cutoff of October 23, 2015, patients with sensitivity to previous endocrine therapy had progression-free survival that was 7.8 months longer in the palbociclib–fulvestrant group than in the placebo–fulvestrant group (hazard ratio for disease progression or death, 0.46; 95% CI, 0.36 to 0.59), whereas patients with intrinsic endocrine resistance had progression-free survival that was 2.3 months longer (hazard ratio, 0.69; 95% CI, 0.43 to 1.09) (Fig. S2 in the Supplementary Appendix).

Among 311 patients with visceral metastatic disease, the median overall survival was 27.6 months (95% CI, 24.4 to 31.2) in the palbociclib–fulvestrant group and 24.7 months (95% CI, 20.8 to 31.8) in the placebo–fulvestrant group (hazard ratio for death, 0.85; 95% CI, 0.64 to 1.13) (Fig. 1B). Among 210 patients without visceral metastatic disease, the median overall survival was 46.9 months (95% CI, 39.3 to could not be estimated) in the palbociclib–fulvestrant group and 35.4 months (95% CI, 24.6 to could not be estimated) in the placebo–fulvestrant group (hazard ratio, 0.69; 95% CI, 0.46 to 1.04; P=0.44 for interaction) (Fig. 1B).

Among 413 postmenopausal patients, the median overall survival was 34.8 months (95% CI, 28.8 to 40.1) in the palbociclib–fulvestrant group and 27.1 months (95% CI, 22.8 to 32.1) in the placebo–fulvestrant group (hazard ratio for death, 0.73; 95% CI, 0.57 to 0.95) (Fig. 1B, and Fig. S3A in the Supplementary Appendix). Among 108 premenopausal or perimenopausal patients, the median overall survival was 38.0 months (95% CI, 24.4 to could not be estimated) in the palbociclib–fulvestrant group and 38.0 months (95% CI, 22.2 to could not be estimated) in the placebo–fulvestrant group (hazard ratio, 1.07; 95% CI, 0.61 to 1.86; P=0.25 for interaction) (Fig. 1B, and Fig. S3B in the Supplementary Appendix).

An exploratory subgroup analysis evaluated overall survival according to *ESR1* and *PIK3CA* mutation status, as assessed in baseline circulating tumor DNA. The median overall survival was longer with palbociclib–fulvestrant than with placebo–fulvestrant among patients with baseline *ESR1* mutations than among those without such mutations (absolute difference, 11.0 months among patients with *ESR1* mutations and 4.7 months among those without such mutations; P=0.60 for interaction) (Fig. 1B). The absolute between-group differences in overall survival were similar among patients with baseline *PIK3CA* mutations and those without such mutations (6.4 months and 5.8 months, respectively; P=0.64 for interaction) (Fig. 1B).

EXPOSURE TO TRIAL INTERVENTION

The median number of cycles of therapy received was 12 (interquartile range, 4 to 21) in the palbociclib–fulvestrant group and 5 (interquartile range, 2 to 12) in the placebo–fulvestrant group. The Kaplan–Meier estimate of the rate of pa-

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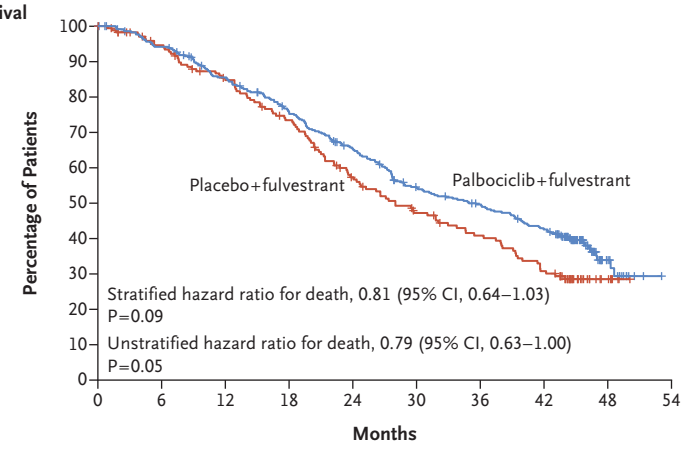
A Overall Survival



	No. of Patients	Median Overall Survival (95% CI)
		mo
Palbociclib+ Fulvestrant	347	34.9 (28.8–40.0)
Placebo+ Fulvestrant	174	28.0 (23.6–34.6)

No. at Risk

Palbociclib+fulvestrant	347	321	286	247	209	165	148	126	17	—
Placebo+fulvestrant	174	155	135	115	86	68	57	43	7	—

B Subgroup Analyses

Subgroup	No. of Patients (%)	Hazard Ratio for Death (95% CI)	Median Overall Survival (95% CI)		P Value for Interaction
			Palbociclib+ fulvestrant	Placebo+ fulvestrant	
			mo		
All patients					
Stratified analysis	521 (100)	0.81 (0.64–1.03)	34.9 (28.8–40.0)	28.0 (23.6–34.6)	
Unstratified analysis	521 (100)	0.79 (0.63–1.00)	34.9 (28.8–40.0)	28.0 (23.6–34.6)	
Sensitivity to previous hormonal therapy					0.12
Yes	410 (79)	0.72 (0.55–0.94)	39.7 (34.8–45.7)	29.7 (23.8–37.9)	
No	111 (21)	1.14 (0.71–1.84)	20.2 (17.2–26.4)	26.2 (17.5–31.8)	
Site of metastatic disease					0.44
Visceral	311 (60)	0.85 (0.64–1.13)	27.6 (24.4–31.2)	24.7 (20.8–31.8)	
Nonvisceral	210 (40)	0.69 (0.46–1.04)	46.9 (39.3–NE)	35.4 (24.6–NE)	
Menopausal status at study entry					0.25
Postmenopausal	413 (79)	0.73 (0.57–0.95)	34.8 (28.8–40.1)	27.1 (22.8–32.1)	
Premenopausal or perimenopausal	108 (21)	1.07 (0.61–1.86)	38.0 (24.4–NE)	38.0 (22.2–NE)	
Age					0.04
<65 yr	392 (75)	0.91 (0.70–1.20)	31.4 (27.4–39.3)	29.7 (24.0–38.0)	
≥65 yr	129 (25)	0.52 (0.33–0.82)	39.7 (30.7–47.0)	23.8 (20.0–33.8)	
Race or ethnic group					0.38
White	385 (74)	0.78 (0.60–1.01)	31.7 (27.6–38.9)	26.2 (21.4–32.1)	
Asian	105 (20)	1.04 (0.57–1.93)	43.7 (28.8–NE)	41.7 (29.7–NE)	
Black or other	29 (6)	0.47 (0.16–1.32)	37.3 (23.8–NE)	19.7 (4.4–NE)	
Hormone-receptor status					0.70
ER-positive and PR-positive	351 (67)	0.77 (0.57–1.03)	39.3 (32.0–45.7)	31.8 (24.0–39.1)	
ER-positive and PR-negative	142 (27)	0.86 (0.56–1.32)	27.6 (22.0–38.9)	24.3 (17.5–37.5)	
Disease-free interval					0.08
≤24 mo	62 (12)	1.31 (0.71–2.44)	19.9 (15.6–27.6)	20.3 (9.3–42.2)	
>24 mo	292 (56)	0.70 (0.52–0.96)	39.3 (31.7–44.5)	29.5 (22.8–38.1)	
Previous chemotherapy					0.66
Neoadjuvant or adjuvant treatment only	214 (41)	0.81 (0.56–1.17)	36.6 (28.9–42.3)	27.4 (22.2–39.5)	
Treatment for metastatic disease	177 (34)	0.91 (0.63–1.32)	25.6 (21.4–30.1)	26.2 (20.0–37.5)	
None	130 (25)	0.68 (0.41–1.15)	46.2 (36.5–NE)	29.7 (22.8–NE)	
Previous lines of therapy for metastatic disease					0.88
0	114 (22)	0.70 (0.43–1.14)	36.1 (27.6–43.7)	24.7 (19.5–34.6)	
1	225 (43)	0.86 (0.60–1.22)	38.0 (27.7–46.5)	33.8 (23.5–41.4)	
2	131 (25)	0.76 (0.48–1.22)	30.0 (23.0–40.1)	24.3 (20.0–29.7)	
≥3	51 (10)	0.64 (0.29–1.40)	34.8 (26.1–NE)	27.1 (5.3–NE)	
ESR1 mutation status					0.60
Positive	106 (20)	0.69 (0.43–1.12)	35.6 (23.6–42.0)	24.6 (19.7–33.0)	
Negative	289 (55)	0.85 (0.61–1.19)	36.5 (28.0–43.1)	31.8 (22.8–39.1)	
PIK3CA mutation status					0.64
Positive	133 (26)	0.74 (0.48–1.14)	28.6 (25.3–39.3)	22.2 (15.7–29.5)	
Negative	262 (50)	0.84 (0.59–1.18)	38.8 (28.9–44.5)	33.0 (24.3–41.6)	

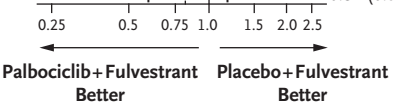


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Figure 1 (facing page). Overall Survival in the Overall Population and According to Subgroup.

Panel A shows overall survival in the intention-to-treat population (all the patients who underwent randomization). Tick marks indicate censored data. Panel B shows a subgroup analysis of overall survival. Boxes represent hazard ratios for death, with error bars indicating 95% confidence intervals, in various subgroups according to characteristics of the patients at baseline. The prespecified stratification factors were the presence or absence of sensitivity to previous endocrine therapy, presence or absence of visceral metastatic disease, and menopausal status at trial entry. Race was reported by the patient; 2 patients (<1%) did not report their race on the case-report form. A total of 6% of the patients had estrogen receptor (ER)–negative, progesterone receptor (PR)–positive tumors. A total of 32% of the patients had received an initial diagnosis of metastatic disease or did not have data regarding a date of the initial diagnosis of early-stage disease, so they were not included in the estimation of values for the disease-free interval. Data regarding *ESR1* (encoding estrogen receptor 1) and *PIK3CA* (encoding phosphatidylinositol 3-kinase catalytic alpha polypeptide) were from a subgroup of patients who had samples of circulating tumor DNA that were tested for the mutations; 25% of the patients did not have adequate circulating tumor DNA for testing. NE indicates that the value could not be estimated.

tients continuing the trial intervention at 24 months was 23% (95% CI, 19 to 28) in the palbociclib–fulvestrant group and 10% (95% CI, 6 to 15) in the placebo–fulvestrant group, and the rate at 36 months was 14% (95% CI, 11 to 18) and 5% (95% CI, 3 to 9), respectively (Fig. 3). At the time of the analysis, 35 patients (10%) were continuing to receive the trial intervention in the palbociclib–fulvestrant group (median duration, 45.4 months; range, 44.2 to 51.4), as compared with 6 patients (3%) in the placebo–fulvestrant group (median duration, 44.7 months; range, 44.2 to 45.6).

DISEASE PROGRESSION AFTER TRIAL INTERVENTION

In the intention-to-treat population, 389 patients (75%) received therapy after the end of trial intervention. The median number of lines of treatment received after disease progression was 2 (range, 1 to 10) in the palbociclib–fulvestrant group and 3 (range, 1 to 10) in the placebo–fulvestrant group. The type of subsequent treatment was similar in the two trial groups, except for subsequent CDK4/6 inhibitor treatment (Table 1). Approximately 40% of the patients in each group received endocrine-based therapy as the immediate subsequent line of treatment.

Although the protocol did not allow patients to cross over to receive palbociclib, treatment with a CDK4/6 inhibitor in the subsequent or following lines of treatment after the trial intervention occurred in 4% of patients in the palbociclib–fulvestrant group and 16% of those in the placebo–fulvestrant group (Table 1). We performed a sensitivity analysis to explore the effect of this crossover on overall survival. The rank-preserving structural-failure time analysis suggested a small decrease in overall survival in the placebo–fulvestrant group after correction for the crossover effect of 27 patients (median overall survival, 27.4 months [95% CI, 23.8 to 35.4]; stratified hazard ratio for death in the palbociclib–fulvestrant group vs. the crossover-corrected placebo–fulvestrant group, 0.78 [bootstrapped 95% CI, 0.61 to 1.04]; unstratified hazard ratio, 0.77 [bootstrapped 95% CI, 0.60 to 1.00]), as compared with a median overall survival of 28.0 months before adjustment.

TIME RECEIVING SUBSEQUENT LINE OF THERAPY

In exploratory analyses, we analyzed the time from randomization to the end of the immediate subsequent line of therapy after disease progression, which was 18.8 months (95% CI, 16.4 to 20.5) in the palbociclib–fulvestrant group and 14.1 months (95% CI, 12.0 to 16.7) in the placebo–fulvestrant group (hazard ratio, 0.68; 95% CI, 0.56 to 0.84; P<0.001). The time from randomization to the first use of chemotherapy after disease progression was 17.6 months (95% CI, 15.2 to 19.7) in the palbociclib–fulvestrant group, as compared with 8.8 months (95% CI, 7.3 to 12.7) in the placebo–fulvestrant group (hazard ratio, 0.58; 95% CI, 0.47 to 0.73; P<0.001). The duration of the immediate subsequent line of therapy, according to type of treatment, was similar in the palbociclib–fulvestrant group and the placebo–fulvestrant group. Details are provided in Figures S4 and S5 in the Supplementary Appendix.

ADVERSE EVENTS

The adverse-event profile of palbociclib–fulvestrant remained consistent with that in the primary analysis (Table S1 in the Supplementary Appendix).[7] Neutropenia of grade 3 or 4 occurred in 70% of the patients receiving palboci-

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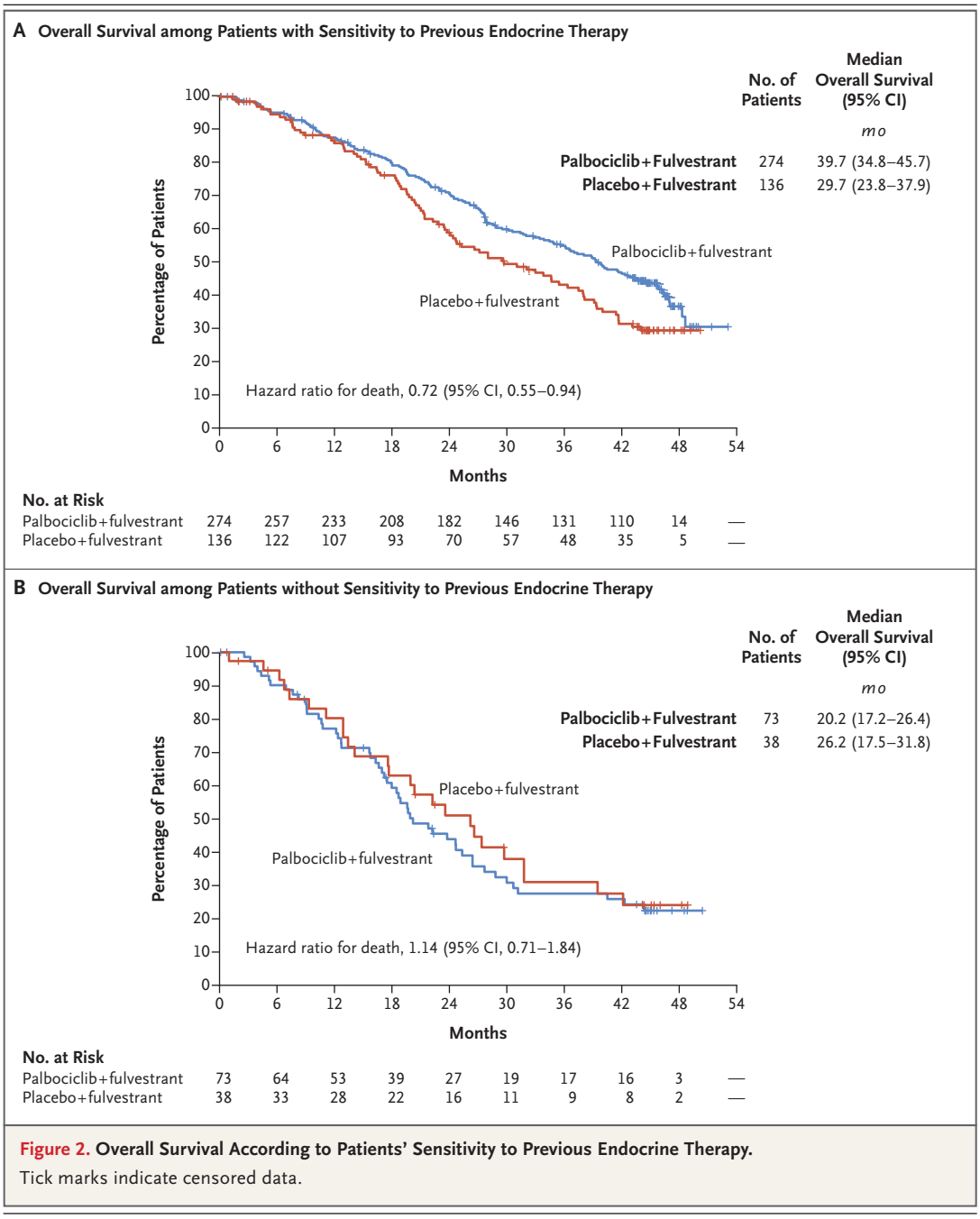

Figure 2. Overall Survival According to Patients' Sensitivity to Previous Endocrine Therapy.
Tick marks indicate censored data.

clib–fulvestrant and in none of the patients receiving placebo–fulvestrant, anemia of grade 3 or 4 occurred in 4% and 2% of the patients, respectively, and thrombocytopenia of grade 3 or 4 occurred in 3% and none of the patients, respectively. Febrile neutropenia remained uncommon, occurring in 1% of the patients (3 of 345 patients) who received palbociclib–fulvestrant and in none of those who received placebo–fulvestrant. Nonhematologic adverse events of grade 3 or 4 were also uncommon. Events of grade 3 or 4 that occurred at a frequency of more than 2% of the patients in the palbociclib–fulvestrant group were infections (in 5% of the patients in the palbociclib–fulvestrant group and in 3% of those in the placebo–fulvestrant group), fatigue (in 3% and 1%, respectively), and elevation in the aspartate aminotransferase level (in 3% and 2%).

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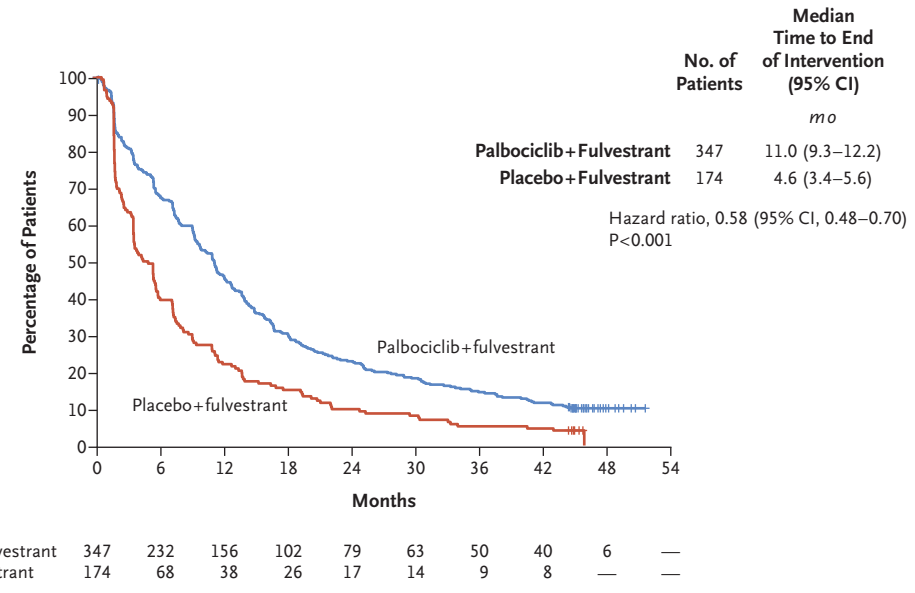

Figure 3. Time from Randomization to the End of the Trial Intervention.
Tick marks indicate censored data.

DISCUSSION

Although the results of the analysis of overall survival did not meet the prespecified threshold for statistical significance, the addition of palbociclib to fulvestrant resulted in an absolute prolongation of overall survival of 6.9 months among patients with hormone-receptor–positive, HER2-negative advanced breast cancer who had disease progression after previous endocrine therapy. This result is consistent with the significant prolongation in progression-free survival that was observed with the addition of palbociclib to fulvestrant (Fig. S6 in the Supplementary Appendix). Among patients with previous sensitivity to endocrine therapy, one of the largest subpopulations enrolled in the trial, overall survival was prolonged by 10.0 months.

Multiple studies have shown that the addition of CDK4/6 inhibitors to endocrine therapy results in substantially prolonged progression-free survival. Improvement has been observed in combination with aromatase inhibitors[6,16-18] and fulvestrant[7,19,20] for palbociclib, ribociclib, and abemaciclib therapy. A key issue has been the extent to which this benefit in progression-free survival translates to a prolongation of overall survival. In the PALOMA-3 trial, we found that the magnitude of improvement in progression-free survival (6.6 months longer with the addition of palbociclib to fulvestrant)[9] translates directly to an improvement in overall survival of similar magnitude in the overall group of trial patients (6.9 months longer), but the difference did not reach statistical significance. This improvement was associated with a longer time from randomization to the end of the immediate subsequent line of therapy after disease progression and a longer time from randomization to the first use of chemotherapy after disease progression among patients treated with palbociclib–fulvestrant than among those who received placebo–fulvestrant. Furthermore, with this longer follow-up, a subgroup of patients who were treated with palbociclib–fulvestrant had a very long duration of disease control, with 14% of the patients continuing in the trial after 3 years of treatment with palbociclib–fulvestrant, as compared with 5% of those receiving placebo–fulvestrant.

Final data regarding overall survival from phase 3 trials of letrozole and CDK4/6 inhibitors are limited. These trials all have lower power for the statistical analysis of overall survival than for the statistical analysis of progression-free survival, and therefore the data presented in this article should be interpreted cautiously when deciding on the timing of CDK4/6 inhibitor therapy. Our data support the use of palbociclib–fulvestrant

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Table 1. Systemic Anticancer Therapies Received as First, Second, and Third or Greater Lines of Subsequent Treatment by More Than 10% of the Patients in Either Trial Group Who Discontinued the Intervention.*

Treatment	Palbociclib–Fulvestrant Group (N=347)			Placebo–Fulvestrant Group (N=174)		
	First Line	Second Line	Third Line or Greater	First Line	Second Line	Third Line or Greater
	number of patients (percent)					
Any†	248 (71)	182 (52)	131 (38)	140 (80)	113 (65)	85 (49)
Chemotherapy						
Any	138 (56)	133 (73)	121 (92)	87 (62)	76 (67)	76 (89)
Eribulin	7 (3)	13 (7)	42 (32)	3 (2)	11 (10)	29 (34)
Paclitaxel	31 (12)	39 (21)	42 (32)	31 (22)	18 (16)	28 (33)
Capecitabine	66 (27)	43 (24)	36 (27)	36 (26)	20 (18)	24 (28)
Doxorubicin	12 (5)	7 (4)	35 (27)	1 (1)	10 (9)	12 (14)
Vinorelbine	6 (2)	8 (4)	23 (18)	7 (5)	5 (4)	21 (25)
Gemcitabine	7 (3)	6 (3)	26 (20)	5 (4)	9 (8)	15 (18)
Cyclophosphamide	13 (5)	9 (5)	23 (18)	8 (6)	4 (4)	8 (9)
Carboplatin	5 (2)	6 (3)	19 (15)	1 (1)	5 (4)	7 (8)
Antihormonal agent						
Any	100 (40)	40 (22)	38 (29)	52 (37)	29 (26)	31 (36)
Exemestane	57 (23)	20 (11)	21 (16)	25 (18)	15 (13)	13 (15)
mTOR kinase inhibitor						
Any	40 (16)	17 (9)	20 (15)	21 (15)	12 (11)	13 (15)
Everolimus	40 (16)	17 (9)	20 (15)	21 (15)	12 (11)	13 (15)
CDK4/6 inhibitor‡						
Any	6 (2)	2 (1)	6 (5)	9 (6)	6 (5)	15 (18)
Palbociclib	4 (2)	2 (1)	5 (4)	7 (5)	6 (5)	13 (15)
Ribociclib	1 (<1)	0	1 (1)	2 (1)	0	1 (1)
Abemaciclib	1 (<1)	0	0	0	0	2 (2)

* Percentages in the first row were calculated on the basis of the number of patients in the intention-to-treat population. Percentages in the remaining rows were calculated on the basis of the number of patients who received any treatment after the discontinuation of the trial intervention (i.e., the values in the first row). The term mTOR denotes mammalian target of rapamycin.

† One patient with missing data or partial information about start and stop dates for all reported follow-up therapies was not included in this analysis.

‡ In the placebo–fulvestrant group, 27 patients received inhibitors of cyclin-dependent kinases 4 and 6 (CDK4/6) after disease progression: 3 patients received ribociclib only; 22 patients received palbociclib only, 2 of whom received palbociclib twice in combination with different endocrine therapies (24 counts in the table); and 2 patients received both palbociclib and subsequent abemaciclib (4 counts in the table).

in patients with disease recurrence during endocrine therapy after at least 2 years of adjuvant therapy or in patients who received endocrine therapy alone for metastatic disease with clinical benefit. For patients for whom first-line aromatase inhibitor–based therapy is a standard of care or those who do not have a relapse while they are receiving an aromatase inhibitor, our findings do not inform the timing of palbociclib therapy.

The results regarding overall survival in the PALOMA-3 trial show the substantial challenges of finding a significant prolongation of overall survival in the context of a disease in which survival after disease progression is substantially longer than the time in the trial.[21] To design a trial in this context that would detect a significant improvement in overall survival to result in a hazard ratio for death of 0.80 would have required a much larger trial. Accordingly, an 80% power calculation would involve more than 700 events, as compared with the approximate 46% power that results from the 310 deaths among the 521 patients who were enrolled in this trial. Future meta-analyses of CDK4/6 inhibitor studies

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may provide a more robust assessment of the effect of this class of drugs on overall survival, including in subgroups of patients. This trial also shows a further challenge of finding a significant benefit, because 16% of the patients in the placebo–fulvestrant group crossed over to receive a CDK4/6 inhibitor as subsequent therapy because of the commercial availability of this class of agents. Crossover to receive an investigational drug after disease progression may attenuate the observed advantage in overall survival[22] and probably resulted in a modest prolongation of overall survival in the control group, thereby further reducing the power of the trial to show a significant benefit.

A planned subgroup analysis of overall survival regarding the three prespecified stratification factors identified the patients who derived the most benefit from palbociclib. In particular, patients with sensitivity to previous endocrine therapy had a substantial benefit, whereas those with intrinsic endocrine resistance had a limited benefit. This differential benefit in terms of overall survival closely mirrors the absolute prolongation of progression-free survival that was observed with palbociclib in these two populations. These data confirm that palbociclib was highly effective in augmenting responses in endocrine-sensitive cancers, but the effect may be more limited in tumors with intrinsic endocrine resistance. However, relatively few patients with intrinsic endocrine resistance were recruited in the trial, which limits the assessment of palbociclib in these patients.

Although palbociclib–fulvestrant resulted in a longer median overall survival than placebo–fulvestrant among postmenopausal patients but not among premenopausal or perimenopausal patients, this disparity can be attributed in part to the small size of the subgroup of premenopausal or perimenopausal patients and may also reflect variance in the proportion of patients with intrinsic endocrine resistance in the two subgroups. In the subgroup of premenopausal or perimenopausal patients, the percentage of patients with intrinsic endocrine resistance was higher than in the postmenopausal subgroup (30% vs. 19%).[23] Because patients with intrinsic endocrine resistance may have limited benefit from endocrine therapy in combination with palbociclib, the overall survival benefit is difficult to ascertain. Furthermore, an imbalance in certain prognostic factors between the palbociclib–fulvestrant group and the placebo–fulvestrant group in the subgroup of premenopausal or perimenopausal patients favored the control group. Premenopausal or perimenopausal patients who had been randomly assigned to the placebo–fulvestrant group had received fewer lines of previous therapy than those who had been randomly assigned to the palbociclib–fulvestrant group (lines of previous therapy, 0 or 1: 72% of the patients in the placebo–fulvestrant group vs. 58% of those in the palbociclib–fulvestrant group), and fewer patients were 40 years of age or younger (22% of patients in the placebo–fulvestrant group vs. 35% of those in the palbociclib–fulvestrant group).[23]

The duration of the immediate subsequent line of therapy after disease progression after the completion of trial intervention was similar in the palbociclib–fulvestrant group and the placebo–fulvestrant group, which shows that standard treatments had similar efficacy after progression while patients were receiving palbociclib or placebo (Fig. S5 in the Supplementary Appendix). Research on the mechanisms of resistance to CDK4/6 inhibitors in the PALOMA-3 trial indicated that disease progression during palbociclib–fulvestrant treatment was due predominantly to endocrine resistance.[24,25] Analysis of circulating tumor DNA in plasma samples obtained at the end of the trial intervention revealed that the genetic profile at the end of the trial intervention was largely similar in patients treated with palbociclib and those who received placebo, with the exception of retinoblastoma (*RB1*) mutations that were selected in 5% of the patients who had progression during palbociclib treatment.[24] The data regarding overall survival in this trial suggest that the low rate of *RB1* mutations selected by palbociclib has no overall detectable effect on either overall survival or sensitivity to subsequent therapies after progression during trial treatment.

Taken together, the data from the PALOMA-3 trial showed that palbociclib in combination with fulvestrant led to a 6.9-month prolongation of overall survival, although the finding did not reach significance in the intention-to-treat population. In the subgroup of patients with sensitivity to previous endocrine therapy, overall survival was 10 months longer with palbociclib–fulvestrant than with placebo–fulvestrant.

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

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

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APPENDIX

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