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Palbociclib in Hormone-Receptor–Positive Advanced Breast Cancer

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ABSTRACT

BACKGROUND

Growth of hormone-receptor–positive breast cancer is dependent on cyclin-dependent kinases 4 and 6 (CDK4 and CDK6), which promote progression from the G1 phase to the S phase of the cell cycle. We assessed the efficacy of palbociclib (an inhibitor of CDK4 and CDK6) and fulvestrant in advanced breast cancer.

METHODS

This phase 3 study involved 521 patients with advanced hormone-receptor–positive, human epidermal growth factor receptor 2–negative breast cancer that had relapsed or progressed during prior endocrine therapy. We randomly assigned patients in a 2:1 ratio to receive palbociclib and fulvestrant or placebo and fulvestrant. Premenopausal or perimenopausal women also received goserelin. The primary end point was investigator-assessed progression-free survival. Secondary end points included overall survival, objective response, rate of clinical benefit, patient-reported outcomes, and safety. A preplanned interim analysis was performed by an independent data and safety monitoring committee after 195 events of disease progression or death had occurred.

RESULTS

The median progression-free survival was 9.2 months (95% confidence interval [CI], 7.5 to not estimable) with palbociclib–fulvestrant and 3.8 months (95% CI, 3.5 to 5.5) with placebo–fulvestrant (hazard ratio for disease progression or death, 0.42; 95% CI, 0.32 to 0.56; P<0.001). The most common grade 3 or 4 adverse events in the palbociclib–fulvestrant group were neutropenia (62.0%, vs. 0.6% in the placebo–fulvestrant group), leukopenia (25.2% vs. 0.6%), anemia (2.6% vs. 1.7%), thrombocytopenia (2.3% vs. 0%), and fatigue (2.0% vs. 1.2%). Febrile neutropenia was reported in 0.6% of palbociclib-treated patients and 0.6% of placebo-treated patients. The rate of discontinuation due to adverse events was 2.6% with palbociclib and 1.7% with placebo.

CONCLUSIONS

Among patients with hormone-receptor–positive metastatic breast cancer who had progression of disease during prior endocrine therapy, palbociclib combined with fulvestrant resulted in longer progression-free survival than fulvestrant alone. (Funded by Pfizer; PALOMA3 ClinicalTrials.gov number, NCT01942135.)

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Approximately 80% of breast cancers express estrogen receptors, progesterone receptors, or both. Endocrine therapies are the mainstay of treatment for these hormone-receptor–positive cancers, substantially reducing the relapse rate after presentation with early-stage cancer.[1] Despite advances in endocrine therapy, many women have a relapse during or after completing adjuvant therapy. The care of these women remains a considerable clinical challenge. Single-agent treatment with an aromatase inhibitor or tamoxifen has shown limited clinical benefit.[2,3] The selective estrogen-receptor degrader fulvestrant has modest activity in this population of patients,[4,5] and the development of effective therapies that can reverse resistance to endocrine therapy is of clinical importance.

Cyclin-dependent kinases 4 and 6 (CDK4 and CDK6), which are activated by D-type cyclins, promote cell-cycle entry by phosphorylating Rb (retinoblastoma protein), among other proteins, to initiate transition from the G1 phase to the S phase.[6] Multiple oncogenic signals in hormone-receptor–positive breast cancer converge to promote expression of cyclin D1 and activation of CDK4 and CDK6 to drive breast-cancer proliferation.[7,8] In vitro evidence suggests that breast cancer that has developed resistance to prior endocrine therapy remains dependent on cyclin D1–CDK4 to promote proliferation.[9,10]

Palbociclib (Ibrance, Pfizer) is an orally bioavailable small-molecule inhibitor of CDK4 and CDK6, with a high level of selectivity for CDK4 and CDK6 over other cyclin-dependent kinases.[11] Palbociclib inhibits CDK4 and CDK6 in vitro, resulting in loss of RB1 phosphorylation. It has high activity in hormone-receptor–positive breast-cancer cell lines and is synergistic in combination with endocrine therapies.[12] Prior phase 2 research suggested that single-agent palbociclib induced responses in hormone-receptor–positive breast cancer.[13] In an open-label, randomized, phase 2 study involving patients with newly diagnosed metastatic estrogen-receptor–positive breast cancer, palbociclib in combination with letrozole was associated with significantly longer progression-free survival than was letrozole alone.[14] The PALOMA3 trial assessed the safety and efficacy of the combination of palbociclib and fulvestrant in premenopausal or postmenopausal women with hormone-receptor–positive advanced breast cancer that progressed during prior endocrine therapy.

Methods

Patients

Women with hormone-receptor–positive, human epidermal growth factor receptor 2 (HER2)–negative advanced breast cancer were eligible if their cancer had relapsed or progressed during prior endocrine therapy. Hormone-receptor status (expression of estrogen receptor, progesterone receptor, or both) and HER2 status were assessed locally with the tumor tissue obtained most recently. Women were eligible regardless of menopausal status; those with postmenopausal breast cancer must have had disease progression during prior aromatase inhibitor therapy, defined as progression during or within 1 month after the end of therapy in the context of metastatic disease or progression during or within 12 months after the completion or discontinuation of adjuvant therapy. Women with premenopausal or perimenopausal breast cancer must have had disease progression during prior endocrine therapy, defined as progression during or within 1 month after the end of prior endocrine therapy in the context of metastatic disease or progression during or within 12 months after discontinuation of adjuvant tamoxifen. Eligible patients were allowed one prior line of chemotherapy in the context of advanced disease. The qualifying endocrine therapy was not required to be the most recent treatment before randomization, but progression during the immediate prior therapy was required for randomization.

Patients had measurable disease according to Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1,[15] or bone-only lytic or mixed lytic and blastic lesions that could be accurately assessed by means of computed tomography (CT) or magnetic resonance imaging (MRI). Patients had adequate organ function and an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 (on a scale of 0 to 5, with 0 indicating no symptoms, 1 indicating mild symptoms, and higher numbers indicating increasing degrees of disability). Prior exposure to fulvestrant or everolimus was not allowed, and patients with uncontrolled brain metastases or symptomatic visceral spread who were at risk

for life-threatening complications were excluded. Women were defined as postmenopausal if they were at least 60 years of age, had undergone bilateral oophorectomy, or were younger than 60 years of age and had had cessation of regular menses for at least 12 consecutive months with no alternative pathologic or physiological cause and had serum levels of estradiol and follicle-stimulating hormone in the postmenopausal range. All other patients were designated as being premenopausal or perimenopausal.

STUDY DESIGN

In this double-blind, phase 3 study, patients were randomly assigned in a 2:1 ratio to receive palbociclib (125 mg per day orally for 3 weeks, followed by 1 week off) and fulvestrant (500 mg intramuscularly per standard of care every 14 days for the first three injections and then every 28 days) or matching placebo and fulvestrant. Premenopausal or perimenopausal patients received goserelin for the duration of study treatment, starting at least 4 weeks before randomization and continuing every 28 days. Randomization was stratified according to the presence or absence of visceral metastasis, menopausal status at study entry (postmenopausal vs. premenopausal or perimenopausal), and sensitivity to prior endocrine therapy. Patients were defined as sensitive to prior endocrine therapy if they had a relapse after 24 months of adjuvant endocrine therapy or had a clinical benefit (objective response [complete or partial] or stable disease lasting ≥24 weeks) from prior endocrine therapy in the context of advanced disease.

Treatment continued until objective demonstration of disease progression, unacceptable toxic effects, or withdrawal of consent. Crossover in the event of disease progression was not allowed. Reduction in the daily dose of palbociclib or placebo owing to adverse events was allowed in stages (to 100 mg, then 75 mg, and then 75 mg on a schedule of 2 weeks on and 2 weeks off), with criteria defined in the study protocol (for dose-modification guidelines, see Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org; the protocol is also available at NEJM.org). Reduction in the dose of fulvestrant was not allowed. Starting a new cycle of palbociclib or placebo was delayed until a reduction in the severity of adverse events to grade 2 or lower. If palbociclib or placebo was delayed, fulvestrant and goserelin were continued on the preplanned schedule.

One cycle was defined as 3 weeks on, followed by 1 week off (palbociclib or placebo). All patients had to provide tumor samples from a biopsy of a recurrent breast cancer (although patients with bone-only disease could provide archival tissue) and blood samples (including samples for analysis of circulating tumor DNA) for future translational research.

PROCEDURES

Imaging (CT, MRI, or both) was performed at screening within 4 weeks before randomization, then repeated every 8±1 weeks until disease progression. Radiographic bone scans were performed at screening and subsequently as clinically indicated or to confirm complete response. Patients who discontinued study drugs without progression continued to have scans every 8 weeks. Biochemical and hematologic laboratory tests were performed on days 1 and 15 of the first two cycles and then on day 1 of subsequent cycles. Vital signs were assessed on day 1 of every cycle; adverse events were recorded and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0, with relationship to study medications recorded.

END POINTS

The primary end point was investigator-assessed progression-free survival according to RECIST, version 1.1.[15] Secondary end points included overall survival; survival probability at 1, 2, and 3 years; objective response; duration of response; rate of clinical benefit; patient-reported outcomes; pharmacokinetics; and safety. Patient-reported outcome end points included health-related quality-of-life scores on the EuroQol Group 5-Dimension Self-Report Questionnaire (EQ-5D), the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Core Module (QLQ-C30), and the EORTC Breast Cancer Module (QLQ-BR23).

STUDY OVERSIGHT

The PALOMA3 study was designed by an academic steering group, including representatives from the sponsor (Pfizer). All the authors con-

firm that the study conformed to the protocol and vouch for the accuracy and completeness of the data. The first draft of the manuscript was prepared by the first and last authors and representatives of the sponsor. Subsequently, all the authors were involved with interpretation of the data and in writing and reviewing the manuscript. A professional medical writer paid by the sponsor provided editorial assistance with incorporation of the authors' revisions into the manuscript. Fulvestrant was provided by AstraZeneca.

The study was approved by an institutional review board, or equivalent, at each site, and all the patients gave written informed consent before enrollment. The study was conducted according to the principles of Good Clinical Practice and the Declaration of Helsinki. A steering committee reviewed the study conduct. An independent data and safety monitoring committee met every 6 months to review safety and pharmacokinetics and to perform the interim analysis.

STATISTICAL ANALYSIS

The primary end point of progression-free survival was assessed with the use of a predefined log-rank test stratified according to the presence or absence of visceral disease and sensitivity to prior endocrine therapy. We estimated that 238 events of progression or death would be required in the two treatment groups for the study to have 90% power to detect a hazard ratio of 0.64 (representing a 56% improvement in median progression-free survival [6.00 months vs. 9.38 months]) with a one-sided significance level of $\alpha = 0.025$. A total sample of 417 patients was to be enrolled. One interim analysis was planned for early stopping of the study owing to efficacy after approximately 60% of the total progression-free survival events were observed with the use of a prespecified Haybittle–Peto efficacy boundary ($\alpha = 0.00135$).[16] The information fraction of the interim analysis was increased, reflecting rapid study enrollment (Fig. S1 in the Supplementary Appendix). Central assessment of progression-free survival was performed with the use of an audit approach involving a random-sample–based, blinded, independent central review to provide assurance that the investigator-assessed primary end point was accurate.[17] A third-party core imaging laboratory performed the blinded review for a randomly selected subgroup of patients (approximately 40%) selected after enrollment completion. All reported P values were two-sided.

RESULTS

PATIENT CLINICAL AND PATHOLOGICAL FEATURES

Between October 7, 2013, and August 26, 2014, a total of 521 patients from 144 centers in 17 countries were randomly assigned to palbociclib and fulvestrant (347 patients) or placebo and fulvestrant (174 patients) (Fig. S2 in the Supplementary Appendix). Baseline characteristics of the intention-to-treat population were well balanced between the study groups (Table 1). The median age was 57 years, 59.7% of the patients had visceral disease, 79.3% were postmenopausal, and 78.7% had cancers that were sensitive to prior endocrine therapy. All patients had HER2-negative disease, 67.0% had both estrogen-receptor–positive and progesterone-receptor–positive disease, and 26.7% had estrogen-receptor–positive but progesterone-receptor–negative disease. A total of 77.9% of the patients had measurable disease, and 23.2% had at least partially lytic bone-only disease. Overall, 122 patients (23.4%) presented with metastatic disease as the initial disease manifestation (86 patients [24.8%] in the palbociclib–fulvestrant group and 36 patients [20.7%] in the placebo–fulvestrant group).

STUDY TREATMENT

By the data cutoff date (December 5, 2014) for the interim analysis, 195 events of disease progression or death had occurred (102 events in the palbociclib–fulvestrant group and 93 in the placebo–fulvestrant group with 2:1 randomization); 238 patients (68.6%) continue to receive treatment with palbociclib–fulvestrant and 75 patients (43.1%) with placebo–fulvestrant. The median relative dose intensity was 91.7% for palbociclib and 99.7% for fulvestrant in the palbociclib–fulvestrant group and 100% for both placebo and fulvestrant in the placebo–fulvestrant group. The palbociclib dose was reduced in 109 of 345 patients (31.6%), whereas the placebo dose was reduced in 3 of 172 patients (1.7%). The main reason for study-treatment discontinuation was disease progression, occurring in 85 patients (24.5%) assigned to palbociclib–fulves-

trant and 87 patients (50.0%) assigned to placebo–fulvestrant. Discontinuation of palbociclib or matching placebo owing to adverse events occurred in 9 patients (2.6%) receiving palbociclib and 3 patients (1.7%) receiving placebo.

ADVERSE EVENTS

The most common adverse events reported for the palbociclib–fulvestrant group were neutropenia, leukopenia, fatigue, and nausea (Table 2). Hematologic adverse events were frequent in the palbociclib–fulvestrant group. Neutropenia (any grade) occurred in 78.8% of the patients receiving palbociclib–fulvestrant versus 3.5% of the patients receiving placebo–fulvestrant, leukopenia in 45.5% versus 4.1%, anemia in 26.1% versus 9.9%, and thrombocytopenia in 19.4% versus 0%. Grade 3 or 4 neutropenia occurred in 62.0% of the patients receiving palbociclib–fulvestrant versus 0.6% of the patients receiving placebo–fulvestrant, leukopenia in 25.2% versus 0.6%, anemia in 2.6% versus 1.7%, and thrombocytopenia in 2.3% versus 0%. Rates of febrile neutropenia were low, occurring in two patients (0.6%) receiving palbociclib–fulvestrant and one patient (0.6%) receiving placebo–fulvestrant.

The most common nonhematologic adverse events were fatigue (38.0% in the palbociclib–fulvestrant group vs. 26.7% in the placebo–fulvestrant group), nausea (29.0% vs. 26.2%), and headache (21.2% vs. 17.4%). A higher incidence of infections was reported in the palbociclib–fulvestrant group than in the placebo–fulvestrant group (34.2% vs. 24.4%); infections were primarily of grade 1 or 2 severity (32.4% vs. 22.7%). The most common infections were upper respiratory infections (19.4% vs. 16.3%). No grade 3 or 4 nonhematologic adverse events occurred in more than 2% of the patients receiving palbociclib.

Serious adverse events (any cause) occurred in 9.6% of the patients in the palbociclib–fulvestrant group and 14.0% of the patients in the placebo–fulvestrant group. No individual serious adverse event occurred in more than 1% of the patients receiving palbociclib. Three patients (0.9%) receiving palbociclib and one patient (0.6%) receiving placebo had pyrexia, and three patients (0.9%) receiving palbociclib and no patients receiving placebo had a pulmonary embolism. During the study-treatment period, there were four deaths in the palbociclib–fulvestrant group (all due to disease progression) and two deaths in the placebo–fulvestrant group (one due to disease progression and one due to intracerebral hemorrhage).

Global quality of life was generally maintained with palbociclib–fulvestrant but deteriorated significantly with placebo–fulvestrant (mean overall change from baseline in QLQ-C30 score [range, 0 to 100, with higher scores indicating a higher quality of life], −0.9 points vs. −4.0 points; P=0.03). Patients receiving palbociclib showed a significant improvement from baseline in emotional functioning as compared with patients receiving placebo (mean overall change from baseline score on the emotional-functioning subscale of the QLQ-C30 scale [range, 0 to 100, with higher scores indicating better emotional functioning], 2.7 points vs. −1.9 points; P=0.002).

EFFICACY OF PALBOCICLIB IN COMBINATION WITH FULVESTRANT

The trial met its primary end point at the interim analysis on the basis of the recommendation by the independent data and safety monitoring committee. The median progression-free survival was 9.2 months (95% confidence interval [CI], 7.5 to not estimable) with palbociclib–fulvestrant and 3.8 months (95% CI, 3.5 to 5.5) with placebo–fulvestrant (hazard ratio for disease progression or death, 0.42; 95% CI, 0.32 to 0.56; P<0.001) (Fig. 1A). Approximately 40% of the patients (211) were randomly selected for central imaging assessment by blinded independent review. The results of the blinded audit were consistent with the investigator-assessed primary end point; the median progression-free survival was not estimable with palbociclib–fulvestrant and was 3.7 months (95% CI, 3.4 to 7.2) with placebo–fulvestrant (hazard ratio for disease progression or death, 0.27; 95% CI, 0.16 to 0.46; P<0.001) (Fig. 1B).

Subgroup analyses of progression-free survival according to stratification factors and demographic or prognostic factors revealed consistent results (Fig. 2). In particular, the relative difference in progression-free survival between palbociclib and placebo was similar in premenopausal or perimenopausal patients and postmenopausal patients (hazard ratio for disease

Table 1. Clinical and Pathological Characteristics of the Patients.*

Characteristic	Palbociclib–Fulvestrant (N=347)	Placebo–Fulvestrant (N=174)
Age		
Median — yr	57	56
Range — yr	30–88	29–80
<65 yr — no. (%)	261 (75.2)	131 (75.3)
≥65 yr — no. (%)	86 (24.8)	43 (24.7)
Race — no. (%)†		
White	252 (72.6)	133 (76.4)
Asian	74 (21.3)	31 (17.8)
Black or other	20 (5.8)	9 (5.2)
Hormone-receptor status — no. (%)		
ER-positive and PR-positive	238 (68.6)	111 (63.8)
ER-positive and PR-negative	91 (26.2)	48 (27.6)
ECOG performance status — no. (%)‡		
0	207 (59.7)	115 (66.1)
1	140 (40.3)	59 (33.9)
Disease-free interval§		
Median — mo	48	51
≤24 mo — no./total no. (%)	42/235 (17.9)	23/124 (18.5)
>24 mo — no./total no. (%)	186/235 (79.1)	95/124 (76.6)
Menopausal status at study entry — no. (%)		
Premenopausal or perimenopausal	72 (20.7)	36 (20.7)
Postmenopausal	275 (79.3)	138 (79.3)
Documented sensitivity to prior hormonal therapy — no. (%)¶		
Yes	274 (79.0)	136 (78.2)
No	73 (21.0)	38 (21.8)
Visceral metastasis — no. (%)‖	206 (59.4)	105 (60.3)
Measurable disease — no. (%)	268 (77.2)	138 (79.3)
Disease stage at study entry — no. (%)**		
Recurrent locally advanced††	49 (14.1)	25 (14.4)
Metastatic	296 (85.3)	146 (83.9)
No. of disease sites — no. of patients (%)‡‡		
1	111 (32.0)	60 (34.5)
2	99 (28.5)	50 (28.7)
≥3	135 (38.9)	62 (35.6)
Prior endocrine therapy — no. (%)§§		
Aromatase inhibitor with or without GnRH agonist	296 (85.3)	151 (86.8)
Tamoxifen with or without GnRH agonist	211 (60.8)	104 (59.8)
Most recent therapy — no. (%)		
Aromatase inhibitor with or without GnRH agonist	238 (68.6)	118 (67.8)
Tamoxifen with or without GnRH agonist	63 (18.2)	30 (17.2)

Table 1. (Continued.)

Characteristic	Palbociclib–Fulvestrant (N=347)	Placebo–Fulvestrant (N=174)
Prior chemotherapy — no. (%)		
Neoadjuvant or adjuvant treatment only¶¶	144 (41.5)	75 (43.1)
Metastatic treatment, with or without prior neoadjuvant or adjuvant therapy	107 (30.8)	63 (36.2)
Prior lines of therapy in the context of metastatic disease — no. of patients (%)		
0	84 (24.2)	45 (25.9)
1	132 (38.0)	70 (40.2)
2	90 (25.9)	43 (24.7)
≥3	41 (11.8)	16 (9.2)

* No significant differences in the clinical and pathological characteristics of the patients were identified between the two treatment groups. ER denotes estrogen receptor, GnRH gonadotropin-releasing hormone, and PR progesterone receptor.
† Race was self-reported. Race was unspecified in one patient in each treatment group.
‡ Eastern Cooperative Oncology Group (ECOG) performance status is scored on a scale of 0 to 5, with 0 indicating no symptoms, 1 indicating mild symptoms, and higher numbers indicating increasing degrees of disability.
§ The disease-free interval was defined as the time from diagnosis of primary breast cancer to first relapse in patients who received adjuvant therapy.
¶ Patients were defined as having sensitivity to prior endocrine therapy if they had a relapse after 24 months of adjuvant endocrine therapy or had a clinical benefit (objective response [complete or partial] or stable disease lasting ≥24 weeks) from prior endocrine therapy in the context of advanced disease.
‖ Visceral metastasis was defined as lung, liver, brain, pleural, or peritoneal involvement.
** Data on disease stage at study entry were missing or unknown for five patients (two in the palbociclib–fulvestrant group and three in the placebo–fulvestrant group).
†† Recurrent locally advanced disease included local and regional recurrences.
‡‡ Data on number of disease sites were missing for four patients (two in each treatment group).
§§ Prior endocrine therapy was defined as any endocrine therapy anytime before study entry.
¶¶ These patients did not receive chemotherapy in the context of metastatic disease.

progression or death, 0.44 and 0.41, respectively; P=0.94 for interaction between the study-drug assignment and menopausal status). Rates of overall objective response were 10.4% (95% CI, 7.4 to 14.1) with palbociclib–fulvestrant and 6.3% (95% CI, 3.2 to 11.0) with placebo–fulvestrant (P=0.16). By the data cutoff date, 31.7% of the patients (35.7% of those in the palbociclib–fulvestrant group and 23.6% of those in the placebo–fulvestrant group) continued to receive study treatment with less than 24 weeks of follow-up; the median duration of follow-up was 5.6 months. The rate of clinical benefit (response or prolonged stable disease) at the interim analysis was 34.0% (95% CI, 29.0 to 39.3) with palbociclib–fulvestrant and 19.0% (95% CI, 13.4 to 25.6) with placebo–fulvestrant (P<0.001). At the time of the interim analysis, data on overall survival were immature, with a total of 28 deaths: 19 patients (5.5%) in the palbociclib–fulvestrant group and 9 (5.2%) in the placebo–fulvestrant group. Double blinding has been maintained after the interim analysis to allow ongoing follow-up of overall survival.

DISCUSSION

This double-blind, phase 3, randomized study showed that adding palbociclib to fulvestrant resulted in substantially longer progression-free survival than fulvestrant alone in patients with advanced hormone-receptor–positive, HER2-negative breast cancer that had progressed during prior endocrine therapy, irrespective of menopausal status. Adverse events observed with palbociclib and fulvestrant were consistent with previously reported data, and a high rate of hematologic adverse events was observed in the palbociclib group. Overall, palbociclib maintained quality of life, and the rate of discontinuation due to adverse events was similar to that observed with placebo.

The findings of this study are consistent with prior results with palbociclib in different set-

Table 2. Adverse Events with an Incidence of 10% or More in the Palbociclib–Fulvestrant Group, Regardless of Relationship to Study Drugs.*

Event	Palbociclib–Fulvestrant (N=345)			Placebo–Fulvestrant (N=172)		
	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
	number of patients (percent)					
Any adverse event	337 (97.7)	202 (58.6)	37 (10.7)	153 (89.0)	28 (16.3)	3 (1.7)
Neutropenia	272 (78.8)	184 (53.3)	30 (8.7)	6 (3.5)	0	1 (0.6)
Leukopenia	157 (45.5)	85 (24.6)	2 (0.6)	7 (4.1)	0	1 (0.6)
Fatigue	131 (38.0)	7 (2.0)	0	46 (26.7)	2 (1.2)	0
Nausea	100 (29.0)	0	0	45 (26.2)	1 (0.6)	0
Anemia	90 (26.1)	9 (2.6)	0	17 (9.9)	3 (1.7)	0
Headache	73 (21.2)	1 (0.3)	0	30 (17.4)	0	0
Thrombocytopenia	67 (19.4)	6 (1.7)	2 (0.6)	0	0	0
Upper respiratory infection†	67 (19.4)	1 (0.3)	0	28 (16.3)	0	0
Diarrhea	66 (19.1)	0	0	30 (17.4)	1 (0.6)	0
Constipation	58 (16.8)	0	0	24 (14.0)	0	0
Alopecia	51 (14.8)‡	NA	NA	10 (5.8)	NA	NA
Hot flushes	51 (14.8)	0	0	28 (16.3)	0	0
Vomiting	50 (14.5)	1 (0.3)	0	21 (12.2)	1 (0.6)	0
Arthralgia	45 (13.0)	1 (0.3)	0	28 (16.3)	0	0
Cough	45 (13.0)	0	0	18 (10.5)	0	0
Decreased appetite	44 (12.8)	3 (0.9)	0	13 (7.6)	0	0
Stomatitis	40 (11.6)	2 (0.6)	0	4 (2.3)	0	0
Back pain	39 (11.3)	3 (0.9)	0	26 (15.1)	4 (2.3)	0
Dizziness	37 (10.7)	1 (0.3)	0	16 (9.3)	0	0
Dyspnea	37 (10.7)	0	1 (0.3)	11 (6.4)	1 (0.6)	0
Pain in extremity	34 (9.9)	0	0	19 (11.0)	3 (1.7)	0

* Adverse events were coded according to the *Medical Dictionary for Regulatory Activities* (MedDRA). Thromboembolic events occurred in less than 2% of patients in the palbociclib–fulvestrant group: two patients (0.6%) had a nonserious event, and four patients (1.2%) had a serious event (three pulmonary emboli and one deep-vein thrombosis). No thromboembolic adverse events were reported in the placebo–fulvestrant group. NA denotes not applicable.

† Upper respiratory infection included influenza, influenza-like illness, laryngitis, nasopharyngitis or pharyngitis, rhinitis, sinusitis, and upper respiratory tract infection.

‡ A total of 13.6% of the patients in the palbociclib–fulvestrant group had grade 1 alopecia, whereas 1.2% had grade 2 alopecia.

tings in hormone-receptor–positive and HER2-negative advanced breast cancer.[13] In the open-label, phase 2 PALOMA1 study involving patients who had not previously received endocrine therapy and those with late relapses after adjuvant endocrine therapy, palbociclib in combination with letrozole resulted in longer progression-free survival than letrozole alone.[14] This finding suggests that palbociclib has activity when combined with endocrine therapy in both patients who have not previously received endocrine therapy and those who have disease that is resistant to such therapy. The ongoing PALOMA2 study (ClinicalTrials.gov number, NCT01740427) is designed to further confirm the efficacy of palbociclib as a first-line treatment for patients who have not previously received endocrine therapy for their advanced disease. Other phase 3,

randomized studies are under way with the dual CDK4 and CDK6 inhibitors ribociclib (NCT01958021) and abemaciclib (NCT02246621). The PALOMA1 study had insufficient power to assess the effect of palbociclib on overall survival,[14] and the number of deaths in the PALOMA3 study at the time of the interim analysis was insufficient to assess overall survival. The effect of palbociclib on overall survival is unknown, and follow-up is ongoing.

Our results support the scientific evidence that the cyclin D1–CDK4–CDK6 dimer is a key downstream effector in hormone-receptor–positive breast cancer[7] and remains so after the development of resistance to endocrine therapy. Targeting CDK4 and CDK6 may represent a therapeutic strategy across diverse mechanisms of acquired resistance to endocrine therapy, including activation of receptor tyrosine kinase signaling,[18] up-regulation of PI3 kinase–mammalian target of rapamycin (mTOR) signaling,[19] and mutation of *ESR1*.[20,21]

The management of advanced hormone-receptor–positive disease has evolved, with several prospective studies indicating the importance of combining endocrine therapies with targeted drugs.[2,14,22] Results observed with palbociclib compare favorably with those observed with other agents licensed for the treatment of postmenopausal women in a similar population.[2] The median progression-free survival observed with placebo–fulvestrant in the PALOMA3 study was inferior to that in the prior studies of endocrine therapy alone,[4] a finding that probably reflects the higher-risk, younger, and more heavily pretreated population recruited into the PALOMA3 study. Translational research efforts to identify markers of sensitivity or resistance to palbociclib in the PALOMA3 study are ongoing.

Guidelines and prior clinical studies suggest that premenopausal and perimenopausal patients with advanced cancer should be treated with ovarian suppression, either biochemically with gonadotropin-releasing hormone analogues or through surgical oophorectomy, and cared for as if they were postmenopausal patients.[3,23-25] Nevertheless, premenopausal patients are frequently excluded from registration trials of current targeted therapies given in combination with hormone therapy. The PALOMA3 study included 108 premenopausal or perimenopausal patients in whom ovarian suppression was induced by goserelin. The relative difference in progression-free survival between palbociclib and placebo was similar in premenopausal or perimenopausal patients and postmenopausal

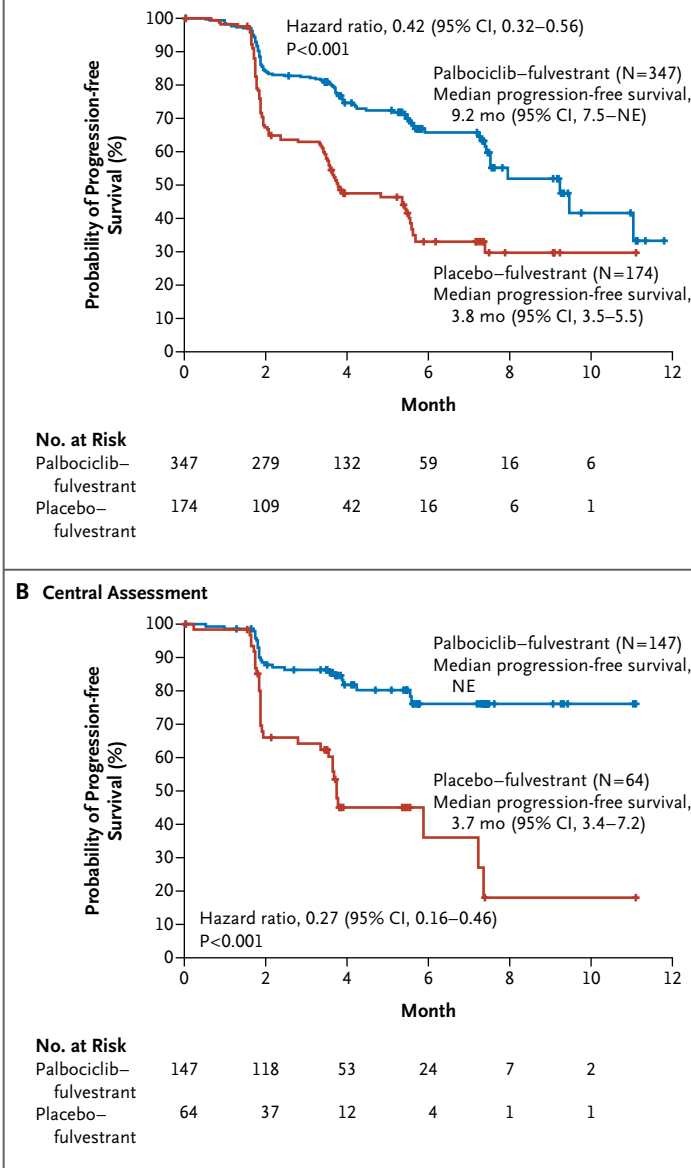

Figure 1. Progression-free Survival.

Panel A shows progression-free survival as assessed by the investigators in the intention-to-treat population (primary analysis), and Panel B shows progression-free survival according to central assessment in a random sample of patients by means of blinded, independent central review. NE denotes not estimable.

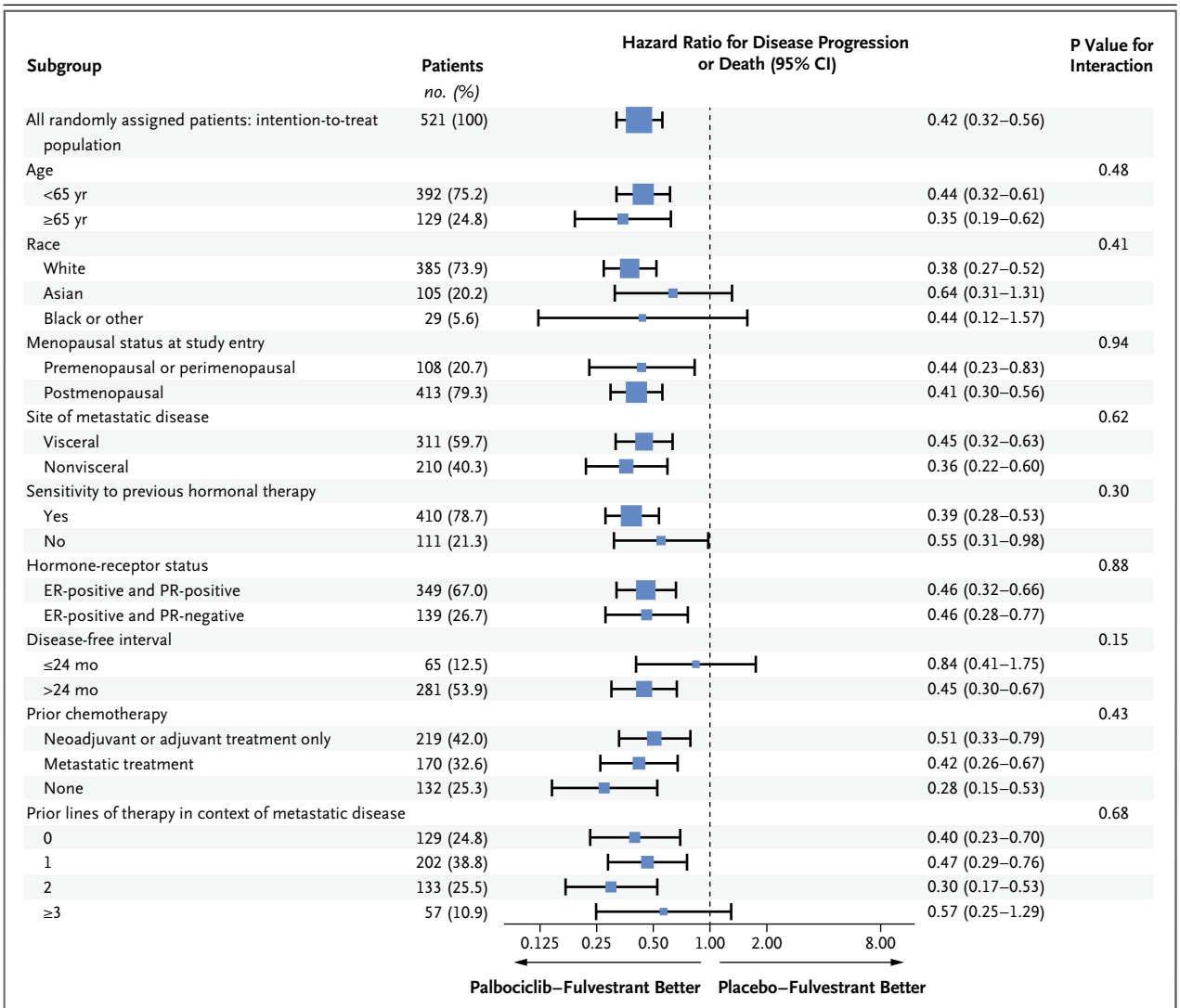

Figure 2. Subgroup Analysis of Progression-free Survival.

The blue boxes represent the hazard ratios with 95% confidence intervals (horizontal lines); the size of each box is proportional to the size of the corresponding subgroup. ER denotes estrogen receptor, and PR progesterone receptor.

patients, a finding that supports treatment guidelines and the inclusion of premenopausal or postmenopausal patients.

In conclusion, the PALOMA3 study showed that palbociclib with fulvestrant resulted in longer progression-free survival and a relatively higher quality of life than fulvestrant alone in patients with advanced hormone-receptor–positive breast cancer that had progressed during prior endocrine therapy, regardless of the patient's menopausal status. Neutropenia was the most common adverse event in patients receiving palbociclib, but a very low incidence of febrile neutropenia was observed in both treatment groups.

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