ORIGINAL ARTICLE

Palbociclib and Letrozole in Advanced Breast Cancer

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Abstract

BACKGROUND

A phase 2 study showed that progression-free survival was longer with palbociclib plus letrozole than with letrozole alone in the initial treatment of postmenopausal women with estrogen-receptor (ER)–positive, human epidermal growth factor receptor 2 (HER2)–negative advanced breast cancer. We performed a phase 3 study that was designed to confirm and expand the efficacy and safety data for palbociclib plus letrozole for this indication.

METHODS

In this double-blind study, we randomly assigned, in a 2:1 ratio, 666 postmenopausal women with ER-positive, HER2-negative breast cancer, who had not had prior treatment for advanced disease, to receive palbociclib plus letrozole or placebo plus letrozole. The primary end point was progression-free survival, as assessed by the investigators; secondary end points were overall survival, objective response, clinical benefit response, patient-reported outcomes, pharmacokinetic effects, and safety.

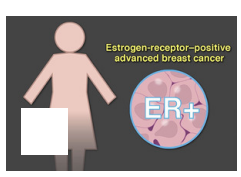
RESULTS

The median progression-free survival was 24.8 months (95% confidence interval [CI], 22.1 to not estimable) in the palbociclib–letrozole group, as compared with 14.5 months (95% CI, 12.9 to 17.1) in the placebo–letrozole group (hazard ratio for disease progression or death, 0.58; 95% CI, 0.46 to 0.72; P<0.001). The most common grade 3 or 4 adverse events were neutropenia (occurring in 66.4% of the patients in the palbociclib–letrozole group vs. 1.4% in the placebo–letrozole group), leukopenia (24.8% vs. 0%), anemia (5.4% vs. 1.8%), and fatigue (1.8% vs. 0.5%). Febrile neutropenia was reported in 1.8% of patients in the palbociclib–letrozole group and in none of the patients in the placebo–letrozole group. Permanent discontinuation of any study treatment as a result of adverse events occurred in 43 patients (9.7%) in the palbociclib–letrozole group and in 13 patients (5.9%) in the placebo–letrozole group.

CONCLUSIONS

Among patients with previously untreated ER-positive, HER2-negative advanced breast cancer, palbociclib combined with letrozole resulted in significantly longer progression-free survival than that with letrozole alone, although the rates of myelotoxic effects were higher with palbociclib–letrozole. (Funded by Pfizer; PALOMA-2 ClinicalTrials.gov number, NCT01740427.)

QUICK TAKE



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Hormone-receptor–positive breast cancer represents the largest therapeutic subtype of the disease, accounting for 60 to 65% of all malignant neoplasms of the breast. For more than 50 years, the treatment of hormone-receptor–positive disease has been focused on targeting the estrogen-receptor signaling pathway.[1] However, both new and acquired resistance to hormonal blockade occurs in a large subset of these cancers, and new approaches are needed.[2]

The cyclin-dependent kinases (CDKs) are a large family of serine–threonine kinases that play an important role in regulating cell-cycle progression. The interaction of cyclin D with CDK4 and CDK6 facilitates the hyperphosphorylation of the retinoblastoma (Rb) gene product, which in turn leads to progression through the G1 checkpoint to the S phase of the cell cycle. Alterations in the cyclin-D–CDK4/6–Rb pathway that result in the loss of regulation of this critical Rb checkpoint have been described in a number of malignant conditions and are associated with endocrine resistance in breast cancer. These alterations include cyclin-D amplification; loss, mutation, or both loss and mutation of Rb itself; and loss of negative regulators of the pathway, such as p16.[3]

Palbociclib (Ibrance, Pfizer) is a small-molecule inhibitor of CDK4 and CDK6.[4] Preclinical studies of palbociclib have shown its ability to preferentially inhibit the growth of estrogen-receptor (ER)–positive breast cancer cells, act synergistically with antiestrogens, and reverse endocrine resistance.[5] These findings led to the design and implementation of PALOMA (Palbociclib: Ongoing Trials in the Management of Breast Cancer)–1, an open-label, randomized, proof-of-concept study that evaluated palbociclib plus letrozole versus letrozole alone as first-line therapy in postmenopausal women with ER-positive, human epidermal growth factor receptor 2 (HER2)–negative advanced breast cancer.[6] PALOMA-1 showed significantly longer progression-free survival with palbociclib plus letrozole than with letrozole alone; this finding supported the accelerated Food and Drug Administration (FDA) approval of the combined use of palbociclib and letrozole for this indication in the United States.[7] PALOMA-2 — a larger study than PALOMA-1 — was designed to confirm the findings of PALOMA-1 and to further assess the safety and efficacy of palbociclib plus letrozole as first-line therapy for postmenopausal women with ER-positive, HER2-negative advanced breast cancer.

Methods

STUDY OVERSIGHT

PALOMA-2 was designed by an academic steering committee that included representatives from Pfizer, the industry sponsor (see the Supplementary Appendix, available with the full text of this article at NEJM.org). Pfizer supplied the investigators with the treatments used in the study. Data were collected by the study investigators and verified by Pfizer. All the authors had access to the data and vouch for the integrity, accuracy, and completeness of the data and analyses and for the fidelity of the study to the protocol, which is available, with the statistical analysis plan, at NEJM.org. The first draft of the manuscript was written by the first and last authors, and all the authors were involved in the interpretation of the data and in the writing and review of subsequent drafts of the manuscript. Two professional writers, paid by the sponsor, provided editorial support. The decision to submit the manuscript for publication rested solely with the authors.

The study was approved by an institutional review board or equivalent ethics committee at each participating site, and all patients provided written informed consent before enrollment. The study was conducted in accordance with the International Conference on Harmonisation Good Clinical Practice guidelines and the provisions of the Declaration of Helsinki. An independent data and safety monitoring committee met every 6 months to review safety data and performed the interim analysis.

STUDY DESIGN

In this double-blind, phase 3 study, patients were randomly assigned, in a 2:1 ratio, to receive 125 mg of palbociclib per day, administered orally in 4-week cycles (3 weeks of treatment followed by 1 week off), or matching placebo; all the patients received 2.5 mg of letrozole per day, administered orally (continuous treatment). Randomization was stratified according to site of disease (visceral or nonvisceral), disease-free interval from the end of adjuvant or neoadjuvant treatment to disease recurrence (newly metastatic disease [referred to as “de novo metastatic” in the protocol; the term applies to patients who had not received any prior systemic therapy, for whom a determination of disease-free interval was not possible], ≤12 months, or >12 months), and status with respect to prior adjuvant or neoadjuvant anticancer therapy (prior receipt or no receipt of hormonal therapy).

The treatment period was from t' ı of objective disease progression according to Respo. n 1.1,[8] the development of unacceptable toxic effects, or withdrawal of consent. Patients could continue the assigned treatment beyond the time of RECIST-defined disease progression if it was considered by the investigator to be in the best interest of the patient. Crossover between study groups was not allowed. Dose reductions of palbociclib or placebo, as specified in the

protocol, were allowed because of adverse events (Table S1 in the Supplementary Appendix). Dose reductions of letrozole were not permitted. The start of a new cycle of palbociclib or placebo was delayed until the severity of an adverse event decreased to grade 2 or lower.

PATIENTS

Women with ER-positive, HER2-negative advanced breast cancer were eligible for enrollment if they had not received prior systemic therapy for advanced disease. ER status was assessed locally. Fresh biopsy specimens of recurrent or metastatic tumors were obtained whenever possible; otherwise, the most recent archival tumor tissue was acceptable for eligibility. HER2 status was determined with the use of an FDA-approved assay. Postmenopausal status was an eligibility criterion; women were considered to be postmenopausal if they had undergone prior bilateral oophorectomy, had had spontaneous cessation of menses for 12 consecutive months or more, or had follicle-stimulating hormone and estradiol levels in postmenopausal ranges without an alternative cause. Prior adjuvant or neoadjuvant treatment with a nonsteroidal aromatase inhibitor was allowed unless disease had recurred while the patient was receiving the therapy or within 12 months after completing therapy. Eligibility criteria also included adequate organ function, an Eastern Cooperative Oncology Group performance status of 0 to 2 (measured on a 5-point scale, with 0 indicating no symptoms and higher numbers indicating greater disability), and measurable disease according to RECIST, version 1.1,[8] or lesions only in the bone (i.e., bone-only disease). Patients with advanced, symptomatic, visceral spread (i.e., spread to the viscera or main organs of the body) who were at risk for short-term, life-threatening complications were excluded from the study.

PROCEDURES

Imaging (computed tomography, magnetic resonance imaging, or both) was used to screen patients within 4 weeks before randomization and was repeated every 11 to 13 weeks after randomization. Bone scans were performed within 12 weeks before randomization and every 23 to 25 weeks after randomization. Imaging and bone scans continued to be performed until disease progression, initiation of a new anticancer therapy, or withdrawal from the study, whichever came first. Laboratory tests were performed on days 1 and 14 of the first two cycles and 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; their suspected causal relationships to a study medication or placebo on the basis of the investigator's judgment were also recorded.

END POINTS

The primary end point was investigator-assessed progression-free survival, which was defined as the time from randomization to radiologically confirmed disease progression, according to RECIST, version 1.1, or death during the study. Secondary end points included overall survival, objective response (defined as a confirmed complete response or partial response), the duration of response, the clinical benefit response (defined as a confirmed complete response, a partial response, or stable disease for ≥24 weeks), patient-reported outcomes, pharmacokinetic effects, safety, and tissue biomarker assessments. Patient-reported outcomes were assessed by health-related quality-of-life scores on the EuroQol Group 5-Dimension Self-Report Questionnaire and the Functional Assessment of Cancer Therapy–Breast; data on these assessments are not included in this article.

STATISTICAL ANALYSIS

The primary end point, progression-free survival, was assessed with the use of a prespecified log-rank test stratified according to the presence or absence of visceral disease. We estimated that a total of 347 events of disease progression or death would be required for the study to have 90% power to detect a hazard ratio of 0.69 (representing a 31% reduction in risk or a 44% longer median progression-free survival with palbociclib plus letrozole than with placebo plus letrozole [13 months vs. 9 months]), at a one-sided alpha level of 0.025. The target sample size was 650 patients. We planned for the data and safety monitoring committee to conduct one interim analysis after approximately 65% of the total number of events of disease progression or death were observed to allow for the study to be stopped early owing either to compelling evidence of efficacy (using a prespecified Haybittle–Peto efficacy boundary with an alpha level of 0.000013) or to a lack of efficacy. The Kaplan–Meier method was used to obtain estimates of median progression-free survival, with corresponding two-sided 95% confidence intervals. Cox proportional-hazards models were used to calculate hazard ratios.

A blinded, independent central review of progression-free survival was performed for all patients as a supportive analysis. Fisher's exact test was used to compare rates of objective response and clinical benefit response between the study groups.

Results

PATIENTS

From February 2013 through July 2014, a total of 666 women at 186 sites in 17 countries were randomly assigned, in a 2:1 ratio, to the palbociclib–letrozole group (444 patients) or to the placebo–letrozole group (222 patients) (Fig. S1 and Table S2 in the Supplementary Appendix). The baseline characteristics of the intention-to-treat population were well balanced between study groups (Table 1). The median age was 62 years in the palbociclib–letrozole group and 61 years in the placebo–letrozole group. Among all the patients, 48.6% had visceral disease, 62.8% had received prior systemic therapy for breast cancer, 37.2% had newly diagnosed advanced breast cancer, 40.7% had a disease-free interval of more than 12 months, and 22.1% had a disease-free interval of 12 months or less. Slightly fewer than half the study patients had received chemotherapy as an adjuvant or neoadjuvant treatment, and 56.3% had received prior adjuvant endocrine therapy with the specific agents listed in Table 1; a total of 22.7% of the patients had bone-only disease.

STUDY TREATMENT

By the data cutoff date for the final analysis (February 26, 2016), a total of 331 events of disease progression or death had occurred (194 [43.7%] events in the palbociclib–letrozole group and 137 [61.7%] in the placebo–letrozole group, in accordance with the 2:1 study-group assignment ratio); 199 patients (44.8%) were still receiving palbociclib plus letrozole, and 61 (27.5%) were still receiving placebo plus letrozole. The median relative dose intensity (the ratio of administered doses to planned doses) was 93% for palbociclib and 100% for letrozole in the palbociclib–letrozole group and 100% for both in the placebo–letrozole group. The dose of palbociclib was reduced according to protocol in 160 of the 444 patients (36.0%) in the palbociclib–letrozole group, whereas matching placebo was reduced in 3 of the 222 patients (1.4%) in the placebo–letrozole group (Tables S1 and S3 in the Supplementary Appendix). The main reason for permanent discontinuation of the study treatment was disease progression, which occurred in 172 patients (38.7%) in the palbociclib–letrozole group and in 125 patients (56.3%) in the placebo–letrozole group. Overall permanent discontinuation of study treatment as a result of adverse events occurred in 43 patients (9.7%) in the palbociclib–letrozole group (palbociclib or both palbociclib and letrozole) and in 13 patients (5.9%) in the placebo–letrozole group (placebo or both placebo and letrozole). Permanent discontinuation of palbociclib or matching placebo as a result of adverse events occurred in 33 patients (7.4%) in the palbociclib–letrozole group and in 10 patients (4.5%) in the placebo–letrozole group.

ADVERSE EVENTS

The most common adverse events in the palbociclib–letrozole group were neutropenia, leukopenia, fatigue, nausea, arthralgia, and alopecia (Table 2). With the exclusion of neutropenia and leukopenia, 57.0% of the patients reported an adverse event with a maximum grade of 1 or 2 and 39.2% of patients reported events of grade 3 or higher. Hematologic adverse events of any grade included neutropenia (occurring in 79.5% of the patients in the palbociclib–letrozole group vs. 6.3% of the patients in the placebo–letrozole group), leukopenia (39.0% vs. 2.3%), anemia (24.1% vs. 9.0%), and thrombocytopenia (15.5% vs. 1.4%). Grade 3 or 4 hematologic adverse events included neutropenia (occurring in 66.4% of patients in the palbociclib–letrozole group vs. 1.4% in the placebo–letrozole group), leukopenia (24.8% vs. 0%), anemia (5.4% vs. 1.8%), and thrombocytopenia (1.6% vs. 0%). Grade 3 or 4 febrile neutropenia occurred in eight patients (1.8%) in the palbociclib–letrozole group and in no patients in the placebo–letrozole group.

The most common nonhematologic adverse events were fatigue (occurring in 37.4% of the patients in the palbociclib–letrozole group vs. 27.5% in the placebo–letrozole g
arthralgia (33.3% vs. 33.8%). A l
among the patients in the palbociclib–letrozole group (grade 1 alopecia occurred in 30.2% and grade 2 in 2.7%) than in the placebo–letrozole group (grade 1 alopecia occurred in 14.9% and grade 2 in 0.9%). Other

TABLE 1

Table 1. Patient Demographic and Clinical Characteristics.*

Characteristic	Palbociclib–Letrozole (N=444)	Placeb (N
Age		
Median (range) — yr	62 (30–89)	61 (28–88)
<65 yr — no. (%)	263 (59.2)	141 (63.5)
≥65 yr — no. (%)	181 (40.8)	81 (36.5)
Race — no. (%)†		
White	344 (77.5)	172 (77.5)
Asian	65 (14.6)	30 (13.5)
Black	8 (1.8)	3 (1.4)
Other	27 (6.1)	17 (7.7)
ECOG performance status — no. (%)‡		
0	257 (57.9)	102 (45.9)
1	178 (40.1)	117 (52.7)
2	9 (2.0)	3 (1.4)
Disease stage at initial diagnosis — no. (%)		
I	51 (11.5)	30 (13.5)
II	137 (30.9)	68 (30.6)
III	72 (16.2)	39 (17.6)
IV	138 (31.1)	72 (32.4)
Unknown	36 (8.1)	12 (5.4)
Other or data missing§	10 (2.3)	1 (0.5)
Recurrence type — no. (%)		
Locoregional	2 (0.5)	2 (0.9)
Local	6 (1.4)	3 (1.4)
Regional	3 (0.7)	1 (0.5)
Distant	294 (66.2)	145 (65.3)
Newly diagnosed	139 (31.3)	71 (32.0)
Disease-free interval — no. (%)¶		
Newly metastatic disease	167 (37.6)	81 (36.5)
≤12 mo	99 (22.3)	48 (21.6)
>12 mo	178 (40.1)	93 (41.9)
Disease site — no. (%)		
Visceral	214 (48.2)	110 (49.5)
Nonvisceral	230 (51.8)	112 (50.5)
Bone only	103 (23.2)	48 (21.6)
No. of disease sites — no. (%)		
1	138 (31.1)	66 (29.7)
2	117 (26.4)	52 (23.4)
3	112 (25.2)	61 (27.5)
≥4	77 (17.3)	43 (19.4)
Prior adjuvant or neoadjuvant therapies — no. (%)		
Chemotherapy	213 (48.0)	109 (49.1)
Neoadjuvant	54 (12.2)	32 (14.4)
Adjuvant	180 (40.5)	89 (40.1)
Adjuvant hormonal therapy‖	249 (56.1)	126 (56.8)
Tamoxifen	209 (47.1)	98 (44.1)
Anastrozole	56 (12.6)	29 (13.1)
Letrozole	36 (8.1)	16 (7.2)
Exemestane	30 (6.8)	13 (5.9)
Goserelin	5 (1.1)	6 (2.7)
Toremifene	7 (1.6)	1 (0.5)
Other	3 (0.7)	4 (1.8)

* There were no significant differences in baseline characteristics between the two treatment groups except for Eastern Cooperative Oncology Group (ECOG) performance status (P=0.004). Some percentages do not sum to 100 because of rounding.
† Race was self-reported.
‡ ECOG performance status is measured on a 5-point scale, with 0 indicating no symptoms and higher numbers indicating increasing disability.
§ "Other" was an option for the site to select on the clinical report form if none of the other available options were applicable; "data missing" means that the site did not complete that field because the information was not available.
¶ Disease-free interval was defined as the time from adjuvant or neoadjuvant therapy to recurrence. Newly metastatic disease (referred to as "de novo metastatic" in the protocol) applies to patients who had not received any prior systemic therapy, for whom a determination of disease-free interval was not possible.
‖ Patients who received anastrozole or letrozole as a component of their adjuvant or neoadjuvant therapy were excluded from the study if they had disease progression while receiving the therapy or within 12 months after completing the therapy.

Patient Demographic and Clinical Characteristics.

TABLE 2

adverse events for which the incidence was higher in the palbociclib–letrozole group than in the placebo–letrozole group were diarrhea (26.1% vs. 19.4%), cough (25.0% vs. 18.9%), and stomatitis (15.3% vs. 5.9%). There was no substantial between-group difference with respect to infections of grade 3 or higher. The incidence of headache was lower in the palbociclib–letrozole group than in the placebo–letrozole group (21.4% vs. 26.1%), as was the incidence of hot flush (20.9% vs. 30.6%). No grade 3 or 4 nonhematologic events occurred in more than 2.5% of patients in the palbociclib–letrozole group.

Serious adverse events from any cause occurred in 19.6% of the patients in the palbociclib–letrozole group and in 12.6% of the patients in the placebo–letrozole group. Febrile neutropenia was reported as serious in seven patients (1.6%) in the palbociclib–letrozole group. No other serious adverse events were reported at an incidence of higher than 1.0% in the palbociclib–letrozole group. Pulmonary embolism occurred in 0.9% of the patients in the palbociclib–letrozole group and in 1.4% in the placebo–letrozole group. During the treatment period, 10 deaths occurred in the palbociclib–letrozole group (2.3%) and 4 deaths occurred in the placebo–letrozole group (1.8%). One death in the placebo–letrozole group was considered to be related to the study regimen.

Table 2. Adverse Events from Any Cause That Occurred in at Least 10% of the Patients in Either Study Group in the As-Treated Population.

Adverse Event	Palbociclib–Letrozole (N=444)			Placebo–Letrozole (N=222)*		
	Any Grade	Grade 3	Grade 4†	Any Grade	Grade 3	Grade 4
	number of patients (percent)					
Any adverse event	439 (98.9)	276 (62.2)	60 (13.5)	212 (95.5)	49 (22.1)	5 (2.3)
Neutropenia‡	353 (79.5)	249 (56.1)	46 (10.4)	14 (6.3)	2 (0.9)	1 (0.5)
Leukopenia§	173 (39.0)	107 (24.1)	3 (0.7)	5 (2.3)	0	0
Fatigue	166 (37.4)	8 (1.8)	0	61 (27.5)	1 (0.5)	0
Nausea	156 (35.1)	1 (0.2)	0	58 (26.1)	4 (1.8)	0
Arthralgia	148 (33.3)	3 (0.7)	0	75 (33.8)	1 (0.5)	0
Alopecia¶	146 (32.9)	0	0	35 (15.8)	0	0
Diarrhea	116 (26.1)	6 (1.4)	0	43 (19.4)	3 (1.4)	0
Cough	111 (25.0)	0	0	42 (18.9)	0	0
Anemia‖	107 (24.1)	23 (5.2)	1 (0.2)	20 (9.0)	4 (1.8)	0
Back pain	96 (21.6)	6 (1.4)	0	48 (21.6)	0	0
Headache	95 (21.4)	1 (0.2)	0	58 (26.1)	4 (1.8)	0
Hot flush	93 (20.9)	0	0	68 (30.6)	0	0
Constipation	86 (19.4)	2 (0.5)	0	34 (15.3)	1 (0.5)	0
Rash**	79 (17.8)	4 (0.9)	0	26 (11.7)	1 (0.5)	0
Asthenia	75 (16.9)	10 (2.3)	0	26 (11.7)	0	0
Thrombocytopenia††	69 (15.5)	6 (1.4)	1 (0.2)	3 (1.4)	0	0
Vomiting	69 (15.5)	2 (0.5)	0	37 (16.7)	3 (1.4)	0
Pain in extremity	68 (15.3)	1 (0.2)	0	39 (17.6)	3 (1.4)	0
Stomatitis	68 (15.3)	1 (0.2)	0	13 (5.9)	0	0
Decreased appetite	66 (14.9)	3 (0.7)	0	20 (9.0)	0	0
Dyspnea	66 (14.9)	5 (1.1)	0	30 (13.5)	3 (1.4)	0
Insomnia	66 (14.9)	0	0	26 (11.7)	0	0
Dizziness	63 (14.2)	2 (0.5)	0	33 (14.9)	0	0
Nasopharyngitis	62 (14.0)	0	0	22 (9.9)	0	0
Upper respiratory tract infection	59 (13.3)	0	0	25 (11.3)	0	0
Dry skin	55 (12.4)	0	0	13 (5.9)	0	0
Pyrexia	55 (12.4)	0	0	19 (8.6)	0	0
Myalgia	53 (11.9)	0	0	20 (9.0)	0	0
Urinary tract infection	53 (11.9)	5 (1.1)	0	17 (7.7)	0	0
Abdominal pain	50 (11.3)	4 (0.9)	0	12 (5.4)	0	0
Peripheral edema	50 (11.3)	0	0	14 (6.3)	0	0
Dysgeusia	45 (10.1)	0	0	11 (5.0)	0	0
Dyspepsia	41 (9.2)	0	0	27 (12.2)	1 (0.5)	0
Anxiety	36 (8.1)	0	0	25 (11.3)	0	0

* One death secondary to lower respiratory tract infection and pulmonary embolism occurred in the placebo–letrozole group and was believed to be treatment related.
† Grade 4 events that were reported in the palbociclib–letrozole group but not shown in the table were increased alanine aminotransferase level, increased blood creatinine level, febrile neutropenia, pulmonary embolism, acute kidney injury, hyperuricemia, acute pancreatitis, pathologic fracture, pericardial effusion, sepsis, increased amylase level, aortic valve stenosis, pulmonary edema, staphylococcal bacteremia, thrombotic cerebral infarction, urosepsis, and increased lipase level; these grade 4 events were reported in one patient each, except for increased lipase level, which was reported in two patients.
‡ Neutropenia was categorized according to the *Medical Dictionary for Regulatory Activities* (MedDRA) preferred terms neutropenia and neutrophil count decreased. Febrile neutropenia was reported in 1.8% of patients in the palbociclib–letrozole group and in no patients in the placebo–letrozole group.
§ Leukopenia was categorized according to the MedDRA preferred terms leukopenia and white blood cell count decreased.
¶ In the palbociclib–letrozole group, 30.2% of the patients had grade 1 alopecia and 2.7% had grade 2. In the placebo–letrozole group, 14.9% of patients had grade 1 alopecia and 0.9% had grade 2.
‖ Anemia was categorized according to the MedDRA preferred terms anemia, hematocrit decreased, and hemoglobin decreased.
** Rash was categorized according to the MedDRA preferred terms dermatitis, dermatitis acneiform, rash, rash erythematous, rash maculopapular, rash papular, rash pruritic, and toxic skin eruption.
†† Thrombocytopenia was categorized according to the MedDRA preferred terms platelet count decreased and thrombocytopenia.

Adverse Events from Any Cause That Occurred in at Least 10% of the Patients in Either Study Group in the As-Treated Population.

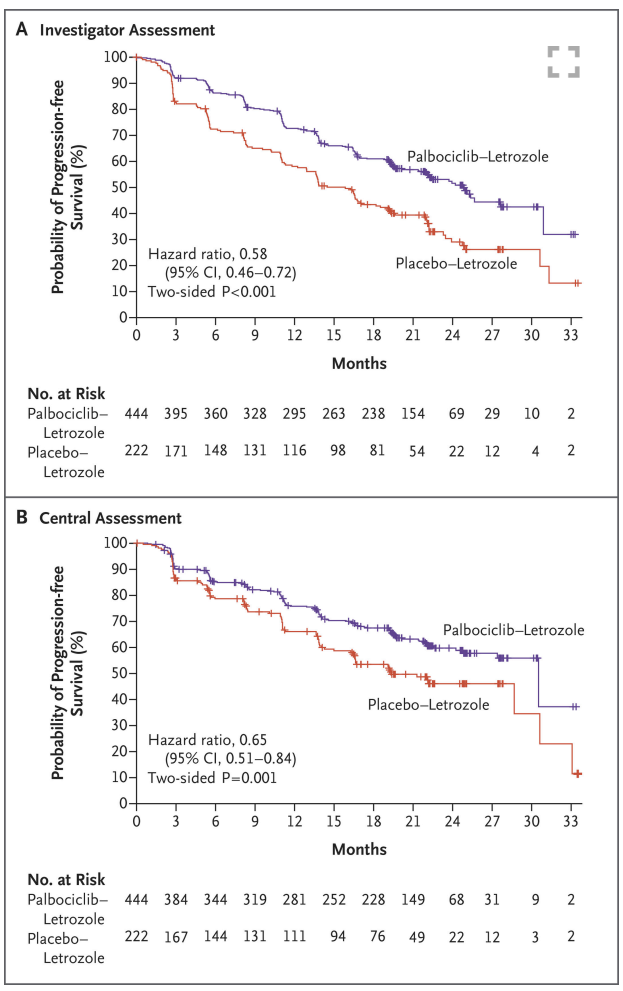
EFFICACY OF PALBOCICLIB PLUS LETROZOLE

PALOMA-2 met its primary end point by showing a median progression-free survival of 24.8 months (95% confidence interval [CI], 22.1 to not estimable) in the palbociclib–letrozole group, as compared with 14.5 months (95% CI, 12.9 to 17.1) in the placebo-letrozole group (hazard ratio for disease progression or death, 0.58; 95% CI, 0.46 to 0.72; two-sided P<0.001) (Figure 1A). The treatment effect of palbociclib combined with letrozole on progression-free survival was also supported by the findings of an independent blinded review in which a hazard ratio for disease progression or death of 0.65 (95% CI, 0.51 to 0.84) was observed (two-sided P=0.001) (Figure 1B). The median duration of follow-up was 23 months.

Subgroup analyses of progression-free survival according to stratification factors and other baseline characteristics confirmed a consistent benefit of palbociclib–letrozole across all subgroups (Figure 2). These analyses included patients with visceral disease (48.2% in the palbociclib–placebo group vs. 49.5% in the placebo–letrozole group; hazard ratio for disease progression or death, 0.63; 95% CI, 0.47 to 0.85), patients with nonvisceral disease (51.8% vs. 50.5%; hazard ratio, 0.50; 95% CI, 0.36 to 0.70), patients who had received prior hormonal therapy (56.1% vs. 56.8%; hazard ratio, 0.53; 95% CI, 0.40 to 0.70), and patients who had not received prior hormonal therapy (43.9% vs. 43.2%; hazard ratio, 0.63; 95% CI, 0.44 to 0.90). With respect to disease-free interval, the risk of disease progression or death was also lower in the palbociclib–letrozole group than in the placebo–letrozole group among patients who had had a disease-free interval of 12 months or less (22.3% vs. 21.6%; hazard ratio, 0.50; 95% CI, 0.33 to 0.76) and among those who had had a disease-free interval of more than 12 months (40.1% vs. 41.9%; hazard ratio, 0.52; 95% CI, 0.36 to 0.73). In the subgroup of patients with newly metastatic disease, patients in the palbociclib–letrozole group also had a significantly lower risk of disease progression or death than those in the placebo–letrozole group (37.6% vs. 36.5%; hazard ratio, 0.67; 95% CI, 0.46 to 0.99).

The rate of confirmed objective response among all the patients who had been randomly assigned to the palbociclib–letrozole group was 42.1% (95% CI, 37.5 to 46.9), and amo
group who had measurable disea
confirmed objective response was 55.3% (95% CI, 49.9 to 60.7); the corresponding rates in the placebo–letrozole group were 34.7% (95% CI,

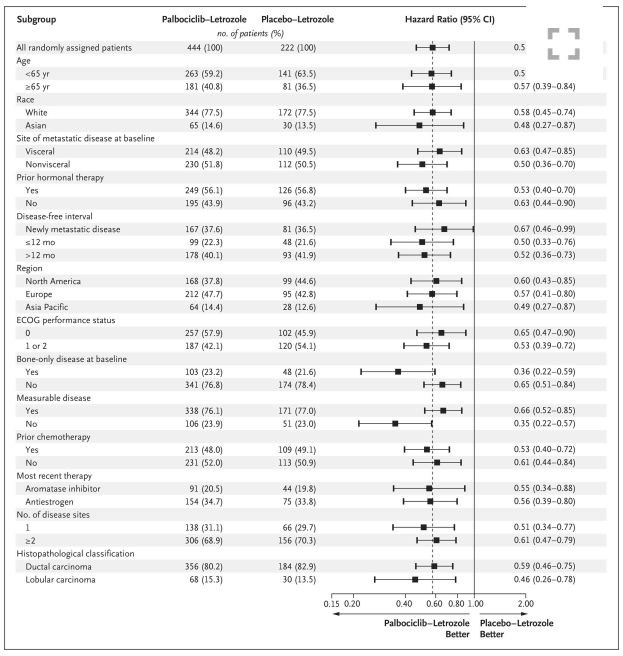
FIGURE 1



Progression-free Survival.

FIGURE 2

28.4 to 41.3) and 44.4% (95% CI, 36.9 to 52.2) (Table 3). The rate of clinical benefit response was 84.9% (95% CI, 81.2 to 88.1) among all the patients who had been randomly assigned to the palbociclib–letrozole group and 70.3% (95% CI, 63.8 to 76.2) among all the patients who had been randomly assigned to the placebo–letrozole group. Data on overall survival were immature at the time of this analysis of the primary end point, and the final overall survival analysis will be performed when a total of 390 deaths occur per protocol and in agreement with regulatory agencies. Double blinding has been maintained to allow ongoing follow-up to assess overall survival.



Subgroup Analysis of Progression-free Survival.

TABLE 3

Table 3. **Best Overall Response in the Intention-to-Treat Population.**

Variable	Palbociclib–Letrozole (N=444)	Placebo–Letrozole (N=222)	Odds Ratio (95% CI)	
All randomly assigned patients — no.	444	222		
Rate of objective response — % (95% CI)*	42.1 (37.5–46.9)	34.7 (28.4–41.3)	1.40 (0.98–2.01)	0.06
Rate of clinical benefit response — % (95% CI)†	84.9 (81.2–88.1)	70.3 (63.8–76.2)	2.39 (1.58–3.59)	<0.001
Median duration of response — mo (95% CI)	22.5 (19.8–28.0)	16.8 (14.2–28.5)‡		
Patients with measurable disease — no.§	338	171		
Rate of objective response — % (95% CI)*	55.3 (49.9–60.7)	44.4 (36.9–52.2)	1.55 (1.05–2.28)	0.03
Rate of clinical benefit response — % (95% CI)†	84.3 (80.0–88.0)	70.8 (63.3–77.5)	2.23 (1.39–3.56)	<0.001
Median duration of response — mo (95% CI)	22.5 (19.8–28.0)	16.8 (15.4–28.5)		

* Rate of objective response was defined as the percentage of patients who had a confirmed complete response or a partial response.
† Rate of clinical benefit response was defined as the percentage of patients who had a confirmed complete response, a partial response, or stable disease for 24 weeks or more.
‡ One patient with bone-only disease at baseline was included; all other patients had measurable disease at baseline.
§ Measurable disease was defined according to Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1.[8]

Best Overall Response in the Intention-to-Treat Population.

Discussion

An intense effort has been made to improve the outcomes of first-line treatment of hormone-receptor–positive advanced breast cancer.[9] PALOMA-2 is a phase 3 study that showed that the addition of a CDK inhibitor to standard endocrine therapy significantly improved outcomes in the first-line treatment of ER-positive, HER2-negative advanced breast cancer.

The development of palbociclib and other CDK4 and CDK6 inhibitors for the treatment of hormone-receptor–positive advanced breast cancer was based on the findings of our preclinical studies that identified a dependence of hormone-receptor–positive breast cancer on CDK4 and CDK6 signaling and a synergistic effect from targeting the ER, cyclin-D–CDK4/6–Rb pathway.[5] This double-blind, placebo-controlled phase 3 study confirmed the efficacy and safety of combining palbociclib with letrozole therapy as first-line treatment for postmenopausal women with ER-positive advanced breast cancer. PALOMA-2 showed that the clinical benefit of palbociclib combined with letrozole occurred irrespective of age, performance status, disease site, prior chemotherapy, prior endocrine therapy, disease-free interval after adjuvant treatment, or histologic subtype.

A high incidence of hematologic adverse events has consistently been observed with palbociclib.[6,10] Although the incidence of neutropenia of any grade in the palbociclib–letrozole group was 79.5% in the current study, the incidence of febrile neutropenia was lower than 2%. In addition, the rate of permanent treatment discontinuation associated with an adverse event did not differ significantly between the two study groups, although dose reductions and interruptions were more common with palbociclib than with placebo. Finally, the higher incidence of pulmonary emboli observed in PALOMA-1[6] was not observed in this larger study. The favorable benefit–risk assessment of the palbociclib–letrozole combination is further supported by a higher objective response rate, a higher rate of clinical benefit response, and a longer duration of response.

The median progression-free survival of 14.5 months in the placebo–letrozole group in PALOMA-2 is consistent with that observed in other recent studies of letrozole in similar populations.[11,12] This efficacy was substantially improved with the addition of palbociclib, and the longer (by 10 months) median progression-free survival with palbociclib–letrozole in PALOMA-2 was consistent with that observed in PALOMA-1. The median progression-free survival of 24.8 months in PALOMA-2 is longer t with advanced breast cancer. Whether this progression-free su until further follow-up is completed.

In conclusion, PALOMA-2 confirmed our earlier findings that palbociclib combined with letrozole results in significantly longer progression-free survival than that with letrozole alone among postmenopausal women with ER-positive, HER2-negative advanced breast cancer and provides additional evidence regarding the efficacy and safety of inhibition of CDK4 and CDK6 as first-line treatment. The addition of palbociclib to letrozole therapy resulted in higher rates of myelotoxic effects than the rates with placebo plus letrozole; thus far, these effects have been successfully managed with appropriate supportive care and dose reductions. Moreover, the results of our study underscore the way in which translating preclinical studies into clinical trial designs can lead to significantly improved outcomes for patients with cancer.

NOTES

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org. Dr. Randolph was employed at Pfizer at the time the study was conducted and the manuscript initiated but is no longer a Pfizer employee.

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SUPPLEMENTARY MATERIAL

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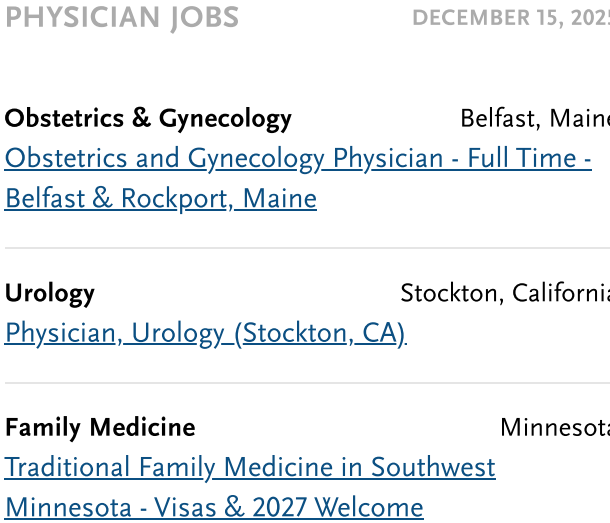

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