ORIGINAL ARTICLE

Palbociclib for Hormone-Receptor–Positive, HER2-Positive Advanced Breast Cancer

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ABSTRACT

BACKGROUND

Dual anti–human epidermal growth factor receptor 2 (HER2) therapy plus chemotherapy followed by maintenance treatment with HER2-targeted and endocrine therapies is standard first-line treatment for hormone-receptor–positive, HER2-positive metastatic breast cancer. On the basis of preclinical and clinical data, the addition of palbociclib (a selective inhibitor of cyclin-dependent kinases 4 and 6) may overcome resistance to both endocrine and HER2-directed therapies.

METHODS

In this phase 3, open-label, randomized trial, we enrolled patients with hormone-receptor–positive, HER2-positive metastatic breast cancer who did not have disease progression after four to eight cycles of chemotherapy plus HER2-targeted therapy. Patients were randomly assigned in a 1:1 ratio to receive maintenance HER2-targeted and endocrine therapies with or without palbociclib. The primary end point was investigator-assessed progression-free survival. Secondary end points included the objective response, clinical benefit, safety, and overall survival.

RESULTS

A total of 518 patients underwent randomization: 261 were assigned to receive palbociclib and 257 to receive standard therapy. At a median follow-up of 53.5 months, patients in the palbociclib group had significantly longer progression-free survival than those in the standard-therapy group (median duration, 44.3 months vs. 29.1 months; hazard ratio for disease progression or death, 0.75; 95% confidence interval, 0.59 to 0.96; two-sided P=0.02). Grade 3 and 4 adverse events, predominantly from neutropenia, occurred in 79.7% and 10.0% of the patients, respectively, in the palbociclib group, as compared with 30.6% and 3.6% of the patients, respectively, in the standard-therapy group.

CONCLUSIONS

The addition of palbociclib to maintenance anti-HER2 and endocrine therapies led to a significant improvement in progression-free survival over standard therapy, with increased toxic effects, mainly neutropenia. (Funded by Pfizer and others; PATINA ClinicalTrials.gov number, NCT02947685.)

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A Quick Take is available at NEJM.org

The identification of human epidermal growth factor receptor 2 (HER2)–positive breast cancer as a distinct clinical subtype has driven the development of transformative HER2-targeted therapies.[1-3] More than 50% of HER2-positive breast cancers coexpress estrogen receptors, progesterone receptors, or both, which forms a biologically distinct subgroup.[4,5]

The current standard first-line treatment for hormone-receptor–positive, HER2-positive metastatic breast cancer consists of induction chemotherapy, combined with trastuzumab and pertuzumab for several cycles, followed by maintenance therapy with dual HER2 blockade and endocrine therapies.[6-9] Preclinical studies have shown crosstalk between HER2 and estrogen-receptor signaling pathways, which can promote resistance when only one pathway is targeted.[10-12] The axis of cyclin D1 and cyclin-dependent kinases 4 and 6 (CDK4/6) has also been implicated as a driver of tumor initiation, proliferation, and survival in HER2-positive breast cancer, as well as of resistance to both endocrine and HER2-directed therapies.[13-18] These findings provide a compelling rationale for concurrent inhibition of HER2, estrogen receptor, and the cell cycle through CDK4/6 inhibition to improve disease control and potentially survival outcomes in patients with hormone-receptor–positive, HER2-positive advanced breast cancer.

Early-phase clinical studies have shown that CDK4/6 inhibition in combination with both HER2-targeted and endocrine therapies is feasible, safe, and may provide additional efficacy in patients with advanced hormone-receptor–positive, HER2-positive breast cancer (i.e., disease that is metastatic or not amenable to resection or radiation therapy with curative intent).[19-23] We therefore hypothesized that the addition of the CDK4/6 inhibitor palbociclib to standard first-line therapy in the maintenance phase would provide longer disease control.

Methods

Trial Design

We conducted the phase 3 PATINA trial (Randomized, Open Label, Clinical Study of the Targeted Therapy, Palbociclib, to Treat Metastatic Breast Cancer) at 123 sites in eight countries. We enrolled patients who were receiving first-line treatment for hormone-receptor–positive, HER2-positive advanced breast cancer. Eligible patients had completed a minimum of four cycles and a maximum of eight cycles of trastuzumab-based induction chemotherapy without evidence of disease progression (i.e., complete response, partial response, or stable disease, as assessed locally). Induction therapy included trastuzumab and pertuzumab plus a taxane. Single-agent HER2 blockade with trastuzumab (i.e., without pertuzumab) was allowed in up to 20% of the patients. For those receiving trastuzumab only, the chemotherapy backbone could be either a taxane or vinorelbine.[24]

Patients were enrolled after induction therapy with no more than 12 weeks between the last induction infusion and the first protocol-assigned therapy. They were randomly assigned in a 1:1 ratio to receive maintenance treatment with anti-HER2 and endocrine therapies with palbociclib (palbociclib group) or without palbociclib (standard-therapy group). Endocrine therapy consisted of either an aromatase inhibitor or fulvestrant; premenopausal patients were required to receive ovarian suppression. Randomization was stratified according to the patient's response to induction therapy (complete or partial response vs. stable disease), previous neoadjuvant or adjuvant anti-HER2 therapy (yes or no), type of endocrine therapy (aromatase inhibitor or fulvestrant), and single or dual HER2 blockade (trastuzumab or trastuzumab plus pertuzumab).

Trial Oversight

The trial was funded by Pfizer (which provided the palbociclib used in the trial) and by an academic collaboration led by Alliance Foundation Trials in partnership with Breast Cancer Trials (Australia and New Zealand), Fondazione Michelangelo, GBG Forschungs, PrECOG Cancer Research Group, SOLTI Breast Cancer Research Group, and Unicancer. Oversight was provided by a multinational steering committee led by Alliance Foundation Trials that included Pfizer representatives. Alliance Foundation Trials coordinated trial operations, including data management and analysis. Efficacy and safety data were monitored by the independent data and safety monitoring board at the Alliance. The protocol (available with the full text of this article at NEJM.org) and its amendments were approved by the institutional review board or ethics committee at each site. All the patients provided written informed consent.

The trial was conducted in accordance with the Good Clinical Practice guidelines of the International Council for Harmonisation and the principles of the Declaration of Helsinki. Data were collected by Alliance Foundation Trials, reviewed by the trial chair (the first author), and analyzed by all the authors in collaboration with the Statistics and Data Center of the Alliance. The first author wrote the first draft of the manuscript, with support from the coauthors and the Statistics and Data Center, and vouches for the accuracy and completeness of the data and for the adherence of the trial to the protocol. No one who is not an author contributed to the writing of the manuscript.

PATIENTS

Eligible patients were women or men who were 18 years of age or older with histologically confirmed hormone-receptor–positive and HER2-positive advanced breast cancer. The hormone receptor with positivity could be either the estrogen or progesterone receptor. Status with respect to hormone receptor and HER2 was assessed locally. Hormone-receptor positivity was defined as at least 1% tumor-cell nuclear staining on immunohistochemical (IHC) analysis. HER2 positivity was defined as an IHC score of 3+ or gene amplification performed by in situ hybridization, according to the guidelines of the American Society of Clinical Oncology and the College of American Pathologists.[25] Eligible patients were required to have a disease-free interval of at least 6 months after any previous neoadjuvant or adjuvant anti-HER2 therapy until metastatic diagnosis and to have received no previous systemic therapy for metastatic disease other than induction therapy. Patients with asymptomatic central nervous system (CNS) metastases at diagnosis were eligible; for those who had received previous CNS radiotherapy, a minimum of 3 weeks was required between completion of CNS radiotherapy and day 1 of cycle 1, with no ongoing requirement for glucocorticoid therapy.

END POINTS

The primary end point was investigator-assessed progression-free survival, which was defined as the time from randomization to documented disease progression or death from any cause, whichever occurred first. Data for patients without progression or death at the time of data cutoff were censored at the date of their last tumor assessment. Secondary end points included a confirmed objective response (as measured from randomization and defined as a complete or partial response that was sustained for at least two consecutive assessments), overall survival, and safety. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.

ASSESSMENTS

Tumor assessments were conducted according to Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1, at baseline (within 28 days before randomization) and every 12 weeks thereafter, until disease progression, unacceptable toxic effects, withdrawal of consent, or death. Brain imaging was not required in asymptomatic patients. Adverse events were recorded until 42 days after the final dose of a trial therapy.

Palbociclib was administered orally at a dose of 125 mg daily for 21 days, followed by 7 days off in 28-day cycles. Dose reductions to 100 mg and 75 mg were permitted according to the protocol, consistent with labeling; treatment was discontinued if further dose reduction was required. Complete blood counts were obtained at baseline, on day 1 of cycles 1 through 4, and every 3 months thereafter. In the palbociclib group, an additional complete blood count was performed on day 22 of cycle 1. Anti-HER2 and endocrine therapies were administered according to standard guidelines, including subcutaneous formulations of trastuzumab and pertuzumab where available. Patients who discontinued any component of therapy for safety reasons were permitted to continue to receive the remaining drugs. The use of growth factor support was not allowed in the trial.

STATISTICAL ANALYSIS

The trial was powered to detect a hazard ratio of 0.667 for investigator-assessed progression-free survival (the palbociclib group vs. the standard-therapy group) on the assumption of a median progression-free survival of 13.0 months in the standard-therapy group and 19.5 months in the palbociclib group. A total of 269 events (disease progression or death) were required to provide 90% power with a one-sided log-rank test at an alpha level of 0.025. Two interim analyses

were planned: a futility analysis after the occurrence of 135 events of progression or death (estimated 50%) and an efficacy analysis after the occurrence of 175 events (estimated 65%). This sample size was estimated to provide 80% power to detect an overall survival benefit from 50 months to 71.4 months (hazard ratio, 0.70) with a one-sided alpha level of 0.025. Overall survival would be tested hierarchically at a one-sided alpha level of 0.0002 if progression-free survival reached significance at the interim or final analysis; otherwise, the final overall survival analysis would be performed after the occurrence of 247 deaths.

Interim analyses for progression-free survival were conducted in July 2021 (for futility) and December 2021 (for efficacy). The final progression-free survival analysis was conducted in October 2024 when 262 of the required 269 events had occurred. This decision was based on mature follow-up data (median, 53.5 months), continued treatment in 131 patients, and a plateauing event rate (approximately one progression or death event per month from October 2023 to October 2024). On the basis of the results of the primary and sensitivity analyses for progression-free survival (Table S1 in the Supplementary Appendix, available at NEJM.org), the data and safety monitoring board recommended the release of the trial data.

Efficacy analyses included all the patients who had undergone randomization. Safety analyses were conducted in the safety population, which was defined as all the patients who had received at least one dose of a protocol-assigned therapy. The primary analyses used unstratified models and were confirmed with stratified models. Two-sided P values are reported for all end points. No methods to adjust for multiplicity were planned in the protocol for secondary end points. Thus, the widths of confidence intervals were not adjusted for multiplicity, so the intervals may not be used in place of hypothesis testing for secondary end points.

All the analyses were conducted at the Statistics and Data Center of Alliance Foundation Trials with a data-cutoff date of October 14, 2024. All analyses were performed with SAS software, version 9.4, and R statistical software, version 4.4.1. Additional statistical details are provided in the protocol and the Supplementary Appendix.

RESULTS

PATIENTS AND TREATMENTS

From June 2017 through July 2021, a total of 518 patients were enrolled and randomly assigned to receive either palbociclib with anti-HER2 and endocrine therapies (261 patients) or anti-HER2 and endocrine therapies alone (257 patients). Approximately 10% of screened patients were deemed to be ineligible for various reasons, including the occurrence of disease progression after previous induction therapy, although the precise number attributable to progression was not recorded (Fig. S1). Baseline characteristics were well balanced between the groups (Table 1). The median age was 53.4 years; 99.4% of the patients were female, and 61.8% were postmenopausal. Most of the patients were White; Black patients were both underrepresented and unevenly assigned. A total of 54.4% of the patients had de novo metastatic disease (which was defined as metastatic disease in a patient who had received no previous anti-HER2 therapy and who enrolled in the trial within 1 year after the diagnosis of the primary breast cancer).

The median number of induction therapy cycles before randomization was six. Overall, 70.1% of the patients had a complete or partial response, and 29.3% had stable disease at the end of induction. The majority of patients (94.0%) were treated with dual anti-HER2 therapy, and 90.7% received an aromatase inhibitor. Of the 29 patients (5.6%) who were treated with trastuzumab without pertuzumab, only 2 received induction with vinorelbine rather than a taxane.

At the end of the trial, the patients who continued to receive the trial therapy included 75 patients (28.7%) in the palbociclib group and 56 (21.8%) in the standard-therapy group. The most common reason for treatment discontinuation was disease progression in 124 patients (47.5%) in the palbociclib group and in 136 patients (52.9%) in the standard-therapy group (Fig. S1).

EFFICACY

At a median follow-up of 53.5 months, the median progression-free survival was 44.3 months (95% confidence interval [CI], 32.4 to 56.8) in the palbociclib group and 29.1 months (95% CI, 23.3 to 38.6) in the standard-therapy group (hazard ratio for disease progression or death, 0.75;

95% CI, 0.59 to 0.96; two-sided unstratified P=0.02 and stratified P=0.03) (Fig. 1A). Estimated progression-free survival at 12, 24, and 48 months was 84.9%, 65.2%, and 46.5% in the palbociclib group and 73.2%, 55.3%, and 38.3% in the standard-therapy group, respectively. Subgroup analyses were underpowered; the data are shown in Figure 1B.

The confirmed response (defined as a complete or partial response that was sustained for at least two consecutive assessments, with the exclusion of patients who had a complete response to induction treatment) was 32.9% (95% CI, 26.9 to 39.4) in the palbociclib group and 24.8% (95% CI, 19.3 to 30.0) in the standard-therapy group (Fig. 2). The median duration of confirmed response was 44.9 months (95% CI, 27.1 to 51.6) in the palbociclib group and 30.8 months (95% CI, 26.0 to nonevaluable due to low number of events) in the standard-therapy group. The percentage of patients who had a complete response was greater in the palbociclib group than in the standard-therapy group (14.3% vs. 11.3%), regardless of previous response to induction therapy (Fig. S2).

The percentage of patients who had a clinical benefit was 88.9% (95% CI, 84.4 to 92.4) in the palbociclib group and 80.9% (95% CI, 75.6 to 85.6) in the standard-therapy group (Fig. S3). At the data cutoff, 123 patients had died (60 in the palbociclib group and 63 in the standard-therapy group), for a hazard ratio for death of 0.86 (95% CI, 0.61 to 1.23) for the secondary end point of overall survival. According to the protocol, the final overall survival analysis will occur after 247 deaths have been reported.

SAFETY

A total of 509 patients were included in the safety population: 261 in the palbociclib group and 248 in the standard-therapy group. A total of 9 patients were excluded from the standard-therapy group: 8 who withdrew consent before starting treatment and 1 who did not receive any treatment.

Adverse events of any grade occurred in all the patients in the palbociclib group and in 94.4% of those in the standard-therapy group. Grade 3 adverse events were more than twice as frequent with palbociclib (79.7% vs. 30.6%), due mainly to neutropenia (55.9% vs. 2.0%) and leukopenia (15.7% vs. 0.8%). Grade 4 adverse events occurred in 10.0% of the patients in the palbociclib group and in 3.6% of those in the standard-therapy group (Table S2). Table 2 lists the adverse events that occurred in at least 10% of the patients in either trial group during treatment or within 42 days after treatment.

Neutropenia was more frequent in the palbociclib group than in the standard-therapy group; grade 2 events were reported in 14.6% and 3.6%, respectively; grade 3 events in 55.9% and 2.0%, respectively; and grade 4 events in 4.6% and 0%, respectively (Table S2). Two patients in the palbociclib group had febrile neutropenia.

Grade 2 or higher fatigue was reported more frequently in the palbociclib group than in the standard-therapy group (grade 2, 22.2% and 12.9%, respectively; and grade 3, 5.0% and 0%, respectively). Diarrhea was more common in the palbociclib group than in the standard-therapy group (grade 2, 27.6% and 10.9%, respectively; and grade 3, 9.6% and 1.2%, respectively), with a median time until onset of grade 2 or 3 diarrhea of 2.3 months in the palbociclib group. Among the patients who had grade 3 diarrhea at any time in the palbociclib group, 30.8% had diarrhea recorded as a baseline symptom before the trial initiation. Stomatitis of grade 2 or 3 was observed in 9.9% of the patients in the palbociclib group and 0.4% of those in the standard-therapy group.

Grade 5 adverse events (fatal events attributed to causes other than the trial treatment) occurred in 3.8% of the patients in the palbociclib group and in 4.4% of those in the standard-therapy group (Table S3); no deaths that were determined by the investigator to be related to a trial treatment were reported. Serious adverse events occurred in 28.7% of the patients in the palbociclib group and in 21.8% of those in the standard-therapy group (Table S4).

The dose of palbociclib was reduced in 57.7% of the patients (once in 27.7% of the treated patients and twice in 30.0%). The median time until the first dose reduction was 3.2 months. Neutropenia was the most common adverse event leading to a dose reduction (in 72.3% of the patients) (Table S5). Adverse events led to the discontinuation of palbociclib in 18.0% of the patients (Table S6). The most common adverse event causing discontinuation was uncomplicated

Table 1. Characteristics of the Patients at Baseline.*

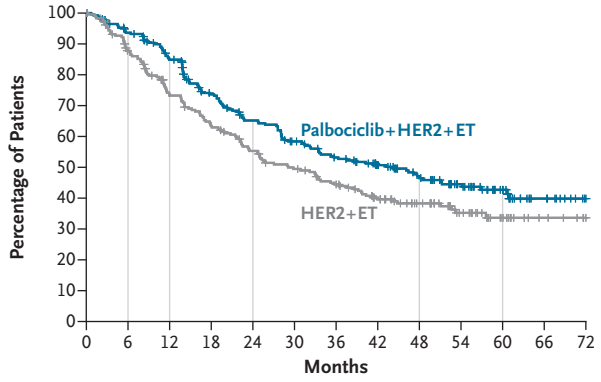
Characteristic	Palbociclib+ HER2+ET (N=261)	HER2+ET (N=257)	Total (N=518)
Age — yr			
Median (IQR)	53.5 (43.6–60.4)	53.0 (45.1–62.8)	53.4 (44.2–61.4)
Range	28.7–81.7	29.9–84.3	28.7–84.3
Race or ethnic group — no. (%)†			
Asian Indian, Chinese, or other Asian	6 (2.3)	4 (1.6)	10 (1.9)
Black	4 (1.5)	11 (4.3)	15 (2.9)
White	207 (79.3)	194 (75.5)	401 (77.4)
Other ethnic group	8 (3.1)	3 (1.2)	11 (2.1)
Missing data	36 (13.8)	45 (17.5)	81 (15.6)
Geographic region — no. (%)			
North America	83 (31.8)	83 (32.3)	166 (32.0)
Western Europe, Australia, or New Zealand	178 (68.2)	174 (67.7)	352 (68.0)
Sex — no. (%)			
Female	259 (99.2)	256 (99.6)	515 (99.4)
Male	2 (0.8)	1 (0.4)	3 (0.6)
ECOG performance-status score — no. (%)‡			
0	150 (57.5)	144 (56.0)	294 (56.8)
1	111 (42.5)	110 (42.8)	221 (42.7)
Missing data	0	3 (1.2)	3 (0.6)
Menopausal status — no. (%)			
NA because of male sex	2 (0.8)	1 (0.4)	3 (0.6)
Postmenopausal	163 (62.5)	157 (61.1)	320 (61.8)
Premenopausal	96 (36.8)	96 (37.4)	192 (37.1)
Missing data	0	3 (1.2)	3 (0.6)
Estrogen-receptor status — no. (%)§			
Negative	10 (3.8)	3 (1.2)	13 (2.5)
Positive	251 (96.2)	251 (97.7)	502 (97.5)
Missing data	0	3 (1.2)	3 (0.6)
Progesterone-receptor status — no. (%)§			
Negative	75 (28.7)	79 (30.7)	154 (29.9)
Positive	185 (70.9)	174 (67.7)	359 (69.3)
Unknown	1 (0.4)	1 (0.4)	2 (0.4)
Missing data	0	3 (1.2)	3 (0.6)
HER2 assessment — no. (%)§¶			
2+, ISH amplified	59 (22.6)	71 (27.6)	130 (25.1)
3+	201 (77.0)	183 (71.2)	384 (74.1)
Missing data	1 (0.4)	3 (1.2)	4 (0.8)

Table 1. (Continued.)

Characteristic	Palbociclib+ HER2+ET (N=261)	HER2+ET (N=257)	Total (N=518)
Site of metastases — no. (%)‖			
Central nervous system	11 (4.2)	9 (3.5)	20 (3.9)
Nonvisceral	57 (21.8)	60 (23.3)	117 (22.6)
Visceral	193 (73.9)	186 (72.4)	379 (73.2)
Missing data	0	2 (0.8)	2 (0.4)
Number of cycles of induction treatment			
Median (IQR)	6.0 (6.0–7.0)	6.0 (6.0–7.0)	6.0 (6.0–7.0)
Range	4.0–8.0	4.0–8.0	4.0–8.0
Missing data	0	3 (1.2)	3 (0.6)
De novo metastatic disease — no. (%)**			
No	124 (47.5)	109 (42.4)	233 (45.0)
Yes	137 (52.5)	145 (56.4)	282 (54.4)
Missing data	0	3 (1.2)	3 (0.6)
Previous adjuvant or neoadjuvant anti-HER2 therapy — no. (%)††			
No	172 (65.9)	174 (67.7)	346 (66.8)
Yes	89 (34.1)	80 (31.1)	169 (32.6)
Missing data	0	3 (1.2)	3 (0.6)
Best response to induction therapy by investigator assessment — no. (%)††‡‡			
Complete or partial response	182 (69.7)	181 (70.4)	363 (70.1)
Stable disease	79 (30.3)	73 (28.4)	152 (29.3)
Missing data	0	3 (1.2)	3 (0.6)
Receipt of dual anti-HER2 therapy — no. (%)††			
No	14 (5.4)	15 (5.8)	29 (5.6)
Yes	247 (94.6)	240 (93.4)	487 (94.0)
Missing data	0	2 (0.8)	2 (0.4)
Type of endocrine therapy — no. (%)††			
Aromatase inhibitor	238 (91.2)	232 (90.3)	470 (90.7)
Fulvestrant	22 (8.4)	22 (8.6)	44 (8.5)
Missing data	1 (0.4)	3 (1.2)	4 (0.8)

* ET denotes endocrine therapy, HER2 human epidermal growth factor receptor 2, IQR interquartile range, and NA not applicable.
† Race or ethnic group was reported by the investigator.
‡ The Eastern Cooperative Oncology Group (ECOG) performance-status score is a measure of the patient's functional ability on a scale of 0 (fully active) to 5 (death).
§ The patient's hormonal status was determined from archival tissue for two patients.
¶ An immunohistochemical (IHC) score of 2+ indicates equivocal HER2 protein expression and requires reflex in situ hybridization (ISH) testing to determine HER2 gene amplification status; an IHC score of 3+ indicates HER2-positive disease.
‖ Baseline sites of disease include those that were identified at the time of the primary tumor diagnosis as well as at the time of randomization.
** De novo metastatic disease was defined as metastatic disease in a patient who had received no previous anti-HER2 therapy and who enrolled in the trial within 1 year after the diagnosis of the primary breast cancer.
†† This category was used as a stratification factor in the analyses.
‡‡ Two of these patients were treated with vinorelbine during the induction phase.

A Progression-free Survival



	No. of Events/Total No. of Patients	Median Progression-free Survival (95% CI)
		mo
Palbociclib+HER2+ET	127/261	44.3 (32.4–56.8)
HER2+ET	135/257	29.1 (23.3–38.6)

Hazard ratio for disease progression or death, 0.75 (95% CI, 0.59–0.96)
Two-sided unstratified P=0.02 by log-rank test

No. at Risk

Palbociclib+HER2+ET	261	230	202	166	144	126	111	92	76	54	33	15	5
HER2+ET	257	197	157	135	115	101	88	68	52	30	15	6	1

B Risk of Progression or Death, According to Subgroup

Subgroup	Palbociclib+HER2+ET	HER2+ET	Hazard Ratio for Disease Progression or Death (95% CI)
	no. of events/total no. of patients		
All patients	127/261	135/257	0.75 (0.59–0.96)
Stratification factors			
Previous anti-HER2 therapy			
No	81/172	87/174	0.78 (0.57–1.05)
Yes	46/89	48/80	0.69 (0.46–1.03)
Best response to induction			
Complete or partial response	89/182	100/181	0.75 (0.56–1.00)
Stable disease	38/79	35/73	0.80 (0.50–1.26)
Endocrine therapy			
Aromatase inhibitor	112/238	122/232	0.74 (0.57–0.96)
Fulvestrant	14/22	13/22	0.64 (0.30–1.36)
Pertuzumab use			
No	7/14	8/15	0.76 (0.26–2.19)
Yes	120/247	127/240	0.75 (0.59–0.96)
Clinical and demographic factors			
Female sex	125/259	135/256	0.74 (0.58–0.94)
Race			
Non-White	9/18	7/18	1.36 (0.51–3.67)
White	104/207	103/194	0.73 (0.56–0.96)
Geographic region			
Australia and New Zealand	13/25	12/24	0.70 (0.32–1.55)
Europe	73/153	79/150	0.82 (0.60–1.12)
North America	41/83	44/83	0.64 (0.42–0.99)
Age			
≤65 yr	110/220	112/211	0.79 (0.61–1.03)
>65 yr	17/41	23/46	0.60 (0.32–1.12)
Menopause status			
Postmenopausal	80/163	79/157	0.82 (0.60–1.12)
Premenopausal	45/96	56/96	0.62 (0.42–0.92)
ECOG performance-status score			
0	69/150	73/144	0.78 (0.56–1.08)
1	58/111	62/110	0.72 (0.50–1.03)
Visceral staus			
Central nervous system	5/11	5/9	0.67 (0.19–2.34)
Nonvisceral	18/57	27/60	0.53 (0.29–0.97)
Visceral	104/193	103/186	0.82 (0.62–1.07)
ER and PR status			
ER+, PR+	87/175	81/171	0.85 (0.63–1.15)
ER+, PR–	35/75	52/79	0.65 (0.42–1.00)
HER2 status			
2+, ISH amplified	30/59	41/71	0.66 (0.41–1.06)
3+	97/201	94/183	0.80 (0.60–1.06)
De novo metastatic disease			
No	66/124	60/109	0.78 (0.55–1.11)
Yes	61/137	75/145	0.72 (0.51–1.00)

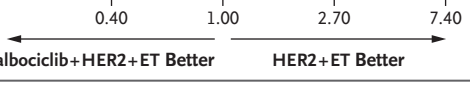


Figure 1 (facing page). Progression-free Survival in the Intention-to-treat Population and According to Stratified and Clinicopathologic Features.

Panel A shows investigator-assessed progression-free survival in the group that received palbociclib plus anti–human epidermal growth factor receptor 2 therapy and endocrine therapy (palbociclib+HER2+ET) as compared with the group that received anti-HER2 therapy and endocrine therapies (HER2+ET) alone. At a median follow-up of 53.5 months, patients in the palbociclib group had significantly longer progression-free survival than those in the standard-therapy group (median duration, 44.3 months vs. 29.1 months; hazard ratio for death or disease progression, 0.75; 95% confidence interval, 0.59 to 0.96; two-sided P=0.02). Tick marks indicate data censoring. Panel B is a forest plot showing hazard ratios and 95% confidence intervals for disease progression or death in predefined subgroups. The data are divided according to stratified subgroups at the time of randomization and according to clinicopathologic features. In the category of pertuzumab use, "no" indicates that patients received only trastuzumab monotherapy and "yes" indicates that patients received both trastuzumab and pertuzumab. The Eastern Cooperative Oncology Group (ECOG) performance-status score is a measure of the patient's functional ability on a scale of 0 (fully active) to 5 (death). An immunohistochemical (IHC) score of 2+ indicates equivocal HER2 protein expression and requires reflex in situ hybridization (ISH) testing to determine HER2 gene amplification status; an IHC score of 3+ indicates HER2-positive disease. De novo metastatic disease was defined as metastatic disease in a patient who had received no previous anti-HER2 therapy and who enrolled in the trial within 1 year after the diagnosis of the primary breast cancer. ER denotes estrogen receptor, and PR progesterone receptor.

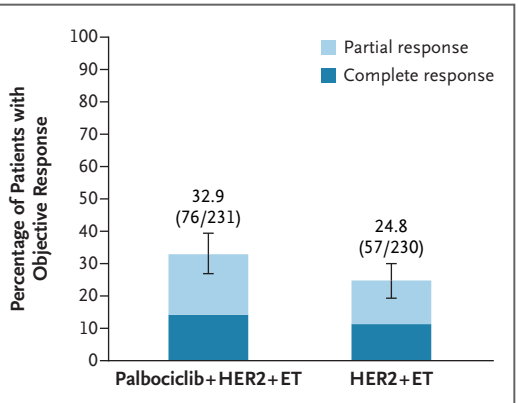


Figure 2. Tumor Response.

Shown is the percentage of patients who had a confirmed objective (partial or complete) response in the group that received palbociclib plus anti-HER2 and endocrine therapies as compared with those who received anti-HER2 and endocrine therapies alone. This analysis does not include patients who had a complete response after they had undergone induction therapy before randomization.

neutropenia (grade 3 or higher in 11 of 26 patients [42.3%]) (Table S7).

DISCUSSION

In the phase 3 PATINA trial, the addition of palbociclib to anti-HER2 and endocrine therapy prolonged progression-free survival by more than 1 year in patients with hormone-receptor–positive, HER2-positive advanced breast cancer. The 29-month median progression-free survival observed in the standard-therapy group was longer than what was initially predicted during the design of the trial. This factor was likely due in part to the mandatory use of endocrine therapy in the two trial groups. Endocrine therapy was required in the trial to align with contemporary clinical guidelines and exploit potential synergies in hormone-receptor–positive disease with CDK4/6 inhibition.[6,7,10-12,19,20,22,26] In addition, the trial excluded the subgroup of patients who had disease progression during induction therapy, thereby potentially enriching the trial population for patients with more favorable disease biology.[2,3] Among the 630 patients who were screened, 62 (10%) were ineligible (Fig. S1), a group that included patients with disease progression among other reasons for noneligibility.

The addition of palbociclib in this population extended the median progression-free survival to 44.3 months from 29.1 months in the standard-therapy group, which represented a significant improvement. With the inclusion of the time that patients received induction therapy, disease control with first-line treatment was extended to a median of more than 4 years in the palbociclib group. The observed benefit probably reflects the biologic convergence of HER2, estrogen receptor, and CDK4/6 signaling and hence the effect of their combined inhibition. In HER2-positive models, persistent cyclin D1–CDK4/6 activity has been implicated in resistance to HER2-targeted therapy, and preclinical studies have shown synergistic effects with dual inhibition of CDK4/6 and HER2.[17,27] Our findings in this trial support the clinical relevance of this mechanistic rationale.

Table 2. Adverse Events.*

Adverse Events	Palbociclib+HER2+ET (N=261)		HER2+ET (N=248)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
	number of patients (percent)			
Neutropenia†	203 (77.8)	158 (60.5)	19 (7.7)	5 (2.0)
Diarrhea	184 (70.5)	25 (9.6)	93 (37.5)	3 (1.2)
Fatigue†	140 (53.6)	13 (5.0)	99 (39.9)	0
Leukopenia†	99 (37.9)	42 (16.1)	12 (4.8)	2 (0.8)
Arthralgia	95 (36.4)	4 (1.5)	119 (48.0)	2 (0.8)
Anemia†	80 (30.7)	8 (3.1)	20 (8.1)	1 (0.4)
Nausea	77 (29.5)	1 (0.4)	38 (15.3)	1 (0.4)
Headache	67 (25.7)	4 (1.5)	45 (18.1)	2 (0.8)
Thrombocytopenia†	65 (24.9)	3 (1.1)	4 (1.6)	0
Abdominal pain†	62 (23.8)	4 (1.5)	19 (7.7)	5 (2.0)
Hot flush†	58 (22.2)	0	70 (28.2)	0
Rash†	58 (22.2)	0	42 (16.9)	0
Covid-19†	57 (21.8)	2 (0.8)	25 (10.1)	0
Pruritus	55 (21.1)	4 (1.5)	41 (16.5)	0
Stomatitis	54 (20.7)	5 (1.9)	11 (4.4)	0
Mucosal inflammation	52 (19.9)	4 (1.5)	10 (4.0)	0
Muscle spasms	51 (19.5)	1 (0.4)	27 (10.9)	0
Epistaxis	49 (18.8)	0	14 (5.6)	0
Pyrexia	43 (16.5)	3 (1.1)	13 (5.2)	1 (0.4)
Cough†	42 (16.1)	0	29 (11.7)	0
Vomiting	41 (15.7)	2 (0.8)	21 (8.5)	3 (1.2)
Dizziness	37 (14.2)	2 (0.8)	23 (9.3)	1 (0.4)
Hypokalemia†	37 (14.2)	3 (1.1)	13 (5.2)	3 (1.2)
Peripheral neuropathy	35 (13.4)	0	21 (8.5)	1 (0.4)
Decreased appetite	34 (13.0)	2 (0.8)	13 (5.2)	0
Aspartate aminotransferase increased	33 (12.6)	3 (1.1)	11 (4.4)	2 (0.8)
Back pain	33 (12.6)	1 (0.4)	33 (13.3)	1 (0.4)
Constipation	33 (12.6)	0	24 (9.7)	0
Upper respiratory tract infection	32 (12.3)	1 (0.4)	18 (7.3)	0
Myalgia	31 (11.9)	0	27 (10.9)	1 (0.4)
Alanine aminotransferase increased	29 (11.1)	7 (2.7)	10 (4.0)	2 (0.8)
Alopecia	28 (10.7)	0	9 (3.6)	0
Insomnia	28 (10.7)	1 (0.4)	30 (12.1)	0
Urinary tract infection	28 (10.7)	2 (0.8)	21 (8.5)	1 (0.4)
Vulvovaginal dryness	28 (10.7)	1 (0.4)	10 (4.0)	0
Ejection fraction decreased	24 (9.2)	1 (0.4)	28 (11.3)	8 (3.2)

* Adverse events that are listed in this table occurred in at least 10% of patients in either trial group during treatment or within 42 days after treatment. Covid-19 denotes coronavirus disease 2019.
† This event was reported as a consolidated term. A detailed list of consolidated terms is provided in the Supplementary Appendix.

The safety profile of this trial was consistent with the known toxic effects of the individual agents.[2,26,28-30] Neutropenia was more frequent with palbociclib, and febrile neutropenia was rare despite the omission of colony-stimulating factor support. Grade 2 or 3 diarrhea in the palbociclib group, particularly early on and among patients who had diarrhea at baseline, may reflect residual toxic effects from chemotherapy or overlapping effects from pertuzumab and palbociclib. No deaths that were determined by the investigator to be related to treatment occurred in either trial group.

Limitations of this trial include its open-label design and the limited racial diversity of the trial population. We are compiling additional data regarding patient-reported outcomes, biomarker data, and outcomes related to the incidence of metastases in the CNS.

The achievement of progression-free survival beyond 44 months with a regimen represents a meaningful clinical advance, and the median follow-up of 53.5 months provides mature and robust estimates of progression-free survival. Although the use of newer, more potent HER2-directed infusional and chemotherapy-based therapies (including antibody–drug conjugates) may be warranted in selected high-risk patients receiving first-line therapy, the sequential use of single-agent taxane therapy plus trastuzumab and pertuzumab followed by endocrine therapy and palbociclib resulted in a long first-line progression-free survival. Early death was uncommon in our trial, which had a 6-month overall survival of more than 99% in the two groups. This outcome reflects the favorable outcomes of patients who had completed induction therapy and entered the maintenance phase.

In our trial, we found that palbociclib in combination with anti-HER2 and endocrine therapy was an effective first-line strategy for patients with hormone-receptor–positive, HER2-positive advanced breast cancer.

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