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Impact of Prior Treatment on Palbociclib Plus Letrozole Efficacy and Safety in Patients with Estrogen Receptor–Positive/Human Epidermal Growth Factor Receptor 2–Negative (ER+/HER2–) First-Line Advanced Breast Cancer: a PALOMA-2 Subgroup Analysis

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BACKGROUND

- Palbociclib is a first-in-class, selective, small-molecule inhibitor of cyclin-dependent kinases (CDKs) 4 and 6, which represent attractive targets for therapeutic intervention in many human cancers, including breast cancer.[1,4]
- Preclinical studies have demonstrated that palbociclib is most active in estrogen receptor–positive (ER+) breast cancer cell lines with luminal features and is synergistic when combined with endocrine therapy.[4]
- The significant clinical efficacy of palbociclib combined with letrozole initially observed in the open-label, randomized, phase 2 PALOMA-1 study (NCT00721409) was then confirmed in the phase 3 PALOMA-2 study (NCT01740427) of postmenopausal women with ER+/human epidermal growth factor receptor 2–negative (HER2–) advanced breast cancer (ABC).[2,5]
- In PALOMA-2, palbociclib plus letrozole significantly prolonged median progression-free survival (PFS) vs placebo plus letrozole in patients receiving first-line treatment for advanced/metastatic disease (24.8 vs 14.5 months; hazard ratio [HR], 0.58; 95% CI, 0.46–0.72; *P*<0.001).[2,5]
- Here, the PALOMA-2 study results have been more deeply analyzed to verify the consistency of the palbociclib plus letrozole efficacy and safety profile across 4 subgroups of patients: (1) pre-treated or (2) not pre-treated with endocrine therapy and (3) treated or (4) not treated with prior chemotherapy in the (neo)adjuvant setting.
- The PALOMA-2 study is still ongoing to collect survival data.

OBJECTIVES

- The objectives of this analysis were to evaluate the efficacy and safety of palbociclib in combination with letrozole across subgroups of patients with ER+/HER2– ABC who were either exposed or not exposed to prior neo(adjuvant) endocrine therapy or chemotherapy following their primary diagnosis.
  - The primary endpoint of the study was investigator-assessed PFS.
  - Key secondary endpoints included objective response (OR), clinical benefit rate (CBR), and duration of response (DOR), as well as a safety assessment between the treatment arms.

METHODS

Study Design and Treatment

- PALOMA-2 is a multicenter, double-blind, placebo-controlled, randomized, phase 3 study that enrolled postmenopausal women with ER+/HER2– ABC previously untreated for advanced/metastatic disease.
- Patients were randomly assigned in a 2:1 ratio to receive either palbociclib (125 mg once daily [QD] orally; 3 weeks on, 1 week off schedule) plus letrozole (2.5 mg QD orally; continuous treatment) or a matching placebo plus letrozole (with the same respective dosing regimen).
- Patients were stratified according to disease site (visceral or nonvisceral), disease-free interval since completion of prior (neo)adjuvant treatment (de novo, ≤12 months, or >12 months), and prior (neo) adjuvant endocrine therapy (yes or no).
- Patients were allowed to have received prior (neo)adjuvant endocrine therapy or chemotherapy with curative intent, but at study entry, were required to be treatment-naive for advanced/metastatic breast cancer.
  - If nonsteroidal aromatase inhibitors were used previously for early breast cancer, patients were required to have a disease-free interval of >12 months from completion of their nonsteroidal aromatase inhibitor-based (neo)adjuvant therapy.
- Once on study, patients received the assigned study treatment until objective disease progression, symptomatic deterioration, unacceptable toxicity, death, or withdrawal of consent.

Eligibility Criteria

- Study eligibility criteria have been reported previously.[5] In brief, eligible patients were postmenopausal with a confirmed diagnosis of ER+/HER2– locoregionally recurrent or metastatic disease inoperable with a curative intent, were not previously treated with any systemic anticancer therapy for advanced disease, and had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2. Inclusion criteria required evidence of measurable disease according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Patients were excluded from study entry in the event of disease recurrence during or within 12 months of completing prior (neo)adjuvant treatment with a nonsteroidal aromatase inhibitor or if they had advanced symptomatic visceral spread.

Efficacy Assessments

- PFS was defined as the time from the date of randomization to the date of the first documentation of objective progression of disease per RECIST version 1.1 or death due to any cause, whichever occurs first.
- An objective response was considered to have been achieved if a patient sustained a complete response (CR) or partial response (PR) according to RECIST version 1.1.
  - A confirmed response was defined as a response that was confirmed by a repeat assessment performed no less than 4 weeks after the criteria of response were first met.
- The CBR was defined as the overall rate of CR, PR, or stable disease ≥24 weeks according to RECIST version 1.1.
- DOR was defined as the time from the first documentation of objective tumor response (CR or PR) to the first documentation of objective tumor progression among patients who had CR/PR.
- PFS, OR rate (ORR), CBR, and DOR were evaluated in each subgroup of patients pretreated or not pretreated with endocrine therapy and/or chemotherapy in the (neo)adjuvant setting.
- Median PFS and median DOR in the subgroups assessed were estimated using the Kaplan-Meier method. HRs for PFS were estimated from the Cox proportional hazards model with a 95% CI.

Safety Assessments

- All patients treated with ≥1 dose of the study treatment (palbociclib plus letrozole or placebo plus letrozole) were included in the safety analysis.
- Adverse events (AEs) were graded for severity according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0).

Other Assessments

- Descriptive statistics were used to summarize patient disposition, baseline characteristics, and treatment exposure.

RESULTS

Baseline Characteristics

- Between February 28, 2013, and July 29, 2014, 666 postmenopausal women were enrolled and randomly assigned (2:1) to the palbociclib plus letrozole arm (n=444) or the placebo plus letrozole arm (n=222).
- Baseline characteristics were well balanced among the subgroups of patients (**Table 1**).
- Across the subgroups of patients that received prior (neo)adjuvant treatment for breast cancer, the median age ranged between 58 and 65 years, and the vast majority of patients were white (75%–81%) and of non-Hispanic or Latino ethnicity (86%–87%).
- The most common endocrine therapies received by patients for their primary diagnosis were tamoxifen (22%-84%), anastrozole (6%-23%), letrozole (4%-15%) and exemestane (2%-12%).
- Median duration of time since diagnosis was markedly longer in patients exposed to previous endocrine therapy or chemotherapy in the (neo)adjuvant setting (8.8 years) than in previously untreated patients (0.2 years; **Table 1**).

Table 1. Baseline Characteristics of the Subgroups Receiving Palbociclib Plus Letrozole Therapy

	Prior Endocrine Therapy[a]		Prior Chemotherapy[a]	
Baseline Characteristic	Yes n=249	No n=195	Yes n=213	No n=231
Median (range) age, years	60 (30–88)	64 (40–89)	58 (30–85)	65 (44–89)
Race[c], n (%)				
White	187 (75)	157 (81)	163 (77)	181 (78)
Asian/Black	43 (17) / 4 (2)	22 (11) / 4 (2)	33 (16) / 4 (2)	32 (14) / 4 (2)
Ethnicity[d], n (%)				
Non-Hispanic or Latino	217 (87)	169 (87)	184 (86)	202 (87)
Hispanic or Latino	20 (8)	19 (10)	20 (9)	19 (8)
Previous endocrine therapy for primary diagnosis[b], n (%)				
Tamoxifen	209 (84)	NA	158 (74)	51 (22)
Anastrozole	56 (23)	NA	42 (20)	14 (6)
Letrozole	36 (15)	NA	28 (13)	8 (4)
Exemestane	30 (12)	NA	25 (12)	5 (2)
Median (range) duration since breast cancer diagnosis[e], years	8.8 (0.84–27.1)	0.2 (0.03–29.4)	8.8 (0.48–29.4)	0.2 (0.03–27.3)

NA=not applicable.
[a]Prior (neo)adjuvant therapy received for the primary diagnosis of breast cancer.
[b]Race data were not reported/missing for between 12–15 patients in each group.
[c]Ethnicity data were not reported/missing for between 7–12 patients in each group.
[d]The 4 most commonly used endocrine therapies shown only.
[e]Duration is defined as time since first histopathological diagnosis of breast cancer (year) to day 1 of study or primary diagnosis (of advanced/metastatic breast cancer) visit date.

Exposure

- Exposure to palbociclib was similar across subgroups with respect to the number of treatment cycles, and the median average dose of palbociclib received in patients pre-treated or not pre-treated with endocrine therapy or chemotherapy was similar (**Table 2**).

Table 2. Median Exposure to Palbociclib in Patient Subgroups

	Prior Endocrine Therapy[a]		Prior Chemotherapy[a]	
	Yes n=249	No n=195	Yes n=213	No n=231
Median (range) number of cycles	18 (1–37)	21 (1–37)	19 (1–37)	21 (1–37)
Median (range) average daily palbociclib dose,[c] mg	125 (77–125)	125 (78–125)	125 (77–125)	125 (78–125)

[a]Prior (neo)adjuvant therapy received for the primary diagnosis of breast cancer.
[c]Average daily dose administered denotes the total dose administered/total days on drug.

Efficacy

- As of the cutoff date (February 26, 2016), the median duration of follow-up was 23 months.
- The addition of palbociclib to letrozole consistently and significantly prolonged median PFS compared with placebo plus letrozole across subgroups, regardless of the prior (neo)adjuvant treatment received (endocrine therapy or chemotherapy; **Table 3**).
- For patients in the palbociclib plus letrozole subgroups:
  - Median PFS was similar for patients pretreated with endocrine therapy or prior chemotherapy (22.2 months and 22.4 months, respectively), while patients previously untreated with either endocrine therapy or chemotherapy had a median PFS of 25.7 months (**Table 3**).

Table 3. Summary of Treatment Efficacy by Patient Subgroups

	Prior Endocrine Therapy[a]		Prior Chemotherapy[a]	
Efficacy endpoints for PAL+LET vs PBO+LET	Yes n=249 vs n=126	No n=195 vs n=96	Yes n=213 vs n=109	No n=231 vs n=113
Median PFS, months	22.2 vs 11.3	25.7 vs 19.6	22.4 vs 13.7	25.7 vs 17.0
Hazard ratio (95% CI)	0.53 (0.40–0.70)	0.63 (0.44–0.90)	0.53 (0.40–0.72)	0.61 (0.44–0.84)
Objective response rate[1], %	33.7 vs 27.0	52.8 vs 44.8	36.2 vs 30.3	47.6 vs 38.9
Odds ratio (95% CI)	1.38 (0.84–2.29)	1.38 (0.82–2.33)	1.30 (0.78–2.22)	1.43 (0.88–2.32)
Clinical benefit rate[1], %	81.5 vs 66.7	89.2 vs 75.0	81.7 vs 70.6	87.9 vs 69.9
Odds ratio (95% CI)	2.21 (1.31–3.70)	2.76 (1.37–5.56)	1.85 (1.04–3.29)	3.12 (1.71–5.71)
Patients with a response (CR/PR), n	84 vs 34	103 vs 43	77 vs 33	110 vs 44
Median DOR (CR/PR), months	22.5 vs 22.5	28.0 vs 16.7	20.1 vs 20.9	28.0 vs 16.7
(95% CI)	(16.6–NE) vs (11.2–NE)	(19.3–28.0) vs (15.4–22.3)	(16.7–NE) vs (11.1–NE)	(20.1–28.0) vs (13.8–NE)

CR=complete response; DOR=duration of response; LET=letrozole; NE=not estimable; PAL=palbociclib; PFS=progression-free survival; PBO=placebo; PR=partial response.
[a]Prior (neo)adjuvant therapy received for the primary diagnosis of breast cancer.
[1]Response was confirmed as defined in Methods.

- For patients in the placebo plus letrozole subgroups:
  - Median PFS was shorter in patients pre-treated with endocrine therapy than in those not treated with prior endocrine therapy (11.3 months and 19.6 months, respectively)
  - The subgroup pretreated with chemotherapy had a shorter median PFS than the subgroup not treated with prior chemotherapy (13.7 months and 17.0 months, respectively; **Table 3**).
- Across all subgroups, patients treated with palbociclib plus letrozole achieved a higher ORR than patients in the control arm, regardless of exposure to either endocrine therapy or chemotherapy (**Table 3**).
- In patients treated with palbociclib–letrozole combination therapy, the ORR and median DOR were lower in the subgroups exposed to prior endocrine therapy or chemotherapy than in the subgroups not pretreated with either therapy (**Table 3**).
- In patients treated with palbociclib plus letrozole:
  - Median DOR among patients who had a CR/PR was 22.5 months in the prior endocrine therapy subgroup (28.0 months in the endocrine therapy–naive subgroup) and 20.1 months in patients with prior chemotherapy (28.0 months in patients previously untreated with chemotherapy; **Table 3**).
  - CBR was not markedly different based on patient exposure to prior endocrine therapy or chemotherapy (>80% in all subgroups; **Table 3**).

Safety

- The incidence of all-causality treatment-emergent AEs (TEAEs) for all grades was similar among the subgroups receiving palbociclib plus letrozole, regardless of receiving or not receiving prior (neo)adjuvant therapy (range, 97.4%–100%; **Table 4**).
  - Neutropenia was the most frequently reported AE among these subgroups (range, 77.9%–81.2%), followed by infections (56.9%–61.8%) and leukopenia (37.7%–40.4%; **Table 4**).
  - The most frequently reported nonhematologic AEs were nausea (range, 30.3%–39.9%), fatigue (36.4%–38.2%), and arthralgia (28.7%–36.9%; **Table 4**).

Table 4. Summary of the Most Common Treatment-Emergent AEs (All Causalities, All Cycles) in Subgroups Receiving Palbociclib Combined With Letrozole

	Prior Endocrine Therapy[a]		Prior Chemotherapy[a]	
Preferred term/clustered preferred terms[1]	Yes n=249	No n=195	Yes n=213	No n=231
All AEs, %	100	97.4	99.1	98.7
Hematologic AEs				
Neutropenia[a]	79.9	79.0	81.2	77.9
Grades 3–5	65.9	67.2	66.2	66.7
Infections[4]	61.8	56.9	58.7	60.6
Grades 3–5	5.2	8.2[5]	5.6[5]	7.4
Leukopenia[a]	38.2	40.0	40.4	37.7
Grades 3–5	24.9	24.6	29.1	20.8
Nonhematologic AEs				
Nausea	39.0	30.3	39.9	30.7
Grades 3–5	0	0.5	0.5	0
Fatigue	38.2	36.4	37.6	37.2
Grades 3–5	1.6	2.1	1.9	1.7
Arthralgia	36.9	28.7	35.7	31.2
Grades 3–5	0.8	0.5	0.5	0.9

AE=adverse event; MedDRA=*Medical Dictionary for Regulatory Activities*; PT=preferred term.
[a]Prior (neo)adjuvant therapy received for the primary diagnosis of breast cancer.
[1]MedDRA (v18.1) coding dictionary applied.
[4]Cluster of PTs: infections includes any event with a PT that is part of the System Organ Class Infections and Infestations; leukopenia includes the PTs leukopenia or white blood cell count decreased; neutropenia includes the PTs neutropenia or neutrophil count decreased.
[5]The data for 1 patient (0.5%) with an infection was missing/unknown and was not graded.

- In all subgroups receiving palbociclib plus letrozole, TEAEs of any grade leading to permanent discontinuation occurred in <10% of patients, regardless of exposure to prior therapy or type of prior therapy if pretreated (**Table 5**).
  - The incidence of permanent discontinuations due to severe (grades 3–5) AEs ranged between 0.8% and 3.5% of patients, with similar frequencies observed in all subgroups.
- In this analysis, no new or unexpected safety signals were observed in the subgroups treated with palbociclib plus letrozole combination therapy.

Table 5. Treatment-Emergent AEs With an Incidence of ≥1% Associated With Permanent Discontinuation of Palbociclib or Placebo

	Prior Endocrine Therapy[a]		Prior Chemotherapy[a]	
Preferred term	Yes n=249	No n=195	Yes n=213	No n=231
All AEs, n (%)	24 (9.6)	17 (8.7)	21 (9.9)	20 (8.7)
Grade 5	4 (1.6)[1]	3 (1.5)[1]	4 (1.9)[1]	3 (1.3)[1]
Grade 4	2 (0.8)	2 (1.0)	2 (0.9)	2 (0.9)
Grade 3	7 (2.8)	5 (2.6)	4 (1.9)	8 (3.5)
Neutropenia, n (%)				
All grades	1 (0.4)	4 (2.1)	1 (0.5)	4 (1.7)
Grade 5	0	0	0	0
Grade 4	0	1 (0.5)	0	1 (0.4)
Grade 3	0	3 (1.5)	0	3 (1.3)
Disease progression, n (%)				
All grades	—	2 (1.0)	—	2 (0.9)
Grade 5	—	2 (1.0)	—	2 (0.9)
Grade 4	—	0	—	0
Grade 3	—	0	—	0

AE=adverse event. Dash denotes not reported for any grade.
[a]Prior (neo)adjuvant therapy received for the primary diagnosis of breast cancer.
[1]Events were acute myocardial infarction, cardiogenic shock, cardiovascular insufficiency, and death (1 event each).
[1]Events were disease progression (2 events) and respiratory failure (1 event).

CONCLUSIONS

- Regardless of prior (neo)adjuvant treatment, palbociclib plus letrozole significantly prolonged PFS vs placebo plus letrozole and demonstrated consistent efficacy in both pretreated and non-pretreated subgroups of postmenopausal patients with ER+/HER2– ABC in a first-line setting.
- Tolerability was similar across subgroups and was consistent with the known safety profile of palbociclib when combined with endocrine therapy.

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