Effect of palbociclib plus endocrine therapy on time to chemotherapy across subgroups of patients with hormone receptor–positive/human epidermal growth factor receptor 2–negative advanced breast cancer: Post hoc analyses from PALOMA-2 and PALOMA-3

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ABSTRACT

Background: Previous analyses from the PALOMA-2 and PALOMA-3 studies showed that palbociclib (PAL) plus endocrine therapy (ET) prolongs time to first subsequent chemotherapy (TTC) versus placebo (PBO) plus ET in the overall population of patients with hormone receptor–positive/human epidermal growth factor receptor 2–negative (HR+/HER2–) advanced breast cancer (ABC). Here, we evaluated TTC in relevant patient subgroups.

Methods: These post hoc analyses evaluated TTC by subgroup using data from 2 randomized, phase 3 studies of women with HR+/HER2–ABC. In PALOMA-2, postmenopausal patients previously untreated for ABC were randomized 2:1 to receive PAL (125 mg/day, 3/1-week schedule) plus letrozole (LET; 2.5 mg/day; n = 444) or PBO plus LET (n = 222). In PALOMA-3, premenopausal or postmenopausal patients whose disease had progressed after prior ET were randomized 2:1 to receive PAL (125 mg/day, 3/1-week schedule) plus fulvestrant (FUL; 500 mg; n = 347) or PBO plus FUL (n = 174).

Results: First subsequent chemotherapy was received by 35.5% and 56.2% in PALOMA-2 and PALOMA-3 after progression on palbociclib plus ET or placebo plus ET. Across all subgroups analyzed, the median progression-free survival (PFS) was longer in the PAL plus ET arm than the PBO plus ET arm. TTC was longer with PAL plus ET versus PBO plus ET across the same patient subgroups in both studies.

Conclusions: Across all subgroups, PAL plus ET versus PBO plus ET had longer median PFS and resulted in prolonged TTC in both the PALOMA-2 and PALOMA-3 studies.

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1. Introduction

Cyclin-dependent kinases (CDKs) belong to the serine-threonine kinases and are activated by D-type cyclins [1,2]. CDKs, particularly CDK4 and CDK6 (CDK4/6), regulate cell cycle progression from the G0 or G1 phase into the S phase by phosphorylating the tumor suppressor gene retinoblastoma and other related proteins like p107 and p130 [1,3]. Palbociclib (Ibrance, Pfizer) is a small molecule inhibitor of CDK4/6 with a high selectivity profile toward CDK4/6 over other CDKs [4,5].

For women with hormone receptor–positive/human epidermal growth factor receptor 2–negative (HR+/HER2–) advanced breast cancer (ABC), CDK4/6 inhibitors in combination with endocrine therapy (ET) have become the standard of care [6,7]. The first-in-class CDK4/6 inhibitor palbociclib in combination with ET is approved to treat patients with HR+/HER– ABC based on the demonstration of prolonged progression-free survival (PFS) and an acceptable safety profile in phase 3 trials in patients with HR+/HER– ABC who were previously untreated (PALOMA-2; NCT01740427) and in patients who had relapsed or progressed during prior ET and could have received 1 prior line of chemotherapy for ABC (PALOMA-3; NCT01942135) [5,8]. In individual analyses of the phase 3 PALOMA-2 and PALOMA-3 trials, time to subsequent chemotherapy (TTC) after discontinuation of study treatment was prolonged in patients in the palbociclib arm compared with the placebo arm [9,10]. In PALOMA-2, the median TTC was 40.4 [95% CI, 34.7–47.3] months versus 29.9 [95% CI, 25.6–35.1] months for patients in the palbociclib plus ET versus placebo plus ET arm, respectively (hazard ratio [HR], 0.74 [95% CI, 0.59–0.92]) [9]. In PALOMA-3, the TTC was 17.6 [95% CI, 15.2–19.7] months versus 8.8 [95% CI, 7.3–12.7] months in the palbociclib plus ET versus placebo plus ET arm, respectively (HR, 0.58 [95% CI, 0.47–0.73]; P < 0.001) [10]. In these post hoc analyses, we evaluated TTC in subgroups of patients with HR+/HER2– ABC from each of the PALOMA-2 and PALOMA-3 trials.

2. Patients and methods

2.1. Study design and patients

PALO-2 and PALOMA-3 were phase 3, double-blind, randomized, placebo-controlled studies of palbociclib plus ET in patients with HR+/HER2– ABC, with previously untreated, estrogen receptor–positive/HER2– ABC randomized 2:1 to receive palbociclib (125 mg daily in 4-week cycles on a 3/1 schedule [3 weeks on/1 week off]) or placebo; patients in both arms received letrozole (LET; 2.5 mg daily; continuous treatment) [8].

In PALOMA-3, women (N = 521) of any menopausal status with HR+/HER2– ABC whose disease had progressed after any number of lines of prior ET and who received up to 1 prior chemotherapy regimen for ABC were randomized 2:1 to receive palbociclib (125 mg daily, 3/1 schedule) plus fulvestrant (FUL; 500 mg every 14 days for the first 3 injections and then every 28 days) or placebo plus FUL [5]. Patients who were premenopausal or perimenopausal received concurrent ovarian suppression with goserelin [5]. Approximately 34% of patients who participated in PALOMA-3 had received prior chemotherapy for their advanced disease at baseline [10].

2.2. Data analysis

Numbers and percentages of patients who received first subsequent chemotherapy after discontinuing study treatment were calculated by treatment group in the PALOMA-2 and PALOMA-3 intent-to-treat (ITT) populations and in subgroups of patients according to demographics and baseline disease characteristics. Separate analyses were performed for the individual studies.

The Kaplan-Meier method was used to estimate median TTC and PFS in the ITT population and in patient subgroups by treatment arm along with corresponding 95% CIs based on the Brookmeyer and Crowley method [9]. Unstratified HRs for PFS and TTC were estimated using the Cox proportional hazards model with associated 95% CIs. HR < 1 indicated a reduction in the hazard rate in favor of palbociclib.

3. Results

3.1. PALOMA-2

In PALOMA-2, at data cut-off (May 31, 2017), a total of 444 women had received palbociclib plus LET and 222 women had received placebo plus LET. After discontinuation of study treatment, 35.5% of patients had received first subsequent chemotherapy (36.6% in palbociclib plus LET group and 34% in placebo plus LET group). Demographics and baseline disease characteristics for patients with versus without first subsequent chemotherapy are presented in Table 1. Patients in both the palbociclib plus LET and placebo plus LET arms were more likely to receive versus not receive first subsequent chemotherapy after discontinuation of study treatment if they had visceral disease, a disease-free interval (DFI) of ≤12 months, or received prior adjuvant or neoadjuvant systemic or hormonal therapy or chemotherapy.

The median PFS was longer in the palbociclib plus LET arm compared with the placebo plus LET arm across the patient subgroups from PALOMA-2 (Table 2), as previously reported [9,11]. Across all subgroups included in this analysis, the TTC was longer with palbociclib plus LET compared with placebo plus LET (Fig. 1). Patients with DFI ≤12 months had a median TTC of 23.6 [95% CI, 18.3–34.7] months in the palbociclib plus LET arm versus 17.0 [95% CI, 13.7–27.3] months in the placebo plus LET arm (HR, 0.76 [95% CI, 0.50–1.16]); for patients with
After a median follow-up of 38 months, approximately 55% of patients in the palbociclib plus LET arm and 73% of patients in the placebo plus LET arm received follow-up post-torial systemic anti-cancer therapy (Supplemental Table 1). Antihormonal therapy (FUL and exemestane) was used in about 60% of patients in both groups for first subsequent therapy and in 36% and 49% of patients, respectively, in the palbociclib plus LET arm and the placebo plus LET arm for second subsequent therapy (Supplemental Table 2). Paclitaxel and capcitabine were the most commonly used chemotherapy agents for both first and second subsequent therapy.

3.2. PALOMA-3

In PALOMA-3, at data cut-off (August 17, 2020), a total of 347 women had received palbociclib plus FUL and 174 women had received placebo plus FUL. After discontinuation of study treatment, 56.6% of patients had received first subsequent chemotherapy (53.6% in palbociclib plus FUL group and 61.1% in placebo plus FUL group). Demographics and baseline disease characteristics for patients with versus without first subsequent chemotherapy after study drug discontinuation are presented in Table 3. A higher percentage of younger patients (< 65 years of age) received versus did not receive first subsequent chemotherapy after discontinuation in the palbociclib plus FUL arm (81.1% vs 71.1%). In the placebo plus FUL arm, a higher percentage of patients with premenopausal or perimenopausal status received versus did not receive first subsequent chemotherapy after treatment discontinuation (29.5% vs 11.6%). Among those with visceral disease, a higher percentage received versus did not receive first subsequent chemotherapy after discontinuation of either palbociclib plus FUL (63.6% vs 53.4%) or placebo plus FUL (69.3% vs 50.0%). A higher percentage of patients who had prior chemotherapy in the metastatic setting received versus did not receive first subsequent chemotherapy in both the palbociclib plus FUL arm (35.7% vs 30.4%) and placebo plus FUL arm (43.2% vs 30.2%). Similar results were observed among those who received prior hormonal therapies.

The median PFS was longer in the palbociclib plus FUL arm compared with the placebo plus FUL arm across the patient subgroups who had disease progression during prior ET from PALOMA-3 (Table 4), as previously reported [11–13]. Across all subgroups from PALOMA-3

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**Table 2**

PFS in patients from PALOMA-2 by subgroup and treatment arm.

| Patient Subgroup | ITT Population, n (%) | mPFS (95% CI), mo | PAL + LET | mPFS (95% CI), mo | PBO + LET | HR (95% CI) |
|------------------|-----------------------|------------------|-----------|------------------|-----------|------------|
| Overall (ITT) population | 666 (100) | 27.6 (22.4–30.3) | 14.5 (12.3–17.1) | 0.56 (0.46–0.69) |
| DFI ≤ 12 mo | 146 (22) | 16.6 (13.9–24.2) | 11.0 (5.6–12.9) | 0.48 (0.32–0.72) |
| DFI > 12 mo | 272 (41) | 30.3 (24.8–NE) | 13.8 (8.8–18.2) | 0.55 (0.40–0.76) |
| DFI > 24 mo | 233 (35) | 38.5 (27.5–NE) | 16.6 (13.7–23.5) | 0.52 (0.36–0.75) |
| De novo metastatic | 248 (37) | 27.9 (22.1–33.4) | 22.0 (13.9–27.4) | 0.61 (0.44–0.85) |
| Visceral | 324 (49) | 19.3 (16.4–24.2) | 12.3 (8.4–16.4) | 0.62 (0.47–0.81) |
| Nonvisceral | 340 (51) | 35.9 (27.7–NE) | 17.0 (13.8–24.8) | 0.50 (0.37–0.67) |
| Bone only | 151 (23) | 36.2 (27.6–NE) | 11.2 (8.2–22.0) | 0.41 (0.26–0.63) |
| Visceral liver involvement | 120 (18) | 13.7 (10.9–16.6) | 8.4 (5.5–12.9) | 0.62 (0.41–0.94) |
| Visceral lung involvement | 253 (38) | 23.2 (17.0–27.8) | 12.9 (8.1–16.6) | 0.58 (0.42–0.80) |

DFI = disease-free interval; HR = hazard ratio; ITT = intent to treat; LET = letrozole; mPFS = (median) progression-free survival; NE = not estimable; PAL = palbociclib; PBO = placebo. Items in bold in the Patient Subgroup column represent stratification factors from PALOMA-2.

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**Fig. 1.** Forest plot of TTC by treatment arm in PALOMA-2, overall and across patient subgroups (ITT population). DFI = disease-free interval; HR = hazard ratio; ITT = intent to treat; LET = letrozole; (m) TTC=(median) time to first subsequent chemotherapy; mo = months; NE = not estimable; PAL = palbociclib; PBO = placebo. Items in bold in the Patient Subgroup column represent stratification factors from PALOMA-2.
Fig. 2. TTC in subgroups of patients from PALOMA-2 with (A) DFI ≤ 12 months and > 12 months and (B) nonvisceral and visceral disease (ITT population). DFI = disease-free interval; HR = hazard ratio; ITT = intent to treat; (m)TTC = (median) time to first subsequent chemotherapy; NE = not estimable.
Table 3
Select patient demographics and baseline disease characteristics for patients who did or did not receive first subsequent CT in PALOMA-3 by treatment arm.

|                          | Without First Subsequent CT | With First Subsequent CT |
|--------------------------|-----------------------------|--------------------------|
|                          | PAL + FUL (n = 204)         | PAL + FUL (n = 143)      |
| Age, median, y           | 56.0 (60.0)                 | 56.0 (76.1)              |
| < 65 y, n (%)            | 145 (64.74)                 | 116 (81.1)               |
| ≥ 65 y, n (%)            | 59 (22.65)                  | 27 (21.39)               |
| Race, n (%)              | 150 (79.1)                  | 102 (65.73)              |
| White                    | (73.5)                      | (71.3)                   |
| Black                    | 8 (4.7)                     | 4 (4.5)                  |
| Asian                    | 40 (16.3)                   | 34 (19.3)                |
| Other                    | 6 (2.9)                     | 2 (1.1)                  |
| Unspecified              | 0                           | 1 (1.1)                  |
| Weight, median, kg       | 69.1 (71.2)                 | 69.0 (68.4)              |
| Menopausal status, n (%) | 39 (10.1)                   | 33 (23.1)                |
| Premenopausal/           | 165 (76.88)                 | 110 (62.05)              |
| Perimenopausal           | (80.9)                      | (76.9)                   |
| Disease site, n (%)      | Visceral 109 (53.4)         | 91 (63.6)                |
|                          | Nonvisceral 95 (46.6)       | 52 (36.4)                |
| Sensitivity to prior ET, n (%) | 162 (79.4)           | 111 (68.73)              |
|                          | No 42 (20.6)                | 22 (22.7)                |
| Prior CT for diagnosis, n (%) | 59 (28.9)            | 35 (24.5)                |
|                          | Yes 145 (69.82)             | 108 (69.84)              |
| Neoadjuvant              | 41 (15.74)                  | 26 (18.2)                |
| Adjuvant                 | 87 (45.58)                  | 64 (44.8)                |
| Metastatic               | 62 (30.62)                  | 51 (35.7)                |
| Missing                  | 0                           | 1 (1.2)                  |
| Prior hormonal therapy, n (%) | 78 (38.2)          | 48 (33.6)                |
|                          | 126 (50.7)                  | 95 (66.4)                |
| Metastatic               | 151 (74.0)                  | 108 (64.72)              |
| Prior lines of therapy for ABC, n (%) | 10 (0.7)       | 10 (0.7)                 |
|                          | 135 (60.9)                  | 63 (37.16)               |
|                          | 69 (33.8)                   | 25 (28.4)                |

ABC = advanced breast cancer; CT = chemotherapy; ET = endocrine therapy; FUL = fulvestrant; PAL = palbociclib; PBO = placebo.

*Other includes not reported/missing patients.

included in this analysis, TTC was longer with palbociclib plus FUL compared with placebo plus FUL. Patients without prior chemotherapy in the ABC setting had a median TTC of 18.4 (95% CI, 16.0–21.5) months versus 11.9 (95% CI, 7.8–14.2) months in the palbociclib plus FUL arm versus the placebo plus FUL arm, respectively (HR, 0.62 [95% CI, 0.48–0.81]; for patients with prior chemotherapy in the ABC setting, the median TTC was 14.3 (95% CI, 11.6–20.3) months versus 7.3 (95% CI, 4.3–10.3) months, respectively (HR, 0.56 [95% CI, 0.39–0.81]; Fig. 4A). Patients with nonvisceral disease had a median TTC of 23.3 (95% CI, 19.1–29.1) months versus 17.0 (95% CI, 8.9–23.3) months in the palbociclib plus FUL arm versus the placebo plus FUL arm, respectively (HR, 0.63 [95% CI, 0.44–0.89]); for patients with visceral disease, the median TTC was 15.2 (95% CI, 12.2–17.3) months versus 6.4 (95% CI, 4.4–9.7) months, respectively (HR, 0.58 [95% CI, 0.44–0.76]; Fig. 4B).

After a median follow-up of 73.3 months, approximately 77% of patients in the palbociclib plus FUL arm and 83% of patients in the placebo plus FUL arm received follow-up post-trial systemic anti-cancer therapy (Supplemental Table 1). Chemotherapy was the most common subsequent therapy in the palbociclib and control groups and increased across first (54%–61%), second (66%–72%), and third (90%–92%) subsequent therapies. Antihormonal therapy ( exemestane and FUL) were commonly used in 20%–43% of patients across first, second, and third subsequent therapies (Supplemental Table 3).

4. Discussion

In the PALOMA-2 and PALOMA-3 studies, after treatment discontinuation, 35.5% and 56.2% of patients had received first subsequent chemotherapy, respectively; across all subgroups, patients treated with palbociclib plus ET had longer median PFS that resulted in prolonged median PFS in patients from PALOMA-3 by subgroup and treatment arm.

Table 4
PFS in patients from PALOMA-3 by subgroup and treatment arm.

| Patient Subgroup | ITT Population, n (%) | mPFS (95% CI), mo | HR (95% CI) |
|------------------|-----------------------|------------------|-------------|
|                  |                       | PAL + FUL        | PBO + FUL   |
| Overall (ITT)    | 521 (100)             | 11.2             | 4.6         | 0.50 (0.40–0.62) |
| population       |                       | (9.5–12.9)       | (3.5–5.6)   |
| ET sensitive     | 412 (79)              | 12.0             | 4.2         | 0.46 (0.37–0.59) |
| (HR, 11.1–13.9)  |                       | (11.1–13.9)      | (3.5–5.6)   |
| ET resistant     | 109 (21)              | 7.4              | 5.1         | 0.69 (0.43–1.09) |
| (HR, 5.5–11.1)   |                       | (1.9–7.4)        |             |
| Without prior CT | 344 (66)              | 12.9             | 5.5         | 0.49 (0.37–0.65) |
| in ABC           |                       | (11.0–15.0)      | (3.6–7.6)   |
| With prior CT in | 177 (34)              | 9.5              | 3.5         | 0.54 (0.37–0.77) |
| ABC              |                       | (7.3–11.3)       | (1.9–5.4)   |
| Without any prior therapy in ABC | 115 (22) | 11.0 | 5.1 | 0.59 (0.37–0.93) |
| Visceral         | 313 (60)              | 9.2              | 3.5         | 0.50 (0.38–0.65) |
| (HR, 7.5–11.1)   |                       | (2.0–5.1)        |             |
| Nonvisceral      | 208 (40)              | 16.6             | 5.6         | 0.48 (0.33–0.71) |
| (HR, 13.2–NE)    |                       | (4.6–10.9)       |             |
| Bone only        | 125 (24)              | 14.3             | 9.2         | 0.63 (0.38–1.06) |
| (HR, 11.2–NE)    |                       | (4.8–20.0)       |             |
| Visceral liver involvement | 203 (39) | 7.5 (5.6–9.2) | 2.4 | 0.49 (0.36–0.68) |
| Visceral lung involvement | 162 (31) | 11.1 | 3.7 | 0.45 (0.31–0.67) |

ABC = advanced breast cancer; CT = chemotherapy; ET = endocrine therapy; FUL = fulvestrant; HR = hazard ratio; ITT = intent to treat; mPFS = median progression-free survival; NE = not estimable; PAL = palbociclib; PBO = placebo. Items in bold in the Patient Subgroup column represent stratification factors from PALOMA-3.
The median PFS and TTC compared with patients with better prognosis (DFI > 12 months, de novo, ET sensitivity, nonvisceral/bone-only, and no prior chemotherapy for ABC). These findings were also observed when examining the demographics and characteristics of patients who went on to receive first subsequent chemotherapy compared with those who did not. Patients who went on to receive first subsequent chemotherapy were more likely to have DFI ≤ 12 months, liver or visceral metastases, and prior chemotherapy in the neoadjuvant, adjuvant, or ABC setting. As expected, patients who received palbociclib plus ET in the first-line setting (ie, no prior therapy for ABC) had a longer median PFS and TTC than patients who received palbociclib plus ET after progressing on ET.

These data from PALOMA-2 and PALOMA-3 should be considered in light of potential study limitations, including the exploratory and post hoc nature of the studies. Considering the small number of patients in some of the subgroups, the data should be interpreted with caution. Taken together, these findings in combination with the current body of literature regarding PFS and TTC benefits with CDK4/6 inhibitors suggest that patients receive greater clinical benefit from palbociclib plus ET compared with ET monotherapy for the treatment of HR+/HER2–ABC.

### Data sharing statement

Upon request, and subject to review, Pfizer will provide the data that support the findings of this study. Subject to certain criteria, conditions and exceptions, Pfizer may also provide access to the related individual de-identified participant data. See [https://www.pfizer.com/science/clinical-trials/trial-data-and-results](https://www.pfizer.com/science/clinical-trials/trial-data-and-results) for more information.

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### Declaration of competing interest

**Hope S. Rugo** reports sponsored research to her institution from Pfizer Inc, Merck, Novartis, Eli Lilly, Roche, Daiichi-Sankyo, Seattle Genetics, Macrogenics, Sermonix, Boehringer Ingelheim, Polyphor, AstraZeneca, Ayala, and Gilead and honoraria from PUMA, Samsung, and Mylan.

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**Fig. 3.** Forest plot of TTC by treatment arm in PALOMA-3, overall and across patient subgroups (ITT population). ABC = advanced breast cancer; CT = chemotherapy; ET = endocrine therapy; FUL = fulvestrant; HR = hazard ratio; ITT = intent to treat; mo = months; (m)TTC = (median) time to first subsequent chemotherapy; PAL = palbociclib; PBO = placebo. Items in bold in the Patient Subgroup column represent stratification factors from PALOMA-3.
Fig. 4. TTC in subgroups of patients from PALOMA-3 (A) with and without prior chemotherapy in ABC and (B) with nonvisceral and visceral disease (ITT population). ABC = advanced breast cancer; CT = chemotherapy; HR = hazard ratio; ITT = intent to treat; (m)TTC=(median) time to first subsequent chemotherapy.
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Appendix A. Supplementary data

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