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Effect of Palbociclib (PAL) + Endocrine Therapy (ET) on Time to Chemotherapy (TTC) Across Subgroups of Patients (pts) With Hormone Receptor–Positive/Human Epidermal Growth Factor Receptor 2–Negative (HR+/HER2–) Advanced Breast Cancer (ABC): Post Hoc Analyses From PALOMA-2 (P2) and PALOMA-3 (P3)

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Objective

- To evaluate time to chemotherapy (TTC) in subgroups of patients with hormone receptor–positive/human epidermal growth factor receptor 2–negative (HR+/HER2–) advanced breast cancer (ABC) from the phase 3 PALOMA-2 and PALOMA-3 trials.

Conclusion

- More patients treated with placebo plus ET received a first subsequent chemotherapy after discontinuation of study treatment compared with those patients treated with palbociclib plus ET.
- Palbociclib plus ET prolonged TTC and PFS compared with placebo plus ET across all patient subgroups included in the analysis.
- Patients who received palbociclib plus ET in the first-line setting (ie, no prior therapy in ABC) had a greater delay to subsequent chemotherapy than patients who received palbociclib plus ET after progressing on ET.

Background

- For women with hormone receptor–positive/human epidermal growth factor receptor 2–negative (HR+/HER2–) advanced breast cancer (ABC), cyclin-dependent kinase 4/6 (CDK4/6) inhibitors in combination with endocrine therapy (ET) have become the standard of care.[1,2]
- 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 of patients with HR+/HER– ABC who were previously untreated (PALOMA-2; NCT01740427) and who had relapsed or progressed during prior ET and could have received 1 prior line of chemotherapy for ABC (PALOMA-3; NCT01942135).[3,4]
- In individual analyses of the phase 3 PALOMA-2 and PALOMA-3 trials, time to subsequent chemotherapy (TTC) after disease progression was prolonged in patients in the palbociclib arm compared with the placebo arm.[5,6]
  - In PALOMA-2, the median TTC was 40.4 vs 29.9 months for patients in the palbociclib plus ET vs placebo plus ET arm, respectively (hazard ratio [HR], 0.74 [95% CI, 0.59–0.92]; *P*<0.005).[5]
  - In PALOMA-3, the TTC was 17.6 vs 8.8 months in the palbociclib plus ET vs placebo plus ET arm (HR, 0.58 [0.47–0.73]; *P*<0.001).[6]
- In post hoc analyses, we evaluated TTC in subgroups of patients with HR+/HER2– ABC from each of the PALOMA-2 and PALOMA-3 trials.

Methods

PATIENTS AND STUDY DESIGN

- PALOMA-2 and PALOMA-3 were phase 3, double-blind, randomized, placebo-controlled studies of palbociclib plus ET in patients with HR+/HER2– ABC.[3,4]

PALOMA-2

- Postmenopausal women (N=666) with previously untreated estrogen receptor–positive/HER2– ABC were randomized 2:1 to receive palbociclib (125 mg daily in 4-week cycles in a 3/1 schedule [3 weeks on/1 week off]) or placebo; patients in both arms received letrozole (2.5 mg daily; continuous treatment).[3]

PALOMA-3

- Women (N=521) of any menopausal status with HR+/HER2– ABC whose disease had progressed after any number of lines of previous ET and who could have received up to one prior chemotherapy regimen for ABC were randomized 2:1 to receive palbociclib (125 mg daily, 3/1 schedule) plus fulvestrant (500 mg every 14 days for the first 3 injections and then every 28 days) or placebo plus fulvestrant.[4]
  - Patients who were pre- or peri-menopausal received concurrent ovarian suppression with goserelin.
- Approximately one-third of patients who participated in PALOMA-3 had received prior chemotherapy for their advanced disease at baseline.

SUBGROUP ANALYSIS

- Numbers and percentages of patients who received a 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 baseline demographic and disease characteristics.
  - Separate analyses were performed for both 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 the corresponding 95% CIs, based on the Brookmeyer and Crowley method.
- Unstratified HRs for PFS and TTC were estimated from the Cox proportional hazards model with associated 95% CI.
  - An HR <1 indicated a reduction in hazard rate in favor of palbociclib.

Results

Table 1. Baseline Demographics and Disease Characteristics for Patients Who Did and Did Not Receive Subsequent Chemotherapy in PALOMA-2, by Treatment Arm

	Without Subsequent CT		With First Subsequent CT	
	PAL+LET (n=295)	PBO+LET (n=118)	PAL+LET (n=149)	PBO+LET (n=104)
Age, median, y	63.0	62.0	58.0	60.5
<65, %	53.2	57.6	71.1	70.2
≥65, %	46.8	42.4	28.9	29.8
Race,[a] %				
White	77.6	79.7	77.2	75.0
Black	1.7	0.8	2.0	1.9
Asian	14.6	11.9	14.8	15.4
Other	6.1	7.6	6.0	7.7
Weight, median, kg	68.0	67.0	69.0	65.5
Disease site, %				
Visceral	47.1	40.7	50.3	59.6
Nonvisceral	52.9	59.3	49.7	40.4
Disease-free completion of prior (neo) adjuvant therapy, %				
De novo metastatic	40.3	42.4	32.2	29.8
DFI ≤12 mo	16.9	16.9	32.2	26.9
DFI >12 mo	42.7	40.7	35.6	43.3
Nature of prior (neo) adjuvant anticancer therapy, %				
Prior systemic therapy				
No	40.3	42.4	32.2	29.8
Yes	59.7	57.6	67.8	70.2
Prior chemotherapy for primary diagnosis				
No	55.6	59.3	45.0	41.3
Yes	44.4	40.7	55.0	58.7
Neoadjuvant	9.2	15.3	18.1	13.5
Adjuvant	38.6	30.5	44.3	51.0
Prior hormonal therapy for primary diagnosis				
No	47.8	50.8	35.6	34.6
Yes	52.2	49.2	64.4	65.4

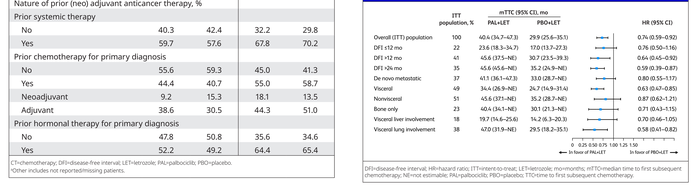
CT=chemotherapy; DFI=disease-free interval; LET=letrozole; PAL=palbociclib; PBO=placebo.
[a]Other includes not reported/missing patients.

Table 2. PFS in Patients From PALOMA-2 by Subgroup and Treatment Arm[5]

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

Figure 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; mo=months; mTTC=median time to first subsequent chemotherapy; NE=not estimable; PAL=palbociclib; PBO=placebo; TTC=time to first subsequent chemotherapy.

Table 3. Select Baseline Patient Demographics and Disease Characteristics for Patients Who Did or Did Not Receive Subsequent Chemotherapy in PALOMA-3, by Treatment Arm

	Without Subsequent CT		With First Subsequent CT	
	PAL+FUL (n=105)	PBO+FUL (n=44)	PAL+FUL (n=242)	PBO+FUL (n=130)
Age, median, y	60	61.5	56	55
<65 y, %	63.6	70.5	80.2	76.9
≥65 y, %	36.2	29.5	19.8	23.1
Race,[a] %				
White	78.1	79.5	70.2	75.4
Black	3.8	6.8	3.3	3.8
Asian	15.2	13.6	24	19.2
Other	2.9	0	2.1	0.8
Weight, median, kg	67.2	71.2	67.6	69
Menopausal status, %				
Pre/peri	15.2	11.4	23.1	23.8
Post	84.8	88.6	76.9	76.2
Disease site, %				
Visceral	61.9	47.7	58.3	64.6
Nonvisceral	38.1	52.3	41.7	35.4
Sensitivity to prior ET, %				
Yes	76.2	68.2	80.2	81.5
No	23.8	31.8	19.8	18.5
Previous chemotherapy for primary diagnosis, %				
No	23.8	13.6	28.5	23.1
Yes	76.2	86.4	71.5	76.9
Neoadjuvant	25.7	27.3	16.5	16.2
Adjuvant	41	56.8	44.6	49.2
Metastatic	36.2	36.4	31	36.9
Previous hormonal therapy, %				
1	42.9	45.5	33.5	39.2
>1	57.1	54.5	66.5	60.8
Metastatic	71.4	68.2	76	75.4
Prior lines of therapy for ABC, %				
0–1	68.6	63.6	59.1	73.8
≥2	31.4	36.4	40.9	26.2

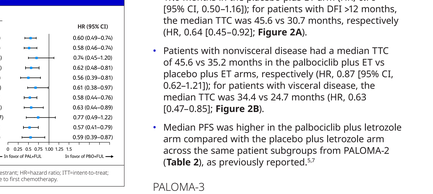
ABC=advanced breast cancer; CT=chemotherapy; ET=endocrine therapy; FUL=fulvestrant; PAL=palbociclib; PBO=placebo.
[a]Other includes not reported/missing patients.

Table 4. PFS in Patients From PALOMA-3 by Subgroup and Treatment Arm[6]

Patient Subgroup	ITT Population, %	mPFS (95% CI), mo		
		PAL+FUL	PBO+FUL	HR (95% CI)
Overall (ITT) population	100	11.2 (9.5–12.9)	4.6 (3.5–5.6)	0.50 (0.40–0.62)
ET sensitive	79	12.0 (11.1–13.9)	4.2 (3.5–5.6)	0.46 (0.36–0.59)
ET resistant	21	7.4 (5.5–11.1)	5.1 (1.9–7.4)	0.69 (0.43–1.09)
Without prior CT in ABC	66	12.9 (11.0–15.0)	5.5 (3.6–7.6)	0.49 (0.37–0.65)
With prior CT in ABC	34	9.5 (7.3–11.3)	3.5 (1.9–5.4)	0.54 (0.37–0.78)
Without any prior therapy in ABC	22	11.0 (7.3–13.2)	5.1 (2.1–9.2)	0.59 (0.37–0.93)
Visceral	60	9.2 (7.5–11.1)	3.5 (2.0–5.1)	0.50 (0.38–0.65)
Nonvisceral	40	16.6 (13.2–NE)	5.6 (4.6–10.9)	0.48 (0.33–0.71)
Bone only	24	14.3 (11.2–NE)	9.2 (4.8–20.0)	0.63 (0.38–1.06)
Visceral liver involvement	39	7.5 (5.6–9.2)	2.4 (1.9–3.6)	0.49 (0.36–0.68)
Visceral lung involvement	31	11.1 (9.2–12.0)	3.7(2.1–7.2)	0.45 (0.31–0.67)

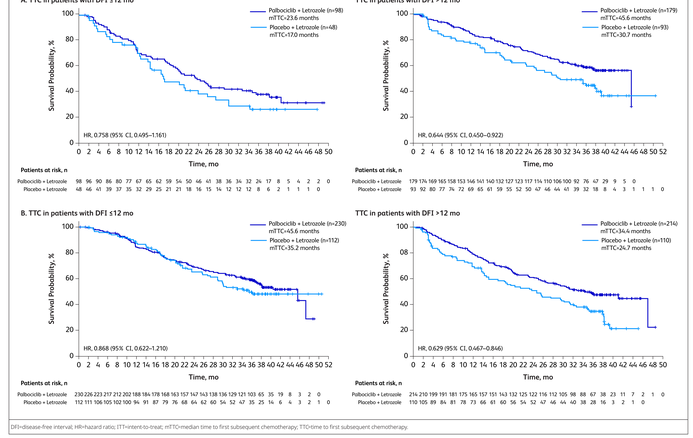
ABC=advanced breast cancer; CT=chemotherapy; ET=endocrine therapy; FUL=fulvestrant; HR=hazard ratio; ITT=intent-to-treat; mPFS=median progression-free survival; NE=not estimable; PAL=palbociclib; PBO=placebo; PFS=progression-free survival.

Figure 3. Forest Plot of TTC by Treatment Arm in PALOMA-3, Overall and Across Patient Subgroups; ITT Population



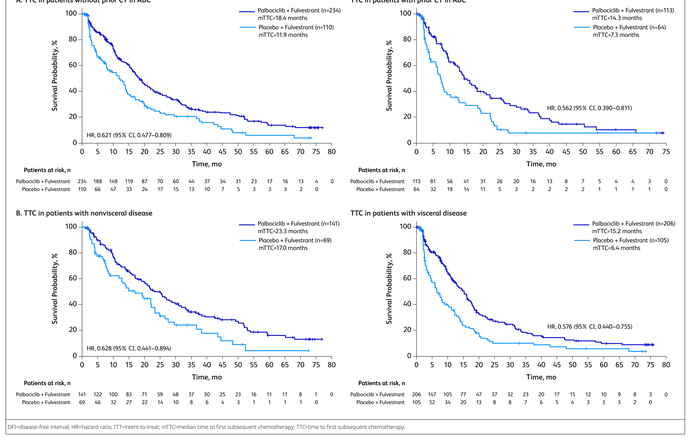
ABC=advanced breast cancer; CT=chemotherapy; ET=endocrine therapy; FUL=fulvestrant; HR=hazard ratio; ITT=intent-to-treat; mTTC=median time to first chemotherapy; PAL=palbociclib; PBO=placebo; TTC=time to first chemotherapy.

Figure 2. TTC in Subgroups of Patients From PALOMA-2 With (A) DFI ≤12 and >12 Months and (B) Nonvisceral and Visceral Disease; ITT Population



DFI=disease-free interval; HR=hazard ratio; ITT=intent-to-treat; mTTC=median time to first subsequent chemotherapy; TTC=time to first subsequent chemotherapy.

Figure 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



DFI=disease-free interval; HR=hazard ratio; ITT=intent-to-treat; mTTC=median time to first subsequent chemotherapy; TTC=time to first subsequent chemotherapy.

PALOMA-2

- More patients in the placebo plus ET vs palbociclib plus ET group received first subsequent chemotherapy after discontinuation of study treatment (46.8% vs 33.6%).
- Baseline demographics and disease characteristics for patients with vs without a subsequent first chemotherapy are presented in **Table 1**.
  - Patients in both the palbociclib plus ET and placebo plus ET arms were more likely to receive vs not receive chemotherapy after discontinuation of study treatment if they were younger (<65 years), had a disease-free interval (DFI) ≤12 months, or had received prior (neo) adjuvant systemic or hormonal therapy or chemotherapy.
  - Patients in the placebo plus ET arm were more likely to receive vs not receive subsequent chemotherapy if they had visceral metastases.
- Across all subgroups included in this analysis, TTC was longer with palbociclib plus letrozole compared with placebo plus letrozole (**Figure 1**).
- Patients with DFI ≤12 months had a median TTC of 23.6 months in the palbociclib plus ET arm vs 17.0 months in the placebo plus ET arm (HR, 0.76 [95% CI, 0.50–1.16]); for patients with DFI >12 months, the median TTC was 45.6 vs 30.7 months, respectively (HR, 0.64 [0.45–0.92]; **Figure 2A**).
- Patients with nonvisceral disease had a median TTC of 45.6 vs 35.2 months in the palbociclib plus ET vs placebo plus ET arms, respectively (HR, 0.87 [95% CI, 0.62–1.21]); for patients with visceral disease, the median TTC was 34.4 vs 24.7 months (HR, 0.63 [0.47–0.85]; **Figure 2B**).
- Median PFS was higher in the palbociclib plus letrozole arm compared with the placebo plus letrozole arm across the same patient subgroups from PALOMA-2 (**Table 2**), as previously reported.[5,7]

PALOMA-3

- In PALOMA-3, more patients in the placebo plus ET vs palbociclib plus ET group received a first subsequent chemotherapy after discontinuation of study treatment (74.7% vs 69.7%).
- Baseline demographics and disease characteristics for patients with vs without a subsequent chemotherapy after study drug discontinuation are presented in **Table 3**.
  - A higher percentage of younger patients (<65 years) received vs did not receive chemotherapy after discontinuation of either palbociclib plus ET or placebo plus ET.
  - Patients with subsequent chemotherapy had more prior hormonal therapies and prior lines of therapy for ABC.
  - In the placebo plus ET arm, a higher percentage of patients with visceral metastasis received vs did not receive subsequent chemotherapy.
- Across all subgroups from PALOMA-3 included in this analysis, TTC was longer with palbociclib plus ET compared with placebo plus ET (**Figure 3**).
- Patients without prior chemotherapy in the ABC setting had a median TTC of 18.4 vs 11.9 months in the palbociclib plus ET arm vs the placebo plus ET 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 vs 7.3 months (HR, 0.56 [0.39–0.81]; **Figure 4A**).
- Patients with nonvisceral disease had a median TTC of 23.3 vs 17.0 months in the palbociclib plus ET and placebo plus ET arm, respectively (HR, 0.63 [95% CI, 0.44–0.89]); for patients with visceral disease, the median TTC was 15.2 vs 6.4 months (HR, 0.58 [0.44–0.76]; **Figure 4B**).
- Median PFS was higher in the palbociclib plus fulvestrant arm compared with the placebo plus fulvestrant arm across the same patient subgroups from PALOMA-3 (**Table 4**), as previously reported.[7,8]

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References: **1.** Cardoso F, et al. ***Ann Oncol***. 2020;31(12):1623-1649. **2.** National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). Breast Cancer. Version 5.2021. National Comprehensive Cancer Network; June 28, 2021. **3.** Rinn RS, et al. ***N Engl J Med***. 2016;375(20):1925-1936. **4.** Turner NC, et al. ***N Engl J Med***. 2015;373(3):209-219. **5.** Rugo HS, et al. ***Breast Cancer Res Treat***. 2019;174(3):719-729. **6.** Turner NC, et al. ***N Engl J Med***. 2018;379(20):1926-1936. **7.** Turner NC, et al. ***Ann Oncol***. 2018;29(3):669-680. **8.** Rugo HS, et al. ***Oncologist***. 2021;[Epub ahead of print; doi:10.1002/onco.13833].

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