Palbociclib in combination with letrozole in patients with estrogen receptor–positive, human epidermal growth factor receptor 2–negative advanced breast cancer: PALOMA-2 subgroup analysis of Japanese patients

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Abstract

Background In PALOMA-2, palbociclib–letrozole significantly improved progression-free survival (PFS) vs placebo–letrozole in women with estrogen receptor–positive, human epidermal growth factor receptor 2–negative (ER+/HER2–) advanced breast cancer (ABC) in the first-line setting. We evaluated the efficacy, safety, and pharmacokinetics of palbociclib in Japanese women in PALOMA-2.

Methods In this phase 3 study, 666 postmenopausal women with ER+/HER2– ABC were randomized 2:1 to palbociclib (125 mg/day [3 weeks on/1 week off]) plus letrozole (2.5 mg daily) or placebo plus letrozole. A prespecified, exploratory, subgroup analysis of Japanese patients (n = 46) was conducted to compare results with those of the overall population.

Results At the February 26, 2016 cutoff, median PFS among the 46 Japanese patients was 22.2 months (95%CI, 13.6–not estimable) with palbociclib–letrozole vs 13.8 months (5.6–22.2) with placebo–letrozole (hazard ratio, 0.59 [95%CI, 0.26−1.34]). The most common adverse events (AEs) were hematologic and more frequent among Japanese patients than the overall population (neutropenia: 93.8% [87.5% grade 3/4] vs 79.5% [66.4%]; leukopenia: 62.5% [43.8%] vs 39.0% [24.8%]); no Japanese patients had febrile neutropenia. Palbociclib dose reductions due to toxicity (mainly neutropenia) were more common in Japanese patients (62.5% vs 36.0%); few permanently discontinued due to AEs. Although mean palbociclib trough concentration was higher in Japanese patients vs non-Asians (95.4 vs 61.7 ng/mL), the range of individual values of the Japanese patients was within that of non-Asians.

Conclusions These results from PALOMA-2 suggest that palbociclib–letrozole merits consideration as a first-line treatment option for postmenopausal Japanese patients with ER+/HER2– ABC. ClinicalTrials.gov: NCT01740427.

Keywords Advanced breast cancer · HER2– · HR+ · Japanese · Letrozole · Palbociclib

Introduction

Breast cancer is the most common cancer and fifth leading cause of cancer-related death in Japan [1]. Hormone receptor–positive (HR+) breast cancer accounts for approximately 71% of new cases worldwide [2]. Endocrine therapy is a mainstay of HR+ breast cancer treatment and is recommended by the Japanese Breast Cancer Society and international guidelines for initial treatment of HR+ disease [3, 4]. However, hormonal blockade alone provides only modest benefit in women with advanced breast cancer (ABC),
with many patients having de novo or acquired resistance to
endocrine therapy [4].

Palbociclib is a selective, oral inhibitor of cyclin-depend-
ent kinases 4 and 6 (CDK4/6) that prevents cell prolifera-
tion by blocking cell cycle progression from the G1 to the S
phase [5]. In the multinational, phase 3 PALOMA-2 study,
median progression-free survival (PFS) was significantly
longer with palbociclib–letrozole than with placebo–letro-
zo as first-line treatment for postmenopausal women with
estrogen receptor–positive (ER+)/human epidermal growth
factor receptor 2−negative (HER2−) ABC, and toxicities
were manageable [6]. Palbociclib is approved in the United
States, the European Union, and Japan for the treatment of
HR+/HER2− ABC in combination with endocrine therapy
[7–9].

Limited data are available on the efficacy and safety of
palbociclib–letrozole in Japanese patients. A phase 1 study
in postmenopausal Japanese women with ER+/HER2− ABC
determined that the optimal dosage of palbociclib is 125 mg
once daily (QD) for 3 weeks on followed by 1 week off (3/1
schedule), the same as in Western patients [10]. A single-
arm, phase 2 study evaluated the efficacy and safety of
palbociclib–letrozole (3/1 regimen) in 42 postmenopausal
Japanese patients with treatment-naive ER+/HER2− ABC;
although follow-up is ongoing, initial results are encour-
aging with a 1-year probability of PFS of 75.0% (90%CI,
61.3%–84.4%) [11].

Data on the efficacy and safety of palbociclib–letrozole in
Asian patients in PALOMA-2 have been reported [12];
however, some patients resided in Western countries, as the
analysis included all patients who reported Asian ethnicity.
Dietary habits and medical environments vary among Asian
countries, and these factors may influence clinical outcomes
[13, 14]. Therefore, additional investigation in Japanese
patients is warranted. This paper presents results of a pre-
specified exploratory analysis of the efficacy—including the
association between efficacy and dose reduction—safety, and
pharmacokinetics (PK) of palbociclib in Japanese women
residing in Japan enrolled in PALOMA-2, as well as ad hoc
analyses in the overall population of factors associated with
neutropenia, the most common adverse event (AE) associ-
ated with palbociclib.

Patients and methods

Study design and patients

The PALOMA-2 study has been described previously [6].
Briefly, postmenopausal women with histologically or cyto-
logically confirmed ER+/HER2− ABC (locoregionally
recurrent or metastatic) not suitable for resection or radiation
therapy with curative intent were randomized 2:1 to receive
palbociclib 125 mg QD (3/1 schedule) plus daily letrozole
2.5 mg or matching placebo plus letrozole. Dose reductions
of palbociclib or placebo due to AEs were allowed; dose
reductions of letrozole were not. Randomization was strati-
fied by disease site (visceral/nonvisceral), disease-free inter-
val from the end of (neo)adjuvant therapy (de novo meta-
static, ≤ 12 months, > 12 months), and prior (neo)adjuvant
hormonal therapy (yes, no). There was no stratification by
country/region.

Patients included in this analysis were residing in Japan.
The study was approved by an institutional review board or
ethics committee at each site (Table S1), and all patients
provided written informed consent. PALOMA-2 was con-
ducted in accordance with the Declaration of Helsinki and
the International Conference on Harmonisation Good Clini-
cal Practice Guidelines.

Outcomes and assessments

The primary endpoint was investigator-assessed PFS. Sec-
ondary endpoints included objective response (confirmed
partial or complete response per RECIST v1.1), clinical ben-
efit response (CBR; objective response or stable disease for
≥ 24 weeks per RECIST v1.1), safety, and PK. Radiological
tumor assessments were performed at screening and every
12 weeks during treatment.

Laboratory analyses were performed on days 1 and 15 of
cycles 1 and 2 then on day 1 of each subsequent cycle. AEs
were assessed according to the National Cancer Institute
Common Terminology Criteria for Adverse Events, version
4.0. Blood samples for PK analysis were obtained predose
on day 15 of cycles 1 and 2. Plasma samples were analyzed
using a validated high-performance liquid chromatography
with tandem mass spectrometry.

Statistical analyses

Estimates of median PFS and corresponding 2-sided 95%
confidence intervals were obtained using the Kaplan–Meier
method. Cox proportional hazard models were used to
calculate HRs [6]. Comparisons of PFS were done using
1-sided unstratified log-rank tests. A blinded independent
central review (BICR) of PFS was conducted for all patients
as a supportive analysis. Safety data are summarized using
descriptive statistics in patients who received ≥ 1 dose of
study treatment (as-treated population). Nominal P
values are presented, and no adjustments were made for multiple
testing. Additional details are published elsewhere [6]. Pear-
son correlation coefficients were calculated for the analy-
eses evaluating the relationship between palbociclib trough
centration (C_{trough}) and body weight/body surface area
(BSA)/body mass index (BMI) and factors associated with
posttreatment neutrophil counts.
Results

Patients and study treatment

Between December 2013 and June 2014, 46 Japanese patients enrolled in PALOMA-2; 32 were randomized to palbociclib–letrozole and 14 to placebo–letrozole. Demographics and baseline disease characteristics of the overall and Japanese populations are in Table 1. Japanese women had a lower median body weight compared with the overall population (palbociclib–letrozole, 53.9 vs 68.0 kg; placebo–letrozole, 57.1 vs 66.8 kg) and a better Eastern Cooperative Oncology Group (ECOG) performance status (palbociclib–letrozole, 84.4% vs 57.9% had ECOG performance status grade 0; placebo–letrozole, 71.4% vs 45.9%). More Japanese patients vs the overall population had visceral disease (palbociclib–letrozole, 62.5% vs 48.2%; placebo–letrozole, 71.4% vs 49.5%) and a disease-free interval > 12 months (palbociclib–letrozole, 59.4% vs 40.1%; placebo–letrozole, 64.3% vs 41.9%). In the palbociclib–letrozole group, more Japanese patients (62.5%) were ≥ 65 years of age (vs 40.8% in the overall population).

In contrast with the overall population, median duration of treatment among Japanese patients was similar with both treatments (palbociclib–letrozole, 13.34 [range, 0.69–26.15] months; placebo–letrozole, 13.60 [2.04–24.87] months; Table 2). More Japanese patients required palbociclib dose reductions (62.5% vs 36.0% overall), leading to a lower relative dose intensity than the overall population (74.3% [44.0%–100.0%] vs 93.0% [40.3%–109.5%]).

Table 1  Demographics and baseline disease characteristics in the overall population and Japanese patients

| Characteristic                       | Overall population | Japanese patients |
|--------------------------------------|--------------------|-------------------|
|                                     | PAL + LET (n = 444) | PBO + LET (n = 222) | PAL + LET (n = 32) | PBO + LET (n = 14) |
| **Age, y**                           |                    |                   |                   |                   |
| Median (range)                       | 62 (30–89)         | 61 (28–88)        | 67 (44–88)        | 61 (51–88)        |
| < 65, n (%)                          | 263 (59.2)         | 141 (63.5)        | 12 (37.5)         | 11 (78.6)         |
| ≥ 65, n (%)                          | 181 (40.8)         | 81 (36.5)         | 20 (62.5)         | 3 (21.4)          |
| **Median (range) weight, kg**        | 68.0 (33.0–156.8)  | 66.8 (35.0–124.8) | 53.9 (33.0–88.0) | 57.1 (43.8–67.4) |
| **ECOG performance status, n (%)**   |                    |                   |                   |                   |
| 0                                    | 257 (57.9)         | 102 (45.9)        | 27 (84.4)         | 10 (71.4)         |
| 1                                    | 178 (40.1)         | 117 (52.7)        | 3 (9.4)           | 4 (28.6)          |
| 2                                    | 9 (2.0)            | 3 (1.4)           | 2 (6.3)           | 0                 |
| **Disease site, n (%)**              |                    |                   |                   |                   |
| Visceralb                            | 214 (48.2)         | 110 (49.5)        | 20 (62.5)         | 10 (71.4)         |
| Nonvisceral                          | 230 (51.8)         | 112 (50.5)        | 12 (37.5)         | 4 (28.6)          |
| Bone-only                            | 103 (23.2)         | 48 (21.6)         | 4 (12.5)          | 1 (7.1)           |
| **Number of disease sites, n (%)**   |                    |                   |                   |                   |
| 1                                    | 138 (31.1)         | 66 (29.7)         | 7 (21.9)          | 5 (35.7)          |
| 2                                    | 117 (26.4)         | 52 (23.4)         | 10 (31.3)         | 4 (28.6)          |
| 3                                    | 112 (25.2)         | 61 (27.5)         | 12 (37.5)         | 3 (21.4)          |
| ≥ 4                                  | 77 (17.3)          | 43 (19.4)         | 3 (9.4)           | 2 (14.3)          |
| **Disease-free interval, n (%)**     |                    |                   |                   |                   |
| Newly metastatic disease             | 167 (37.6)         | 81 (36.5)         | 8 (25.0)          | 3 (21.4)          |
| ≤ 12 months                          | 99 (22.3)          | 48 (21.6)         | 5 (15.6)          | 2 (14.3)          |
| > 12 months                          | 178 (40.1)         | 93 (41.9)         | 19 (59.4)         | 9 (64.3)          |
| **Prior (neo)adjuvant therapy, n (%)**|                    |                   |                   |                   |
| Hormonal therapy                     | 249 (56.1)         | 126 (56.8)        | 21 (65.6)         | 10 (71.4)         |
| Chemotherapy                         | 213 (48.0)         | 109 (49.1)        | 15 (46.9)         | 8 (57.1)          |

ECOG Eastern Cooperative Oncology Group, LET letrozole, PAL palbociclib, PBO placebo

*Based on case report form data

bRefers to lung (including pleura) or liver involvement

*Calculated as the time between end of neoadjuvant or adjuvant treatment and onset of metastatic disease or disease recurrence
Efficacy

Median duration of follow-up was similar in the overall (palbociclib–letrozole: 23.0 months; placebo–letrozole: 22.3 months) and Japanese (21.6 and 22.3 months, respectively) populations (data cutoff: February 26, 2016). In the overall population, median PFS was significantly improved with palbociclib–letrozole vs placebo–letrozole (Fig. 1a) [6]. Among Japanese patients, median PFS was 22.2 months (95%CI, 13.6–not estimable) with palbociclib–letrozole vs 13.8 months (5.6–22.2) with placebo–letrozole (HR, 0.59 [95%CI, 0.26–1.34]; 1-sided \( P = 0.103 \)) (Fig. 1b). By BICR, median PFS was 30.5 months (95%CI, 27.4–not estimable) with palbociclib–letrozole vs 19.3 months (16.4–30.6) with placebo–letrozole in the overall population (HR, 0.65 [95%CI, 0.51–0.84]; 1-sided \( P < 0.001 \); Fig. 2a) [6]. In Japanese patients, BICR median PFS was not reached (95%CI, 14.1 months–not estimable) with palbociclib–letrozole and 16.6 months (5.4–19.3) with placebo–letrozole (HR, 0.45 [95%CI, 0.18–1.12]; 1-sided \( P = 0.039 \)) (Fig. 2b). The PFS with palbociclib was consistent in other Asian patients (excluding Japanese) as well as non-Asians (Fig. S1).

Confirmed objective response rate (ORR) was numerically higher with palbociclib–letrozole vs placebo–letrozole in both the overall (55.3% [95%CI, 49.9–60.7] vs 44.4% [36.9–52.2]) and Japanese populations (46.4% [27.5–66.1] vs 38.5% [13.9–68.4]) in patients with measurable disease (Table 3). The degree of improvement in ORR with palbociclib was similar in the intent-to-treat (ITT) population. CBR was higher with palbociclib–letrozole vs placebo–letrozole in the overall population (84.3% [95%CI, 80.0–88.0] vs 70.8% [63.3–77.5]) in patients with measurable disease, but not in Japanese patients (75.0% [95%CI, 55.1–89.3] vs 84.6% [54.6–98.1]); results were similar in the ITT population (Table 3).

Using an updated data cutoff (May 31, 2017), with approximately 37-month median follow-up [15], median investigator-assessed PFS in Japanese patients was 24.9 months (95%CI, 13.6–38.6) with palbociclib–letrozole vs 13.8 months (5.6–not estimable) with placebo–letrozole (HR, 0.67 [95%CI, 0.31–1.47]) (Fig. 3a); median PFS by BICR was 27.9 months (95%CI, 16.4–not estimable) vs 16.6 months (5.4–33.2), respectively (HR, 0.55 [95%CI, 0.23–1.29]) (Fig. 3b). Data for overall survival are not yet mature.

In the evaluation of the association between efficacy and dose reduction, Japanese patients in the palbociclib–letrozole group who required dose reduction to 100 mg QD or 75 mg QD also showed long PFS (Fig. 4).

### Table 2 Exposure to study drug in the overall population and Japanese patients

|                  | Overall population | Japanese patients |
|------------------|--------------------|-------------------|
|                  | PAL + LET (n = 444) | PBO + LET (n = 222) | PAL + LET (n = 32) | PBO + LET (n = 14) |
| **Duration of treatment**, median (range), months | 19.81 (0.03–34.07) | 13.57 (0.33–35.18) | 13.34 (0.69–26.15) | 13.60 (2.04–24.87) |
| **Average daily dose, median (range), mg** | 125.0 (76.6–125.2) | 125.0 (104.7–125.6) | 112.4 (84.4–125.0) | 125.0 (109.6–125.6) |
| **Dose reductions, \( n \) (%)** | 160 (36.0) | 3 (1.4) | 20 (62.5) | 1 (7.1) |
| **Reduction to 100 mg** | 97 (21.8) | 3 (1.4) | 11 (34.4) | 1 (7.1) |
| **Reduction to 75 mg** | 63 (14.2) | 0 | 9 (28.1) | 0 |
| **Time to first dose reduction**, median (range), days | 90 (28–785) | 42 (29–198) | 63 (29–785) | 42 |
| **Dose interruption, \( n \) (%)** | 297 (66.9) | 92 (41.4) | 22 (68.8) | 6 (42.9) |
| **Relative dose intensity, median (range), %** | 93.0 (40.3–109.5) | 99.6 (56.1–104.5) | 74.3 (44.0–100.0) | 99.2 (56.1–100.0) |
| **LET** | 233 (52.5) | 97 (43.7) | 20 (62.5) | 9 (64.3) |
| **Relative dose intensity, median (range), %** | 99.9 (73.4–100.2) | 100.0 (79.0–100.0) | 99.8 (77.8–100.0) | 99.9 (93.2–100.0) |
Pharmacokinetics

The geometric mean (geometric CV%) palbociclib $C_{\text{trough}}$ at steady state was higher in Japanese (95.4 ng/mL [31.3]) and other Asians (90.1 ng/mL [36.0]) relative to non-Asians (61.7 ng/mL [59.1]), indicating greater palbociclib exposure. However, individual palbociclib $C_{\text{trough}}$ values in each of the 3 groups were generally within a similar range (Fig. 5). No apparent correlation was observed between steady state $C_{\text{trough}}$ and body weight (Fig. 6) or BSA/BMI (data not shown) in Japanese, Asian (excluding Japanese), and non-Asian patients.

Safety

Hematologic AEs were the most common toxicities reported with palbociclib–letrozole in the overall and Japanese populations (Table 4). With the exception of neutropenia and leukopenia, most hematologic AEs were of grade 1 or 2 severity. The incidence of any-grade hematologic AEs with combination therapy was higher in the Japanese than in the overall population (neutropenia, 93.8% vs 79.5%; leukopenia, 62.5% vs 39.0%; and thrombocytopenia, 37.5% vs 15.5%, respectively). Grade 3/4 events were more common with palbociclib–letrozole among Japanese patients vs the overall population (neutropenia, 87.5% vs 66.4%; leukopenia, 43.8% vs 24.8%; and thrombocytopenia, 6.3% vs 1.6%).
Neutropenia was manageable with dose modifications, and only 3 Japanese women (9.4%) permanently discontinued palbociclib because of this AE. No febrile neutropenia was observed among Japanese patients.

The most common (> 20% incidence) nonhematologic AEs reported with palbociclib–letrozole in the Japanese patients were stomatitis (53.1% vs 30.4% in the overall population, respectively), nasopharyngitis (43.8% vs 14.0%), nausea (28.1% vs 35.1%), alopecia (25.0% vs 32.9%), and increased alanine aminotransferase (21.9% vs 9.9%) (Table 4). Stomatitis and nasopharyngitis were substantially (> 20% difference) more common among the Japanese vs overall population, whereas fatigue (15.6% vs 37.4%) was less common. Few patients had grade 3/4 nonhematologic AEs.

The overall incidence of AEs associated with dose reductions was higher in the Japanese vs overall population (62.5% vs 36.0%, respectively) (Table S2). Neutropenia (31.3%) and decreased neutrophil count (28.1%) were the only AEs associated with dose reductions in > 1 Japanese patient. Five Japanese patients permanently discontinued palbociclib because of AEs (neutropenia in 1 patient, neutrophil count decreased in 2 patients, cerebral hemorrhage and pulmonary fibrosis in 1 patient each). Posttreatment (Cycle 1, Day 15) absolute neutrophil counts (ANCs) correlated with baseline ANC in Japanese patients, other Asians (excluding Japanese), and non-Asians [overall correlation

Fig. 2 BICR-assessed PFS in the a overall population and b Japanese patients (ITT population). BICR blinded independent central review, CI confidence interval, HR hazard ratio, ITT intent-to-treat, LET letrozole, NE not estimable, NR not reached, PAL palbociclib, PBO placebo, PFS progression-free survival. a HR stratified by disease site (visceral vs nonvisceral) at baseline. b Unstratified HR.
No apparent correlation was observed between posttreatment ANC and steady state C\textsubscript{trough} (Fig. 7b), body weight (Fig. 7c), BSA/BMI (data not shown), or age (Fig. 7d).

**Discussion**

This prespecified, exploratory subgroup analysis of PAL-OMA-2 suggests that palbociclib–letrozole is effective for postmenopausal Japanese women with ER+/HER2– ABC who have not received prior systemic treatment for ABC. The addition of palbociclib numerically increased PFS in Japanese patients, with a median investigator-assessed PFS of 22.2 vs 13.8 months with placebo–letrozole (HR, 0.59 [95%CI, 0.26–1.34]; 1-sided \( P = 0.1027 \)). For other Asian patients (excluding Japanese) and for non-Asians, PFS was similar with palbociclib–letrozole (Fig. S1).

Based on the most recent data cutoff, median investigator-assessed PFS in Japanese patients was 24.9 months with palbociclib–letrozole vs 13.8 months with placebo–letrozole, while median PFS by BICR was 27.9 vs 16.6 months.

### Table 3  Tumor response in the ITT population and in patients with measurable disease

| ITT Population | Overall population | Japanese patients |
|----------------|--------------------|-------------------|
|                | PAL + LET (n = 444) | PBO + LET (n = 222) | PAL + LET (n = 32) | PBO + LET (n = 14) |
| Best overall response, n (%) | | | | |
| Complete response | 9 (2.0) | 5 (2.3) | 1 (3.1) | 0 |
| Partial response | 178 (40.1) | 72 (32.4) | 12 (37.5) | 5 (35.7) |
| Stable disease (weeks) | 210 (47.3) | 96 (43.2) | 13 (40.6) | 8 (57.1) |
| \( \geq 24 \) | 190 (42.8) | 79 (35.6) | 12 (37.5) | 7 (50.0) |
| < 24 | 20 (4.5) | 17 (7.7) | 1 (3.1) | 1 (7.1) |
| Disease progression | 34 (7.7) | 37 (16.7) | 5 (15.6) | 1 (7.1) |
| Indeterminate | 13 (2.9) | 12 (5.4) | 1 (3.1) | 0 |
| ORR,a,b % (95%CI) | 42.1 (37.5–46.9) | 34.7 (28.4–41.3) | 40.6 (23.7–59.4) | 35.7 (12.8–64.9) |
| Odds ratio\(^c\) (95%CI) | 1.40 (0.98–2.01) | 1.23 (0.29–5.79) | \(0.0310\) | 0.5095 |
| CBR,b,d % (95%CI) | 84.9 (81.2–88.1) | 70.3 (63.8–76.2) | 78.1 (60.0–90.7) | 85.7 (57.2–98.2) |
| Odds ratio\(^c\) (95%CI) | 2.39 (1.58–3.59) | 0.60 (0.05–3.86) | \(0.0001\) | 0.8409 |

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CBR clinical benefit response, CI confidence interval, ITT intent-to-treat, LET letrozole, ORR objective response rate, PAL palbociclib, PBO placebo

\(^a\)Confirmed complete and partial response

\(^b\)Exact method based on binomial distribution

\(^c\)Stratified and unstratified odds ratio in the overall population and Japanese patients, respectively

\(^d\)Confirmed complete and partial response plus stable disease \( \geq 24 \) weeks
respectively (Fig. 3). The difference between investigator- and BICR-assessed median PFS was also observed in the overall population (Figs. 1a, 2a), and was largely due to a higher censoring rate in the BICR analysis. Patients with investigator-diagnosed progressive disease were removed from study treatment and often switched to subsequent therapies with no further tumor assessment in the study. If progressive disease could not be confirmed on central review, the patient would be censored in the BICR analysis. Despite the difference in censoring rates, the results of BICR analysis showed preferable clinical benefit with palbociclib–letrozole and supported the findings of primary analysis.

Consistent with the overall population, ORR was higher in Japanese patients treated with palbociclib–letrozole; however, CBR was lower with palbociclib–letrozole than with placebo–letrozole. This discrepancy reflects differences in the number of Japanese patients who experienced disease progression within 24 weeks of randomization: 5 patients in the palbociclib–letrozole group vs 1 in the placebo–letrozole group.

In a single-arm phase 2 study of palbociclib–letrozole in Japanese women with treatment-naive ER+/HER2–ABC, the probability of PFS at 1 year was 75.0% (90% CI, 61.3%–84.4%). Median PFS was not yet reached (lower limit of 95% CI was 21.7 months) and follow-up is ongoing [11].

In PALOMA-2, the geometric mean palbociclib C_{trough} at steady state was higher in Japanese (95.4 ng/mL) and other Asian patients (90.1 ng/mL) relative to non-Asians; however, individual values within each group were generally
within range of one another. Although Japanese patients in the palbociclib–letrozole arm had a lower body weight relative to the overall population (median, 53.9 kg vs 68.0 kg), no apparent relationships were observed between C\text{trough} and lower body weight/BSA/BMI. These results are consistent with those of a population PK analysis using data from other multinational studies of palbociclib, which showed that body weight had no clinically important effect on palbociclib PK and suggest there is no need for weight-based dosing [16].

Palbociclib is metabolized primarily by cytochrome P450 isozyme (CYP)3A and sulfotransferase (SULT) enzyme SULT2A1 [7]. There is wide interindividual variability in CYP3A metabolism, and analyses of cytochrome P450 activity among native Japanese, Chinese, Korean, and Caucasian populations indicate that CYP3A metabolism is independent of ethnicity and genotypes [17–19]. Although specific reasons were not identified for the observed difference in C\text{trough} between the two populations in PALOMA-2, the interindividual variability of CYP3A might be a factor.

In the aforementioned open-label phase 2 study of palbociclib–letrozole in Japanese patients, full PK analysis in a palbociclib PK profile subset (n = 6) showed a remarkable similarity to that in non-Japanese patients enrolled in PALOMA-1 [11, 20]. In addition, in the global phase 3 study of palbociclib–fulvestrant (PALOMA-3), the within-patient mean steady state palbociclib C\text{trough} in Japanese,

![Fig. 4 Duration of PFS in 32 Japanese patients treated with palbociclib–letrozole. OR objective response, LET letrozole, PD progressive disease, PFS progression-free survival](image)

![Fig. 5 Palbociclib C\text{trough} at steady state in non-Asian, Asian (excluding Japanese), and Japanese patients. Black diamonds represent the subpopulation arithmetic mean values and open circles represent individual patient values. The dashed blue line represents the arithmetic mean value of all data from all patients. The box plot provides median and 25%/75% quartiles with whiskers to the last point within 1.5 times interquartile range. C\text{trough} trough concentration](image)

![Fig. 6 Palbociclib C\text{trough} at steady state vs body weight in non-Asian, Asian (excluding Japanese), and Japanese patients. Pearson product-moment correlation coefficient (R) is presented. Within-patient palbociclib C\text{trough} are shown. C\text{trough} trough concentration](image)
Table 4  Adverse events occurring in ≥ 15% of Japanese patients in either arm (all-causality; as-treated population)

| Adverse Event | Overall population | Japanese patients |
|---------------|--------------------|-------------------|
|               | PAL + LET (n=444)  | PBO + LET (n=222) | PAL + LET (n=32)  | PBO + LET (n=14)  |
|               | Any Grade | Grade 3 | Grade 4 | Any Grade | Grade 3 | Grade 4 | Any Grade | Grade 3 | Grade 4 | Any Grade | Grade 3 | Grade 4 |
| Any AE, n (%) | 439 (98.9) | 276 (62.2) | 60 (13.5) | 212 (95.5) | 49 (22.1) | 5 (2.3) | 32 (100) | 19 (59.4) | 11 (34.4) | 13 (92.9) | 4 (28.6) | 0 |
| Hematologic AEs | | | | | | | | | | | | |
| Neutropeniaa | 353 (79.5) | 249 (56.1) | 46 (10.4) | 14 (6.3) | 2 (0.9) | 1 (0.5) | 30 (93.8) | 17 (53.1) | 11 (34.4) | 2 (14.3) | 0 | 0 |
| Leukopeniaa | 173 (39.0) | 107 (24.1) | 3 (0.7) | 5 (2.3) | 0 | 0 | 20 (62.5) | 14 (43.8) | 0 | 1 (7.1) | 0 | 0 |
| Thrombocytopeniaa | 69 (15.5) | 6 (1.4) | 1 (0.2) | 3 (1.4) | 0 | 0 | 12 (37.5) | 2 (6.3) | 0 | 0 | 0 | 0 |
| Anemiaa | 107 (24.1) | 23 (5.2) | 1 (0.2) | 20 (9.0) | 4 (1.8) | 0 | 9 (28.1) | 3 (9.4) | 0 | 3 (21.4) | 1 (7.1) | 0 |
| Nonhematologic AEs | | | | | | | | | | | | |
| Stomatitasa | 135 (30.4) | 4 (0.9) | 0 | 30 (13.5) | 0 | 0 | 17 (53.1) | 0 | 0 | 4 (28.6) | 0 | 0 |
| Nasopharyngitis | 62 (14.0) | 0 | 0 | 22 (9.9) | 0 | 0 | 14 (43.8) | 0 | 0 | 2 (14.3) | 0 | 0 |
| Nausea | 156 (35.1) | 1 (0.2) | 0 | 58 (26.1) | 4 (1.8) | 0 | 9 (28.1) | 0 | 0 | 1 (7.1) | 1 (7.1) | 0 |
| Alopecia | 146 (32.9) | – | – | 35 (15.8) | – | – | 8 (25.0) | – | – | 0 | – | – |
| ALT increase | 44 (9.9) | 9 (2.0) | 1 (0.2) | 9 (4.1) | 0 | 0 | 7 (21.9) | 2 (6.3) | 0 | 1 (7.1) | 0 | 0 |
| AST increase | 43 (9.7) | 11 (2.5) | 0 | 11 (5.0) | 2 (0.9) | 0 | 6 (18.8) | 1 (3.1) | 0 | 1 (7.1) | 0 | 0 |
| Decreased appetite | 66 (14.9) | 3 (0.7) | 0 | 20 (9.0) | 0 | 0 | 6 (18.8) | 1 (3.1) | 0 | 0 | 0 | 0 |
| Rasha | 79 (17.8) | 4 (0.9) | 0 | 26 (11.7) | 1 (0.5) | 0 | 6 (18.8) | 0 | 0 | 2 (14.3) | 0 | 0 |
| Arthralgia | 148 (33.3) | 3 (0.7) | – | 75 (33.8) | 1 (0.5) | – | 5 (15.6) | 0 | – | 3 (21.4) | 0 | – |
| Dry skin | 55 (12.4) | 0 | – | 13 (5.9) | 0 | – | 5 (15.6) | 0 | – | 0 | 0 | – |
| Fatigue | 166 (37.4) | 8 (1.8) | 0 | 61 (27.5) | 1 (0.5) | 0 | 5 (15.6) | 0 | 0 | 1 (7.1) | 0 | 0 |
| Hot flush | 93 (20.9) | 0 | – | 68 (30.6) | 0 | – | 2 (6.3) | 0 | – | 4 (28.6) | 0 | – |

– grade not available, AE adverse event, ALT alanine aminotransferase, AST aspartate aminotransferase, LET letrozole, PAL palbociclib, PBO placebo

aClusters of preferred terms were used to represent multiple preferred terms

bOne treatment-related death with lower respiratory tract infection and pulmonary embolism occurred in the PBO + LET group
Asian (excluding Japanese), and non-Asian patients demonstrated relative consistency in the central tendency and range of observed values across groups, indicating similar palbociclib exposure in these subpopulations [21]. Considered together, these data suggest there is no clinically relevant difference in PK between Japanese and non-Japanese patients.

Palbociclib–letrozole was well tolerated in Japanese patients, consistent with other palbociclib studies [6, 10, 11, 22, 23]; the most common AEs were neutropenia and leukopenia. A higher percentage of Japanese patients receiving palbociclib–letrozole experienced grade ≥ 3 neutropenia and grade ≥ 3 leukopenia compared with the overall population (87.5% vs 66.4% and 43.8% vs 24.8%, respectively); however, no febrile neutropenia was observed among Japanese patients.

Neutrophil counts vary among different ethnicities and ANC is generally lower in Asians vs non-Asians [24–26]. While historical comparisons must be interpreted cautiously, mean neutrophil counts reported for Japanese men (n = 3356) and women (n = 6027) were 3.8 (standard deviation, 1.3) × 10^3/mm^3 and 3.5 (1.3) × 10^3/mm^3, respectively [27], which are slightly lower than neutrophil counts previously observed in a non-Hispanic white population (n = 4270; 4.35 × 10^3/mm^3 [95%CI, 4.27–4.44]) [25]. In PALOMA-2, Japanese and most other Asians had baseline ANCs of < 6000/mm^3, whereas many non-Asians had ANCs > 6000/mm^3 (Fig. 7a). Lower baseline neutrophil counts in Japanese and other Asians could potentially explain the higher rate of neutropenia observed in these patients. Posttreatment ANC correlated with baseline neutrophil counts in all 3 groups (R = 0.527). Together, the data suggest that the higher incidence of neutropenia among Japanese patients was not related to a higher C_{trough} or lower body weight/BSA/BMI.

Although febrile neutropenia was not observed in Japanese patients in PALOMA-2, eight patients (1.8%, all non-Asian) in the overall population reported febrile neutropenia.

Fig. 7 Posttreatment absolute neutrophil counts vs a baseline absolute neutrophil count, b palbociclib C_{trough}, c body weight, and d age. Pearson product-moment correlation coefficients (R) are presented.
Baseline neutrophil counts in these patients were relatively low: median 2430/mm³ (range, 1450–3300). These data suggest that lower baseline neutrophil counts may be a risk factor for febrile neutropenia as well as neutropenia with palbociclib, consistent with the widely reported association between lower baseline neutrophil counts and neutropenia/febrile neutropenia in patients receiving chemotherapy [28–30]. In vitro studies indicate that palbociclib causes reversible bone marrow suppression, clearly differentiating it from apoptotic cell death caused by cytotoxic chemotherapeutic agents [31]. This may explain the reduced frequency of febrile neutropenia seen with palbociclib vs cytotoxic chemotherapies.

Although common, neutropenia was effectively managed with dose modifications, and few Japanese patients permanently discontinued palbociclib because of this AE. In addition, the duration of PFS in Japanese patients was not affected by dose reduction to 100 or 75 mg QD (Fig. 4). Results from the open-label phase 2 study also suggest that dose reductions are unlikely to affect the efficacy of palbociclib in Japanese patients, although data from this study are immature and the impact of dose reductions on treatment response will require further evaluation [11]. Of note, dose reductions did not appear to compromise PFS in the overall populations of PALOMA-2 [32, 33] or PALOMA-3 [34, 35].

Stomatitis and nasopharyngitis were more commonly reported among Japanese patients receiving palbociclib–letrozole. All reported events in Japanese patients were grade 1 or 2, and no patients discontinued treatment or required dose reductions because of these AEs. The underlying cause for higher incidences of some AEs in Japanese patients is not clear. As described above, a lower body weight/BSA/BMI in Japanese patients does not necessitate dose adjustments, indicating that it is unlikely that these characteristics contributed to the higher incidence of certain AEs. Rather, differences in genetics, diet, or AE monitoring could possibly contribute to the observed differences.

This analysis suggests that the addition of palbociclib improved clinical outcomes in Japanese patients with ER+/HER2– ABC. However, these results should be interpreted cautiously, as the small sample size lacks the power to draw definitive conclusions, particularly regarding efficacy. The safety profile of palbociclib–letrozole was consistent with those reported previously. Hematologic toxicities were more common among Japanese patients than in the overall population, but were successfully managed with dose modifications. Taken together, the results seen in the Japanese and overall populations in PALOMA-2 suggest that palbociclib–letrozole merits consideration as a first-line treatment option for postmenopausal Japanese patients with ER+/HER2– ABC.

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Compliance with ethical standards

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