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Brief Communication

Palbociclib Plus Fulvestrant in Korean Patients from PALOMA-3 With Hormone Receptor-Positive/Human Epidermal Growth Factor Receptor 2–Negative Advanced Breast Cancer

Jee Hyun Kim [1], **Seock-Ah Im** [2], **Sung Hoon Sim** [3], **Eustratios Bananis** [4], **Xin Huang** [5], **Hyun Seon Kim** [6], **Sung-Bae Kim** [7]

[1]Division of Hematology & Medical Oncology, Department of Internal Medicine, Seoul National University Bundang Hospital, Seoul National University College of Medicine, Seoul, Korea
[2]Division of Hematology & Medical Oncology, Department of Internal Medicine, Seoul National University Hospital, Cancer Research Institute, Seoul National University College of Medicine, Seoul, Korea
[3]Department of Internal Medicine, National Cancer Center Korea, Goyang, Korea
[4]Pfizer Inc., New York, USA
[5]Pfizer Inc., San Diego, USA
[6]Pfizer Korea, Seoul, Korea
[7]Department of Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea

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Correspondence to
Seock-Ah Im
Division of Hematology & Medical Oncology, Department of Internal Medicine, Seoul National University Hospital, Cancer Research Institute, Seoul National University College of Medicine, 101 Daehak-ro, Jongro-gu, Seoul 03080, Korea.
E-mail: moisa@snu.ac.kr

ORCID iDs
Jee Hyun Kim
https://orcid.org/0000-0003-1336-3620
Seock-Ah Im
https://orcid.org/0000-0002-5396-6533
Sung Hoon Sim
https://orcid.org/0000-0002-1503-1075
Eustratios Bananis
https://orcid.org/0000-0001-6553-7114
Xin Huang
https://orcid.org/0000-0003-3285-365X
Hyun Seon Kim
https://orcid.org/0000-0003-4844-5175
Sung-Bae Kim
https://orcid.org/0000-0001-5588-8332

ABSTRACT

In the PALOMA-3 trial, the median progression-free survival (PFS) was longer among patients with hormone receptor-positive (HR+)/human epidermal growth factor receptor 2-negative (HER2−) advanced breast cancer (ABC) treated with palbociclib plus fulvestrant than those treated with placebo plus fulvestrant. This subgroup analysis examined the efficacy and safety of palbociclib among Korean patients enrolled in PALOMA-3 (n = 43 [palbociclib group, n = 24; placebo group, n = 19]). In both groups, > 40% of patients were pre/perimenopausal at enrollment. The median PFS was significantly prolonged with palbociclib vs. placebo (12.3 [95% confidence interval (CI), 9.1–not estimable] vs. 5.4 months [95% CI, 1.9–9.2]; hazard ratio, 0.40 [95% CI, 0.19–0.83]; one-sided $p = 0.005$), and the confirmed objective response was 21.1% and 11.8%, respectively (odds ratio, 2.0 [95% CI, 0.24–24.8]). Neutropenia was the most common adverse event associated with palbociclib. Overall, palbociclib plus fulvestrant was effective and generally safe among Korean patients with HR+/HER2− ABC, regardless of menopausal status.

Keywords: Breast neoplasms; Fulvestrant; Korea; Palbociclib, Progression-free survival

In 2017, the age-standardized incidence rate of breast cancer in Korea was 55.6 per 100,000 women, with an age-standardized mortality rate of 5.5 per 100,000 women [1]. In addition, 46.5% of newly diagnosed breast cancer patients in Korea in 2015 were premenopausal [2,3]. According to the 8th Korean Clinical Practice Guidelines for Breast Cancer, the addition of a cyclin-dependent kinase 4/6 (CDK4/6) inhibitor to endocrine therapy is the preferred treatment for pre- and postmenopausal women with hormone receptor-positive/human epidermal growth factor receptor 2-negative (HR+/HER2−) advanced breast cancer

Data Availability

Upon request, and subject to certain criteria, conditions, and exceptions (see https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information), Pfizer will provide access to individual de-identified participant data from Pfizer-sponsored global interventional clinical studies conducted for medicines, vaccines, and medical devices (1) for indications that have been approved in the US and/or EU or (2) in programs that have been terminated (i.e., development for all indications has been discontinued). Pfizer will also consider requests for the protocol, data dictionary, and statistical analysis plan. Data may be requested from Pfizer trials 24 months after study completion. The de-identified participant data will be made available to researchers whose proposals meet the research criteria and other conditions, and for which an exception does not apply, via a secure portal. To gain access, data requestors must enter into a data access agreement with Pfizer.

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Author Contributions

Conceptualization: Kim JH, Sim SH, Bananis E, Kim HS; Data curation: Huang X, Kim SB; Formal analysis: Huang X; Methodology: Huang X; Writing - original draft: Kim JH; Writing - review & editing: Kim JH, Im SA, Sim SH, Bananis E, Huang X, Kim HS, Kim SB.

(ABC) [4]. Palbociclib was the first CDK4/6 inhibitor, in combination with letrozole in the first-line setting or fulvestrant in the second and later line settings, to be approved in many countries, including Korea [5-7]. Although accumulating evidence indicates that palbociclib has comparable clinical benefit in Asian and non-Asian patients [8,9], guideline for its use in Asian women remains unclear due to the limited clinical data [10].

The phase 3 PALOMA-3 trial showed significant improvement in progression-free survival (PFS) in the palbociclib plus fulvestrant group versus the placebo plus fulvestrant group in pre/perimenopausal and postmenopausal women with HR+/HER2− ABC, who had progressed on prior endocrine therapy [11,12]. The efficacy and safety of palbociclib in the Asian population of PALOMA-3 have previously been described. However, limited data exist on the use of palbociclib plus fulvestrant in patients from Korea with HR+/HER2− ABC as this combination was not covered by health insurance until after June 1, 2020. The aim of this study was to assess the efficacy and safety of palbociclib plus fulvestrant versus placebo plus fulvestrant among Korean patients enrolled in PALOMA-3 who had progressed after receiving prior endocrine therapy.

PALOMA-3 was a phase 3, international, multicenter, randomized, double-blind, placebo-controlled clinical study (NCT01942135); study design and inclusion/exclusion criteria were described previously [12]. The study was approved by an institutional review board or independent ethics committee at each study site and conducted according to the International Ethical Guidelines for Biomedical Research Involving Human Subjects, Guidelines for Good Clinical Practice, and the Declaration of Helsinki. All patients provided written informed consent. The efficacy and safety of palbociclib plus fulvestrant (AstraZeneca, Wilmington, USA) compared to that of placebo plus fulvestrant was analyzed among patients from Korea and the Asia-Pacific region (inclusive of Korea, Australia, Japan, and Taiwan). Patients were randomized 2:1 to receive palbociclib (125 mg) orally once daily (for 21 days followed by 7 days off treatment for each 28-day cycle [3 weeks on/1 week off schedule]) and fulvestrant (500 mg) intramuscularly (every 14 days for the first three injections and then every 28 days) or matching placebo and fulvestrant. Pre- and perimenopausal women received goserelin or a luteinizing hormone-releasing hormone (LHRH) agonist ≥ 4 weeks before randomization. If patients had not received goserelin as their LHRH before study enrollment, they were switched to goserelin for the duration of the study.

All outcomes were based on radiologic assessments of tumor burden and on the local radiologist's or investigator's assessment. Median PFS was defined as the time from randomization to the date of first documentation of objective progression of disease (PD) or death due to any cause in the absence of documented PD, whichever occurred first. Objective response (OR) was analyzed among patients with measurable baseline disease and was defined as a complete response (CR) or partial response (PR) according to RECIST v.1.1 from randomization until disease progression or death due to any cause. Clinical benefit response (CBR) was defined as CR, PR, or stable disease (SD) ≥ 24 weeks according to the RECIST v.1.1 between randomization and disease progression or death due to any cause. Adverse events (AEs) were classified using Medical Dictionary for Regulatory Activities (MedDRA) v.17.1; severity of the toxicities was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events v4.0. AEs were summarized by treatment and frequency of patients experiencing treatment-emergent AEs (TEAEs) corresponding to body systems and MedDRA preferred term.

A data cutoff date of October 23, 2015, was used for PFS, best overall tumor response, and safety analyses. A data cutoff date of April 13, 2018, was used for subsequent systemic anticancer therapy analyses. The intent-to-treat population included all randomized patients; patient characteristics, efficacy endpoints, and subsequent systemic anticancer treatments were evaluated in this population. The as-treated population included all patients who received ≥ 1 dose of study treatment; treatment administration and safety were evaluated in this population. The Kaplan-Meier method was used to estimate median PFS. The Cox proportional hazards model was used to compute the hazard ratio and corresponding 95% confidence interval (CI). Odds ratios and the corresponding 95% CI were calculated using the exact Clopper-Pearson method.

A total of 114 patients from the Asia-Pacific region were treated in the PALOMA-3 trial (palbociclib plus fulvestrant group, n = 78; placebo plus fulvestrant group, n = 36; **Table 1**). Among the 43 patients from Korea, 24 received palbociclib plus fulvestrant, and 19 received placebo plus fulvestrant. A total of 32 (74.4%) Korean patients discontinued the study; 15 (62.5%) patients in the palbociclib group and 16 (84.2%) in the placebo group permanently discontinued due to objective disease progression or relapse, and one (4.2%) patient in the palbociclib group discontinued due to an AE. The median age of patients in the Korean cohort was 51.5 years in the palbociclib group, and 49.0 years in the placebo group, which was younger than the median age in the overall PALOMA-3 population (palbociclib group, 57.0 years; placebo group, 56.0 years) [12]. In both treatment groups, more than 40% of Korean patients were pre/perimenopausal at baseline. The median weight was similar among Korean patients regardless of treatment assignment (palbociclib group, 54.8 kg; placebo group, 55.7 kg), but was lower than that of the overall PALOMA-3 study population (palbociclib group, 67.2 kg; placebo group, 69.8 kg). The majority of Korean patients in each treatment group had documented sensitivity to prior hormone therapy (> 75%).

In Korean patients, the median PFS was significantly longer with palbociclib plus fulvestrant than with placebo plus fulvestrant (12.3 months [95% CI, 9.1–not estimable (NE)] vs. 5.4 months [95% CI, 1.9–9.2]; hazard ratio, 0.40 [95% CI, 0.19–0.83]; one-sided $p = 0.005$; **Figure 1**). Among the 114 Asian-Pacific patients, median PFS was 12.9 (95% CI, 9.2–15.5) and 5.8 months (95% CI, 3.6–9.2) in the palbociclib and placebo groups, respectively (hazard ratio, 0.51 [95% CI, 0.32–0.82]; **Figure 1**). Due to the large number of pre/perimenopausal patients in the Korean subgroup, median PFS was analyzed according to menopausal status. Among 18 pre/perimenopausal Korean patients, median PFS was not reached in the palbociclib plus fulvestrant group (95% CI, 5.8–NE) and was 5.3 months (95% CI, 0.9–11.3) in the placebo plus fulvestrant group (hazard ratio, 0.25 [95% CI, 0.08–0.83]; **Figure 2**). Among 25 postmenopausal Korean patients, the median PFS was 10.4 (95% CI, 2.1–NE) and 5.4 months (95% CI, 1.9–9.2) in the palbociclib and placebo groups, respectively (hazard ratio, 0.58 [95% CI, 0.23–1.49]; **Figure 2**). In the pre/perimenopausal cohort (n = 43) of Asian-Pacific patients, the median PFS was longer with palbociclib plus fulvestrant than with placebo plus fulvestrant (13.6 months [95% CI, 9.2–NE] vs. 8.2 months [95% CI, 1.7–11.3]; hazard ratio, 0.38 [95% CI, 0.17–0.83]; **Figure 2**). Among postmenopausal Asian-Pacific patients (n = 71), median PFS was 11.3 (95% CI, 5.6–16.6) and 5.5 months (95% CI, 3.6–8.5) in the palbociclib plus fulvestrant and placebo plus fulvestrant groups, respectively (hazard ratio, 0.64 [95% CI, 0.35–1.16]; **Figure 2**).

The confirmed OR rate (CR + PR) was 21.1% (95% CI, 6.1–45.6) among Korean patients with measurable disease at baseline who received palbociclib plus fulvestrant (n = 19) and 11.8% (95% CI, 1.5–36.4) among those who received placebo plus fulvestrant (n = 17; odds ratio, 2.0

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Table 1. Demographic and baseline characteristics (intent-to-treat population)

Characteristic	Korean patients		Asian-Pacific patients	
	Palbociclib + fulvestrant (n = 24)	Placebo + fulvestrant (n = 19)	Palbociclib + fulvestrant (n = 78)	Placebo + fulvestrant (n = 36)
Age (yr)				
< 65	22 (91.7)	16 (84.2)	67 (85.9)	28 (77.8)
≥ 65	2 (8.3)	3 (15.8)	11 (14.1)	8 (22.2)
Median (range)	51.5 (36–79)	49.0 (39–72)	53.0 (33–79)	51.0 (39–80)
Race				
Asian	24 (100)	19 (100)	58 (74.4)	28 (77.8)
White	0	0	18 (23.1)	8 (22.2)
Other	0	0	2 (2.6)	0
Weight (kg)				
Median (range)	54.8 (35.6–73.5)	55.7 (35.1–71.2)	57.8 (35.6–116.1)	57.3 (35.1–117.3)
Height (cm)				
Median (range)	156.3 (139.8–166.0)	157.1 (151.4–174.0)	156.8 (139.8–174.0)	157.0 (145.1–174.0)
Pre/perimenopausal	10 (41.7)	8 (42.1)	31 (39.7)	12 (33.3)
Postmenopausal	14 (58.3)	11 (57.9)	47 (60.3)	24 (66.7)
Involved disease sites*				
Bone	18 (75.0)	12 (63.2)	60 (76.9)	23 (63.9)
Lymph node	9 (37.5)	9 (47.4)	27 (34.6)	14 (38.9)
Liver	7 (29.2)	8 (42.1)	29 (37.2)	18 (50.0)
Breast	7 (29.2)	2 (10.5)	20 (25.6)	6 (16.7)
Lung	6 (25.0)	3 (15.8)	20 (25.6)	7 (19.4)
Other	6 (25.0)	12 (63.2)	13 (16.7)	19 (52.8)
Visceral metastases at baseline	12 (50.0)	11 (57.9)	41 (52.6)	24 (66.7)
No. involved sites*				
1	10 (41.7)	5 (26.3)	27 (34.6)	11 (30.6)
2	6 (25.0)	7 (36.8)	24 (30.8)	12 (33.3)
3	3 (12.5)	3 (15.8)	12 (15.4)	6 (16.7)
> 3	5 (20.8)	4 (21.1)	14 (17.9)	7 (19.4)
Not reported	0	0	1 (1.3)	0
Prior surgery	19 (79.2)	16 (84.2)	63 (80.8)	30 (83.3)
Prior radiotherapy	18 (75.0)	11 (57.9)	49 (62.8)	24 (66.7)
Prior systemic therapies				
1	4 (16.7)	3 (15.8)	17 (21.8)	7 (19.4)
2	9 (37.5)	6 (31.6)	27 (34.6)	12 (33.3)
3	5 (20.8)	6 (31.6)	18 (23.1)	8 (22.2)
> 3	6 (25.0)	4 (21.1)	16 (20.5)	9 (25.0)
Prior hormone therapy lines				
1	5 (20.8)	5 (26.3)	23 (29.5)	11 (30.6)
> 1	19 (79.2)	14 (73.7)	55 (70.5)	25 (69.4)
Prior chemotherapy	19 (79.2)	17 (89.5)	54 (69.2)	26 (72.2)
For advanced/metastatic disease†	6 (25.0)	12 (63.2)	19 (24.4)	15 (41.7)
Prior tamoxifen or tamoxifen citrate	17 (70.8)	16 (84.2)	2 (2.6)‡	1 (2.8)‡
Prior aromatase inhibitors§	18 (75.0)	14 (73.7)	6 (7.7)¶	3 (8.3)¶
Documented sensitivity to prior hormone therapy	18 (75.0)	17 (89.5)	62 (79.5)	31 (86.1)

Values are presented as number (%).
*Involved sites include both target and nontarget sites. Sites with multiple lesions are counted once; †Chemotherapies reported as "palliative" oncology treatment type are classified as "advanced/metastatic."; ‡Data representative of Asian-Pacific patients who received tamoxifen or tamoxifen citrate only; §Aromatase inhibitors included anastrozole, letrozole, and exemestane; ¶Data representative of Asian-Pacific patients who received aromatase inhibitors only.

[95% CI, 0.24–24.8]). Similar results were observed in Asian-Pacific patients, with a confirmed OR rate of 21.7% (95% CI, 12.1–34.2) and 12.1% (95% CI, 3.4–28.2) in the palbociclib (n = 60) and placebo (n = 33) groups, respectively (odds ratio, 2.0 [95% CI, 0.55–9.19]). The CBR rate (SD ≥ 24 weeks or CR + PR) for the palbociclib and placebo groups was 78.9% (95% CI, 54.4–93.9) and 35.3% (95% CI, 14.2–61.7), respectively, among Korean patients (odds ratio, 6.9 [95% CI, 1.3–40.3]), whereas among Asian-Pacific patients it was 65.0% (95% CI, 51.6–76.9) and 45.5% (95% CI, 28.1–63.6), respectively (odds ratio, 2.2 [95% CI, 0.86–5.8]).

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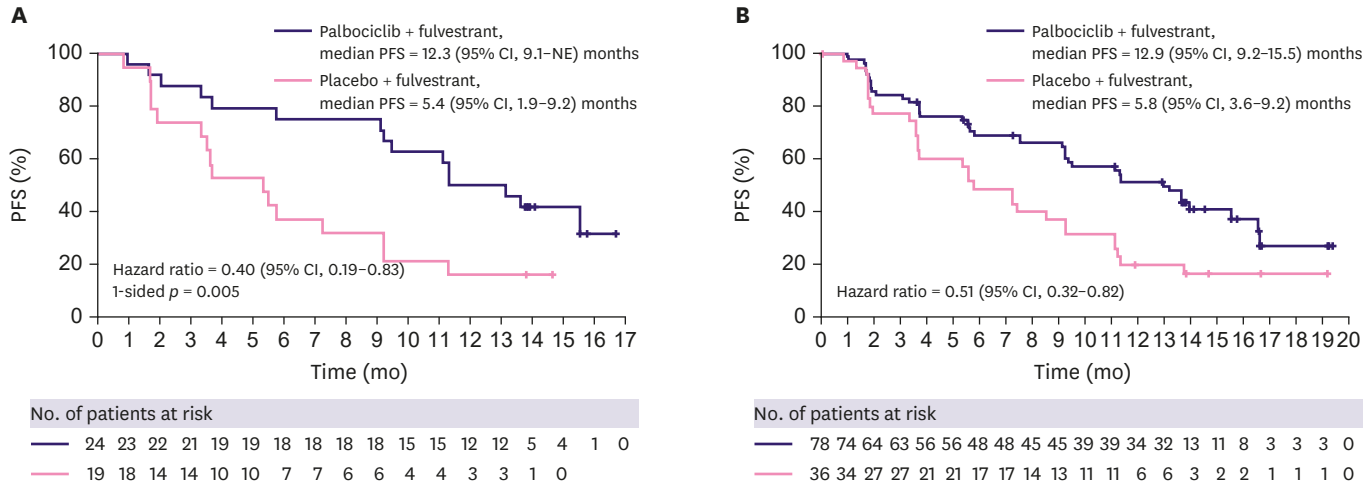

Figure 1. Investigator-assessed PFS among (A) Korean patients and (B) Asian-Pacific patients (intent-to-treat population).
NE = not estimable; PFS = progression-free survival; CI = confidence interval.

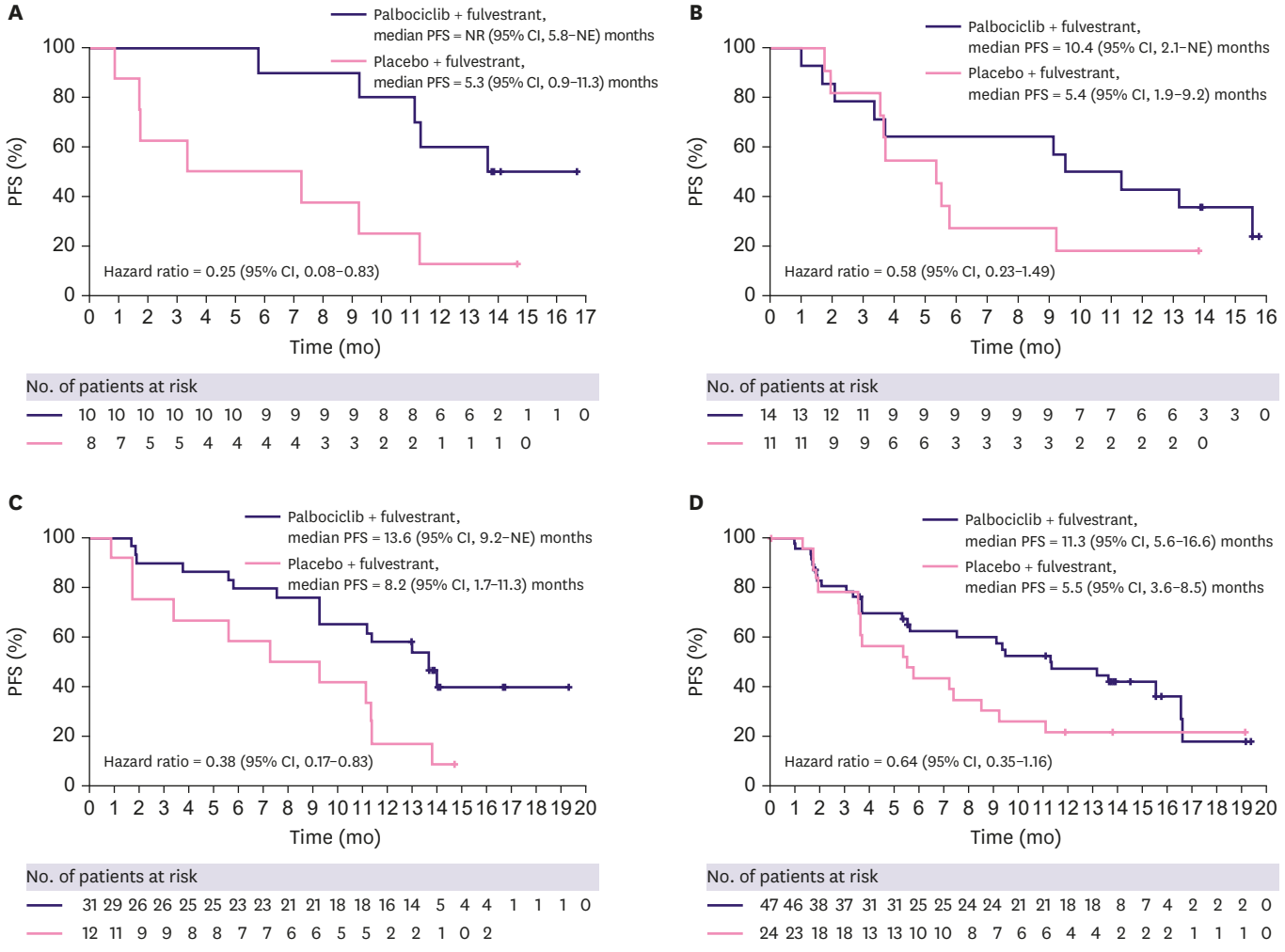

Figure 2. Investigator-assessed progression-free survival among (A) pre/perimenopausal Korean patients, (B) postmenopausal Korean patients, (C) pre/perimenopausal Asian-Pacific patients and (D) postmenopausal Asian-Pacific patients.
PFS = progression-free survival; CI = confidence interval; NE = not estimable.

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The median duration of treatment in Korean patients was 11.2 months (range, < 1–17.8 months) among those who received palbociclib plus fulvestrant and 5.3 months (range, < 1–15.3 months) among those who received placebo plus fulvestrant. The relative dose intensity of palbociclib was similar in the Korean (88.3% [range, 66.0%–100.0%]) and Asian-Pacific populations (86.5% [range, 22.0%–102.0%]). A total of 14 Korean patients (58.3%) had at least one palbociclib dose reduction. In the palbociclib plus fulvestrant group, 13 (54.2%) Korean patients experienced a dose reduction due to a TEAE, while 24/24 (100.0%) patients experienced a dose interruption due to a TEAE. In the placebo plus fulvestrant group, three (15.8%) patients experienced a dose interruption due to a TEAE, and no patient had a dose reduction; one Korean patient permanently discontinued the treatment owing to a suicide attempt. In general, the safety profile among Korean patients was similar to that of Asian-Pacific patients (**Table 2**). In Korean and Asian-Pacific patients, neutropenia was the most common TEAE (95.8% and 94.8%, respectively) and grade 3/4 TEAE (95.8% and 90.9%) was noted in the palbociclib plus fulvestrant group. Febrile neutropenia was observed in 1 Korean patient and 2 Asian-Pacific patients treated with palbociclib plus fulvestrant.

Table 2. All-causality treatment-emergent adverse events that occurred in ≥ 15% of Korean or Asian-Pacific patients in either treatment arm (AT population)

AE	Korean patients						Asian-Pacific patients					
	Palbociclib + fulvestrant (n = 24)			Placebo + fulvestrant (n = 19)			Palbociclib + fulvestrant (n = 77)			Placebo + fulvestrant (n = 36)		
	Any grade	Grade 3	Grade 4	Any grade	Grade 3	Grade 4	Any grade	Grade 3	Grade 4	Any grade	Grade 3	Grade 4
Patients with any AE	24 (100.0)	18 (75.0)	5 (20.8)	17 (89.5)	3 (15.8)	0	77 (100.0)	56 (72.7)	18 (23.4)	33 (91.7)	8 (22.2)	0
Neutropenia*	23 (95.8)	19 (79.2)	4 (16.7)	0	0	0	73 (94.8)	54 (70.1)	16 (20.8)	3 (8.3)	0	0
Rash†	9 (37.5)	0	0	0	0	0	21 (27.3)	1 (1.3)	0	1 (2.8)	0	0
Stomatitis‡	9 (37.5)	0	0	1 (5.3)	0	0	30 (39.0)	0	0	4 (11.1)	0	0
Leukopenia§	8 (33.3)	8 (33.3)	0	0	0	0	44 (57.1)	30 (39.0)	1 (1.3)	3 (8.3)	0	0
Cough	7 (29.2)	0	0	2 (10.5)	0	0	12 (15.6)	0	0	2 (5.6)	0	0
Decreased appetite	7 (29.2)	0	0	0	0	0	14 (18.2)	0	0	1 (2.8)	1 (2.8)	0
Infections¶	7 (29.2)	1 (4.2)	0	3 (15.8)	0	0	36 (46.8)	2 (2.6)	0	13 (36.1)	1 (2.8)	0
Nausea	7 (29.2)	0	0	3 (15.8)	0	0	24 (31.2)	0	0	8 (22.2)	0	0
Anemia**	6 (25.0)	0	0	1 (5.3)	1 (5.3)	0	19 (24.7)	3 (3.9)	0	4 (11.1)	2 (5.6)	0
Diarrhea	6 (25.0)	0	0	3 (15.8)	0	0	18 (23.4)	0	0	5 (13.9)	1 (2.8)	0
Fatigue	6 (25.0)	0	0	3 (15.8)	0	0	27 (35.1)	1 (1.3)	0	6 (16.7)	0	0
Headache	6 (25.0)	0	0	3 (15.8)	0	0	15 (19.5)	0	0	7 (19.4)	0	0
Alopecia	5 (20.8)	0	0	0	0	0	13 (16.9)	0	0	1 (2.8)	0	0
Asthenia	5 (20.8)	0	0	0	0	0	6 (7.8)	0	0	0	0	0
Insomnia	5 (20.8)	0	0	2 (10.5)	0	0	7 (9.1)	0	0	3 (8.3)	0	0
Musculoskeletal pain	5 (20.8)	0	0	0	0	0	9 (11.7)	0	0	0	0	0
Pruritus	5 (20.8)	0	0	2 (10.5)	0	0	6 (7.8)	0	0	3 (8.3)	0	0
Constipation	4 (16.7)	0	0	2 (10.5)	0	0	12 (15.6)	0	0	5 (13.9)	0	0
Dyspepsia	4 (16.7)	0	0	2 (10.5)	0	0	4 (5.2)	0	0	2 (5.6)	0	0
Pyrexia	4 (16.7)	0	0	0	0	0	13 (16.9)	0	0	1 (2.8)	0	0
Upper respiratory tract infection	4 (16.7)	1 (4.2)	0	0	0	0	11 (14.3)	1 (1.3)	0	1 (2.8)	0	0
Abdominal pain	3 (12.5)	0	0	2 (10.5)	0	0	4 (5.2)	0	0	3 (8.3)	0	0
Thrombocytopenia††	3 (12.5)	1 (4.2)	0	0	0	0	19 (24.7)	1 (1.3)	0	0	0	0
Vomiting	3 (12.5)	2 (8.3)	0	0	0	0	13 (16.9)	2 (2.6)	0	3 (8.3)	0	0
Abdominal pain upper	1 (4.2)	0	0	3 (15.8)	0	0	4 (5.2)	1 (1.3)	0	4 (11.1)	0	0
Injection site pain	1 (4.2)	0	0	3 (15.8)	0	0	3 (3.9)	0	0	5 (13.9)	0	0
Nasopharyngitis	1 (4.2)	0	0	1 (5.3)	0	0	15 (19.5)	0	0	4 (11.1)	0	0
Pain	1 (4.2)	0	0	1 (5.3)	0	0	1 (1.3)	0	0	5 (13.9)	1 (2.8)	0

Values are presented as number (%).
AE = adverse event; AT = as-treated.
*Neutropenia includes the following Preferred Terms: Neutropenia, Neutrophil count decreased; †Rash includes the following Preferred Terms: Dermatitis, Dermatitis acneiform, Rash, Rash erythematous, Rash maculopapular, Rash papular, Rash pruritic, Toxic skin eruption; ‡Stomatitis includes the following Preferred Terms: Aphthous stomatitis, Cheilitis, Glossitis, Glossodynia, Mouth ulceration, Mucosal inflammation, Oral pain, Oropharyngeal discomfort, Oropharyngeal pain, Stomatitis; §Leukopenia includes the following Preferred Terms: Leukopenia, White blood cell count decreased; ¶Infections includes the following Preferred Terms: any event having a Preferred Term part of the System Organ Class Infections and infestations; **Anemia includes the following Preferred Terms: Anemia, Hematocrit decreased, Hemoglobin decreased; ††Thrombocytopenia includes the following Preferred Terms: Platelet count decreased, Thrombocytopenia.

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In the palbociclib and placebo groups, 19 (79.2%) and 16 (84.2%) Korean patients, respectively, received at least one subsequent anticancer therapy. Among patients treated with palbociclib plus fulvestrant, 13 (54.2%) patients received two subsequent anticancer therapies and 8 (33.3%) received three subsequent anticancer therapies. In the placebo group, 15 (78.9%) and 13 (68.4%) patients received two and three subsequent anticancer therapies, respectively. The majority of patients in each group received chemotherapy as a first subsequent anticancer treatment (palbociclib group, n = 12 [63.2%]; placebo group, n = 9 [56.3%]). Among patients who received antihormonal therapy as a first subsequent anticancer treatment (n = 6 in each treatment group), 4 patients (66.7%) in the palbociclib group and 6 patients (100.0%) in the placebo group received exemestane in combination with everolimus.

Similar to the results from the overall population of PALOMA-3, palbociclib plus fulvestrant was an effective treatment in Korean patients with HR+/HER2− ABC who progressed following prior endocrine therapy [13]. In this patient cohort, the median PFS was significantly prolonged in the palbociclib plus fulvestrant group compared to that in the placebo plus fulvestrant group, regardless of menopausal status, and the confirmed OR rate was greater with palbociclib combination treatment (21.1% vs. 11.8%). The CBR rate among patients in the palbociclib group was more than double of that observed in the placebo group (78.9% vs. 35.3%). Palbociclib plus fulvestrant was well tolerated, with neutropenia being the most frequently reported TEAE. Additionally, the efficacy and safety profile of palbociclib in Korean patients was consistent with that observed in the Asian-Pacific population.

Overall, Korean patients from PALOMA-3 were heavily pretreated. The majority of patients in either treatment group received prior chemotherapy (palbociclib group, 79.2%; placebo group, 89.5%) and had > 1 prior line of hormone therapy (palbociclib group, 79.2%; placebo group, 73.7%). Additionally, the majority of Korean patients had sensitivity to prior endocrine therapy. Recent subgroup analyses of PALOMA-3 showed that overall survival (OS) among patients with sensitivity to previous endocrine therapy was 10 months longer in the palbociclib plus fulvestrant group than that in the placebo plus fulvestrant group [14]. Additional subgroup analyses of PALOMA-3 suggest that endocrine sensitivity and the lack of prior chemotherapy for ABC are prognostic factors for OS [15].

The efficacy and safety results observed in Korean patients are generally similar to those observed in the overall population and in subgroup analyses of Japanese and Asian patients from PALOMA-3 [9,11,13,16]. The relative dose intensity for palbociclib was 88.3% in the Korean population and 91.7% in the overall population. In both populations, neutropenia was the most common TEAE with palbociclib therapy, although a higher percentage of Korean patients experienced any grade (95.8% and 80.9%) and grade 3/4 neutropenia (95.8% and 64.3%) than the overall PALOMA-3 population [13]. Palbociclib-associated neutropenia has been previously shown to be manageable by dose modification with no negative impact on efficacy [8,17-20].

A notable difference between the Korean subgroup and the overall population of PALOMA-3 is the percentage of pre/perimenopausal women at study entry. In general, the percentage of premenopausal women with breast cancer is higher among Asian patients than among non-Asian patients. In the Korean population, 41.7% and 42.1% of patients were pre/perimenopausal at baseline in the palbociclib and placebo groups, respectively; whereas in the overall population of PALOMA-3, 20.7% of patients in both treatment groups were pre/

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perimenopausal [12]. The median PFS among pre/perimenopausal women in the overall and Korean population of PALOMA-3 was significantly longer in the palbociclib group than that in the placebo group, suggesting that palbociclib combination therapy was an effective option in this patient subgroup. In a subgroup analysis of the overall population, palbociclib plus fulvestrant was also effective in pre/perimenopausal patients with prior sensitivity to endocrine therapy (OS: 48.3 vs. 34.6 months; HR, 0.73 [95% CI, 0.37–1.46]; PFS: 13.6 vs. 5.6 months; HR, 0.38 [95% CI, 0.21–0.68]) [15].

In summary, palbociclib plus fulvestrant was an effective and generally safe treatment option in Korean patients with HR+/HER2− ABC whose disease progressed following prior endocrine therapy. The safety profile among Korean and Asian-Pacific patients was similar to that observed in the overall population enrolled in PALOMA-3.

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REFERENCES

1. Hong S, Won YJ, Park YR, Jung KW, Kong HJ, Lee ES, et al. Cancer statistics in Korea: incidence, mortality, survival, and prevalence in 2017. Cancer Res Treat 2020;52:335-50.
PUBMED | CROSSREF
2. Kang SY, Kim YS, Kim Z, Kim HY, Lee SK, Jung KW, et al. Basic findings regarding breast cancer in Korea in 2015: data from a breast cancer registry. J Breast Cancer 2018;21:1-10.
PUBMED | CROSSREF
3. Kang SY, Kim YS, Kim Z, Kim HY, Lee SK, Jung KW, et al. Erratum: Basic findings regarding breast cancer in Korea in 2015: data from a breast cancer registry. J Breast Cancer 2019;22:153.
PUBMED | CROSSREF
4. Korean Breast Cancer Society. The 8th Korean Clinical Practice Guideline for Breast Cancer. Seoul: Korean Breast Cancer Society; 2019.
5. Beaver JA, Amiri-Kordestani L, Charlab R, Chen W, Palmby T, Tilley A, et al. FDA approval: palbociclib for the treatment of postmenopausal patients with estrogen receptor-positive, HER2-negative metastatic breast cancer. Clin Cancer Res 2015;21:4760-6.
PUBMED | CROSSREF
6. IBRANCE® Capsules (palbociclib). Full Prescribing Information. New York: Pfizer Inc.; 2019.
7. IBRANCE® Capsules (palbociclib) Locally Approved Prescribing Information. Seoul: Pfizer Pharmaceuticals Korea Limited; 2020.
8. Im SA, Mukai H, Park IH, Masuda N, Shimizu C, Kim SB, et al. Palbociclib plus letrozole as first-line therapy in postmenopausal Asian women with metastatic breast cancer: results from the phase III, randomized PALOMA-2 study. J Glob Oncol 2019;5:1-19.
PUBMED | CROSSREF
9. Iwata H, Im SA, Masuda N, Im YH, Inoue K, Rai Y, et al. PALOMA-3: phase III trial of fulvestrant with or without palbociclib in premenopausal and postmenopausal women with hormone receptor–positive, human epidermal growth factor receptor 2–negative metastatic breast cancer that progressed on prior endocrine therapy—safety and efficacy in Asian patients. J Glob Oncol 2017;3:289-303.
PUBMED | CROSSREF
10. Dawood S, Chiu JW, Huang CS, Nag S, Sookprasert A, Yap YS, et al. Palbociclib and beyond for the treatment of HR + HER2- metastatic breast cancer: an Asian-Pacific perspective and practical management guide on the use of CDK4/6 inhibitors. Curr Med Res Opin 2020;36:1363-73.
PUBMED | CROSSREF

11. Cristofanilli M, DeMichele A, Giorgetti C, Turner NC, Slamon DJ, Im SA, et al. Predictors of prolonged benefit from palbociclib plus fulvestrant in women with endocrine-resistant hormone receptor-positive/human epidermal growth factor receptor 2-negative metastatic breast cancer in PALOMA-3. Eur J Cancer 2018;104:21-31.
PUBMED | CROSSREF
12. Turner NC, Ro J, André F, Loi S, Verma S, Iwata H, et al. Palbociclib in hormone-receptor–positive advanced breast cancer. N Engl J Med 2015;373:209-19.
PUBMED | CROSSREF
13. Cristofanilli M, Turner NC, Bondarenko I, Ro J, Im SA, Masuda N, et al. Fulvestrant plus palbociclib versus fulvestrant plus placebo for treatment of hormone-receptor-positive, HER2-negative metastatic breast cancer that progressed on previous endocrine therapy (PALOMA-3): final analysis of the multicentre, double-blind, phase 3 randomised controlled trial. Lancet Oncol 2016;17:425-39.
PUBMED | CROSSREF
14. Turner NC, Slamon DJ, Ro J, Bondarenko I, Im SA, Masuda N, et al. Overall survival with palbociclib and fulvestrant in advanced breast cancer. N Engl J Med 2018;379:1926-36.
PUBMED | CROSSREF
15. Rugo HS, Cristofanilli M, Loibl S, Harbeck N, DeMichele A, Iwata H, et al. Prognostic factors for overall survival in patients with hormone receptor-positive/human epidermal growth factor receptor 2-negative advanced breast cancer: analyses from PALOMA-3. Ann Oncol 2020;31:S372-3.
CROSSREF
16. Masuda N, Inoue K, Nakamura R, Rai Y, Mukai H, Ohno S, et al. Palbociclib in combination with fulvestrant in patients with hormone receptor-positive, human epidermal growth factor receptor 2-negative advanced breast cancer: PALOMA-3 subgroup analysis of Japanese patients. Int J Clin Oncol 2019;24:262-73.
PUBMED | CROSSREF
17. Diéras V, Harbeck N, Joy AA, Gelmon K, Ettl J, Verma S, et al. Palbociclib with letrozole in postmenopausal women with ER+/HER2-advanced breast cancer: hematologic safety analysis of the randomized PALOMA-2 Trial. Oncologist 2019;24:1514-25.
PUBMED | CROSSREF
18. Ettl J, Im SA, Ro J, Masuda N, Colleoni M, Schnell P, et al. Hematologic adverse events following palbociclib dose reduction in patients with hormone receptor-positive/human epidermal growth factor receptor 2-negative advanced breast cancer: pooled analysis from randomized phase 2 and 3 studies. Breast Cancer Res 2020;22:27.
PUBMED | CROSSREF
19. Verma S, Bartlett CH, Schnell P, DeMichele AM, Loi S, Ro J, et al. Palbociclib in combination with fulvestrant in women with hormone receptor-positive/HER2-negative advanced metastatic breast cancer: detailed safety analysis from a multicenter, randomized, placebo-controlled, phase III study (PALOMA-3). Oncologist 2016;21:1165-75.
PUBMED | CROSSREF
20. Wilkie J, Schickli MA, Berger MJ, Lustberg M, Reinbolt R, Noonan A, et al. Progression-free survival for real-world use of palbociclib in hormone receptor-positive metastatic breast cancer. Clin Breast Cancer 2020;20:33-40.
PUBMED | CROSSREF