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Original Article

Implications of Tamoxifen Resistance in Palbociclib Efficacy for Patients with Hormone Receptor–Positive, HER2-Negative Metastatic Breast Cancer: Subgroup Analyses of KCSG-BR15-10 (YoungPEARL)

Jiyun Lee[1], **Seock-Ah Im**[2], **Gun Min Kim**[3], **Kyung Hae Jung**[4], **Seok Yun Kang**[5], **In Hae Park**[6], **Jee Hyun Kim**[7], **Hee Kyung Ahn**[8], **Yeon Hee Park**[1]

[1]*Division of Hematology-Oncology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul,* [2]*Department of Internal Medicine, Seoul National University Hospital, Cancer Research Institute, Seoul National University College of Medicine, Seoul,* [3]*Division of Medical Oncology, Department of Internal Medicine, Yonsei University College of Medicine, Seoul,* [4]*Department of Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul,* [5]*Department of Hematology-Oncology, Ajou University School of Medicine, Suwon,* [6]*Center for Breast Cancer, National Cancer Center, Goyang,* [7]*Department of Internal Medicine, Seoul National University Bundang Hospital, Seoul National University College of Medicine, Seongnam,* [8]*Division of Medical Oncology, Department of Internal Medicine, Gachon University Gil Medical Center, Incheon, Korea*

Purpose YoungPEARL (KCSG-BR15-10) trial demonstrated a significant progression-free survival (PFS) benefit for premenopausal patients with hormone receptor–positive/human epidermal growth factor receptor 2–negative (HR+/HER2–) metastatic breast cancer (MBC) for palbociclib plus exemestane with ovarian function suppression compared to capecitabine. However, the number of tamoxifen-sensitive premenopausal patients was small because most recurrences occurred early during adjuvant endocrine therapy (ET), with tamoxifen being the only drug used; hence, the data for these patients were limited. Here we present a subgroup analysis according to tamoxifen sensitivity from the YoungPEARL study.

Materials and Methods Patients were randomized 1:1 to receive palbociclib+ET (oral exemestane 25 mg/day for 28 days, palbociclib 125 mg/day for 21 days, plus leuprolide 3.75 mg subcutaneously every 4 weeks) or chemotherapy (oral capecitabine 1,250 mg/m^2 twice daily for 14 days every 3 weeks). Tamoxifen resistance was defined as: relapse while on adjuvant tamoxifen, relapse within 12 months of completing adjuvant tamoxifen, or progression while on first-line tamoxifen within 6 months for MBC.

Results In total, 184 patients were randomized and 178 were included in the modified intention-to-treat population. PFS improvement in the palbociclib+ET group was observed in tamoxifen-sensitive patients (hazard ratio, 0.38; 95% confidence interval, 0.12 to 1.19). Furthermore, palbociclib+ET prolonged median PFS compared with capecitabine in tamoxifen-sensitive (20.5 months vs. 12.6 months) and tamoxifen-resistant (20.1 months vs. 14.5 months) patients. Palbociclib+ET demonstrated a higher rate of objective response, disease control, and clinical benefit in tamoxifen-sensitive patients.

Conclusion This *post hoc* exploratory analysis suggests that palbociclib+ET is a promising therapeutic option for premenopausal HR+/HER2– MBC patients irrespective of tamoxifen sensitivity.

Key words Breast neoplasms, Tamoxifen, CDK4/6 inhibitor, Palbociclib, Endocrine therapy

Introduction

CDK4/6 inhibitors in combination with endocrine therapy have become the standard of treatment for patients with hormone receptor–positive/human epidermal growth factor receptor 2–negative (HR+/HER2–) metastatic breast cancer (MBC) [1-3]. Palbociclib, a first-in-class CDK4/6 inhibitor, demonstrated anticancer activity in preclinical tests and has been approved for the treatment of patients with HR+/HER2– MBC in combination with endocrine therapy [4,5]. The YoungPEARL (KCSG-BR15-10, NCT02592746) trial demonstrated the efficacy and safety of palbociclib plus exemestane with gonadotropin-releasing hormone (GnRH) agonist in premenopausal patients with HR+/HER2– MBC, who have been pretreated with tamoxifen [6]. Progression-free survival (PFS) was significantly longer for patients in the palbociclib arm compared to those in the capecitabine arm (median PFS, 20.1 months vs. 14.4 months; hazard ratio [HR], 0.66; 95% confidence interval [CI], 0.44 to 0.99; p=0.024).

Despite the current clinical guidelines which recommend endocrine therapy as the standard treatment of choice for patients with HR+/HER2– MBC, the treatment patterns have differed in South Korea: for premenopausal women, the availability of endocrine therapies apart from tamoxifen and

Correspondence: Yeon Hee Park
Division of Hematology-Oncology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, 81 Irwon-ro, Gangnam-gu, Seoul 06351, Korea
Tel: 82-2-3410-1780 Fax: 82-2-3410-1754 E-mail: yeonh.park@samsung.com
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Table 1. Baseline characteristics

Variable	ITT population		Tamoxifen sensitive (n=25)[a]		Tamoxifen resistant (n=153)	
	Palbociclib plus ET group (n=92)	Capecitabine group (n=86)	Palbociclib plus ET group (n=16)	Capecitabine group (n=9)	Palbociclib plus ET group (n=76)	Capecitabine group (n=77)
Age, median (yr)	44	44	48	46	43	44
Hormone receptor status						
ER+/PR+	70 (76.1)	64 (74.4)	14 (87.5)	8 (88.9)	56 (73.7)	56 (72.7)
ER+/PR–	22 (23.9)	22 (25.6)	2 (12.5)	1 (11.1)	20 (26.3)	21 (27.3)
ECOG PS						
0	54 (58.7)	48 (55.8)	9 (56.3)	4 (44.4)	45 (59.2)	44 (57.1)
1-2	38 (41.3)	38 (44.2)	7 (43.7)	5 (55.6)	31 (40.8)	33 (42.9)
Disease status						
Recurrent	64 (69.6)	60 (69.8)	10 (62.5)	5 (55.6)	54 (71.1)	55 (71.4)
De-novo	28 (30.4)	26 (30.2)	6 (37.5)	4 (44.4)	22 (28.9)	22 (28.6)
Metastases site						
Visceral	45 (48.9)	43 (50.0)	6 (37.5)	6 (66.7)	39 (51.3)	37 (48.1)
Non-visceral only	47 (51.1)	43 (50.0)	10 (62.5)	3 (33.3)	37 (48.7)	40 (51.9)
No. of metastatic organs						
1	50 (54.3)	38 (44.2)	12 (75.0)	4 (44.4)	38 (50.0)	34 (44.2)
≥ 2	42 (45.7)	48 (55.8)	4 (25.0)	5 (55.6)	38 (50.0)	43 (55.8)
Previous treatment for MBC						
Yes	46 (50.0)	41 (47.7)	9 (56.3)	5 (55.6)	37 (48.7)	36 (46.8)
No	46 (50.0)	45 (52.3)	7 (43.7)	4 (44.4)	39 (51.3)	41 (53.2)
Previous CTx for MBC						
Yes	22 (23.9)	18 (20.9)	6 (37.5)	5 (55.6)	16 (21.1)	13 (16.9)
No	70 (76.1)	68 (79.1)	10 (62.5)	4 (44.4)	60 (78.9)	64 (83.1)

Values are presented as number (%). CTx, cytotoxic chemotherapy; ECOG, Eastern Cooperative Oncology Group; ER, estrogen receptor; ET, endocrine therapy; ITT, intention-to-treat; MBC, metastatic breast cancer; PR, progesterone receptor; PS, performance status. [a]Four patients in the palbociclib arm and five patients in the capecitabine arm had not received prior tamoxifen.

GnRH agonist has been limited due to poor accessibility of pharmacy and a concern for poor prognosis [7,8]. In reality, premenopausal women tended to receive cytotoxic chemotherapy rather than endocrine treatment with ovary function suppression. This non-adherence to guidelines in Korea was partially due to the aggressive biologic features, or the lack of available endocrine treatment for premenopausal women. Tamoxifen with or without the GnRH agonist has been the only endocrine therapy available until the GnRH agonist plus aromatase inhibitor became approved and reimbursed in 2017. Hence, premenopausal women who showed disease recurrence during adjuvant tamoxifen treatment had to receive cytotoxic chemotherapy, and this "tamoxifen-pretreated" population became increasingly important.

The PALOMA-2 trial, which included post-menopausal patients with HR+/HER2– breast cancer, demonstrated a favorable outcome with palbociclib plus letrozole compared to letrozole alone, despite the fact that 10% of tamoxifen-pretreated patients had primary endocrine refractory disease [4,9]. Hence, in this *post hoc* analysis, we aimed to investigate whether tamoxifen-pretreated patients from the YoungPEARL study also had favorable outcomes. We wanted to elucidate whether the efficacy of palbociclib was also applicable in premenopausal patients with HR+/HER2– MBC who were previously treated with tamoxifen.

Materials and Methods

1. Study design

The YoungPEARL study design has been previously published [6]. In brief, premenopausal women with HR+/HER2– metastatic or recurrent breast cancer, whose disease had progressed on prior tamoxifen irrespective of treatment-free interval, were randomized 1:1 to receive either palbociclib plus combination endocrine therapy (oral exemestane 25 mg/day for 28 days and oral palbociclib 125 mg/day for 21 days every 4 weeks plus leuprolide 3.75 mg subcutaneously

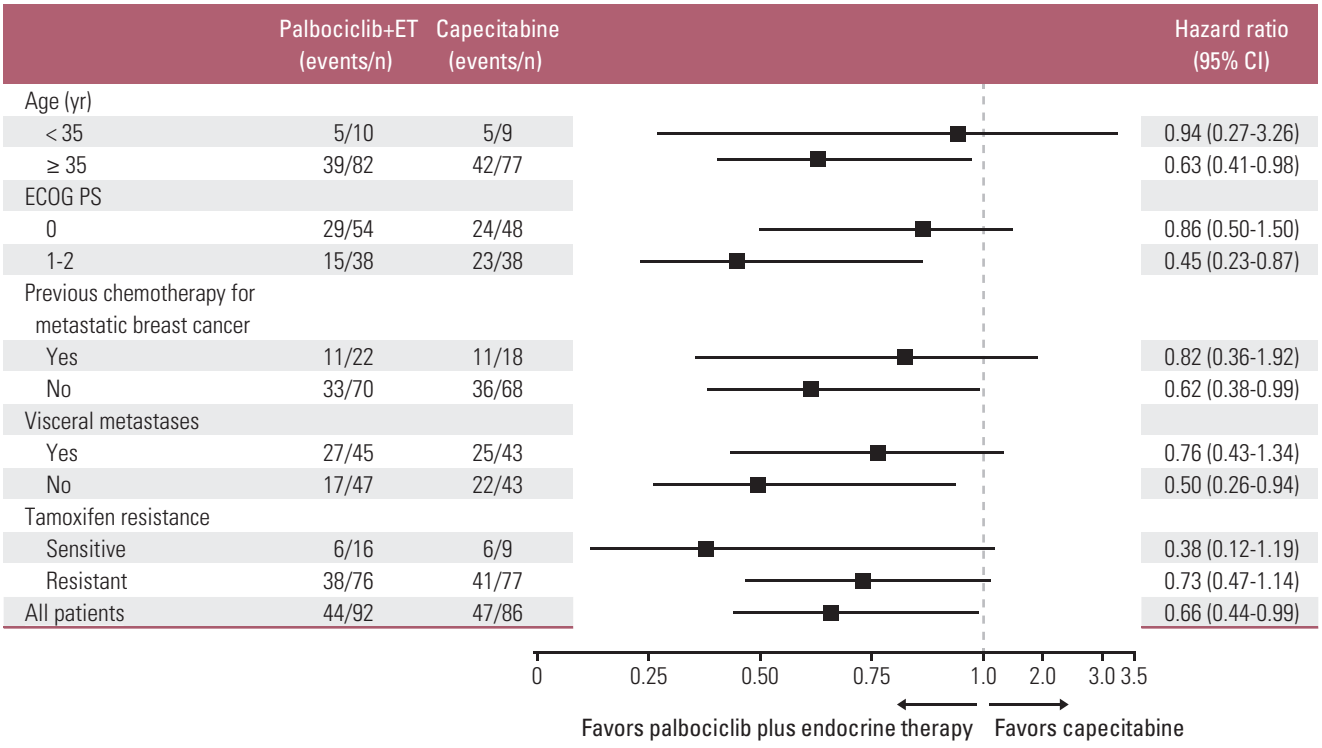

Fig. 1. Forest plot of subgroup analysis for progression-free survival. CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; ET, endocrine therapy; PS, performance status.

every 4 weeks) or chemotherapy (oral capecitabine 1,250 mg/m^2 twice daily for 2 weeks every 3 weeks).

Premenopausal status was defined as having had the most recent menstrual period within the past 12 months in any patients (irrespective of previous treatment received); for patients on tamoxifen, a period within the previous 3 months, a plasma estradiol concentration higher than 10 pg/mL, follicle-stimulating hormone (FSH) concentration of at least 40 IU/L, or plasma estradiol and FSH concentrations within the laboratory-defined premenopausal range; or in patients with chemotherapy-induced amenorrhea, a plasma estradiol concentration higher than 10 pg/mL, FSH concentration of at least 40 IU/L, or plasma estradiol and FSH concentrations within the laboratory-defined premenopausal range.

2. Outcomes and assessments

The primary endpoint of this study was investigator-assessed PFS; additional endpoints included overall survival (OS), quality of life, toxicity, the proportion of patients with objective responses, and the proportion of patients with clinical benefit, some of which have been published previously [6]. In this *post hoc* analysis, PFS was analyzed for patients with and without tamoxifen resistance in the modified intention-to-treat (ITT) population.

Tamoxifen resistance was defined as: (1) relapse while on adjuvant tamoxifen, (2) relapse within 12 months of completing adjuvant tamoxifen, or (3) progression while on first-line tamoxifen within 6 months for MBC [10]. Patients who did not match any of the criteria above were defined as tamoxifen-sensitive.

3. Statistical analyses

Descriptive statistics were used to summarize patient and treatment characteristics. PFS were calculated using the Kaplan-Meier method and compared using the log-rank test. Univariate/multivariate models for clinical characteristics in association with PFS were based on Cox proportional hazards regression analyses. Results were presented as HRs with 95% CIs. All analyses were performed using IBM SPSS Statistics ver. 25 (IBM Corp., Armonk, NY) and GraphPad Prism 6 (La Jolla, CA).

Results

1. Baseline demographic and disease characteristics

The ITT population in YoungPEARL was comprised of 178 randomized patients (palbociclib plus endocrine therapy

arm, n=92; capecitabine arm, n=86) [6]. The baseline demographic and disease characteristics were generally similar among the treatment groups (Table 1). Most of the patients in both groups who had recurrent disease had received tamoxifen as adjuvant endocrine therapy with or without a GnRH agonist. Among the 124 patients who had recurrent disease after curative surgery, we identified 12 patients and four patients from the palbociclib plus endocrine therapy arm and the capecitabine arm, respectively, who had a tamoxifen-sensitive recurrence. An additional four and five patients with tamoxifen-naïve disease were identified from the palbociclib plus endocrine therapy arm and the capecitabine arm, respectively, revealing a total of 25 patients with tamoxifen-sensitive MBC.

In the ITT population of the YoungPEARL study, the improvement in PFS in the palbociclib plus endocrine therapy group was previously observed in patients older than 35 years, in patients with worse Eastern Cooperative Oncology Group performance statuses, in those who had not previously received chemotherapy in a metastatic setting, and in those with non-visceral disease in subgroup analyses [6]. In this *post hoc* subgroup analysis, we identified a greater improvement in PFS for patients who were sensitive to tamoxifen (unstratified HR, 0.38 [95% CI, 0.12 to 1.19]; p=0.097) compared to those who were resistant to tamoxifen (unstratified HR, 0.73 [95% CI, 0.47 to 1.14]; p=0.167) (Fig. 1).

2. Efficacy in patients with/without tamoxifen-resistance

To better understand the impact of tamoxifen resistance on the PFS benefits provided by palbociclib, the duration of PFS were analyzed in subgroups of patients according to tamoxifen sensitivity. The median PFS have been previously reported in the ITT population as 20.1 months (95% CI, 14.2 to 21.8) vs. 14.4 (12.1 to 17.0) in the palbociclib plus endocrine therapy and capecitabine arms, respectively (HR, 0.66 [95% CI, 0.44 to 0.99]; p=0.024). In this *post hoc* analysis, we found no significant difference in PFS according to tamoxifen sensitivity in the ITT population, palbociclib plus endocrine therapy arm, and capecitabine arm (Fig. 2A-C). However, for the subgroup of patients who were sensitive to tamoxifen, the median PFS were 20.5 months (95% CI, not available [NA] to NA) and 12.6 (95% CI, 6.7 to 18.6) in the palbociclib plus endocrine therapy and the capecitabine arms, respectively, resulting in an absolute difference of 7.9 months in favor of palbociclib plus endocrine therapy (Fig. 2D). For tamoxifen-resistant patients, the median PFS were 20.1 months (95% CI, 14.2 to 26.0) with palbociclib plus endocrine therapy and 14.5 months (95% CI, 12.4 to 16.5) with capecitabine, resulting in an absolute difference of 5.6 months (Fig. 2D). In this exploratory analysis, the median PFS was prolonged with palbociclib plus endocrine therapy compared to capecitabine regardless of tamoxifen sensitivity. Consistently, a longer duration of response (DOR) was demonstrated in patients treated with palbociclib plus endocrine therapy compared to those treated with capecitabine for both tamoxifen-sensitive (18.9 months [95% CI, 2.6 to 35.2] vs. 6.6 [95% CI, NA to NA]) and tamoxifen-resistant groups (17.1 months [95% CI, 9.5 to 24.8] vs. 13.1 [95% CI, 6.8 to 19.5]) (Table 2).

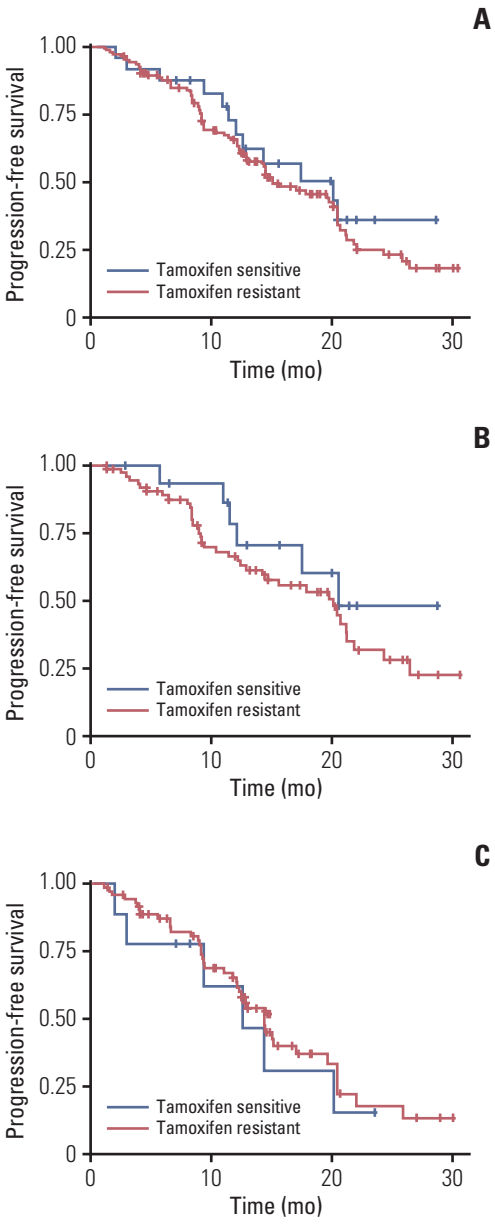

Fig. 2. Progression-free survival curves according to tamoxifen sensitivity for ITT population (20.2 months vs. 15.1 months) (A), palbociclib plus endocrine therapy arm (20.5 months vs. 20.1 months) (B), and capecitabine arm (12.6 months vs. 14.5 months) (C). *(Continued to the next page)*

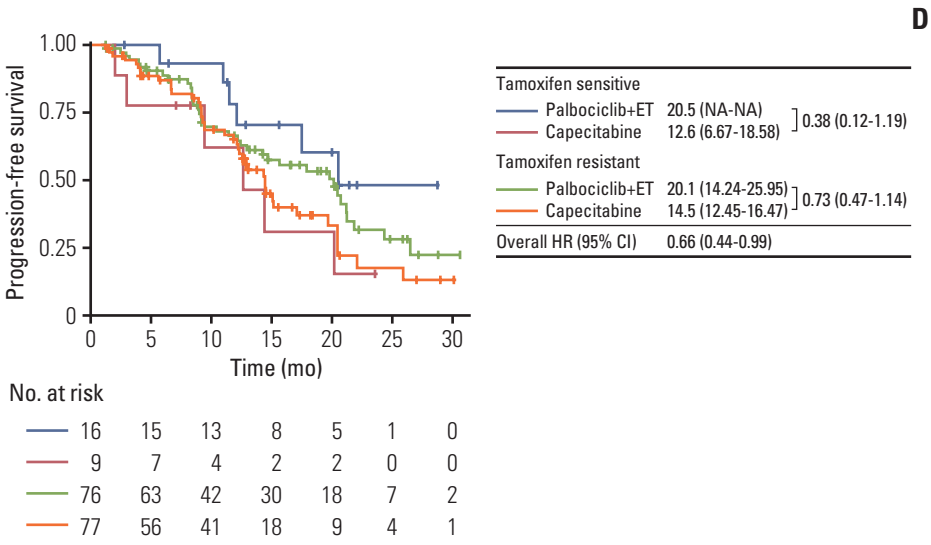

Fig. 2. *(Continued from the previous page)* (D) Progression-free survival curves according to tamoxifen sensitivity and treatment arms. CI, confidence interval; ET, endocrine therapy; HR, hazard ratio; ITT, intention-to-treat; NA, not available.

Table 2. Summary of treatment efficacy

	Tamoxifen sensitive (n=25)			Tamoxifen resistant (n=153)		
	Palbociclib plus ET group (n=16)	Capecitabine group (n=9)	p-value	Palbociclib plus ET group (n=76)	Capecitabine group (n=77)	p-value
Objective response, n (%)	7 (43.8)	2 (22.2)	0.401	27 (35.5)	27 (35.1)	> 0.99
Disease control, n (%)	16 (100)	8 (88.9)	0.360	73 (96.1)	70 (90.9)	0.717
Clinical benefit, n (%)	14 (87.5)	7 (77.8)	0.602	60 (78.9)	51 (66.2)	0.194
PFS (95% CI, mo)	20.5 (NA-NA)	12.6 (6.7-18.6)	0.086	20.1 (14.2-26.0)	14.5 (12.4-16.5)	0.164
PFS HR (95% CI)	0.38 (0.12-1.19)	-	0.097	0.73 (0.47-1.14)	-	0.167
DOR (95% CI, mo)	18.9 (2.6-35.2)	6.6 (NA-NA)	0.458	17.1 (9.5-24.8)	13.1 (6.8-19.5)	0.217
DOR HR (95% CI)	0.37 (0.02-5.86)	-	0.477	0.59 (0.25-1.39)	-	0.223

CI, confidence interval; DOR, duration of response; ET, endocrine therapy; HR, hazard ratio; NA, not applicable; PFS, progression-free survival.

In the tamoxifen-sensitive group, seven of 16 patients (43.8%) treated with palbociclib plus endocrine therapy and two of nine (22.2%) treated with capecitabine achieved an objective response; in addition, 16 of 16 (100.0%) treated with palbociclib plus endocrine therapy and eight of nine (88.9%) treated with capecitabine achieved disease control (Table 2). The proportion of patients who achieved clinical benefit were 87.5% (14 of 16) and 77.8% (7 of 9) for those treated with palbociclib plus endocrine therapy and with capecitabine, respectively. In the tamoxifen-resistant group, the proportions of patients who achieved objective response (35.5% vs. 35.1%) and disease control (96.1% vs. 90.9%) did not differ markedly between the treatment arms (Table 2).

3. Prognostic factors for PFS

Multivariate analysis was performed to identify prognostic factors associated with PFS, and we found that tamoxifen sensitivity was not associated with PFS benefit. The only factor significantly associated with favorable PFS, other than non-visceral metastases, was palbociclib plus endocrine therapy over capecitabine (multivariate HR, 0.67; 95% CI, 0.44 to 1.01; p=0.054), as demonstrated in the original YoungPEARL trial (Table 3).

Table 3. Univariate and multivariate analyses for progression-free survival

Variable	Univariate analysis		Multivariate analysis	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Age (yr)				
< 35	1		-	
≥ 35	0.92 (0.47-1.77)	0.794	-	-
ECOG PS				
0-1	1		-	
≥ 2	1.03 (0.68-1.56)	0.903	-	-
Previous chemotherapy for metastatic breast cancer				
Yes	1		-	
No	0.84 (0.52-1.35)	0.468	-	-
Visceral metastases				
Yes	1		1	
No	0.56 (0.37-0.85)	0.007	0.56 (0.37-0.86)	0.007
Tamoxifen resistance				
Sensitive	1		-	
Resistant	1.27 (0.69-2.32)	0.449	-	-
Treatment arm				
Capecitabine	1		1	
Palbociclib+ET	0.66 (0.44-0.99)	0.049	0.67 (0.44-1.01)	0.054

CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; ET, endocrine therapy; HR, hazard ratio; PS, performance status.

Discussion

A previous study has reported that a GnRH agonist (goserelin) versus ovariectomy demonstrated similar failure-free survival and OS in premenopausal women with HR+/HER2– breast cancer [11]. The YoungPEARL study was designed to compare the combination of palbociclib plus exemestane with ovarian suppression to single-agent chemotherapy in premenopausal women who had disease progression or relapse during or after previous endocrine therapy with tamoxifen [6]. Its unique strength lay in the study design, which explicitly recruited premenopausal women with HR+/HER2– MBC, the patient population which has been under-represented in most clinical trials other than MONALEESA-7. We hypothesized that palbociclib in combination with endocrine therapy would be more efficacious than a commonly used chemotherapeutic agent, capecitabine, which has been preferentially used in the context of a lack of endocrine options in the premenopausal population.

Premenopausal women with HR+/HER2– MBC constitute a distinctive patient population; they are more commonly found in Eastern countries compared to Western countries, owing to different ethnic background along with environmental and social factors [12-16]. In many Asian countries, the peak incidence of breast cancer occurs at the age range of 40-50 years, leading to about half of the patients being premenopausal. Other studies have reported that the patients in the younger age group exhibit higher risk for mortality, which is attributable to aggressive tumor behavior requiring rapid response [7,17-19]. Nevertheless, these patients have been under-represented, or even marginalized, in most clinical trials leading to a lack of evidence and limited treatment options.

In Asian countries, including South Korea, tamoxifen has been the only endocrine therapy, other than GnRH agonists, approved for premenopausal women, and hence most patients who received endocrine therapy at the time of enrolment were treated with tamoxifen in adjuvant or metastatic settings [20]. Under these circumstances, 25 of the total 178 patient population (14%) included in YoungPEARL had a tamoxifen-sensitive disease at study enrolment. In this *post hoc* subgroup analysis, we revealed that tamoxifen sensitivity did not significantly influence the survival benefit associated with palbociclib plus endocrine therapy compared to capecitabine. Both patient groups with and without tamoxifen resistance demonstrated a longer median PFS (tamoxifen-sensitive: 20.5 months vs. 12.6 months; HR, 0.38; tamoxifen-resistant: 20.1 vs. 14.5; HR, 0.73) and DOR (tamoxifen-sensitive: 18.9 months vs. 6.6 months; HR, 0.37; tamoxifen-resistant: 17.1 vs. 13.1; HR, 0.59) with palbociclib plus endocrine therapy compared to capecitabine. The proportion of patients achieving an objective response (44% vs. 22%), disease control (100% vs. 89%), and clinical benefit (88% vs. 78%) were consistently higher with palbociclib plus

endocrine therapy compared to capecitabine, in patients with tamoxifen-sensitive disease.

The MONALEESA-7 trial was the first study to evaluate the efficacy of ribociclib, another important CDK4/6 inhibitor, in addition to endocrine therapy in premenopausal patients. It included 268 of a total 672 patients (40%) who received previous (neo)adjuvant endocrine therapy, among whom 205 (77%) had disease progression within 12 months and 60 (22%) had disease progression after 12 months from the end of endocrine treatment [21]. In subgroup analysis, ribociclib was significantly favored for PFS benefit with HR 0.59 (95% CI, 0.40 to 0.87) for patients with treatment-free interval of less than 12 months. However, PFS benefit for those with a treatment-free interval of more than 12 months was rather doubtful with an HR of 0.75 (95% CI, 0.28 to 2.02) and the upper limit of the 95% CI notably crossing over 1.0. In the subsequent report on OS, the patients with a treatment-free interval of more than 12 months showed an HR of 1.53 (95% CI, 0.44 to 5.34), favoring a placebo over ribociclib [22]. The worrisome results from the subgroup analysis on PFS benefit failed to translate into any OS benefits for patients with treatment-free survivals of more than 12 months with ribociclib treatment.

For palbociclib, an enthusiasm for clinical benefit for patients with endocrine sensitivity was glimpsed in the PALOMA-3 trial which analyzed patients with any menopausal status and endocrine-resistant HR+/HER2– breast cancer [5]. This study included 410 of total 521 patients (79%) who had a documented clinical benefit from at least one previous endocrine therapy. A subgroup analysis for patients with sensitivity to previous hormonal therapy demonstrated a favorable outcome with palbociclib over a placebo in both PFS (10.2 months [95% CI, 9.4 to 11.2] vs. 4.2 months [95% CI, 3.5 to 5.6]; HR, 0.42 [95% CI, 0.32 to 0.56]) and OS (39.7 months [95% CI, 34.8 to 45.7] vs. 29.7 months [95% CI, 23.8 to 37.9]; HR, 0.72 [95% CI, 0.55 to 0.94]) [5,23]. Taken together with our results, these findings suggest that palbociclib is a promising therapeutic option for patients with tamoxifen-sensitive MBC. Further data on OS for patients included in the YoungPEARL trial, in regard to tamoxifen sensitivity, are highly anticipated.

This study has several limitations including its exploratory, *post hoc* nature and the small number of patients analyzed. As such, these data must be interpreted with caution. Despite these limitations, the significant PFS benefit with palbociclib therapy demonstrated in this *post hoc* analysis from the YoungPEARL study holds a robust clinical significance for making treatment decisions in this patient subgroup. In conclusion, palbociclib plus exemestane with ovarian suppression is an active treatment option in tamoxifen-sensitive, as well as tamoxifen-resistant, premenopausal patients with HR+/HER2– MBC who are candidates for cytotoxic chemotherapy.

Ethical Statement

The study was approved by the institutional ethics committees of each hospital and by the Korean Cancer Study Group Institutional Review Board. Written informed consent was obtained from each participant.

Author Contributions

Conceived and designed the analysis: Lee J, Im SA, Kim GM, Jung KH, Kang SY, Park IH, Kim JH, Ahn HK, Park YH.
Collected the data: Lee J, Im SA, Kim GM, Jung KH, Kang SY, Park IH, Kim JH, Ahn HK, Park YH.
Contributed data or analysis tools: Lee J, Im SA, Kim GM, Jung KH, Kang SY, Park IH, Kim JH, Ahn HK, Park YH.
Performed the analysis: Lee J, Im SA, Kim GM, Jung KH, Kang SY, Park IH, Kim JH, Ahn HK, Park YH.
Wrote the paper: Lee J, Im SA, Kim GM, Jung KH, Kang SY, Park IH, Kim JH, Ahn HK, Park YH.

Conflicts of Interest

Conflict of interest relevant to this article was not reported.

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