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Real-World Comparative Effectiveness of Palbociclib Plus Letrozole vs Letrozole in Older Patients With Metastatic Breast Cancer

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- In older patients with a median age of 74 years, first-line palbociclib plus letrozole significantly prolonged median rwPFS (22.2 [95% CI, 20.0–30.4] vs 15.8 [95% CI, 12.9–18.9] months; HR = 0.59 [95% CI, 0.47–0.74]; *P*<0.0001) and OS (not reached vs 43.4 [95% CI, 30.0–NE] months; HR = 0.55 [95% CI, 0.42–0.72], *P*<0.0001) compared with letrozole alone.
- rwBTR was significantly higher in the group that received palbociclib plus letrozole vs the group that received letrozole alone (52.4% vs 22.1%, odds ratio=2.0 [95% CI, 1.4–2.7], *P*<0.0001).
- These findings complement the efficacy of palbociclib plus letrozole vs letrozole plus placebo demonstrated in older patients in the PALOMA clinical trials.

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Background

- Palbociclib was the first clinically available cyclin-dependent kinase 4/6 (CDK4/6) inhibitor and, in combination with endocrine therapy, is indicated for HR+/HER2– MBC.[1]
- In the phase 3 PALOMA-2 trial, palbociclib in combination with letrozole compared with letrozole plus placebo as a first-line therapy in postmenopausal women with HR+/HER2– MBC significantly prolonged progression-free survival (PFS; 27.6 vs 14.5 months, hazard ratio [HR] = 0.56 [95% CI, 0.46–0.69]; *P*<0.001).[2]
- Emerging real-world data have demonstrated the safety and effectiveness of palbociclib in combination with endocrine therapy in routine clinical practice.[3-5]
- In pooled analyses from the PALOMA-1 and PALOMA-2 trials, palbociclib in combination with letrozole compared with letrozole plus placebo as a first-line therapy also demonstrated significantly prolonged PFS in patients aged 65–74 years (27.5 vs 21.8 months; HR = 0.66 [95% CI, 0.45–0.97]; *P*<0.016) and in patients aged ≥75 years (not reached vs 10.9 months; HR = 0.31 [95% CI, 0.16–0.61]; *P*<0.001).[2]
- However, data on the comparative effectiveness of palbociclib therapy vs endocrine therapy alone in older patients in a real-world clinical setting are limited.

Objective

- To describe patient characteristics and compare real-world best tumor response (rwBTR), real-world progression-free survival (rwPFS), and overall survival (OS) of palbociclib plus letrozole vs letrozole alone as a first-line therapy in older patients with hormone receptor–positive/human epidermal growth factor receptor 2–negative (HR+/HER2–) metastatic breast cancer (MBC) in routine clinical practice in the United States.

Methods

STUDY DESIGN AND DATABASE

- This retrospective study used data from Flatiron Health's (New York, NY) longitudinal database, which includes de-identified structured and unstructured electronic health records (EHRs) from > 280 cancer clinics, representing 2.4 million patients with cancer actively being treated in the United States.

PATIENTS

- Women aged ≥65 years diagnosed with HR+/HER2– MBC and initiating palbociclib plus letrozole or letrozole alone in the first-line setting between February 2015 and September 2018 were included.
- Patients were evaluated from the start of therapy with palbociclib plus letrozole or letrozole alone to December 2018, death, or last visit, whichever came first.
- Patients were excluded if they had previously been treated with another CDK4/6 inhibitor, with an AI, or with tamoxifen, raloxifene, toremifene, or fulvestrant for MBC.
- Patients were also excluded if they were treated with a CDK4/6 inhibitor as part of a clinical trial and those whose first structured activity was >90 days after their MBC diagnosis date were also excluded.

OUTCOMES

- rwPFS was defined as the time from start of treatment to death or disease progression.[4]
  - Disease progression was concluded by the treating clinician based on radiology, pathology, or laboratory evidence or clinical assessment, whichever came first. If patients did not die or have disease progression, they were censored at the date of initiation of the next line of therapy for patients with ≥2 lines of therapy or their last visit date during the study period for patients with only 1 line of therapy.
- OS was defined as the months from the start of treatment to the date of death. Patients who did not die during that period were censored at the time of data cutoff.
- Real-world tumor responses were assessed based on the treating clinician's assessment of radiologic evidence for change in burden of disease over the course of treatment.[3]
  - Complete response: complete resolution of all visible disease
  - Partial response: partial reduction in size of visible disease in some or all areas without any areas of increase in visible disease
  - Stable disease: no change in overall size of visible disease; also included cases in which some lesions increased in size and some lesions decreased in size
  - Progressive disease: an increase in visible disease and/or presence of any new lesions; included cases in which the clinician indicated progressive disease

STATISTICAL ANALYSIS

- Comparative analyses were conducted with an unadjusted method (without controlling for confounders) method and a stabilized inverse probability treatment weighting (sIPTW) (used to balance patient characteristics).
- Survival time was calculated using Kaplan-Meier survival analysis. To compare the risk of rwPFS and OS between the study cohorts, Cox proportional hazards models with a robust sandwich estimator were used.
- Logistic regression was used to estimate the odds of real-world tumor responses in the group receiving palbociclib plus letrozole compared with the group receiving letrozole alone.

Results

PATIENTS

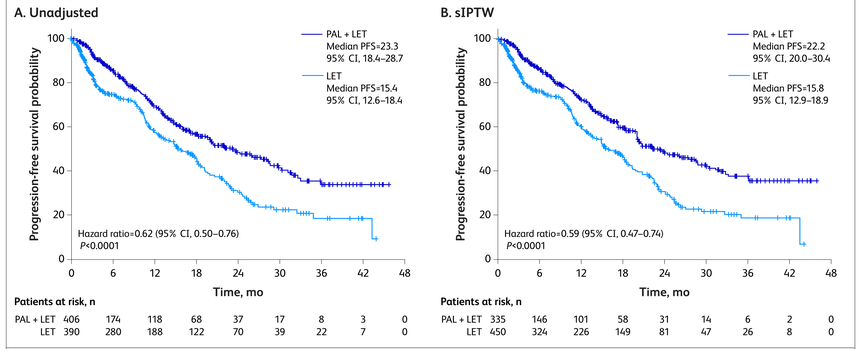
- A total of 796 women with HR+/HER2– MBC aged ≥65 years were included.
- In the unadjusted cohort, patient demographic and clinical characteristics differed between the groups receiving palbociclib plus letrozole and letrozole alone (**Table 1**).
- After sIPTW, patient demographic and clinical characteristics were generally well balanced.
  - The median age was 74.0 years in each treatment group, and approximately 71% of patients were White (**Table 1**).
- The median duration of follow-up was 18.6 months in the group receiving letrozole alone and 20.2 months in the group receiving palbociclib plus letrozole.

Table 1. Patient Characteristics

	Unadjusted			sIPTW		
Characteristic	Letrozole (n=406)	Palbociclib + Letrozole (n=390)	Standardized Difference	Letrozole (n=335)	Palbociclib + Letrozole (n=450)	Standardized Difference
Age, y						
Mean (SD)	75.8 (6.2)	73.2 (5.9)	0.444	74.9 (5.7)	74.4 (6.5)	0.077
Median (IQR)	77.0 (12.0)	72.0 (10.0)		74.0 (12.0)	74.0 (10.0)	
Age group, y						
65–74	175 (43.1)	245 (62.8)	–0.403	175 (52.3)	231 (51.4)	0.018
≥75	231 (56.9)	145 (37.2)		160 (47.7)	219 (48.6)	
Race						
White	287 (70.7)	269 (69.0)	0.037	237 (70.8)	318 (70.7)	0.002
Black	32 (7.9)	24 (6.2)	0.068	23 (6.8)	27 (6.0)	0.034
Asian	6 (1.5)	8 (2.0)	–0.044	5 (1.4)	7 (1.5)	–0.013
Hispanic or Latino	11 (2.7)	9 (2.3)	0.026	8 (2.5)	11 (2.4)	0.005
Other/unknown	70 (17.2)	80 (20.5)	–0.084	62 (18.6)	87 (19.4)	–0.021
Practice type						
Community	389 (95.8)	375 (96.2)	–0.017	322 (96.4)	435 (96.5)	–0.010
Academic	17 (4.2)	15 (3.8)		12 (3.6)	16 (3.5)	
Disease stage at initial diagnosis						
I or II	145 (35.7)	145 (37.2)	–0.030	117 (35.1)	163 (36.1)	–0.022
III	46 (11.3)	44 (11.3)	0.002	39 (11.6)	52 (11.6)	–0.000
IV	166 (40.9)	159 (40.8)	0.002	139 (41.5)	180 (40.0)	0.031
Not documented	49 (12.1)	42 (10.8)	0.041	40 (11.8)	55 (12.3)	–0.014
ECOG performance status						
0	93 (22.9)	147 (37.7)	–0.326	100 (30.0)	137 (30.4)	–0.008
1	88 (21.7)	94 (24.1)	–0.058	78 (23.2)	106 (23.6)	–0.009
2	41 (10.1)	35 (9.0)	0.038	32 (9.4)	44 (9.7)	–0.010
3 or 4	18 (4.4)	3 (0.8)	0.232	9 (2.6)	8 (1.9)	0.053
Not documented	166 (40.9)	111 (28.5)	0.263	116 (34.7)	155 (34.4)	0.006
Visceral disease*	137 (33.7)	170 (43.6)	–0.203	129 (38.7)	172 (38.3)	0.008
No visceral disease*	269 (66.3)	220 (56.4)		205 (61.3)	278 (61.7)	
Bone–only disease†	162 (39.9)	134 (34.4)	0.115	124 (37.0)	163 (36.2)	0.017
Brain metastases	14 (3.4)	8 (2.0)	0.086	9 (2.8)	10 (2.3)	0.029
Number of metastatic sites‡						
1	215 (53.0)	182 (46.7)	0.126	165 (49.4)	214 (47.6)	0.036
2	90 (22.2)	118 (30.3)	–0.185	90 (26.8)	119 (26.4)	0.009
3	43 (10.6)	58 (14.9)	–0.129	42 (12.7)	57 (12.7)	0.000
4+	22 (5.4)	26 (6.7)	–0.052	19 (5.8)	26 (5.9)	–0.003

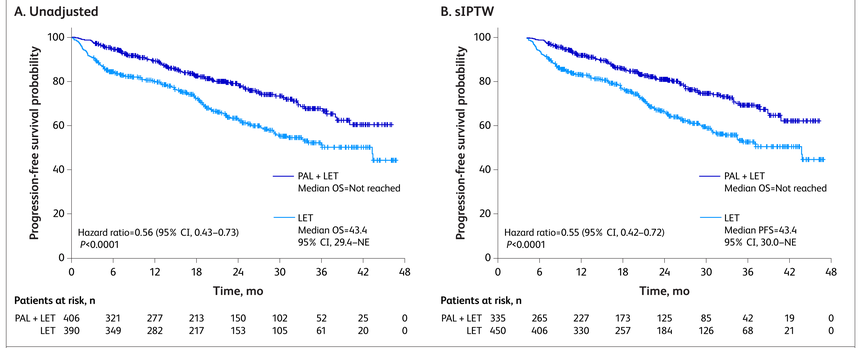
ECOG=Eastern Cooperative Oncology Group; IQR=interquartile range; sIPTW=stabilized inverse probability treatment weighting.
All data are n (%) unless otherwise noted.
*Visceral disease was defined as metastatic disease in the lung and/or liver; patients could have had other sites of metastases. No visceral disease was defined as no lung or liver metastases.
†Bone-only disease was defined as metastatic disease in the bone only.
‡Multiple metastases at the same site were counted as 1 site (eg, if a patient had 3 bone metastases in the spine, it was considered only 1 site).

Figure 1. Kaplan-Meier Curves of Real-World Progression-Free Survival



LET=letrozole; PAL=palbociclib; PFS=progression-free survival; sIPTW=stabilized inverse probability treatment weighting.

Figure 2. Kaplan-Meier Curves of Overall Survival



LET=letrozole; NE=not estimable; OS=overall survival; PAL=palbociclib; sIPTW=stabilized inverse probability treatment weighting.

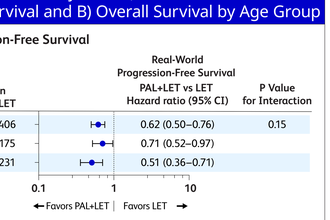
OUTCOMES

- Median rwPFS was significantly longer among the older patients who received palbociclib plus letrozole vs letrozole alone in both the unadjusted (23.3 [95% CI, 18.4–28.7] vs 15.4 [95% CI, 12.6–18.4] months; HR = 0.62 [95% CI, 0.50–0.76]; *P*<0.0001) and sIPTW adjusted (22.2 [95% CI, 20.0–30.4] vs 15.8 [95% CI, 12.9–18.9] months; HR = 0.59 [95% CI, 0.47–0.74]; *P*<0.0001) analyses (**Figure 1**).
- Median OS was significantly longer among the older patients who received palbociclib plus letrozole vs the group that received letrozole alone in both the unadjusted (not reached vs 43.4 [95% CI, 29.4–not estimable (NE)] months; HR = 0.56 [95% CI, 0.43–0.73], *P*<0.0001) and sIPTW adjusted (not reached vs 43.4 [95% CI, 30.0–NE] months; HR = 0.55 [95% CI, 0.42–0.72], *P*<0.0001) analyses (**Figure 2**).
- When analyzed by age group, median rwPFS and median OS remained longer in patients who received palbociclib plus letrozole vs letrozole alone in both the 65–74 and the ≥75 year old age groups (**Figure 3**). No interactions between age groups and treatment group were observed for rwPFS or OS (**Figure 3**).

Figure 3. Forest Plots of Unadjusted A) Real-World Progression-Free Survival and B) Overall Survival by Age Group

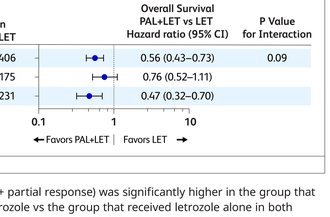
A. Real-World Progression-Free Survival

Subgroup	Patients, n PAL+LET	Patients, n LET	Real-World Progression-Free Survival PAL+LET vs LET Hazard ratio (95% CI)	P Value for Interaction
All patients	390	406	0.62 (0.50–0.76)	0.15
Age 65–74 y	245	175	0.71 (0.52–0.97)	
Age >75 y	145	231	0.51 (0.36–0.71)	



B. Overall Survival

Subgroup	Patients, n PAL+LET	Patients, n LET	Overall Survival PAL+LET vs LET Hazard ratio (95% CI)	P Value for Interaction
All patients	390	406	0.56 (0.43–0.73)	0.09
Age 65–74 y	245	175	0.76 (0.52–1.11)	
Age >75 y	145	231	0.47 (0.32–0.70)	



LET=letrozole; PAL=palbociclib.

- rwBTR (complete response + partial response) was significantly higher in the group that received palbociclib plus letrozole vs the group that received letrozole alone in both the unadjusted (52.0% vs 21.4%, odds ratio=2.2 [95% CI, 1.6–3.1], *P*<0.0001) and sIPTW adjusted (52.4% vs 22.1%, odds ratio=2.0 [95% CI, 1.4–2.7], *P*<0.0001) analyses (**Table 2**).

Table 2. Real-World Best Tumor Responses

	Unadjusted			sIPTW		
	Letrozole (n=406)	Palbociclib + Letrozole (n=390)	*P* Value	Letrozole (n=335)	Palbociclib + Letrozole (n=450)	*P* Value
CR	17 (4.2)	32 (8.2)	<0.0001	13 (4.0)	45 (10.1)	<0.0001
PR	70 (17.2)	171 (43.8)		60 (18.0)	190 (42.3)	
Stable disease	53 (13.0)	86 (22.0)		44 (13.0)	98 (21.8)	
Progressive disease	68 (16.8)	47 (12.0)		52 (15.6)	57 (12.7)	
Indeterminate	13 (3.2)	8 (2.1)		10 (3.0)	7.4 (1.6)	
Missing	185 (45.6)	46 (11.8)		155 (46.4)	52 (11.5)	
Best overall response (CR+PR)	87 (21.4)	203 (52.0)	<0.0001	74 (22.1)	236 (52.4)	<0.0001

CR=complete response; PR=partial response, rwBTR=real-world best tumor response.
All data are n (%) unless otherwise noted.

LIMITATIONS

- EHRs have the potential for missing or incomplete data and the quality of information extracted from the EHR depends on the quality of information entered by the clinician.
- Tumor response assessments in routine practice were not scheduled and tumor responses were limited by the clinician's interpretation and documentation of tumor response based on radiologic evidence for change in burden of disease. Tumor response assessment was not based on Response Evaluation Criteria in Solid Tumors (RECIST).
- Other variables unavailable in the database could not be statistically controlled.
- Findings from patients in the Flatiron database may not be generalized to other patient populations.
- This is a retrospective analysis of data from an EHR database and causal relationships to treatment cannot be determined.

References: 1. Hui R, et al. *Asia Pac J Clin Oncol.* 2021;17 Suppl 1:3-14. **2.** Rugo HS, et al. *Breast Cancer Res Treat.* 2019;174(3):719-729. **3.** Brufsky A, et al. *Target Oncol.* 2021. **4.** DeMichele A, et al. *Breast Cancer Res.* 2021;23(1):37. **5.** Varella L, et al. *Breast Cancer Res Treat.* 2019;176(2):429-434.

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