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Overall Survival With First-Line Palbociclib Plus an Aromatase Inhibitor (AI) vs AI in Metastatic Breast Cancer: A Large Real-World Database Analysis

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Objective

- To compare the survival outcomes of patients with hormone receptor positive/human epidermal growth factor receptor 2–negative metastatic breast cancer (HR+/HER2– MBC) treated with first-line palbociclib + AI versus AI alone in routine clinical practice in the United States.

Conclusions

- This real-world comparative effectiveness study—the largest conducted in MBC to date—demonstrated that palbociclib + AI versus AI alone was significantly associated with both prolonged overall survival (OS; after stabilized inverse probability treatment weighting [sIPTW], hazard ratio [HR] = 0.76 [95% CI, 0.65–0.87]; $P = 0.0001$) and real-world progression-free survival (rwPFS; after sIPTW, HR = 0.70 [95% CI, 0.62–0.78]; $P < 0.0001$) in a heterogeneous population of postmenopausal women and of men with HR+/HER2– MBC.
- These findings continue to support first-line palbociclib + AI as a standard of care for patients with HR+/HER2– MBC.

Electronic Poster, Video Poster, and Supplementary Material

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Abstract Plain Language Summary

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References: 1. IBRANCE® capsules (palbociclib). Full Prescribing Information, Pfizer Inc, New York, NY, 2019. **2.** Finn RS, et al. *N Engl J Med*. 2016;375:1925-1936. **3.** Rugo HS, et al. *Breast Cancer Res Treat*. 2019;174:719-729. **4.** DeMichele A, et al. *Breast Cancer Res*. 2021;23:37. **5.** Brufsky A, et al. *Target Oncol*. 2021;16:601-611. **6.** Harbeck N, et al. *Future Oncol*. 2021;17:2107-2122.

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Background

- Palbociclib is a cyclin-dependent kinase 4/6 (CDK4/6) inhibitor approved for HR+/HER2– advanced breast cancer in combination with an AI or fulvestrant.[1]
- The randomized, double-blind, placebo-controlled, phase 3 PALOMA-2 trial supported the approval of first-line palbociclib + AI in patients with HR+/HER2– MBC by demonstrating a significant PFS benefit with palbociclib + letrozole versus placebo + letrozole (27.6 vs 14.5 months; HR = 0.56, 95% CI, 0.461–0.687; $P < 0.0001$).[1-3]
- Recent small or short follow-up real-world studies support the clinical benefit of palbociclib in routine clinical practice;[4-6] however, further investigation on the relative effectiveness of palbociclib + AI vs AI alone in the real-world clinical setting is warranted.
- This retrospective analysis evaluated the effectiveness of first-line palbociclib + AI, as compared with AI alone, in patients with HR+/HER2– MBC treated in real-world clinical practice in the United States.

Materials and Methods

STUDY DESIGN

- This retrospective cohort study (P-REALITY X: Palbociclib REAl-world first-LIne comparaTive effectiveness studY eXtended) included patients with HR+/HER2– MBC in the Flatiron Health longitudinal database, which represents >3 million records of patients with cancer in the United States.
  - The study included 2888 postmenopausal women and men aged ≥18 years who started first-line palbociclib + AI or AI therapy for HR+/HER2– MBC from February 3, 2015, to March 31, 2020.
  - Patients were evaluated from the start of palbociclib + AI or AI to September 30, 2020, death, or the last visit, whichever came first.
- The primary endpoint was OS, defined as the time in months from the start of palbociclib + AI or AI alone to death from any cause.
- The secondary endpoint was rwPFS, defined as the number of months from the start of treatment with palbociclib + AI or AI alone to the date of the first documentation of disease progression by the treating clinician based on radiology, laboratory evidence, pathology, or clinical assessment or death due to any cause, whichever occurred first.

STATISTICAL METHODS

- Unadjusted analyses (without controlling for baseline patient characteristics) were first conducted.
- sIPTW as the primary analysis was performed to balance patient demographic and baseline clinical characteristics.
- 1:1 propensity score matching (PSM) was conducted as sensitivity analysis.
- Median survival times and 95% CIs for OS and rwPFS were estimated using the weighted Kaplan-Meier method.
- Cox proportional hazards model was used to compute the HR and the corresponding 95% CI.

Results

PATIENT CHARACTERISTICS

- Of the 2888 eligible patients included in the analysis, 1324 received treatment with palbociclib + AI and 1564 received treatment with an AI alone.
- Overall, the median age of patients was 70.0 years, 67.8% were white, 34.8% had de novo MBC, 29.4% had lung or liver involvement, and 38.7% had bone-only disease (**Table 1**).
  - Baseline characteristics were generally similar between both treatment groups after sIPTW and 1:1 PSM (please scan the QR code for **Supplementary Table 1**).
  - Most patients (>90%) were treated in the community versus academic setting, and the percentage of patients with different insurance plans was similar between treatment groups (please scan the QR code for **Supplementary Table 1**).
- After sIPTW, median follow-up was 23.9 months in the palbociclib + AI group and 24.5 months in the AI group (**Table 1**).

OS AND rwPFS

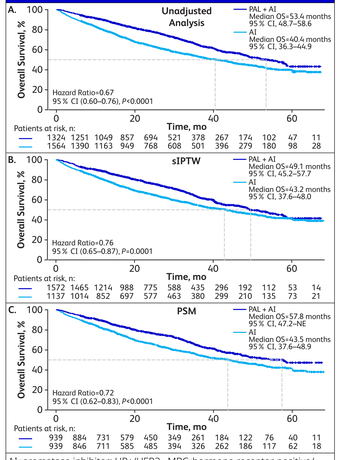
- Both unadjusted and adjusted analyses consistently demonstrated that palbociclib + AI was significantly associated with prolonged median OS and rwPFS compared with AI alone among patients with HR+/HER2– MBC in real-world clinical practice (**Figures 1** and **2**).
  - After sIPTW and 1:1 PSM, a consistent OS benefit with palbociclib + AI versus AI alone was generally observed across most subgroups examined; benefits were observed regardless of race and among patients with and without visceral or bone-only disease (please scan the QR code for **Supplementary Figures 1** and **2**).
- A total of 48.9% and 65.1% of patients in the palbociclib group and AI alone group, respectively, had subsequent treatments (sIPTW analysis); of which 43.1% and 50.5%, respectively, received a CDK4/6 inhibitor as second-line treatment (please scan the QR code for **Supplementary Table 2**).

Table 1. Patient Characteristics

	Unadjusted Total Cohort		Cohort After sIPTW		Cohort After PSM	
Characteristic	**Palbociclib + AI (n=1324)**	**AI Alone (n=1564)**	**Palbociclib + AI (n=1572)**	**AI Alone (n=1137)**	**Palbociclib + AI (n=939)**	**AI Alone (n=939)**
Median (IQR) age, y	67 (61–74)	72 (64–80)	70 (63–78)	70 (63–79)	69 (63–76)	70 (63–78)
Age ≥75 y,* n (%)	313 (23.6)	648 (41.4)	559 (35.6)	380 (33.5)	280 (29.8)	292 (31.1)
Female sex, n (%)	1,314 (99.2)	1,545 (98.8)	1,555 (98.9)	1,125 (99.0)	931 (99.2)	929 (98.9)
Race/ethnicity,* n (%)						
White	900 (68.0)	1059 (67.7)	1063 (67.6)	766 (67.4)	591 (62.9)	636 (67.7)
Black	107 (8.1)	136 (8.7)	134 (8.5)	96 (8.5)	83 (8.8)	71 (7.6)
Other/unknown	317 (23.9)	369 (23.6)	375 (23.9)	274 (24.1)	265 (28.2)	232 (24.7)
ECOG PS,* n (%)						
0	499 (37.7)	397 (25.4)	472 (30.1)	348 (30.6)	273 (29.1)	304 (32.4)
1	318 (24.0)	334 (21.4)	362 (23.0)	259 (22.8)	228 (24.3)	225 (24.0)
2, 3, or 4	153 (11.6)	271 (17.3)	251 (15.9)	169 (14.9)	137 (14.6)	118 (12.6)
Not documented	354 (26.7)	562 (35.9)	487 (31.0)	361 (31.7)	301 (32.1)	292 (31.1)
Visceral disease,*[‡1] n (%)	444 (33.5)	404 (25.8)	460 (29.3)	337 (29.7)	295 (31.4)	293 (31.2)
Bone-only disease,*[‡1] n (%)	519 (39.2)	599 (38.3)	589 (37.5)	440 (38.7)	373 (39.7)	403 (42.9)
Brain metastases, n (%)	26 (2.0)	50 (3.2)	26 (1.7)	43 (3.8)	18 (1.9)	39 (4.2)
Interval from initial BC Dx to MBC Dx,* n (%), y						
De novo	541 (40.9)	464 (29.7)	530 (33.7)	390 (34.3)	323 (34.4)	323 (34.4)
≤1	40 (3.0)	66 (4.2)	74 (4.7)	43 (3.8)	34 (3.6)	41 (4.4)
>1–5	191 (14.4)	429 (27.4)	271 (17.2)	288 (25.4)	151 (16.1)	230 (24.5)
>5	551 (41.6)	601 (38.4)	696 (44.3)	414 (36.4)	430 (45.8)	343 (36.5)
Not documented	1 (0.08)	4 (0.3)	1 (0.05)	2 (0.2)	1 (0.11)	2 (0.21)
NCI comorbidity index, mean (SD)	0.29 (0.47)	0.39 (0.52)	0.33 (0.57)	0.36 (0.42)	0.31 (0.5)	0.34 (0.5)
Number of metastatic sites,*[‡] n (%)						
1	654 (49.4)	843 (53.9)	793 (50.4)	589 (51.8)	498 (53.0)	526 (56.0)
2	367 (27.7)	291 (18.6)	352 (22.4)	261 (22.9)	244 (26.0)	222 (23.6)
3	178 (13.4)	133 (8.5)	158 (10.1)	129 (11.3)	106 (11.3)	107 (11.4)
≥4	89 (6.7)	53 (3.4)	84 (5.3)	47 (4.1)	55 (5.9)	48 (5.1)
Not documented	36 (2.7)	244 (15.6)	186 (11.8)	111 (9.8)	36 (3.8)	36 (3.8)
Median follow-up duration (IQR), mo	25.0 (13.8–38.3)	23.3 (11.8–42.3)	23.9 (12.8–38.0)	24.5 (12.0–42.9)	23.4 (13.1–37.8)	24.94 (12.4–44.4)

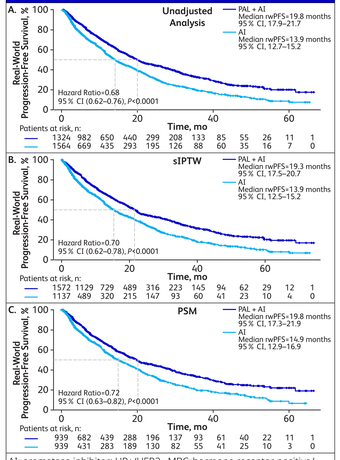
AI=aromatase inhibitor; BC=breast cancer; Dx=diagnosis; ECOG PS=Eastern Cooperative Oncology Group performance status; IQR=interquartile range; MBC=metastatic breast cancer; NCI=National Cancer Institute; PSM=propensity score matching; sIPTW= stabilized inverse probability treatment weighting.
*Variable used in PS computation model.
[‡1]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.
[‡]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 OS for Patients With HR+/HER2– MBC Treated With Palbociclib + AI or AI Alone According to (A) Unadjusted, (B) sIPTW, and (C) PSM Analyses



AI=aromatase inhibitor; HR+/HER2– MBC=hormone receptor positive/human epidermal growth factor receptor 2–negative metastatic breast cancer; NE=not evaluable; OS=overall survival; PAL=palbociclib; PSM=propensity score matching; sIPTW=stabilized inverse probability treatment weighting.

Figure 2. Kaplan-Meier Curves of rwPFS for Patients With HR+/HER2– MBC Treated With Palbociclib + AI or AI Alone According to (A) Unadjusted, (B) sIPTW, and (C) PSM Analyses



AI=aromatase inhibitor; HR+/HER2– MBC=hormone receptor positive/human epidermal growth factor receptor 2–negative metastatic breast cancer; PAL=palbociclib; PSM=propensity score matching; rwPFS=real-world progression-free survival; sIPTW=stabilized inverse probability treatment weighting.

LIMITATIONS

- This study is a retrospective database study of electronic health records, which may have missing or erroneous data entry and cannot determine causal relationship.
- Disease progression was based on the treating physician's clinical assessment or interpretation of radiographic or pathologic results rather than standard criteria (eg, Response Evaluation Criteria in Solid Tumors).
- While sIPTW and PSM were used to balance baseline and clinical patient characteristics, unobserved variables cannot be fully addressed through these methods.
- Some subgroups analyzed may not have sufficient power due to sample size (eg, younger patients aged <50 years).
- Findings presented here may not be generalizable to patient populations not represented in the Flatiron Database.