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Real-world treatment patterns for palbociclib plus an aromatase inhibitor, or an aromatase inhibitor alone, for patients with metastatic breast cancer in the Flatiron Database

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Abstract

There are limited real-world comparative effectiveness data for palbociclib plus an aromatase inhibitor (AI) as a first-line (1L) treatment examining endpoints that require long term follow-up and post 1L progression. The Flatiron Health Analytic Database was used to characterize treatment and dosing patterns in patients with hormone receptor-positive/human epidermal growth factor 2-negative (HR+/HER2−) metastatic breast cancer (mBC) receiving palbociclib plus an AI vs an AI alone in routine US clinical practice. In addition, time to chemotherapy (TTC) and real-world progression-free survival (rwPFS) when combining 1L and second-line of therapy (rwPFS2) were assessed. Of 1324 patients who received palbociclib plus an AI between February 3, 2015 and March 31, 2020, 1110 (83.8%) started palbociclib at the recommended 125 mg/day dose. After stabilized inverse probability treatment-weighting (sIPTW), median TTC in patients treated with palbociclib plus an AI and AI alone was 37.4 months (95% confidence interval [CI], 33.7-40.7) and 29.2 months (95% CI, 26.8-33.5), respectively (hazard ratio [HR] = 0.77 [95% CI, 0.69-0.86], $P < .0001$); median rwPFS2 was 32.6 months (95% CI, 29.4-35.2) and 20.7 months (95% CI, 18.9-22.6), respectively (HR = 0.62 [95% CI, 0.54-0.70], $P < .0001$). Sensitivity analyses with propensity score matching showed similar results to sIPTW analyses. Results from this large real-world study examining additional effectiveness outcomes beyond 1L rwPFS and overall survival support the use of palbociclib plus an AI as a 1L treatment for patients with HR+/HER2− mBC.

KEYWORDS
CDK4/6 inhibitor, HR+/HER2−, metastatic breast cancer, palbociclib, real-world progression-free survival

Abbreviations list: 1L/2L, first line/second line; AI, aromatase inhibitor; BC, breast cancer; CDK4/6, cyclin-dependent kinase 4/6; CI, confidence interval; HER2−, human epidermal growth factor 2-negative; HR, hazard ratio; HR+, hormone receptor-positive; OS, overall survival; PFS, progression-free survival; PSM, propensity score matching; rwPFS, real-world progression-free survival; rwPFS2, real-world progression-free survival when combining first and second lines of therapy; sIPTW, stabilized inverse probability treatment weighting; TTC, time to chemotherapy; US, United States.

What's new?

There are limited data on the real-world comparative effectiveness of combination therapy involving the cyclin-dependent kinase inhibitor palbociclib and an aromatase inhibitor (AI) for hormone receptor-positive/human epidermal growth factor 2-negative (HR+/HER2−) metastatic breast cancer (mBC). In this study, the authors assessed time to chemotherapy (TTC) and real-world progression-free survival when combining first-line and second-line therapy (rwPFS2) in men and postmenopausal women with HR+/HER2− mBC treated with palbociclib plus an AI vs an AI alone. Combination therapy involving palbociclib plus an AI was associated with longer TTC and rwPFS2 compared to treatment with AI alone. The findings support the use of palbociclib plus AI combination treatment for HR+/HER2− mBC patients in real-world clinical practice.

1 | INTRODUCTION

In 2022, there were approximately 4.1 million women living in the United States (US) with a history of breast cancer; the hormone receptor-positive/human epidermal growth factor receptor 2-negative (HR+/HER2−) subtype accounts for 68% of all breast cancer cases.[1] About 4% of those living with breast cancer are projected to have metastatic disease,[2] which has a 5-year survival rate of approximately 30%.[1]

The standard of care for patients with HR+/HER2− metastatic breast cancer (mBC) is a cyclin-dependent kinase 4/6 (CDK4/6) inhibitor plus an aromatase inhibitor (AI) as first-line (1L) therapy or with fulvestrant after prior endocrine therapy (ET).[3] Palbociclib, the first-in-class CDK4/6 inhibitor, was approved in the US in February 2015 as 1L treatment in combination with letrozole for patients with HR+/HER2− mBC based on findings from the phase 2 PALOMA-1 trial.[4,5] Subsequently, the phase 3 PALOMA-2 trial demonstrated clinically and statistically significant improvement in the primary endpoint of progression-free survival (PFS) in patients with HR+/HER2− mBC treated with palbociclib in combination with letrozole vs placebo plus letrozole as 1L therapy.[6,7] However, the secondary endpoint of overall survival (OS) in the PALOMA-2 trial was numerically longer but was not statistically significantly different between the treatment arms.[8]

Controlled clinical trials can limit the clinical and demographic characteristics of patients who are studied due to strict inclusion and exclusion criteria and as a result may have limited patients with worse Eastern Cooperative Oncology Group (ECOG) performance status, multiple comorbidities, or who are elderly or frail. Importantly, real-world studies can help us understand treatment patterns and clinical effectiveness or safety in a heterogeneous population in routine clinical practice, which can be informative for clinical treatment decisions.[9-12] In the case of palbociclib, real-world data added support to the clinical data in male breast cancer patients for a label expansion in 2019 to include men with HR+/HER2− mBC.[13-15] Over 8 years of post-approval real-world patient experience and more than 665 000 patients prescribed palbociclib globally (including nearly 173 000 in the US as of June 2020) make it possible to study comparative effectiveness in a large and diverse population of patients with HR+/HER2− mBC within the US. Patt et al[16] recently reported real-world treatment patterns with respect to dosing regimens, tumor response and time to chemotherapy (TTC) supporting the 1L use of palbociclib plus an AI in women with HR+/HER2− mBC. However, this study was limited by the lack of a comparator arm. To date, only four real-world studies have provided comparative effectiveness data for palbociclib plus an AI vs an AI alone.[17-20] A recent independent study from the Survey Epidemiology and End Results-Medicare database demonstrated an OS benefit in women aged ≥65 years with de novo HR+/HER2− mBC receiving 1L treatment with a CDK4/6 inhibitor plus ET vs ET alone (adjusted HR, 0.590 [95% confidence interval [CI], 0.423-0.823]);[21] of note, palbociclib was the predominant CDK4/6 inhibitor used and accounted for 90% of CDK4/6 inhibitor use in this study.[21,22] Currently, real-world comparative effectiveness data on palbociclib are still limited, potentially due to the challenges of finding enough patients in a single quality data source.

In the real-world study, Palbociclib REAl-world first-LIne comparaTive effectiveness studY eXtended (P-REALITY X), the diversity and size of the Flatiron Health Analytics Database, allowed an analysis of a large sample of patients treated with palbociclib with up to 68 months follow up.[20] P-REALITY X analysis has demonstrated significantly longer median OS and rwPFS in patients with HR+/HER2− mBC treated with 1L palbociclib plus an AI. After stabilized inverse probability treatment weighting (sIPTW), the median OS was 49.1 months (95% CI, 45.2-57.7) with palbociclib plus an AI (n = 1572) vs 43.2 months (95% CI, 37.6-48.0) with an AI alone (n = 1137), resulting in a 24% reduction in risk of death (hazard ratio [HR] = 0.76; 95% CI, 0.65-0.87; $P < .0001$). The median rwPFS after sIPTW was 19.3 months (95% CI, 17.5-20.7) with palbociclib plus an AI vs 13.9 months (95% CI 12.5-15.2) with an AI alone, resulting in a 30% risk reduction in disease progression (HR, 0.70; 95% CI, 0.62-0.78; $P < .0001$).

Here we present additional real-world analyses from the P-REALITY X study. Detailed analysis of treatment patterns of palbociclib plus an AI, including initial dose and dose modifications, were evaluated for men and postmenopausal women with HR+/HER2− mBC. Additionally, TTC and real-world progression-free survival 2 (rwPFS2), which was the rwPFS in 1L combined with second-line (2L) therapy, were compared for patients receiving palbociclib plus an AI vs an AI alone.

2 | METHODS

2.1 | Study design and data source

This study was a retrospective analysis of the Flatiron Health Analytic Databases nationwide longitudinal electronic health records from over

280 cancer clinics representing more than 3 million patients with cancer actively treated in the US. Detailed methods have been previously published.[20]

2.2 | Patients

In this analysis of men and postmenopausal women, key inclusion criteria were age ≥ 18 years, presence of HR+/HER2− mBC, and date of first prescription (index date) for palbociclib as 1L therapy or AI alone for mBC occurring between February 2015 and March 2020. Patients were followed from start of therapy to September 2020, death, or last visit, whichever came first.

2.3 | Outcomes

Outcomes included palbociclib treatment patterns (starting dose and dose adjustments), TTC, and rwPFS2. Treatment patterns were captured from patient medical records during the observation period. TTC was defined as the length of time from the start of treatment to the beginning of chemotherapy, death from any cause, last visit, or end of study, whichever came first. rwPFS2 was defined as the number of months from the start of palbociclib plus an AI or AI alone to disease progression on the 2L of therapy, as determined by the treating physician, or death from any cause, whichever occurred first. Patients who received 3 or more lines of therapy, did not die and were without disease progression in the 2L of therapy, were censored at the date of initiation of the third line (3L) of therapy. Patients with only the 1L or 2L of therapy, who did not die and were without disease progression in the 2L of therapy were censored at the date of their last visit during the study period (February 2015 to September 2020). Disease progression in the 1L of therapy was not counted as either an event or censored.

2.4 | Statistical analysis

Descriptive analyses were conducted to describe treatment dosing patterns. Time-to-event endpoints were summarized using the weighted Kaplan-Meier method and displayed graphically. The weighted Cox proportional hazards model was used to compute HRs and corresponding 95% CI. Three methods were used for comparative analysis: (1) an unadjusted analysis without controlling for baseline patient characteristics, (2) the sIPTW method (the primary analysis) to balance baseline demographic and clinical characteristics between treatment groups and control for confounding variables and (3) 1:1 propensity score matching (PSM) as a sensitivity analysis. The sIPTW and PSM are both based on propensity scores, defined as the probability of assignment to treatment conditional on a set of observed baseline covariates.[23,24] A multivariable binomial logistic regression model was used to compute propensity scores. Variables included in the model were age group, sex, race/ethnicity, practice type, disease stage at initial diagnosis, ECOG performance status, bone disease, visceral disease, interval from initial breast cancer diagnosis to mBC diagnosis, and number of metastatic sites (Table S1).

3 | RESULTS

3.1 | Patients

A total of 2888 men and postmenopausal women with HR+/HER2− mBC were included in the analysis. Of these, 1324 patients were treated with palbociclib plus an AI and 1564 patients were treated with AI alone as 1L therapy. In the unadjusted cohort for both groups combined, the mean age was 69.0 years, 67.8% were White, 34.8% had de novo mBC, 29.4% had visceral disease, and 38.7% had bone-only disease (Table 1). Patient characteristics were generally balanced after sIPTW and PSM analyses (standardized mean difference < 0.1) (Table S1). After sIPTW, median follow up was 23.9 months in the palbociclib plus an AI arm and 24.5 months in the AI alone arm

3.2 | Palbociclib starting dose and dose adjustments

Of 1324 patients receiving palbociclib plus an AI, 1110 (83.8%) patients were started on palbociclib at 125 mg/day, 144 (10.9%) at 100 mg/day and 48 (3.6%) at 75 mg/day (Table 1). The median age of those starting palbociclib at the recommended dose of 125 mg/day was 67.0 years; the median ages for those starting palbociclib at 100 mg/day and 75 mg/day were 71.5 and 73.5 years, respectively. A greater proportion of patients who started on lower doses of palbociclib (16.7% on 100 mg/day and 22.9% on 75 mg/day) had an ECOG performance status of 2-4 than those who started on 125 mg/day (10.5%). Of the patients who started on palbociclib at 125, 100 and 75 mg/day, 41.1%, 36.8% and 31.3% experienced dose adjustments, respectively (Table 2 and Figure 1). Of the patients who started palbociclib at 125 mg/day and had a dose modification (n = 456), 421 (92.3%) had their dose reduced. Of the patients who started palbociclib at 100 mg/day and had a dose modification (n = 53), 32 (60.4%) had their dose reduced, while 10 (18.9%) had their dose increased. Of the patients who started palbociclib at 75 mg/day, 6 (12.5%) had their dose increased. For 125, 100, and 75 mg/day palbociclib doses at initiation, the median numbers of days to the first dose adjustment were 85, 95, and 112 days, respectively.

3.3 | Time to chemotherapy

In the unadjusted analysis of the full cohort, median TTC was 38.1 months (95% CI, 35.0-41.1) in the palbociclib plus an AI group and 28.1 months (95% CI, 25.5-30.9) in the AI alone group (HR = 0.74 [0.66-0.82]; $P < .0001$; Figure 2A). After sIPTW, median TTC was

TABLE 1 Patient demographics and clinical characteristics.

Characteristic	Unadjusted total cohort		Initial Palbociclib dose		
	Palbociclib + AI (n = 1324)	AI Alone (n = 1564)	125 mg (n = 1110)	100 mg (n = 144)	75 mg (n = 48)
Median age (IQR), years	67 (61-74)	72 (64-80)	67 (60-73)	71.5 (64-78)	73.5 (65.5-81.5)
Age ≥ 75 years, n (%)	313 (23.6)	648 (41.4)	230 (20.7)	53 (36.8)	23 (47.9)
Female sex, n (%)	1314 (99.2)	1545 (98.8)	1101 (99.2)	143 (99.3)	48 (100)
Race/ethnicity, n (%)					
White	900 (68.0)	1059 (67.7)	795 (71.6)	89 (61.8)	29 (60.4)
Black	107 (8.1)	136 (8.7)	93 (8.4)	7 (4.9)	7 (14.6)
Other/unknown[a]	317 (23.9)	369 (23.6)	222 (20)	48 (33.3)	12 (25)
ECOG PS, n (%)					
0	499 (37.7)	397 (25.4)	436 (39.3)	42 (29.2)	13 (27.1)
1	318 (24.0)	334 (21.4)	261 (23.5)	40 (27.8)	12 (25)
2, 3, or 4	153 (11.6)	271 (17.3)	117 (10.5)	24 (16.7)	11 (22.9)
Not documented	354 (26.7)	562 (35.9)	296 (26.7)	38 (26.4)	12 (25)
Visceral disease,[b] n (%)	444 (33.5)	404 (25.8)	371 (33.4)	51 (35.4)	16 (33.3)
Bone-only disease,[c] n (%)	519 (39.2)	599 (38.3)	435 (39.2)	59 (41)	18 (37.5)
Brain metastases, n (%)	26 (2.0)	50 (3.2)	23 (2.1)	2 (1.4)	1 (2.1)
Interval from initial BC diagnosis to mBC diagnosis, n (%), years					
De novo	541 (40.9)	464 (29.7)	454 (40.9)	60 (41.7)	20 (41.7)
≤1	40 (3.0)	66 (4.2)	32 (2.9)	7 (4.9)	0 (0.0)
>1–5	191 (14.4)	429 (27.4)	156 (14.1)	18 (12.5)	12 (25)
>5	551 (41.6)	601 (38.4)	467 (42.1)	59 (41.0)	16 (33.3)
Not documented	1 (0.08)	4 (0.3)	1 (0.09)	0 (0.0)	0 (0.0)
NCI Comorbidity Index, mean (SD)	0.29 (0.47)	0.39 (0.52)	0.28 (0.47)	0.31 (0.45)	0.41 (0.57)
Number of metastatic sites,[d] n (%)					
1	654 (49.4)	843 (53.9)	543 (48.9)	75 (52.1)	24 (50.0)
2	367 (27.7)	291 (18.6)	316 (28.5)	32 (22.2)	14 (29.2)
3	178 (13.4)	133 (8.5)	150 (13.5)	21 (14.6)	4 (8.3)
4	56 (4.2)	31 (2.0)	48 (4.3)	6 (4.2)	2 (4.2)
≥5	33 (2.5)	22 (1.4)	25 (2.3)	6 (4.2)	2 (4.2)
Not documented	36 (2.7)	244 (15.6)	28 (2.5)	4 (2.8)	2 (4.2)
Median follow-up duration (IQR), months	25.0 (13.8-38.3)	23.3 (11.8-42.3)	25.6 (14.0-39.0)	24.7 (13.5-36.2)	22.9 (12.2-38.6)

[a]Other/unknown also includes Asian, Hispanic, or Latino.
[b]Visceral disease was defined as metastatic disease in the lung and/or liver; patients could have other sites of metastases. No visceral disease was defined as no lung or liver metastases.
[c]Bone-only disease was defined as metastatic disease in the bone only.
[d]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).
Abbreviations: AI, aromatase inhibitor; BC, breast cancer; ECOG PS, Eastern Cooperative Oncology Group Performance Status; IQR, interquartile range; mBC, metastatic breast cancer; NCI, National Cancer Institute.

significantly longer for patients treated with palbociclib plus an AI (37.4 months [95% CI, 33.7-40.7]) when compared with patients treated with an AI alone (29.2 months [95% CI, 26.8-33.5]; HR = 0.77 [0.69-0.86]; $P < .0001$; Figure 2B). After PSM, median TTC was 37.8 months (95% CI, 33.7-41.3) in the palbociclib plus an AI group and 30.7 months (95% CI, 27.2-35.7) in the AI alone group (HR = 0.78 [95% CI, 0.68-0.89]; $P = .0002$; Figure 2C).

3.4 | Real-world progression-free survival 2

In the unadjusted analysis of the full cohort, median rwPFS2 was 32.3 months (95% CI, 29.8-34.8) among patients in the palbociclib plus an AI group and 19.6 months (95% CI, 18.3-21.7) in the AI alone group (HR = 0.58 [0.52-0.64]; $P < .0001$; Figure 3A). After sIPTW, median rwPFS2 was significantly longer among patients treated with

TABLE 2 Palbociclib dose adjustments.

Dose modification	Initial dose 125 mg (n = 1110)	Dose modification	Initial dose 100 mg (n = 144)	Dose modification	Initial dose 75 mg (n = 48)
Dose change, n (%)	456 (41.1)		53 (36.8)		15 (31.3)
125 to 100 only, n (%)	247 (22.3)	100 to 75 only, n (%)	32 (22.2)	75 to 100 only, n (%)	4 (8.3)
125 to 100 to 75 only, n (%)	132 (11.9)	100 to 125 only, n (%)	10 (6.9)	75 to 100 to 125 only, n (%)	2 (4.2)
125 to 75 only, n (%)	42 (3.8)			75 to 125 only, n (%)	0 (0)
Other change, n (%)	35 (3.2)		11 (7.6)		9 (18.8)
Reduction, n (%)	421 (37.9)	Adjustment, n (%)	42 (29.2)	Increase, n (%)	6 (12.5)
Median days to first adjustment (IQR)	85 (52-195)		95 (39-236)		112 (39-171)
Number of adjustments					
Median	0		0		0
Mean (SD)	0.60 (0.85)		0.47 (0.74)		0.69 (1.21)
Range	0–6		0–4		0–5

Abbreviation: IQR, interquartile range.

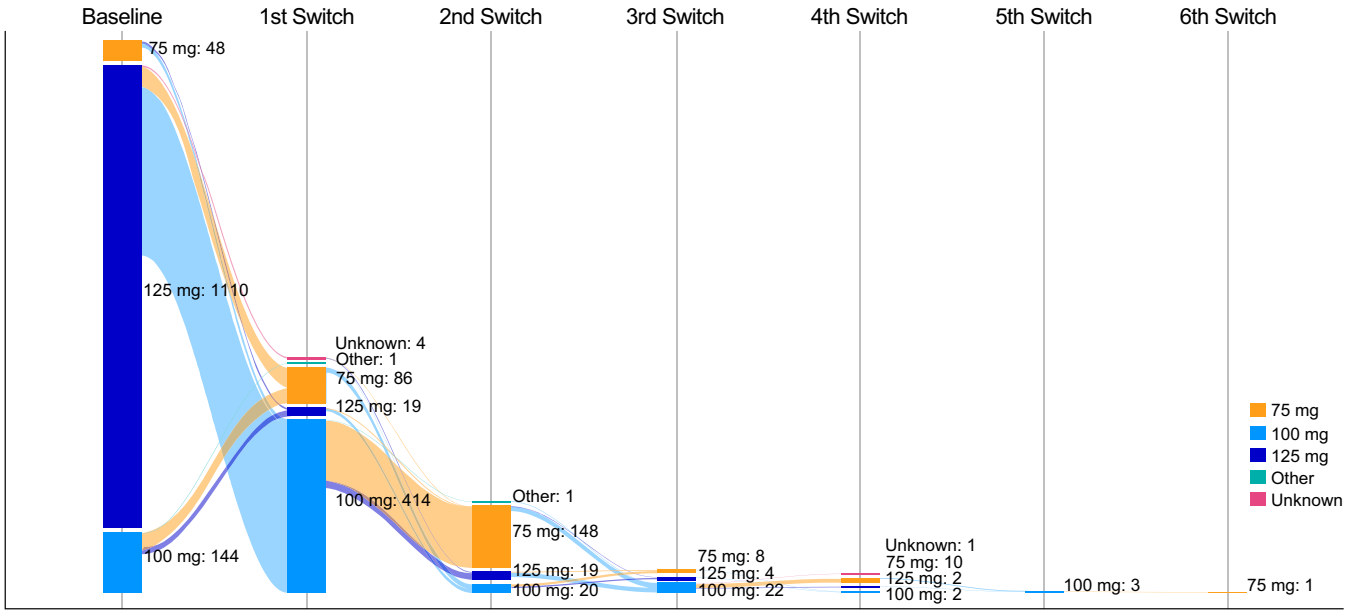
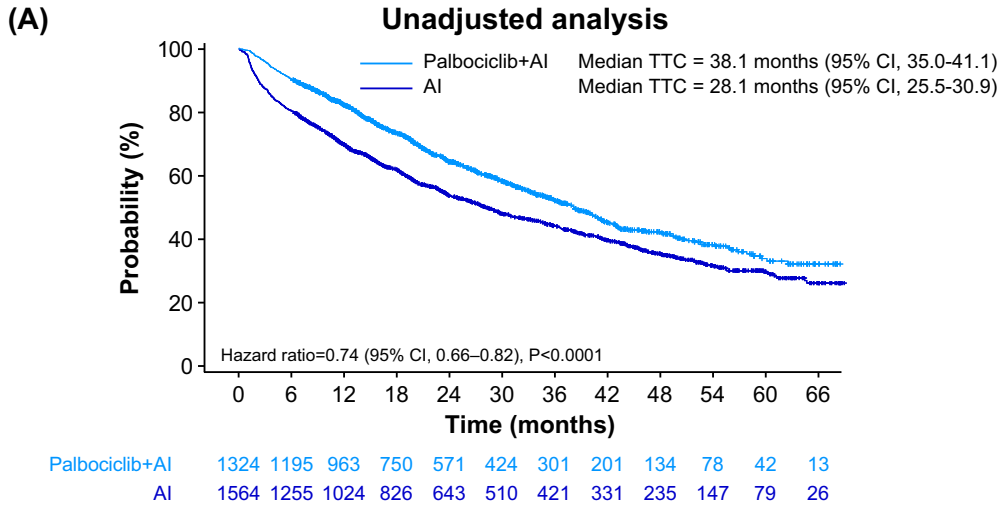


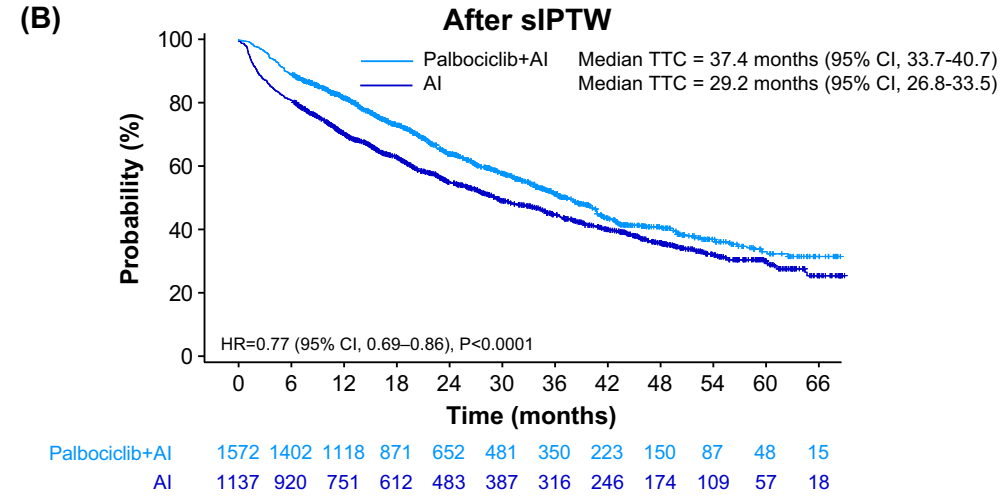
FIGURE 1 Sankey diagram indicating the dose adjustments in patients treated with palbociclib in combination with an aromatase inhibitor during a median follow-up period of 25 months.

palbociclib plus an AI (32.6 months [95% CI, 29.4-35.2]) when compared with patients treated with an AI alone (20.7 months [95% CI, 18.9-22.6]), resulting in a 38% reduction in the risk of disease progression (HR = 0.62; 95% CI, 0.54-0.70; $P < .0001$; Figure 3B). After PSM, median rwPFS2 was 32.2 months (95% CI, 29.3-35.2) for patients receiving palbociclib plus an AI compared with 22.0 months (95% CI, 19.8-24.3) for patients receiving an AI alone (HR = 0.64; 95% CI, 0.56-0.73; $P < .0001$; Figure 3C).

4 | DISCUSSION

Real-world studies provide an important perspective from a treatment experience in a non-clinical trial setting where specific safety monitoring, follow-up visits, or allowed concomitant medications are not protocol driven. Real-world studies can provide additional insights to the data generated in a randomized controlled trial setting. While the diversity of patients in clinical trials can be limited by strict inclusion and exclusion criteria, real-world studies are more generalizable to actual patient populations in clinical practice. In this retrospective analysis of 2888 patients in the Flatiron Health Analytic Database, we found that the majority (83.8%) of patients initiated palbociclib at the recommended dose of 125 mg/day; of these patients, 41.1% had a dose modification and the median number of days until the first dose adjustment was 85 days. Treatment with palbociclib plus an AI was associated with a delay in TTC and a rwPFS2 benefit when compared to treatment with AI alone in this large cohort of men and postmenopausal women with HR+/HER2− mBC.





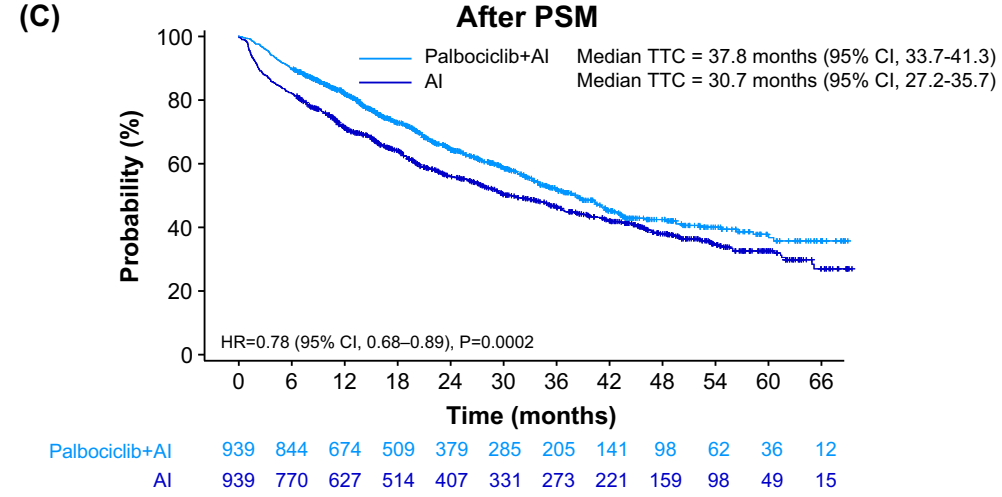


FIGURE 2 Kaplan-Meier curves of time to chemotherapy. (A) Unadjusted analysis, (B) After sIPTW, (C) After PSM. AI, aromatase inhibitor; HR, hazard ratio; PAL, palbociclib; PSM, propensity score matching; sIPTW, stabilized inverse probability of treatment weighting; TTC, time to chemotherapy. Statistical significance was analyzed by a weighted Cox proportional hazards model.

In real-world US clinical practice, treatment decisions may differ from those in a clinical trial due to differences including the patient population, considerations for adverse events, and local setting factors. In the PALOMA-2 trial, patients in the palbociclib + letrozole arm started palbociclib at 125 mg/day.[6] Per the current drug label, the recommended starting dose for palbociclib is 125 mg/day unless patients have severe liver impairment or external factors predispose them to decreased palbociclib clearance from plasma.[25] In our study, 14.7% of patients started palbociclib at a lower-than-recommended dose. Patients that started palbociclib at lower-than-recommended

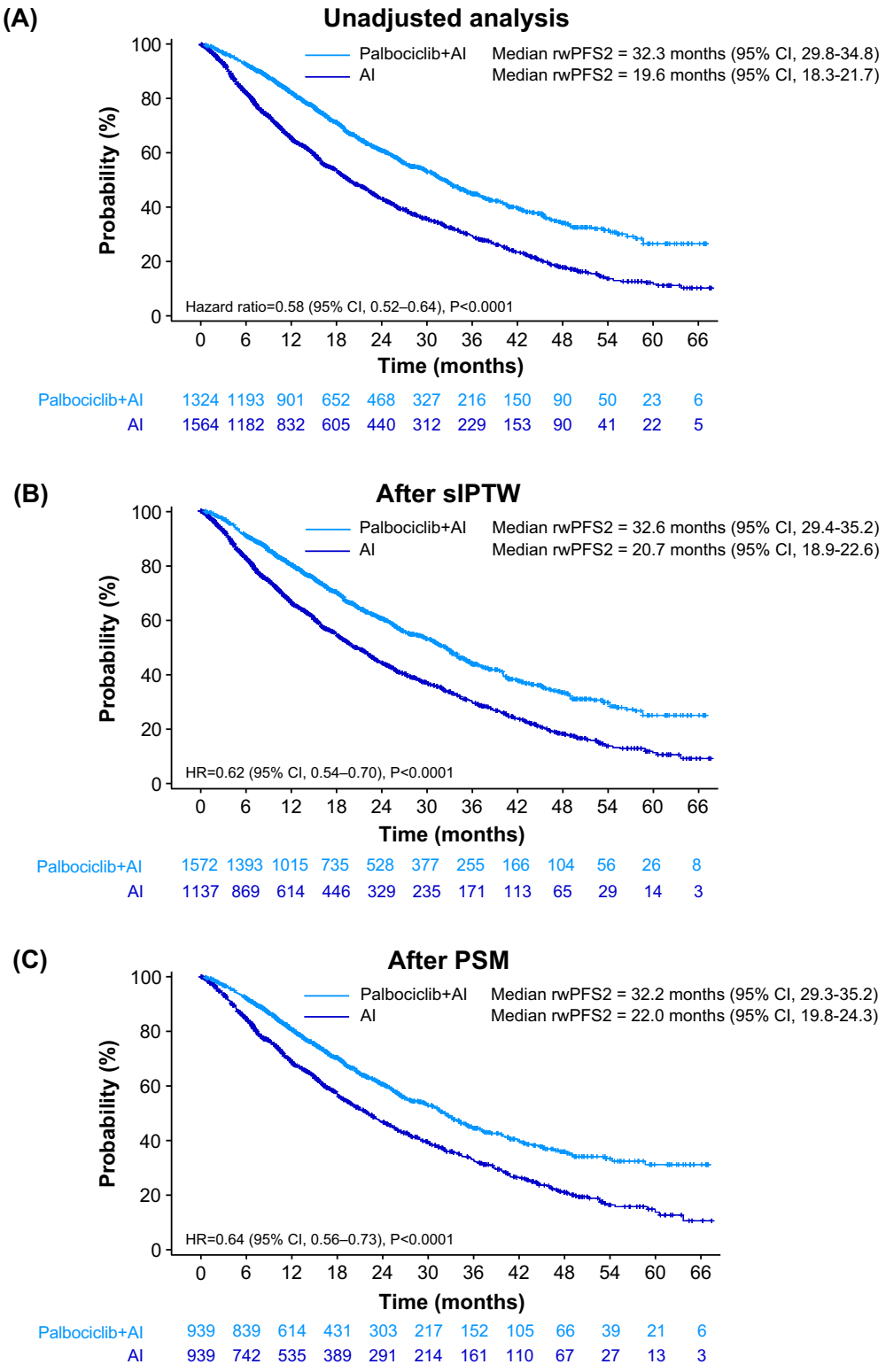


FIGURE 3 Kaplan-Meier curves of real-world progression free survival 2. (A) Unadjusted analysis, (B) After sIPTW and (C) After PSM. AI, aromatase inhibitor; HR, hazard ratio; PAL, palbociclib; PSM, propensity score matching; sIPTW, stabilized inverse probability of treatment weighting; rwPFS2, real-world progression-free survival 2. Statistical significance was analyzed by a weighted Cox proportional hazards model.

doses were older (median age 71.5 and 73.5 years starting at 100 and 75 mg/day, respectively) compared with those starting at 125 mg/day (median age 67.0 years). Furthermore, a greater proportion of patients who were started on a lower dose of palbociclib had ECOG performance status 2-4 than those that started at the recommended dose. Of note, some patients who started at lower-than-recommended doses had their dose increased, 6.9% for those starting on 100 mg/day and 12.5% for those starting on 75 mg/day. This is noteworthy because outcomes data on lower starting doses and their modifications are limited owing to the usage of the recommended 125 mg/day starting dose in palbociclib clinical trials. Percentages of patients starting palbociclib at lower than 125 mg/day reported in other real-world

studies range from 0% to 27.3%.[16,26-31] While patients in the PALOMAGE were aged 70.0 years or older, similar to our study, 27.3% of patients (vs 14.7% of patients in our study) were started on palbociclib at a lower initial dose.[26]

Here, of the patients who started palbociclib treatment at 125 mg/day, 37.9% experienced dose reductions. Other US-based real-world-evidence studies reported dose reductions as follows: 20.1% of patients (using data from 1 year after approval of palbociclib);[27] 34.0% of patients (using data from the expanded-access program),[28] 19.7% of patients in the IRIS study;[31] and 39.2% with dose reductions in a smaller cohort from the Flatiron Health Analytics database.[16] While direct comparisons cannot be made between findings from real-world data and randomized clinical trials, the dose reduction results presented here are in alignment with the PALOMA-1 and PALOMA-2 clinical trials, wherein 39.8% and 39.4% of patients, respectively, had dose reductions,[5,7] despite differences in the patient characteristics such as median age (patients in P-REALITY X are older), and treatment setting (academic setting in the PALOMA trials vs community setting in P-REALITY X).[20]

While not all patients started palbociclib at the recommended dose of 125 mg/day and 37.9% had their dose reduced, studies have shown that dose reduction does not adversely affect PFS. Clifton et al[32] reported more dose reductions in older adults (aged >65.0 years); however, they found rwPFS to be longer (but not significantly so after adjustment) for patients who experienced dose reductions;[32] while patients with pre-existing conditions often experienced dose reductions, they still obtained a PFS benefit.[33] In a real-world study of patients receiving palbociclib with fulvestrant in the 2L or greater treatment setting, median rwPFS did not differ among patients with neutropenia-related dose reductions and interruptions and those without dose modifications.[34] While these studies report no adverse effect of lower doses, at least one study observed that patients starting palbociclib at the recommended dose had a higher rwPFS and real-world best tumor responses than the small proportion of patients who started at lower doses.[16] Data from the PALOMA trials additionally showed that dose reductions did not impact PFS;[35,36] however, dose reductions within all trials are based on individual tolerability and follow a protocol-specific algorithm with all beginning at the recommended starting dose.[37]

An increase in the median TTC means a longer time before patients are exposed to a treatment option with more toxicity, which can have a substantial impact on quality of life. Notably, in our study, with a median follow-up period of over 25 months, consistent improvements in median TTC favoring treatment with palbociclib plus an AI vs an AI alone across the unadjusted, primary sIPTW statistical approach and PSM sensitivity analysis are reported. For context, the P-REALITY X study showed a 5.4-month rwPFS benefit (HR = 0.70 [95% CI, 0.62-0.78]; $P < .0001$) for palbociclib plus an AI (19.3 months [95% CI, 17.5-20.7] vs 13.9 months [95% CI, 12.5-15.2] for AI alone). Here, TTC was improved (HR = 0.77 [95% CI, 0.69-0.86]; $P < .0001$) by more than 8 months (37.4 months [95% CI, 33.7-40.7] for palbociclib plus an AI vs 29.2 months [95% CI, 26.8-33.5] for an AI alone). Median TTC reported in Patt et al[16] was also comparable (36.6 months) with a shorter median follow-up (21 months). These data are generally consistent with results from the PALOMA-1[38] and PALOMA-2[7] trials where palbociclib plus letrozole treatment increased median TTC by 9.0 months (26.7 months [95% CI, 19.2-32.7] for palbociclib plus letrozole vs 17.7 months [95% CI, 16.1-24.2], for letrozole alone; HR = 0.66 [95% CI, 0.45-0.99]) and 10.5 months (40.4 months [95% CI, 34.7-47.3] for palbociclib plus letrozole vs 29.9 months [95% CI, 25.6-35.1] for placebo plus letrozole; HR = 0.74 [95% CI, 0.59-0.92]), respectively. PALOMA-3 also showed a TTC benefit for palbociclib post-endocrine treatment failure of 8.8 months (17.6 months [95% CI, 15.2-19.7] for palbociclib plus fulvestrant vs 8.8 months [95% CI, 7.3-12.7] for placebo plus fulvestrant; HR = 0.58 [95% CI, 0.47-0.73]; $P < .001$).[39] Additional clinical trials have shown a TTC benefit for other CDK4/6 inhibitors, including ribociclib (MONALEESA-2 and MONALEESA-7), and abemaciclib (MONARCH-3) in combination with ET when used in the 1L of therapy.[40]

PFS2 assesses the maintenance of benefits of sequential treatment (ie, whether PFS after the subsequent treatment a patient receives is impacted by their 1L treatment), thus informing on the benefits of sequential therapy.[41] PFS2 may be a surrogate measure in clinical trials to measure long-term benefits where delays in OS maturation make OS difficult to assess.[42,43] Whereas post-progression therapeutic options and crossover to receive investigational drugs can also confound study endpoints like OS, PFS2 is able to circumvent the confounding effects of subsequent lines of therapy.[43] Here, the median time to disease progression on the 2L of therapy was significantly longer for patients who initiated palbociclib plus an AI compared with those who initiated an AI alone for 1L treatment. The definition of PFS2 varies across clinical trials with very few having evaluated PFS2 as defined here. In MONALEESA-7, median PFS2 (time from randomization to investigator-assessed disease progression on 2L therapy, or death from any cause, whichever occurred first) in pre- or perimenopausal women with HR+/HER2− advanced breast cancer favored ribociclib plus ET over placebo plus ET (not evaluable vs 32.3 months, respectively; HR = 0.69; 95% CI, 0.55-0.87).[40,44] The phase 3 MONALEESA-3 trial evaluating PFS2 (defined as in MONALEESA-7) in women with postmenopausal HR+/HER2− advanced breast cancer treated in the 1L or 2L setting observed favorable median PFS2 outcomes for those treated with ribociclib plus fulvestrant (37.4 months) vs placebo plus fulvestrant (28.1 months) (HR = 0.71; 95% CI, 0.57-0.84).[45] PFS2 was not evaluated in PALOMA-2 but PALOMA-3 reported a statistically significant difference in median PFS2 between the two arms (18.8 months vs 14.1 months, respectively [HR = 0.68; 95% CI, 0.56-0.84; $P < .001$]).[39] However, PFS2 in PALOMA-3 was defined as the time from randomization to the end of the immediate subsequent line of therapy after disease progression.[39] Importantly, now for the first time in a real-world setting, results suggest that treatment with palbociclib did not detrimentally affect subsequent treatment, that is, a tumor does not become tolerant or less responsive to subsequent treatment after 1L treatment with palbociclib.

This study has several strengths including the scale and diversity of the Flatiron Health Analytics Database population. While relatively few breast cancer clinical trials include men, the approximately 1% of men included in the Flatiron Health Analytics Database is representative of

the expected real-world male: female breast cancer incidence ratio.[1,3,13] This along with the diverse study population (32%, non-White) as well as percentage of elderly patients (33%, ≥75 years) in this study further adds to its strength. To our knowledge, the P-REALITY X study is the largest real-world study to date to evaluate the comparative effectiveness of a CDK4/6 inhibitor combination treatment for people with HR+/HER2− mBC across multiple sites in the real-world setting. The baseline demographic and clinical characteristics of the patients in the overall Flatiron database are comparable to data from the National Cancer Institute's Surveillance, Epidemiology, and End Results program or the Centers for Disease Control's National Program of Cancer Registries.[46] The large sample size and long median follow-up duration made this dataset fit for the purposes of assessing the comparative effectiveness of palbociclib combination treatment with respect to endpoints requiring longer follow-up such as PFS2 and TTC. Importantly, the significant results in the unadjusted and PSM analyses were consistent with the primary sIPTW findings of this study. The consistent statistically significant results across clinically meaningful endpoints—rwPFS, OS, rwPFS2 and TTC—further strengthen the P-REALITY X study conclusions. Additionally, our results are in alignment with other real-world evidence studies evaluating palbociclib.

Owing to the retrospective nature of the study, typical limitations of a data source in which the primary purpose was not research are present, including potential bias in treatment selection, incomplete or missing data, limited data on comorbidities, and the potential for inaccurate data capture. Unlike in clinical trials, disease progression based on scans was not assessed according to a pre-defined schedule and was not based on Response Evaluation Criteria in Solid Tumors; therefore, the data are limited by the treating physician's interpretation of radiographic scans or pathology results. Results from this analysis may not be generalizable to patients outside the Flatiron network or to non-US healthcare systems. In this study, it was not known if patients who started palbociclib at lower than recommended doses did so due to hepatic impairment or other intrinsic factors that reduce palbociclib clearance.

In conclusion, there is an accumulating body of real-world evidence studies that have evaluated palbociclib in combination with an AI in patients with HR+/HER2− mBC in the 1L.[16-18,20,27-29,31,47-52] The results here add to the understanding and support of the benefit of palbociclib plus an AI in the 1L for people with HR+/HER2− mBC in the real world setting. In addition to significantly prolonged OS and rwPFS, treatment with palbociclib plus an AI in a heterogeneous population of men and postmenopausal women with HR+/HER2− mBC was associated with a longer TTC. Furthermore, palbociclib in combination with an AI continued to provide a PFS benefit when combining 1L and 2L of treatment, thus further supporting the timing of palbociclib as a 1L therapy. These additional outcomes are important to healthcare practitioners and patients when considering treatment options.

AUTHOR CONTRIBUTIONS

The work reported in the paper has been performed by the authors, unless clearly specified in the text. Conceptualization: Hope S. Rugo, Xianchen Liu, Benjamin Li, Lynn McRoy and Connie Chen. Formal analysis: Hope S. Rugo, Adam Brufsky, Rachel M. Layman, Xianchen Liu, Benjamin Li, Lynn McRoy and Connie Chen. Writing—review & editing: Hope S. Rugo, Adam Brufsky, Rachel M. Layman, Xianchen Liu, Benjamin Li, Lynn McRoy and Connie Chen.

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CONFLICT OF INTEREST STATEMENT

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DATA AVAILABILITY STATEMENT

Upon request, and subject to review, Pfizer will provide the data that support the findings of this study. Subject to certain criteria, conditions and exceptions, Pfizer may also provide access to the related individual de-identified participant data. See https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information. Further information is available from the corresponding author upon request.

ETHICS STATEMENT

This retrospective database analysis was conducted in accordance with the Guidelines for Good Pharmacoepidemiology Practice, Good Practices for Outcomes Research issued by the International Society for Pharmacoeconomics and Outcomes Research, and Good Practices for Real-world Data Studies of Treatment and/or Comparative Effectiveness. As this study is retrospective and non-interventional and uses anonymized data, it is exempt from institutional review board approval and included a waiver of informed consent. Trial registration number: NCT05361655.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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