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Real-world progression-free survival 2 (rwPFS2) and tumor response with CDK4/6is + aromatase inhibitor (AI) in patients (pts) with HR+/HER2– metastatic breast cancer (mBC)

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Objective

To compare real-world progression-free survival 2 (rwPFS2) and real-world tumor response (rwTR) with palbociclib, ribociclib, or abemaciclib in combination with an aromatase inhibitor (AI), as first-line (1L) treatment for hormone receptor-positive/human epidermal growth factor receptor 2-negative (HR+/HER2–) metastatic breast cancer (mBC) in routine clinical practice in the United States (US).

Conclusions

This large real-world comparative analysis suggests that there are no significant differences in rwPFS2 and rwTR between 1L palbociclib plus AI, ribociclib plus AI, and abemaciclib plus AI in patients with HR+/HER2– mBC.

These findings align with previous P-VERIFY analyses, which also suggested no significant differences in overall survival (OS) and real-world progression-free survival (rwPFS) among the 3 CDK4/6 inhibitors for this patient group.

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Background

- Cyclin-dependent kinase 4/6 (CDK4/6) inhibitors, including palbociclib, ribociclib, and abemaciclib, in combination with endocrine therapy are the standard of care for 1L treatment of HR+/HER2– mBC.[1]
- In the absence of head-to-head randomized controlled trials, there has been an emerging body of real-world evidence for the relative effectiveness of CDK4/6 inhibitors in terms of PFS and OS in patients with HR+/HER2– mBC.[2–10]
- P-VERIFY is the largest real-world study to date to compare relative effectiveness of the 3 CDK4/6 inhibitors.[11,12]
  - Previously reported results from P-VERIFY showed no significant OS and rwPFS differences between 1L CDK4/6 inhibitors (palbociclib, ribociclib, or abemaciclib) when used in combination with AI for patients with HR+/HER2– mBC in routine clinical practice in the US.[11,12]
- There remains a lack of real-world studies evaluating relative CDK4/6 inhibitor effectiveness for other important clinical outcomes such as rwPFS2 and rwTR.
- Here, we report comparative rwPFS2 and rwTR data from the P-VERIFY study between 3 CDK4/6 inhibitors plus AI.

Methods

STUDY DESIGN AND DATA SOURCE

- P-VERIFY (NCT06495164) was a retrospective comparative effectiveness study using the US nationwide Flatiron Health electronic health record-derived deidentified longitudinal database, comprised of patient-level data originating from ~280 US clinics and curated via technology enabled abstraction.[13–15]
- This study included all eligible patients with HR+/HER2– mBC who received 1L treatment with a CDK4/6 inhibitor plus an AI between February 2015 and November 2023.
- Patients were observed from the start of index treatment (palbociclib plus AI, ribociclib plus AI, or abemaciclib plus AI) to the end of May 2024 (data cutoff), death, or last medical activity, whichever came first.

OUTCOMES

- Real-world PFS2 was defined as the time from 1L CDK4/6 inhibitor plus AI initiation to disease progression (based on clinical assessment, radiographic scan, or tissue biopsy) on second-line (2L) treatment or death from any cause, whichever came first.[16]
  - Patients who were alive and did not have disease progression on 2L treatment were censored at the date of initiation of the third line of therapy, the date of their last medical activity, or the data cutoff date, whichever occurred first.
- Real-world TR was defined as the change in burden of disease over the course of 1L index treatment after 1 month of treatment initiation based on the treating clinician's assessment of radiological evidence.[17]
- The rwTR rate was defined as the percentage of patients who had a complete tumor response or partial response in 1L.
- Clinical benefit rate (CBR) was defined as the percentage of patients who achieved either a complete response or partial response or had stable disease in 1L.

STATISTICAL ANALYSIS

- Descriptive statistics were used to describe patient baseline characteristics.
- All study patients were included in the rwPFS2 analysis. In rwTR analysis, only patients who had at least 1 tumor response assessment were included.
- rwPFS2 was estimated using the Kaplan–Meier method; Cox proportional hazards models were used to compute hazard ratios (HRs) and their corresponding 95% confidence intervals (CIs).
- Logistic regression analyses were applied to compare the response rates between treatment groups. Odds ratios (OR) and 95% CIs were reported.
- Three methods were used for comparative analysis: (1) unadjusted analysis; (2) the stabilized inverse probability of treatment weighting (sIPTW) method (primary analysis) to balance baseline patient characteristics; (3) multivariable Cox proportional hazards model (sensitivity analysis).
- A separate analysis was conducted for patients who initiated treatment in 2017 or later, corresponding to when all three CDK4/6 inhibitors were approved and available in the US.

Results

PATIENTS

- Of the 9146 patients with HR+/HER2– mBC who were eligible for rwPFS2 analysis, 6831, 1279, and 1036 patients received treatment with palbociclib plus AI, ribociclib plus AI, and abemaciclib plus AI, respectively.
  - After sIPTW, baseline demographics and patient characteristics were generally balanced between the 3 groups (standardized difference < 0.1; **Table 1**).

Table 1. Patient characteristics after sIPTW

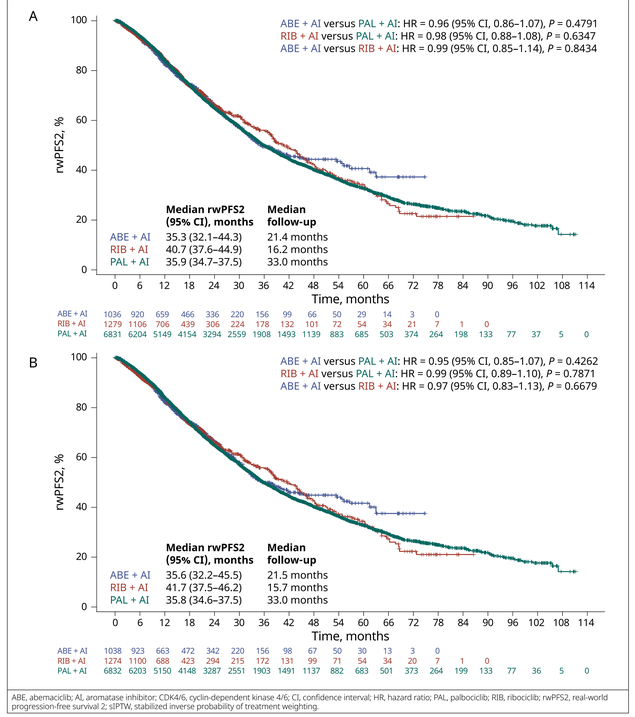
Characteristic	rwPFS2 analysis cohort			rwTR analysis cohort		
	PAL + AI (n = 6832)	RIB + AI (n = 1274)	ABE + AI (n = 1038)	PAL + AI (n = 6086)	RIB + AI (n = 1044)	ABE + AI (n = 877)
Mean age at mBC diagnosis, years (SD)	65.0 (11.7)	64.6 (12.0)	64.7 (12.1)	64.8 (11.7)	64.3 (12.1)	64.5 (12.1)
Female sex, n (%)	6762 (99.0)	1263 (99.1)	1026 (98.9)	6022 (98.9)	1034 (99.1)	867 (98.9)
Race, n (%)						
White	4272 (62.5)	797 (62.6)	654 (63.0)	3851 (63.3)	659 (63.1)	558 (63.7)
Black	638 (9.3)	117 (9.2)	94 (9.1)	577 (9.5)	97 (9.3)	82 (9.4)
Other	1922 (28.1)	360 (28.3)	290 (27.9)	1659 (27.3)	288 (27.6)	237 (27.0)
Practice type, n (%)						
Community	5782 (84.6)	1085 (85.2)	872 (84.0)	5183 (85.2)	897 (85.9)	743 (84.7)
Academic	1050 (15.4)	189 (14.8)	166 (16.0)	903 (14.8)	147 (14.1)	134 (15.3)
Disease stage at initial diagnosis, n (%)						
I	720 (10.5)	136 (10.7)	112 (10.8)	646 (10.6)	110 (10.5)	95 (10.9)
II	1538 (22.5)	287 (22.5)	238 (22.9)	1382 (22.7)	238 (22.8)	203 (23.2)
III	731 (10.7)	136 (10.7)	110 (10.6)	644 (10.6)	113 (10.8)	90 (10.2)
IV	3473 (50.8)	645 (50.6)	523 (50.4)	3098 (50.9)	529 (50.7)	443 (50.5)
Not documented	370 (5.4)	70 (5.5)	56 (5.4)	316 (5.2)	55 (5.2)	46 (5.2)
ECOG PS, n (%)						
0	2444 (35.8)	457 (35.9)	369 (35.5)	2234 (36.7)	387 (37.1)	321 (36.6)
1	1806 (26.4)	329 (25.9)	275 (26.5)	1634 (26.9)	274 (26.2)	235 (26.8)
2, 3, or 4	780 (11.4)	147 (11.5)	119 (11.5)	652 (10.7)	112 (10.7)	95 (10.8)
Not documented	1801 (26.4)	341 (26.7)	275 (26.5)	1566 (25.7)	271 (25.9)	226 (25.7)
Disease-free interval, n (%)						
De novo mBC	3473 (50.8)	645 (50.6)	523 (50.4)	3098 (50.9)	529 (50.7)	443 (50.5)
≤ 1 year	276 (4.0)	52 (4.1)	42 (4.1)	246 (4.0)	42 (4.0)	36 (4.1)
> 1–5 years	1082 (15.8)	202 (15.8)	162 (15.6)	942 (15.5)	161 (15.4)	134 (15.3)
> 5 years	2001 (29.3)	376 (29.5)	311 (30.0)	1799 (29.6)	312 (29.9)	264 (30.1)
Visceral metastasis,[a] n (%)	2374 (34.7)	443 (34.8)	358 (34.5)	2104 (34.6)	357 (34.2)	301 (34.3)
Bone-only metastasis,[b] n (%)	3171 (46.4)	591 (46.4)	481 (46.3)	2868 (47.1)	494 (47.3)	412 (47.0)
Number of metastatic sites,[c] n (%)						
1	4010 (58.7)	745 (58.5)	611 (58.8)	3615 (59.4)	620 (59.4)	521 (59.4)
2	1585 (23.2)	304 (23.9)	240 (23.1)	1402 (23.0)	245 (23.5)	201 (23.0)
≥ 3	615 (9.0)	111 (8.7)	92 (8.9)	534 (8.8)	87 (8.3)	77 (8.8)
Not documented	622 (9.1)	114 (8.9)	95 (9.2)	535 (8.8)	92 (8.8)	78 (8.9)
Menopausal status at initial diagnosis, n (%)						
Premenopausal	1265 (18.5)	279 (21.9)	204 (19.6)	1149 (18.9)	239 (22.9)	172 (19.6)
Postmenopausal	5138 (75.2)	919 (72.1)	762 (73.4)	4561 (74.9)	736 (70.5)	645 (73.6)
Not documented	359 (5.2)	65 (5.1)	61 (5.9)	311 (5.1)	60 (5.7)	50 (5.7)
Not applicable (patient is male)	70 (1.0)	11 (0.9)	11 (1.1)	64 (1.1)	10 (0.9)	10 (1.1)
Year of index date, n (%)						
2015	440 (6.4)	0	0	395 (6.5)	0	0
2016	657 (9.6)	0	0	595 (9.8)	0	0
2017	713 (10.4)	70 (5.5)	0	639 (10.5)	52 (5.0)	0
2018	789 (11.6)	122 (9.6)	58 (5.6)	713 (11.7)	91 (8.7)	56 (6.4)
2019	870 (12.7)	102 (8.0)	125 (12.0)	774 (12.7)	91 (8.8)	110 (12.5)
2020	928 (13.6)	92 (7.2)	146 (14.0)	833 (13.7)	67 (6.4)	122 (14.0)
2021	1026 (15.0)	80 (6.3)	189 (18.2)	906 (14.9)	56 (5.4)	160 (18.3)
2022	870 (12.7)	226 (17.7)	247 (23.8)	766 (12.6)	190 (18.2)	201 (22.9)
2023	539 (7.9)	582 (45.7)	273 (26.3)	466 (7.7)	496 (47.5)	228 (26.0)
Median follow-up duration (IQR), months	33.0 (34.7)	15.7 (20.8)	21.5 (25.0)	34.2 (34.4)	16.4 (19.9)	22.6 (24.3)

[a]Visceral disease is defined as metastatic disease in the lung and/or liver; patients could have had other sites of metastases.
[b]Bone-only disease is defined as metastatic disease in the bone only.
[c]Multiple metastases at the same site were counted as one site (eg, 3 bone metastases in the spine was considered only one site).
ABE, abemaciclib; AI, aromatase inhibitor; ECOG PS, Eastern Cooperative Oncology Group performance status; IQR, interquartile range; mBC, metastatic breast cancer; PAL, palbociclib; RIB, ribociclib; rwPFS2, real-world progression-free survival 2; rwTR, real-world tumor response; SD, standard deviation; sIPTW, stabilized inverse probability of treatment weighting.

rwPFS2

- Median rwPFS2 after sIPTW was 35.8 (95% CI, 34.6–37.5) months for palbociclib plus AI; 41.7 (95% CI, 37.5–46.2) months for ribociclib plus AI; and 35.6 (95% CI, 32.2–45.5) months for abemaciclib plus AI. Similar rwPFS2 findings were found in the unadjusted analysis (**Figure 1**).
- There were no significant differences in rwPFS2 after sIPTW when comparing the ribociclib and palbociclib groups (HR = 0.99 [95% CI, 0.89–1.10]; P = 0.7871), the abemaciclib and palbociclib groups (HR = 0.95 [95% CI, 0.85–1.07]; P = 0.4262), and the abemaciclib and ribociclib groups (HR = 0.97 [95% CI, 0.83–1.13]; P = 0.6679). Similar findings were found in the unadjusted analysis (**Figure 1**).

Figure 1. rwPFS2 (A) in unadjusted analysis and (B) after sIPTW among the 3 CDK4/6 inhibitors



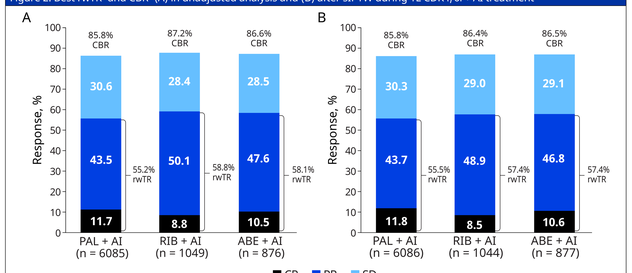
ABE, abemaciclib; AI, aromatase inhibitor; CDK4/6, cyclin-dependent kinase 4/6; CI, confidence interval; HR, hazard ratio; PAL, palbociclib; RIB, ribociclib; rwPFS2, real-world progression-free survival 2; sIPTW, stabilized inverse probability of treatment weighting.

- Results from the subgroup analysis by patient characteristics showed that rwPFS2 after sIPTW were generally consistent with those from the overall cohort for each treatment group comparison (data not shown).
- Multivariable Cox proportional-hazards regression analysis also showed no significant differences in rwPFS2 between treatment groups (HR range, 0.96 to 0.99; all P >0.4).
- In a separate analysis of patients who first received index treatment from 2017 onward (N = 8050; palbociclib n = 5735; ribociclib n = 1279; abemaciclib n = 1036), there were no significant differences in rwPFS2 observed between treatment groups after sIPTW (HR range, 0.97–1.00; all P >0.6), in unadjusted analysis (HR range, 0.98–0.99; all P >0.6), and in sensitivity analysis (HR range, 0.97–1.00; all P >0.6).

rwTR

- Among the overall population, 8010 (87.6%) patients had at least 1 tumor response assessment and were eligible for the rwTR analysis (palbociclib plus AI: n = 6085; ribociclib plus AI: n = 1049; abemaciclib plus AI: n = 876).
  - Patient characteristics after sIPTW were generally balanced between the 3 treatment groups (standardized difference < 0.1; **Table 1**).
- Best overall rwTR rates after sIPTW were 55.5% for palbociclib plus AI, 57.4% for ribociclib plus AI, and 57.4% for abemaciclib plus AI (**Figure 2**).
- The CBR after sIPTW was 85.8% for palbociclib plus AI, 86.4% for ribociclib plus AI, and 86.5% for abemaciclib plus AI.
- Best rwTR rate and CBR after sIPTW were generally consistent with the results from the unadjusted analysis (**Figure 2**).

Figure 2. Best rwTR[a] and CBR[a] (A) in unadjusted analysis and (B) after sIPTW during 1L CDK4/6i + AI treatment



[a]rwTR is calculated as CR + PR; CBR is calculated as CR + PR + SD.
ABE, abemaciclib; AI, aromatase inhibitor; CBR, clinical benefit rate; CDK4/6, cyclin-dependent kinase 4/6; CR, complete response; PAL, palbociclib; PR, partial response; RIB, ribociclib; rwTR, real-world tumor response; SD, stable disease; sIPTW, stabilized inverse probability of treatment weighting.

- After sIPTW, no significant associations were found in the comparisons of rwTR between CDK4/6 inhibitor treatment groups (ribociclib vs palbociclib: OR = 1.079 [95% CI, 0.945–1.232], P = 0.2617; abemaciclib vs palbociclib: OR = 1.082 [95% CI, 0.938–1.248], P = 0.2806; abemaciclib vs ribociclib: OR = 1.003 [95% CI, 0.836–1.202], P = 0.9760). Similar findings were observed in the unadjusted analysis.
- In a separate analysis of patients who first received index treatment from 2017 onward and had at least one tumor response assessment (N = 7023; palbociclib n = 5098; ribociclib n = 1049; abemaciclib n = 876), best overall rwTR rates and CBR were similar across treatment groups both after sIPTW and in the unadjusted analysis.
  - No significant differences in rwTR were observed between treatment groups after sIPTW (OR range, 1.0–1.1; all P >0.1). In the unadjusted analysis, a significant difference was observed between the ribociclib and palbociclib groups (OR = 1.16; P = 0.028), while differences between the abemaciclib and palbociclib groups (OR = 1.13; P = 0.1), and the abemaciclib and ribociclib groups (OR = 0.97; P = 0.752) showed no significant differences.

LIMITATIONS

- This study was a retrospective database analysis, which inherently carries the potential for treatment selection bias and inaccurate, missing or incomplete data. Due to the retrospective design, causality cannot be inferred.
- Although statistical methodologies were used to balance baseline characteristics between treatment groups, these cannot account for potential unmeasured confounders.
- Disease progression and tumor response were based on treating physicians' clinical assessments or interpretation of radiographic scans after assessments, rather than standard criteria such as Response Evaluation Criteria in Solid Tumors.
- The ribociclib and abemaciclib groups had short follow-up times and small sample sizes relative to the palbociclib group.
- Results may not be generalizable to patient populations that were not represented in the Flatiron Health database.

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