PS2-03

Comparative Overall Survival of CDK4/6 inhibitors Plus an Aromatase Inhibitor in HR+/HER2– Metastatic Breast Cancer in the US Real-World Setting

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Objective

To compare overall survival (OS) in patients receiving 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 study represents the largest RW comparative analysis of OS between the CDK4/6 inhibitors in combination with an AI conducted to date.
- Our findings suggest that there are no significant OS differences between 1L palbociclib, ribociclib, or abemaciclib used in combination with an AI for patients with HR+/HER2– mBC in routine clinical practice in the US.

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References: 1. Gradishar WJ, et al. *J Natl Compr Canc Netw*. 2023;21(6):594-608. **2.** U.S. Food and Drug Administration. IBRANCE (palbociclib). Prescribing Information. Accessed: Aug 19, 2024. **3.** U.S. Food and Drug Administration. KISQALI (ribociclib). Prescribing Information. Accessed: Aug 19, 2024. **4.** U.S. Food and Drug Administration. VERZENIO (abemaciclib). Prescribing Information. Accessed: Aug 19, 2024. **5.** Cejuela M, et al. *Int J Mol Sci*. 2023;24(10):8488. **6.** Kahraman S, et al. *Future Oncol*. 2023;19(10):727-736. **7.** Buller W, et al. *J Oncol Pharm Pract*. 2023;29(8):1825-1835. **8.** Vernieri C, et al. *J Clin Oncol*. 2024;42:1014. **9.** Gehrchen ML, et al. *BJC Reports*. 2024;2(1):44. **10.** Abdallah HMA, et al. *Ann Oncol*. 2023;34:S369-S370. **11.** Thill M, et al. *Cancer Res*. 2024;84(9_Suppl):PO1-04-12. **12.** Al-Ziftawi NH, et al. *Front Oncol*. 2023;13:1203684. **13.** Miron AI, et al. *Diagnostics (Basel)*. 2023;13(11):1938. **14.** Tang H, et al. *Cancers (Basel)*. 2023;15(21):5164. **15.** Ma X, et al. *medRxiv*. 2023:2020.03.16.20037143. **16.** Birnbaum B, et al. *arXiv*. 2020:2001.09765.

Acknowledgments: This study was funded by Pfizer Inc. Medical writing support was provided by Diana Avery, PhD, of Oxford PharmaGenesis Inc., Newtown, PA, USA, and was funded by Pfizer Inc., USA.

Funding source: Study sponsored by Pfizer Inc.

Presented at the San Antonio Breast Cancer Symposium® • December 10–13, 2024 • San Antonio, TX

GCMA Code: PP-IBR-IRL-0732 Date of prep: December 2024

Introduction

- The combination of a cyclin-dependent kinase 4/6 (CDK4/6) inhibitor with endocrine therapy is a standard-of-care 1L treatment for patients with HR+/HER2– mBC.[1]
  - Palbociclib was the first CDK4/6 inhibitor approved in the US in 2015, followed by ribociclib and abemaciclib in 2017.[2-4]
- In the absence of head-to-head randomized clinical trials, several real-world (RW) studies have evaluated comparative effectiveness between the 3 CDK4/6 inhibitors.[5-14]
  - Findings were inconsistent across these studies, limited by small sample sizes and short follow-up.
  - Most did not show significant differences in RW progression-free survival and/or OS among CDK4/6 inhibitors.
- Large-scale, RW comparative studies with longer follow-up are needed to further elucidate the relative effectiveness of the 3 approved CDK4/6 inhibitors.

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 cancer clinics (~800 sites of care) and curated via technology-enabled abstraction.[15,16]
- This study included all eligible patients with HR+/HER2– mBC who initiated 1L treatment with a CDK4/6 inhibitor plus an AI between February 2015 and November 2023.
- Patients were followed 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

- The primary outcome was OS, defined as the number of months from start of index treatment to death.
- Date of death was a consensus mortality endpoint based on electronic health record, Social Security Death Index, and obituary data, validated against the National Death Index.
- Patients still alive were censored at the end of the study.

STATISTICAL ANALYSIS

- Descriptive statistics were used to describe patient baseline characteristics.
- Median OS (95% confidence interval [CI]) and landmark OS rates were estimated using the Kaplan–Meier method and displayed graphically.
- The Cox proportional hazards model was used to compute hazard ratios (HRs) and corresponding 95% CIs.
- Four methods were used for comparative analysis: (1) unadjusted analysis without adjusting for baseline patient characteristics; (2) the stabilized inverse probability of treatment weighting (sIPTW) method (primary analysis); (3) multivariable Cox proportional hazards model (sensitivity analysis); and (4) 1:1 exact matching (sensitivity analysis).

Results

PATIENTS

- Of 9146 patients eligible for this 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 clinical characteristics were generally balanced between the 3 groups (standardized difference < 0.1; **Table 1**).
- Median duration of follow-up before and after sIPTW was 33 months for patients treated with palbociclib plus AI, approximately 16 months for patients treated with ribociclib plus AI, and approximately 21 months for patients treated with abemaciclib plus AI (**Table 1**).

Table 1. Patient characteristics after sIPTW

Characteristic	Cohort			Standardized Difference		
	PAL + AI (n = 6832)	RIB + AI (n = 1274)	ABE + AI (n = 1038)	RIB + AI vs PAL + AI	ABE + AI vs PAL + AI	ABE + AI vs RIB + AI
Age at mBC diagnosis, years						
Mean (SD)	65.0 (11.7)	64.6 (12.0)	64.7 (12.1)	–0.0297	–0.0198	0.0097
Median (IQR)	66.0 (17.0)	66.0 (17.0)	66.0 (17.0)			
Sex, n (%)						
Male	70 (1.0)	11 (0.9)	11 (1.1)	–0.0178	0.0068	0.0245
Female	6762 (99.0)	1263 (99.1)	1026 (98.9)			
Race, n (%)						
White	4272 (62.5)	797 (62.6)	654 (63.0)	0.0008	0.0093	0.0086
Black	638 (9.3)	117 (9.2)	94 (9.1)	–0.0063	–0.0081	–0.0018
Other	1922 (28.1)	360 (28.3)	290 (27.9)	0.0032	–0.0048	–0.0081
Practice type, n (%)						
Community	5782 (84.6)	1085 (85.2)	872 (84.0)	0.0154	–0.0169	–0.0323
Academic	1050 (15.4)	189 (14.8)	166 (16.0)			
Disease stage at initial diagnosis, n (%)						
I	720 (10.5)	136 (10.7)	112 (10.8)	0.0052	0.0091	0.0039
II	1538 (22.5)	287 (22.5)	238 (22.9)	0.0005	0.0092	0.0088
III	731 (10.7)	136 (10.7)	110 (10.6)	–0.0003	–0.0044	–0.0041
IV	3473 (50.8)	645 (50.6)	523 (50.4)	–0.0046	–0.0096	–0.0050
Not documented	370 (5.4)	70 (5.5)	56 (5.4)	0.0027	–0.0023	–0.0051
ECOG PS, n (%)						
0	2444 (35.8)	457 (35.9)	369 (35.5)	0.0025	–0.0050	–0.0075
1	1806 (26.4)	329 (25.9)	275 (26.5)	–0.0133	0.0008	0.0141
2, 3, or 4	780 (11.4)	147 (11.5)	119 (11.5)	0.0032	0.0018	–0.0015
Not documented	1801 (26.4)	341 (26.7)	275 (26.5)	0.0082	0.0035	–0.0048
Disease-free interval,[a] n (%)						
De novo mBC	3473 (50.8)	645 (50.6)	523 (50.4)	–0.0046	–0.0096	–0.0050
≤ 1 year	276 (4.0)	52 (4.1)	42 (4.1)	0.0014	0.0007	–0.0007
> 1–5 years	1082 (15.8)	202 (15.8)	162 (15.6)	0.0000	–0.0065	–0.0065
> 5 years	2001 (29.3)	376 (29.5)	311 (30.0)	0.0044	0.0154	0.0109
Visceral metastases,[b] n (%)						
No	4458 (65.3)	831 (65.2)	680 (65.5)	–0.0006	0.0060	0.0066
Yes	2374 (34.7)	443 (34.8)	358 (34.5)			
Bone-only metastases, n (%)						
No	3661 (53.6)	683 (53.6)	557 (53.7)	0.0004	0.0020	0.0016
Yes	3171 (46.4)	591 (46.4)	481 (46.3)			
Number of metastatic sites,[c] n (%)						
1	4010 (58.7)	745 (58.5)	611 (58.8)	–0.0040	0.0029	0.0069
2	1585 (23.2)	304 (23.9)	240 (23.1)	0.0158	–0.0025	–0.0183
≥ 3	615 (9.0)	111 (8.7)	92 (8.9)	–0.0112	–0.0036	0.0076
Not documented	622 (9.1)	114 (8.9)	95 (9.2)	–0.0055	0.0023	0.0078
Menopausal status at initial diagnosis, n (%)						
Premenopausal	1265 (18.5)	279 (21.9)	204 (19.6)	0.0849	0.0279	–0.0570
Postmenopausal	5138 (75.2)	919 (72.1)	762 (73.4)	–0.0702	–0.0415	0.0286
Not documented	359 (5.2)	65 (5.1)	61 (5.9)	–0.0066	0.0283	0.0349
Not applicable (patient is male)	70 (1.0)	11 (0.9)	11 (1.1)	–0.0178	0.0068	0.0245
Year of index date, n (%)						
2015	440 (6.4)	0	0	–0.3711	–0.3711	
2016	657 (9.6)	0	0	–0.4612	–0.4612	
2017	713 (10.4)	70 (5.5)	0	–0.1839	–0.4826	–0.3403
2018	789 (11.6)	122 (9.6)	58 (5.6)	–0.0633	–0.2151	–0.1529
2019	870 (12.7)	102 (8.0)	125 (12.0)	–0.1550	–0.0209	0.1343
2020	928 (13.6)	92 (7.2)	146 (14.0)	–0.2102	0.0129	0.2229
2021	1026 (15.0)	80 (6.3)	189 (18.2)	–0.2860	0.0858	0.3699
2022	870 (12.7)	226 (17.7)	247 (23.8)	0.1393	0.2897	0.1505
2023	539 (7.9)	582 (45.7)	273 (26.3)	0.9435	0.5050	–0.4115
Median follow-up duration (IQR), months	33.0 (34.7)	15.7 (20.8)	21.5 (25.0)			

[a]Disease-free interval was defined as the interval from initial breast cancer diagnosis to mBC diagnosis.
[b]Visceral metastases were defined as metastatic disease in the lung and/or liver; patients could have had other sites of metastases. No visceral metastasis was defined as no metastatic disease in the lung or liver.
[c]Multiple metastases at the same site were counted as 1 site (e.g., 3 bone metastases in a patient's spine were counted as 1 site only).
ABE, abemaciclib; AI, aromatase inhibitor; ECOG PS, Eastern Cooperative Oncology Group performance status; IQR, interquartile range; mBC, metastatic breast cancer; PAL, palbociclib; RIB, ribociclib; SD, standard deviation; sIPTW, stabilized inverse probability treatment weighting.

OVERALL SURVIVAL

- Among 9146 patients in the unadjusted analysis, a total of 3714 deaths were observed: 3096 of 6831 (45.3%) in the palbociclib group, 328 of 1279 (25.6%) in the ribociclib group, and 290 of 1036 (28.0%) in the abemaciclib group.
  - A total of 5432 patients were censored, including 3735 of 6831 (54.7%) in the palbociclib group, 951 of 1279 (74.4%) in the ribociclib group, and 746 of 1036 (72.0%) in the abemaciclib group.
- There were no significant differences in OS between treatment groups in the unadjusted analysis (**Figure 1A**).
- Similarly, no significant differences in OS were found between treatment groups after sIPTW (**Figure 1B**).
  - The adjusted HR was 0.98 (95% CI, 0.87–1.10; $P = 0.7531$) for the ribociclib vs palbociclib comparison, 0.95 (95% CI, 0.84–1.08; $P = 0.4292$) for the abemaciclib vs palbociclib comparison, and 0.97 (95% CI, 0.82–1.14; $P = 0.6956$) for the abemaciclib vs ribociclib comparison.
- After sIPTW, 12-, 24-, and 30-month OS rates in the treatment groups were: palbociclib, 89.7%, 77.5%, and 71.4%; ribociclib, 89.2%, 77.3%, and 72.2%; abemaciclib, 88.2%, 76.1%, and 71.5% (**Figure 1B**).
- Results from the subgroup analysis of OS after sIPTW in each of the pairwise group comparisons (**Figure 2**) were generally consistent with results from the overall cohort.

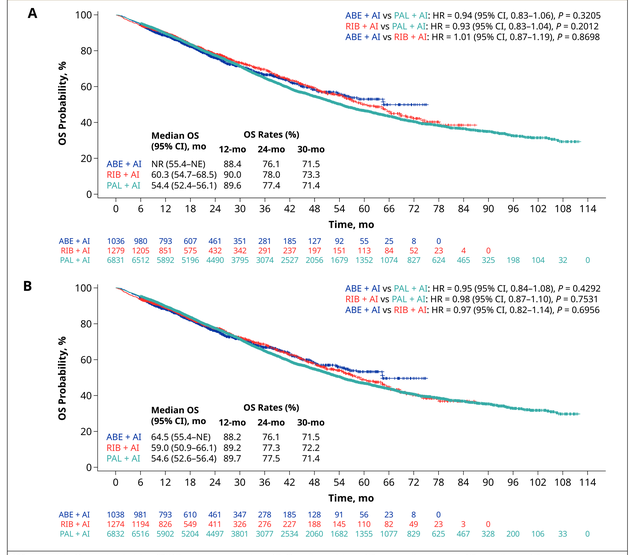
SENSITIVITY ANALYSES

- Multivariable Cox proportional hazards regression analysis also showed no significant differences in OS between treatment groups.
  - The adjusted HR was 0.94 (95% CI, 0.84–1.06; $P = 0.3216$) when comparing the ribociclib group vs the palbociclib group, 0.94 (95% CI, 0.84–1.07; $P = 0.3603$) when comparing the abemaciclib group vs the palbociclib group, and 1.00 (95% CI, 0.85–1.17; $P = 0.9851$) when comparing the abemaciclib group vs the ribociclib group.
- After 1:1 exact matching, there were no significant differences in OS between treatment groups.
  - The adjusted HR was 0.99 (95% CI, 0.85–1.15; $P = 0.8519$) when comparing the ribociclib group vs the palbociclib group, 0.95 (95% CI, 0.80–1.13; $P = 0.5898$) when comparing the abemaciclib group vs the palbociclib group, and 0.96 (95% CI, 0.75–1.24; $P = 0.7630$) when comparing the abemaciclib group vs the ribociclib group.

SUBANALYSIS OF PATIENTS WHO STARTED INDEX TREATMENT IN 2017 OR LATER

- This subanalysis included 5735, 1279, and 1036 patients treated with palbociclib plus AI, ribociclib plus AI, and abemaciclib plus AI, respectively.
- After sIPTW, the adjusted HR was 1.00 (95% CI, 0.89–1.13; P = 0.9728) for the ribociclib vs palbociclib comparison, 0.96 (95% CI, 0.84–1.09; P = 0.5326) for the abemaciclib vs palbociclib comparison, and 0.96 (95% CI, 0.81–1.13; P = 0.6077) for the abemaciclib vs ribociclib comparison.

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

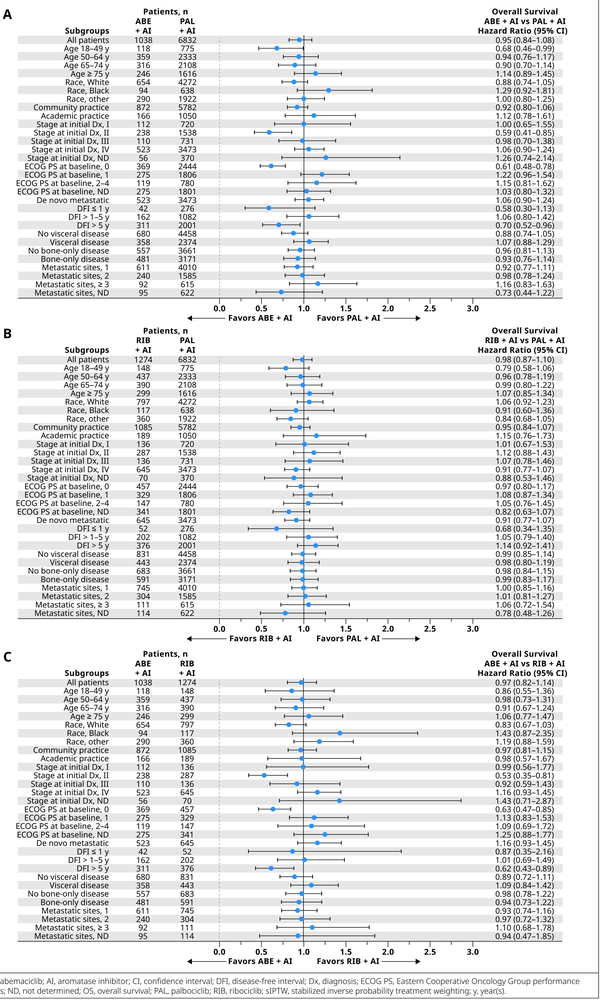


ABE, abemaciclib; AI, aromatase inhibitor; CDK4/6, cyclin-dependent kinase 4/6; CI, confidence interval; HR, hazard ratio; mo, month; NE, not estimable; NR, not reached; OS, overall survival; PAL, palbociclib; RIB, ribociclib; sIPTW, stabilized inverse probability treatment weighting.

Limitations

- The study was a retrospective database analysis, which inherently carries the potential for treatment selection bias and inaccurate or incomplete data capture.
- Although statistical methodologies were used to balance baseline characteristics between treatment groups, these cannot account for potential unmeasured confounders.
- The ribociclib and abemaciclib groups had small sample sizes and short follow-up times relative to the palbociclib group, which may cause point estimates to be unstable beyond 30 months of follow-up.
- Results may not be generalizable to patient populations that were not represented in the Flatiron Health database.

Figure 2. Forest plot of OS by subgroup after sIPTW: (A) abemaciclib + AI vs palbociclib + AI, (B) ribociclib + AI vs palbociclib + AI, and (C) abemaciclib + AI vs ribociclib + AI



ABE, abemaciclib; AI, aromatase inhibitor; CI, confidence interval; DFI, disease-free interval; Dx, diagnosis; ECOG PS, Eastern Cooperative Oncology Group performance status; ND, not determined; OS, overall survival; PAL, palbociclib; RIB, ribociclib; sIPTW, stabilized inverse probability treatment weighting; y, year(s).