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Original Article

Comparative efficacy of CDK4/6 inhibitors palbociclib, ribociclib, and abemaciclib in HR$^+$/HER2$^-$ advanced breast cancer

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Abstract: This study aimed to explore the clinical efficacy of palbociclib, ribociclib, and abemaciclib in hormone receptor-positive, human epidermal growth factor receptor 2-negative (HR$^+$/HER2$^-$) advanced breast cancer (ABC) and to identify factors influencing treatment outcomes. A retrospective analysis was conducted on the clinicopathological data from 240 patients treated between January 2022 and June 2023. Patients were divided into three groups: Group A (n=69, palbociclib 125 mg orally, 3 weeks on/1 week off, plus fulvestrant), Group B (n=72, ribociclib 600 mg orally, 3 weeks on/1 week off, plus fulvestrant), Group C (n=99, abemaciclib 150 mg orally, twice daily, plus fulvestrant). The primary endpoint was real-world progression-free survival (rwPFS); secondary endpoints included objective response rate (ORR), clinical benefit rate (CBR), duration of response (DoR), patient-reported outcomes (PROs), and adverse events (AEs). Multivariate Cox regression analysis was performed to identify prognostic factors. Baseline characteristics were comparable among groups (P>0.05). In first-line treatment, ribociclib and abemaciclib showed a trend toward longer rwPFS compared with palbociclib. Abemaciclib had a higher 24-month ORR compared to palbociclib (P=0.049) and the longest DoR (all P<0.05), but was associated with the greatest decline in PRO (31.31% meaningful deterioration). The most common AEs were neutropenia with palbociclib, hepatotoxicity/QT prolongation with ribociclib, and diarrhea with abemaciclib. In the first-line treatment of HR$^+$/HER2$^-$ ABC, ribociclib and abemaciclib may offer a modest advantage in PFS, while abemaciclib may be superior in inducing objective tumor responses. However, neither drug exhibits comprehensive superiority across all endpoints. Therefore, clinical treatment decisions should take consideration of multiple factors based on individualized medicine protocol.

Keywords: CDK4/6 inhibitors, real-world progression-free survival (rwPFS), hormone receptor-positive breast cancer

Introduction

Cancer is a major global health burden, with breast cancer being the most prevalent malignancy among women [1]. According to 2022 global cancer statistics, breast cancer accounts for 11.6% of all new cancer cases and 6.9% of all cancer-related deaths worldwide; among women, it constitutes approximately 24% of new cancer cases and 15% of cancer-related deaths [2]. Most breast cancers are hormone-driven, with about 70% expressing hormone receptors such as estrogen receptor (ER) [3]. For patients with hormone receptor-positive (HR$^+$) advanced breast cancer (ABC), endocrine therapy has long been the standard treatment due to its favorable efficacy-toxicity profile [4]. However, 30-50% of patients eventually develop acquired resistance within 12-24 months, leading to disease progression [5]. Mechanistically, drug resistance involves adaptive changes in cancer cells, including modification of estrogen receptors or activation of compensatory signaling pathways, which promote tumor growth even under continuous treatment [6].

Cyclin-dependent kinases 4 and 6 (CDK4/6) are key regulators of cell cycle progression, and their hyperactivation in breast cancer drives uncontrolled cellular proliferation [7]. Endocrine therapy alone often fails to fully suppress this pathway, contributing to treatment resistance.

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Mechanistically, CDK4/6 complexes with cyclin D to phosphorylate and inactivate retinoblastoma protein (Rb), facilitating G1-to-S phase transition [8, 9].

Currently, three CDK4/6 inhibitors - palbociclib, ribociclib, and abemaciclib - are approved globally for HR+/HER2- ABC and have become the standard of care when combined with endocrine therapy [10, 11]. Despite targeting the same pathway, these agents differ in kinase selectivity, target engagement, half-life, tissue distribution, and dosing schedules, which may translate into variable efficacy and safety, particularly in endocrine-resistant settings. However, direct head-to-head comparative studies among the three inhibitors remain lacking [12, 13]. Moreover, prior phase III trials differed substantially in patient populations, endpoint definitions, and follow-up durations, complicating cross-trial comparisons [14]. Strict eligibility criteria in these trials often excluded patients with significant comorbidities or advanced age, limiting the generalizability of trial findings to real-world practice [15, 16]. Therefore, comparative studies capturing not only efficacy and safety but also patient-reported outcomes are warranted to inform individualized treatment decisions [17, 18].

In this study, we compared treatment responses among 240 patients with HR+/HER2- ABC who received a combination of CDK4/6 inhibitors and fulvestrant. The aim of this study is to provide evidence to support personalized therapeutic strategies that optimize both patient quality of life and long-term prognosis.

Research methods

Research subjects

This retrospective study included 240 patients diagnosed with hormone receptor-positive, human epidermal growth factor receptor 2-negative (HR+/HER2-) ABC. All patients were treated at our hospital from January 2022 to June 2023. Based on the CDK4/6 inhibitor administered, the patients were divided into three cohorts: Group A (n=69) received palbociclib, Group B (n=72) treated with ribociclib, and Group C (n=99) treated with Abemaciclib.

Inclusion criteria

1. Age ≥18 years, female (male breast cancer patients excluded due to extremely limited sample size); 2. Pathologically confirmed breast cancer via histology or cytology, with immunohistochemistry demonstrating HR-positive and HER2- negative status; 3. Diagnosis of advanced breast cancer (presence of local recurrence or distant metastasis, with measurable or evaluable lesions per RECIST 1.1); 4. Receiving first-line treatment (defined as no prior systemic anticancer therapy at advanced stage, or recurrence/metastasis occurring ≥1 year after completion of adjuvant endocrine therapy); 5. Eastern Cooperative Oncology Group (ECOG) performance status (PS) score of 0-2; 6. Baseline cardiac, hepatic, and renal function within normal limits; 7. Complete clinical documentation, including pathology reports, imaging studies, treatment records, and follow-up data [19, 20].

Exclusion criteria

1. Concurrent malignant tumors (excluding curable tumors); 2. Active infections (e.g., sepsis, active tuberculosis) or severe systemic diseases (e.g., severe heart failure, decompensated cirrhosis); 3. History of QT interval prolongation, congenital long QT syndrome, or concurrent use of medications known to prolong the QT interval (e.g., fluconazole, erythromycin); 4. Pregnant or lactating women; 5. Hypersensitivity to palbociclib, ribociclib, abemaciclib, or fulvestrant components; 6. Treatment interruption exceeding 2 weeks due to non-progression-related reasons (e.g., severe adverse reactions) without resumption of therapy; 7. Incomplete follow-up data preventing efficacy or safety assessment [20, 21].

Ethical statement

This study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki [22] and was approved by the ethics committee of Ganzhou Fifth People's Hospital. Due to the retrospective design, the requirement for informed consent was waived by the ethics committee, and all patient data were anonymized prior to analysis.

Research design

All patients received CDK4/6 inhibitor therapy in combination with fulvestrant, with specific regimens as follows [23, 24]:

1. Group A (Palbociclib Group): Palbociclib (125 mg/tablet, Pfizer Pharmaceuticals Co., Ltd.,

National Drug Approval Number J20180042): 125 mg orally once daily for 21 consecutive days, followed by a 7-day drug-free interval, constituting one cycle; Fulvestrant (500 mg/vial, AstraZeneca Pharmaceuticals Co., Ltd., National Drug Approval Number J20190024): 500 mg intramuscular injection (alternating sides of the buttocks) on Days 1, 15, and 29 of Cycle 1; 500 mg injection on Day 1 of each subsequent 30-day cycle.

2. Group B (Ribociclib Group): Ribociclib (200 mg/tablet, Novartis Pharmaceuticals Co., Ltd., National Drug Approval No. J20200009): 600 mg orally once daily for 21 consecutive days, followed by a 7-day drug-free interval to complete one cycle. Fulvestrant: 500 mg intramuscular injection (alternating sides of the buttocks) on Days 1, 15, and 29 of Cycle 1; 500 mg injection on Day 1 of each subsequent 28-day cycle (dose adjustment same as Group A).

3. Group C (Abemaciclib Group): Abemaciclib (150 mg/tablet, Eli Lilly and Company, China Drug Approval No. J20210018): 150 mg orally twice daily continuously (no drug-free interval). In the event of Grade ≥3 adverse reactions, the dose was reduced to 100 mg twice daily; if intolerance persisted, the dose was further reduced to 50 mg twice daily. Fulvestrant administration follows Group A protocol.

The sample size was determined based on the total number of eligible patients treated at our center during the study period. To ensure adequate statistical power for the primary endpoint (real-world progression-free survival [rwPFS]), a minimum of 210 patients was estimated, assuming a two-sided significance level of 0.05, a power of 80%, and an expected hazard ratio of 0.65 between treatment groups. Ultimately, 240 eligible patients were included.

All patients received supportive care tailored to their assigned therapy. Palbociclib group: prophylactic use of granulocyte colony-stimulating factor (G-CSF) if prior Grade 3 neutropenia occurred; Ribociclib group: regular monitoring of liver function and electrocardiogram; Abemaciclib group: prophylactic use of loperamide after first episode of diarrhea.

Observation indicators

Baseline data: Pre-treatment collection of patient demographics (age, body mass index [BMI], ECOG PS score), pathological characteristics (histological type, ER/PR positivity intensity), disease features (metastatic sites: visceral metastases including lung, liver, brain metastases; bone metastases; lymph node metastases), endocrine resistance status and comorbidities (e.g., hypertension, diabetes), and comorbidities (e.g., hypertension, diabetes).

Primary endpoint: rwPFS [25]: Defined as the time from treatment initiation to the first documented evidence of disease progression or death from any cause, based on routine clinical assessments, including imaging reports and clinical records, rather than protocol-scheduled radiological evaluations. Patients without progression or death by the last follow-up were censored at the date of last contact. This definition reflects the variability in real-world assessment intervals and clinical practice patterns.

Secondary endpoints: (1) Objective Response Rate (ORR) [25]: Proportion of patients achieving a complete response (CR) or a partial response (PR), as defined by the RECIST 1.1 criteria; (2) Clinical Benefit Rate (CBR) [26]: Proportion of patients achieving CR, PR, or stable disease (SD) for ≥6 months; (3) Duration of Response (DoR) [27]: Time from the first CR or PR to disease progression or death, censored at last assessment for patients without progression; (4) Patient-Reported Outcomes (PROs) [28]: Assessed using the EORTC QLQ-C30 (Version 3.0), including the Overall Quality of Life Score (0-100 points). Clinically significant deterioration was defined as a ≥10 points decrease in the Overall Quality of Life Score; (5) Safety endpoints [29]: Adverse events were recorded according to the CTCAE version 5.0, including: incidence rates calculated based on the drug-exposed population; (6) Cox multivariate analysis: Variables potentially influencing rwPFS (age, ECOG PS score, visceral metastasis, bone metastasis, lymph node metastasis, endocrine resistance, treatment regimen) were internally analyzed using univariate Cox analysis. Variables with $P<0.1$ were included in the multivariate Cox proportional hazards regression analysis.

Statistical analysis

Statistical analyses were performed using SPSS 25.0. Quantitative variables with normal distribution were reported as mean ± standard deviation ($x \pm s$) and compared between groups

Table 1. Comparison of baseline characteristics among three groups [mean ± SD, *n* (%)]

Variable	A (Palbociclib, n=69)	B (Ribociclib, n=72)	C (Abemaciclib, n=99)	Test	F/χ^2	*P*
Age (years)	54.15±8.65	53.81±9.15	55.14±8.33	ANOVA	0.543	0.582
BMI (kg/m^2)	23.51±3.12	22.91±2.86	23.24±3.05	ANOVA	0.707	0.494
ECOG PS Score, n (%)				Chi-Square Test	0.479	0.976
0	41 (59.42)	45 (62.50)	62 (62.63)			
1	24 (34.78)	23 (31.94)	33 (33.33)			
2	4 (5.80)	4 (5.56)	4 (4.04)			
Pathological Type, n (%)				Chi-Square Test	0.376	0.984
Ductal carcinoma	52 (75.36)	55 (76.39)	76 (76.77)			
Lobular carcinoma	12 (17.39)	13 (18.06)	18 (18.18)			
Other	5 (7.25)	4 (5.56)	5 (5.05)			
ER Positive Intensity, n (%)				Chi-Square Test	0.438	0.979
Strong positive (≥75%)	38 (55.07)	40 (55.56)	56 (56.57)			
Positive (10%-74%)	25 (36.23)	27 (37.50)	37 (37.37)			
weak positive (1%-9%)	6 (8.70)	5 (6.94)	6 (6.06)			
PR Positive Intensity, n (%)				Chi-Square Test	0.418	0.981
Strong positive (≥75%)	32 (46.38)	33 (45.83)	45 (45.45)			
Positive (10%-74%)	26 (37.68)	28 (38.89)	41 (41.41)			
weak positive (1%-9%)	11 (15.94)	11 (15.28)	13 (13.13)			
Transfer site, n (%)						
Visceral metastasis	31 (44.93)	33 (45.83)	45 (45.45)	Chi-Square Test	0.012	0.994
Bone metastasis	28 (40.58)	30 (41.67)	42 (42.42)	Chi-Square Test	0.057	0.972
Lymph node metastasis	25 (36.23)	27 (37.50)	38 (38.38)	Chi-Square Test	0.080	0.961
Endocrine resistance, n (%)	22 (31.88)	24 (33.33)	32 (32.32)	Chi-Square Test	0.036	0.982
Comorbidities, n (%)						
Hypertension	18 (26.09)	19 (26.39)	28 (28.28)	Chi-Square Test	0.124	0.940
Diabetes	12 (17.39)	13 (18.06)	17 (17.17)	Chi-Square Test	0.023	0.988

Note: BMI, body mass index; ECOG PS, Eastern Cooperative Oncology Group performance status; ER, estrogen receptor; PR, progesterone receptor.

using one-way analysis of variance (ANOVA). Non-normally distributed continuous data were presented as median (interquartile range, IQR), and categorical data as n (%). Multiple pairwise comparisons among the three treatment groups (palbociclib, ribociclib, and abemaciclib) were adjusted using the Bonferroni correction to control family-wise type I error. Group comparisons for categorical variables were conducted using the chi-square test. Survival analyses were conducted using Kaplan-Meier curves, with group differences assessed using the log-rank test. Variables with a *P*-value <0.1 in univariate analysis were incorporated into a multivariate Cox proportional hazards regression model to identify independent prognostic factors.

Results

Baseline characteristics

No statistically significant differences were observed among the three groups in terms of age, BMI, ECOG PS score, histological type, ER/PR positivity intensity, metastatic sites (visceral, bone, lymph node), endocrine resistance status, or comorbidities (hypertension, diabetes) (all P>0.05) (**Table 1**).

Primary efficacy outcome (rwPFS)

During 24-month follow-up, 89 patients (37.1%) experienced disease progression, and 12 patients (5.0%) died. Kaplan-Meier analysis (**Figure 1**) revealed: Group B (Ribociclib) had a

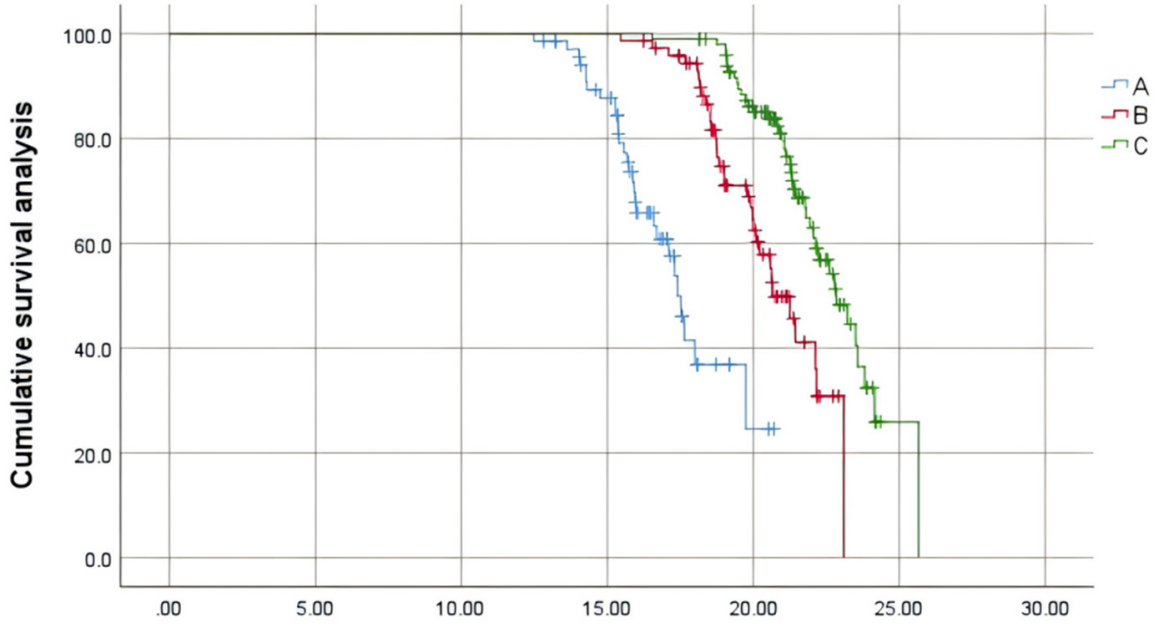

Figure 1. Comparison of rwPFS among three groups.

median rwPFS of 20.6 months (95% CI: 19.8-21.5 months); Group C (Abemaciclib) had a median rwPFS of 22.8 months (95% CI: 21.1-23.8 months). Log-rank test results showed: Group B demonstrated a significant prolongation of rwPFS compared to Group A (χ^2=30.878, P=0.000); Group C demonstrated a significant prolongation of rwPFS compared to Group A (χ^2=67.946, P=0.000); Groups B and C showed no significant difference (χ^2=6.569, P=0.220).

Secondary efficacy outcomes

Objective Response Rate (ORR) and Clinical Benefit Rate (CBR): **Table 2** summarizes ORR and CBR across the three groups. Regarding ORR: Group C (45.5%) was significantly higher than Group A (30.4%) (χ^2=3.846, P=0.049), but not significantly different from Group B (34.7%) (χ^2=1.986, P=0.159). The overall comparison among the three groups was not statistically significant (χ^2=4.343, P=0.114). Regarding CBR: the rate was 69.6% in Group A, 72.2% in Group B, and 74.7% in Group C, with no significant difference (χ^2=0.552, P=0.759).

Duration of Relief (DoR): Among patients achieving CR/PR (Group A: 21 cases, Group B: 25 cases, Group C: 45 cases), the median DoR was was 14.3 months (95% CI: 12.7-15.8 months) in Group A, 15.6 months (95% CI: 14.9-16.3 months) in Group B, and 19.8 months (95% CI: 18.9-20.6 months) in Group C. Intergroup comparisons revealed that Group C had a significantly longer DoR than Group A (Log-rank χ^2=12.496, P=0.002) and Group B (Log-rank χ^2=9.037, P=0.009). No significant difference was observed between Groups A and B (Log-rank χ^2=2.521, P=0.117) (**Table 3**).

PROs

Table 4 shows the changes in overall quality of life (QoL) scores before and after treatment across the three groups. There was no significant difference in overall QoL scores among the three groups prior to treatment (P=0.773); At 3 months, 6 months, and at the end of treatment, all groups experienced a decline from baseline, with Group C (-12.81±10.57) exhibiting a significantly greater decline than Group A (-5.31±11.27) and Group B (-4.81±12.10) (all P<0.05). The proportion of patients experiencing clinically significant deterioration (≥10-point decrease) was significantly higher in Group C (31.31%) than in Groups A (15.94%) and B (18.06%) χ^2=6.814, P=0.033).

Safety profile

All three groups completed at least two treatment cycles, and no patients discontinued ther-

Table 2. Comparison of ORR and CBR among three groups [n (%)]

Variable	A (n=69)	B (n=72)	C (n=99)	Test	χ^2	*P*
ORR				Chi-Square Test	4.343	0.114
CR	3 (4.35)	4 (5.56)	8 (8.08)			
PR	18 (26.09)	21 (29.17)	37 (37.37)			
Total	21 (30.43)	25 (34.72)	45 (45.45)			
CBR				Chi-Square Test	0.552	0.759
CR+PR	21 (30.43)	25 (34.72)	45 (45.45)			
SD ≥6 months	27 (39.13)	27 (37.50)	29 (29.29)			
Total	48 (69.56)	52 (72.22)	74 (74.75)			

Note: CR, complete response; PR, partial response; SD, stable disease.

Table 3. Comparison of median DoR among three groups

Group	Number of instances (n)	Median DoR (months)	95% CI	Log-rank χ^2	value
A	21	14.3	12.7-15.8	vs C: 12.496	vs C: 0.002
				Vs B: 2.521	vs B: 0.117
B	25	15.6	14.9-16.3	Vs C: 9.037	vs C: 0.009
				-	-
C	45	19.8	18.9-20.6	-	-

Note: DoR, duration of response.

Table 4. Comparison of overall QoL scores among three groups before and after treatment (x±s, points)

Time	A (n=69)	B (n=72)	C (n=99)	Test	Effect size	*P*-value
Baseline	80.21±9.75	81.32±9.86	81.24±9.81	ANOVA	0.257	0.773
Treatment at 3 months	77.66±11.18	78.65±10.91	73.23±11.76	ANOVA	5.614	0.004
Treatment at 6 months	76.43±11.86	77.23±11.29	70.14±12.14	ANOVA	9.434	0.001
Treatment completion	74.96±11.05	76.50±10.44	68.42±10.41	ANOVA	14.237	<0.001
Change value (end - baseline)	-5.31±11.27	-4.81±12.10	-12.81±10.57	ANOVA	13.864	<0.001
Clinical significance deterioration [n (%)]	11 (15.94)	13 (18.06)	31 (31.31)	Chi-Square Test	6.814	0.033

Note: QoL, quality of life.

apy due to severe adverse reactions (AEs). **Table 5** presents the incidence of AEs across the three groups. Grade 3-4 AEs: 50.72% (35/69) in Group A, 44.44% (32/72) in Group B, and 38.38% (38/99) in Group C, with no significant intergroup differences (P=0.281).

Hematologic toxicity: The incidence of Grade 3-4 neutropenia in Group A (40.58%) was significantly higher than that in Group B (20.83%) and Group C (10.10%) (χ^2=22.04, P<0.001); Hepatotoxicity: The incidence of Grade 3-4 ALT/AST elevation in Group B (16.67%) was significantly higher than in Group A (5.80%) and Group C (6.06%) (χ^2=6.952, P=0.031); Cardiovascular toxicity: QTcF ≥470 ms was observed more frequently in Group B (11.11%) than in Group A (2.90%) and Group C (3.03%) (χ^2=6.356, P=0.042); No QT interval-related arrhythmias were reported; Gastrointestinal toxicity: Grade 3-4 diarrhea was more frequent in Group C (13.13%) compared with Group A (2.90%) and Group B (5.56%) (χ^2=6.505, P=0.039); Other adverse events (e.g., fatigue, nausea, alopecia) were predominantly Grade 1-2, with no significant differences among the three groups (all P>0.05).

Multivariate Cox regression analysis of factors affecting rwPFS

Univariate analysis: Univariate Cox regression was performed to assess potential factors influencing rwPFS, including rwPFS, ECOG PS

Table 5. Comparison of the incidence of Grade 3-4 adverse events among three groups [n (%)]

Adverse events	A (n=69)	B (n=72)	C (n=99)	Test	Effect size	*P*-value
Hematologic Toxicity						
Neutropenia	28 (40.58)	15 (20.83)	10 (10.10)	Chi-Square Test	22.045	<0.001
Thrombocytopenia	3 (4.35)	2 (2.78)	3 (3.03)	Chi-Square Test	0.318	0.853
Anemia	2 (2.90)	1 (1.39)	2 (2.02)	Chi-Square Test	0.397	0.820
Hepatotoxicity						
Elevated ALT/AST	4 (5.80)	12 (16.67)	6 (6.06)	Chi-Square Test	6.952	0.031
Elevated bilirubin	1 (1.45)	2 (2.78)	1 (1.01)	Chi-Square Test	0.796	0.672
Cardiovascular toxicity						
QT interval prolongation	2 (2.90)	8 (11.11)	3 (3.03)	Chi-Square Test	6.356	0.042
Hypertension	3 (4.35)	4 (5.56)	5 (5.05)	Chi-Square Test	0.109	0.947
Gastrointestinal Toxicity						
Diarrhea	2 (2.90)	4 (5.56)	13 (13.13)	Chi-Square Test	6.503	0.039
Nausea and Vomiting	3 (4.35)	2 (2.78)	4 (4.04)	Chi-Square Test	0.280	0.869
Other						
Fatigue	4 (5.80)	5 (6.94)	7 (7.07)	Chi-Square Test	0.119	0.942
Hair loss	5 (7.25)	6 (8.33)	8 (8.08)	Chi-Square Test	0.063	0.969
Total Grade 3-4 adverse events	35 (50.72)	32 (44.44)	38 (38.38)	Chi-Square Test	2.536	0.281

Note: AE, adverse event; ALT/AST, alanine aminotransferase/aspartate aminotransferase; QT interval, QT interval corrected for heart rate.

score, visceral metastasis, bone metastasis, lymph node metastasis, endocrine resistance, treatment regimen (**Table 6**). The analysis revealed that treatment regimen was significantly associated with rwPFS: ribociclib vs. palbociclib (HR=0.177, 95% CI: 0.101-0.314, P<0.001); abemaciclib vs. palbociclib (HR=0.069, 95% CI: 0.038-0.127, P<0.001). Other variables, including ECOG PS score ≥1, visceral metastasis, endocrine resistance, lymph node metastasis, and bone metastasis, were not statistically significant (all P>0.05) and therefore not included in the multivariate model.

Multivariate analysis: Multivariate Cox regression analysis (**Table 7**) confirmed that treatment regimen remained the only independent factor associated with rwPFS. Specifically, compared with palbociclib, ribociclib (HR=0.177, 95% CI: 0.101-0.314, P<0.001) and abemaciclib (HR=0.069, 95% CI: 0.038-0.127, P<0.001) were both independently associated with significantly longer rwPFS. No other clinical variables, including visceral metastasis, endocrine resistance, or ECOG PS score, were retained in the final multivariate model, consistent with the univariate results.

Discussion

This study retrospectively analyzed real-world data from 240 patients with HR+/HER2- ABC. To our knowledge, it represents one of the first single-center direct comparisons of the efficacy, safety, and PROs among the three CDK4/6 inhibitors - palbociclib, ribociclib, and abemaciclib - each combined with fulvestrant.

In terms of the primary endpoint of rwPFS, both ribociclib and abemaciclib demonstrated significant prolongation compared with palbociclib, whereas no statistically significant difference was observed between ribociclib and abemaciclib. These finding suggest that, in the first-line treatment of HR+/HER2- ABC, both ribociclib and abemaciclib may offer a marginal advantage over palbociclib in delaying disease progression. However, the absence of a significant difference between ribociclib and abemaciclib indicates that neither agent can be conclusively regarded as superior to the other based solely on rwPFS [30].

Regarding secondary efficacy endpoints, abemaciclib demonstrated a higher ORR and a significantly longer DoR. These results indicate

Table 6. Univariate Cox regression analysis of factors affecting rwPFS in HR+/HER2- advanced breast cancer patients

Variables	B	SE	Wald	HR	95% CI	*P* value
Age	0.008	0.012	0.489	1.008	0.985-1.032	0.485
ECOG PS Score ≥1	-0.170	0.205	0.686	0.844	0.565-1.261	0.407
Visceral Metastasis	-0.045	0.202	0.049	0.956	0.643-1.421	0.825
Endocrine Resistance	0.189	0.221	0.737	1.209	0.784-1.863	0.391
Lymph Node Metastasis	-0.037	0.205	0.032	0.964	0.644-1.441	0.857
Bone Metastasis	0.023	0.203	0.012	1.023	0.688-1.522	0.911
Treatment Regimen						
Ribociclib vs. Palbociclib	-1.728	0.291	35.329	0.177	0.101-0.314	<0.001
Abemaciclib vs. Palbociclib	-2.669	0.310	73.955	0.069	0.038-0.127	<0.001

Table 7. Multivariate Cox regression analysis of factors affecting rwPFS in HR+/HER2- advanced breast cancer patients

Variables	B	SE	Wald	HR	95% CI	P
Treatment Regimen						
Ribociclib vs. Palbociclib	-1.728	0.291	35.329	0.177	0.101-0.314	<0.001
Abemaciclib vs. Palbociclib	-2.669	0.310	73.955	0.069	0.038-0.127	<0.001

that, while abemaciclib may be more effective in inducing tumor shrinkage and maintaining response among patients achieving an objective response, this advantage did not translate into a statistically significant improvement in rwPFS compared with ribociclib. No significant differences in CBR were observed among the three groups.

The differential efficacy profiles observed across endpoints may be attributable to distinct pharmacological properties of these agents. Abemaciclib is administered continuously (twice daily without a drug-free interval), whereas palbociclib and ribociclib follow a 3-weeks-on/1-week-off schedule. Preclinical studies have suggested that continuous CDK4/6 inhibition may provide more sustained suppression of tumor cell proliferation [8]. Additionally, abemaciclib targets multiple intracellular kinases beyond CDK4/6, including CDK9 and PIM kinases. Clinically, ribociclib has been associated with the highest risk of hepatotoxicity among the three inhibitors, a phenomenon that may be related to its inhibitory effects on hepatic transporters rather than differences in metabolic pathways [31-34]. However, these mechanisms were not directly tested in our study and should be interpreted cautiously as potential explanatory factors rather than conclusions drawn from the present data.

In terms of safety, three CDK4/6 inhibitors exhibited distinct toxicity profiles consistent with findings from phase III trials. Palbociclib was associated with the highest incidence of grade 3-4 neutropenia (40.58%), which is consistent with its potent inhibitory activity against CDK4/6 in hematopoietic stem cells [35]. Ribociclib showed a higher incidence of grade 3-4 hepatotoxicity (16.67%) and QTc interval prolongation (11.11%), highlighting the need for regular monitoring of liver function and electrocardiograms during treatment. Abemaciclib was associated with a significantly higher incidence of grade 3-4 diarrhea (13.13%), emphasizing the importance of proactive gastrointestinal management. These distinct safety profiles underscore the importance of individualized treatment selection based on patient comorbidities and tolerance, as no single agent demonstrated a uniformly favorable safety profile.

A key contribution of this study is the inclusion of PROs, which revealed significant differences in quality of life among the three groups. Although baseline overall QoL scores were comparable, the abemaciclib group experienced a significantly greater decline at 3 months, 6 months, and at the end of treatment compared with the palbociclib and ribociclib groups. The proportion of patients experiencing clinically

meaningful deterioration was also significantly higher in the abemaciclib group (31.31%) than in the palbociclib (15.94%) and ribociclib (18.06%) groups. These findings suggest that the superior efficacy of abemaciclib in terms of ORR and DoR may come at the cost of a more pronounced negative impact on patients' daily functioning and well-being, likely attributable to its higher incidence of diarrhea and other treatment-related symptoms. This trade-off between efficacy and quality of life should be carefully considered in clinical decision-making, particularly for patients with lower symptom burden or higher baseline quality of life expectations [36].

In this study, both univariate and multivariate Cox regression analyses showed that treatment regimen (ribociclib or abemaciclib vs. palbociclib) was the only factor independently associated with rwPFS. Other clinical variables, including visceral metastasis, endocrine resistance, and ECOG PS score, did not reach statistical significance in our cohort. Collectively, our findings suggest that while ribociclib and abemaciclib may offer advantages over palbociclib in terms of rwPFS, and abemaciclib demonstrates superiority in ORR and DoR, no single CDK4/6 inhibitor exhibits comprehensive superiority across efficacy, safety, and PRO endpoints. The choice of agent should therefore be individualized, taking into account not only efficacy considerations but also patient-specific factors such as comorbidity profile, tumor characteristics, and patient preferences regarding quality of life and treatment-related side effects.

Research limitations

There are several limitations of this study. First of all, single-center design may introduce selection bias, as treatment decisions are often influenced by the patient comorbidities. Second, reliance on medical records and imaging follow-up may result in data inconsistency, potentially affecting the accuracy of efficacy assessments. The relatively small sample size and the homogeneous patient population limit the generalizability of the findings. Third, the follow-up time was relatively short, making it difficult to assess the long-term efficacy differences. In addition, key biomarker analyses (such as ER mutations) were not included, precluding more individualized treatment evaluation. Only a single questionnaire was used for the QoL assessment, which may be insufficiently comprehensive and subject to influence by patient mood and educational level, potentially introducing additional bias.

Conclusion

In real-world clinical practice, ribociclib and abemaciclib combined with fulvestrant may offer prolonged rwPFS compared with palbociclib in patients with HR+/HER2- advanced breast cancer. Abemaciclib was associated with higher objective response rates and longer duration of response, but also greater decline in quality of life. Given the absence of a single agent demonstrating comprehensive superiority, treatment selection should be guided by individualized considerations, including efficacy priorities, safety profiles, and patient-reported outcomes.

Disclosure of conflict of interest

None.

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