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ORIGINAL ARTICLE

Real-world effectiveness comparison of first-line palbociclib, ribociclib or abemaciclib plus endocrine therapy in advanced HR-positive/HER2-negative BC patients: results from the multicenter PALMARES-2 study

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Background: The cyclin-dependent kinase 4/6 inhibitors (CDK4/6is) palbociclib, ribociclib and abemaciclib in combination with endocrine therapy (ET) are the standard-of-care, first-line treatment for patients with hormone receptor-positive, human epidermal growth factor receptor 2-negative advanced breast cancer (HR-positive/HER2-negative aBC). However, no large head-to-head comparisons of the three CDK4/6is have been conducted so far.

Patients and methods: We carried out a multicenter, observational, population-based study to compare the effectiveness of first-line palbociclib, ribociclib and abemaciclib in combination with ET in consecutive HR-positive/HER2-negative aBC patients who initiated the treatment between January 2016 and September 2023 in 18 Italian cancer centers. The primary endpoint of this analysis was real-world progression-free survival (rwPFS). Multivariable Cox regression models were used to adjust the association between individual CDK4/6i and rwPFS for clinically relevant variables.

Results: Of 1982 patients enrolled in the PALMARES-2 study, 789, 736 and 457 patients received palbociclib, ribociclib and abemaciclib, respectively. Median rwPFS was 34.1 months. In the whole study cohort, abemaciclib and ribociclib were associated with better rwPFS when compared with palbociclib [adjusted hazard ratio (aHR) 0.76, 95% confidence interval (CI) 0.63-0.92, $P = 0.004$ and aHR 0.83, 95% CI 0.73-0.95, $P = 0.007$, respectively]. In patients with endocrine-sensitive disease, only abemaciclib was associated with better rwPFS when compared with palbociclib. On the contrary, abemaciclib and ribociclib were more effective than palbociclib in patients who were premenopausal or had endocrine-resistant or luminal B-like disease, while abemaciclib was more effective than ribociclib and palbociclib in patients with *de novo* metastatic disease, and more effective than palbociclib in patients with poorer Eastern Cooperative Oncology Group performance status. The three CDK4/6i were similarly effective in patients who had bone-only disease.

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Conclusions: Palbociclib, ribociclib and abemaciclib have different real-world effectiveness in HR-positive/HER2-negative aBC patients. Our findings can support clinicians in choosing the most appropriate CDK4/6i in specific clinical contexts.

Key words: HR-positive/HER2-negative advanced breast cancer, real-world evidence, progression-free survival, palbociclib, ribociclib, abemaciclib

INTRODUCTION

Breast cancer (BC) is the most common malignancy in women worldwide, with a critical impact on public health due to its incidence, prevalence and global disease burden.[1-4] Despite impressive improvements in BC treatment, advanced BC (aBC) remains an almost invariably deadly disease.[5]

Hormone receptor-positive (HR-positive), human epidermal growth factor receptor 2-negative (HER2-negative) aBC is the most common aBC subtype, and it is responsible for the majority of aBC-related deaths.[6] In the past decade, the introduction of cyclin-dependent kinase 4/6 inhibitors (CDK4/6is), namely palbociclib, ribociclib and abemaciclib, in combination with endocrine therapies (ETs) remarkably improved patient progression-free survival (PFS)[7-13] and, in some studies, also overall survival (OS) when compared with ET alone.[14-17] For these reasons, CDK4/6is plus ET represent the standard-of-care, first-line treatment for the vast majority of HR-positive/HER2-negative aBC patients in both endocrine-sensitive and endocrine-resistant settings.

However, the efficacy of palbociclib, ribociclib and abemaciclib has not been directly compared in large clinical studies. Indeed, most published real-world studies evaluated the effectiveness of each of the three CDK4/6is, but no large effectiveness comparisons of palbociclib, ribociclib and abemaciclib have been conducted so far.[18-23] Since these three drugs have different safety profiles, costs, impact on quality of life and drug—drug interactions,[24,25] investigating which CDK4/6i may be more effective in specific contexts is a highly clinically relevant issue.

Here, we carried out a head-to-head effectiveness comparison of first-line palbociclib, ribociclib and abemaciclib, each used in combination with ET, in the context of the real-world, observational study PALMARES-2.

PATIENTS AND METHODS

Study design and patient population

PALMARES-2 is a retrospective/prospective, multicenter, observational Italian study that is collecting data about the antitumor activity and effectiveness of first-line treatments and subsequent lines of therapy in HR-positive/HER2-negative aBC patients. In the present study, we compared the real-world effectiveness of first-line palbociclib, ribociclib and abemaciclib in combination with ET. The present analysis was conducted at the first study data cut-off (31 January 2024), with 18 participating Italian centers. Patients received ET plus CDK4/6is as first-line treatment for HR-positive/HER2-negative aBC. Detailed enrollment criteria are described in the Supplementary Materials, available at https://doi.org/10.1016/j.annonc.2025.03.023.

This study was conducted in accordance with the Declaration of Helsinki, and it was approved by the Institutional Review Board and Ethics Committee of the 'Fondazione IRCCS Istituto Nazionale dei Tumori' of Milan (INT 101/23). Patients alive at the time of data collection and/or analysis signed a specific informed consent form for the use of their personal data for research purposes. The Ethics Committee authorized the collection and analysis of data from patients who were not alive when the study was conducted and who already authorized the use of data collected as per clinical practice for research purposes.

Study objectives and endpoints

The main objective of this analysis was to compare the real-world effectiveness of palbociclib, ribociclib and abemaciclib plus ET as first-line treatment in HR-positive/HER2-negative aBC patients. Due to the observational nature of the study, the specific CDK4/6i drug as well as the specific type of ET were prescribed according to the choice of the treating physician. Radiological tumor assessment was carried out every 3-4 months through computed tomography (CT) or [^{18}F]2-fluoro-2-deoxy-D-glucose—positron emission tomography (PET) according to local practice.

The primary endpoint of this analysis was real-world PFS (rwPFS), defined as the time interval between the initiation of ET plus CDK4/6is and the detection of disease progression, as evaluated according to radiological (CT/PET scans), clinical (clinical tumor measurements and evolution of patient status) or biochemical criteria (CA15.3 measurements), or patient death, whichever occurred first.[26] We compared rwPFS in patients treated with palbociclib, ribociclib or abemaciclib in the whole study cohort, as well as in patients with endocrine-sensitive or endocrine-resistant disease. Patients without an rwPFS event were censored at the time of data cut-off or last follow-up, if the latter occurred before data cut-off. Secondary objectives of this analysis were to compare the rwPFS associated with the three CDK4/6is in clinically relevant patient cohorts, such as premenopausal patients, older patients (age >75 years at the time of CDK4/6i initiation) or patients with liver metastases, bone-only disease, luminal B-like tumors [defined as progesterone receptor (PgR) expression <1% and/or Ki-67 >20%[27]], *de novo* metastatic disease or poor Eastern Cooperative Oncology Group performance status (ECOG PS) (≥1).

As exploratory endpoints of the present analysis, we evaluated: (i) time to next treatment or death (TTNT-D), defined as the time interval between the initiation of ET

plus CDK4/6is and the initiation of the next line of systemic treatment or death, whichever occurred first; (ii) time to chemotherapy or death (TTC-D), defined as the time between CDK4/6i start and the initiation of the first chemotherapy or patient death, whichever occurred first; and (iii) OS, defined as the time interval between treatment initiation and patient death from any reason.

Data collection

Patient- and tumor-related variables from consecutive patients were retrieved from electronic health records in each participating center, and they were annotated in a predefined database. Patients from each center were assigned a progressive numeric code, and pseudo-anonymized data were shared with the Sponsor (Fondazione IRCCS Istituto Nazionale dei Tumori, Milan) for the study analyses. We collected 47 clinical features at baseline (i.e. before the initiation of ET plus CDK4/6is), including demographic and tumor biology data, and information on previous treatments for early-stage disease, metastatic sites and blood parameters. A full list of baseline features collected within the PALMARES-2 study is included in the Supplementary Materials, available at https://doi.org/10.1016/j.annonc.2025.03.023.

Statistical methods and analyses

The median and interquartile ranges (IQRs) were reported for continuous variables. Categorical variables were summarized as percentages of available data. To evaluate differences, in terms of clinicopathological characteristics, among different CDK4/6i groups, we used the Kruskal—Wallis rank sum test for continuous variables, and the chi-square and Fisher's exact tests for categorical variables. Survival curves were extrapolated using the Kaplan—Meier method. Measures of median survival outcomes (in months) and relative 95% confidence intervals (CIs) were provided for the whole study cohort. Follow-up time was estimated using the reverse Kaplan—Meier method.

rwPFS, TTNT-D, TTC-D and OS differences in patients treated with different CDK4/6is were tested using Cox proportional hazards regression models adjusting for acknowledged prognostic variables.[28-35] For each covariate, we provided adjusted hazard ratios (aHRs) and relative 95% CIs. Confounder-adjusted survival curves were estimated and plotted. We used the 'cluster' function from the 'survival' package in R to account for the random effects related to the multicenter nature of the study[36,37]; centers were clustered according to the number of enrolled patients (high- versus intermediate- versus low-volume centers). To test if features selected on the basis of their clinical relevance actually represent the most informative prognostic characteristics, for rwPFS analyses we also carried out a model-based feature selection through a backward stepwise approach using the Akaike information criterion, and we fitted an additional Cox regression model with the variables selected through the model-based feature selection.[38,39] To confirm results of Cox regression analysis, we used inverse probability of treatment weighting (IPTW) adjustment to balance clinicopathological characteristics among the three CDK4/6i patient cohorts. Propensity scores used for the IPTW analysis were estimated through a generalized boosted model adopting the same variables used in the original model. Estimated weights were incorporated into a weighted Cox regression model to estimate rwPFS.[40,41]

Patients with missing data about the date of their last follow-up, disease progression and death were excluded from the analysis. Covariates whose values were missing in $<5\%$ of patients were imputed by using median or mode values (for numerical or categorical variables, respectively), while covariates with missing values exceeding 5% were excluded from the present analysis.[42] All statistical tests were two-tailed, and a P value <0.05 was considered as significant. Statistical analyses were carried out using R software and R Studio (version 4.1.2) (RStudio: PBC, Boston, MA), with the following packages: 'readxl', 'dplyr', 'tidyr', 'lubridate', 'stringr', 'data.table', 'gtsummary', 'survival', 'survminer', 'ggplot2', 'pec', 'adjustedCurves', 'forestploter', 'twang'.

RESULTS

Patient characteristics and CDK4/6i dose reduction, interruption or switch

At the data cut-off of 31 January 2024, after excluding three patients for whom the date of last follow-up, disease progression or death was not available, we included 1982 patients who initiated first-line ET plus CDK4/6i treatment between 1 January 2016 and 30 September 2023. Palbociclib was the most commonly used CDK4/6i ($n = 789$, 39.8%), followed by ribociclib ($n = 736$, 37.1%) and abemaciclib ($n = 457$, 23.1%). The study flow chart is shown in Supplementary Figure S1, available at https://doi.org/10.1016/j.annonc.2025.03.023.

The median patient age was 63 years. Of 1982 patients included in this analysis, 33% had endocrine-resistant tumors, 18% were premenopausal and 30% had *de novo* metastatic disease (Table 1). All premenopausal patients underwent ovarian function suppression in combination with ET plus CDK4/6is. Covariate distribution according to the specific CDK4/6i and to tumor ET sensitivity/resistance is displayed in Table 2. Abemaciclib-treated patients were more likely to have endocrine-resistant disease, liver metastases and lower PgR tumor expression, while patients receiving ribociclib were younger and more likely to be premenopausal; finally, palbociclib was more commonly prescribed to patients with a poorer ECOG PS (Tables 1 and 2).

In the whole study cohort, CDK4/6i dose reduction or permanent CDK4/6i discontinuation occurred in 977 (50.4%) and 957 (48.3%) patients, respectively. Any dose reduction occurred with similar frequency in patients receiving palbociclib (395, 50.9%), ribociclib (349, 48.7%) and abemaciclib (233, 52.4%), while permanent CDK4/6i discontinuation rates for any reason were 484 (61.5%), 290 (39.4%) and 183 (40.0%), respectively

Table 1. Patient characteristics in the overall study population and in the three CDK4/6i cohorts, after imputation of missing values

Characteristic	Total $n = 1982$	Palbociclib $n = 789$	Ribociclib $n = 736$	Abemaciclib $n = 457$	*P* value
Age (years)	63 (53-72)	66 (56-74)	59 (50-69)	64 (56-71)	<0.001
Menopausal status, *n* (%)					<0.001
Postmenopausal	1628 (82)	689 (87)	538 (73)	401 (88)	
Premenopausal	354 (18)	100 (13)	198 (27)	56 (12)	
Na	2	1	1	0	
ECOG PS, *n* (%)					<0.001
0	1504 (76)	561 (71)	595 (81)	348 (76)	
1	413 (21)	197 (25)	122 (17)	94 (21)	
≥2	65 (3)	31 (3.9)	19 (2.6)	15 (3.3)	
NA	35	12	16	7	
Histology, *n* (%)					0.001
NST	1481 (75)	580 (74)	579 (79)	322 (70)	
ILC	367 (19)	143 (18)	115 (16)	109 (24)	
Other	134 (6)	66 (8.4)	42 (5.7)	26 (5.7)	
NA	56	19	24	13	
ER expression (%)	90 (90-95)	95 (90-95)	90 (90-95)	90 (80-98)	0.3
NA	28	16	6	6	
PgR expression (%)	40 (4-80)	40 (5-80)	50 (7-85)	20 (0-75)	<0.001
NA	35	21	8	6	
Ki-67 expression (%)	20 (15-30)	20 (14-30)	20 (15-30)	20 (15-30)	0.2
NA	79	39	25	15	
HER2 expression, *n* (%)					0.6
0	855 (43)	330 (42)	328 (45)	197 (43)	
Low	1127 (57)	459 (58)	408 (55)	260 (57)	
NA	59	27	19	13	
De novo metastatic (yes), *n* (%)	581 (29)	208 (26)	264 (36)	109 (24)	<0.001
Endocrine resistance (yes), *n* (%)	649 (33)	310 (39)	169 (23)	170 (37)	<0.001
ET partner, *n* (%)					<0.001
AI	1347 (68)	503 (64)	584 (79)	260 (57)	
Fulvestrant	633 (32)	285 (36)	152 (21)	196 (43)	
Tamoxifen	2 (<1)	1 (<1)	0	1 (<1)	
Liver metastases (yes), *n* (%)	413 (21)	170 (22)	120 (16)	123 (27)	<0.001
Bone metastases (yes), *n* (%)	1378 (70)	535 (68)	532 (72)	311 (68)	0.12
Lung metastases (yes), *n* (%)	535 (27)	208 (26)	197 (27)	130 (28)	0.7

NA refers to the absolute number of patients for whom specific variables were missing before imputation.
AI, aromatase inhibitor; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; ECOG PS, Eastern Cooperative Oncology Group performance status; ER, estrogen receptor; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; ILC, invasive lobular carcinoma; NA, not available; NST, no special type; PgR, progesterone receptor.

(Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2025.03.023). While any drug dose reduction occurred with similar frequency in patients receiving the three CDK4/6i drugs, toxicities causing two dose reductions occurred more commonly in patients receiving palbociclib and abemaciclib when compared with ribociclib (16.8% and 15.5% versus 7.5%, respectively) (Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2025.03.023). Treatment discontinuation occurred because of disease progression ($n = 864$, 43.6%), hematological, gastrointestinal and/or liver toxicities ($n = 50$, 2.5%) or other toxicities/reasons ($n = 43$, 2.2%); reasons for treatment discontinuation in each CDK4/6i cohort are summarized in Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2025.03.023.

Significantly more patients in the ribociclib and abemaciclib groups underwent a switch in the type of CDK4/6is ($n = 62$, 8.7% and $n = 33$, 7.4%, respectively) when compared with patients treated with palbociclib ($n = 11$, 1.4%) (Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2025.03.023). The main reason for switching from a CDK4/6i to another one was treatment-induced toxicity (85.9%).

rwPFS comparisons of palbociclib, ribociclib and abemaciclib

Median patient follow-up was 31.3 months (IQR 16.9-49.8 months) in the whole study cohort, and it was lower in patients treated with abemaciclib (22.4 months; IQR 12.3-33.8 months) or ribociclib (25.2 months; IQR 12.7-44.4 months) than in patients receiving palbociclib (45.7 months; IQR 28.0-59.6 months). With 864 rwPFS events and 464 death events, median rwPFS (mrwPFS) and OS in the whole study cohort were 34.1 months (IQR 13.9-86.3 months) and 65.9 months (IQR 36.7 months-not reached), respectively (Supplementary Table S2 and Figure S2, available at https://doi.org/10.1016/j.annonc.2025.03.023).

In the multivariable Cox regression model fitted in the whole study cohort, abemaciclib and ribociclib were associated with better rwPFS when compared with palbociclib (abemaciclib versus palbociclib: aHR 0.76, 95% CI 0.63-0.92, $P = 0.004$; ribociclib versus palbociclib: aHR 0.83, 95% CI 0.73-0.95, $P = 0.007$), whereas we found no significant rwPFS differences between abemaciclib and ribociclib (abemaciclib versus ribociclib: aHR 0.91, 95% CI 0.73-1.14, $P = 0.425$) (Supplementary Figure S3, available at https://doi.org/10.1016/j.annonc.2025.03.023; Figure 1).

Table 2. Clinical characteristics according to CDK4/6is and endocrine sensitivity

Characteristic	Palbociclib *n* = 479	Ribociclib *n* = 567	Abemaciclib *n* = 287	*P* value	Palbociclib *n* = 310	Ribociclib *n* = 169	Abemaciclib *n* = 170	*P* value
	Endocrine sensitive				Endocrine resistant			
Age (years)	68 (57-75)	59 (50-70)	64 (57-71)	<0.001	63 (55-71)	58 (49-66)	62 (53-71)	<0.001
Menopausal status, *n* (%)				<0.001				<0.001
Postmenopausal	420 (88)	417 (74)	261 (91)		268 (86)	121 (72)	140 (82)	
Premenopausal	59 (12)	150 (26)	26 (9)		42 (14)	48 (28%)	30 (18)	
ECOG PS, *n* (%)				0.004				0.029
0	337 (70)	455 (80)	207 (72)		224 (72)	140 (83)	141 (83)	
1	120 (25)	96 (17)	69 (24)		77 (25)	26 (15)	25 (15)	
≥2	22 (5)	16 (3)	11 (4)		9 (3)	3 (2)	4 (2)	
Histology, *n* (%)				0.004				0.032
NST	348 (73)	456 (80)	202 (70)		232 (75)	123 (73)	120 (71)	
ILC	93 (19)	78 (14)	66 (23)		50 (16)	37 (22)	43 (25)	
Other	38 (8)	33 (6)	19 (7)		28 (9)	9 (5)	7 (4)	
ER expression (%)	95 (90-95)	90 (90-95)	90 (90-98)	0.5	90 (86-95)	90 (80-95)	90 (80-95)	0.3
PgR expression (%)	50 (10-85)	50 (10-85)	40 (1-80)	0.004	20 (0-70)	30 (0-80)	5 (0-60)	0.011
Ki-67 expression (%)	20 (14-30)	20 (15-30)	20 (15-30)	0.2	20 (13-30)	23 (15-35)	25 (15-35)	0.3
HER2 expression, *n* (%)				0.9				0.6
0	204 (43)	251 (44)	126 (44)		126 (41)	77 (46)	71 (42)	
Low	275 (57)	316 (56)	161 (56)		184 (59)	92 (54)	99 (58)	
De novo disease (yes), *n* (%)	206 (43)	264 (47)	109 (38)	0.056	NA	NA	NA	NE
ET partner, *n* (%)				0.044				<0.001
AI	430 (90)	525 (93)	247 (86)		73 (23)	59 (35)	13 (8)	
Fulvestrant	48 (10)	42 (7)	39 (14)		237 (77)	110 (65)	157 (92)	
Tamoxifen	1 (<1)	0	1 (<1)		0	0	0	
Liver metastasis (yes), *n* (%)	88 (18)	82 (14)	67 (23)	0.005	82 (26)	38 (22)	56 (33)	0.09
Bone metastasis (yes), *n* (%)	340 (71)	413 (73)	200 (70)	0.6	195 (63)	119 (70)	111 (65)	0.3

AI, aromatase inhibitor; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; ECOG PS, Eastern Cooperative Oncology Group performance status; ER, estrogen receptor; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; ILC, invasive lobular carcinoma; NST, no special type; PgR, progesterone receptor.

These findings were confirmed by multivariable Cox regression model adjusting for covariates that were identified through backward selection (see 'Patients and Methods' section) (Supplementary Figures S4 and S5, available at https://doi.org/10.1016/j.annonc.2025.03.023). Consistent with these results, IPTW-adjusted analyses showed that both abemaciclib and ribociclib were associated with longer rwPFS when compared with palbociclib (abemaciclib versus palbociclib: HR 0.78, 95% CI 0.64-0.95, $P = 0.015$; ribociclib versus palbociclib: HR 0.83, 95% CI 0.71-0.97, $P = 0.02$) (Supplementary Figure S6, available at https://doi.org/10.1016/j.annonc.2025.03.023).

Due to the different year of registration of the three CDK4/6is in Italy, the percentage of individual CDK4/6i prescribed during each year changed over time, with a progressive increase of ribociclib and abemaciclib prescriptions, paralleled by a decrease of palbociclib prescriptions (Supplementary Figure S7, available at https://doi.org/10.1016/j.annonc.2025.03.023). In 2021 as the number of patients initiating first-line ET plus CDK4/6is was numerically similar in the three cohorts (palbociclib: $n = 119$, ribociclib: $n = 147$ or abemaciclib: $n = 125$), we conducted a sensitivity analysis by fitting a multivariable Cox regression model that only included patients who

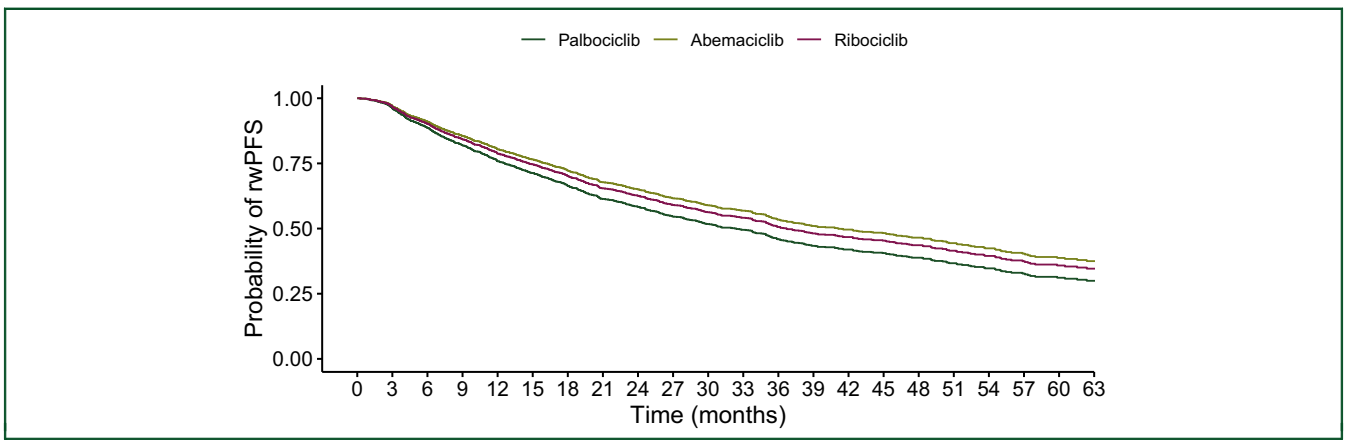

Figure 1. Adjusted rwPFS curves in the whole study cohort. Multivariable Cox model-adjusted rwPFS curves of palbociclib, ribociclib and abemaciclib. rwPFS, real-world progression-free survival.

initiated CDK4/6i therapy during 2021. In this cohort, abemaciclib and ribociclib were associated with significantly better rwPFS when compared with palbociclib (Supplementary Figures S8 and S9, available at https://doi.org/10.1016/j.annonc.2025.03.023).

Then, we compared the effectiveness of the three CDK4/6is in patients with endocrine-sensitive or endocrine-resistant disease. In the endocrine-sensitive setting, abemaciclib was associated with better rwPFS when compared with palbociclib (abemaciclib versus palbociclib: aHR 0.75, 95% CI 0.64-0.87, $P < 0.001$), whereas ribociclib was not (ribociclib versus palbociclib: aHR 0.88, 95% CI 0.63-1.22, $P = 0.443$) (Figure 2). In patients with endocrine-resistant disease, both abemaciclib and ribociclib were associated with better rwPFS when compared with palbociclib (abemaciclib versus palbociclib: aHR 0.77, 95% CI 0.63-0.93, $P = 0.008$; ribociclib versus palbociclib: aHR 0.75, 95% CI 0.58-0.98, $P = 0.034$) (Figure 2). Abemaciclib and ribociclib were not associated with significantly different risk of disease progression in both endocrine-sensitive (aHR 0.85, 95% CI 0.59-1.24, $P = 0.401$) and endocrine-resistant settings (aHR 1.02, 95% CI 0.95-1.09, $P = 0.624$). Adjusted Kaplan–Meier rwPFS curves in these settings are shown in Figure 3.

Impact of palbociclib, ribociclib and abemaciclib on TTNT-D, TTC-D or OS

To strengthen the results of rwPFS analyses, in the whole study cohort, we fitted multivariable Cox regression models to compare palbociclib, ribociclib and abemaciclib in terms of another two clinically relevant endpoints, namely TTNT-D and TTC-D (Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2025.03.023). When compared with palbociclib, both abemaciclib and ribociclib were associated with better TTNT-D (abemaciclib versus palbociclib: aHR 0.80, 95% CI 0.64-0.99, $P = 0.049$; ribociclib versus palbociclib: aHR 0.86, 95% CI 0.74-0.99, $P = 0.033$) and TTC-D (abemaciclib versus palbociclib: HR 0.79, 95% CI 0.69-0.90, $P < 0.001$; ribociclib versus palbociclib: HR 0.84, 95% CI 0.73-0.97, $P = 0.016$; Supplementary Figure S10, available at https://doi.org/10.1016/j.annonc.2025.03.023).

Although OS data are still immature (464 death events; 23.4%; Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2025.03.023), we also carried out an exploratory OS comparison between the three CDK4/6is. Multivariable Cox regression model including clinically relevant covariates showed that both abemaciclib and ribociclib were associated with a lower risk of death when

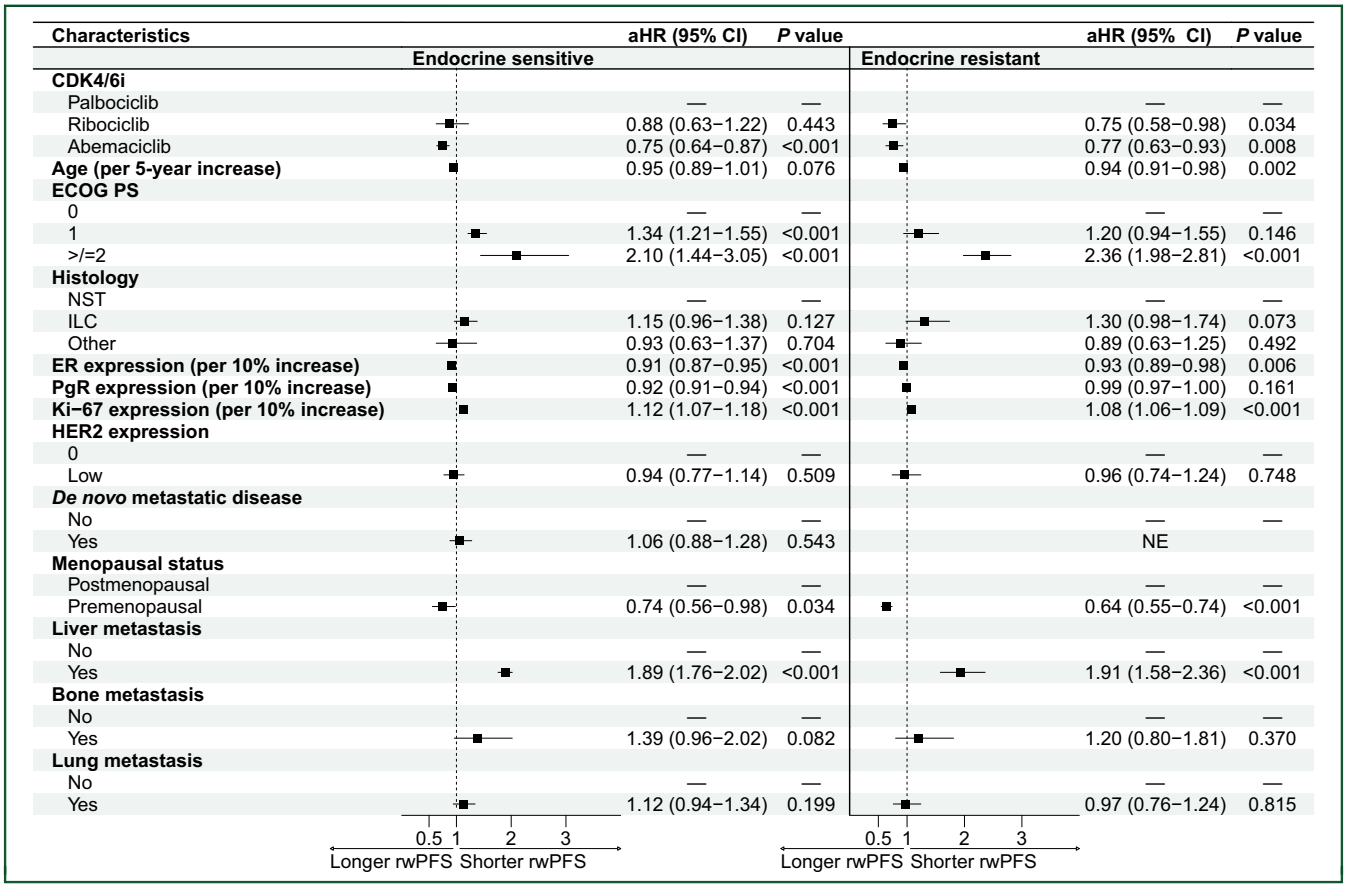

Figure 2. Forest plots of rwPFS multivariable model in endocrine-sensitive and endocrine-resistant cohorts. Forest plots illustrating the results of multivariable Cox regression models (aHR, 95% CI, *P* value) in patients with endocrine-sensitive (left) or endocrine-resistant (right) disease.
aHR, adjusted hazard ratio; CDK4/6i, cyclin-dependent kinase 4/6 inhibitors; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; ILC, invasive lobular carcinoma; NE, not evaluable; NST, no special type; PgR, progesterone receptor; rwPFS, real-world progression-free survival.

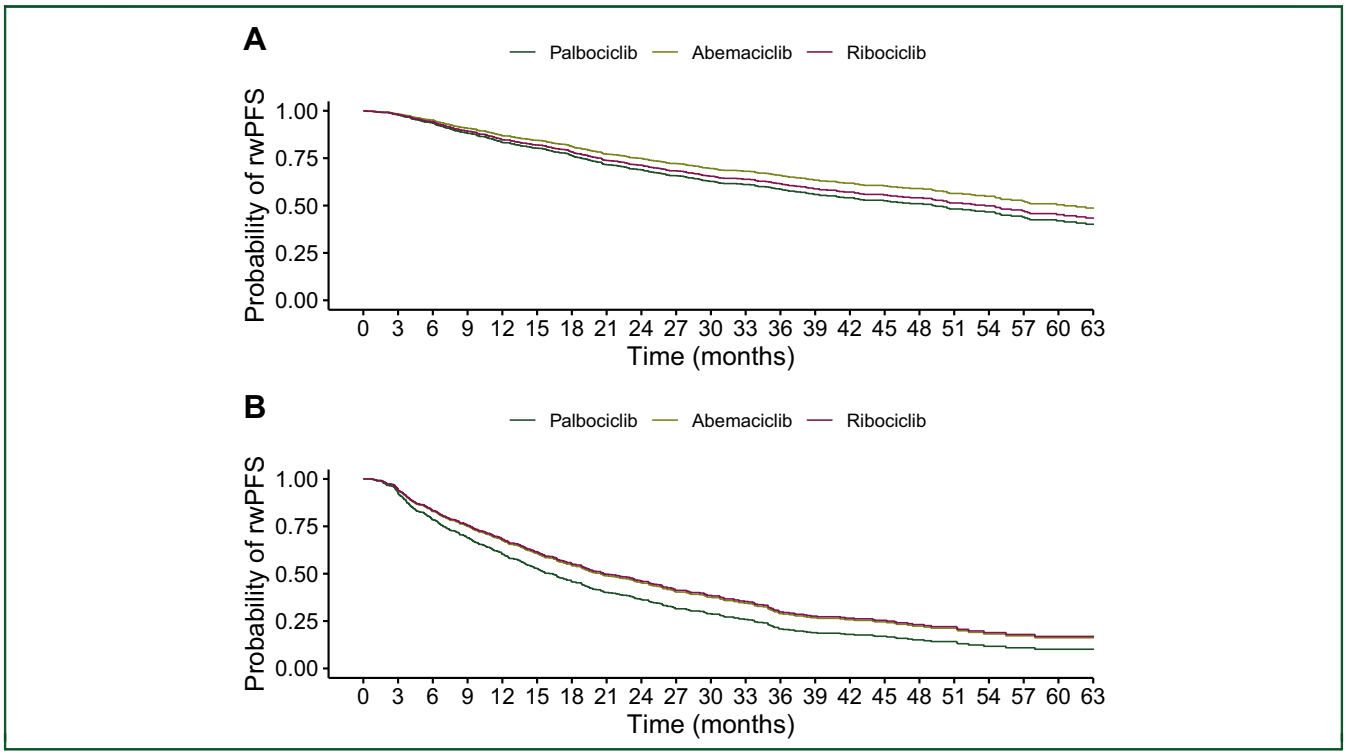

Figure 3. Adjusted rwPFS curves in patients with endocrine-sensitive or endocrine-resistant disease. Cox regression model-based adjusted Kaplan–Meier rwPFS curves in patients treated with palbociclib, ribociclib or abemaciclib according to tumor endocrine sensitivity (A) or endocrine resistance (B).
rwPFS, real-world progression-free survival.

compared with palbociclib (abemaciclib versus palbociclib: HR 0.85, 95% CI 0.74-0.97, $P = 0.014$; ribociclib versus palbociclib: HR 0.83, 95% CI 0.81-0.84, $P < 0.001$; Supplementary Figure S10, available at https://doi.org/10.1016/j.annonc.2025.03.023).

rwPFS comparison of palbociclib, ribociclib and abemaciclib in clinically relevant settings

We fitted eight Cox multivariable sub-models in patients who were older (>75 years of age), premenopausal or in patients with endocrine-resistant disease, luminal B-like disease, worse ECOG PS (≥1), bone-only disease, *de novo* metastatic disease or liver metastases. Data were adjusted for the same covariates adopted in the main rwPFS model (Supplementary Table S3, available at https://doi.org/10.1016/j.annonc.2025.03.023), except for the variable characterizing that specific model. The radar plot in Figure 4 illustrates aHRs of abemaciclib versus palbociclib, ribociclib versus palbociclib or abemaciclib versus ribociclib, in each of these patient sub-cohorts. Abemaciclib was more effective than palbociclib in premenopausal women (aHR 0.59, 95% CI 0.39-0.89, $P = 0.013$), as well as in patients with *de novo* metastatic disease (aHR 0.52, 95% CI 0.37-0.73, $P < 0.001$), luminal B-like tumors (aHR 0.76, 95% 0.65-0.90, $P = 0.002$) or worse ECOG PS (aHR 0.74, 95% CI 0.55-0.99, $P = 0.048$) (Figure 4; Supplementary Table S3, available at https://doi.org/10.1016/j.annonc.2025.03.023). Ribociclib was more effective than palbociclib in premenopausal women (aHR 0.57, 95% CI 0.46-0.70, $P < 0.001$) and in patients with *de novo* metastatic disease (aHR 0.76, 95% CI 0.61-0.94, $P = 0.010$), liver metastases (aHR 0.89, 95% CI 0.79-0.99, $P = 0.036$) or luminal B-like disease (aHR 0.81, 95% CI 0.75-0.88, $P < 0.001$), but it was less effective than palbociclib in older patients (aHR 1.09, 95% CI 1.02-1.17, $P = 0.008$). Abemaciclib was more effective than ribociclib in patients with *de novo* metastatic disease (aHR 0.69, 95% CI 0.60-0.79, $P < 0.001$). Finally, the three CDK4/6is showed similar effectiveness in patients with bone-only disease (Figure 4; Supplementary Table S3, available at https://doi.org/10.1016/j.annonc.2025.03.023).

DISCUSSION

In this multicenter, observational, real-world Italian study, abemaciclib showed higher effectiveness when compared with palbociclib in patients with endocrine-sensitive HR-positive/HER2-negative aBC, whereas both abemaciclib and ribociclib were associated with better rwPFS when compared with palbociclib in patients with endocrine-resistant disease. The three CDK4/6is showed different effectiveness profiles in clinically relevant settings.

In patients with endocrine-sensitive disease, published phase III randomized controlled trials (RCTs) showed that all the three CDK4/6is in combination with ET improve PFS when compared with ET alone.[7,8,10] Ribociclib also improved patient OS in MONALEESA-2/3/7 trials,[14-16] whereas abemaciclib resulted in clinically relevant, although not statistically significant, OS prolongation in the MONARCH 3 trial.[43] Finally, palbociclib did not improve OS in the PALOMA-2 trial.[7,44] Based on OS data of RCTs, ribociclib is the only CDK4/6i supported by category 1

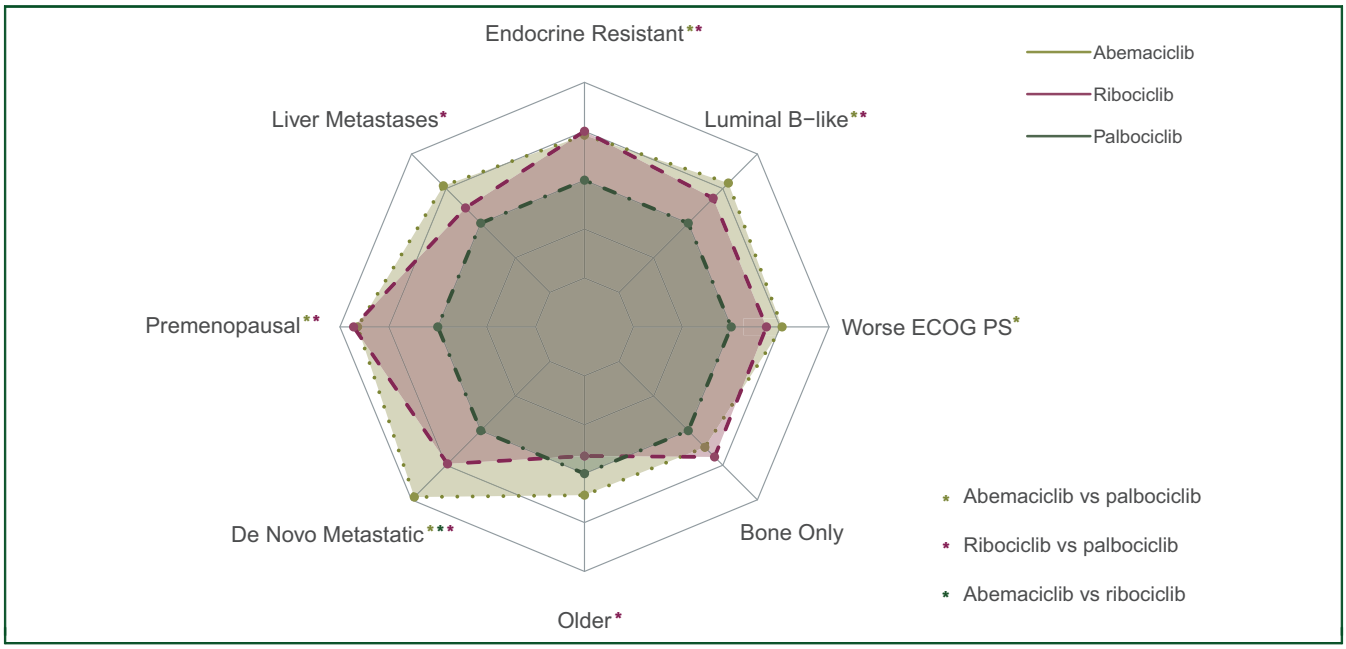

Figure 4. Radar plot summarizing aHR of rwPFS comparisons of the three CDK4/6is in clinically relevant subgroups. Radar plot representing the aHR for rwPFS of ribociclib versus palbociclib, abemaciclib versus palbociclib or abemaciclib versus ribociclib in the subsets of patients with: endocrine-resistant disease; luminal B-like disease; poor ECOG PS; bone-only disease; older patients; *de novo* metastatic disease; premenopausal women; patients with liver metastases. The inner line of the radar plot corresponds to an aHR of 0.50, whereas the outer line corresponds to an aHR of 1.50. Palbociclib line was retained as reference (aHR 1.00). Maroon and olive green asterisks indicate the ribociclib versus palbociclib or abemaciclib versus palbociclib comparisons when they reached statistical significance; the dark green asterisk marks the subgroup in which abemaciclib and ribociclib were associated with significantly different rwPFS. The direction of each comparison is indicated by the position of points corresponding to each CDK4/6i on individual radial lines.
aHR, adjusted hazard ratio; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; ECOG PS, Eastern Cooperative Oncology Group performance status.

recommendation for patients with endocrine-sensitive disease according to the National Comprehensive Cancer Network (NCCN) guidelines.[45] However, no large head-to-head rwPFS comparisons of the three CDK4/6is have been published in this setting, thus limiting the utility of data from RCTs in choosing the most appropriate CDK4/6i. In this scenario, our real-world data showing statistically significant rwPFS benefit of abemaciclib versus palbociclib in patients with endocrine-sensitive disease support the use of abemaciclib as a valid therapeutic option in this setting. Future OS follow-up of this study will be crucial to confirm and strengthen the clinical relevance of our findings.

In patients with endocrine-resistant disease enrolled in MONALEESA-3 and MONARCH 2 trials, both ribociclib and abemaciclib improved patient PFS and OS,[12,13,16,17] whereas in the PALOMA-3 trial palbociclib improved patient PFS, but not OS.[46] Our rwPFS data, which are consistent with OS results from phase III RCTs, support the use of ribociclib or abemaciclib as preferred CDK4/6i in patients with endocrine-resistant HR-positive/HER2-negative aBC.

In this study, we also carried out subgroup analysis to compare the real-world effectiveness of the three CDK4/6is in settings of special clinical interest, and in which it is not clear whether specific CDK4/6i may be more effective than others on the basis of results of published phase III RCTs.

In premenopausal women, the MONALEESA-7 trial demonstrated that ribociclib improves PFS and OS in combination with ET.[9,15] Similarly, abemaciclib prolonged PFS and OS in premenopausal women enrolled in the MONARCH 2 trial.[13,17] On the contrary, palbociclib improved PFS but not OS in premenopausal patients enrolled in the PALOMA-3 trial.[11,46] Here, we showed that abemaciclib and ribociclib are associated with better rwPFS when compared with palbociclib; these data, which are consistent with OS data from RCTs, indicate that abemaciclib and ribociclib are preferable treatment choices for premenopausal women with HR-positive/HER2-negative aBC.

Luminal B-like BC is a biologically distinct HR-positive/HER2-negative BC subtype that is associated with higher clinical aggressiveness, poorer response to ET and worse clinical outcomes.[47] Exploratory analyses from RCTs showed that palbociclib and ribociclib improve PFS in patients with both luminal A and luminal B disease,[48,49] while ribociclib also provided OS benefit in patients with luminal B disease.[50] In sub-analyses of the MONARCH 2/3 trials, abemaciclib improved PFS in patients with tumors lacking PgR expression, a feature that contributes to the definition of luminal B-like disease.[10,13] Although in our study the definition of luminal B-like disease did not take into account gene expression profiles, our findings indicate that patients with low intratumor PgR and/or high Ki-67 expression may achieve higher clinical benefit from abemaciclib or ribociclib than from palbociclib.

Patients with *de novo* metastatic HR-positive/HER2-negative aBC accounted for ∼30% of our study cohort, which is consistent with data from previously published clinical trials and real-world case series.[7,13,21,22] In this setting, ribociclib and abemaciclib improved both PFS and OS in the MONALEESA-2/7 and MONARCH 3 trials, respectively, whereas palbociclib improved PFS, but not OS,

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in the PALOMA-2 trial.[7-10,14,44] In our study, ribociclib was more effective than palbociclib in patients with *de novo* metastatic disease, whereas abemaciclib was associated with better rwPFS when compared with both ribociclib and palbociclib. Our findings, along with results of RCTs, point to abemaciclib as a preferred treatment choice in patients with *de novo* metastatic disease.

Liver metastases are a bad prognostic factor in HR-positive/HER2-negative aBC patients.[23] In our study, both ribociclib and abemaciclib showed a trend toward higher effectiveness when compared with palbociclib in patients with liver metastases, but this difference reached statistical significance only in patients treated with ribociclib. In the MONALEESA-2/3/7 trials, ribociclib improved both PFS and OS in patients with liver metastases,[7-9,12,14,15] while abemaciclib resulted in PFS and OS advantage in patients with visceral metastases enrolled in MONARCH 2/3 trials.[10,13,17,43] However, the efficacy of palbociclib and abemaciclib in patients with liver metastases enrolled in the PALOMA-2/3 and MONARCH 2/3 trials was not reported. Our findings are consistent with data from RCTs,[8,9] and they point to ribociclib as highly effective treatment in HR-positive/HER2-negative aBC patients with liver metastases.

Balancing treatment effectiveness, tolerability and sustainability is crucial in the management of a chronic, but still almost invariably deadly disease, such as HR-positive/HER2-negative aBC.[51] Among the three available CDK4/6is, palbociclib has the best safety profile and the highest manageability.[52-54] Our observation that palbociclib is more effective than ribociclib, and not less effective than abemaciclib in older patients, is of potential clinical relevance. Indeed, older patients more commonly present concomitant comorbidities that could be worsened by the use of ribociclib, which is associated with an increased risk of causing cardiac/liver toxicities and drug—drug interactions, or abemaciclib, which frequently causes gastrointestinal adverse events. The non-inferiority of palbociclib in older patients, as well as in patients with less clinically aggressive disease, such as patients with bone-only disease, should be taken into account to guide the choice regarding the specific CDK4/6i to be used.

The results of our study are unique in the field. Indeed, published works comparing the three CDK4/6is in the real-world setting mostly consist of relatively small case series lacking sufficient power for effectiveness comparisons, and many of them did not employ adequate methodology for covariate adjustment to homogenize treatment cohorts.[55-59] To date, only four large real-world comparisons of the three CDK4/6is have been conducted and presented at international congresses or published in peer-reviewed journals.[60-63] The study by Pantano et al., which enrolled 1184 patients and employed propensity score weighting for covariate adjustment, showed that both abemaciclib and ribociclib were associated with better PFS when compared with palbociclib in the endocrine-sensitive setting, while abemaciclib was associated with better PFS when compared with both ribociclib and palbociclib in patients with endocrine-resistant disease.[60] When compared with our analysis, the study by Pantano et al. enrolled a lower number of patients, and in particular an especially low number of patients treated with abemaciclib ($n = 158$); in addition, the study has not been published in full yet. Another large study recently presented at the American Society of Clinical Oncology (ASCO) 2024 annual meeting included 1511 HR-positive/HER2-negative aBC patients treated with ET + CDK4/6is as first or second line treatment[61]; in this study, fulvestrant plus ribociclib was associated with better PFS and OS when compared with both fulvestrant plus palbociclib and fulvestrant plus abemaciclib. However, the strength of these conclusions is limited by the facts that (i) survival data were not adjusted for clinically relevant covariates; (ii) patients were treated in different lines of therapy for advanced disease; (iii) ∼10% of patients received chemotherapy before ET plus CDK4/6is; and (iv) the study findings have not been published in full yet. A recent Danish retrospective study included 2069 patients, of whom 1554 received first-line ET plus CDK4/6is. In this study, median PFS in the whole study cohort was 35.1 months (95% CI 32.6-38.6 months), which is consistent with mrwPFS results from our study. Patients treated with ribociclib and abemaciclib had better PFS when compared with patients treated with palbociclib (abemaciclib versus palbociclib: HR 0.74, 95% CI 0.60-0.90, $P = 0.005$; ribociclib versus palbociclib: HR 0.80, 95% CI 0.68-0.96, $P = 0.01$). However, the limited number of covariates collected in this dataset only allowed the adjustment for patient age, endocrine sensitivity, ET backbone and sites of metastases (visceral versus non-visceral versus bone-only disease), thus potentially limiting the study conclusions given the large amount of clinically significant variables that could be unbalanced in the different study cohorts, and which were not evaluated as adjustment covariates in this study.[62] More recently, a large real-world study conducted in the United States showed that the three CDK4/6is are associated with similar OS after stabilized inverse probability of treatment weighting covariate balancing and Cox regression model covariate adjustment.[63] However, no rwPFS comparisons of the three CDK4/6is were presented in this study; in addition, the palbociclib cohort was much more numerous than the ribociclib and abemaciclib cohorts in terms of enrolled patients and clinical events; finally, the lack of a fully annotated dataset did not allow a proper adjustment for prognostically relevant variables, such as endocrine resistance, the presence of liver metastases and biological factors such as quantitative HRs and Ki-67 expression.[63]

Our study has several limitations. Firstly, its retrospective and observational nature, which comes with the consequence that patients were not randomly assigned to receive palbociclib, ribociclib or abemaciclib, resulted in an unbalanced distribution of clinically relevant patient- and tumor-related covariates in the three treatment cohorts. As in other real-world studies, the prescription of one or another CDK4/6i may have been influenced by several factors, including: (i) the time of approval and registration of individual molecules, since palbociclib was the first CDK4/6i to be registered and used in Italy; (ii) the publication of

long-term results of RCTs, in particular MONALEESA-2/3/7 and MONARCH 2; (iii) preferences of individual physicians; (iv) patient characteristics, e.g. the common use of ribociclib in premenopausal patients, since MONALEESA-7 was the only RCT that showed PFS and OS advantage from adding ribociclib to ET in this population; (v) patient comorbidities (e.g. the less common prescription of ribociclib in patients with comorbidities, or abemaciclib in patients with gastrointestinal diseases, such as inflammatory bowel diseases); and (vi) concomitant medications, which could differently interact with palbociclib, ribociclib or abemaciclib. To address this non-random allocation of CDK4/6is in the three treatment groups, we used different statistical techniques, such as multivariable Cox regression models and IPTW analysis, to adjust the association between individual CDK4/6i and clinical outcomes for covariates that were unbalanced in the three patient groups. However, due to the lack of a formal statistical plan for conducting rwPFS comparisons, our findings should be interpreted with caution. Secondly, tumor progression reported by clinicians was not assigned according to established radiological criteria (e.g. RECIST 1.1), thus potentially resulting in heterogeneous PFS assessment across participating centers and investigators. To minimize the impact of this limitation on the study findings, we evaluated several real-world endpoints that were previously shown to be trustworthy surrogates of clinical endpoints commonly used in clinical trials, namely rwPFS, TTNT-D and TTC-D,[64-67] and we consistently found that abemaciclib and ribociclib are associated with higher effectiveness when compared with palbociclib in the whole study cohort. We also used the 'cluster' function in multivariable models to account for the participation of heterogeneous Italian institutions in terms of number of patients enrolled (high, medium, low). Thirdly, median follow-up was lower in patients treated with abemaciclib or ribociclib than in patients treated with palbociclib. This reflects the fact that palbociclib was the first CDK4/6i to be approved and registered in Italy, in line with results of other recently published real-world studies comparing the effectiveness of the three CDK4/6is.[63] Fourthly, TTC-D and OS results must be interpreted with caution due to the low maturity of patient follow-up; however, preliminary TTC-D and OS findings were in line with the ones observed with rwPFS and other intermediate real-world endpoints. Fifthly, even though the PALMARES-2 dataset collected baseline genomic data from tumor tissue or blood samples, this information was only available from a minority of patients (4.3% of the whole study cohort), consistent with the fact that tumor genomic characterization of HR-positive/HER2-negative aBC patients who are candidate to receive first-line ET + CDK4/6is is not routinely carried out in Italy. Future PALMARES-2 study follow-up, with the inclusion of more patients with available genomic data, may potentially provide more reliable information about the prognostic role of specific genomic alterations in the whole study cohort, as well as in patients treated with palbociclib, ribociclib or abemaciclib. Finally, only four patients (<1%) included in the current analysis had received CDK4/6is in the adjuvant setting; therefore, in this study, we were unable to investigate the effectiveness of any CDK4/6i, or to compare the effectiveness of palbociclib, ribociclib or abemaciclib, in patients previously exposed to adjuvant abemaciclib or ribociclib. Future follow-up of the PALMARES-2 study will be crucial to confirm and reinforce the clinical findings of our study, as well as to provide evidence about the effectiveness of CDK4/6is in the metastatic setting after the use of adjuvant CDK4/6is.

In conclusion, the three CDK4/6is are associated with different real-world effectiveness. In the perspective of individualizing first-line treatment for HR-positive/HER2-negative aBC patients on the basis of specific patient- and tumor-related characteristics, and in particular of balancing the efficacy, safety profile and costs of individual drugs, we provided the first, large-scale, real-world evidence to support clinicians in the selection of specific CDK4/6i in their daily practice.

APPENDIX

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DISCLOSURE

MVD: personal fees for consultancy/advisory role from Eli Lilly, Pfizer, Novartis, Seagen, Gilead, MSD, Exact Sciences, AstraZeneca, Daiichi Sankyo, Roche. GC: consulting fees from Roche, Novartis, Lilly, Pfizer, AstraZeneca, Daichii Sankyo, Ellipsis, Veracyte, Exact Science, Celcuity, Merck, BMS, Gilead, Sanofi, Menarini; payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events by Lilly, Pfizer, Relay, Gilead, Novartis and support for attending meetings and/or travel from Daichii Sankyo. MGiu: consulting/advisory role for Roche, AstraZeneca, Lilly, Daichii Sankyo, Novartis, Pfizer, Seagen, MSD, Eisai; honoraria from Novartis, Pfizer, Lilly, AstraZeneca, Daichii Sankyo; travel, accommodation, expenses from Lilly, Pfizer, AstraZeneca. ML: advisory role for Roche, Lilly, Novartis, AstraZeneca, Pfizer, Seagen, Gilead, MSD, Pierre Fabre, Menarini and Exact Sciences; speaker honoraria from Roche, Lilly, Novartis, Pfizer, Sandoz, Libbs, Daiichi Sankyo, Takeda, Knight, Ipsen, Menarini and AstraZeneca; travel grants from Gilead, Roche and Daiichi Sankyo; receiving research funding (to his institution) from Gilead; and nonfinancial interests as the chair of the European Society for Medical Oncology (ESMO) Young Oncologists Committee (YOC) and as a member of the national council of the Italian Association of Medical Oncology. NLV: grant from Eisai; speaker bureau from GSK; travel expenses for conference from Gentili, Celgene and Pfizer; advisory role from Novartis and Celgene; advisory role, travel expenses for conference from Pfizer; advisory board from MSD, Roche, Novartis, AstraZeneca and Daiichi Sankyo. AG: research grants from Pharmanutra, AAA; advisory boards, activities as a speaker, travel grants, consultancy from Roche, Novartis, Pfizer, Eli Lilly, Daiichi Sankyo, AstraZeneca, MSD, Seagen, Gilead, Pierre Fabre, Eisai, Exact Sciences, Stemline. AZ: honoraria for advisory board and consultancy for Roche, Novartis, Lilly, Pfizer, Seagen, Daiichi Sankyo, AstraZeneca, Gilead, Merck, Exact Sciences, Gentili, Menarini Stemline. AT: advisory role for Lilly, Novartis, AstraZeneca, Pfizer, Seagen, Gilead and MSD; speaker honoraria from Lilly, Novartis, Pfizer; travel grants from Gilead, Daiichi Sankyo and Novartis. MP: travel support from Pfizer and Novartis. BT: speaker honoraria from Novartis, Daiichi Sankyo, Eli Lilly, Pfizer, Seagen; travel grants from Novartis, Roche, Pfizer, Daiichi Sankyo. DG: consulting/advisor for Roche, Lilly, Novartis, Pfizer, Menarini, Stellantis; honoraria from Novartis, Pfizer, Lilly, AstraZeneca, Roche, Istituto Gentili; travel/accommodation from Novartis, Lilly, Pfizer, Roche. VG: honoraria from Eli Lilly, Daiichi Sankyo, GSK, Gilead, Novartis, Exact Sciences, Roche, AstraZeneca, Menarini Stemline, Zentiva; advisory role for Eli Lilly, Daiichi Sankyo, Menarini Stemline, Exact Sciences, Gilead, Astra Zeneca, MSD, Novartis, Olema Oncology, Pierre Fabre, Pfizer-Seagen, Roche; payment for expert testimony from Eli Lilly; patents for HER2DX (institution); travel support from Gilead, AstraZeneca. GG: invited speaker for Novartis, Eli Lilly, MSD; advisory role for Gilead, Seagen, Menarini. CCr: personal fees for consulting, advisory role and speakers' bureau from Lilly, Roche, Novartis, MSD, Seagen, Daiichi Sankyo, AstraZeneca, Gilead and Pfizer. CDA: advisory role for Roche, Lilly, Novartis, AstraZeneca, Pfizer, Seagen, Daiichi Sankyo, Gilead and GSK and speaker honoraria from Roche, Lilly, Novartis, Pfizer, Seagen, GSK, GILEAD and Daiichi Sankyo; travel grants from Gilead and research support (to the institution) from Novartis, Gilead and Daiichi Sankyo outside the submitted work. GA: honoraria from Roche, Pfizer, AstraZeneca, Novartis, Celgene, Eli Lilly, Amgen and Eisai. GP: personal fees from Foundation One, Illumina and Lilly. SS: speaker fees from Novartis, Pfizer, Roche, Lilly, BMS and MSD. SP: speaker for Novartis, Eli Lilly, Pfizer, Roche, Gilead, Gentili, Sophos; advisory board for Seagen, Daichii-AstraZeneca. CV: role in advisory boards for Pfizer, Novartis, Eli Lilly, Daiichi Sankyo, AstraZeneca, Menarini Stemline; consultancy activity for Eli Lilly and Novartis; honoraria as a speaker from Novartis, Eli Lilly, Pfizer, AstraZeneca, Menarini Stemline, MSD, Istituto Gentili, Accademia Nazionale di Medicina; research grants from Roche (to the institution). All other authors have declared no conflicts of interest.

DATA SHARING

The datasets generated and/or analyzed during the current study are available from the corresponding author upon a reasonable request.

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