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Real-world effectiveness of palbociclib plus fulvestrant in advanced breast cancer: Results from a population-based cohort study

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ABSTRACT

Background: Real-world (RW) data may provide valuable information on the effectiveness and safety of medicines, which is particularly relevant for clinicians, patients and third-party payers. Evidence on the effectiveness of palbociclib plus fulvestrant is scarce, which highlights the need of additional studies. The aim of this study was to evaluate the effectiveness of palbociclib plus fulvestrant in advanced breast cancer (ABC).

Materials and methods: We conducted a population-based retrospective cohort study and cases of interest were identified through the Portuguese National Cancer Registry database and additional data sources. Patients aged≥18 years, diagnosed with ABC and exposed to palbociclib plus fulvestrant between May 31, 2017 and March 31, 2019 were included. Patients were followed-up until death or cut-off date (February 28, 2021). Primary outcome was rw-progression-free survival (rwPFS). Secondary outcomes were rw-overall survival (rwOS), rw-time to palbociclib failure (rwTPF) and rw-time to next treatment (rwTTNT).

Results: A total of 210 patients were included. Median age was 58 years (range 29–83) and 99.05% were female. Median follow-up time was 23.22 months and, at cut-off date, treatment had been discontinued in 189 patients, mainly due to disease progression (n = 152). Median rwPFS was 7.43 months (95% confidence interval [CI] 6.28–9.05) and 2-year rwPFS was 16.65% (95%CI 11.97–22.00). Median rwOS was 24.70 months (95%CI 21.58–29.27), median rwTPF was 7.5 months (95%CI 6.51–9.08) and median rwTTNT was 11.74 months (95% CI 10.33–14.08).

Conclusion: Palbociclib plus fulvestrant seems an effective treatment for ABC in real-world context. Compared to registrations studies, rwPFS and rwOS were shorter in real-life setting.

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1. Introduction

Breast cancer (BC) is the most frequently diagnosed malignancy and the leading cause of cancer death among women worldwide [1]. Although incidence varies significantly globally, the most recent global cancer burden figures estimate that there were 2.26 million incident breast cancer cases in 2020 [2]. In Portugal, 7,437 new BC cases were diagnosed in 2018 and the age-standardized incidence rate was 40.98 per 100,000 world population [3].

Although 90–95% of BC cases are diagnosed in early stages, advanced breast cancer (ABC) remains an incurable disease with 3- and 5-year survival rates of 35–55% and 25%, respectively [4,5]. Furthermore, recent improvements in overall survival (OS) seem to be mostly associated with human epidermal growth factor receptor 2 (HER2)--positive ABC [6], which highlights the need to improve the outcomes of patients with HER2-negative tumours.

Cyclin-dependent kinase 4/6 (CDK4/6) inhibitors were a substantial breakthrough in the management of estrogen receptor (ER)-positive, HER2-negative ABC, and redefined the standard of care [7]. Palbociclib was approved in 2016 for the treatment of hormone receptor (HR)-positive, HER2-negative ABC in combination with an aromatase inhibitor (AI) as first line treatment or in combination with fulvestrant in women who have received prior endocrine therapy (AI resistant-disease).

The association of palbociclib plus fulvestrant was evaluated in PALOMA-3 clinical trial. Women with HR–positive and HER2-negative ABC were randomly assigned to receive palbociclib-fulvestrant or placebo-fulvestrant. Primary outcome was progression-free survival and significant differences were found. Moreover, while the median OS was not significantly different in the overall cohort, the experimental arm presented a significantly longer OS in patients with sensitivity to previous endocrine therapy [39.7 months (95%CI 34.8–45.7) vs 29.7 months (95%CI 23.8–37.9) [hazard ratio (HR) for death, 0.72; 95%CI 0.55–0.94] [8].

Clinical trials demonstrated the efficacy of palbociclib plus fulvestrant, however real-world data may provide valuable information on the long-term effectiveness and safety of medicines, which is particularly relevant for patients, clinicians and third-party payers. Although some evidence on the effectiveness of this association already exists, the great majority is from single-centre/healthcare institution studies, having limited sample sizes and/or short follow-up times [9,10]. Consequently, the generalizability of results may be considerably reduced, highlighing the need for additional evidence arising from multicentre/population-based studies with longer follow-up periods. The aim of this study was to evaluate the effectiveness of palbociclib plus fulvestrant in real-world clinical setting resorting to a population-based cohort exposed to the study treatment within the palbociclib early access program timeframe.

2. Material and methods

2.1. Study design

This is a retrospective cohort study conducted in agreement with the Declaration of Helsinki and reported according to STROBE guideline [11].

2.2. Setting and data sources

This study used data from the Portuguese National Cancer Registry (Registo Oncológico Nacional, RON)'s database, which has been described in detail elsewhere [12–14]. Briefly, RON is a nationwide population-based cancer registry and its database comprises international recommendations stated by the International Agency for Research on Cancer [15] and collects relevant information since cancer diagnosis until patient's death.

Cases of interest were identified through RON's database. To ensure cases exhaustiveness, patients granted early access to palbociclib plus fulvestrant by the National Authority of Medicines and Health Products (INFARMED) were also identified recurring to the palbociclib early access program database. For private health institutions, not included in the early access program, cases of interest were likewise complemented resorting to hospital pharmacies databases. These additional cases of interest were registered in RON's database.

2.3. Ethics

The study was approved by the *Instituto Português de Oncologia de Lisboa Francisco Gentil* Ethics Committee on September 9, 2021 (UIC/1441). Informed consent waiver was granted with the observational and retrospective nature of the study where all variables used are already part of the RON's database as foreseen by law to accomplish registry purposes.

2.4. Study population and information of interest

Adults (≥18 years) diagnosed with ABC (stages IIIC and IV) and initiating palbociclib plus fulvestrant between May 31, 2017 and March 31, 2019 were included. Patients were followed-up between treatment initiation and death or cut-off date (February 28, 2021). Information of interest included: (a) demographic and clinical characteristics (sex, age, stage at diagnosis, morphology, stage at treatment initiation, metastasis location at treatment initiation, Eastern Cooperative Oncology Group Performance Status (ECOG PS) at treatment initiation, hormone receptor status, HER2 status, previous therapies for advanced disease); (b) palbociclib plus fulvestrant exposure (treatment initiation date, concomitant therapies, dose, dose reduction, date and reason for treatment discontinuation, adverse events (AEs) leading to treatment discontinuation); (c) outcomes and post-treatment characterization (disease progression and date, subsequent treatments, vital status and date of last known contact/death).

2.5. Study outcomes and definitions

The primary outcome was real-world progression-free survival (rwPFS), calculated as the time elapsed between palbociclib plus fulvestrant initiation and disease progression or death. Secondary outcomes were real-world overall survival (rwOS), computed as the time elapsed between palbociclib plus fulvestrant initiation and death due to any cause; real-world time to palbociclib failure (rwTPF), defined as the time from palbociclib plus fulvestrant initiation to date of palbociclib discontinuation due to any cause; and real-world time to next treatment (rwTTNT), defined as the time from palbociclib plus fulvestrant initiation to the initiation of a new treatment line for ABC.

Disease progression was defined as the occurrence of imagiological progression, clinical progression or initiation of a new treatment line for ABC. A hierarchical consideration was used according to available information and the following sequence: imagiological disease progression, clinical disease progression and initiation of a new treatment line for ABC. A new treatment line was defined as the initiation of chemotherapy, endocrine therapy or target therapy for ABC. AEs leading to treatment discontinuation were coded according to The Medical Dictionary for Regulatory Activities [16].

Menopausal status at treatment initiation was considered as a post-hoc additional covariate. As in Portugal median age at menopause is estimated to be 48 years (IQR 44–52) [17], female patients aged ≤50 years were classified as pre/peri-menopausal and aged >55 years were categorized as post-menopausal. For female patients aged 51–55, the use of LHRH agonists in association with palbociclib and fulvestrant was considered, and if the patient had concomitant treatment with a luteinizing hormone-releasing hormone (LHRH) agonist, the case was classified as pre/perimenopause; otherwise, the patient was categorized as

post-menopausal. Furthermore, metastases' locations were clustered in three different categories: visceral metastases, defined as the presence of at least one of the following locations: lung/pleura, liver, peritoneum or brain; bone-only metastases, defined based on the presence of bone metastases exclusively; non visceral metastases, identified as the absence of visceral and bone metastases.

2.6. Statistical analysis

Data registered in RON's database were exported in a pseudonymized format. Prior to statistical analyses, data were validated considering missing data and cross-variable validation. Clinical characteristics and treatment patterns were summarized using descriptive statistics. Median follow-up and treatment times were computed simply, as the median of all survival or treatment times (ignoring censoring), respectively. Time to event outcomes (rwPFS, rwOS, rwTPF and rwTTNT) were estimated using the Kaplan-Meier estimator. Median time to event, 1- and 2-year estimates were reported considering a 95% confidence interval (CI). A prespecified sensitivity analysis was conducted to assess the impact on rwPFS and rwOS of the inclusion of patients for whom prior endocrine therapy for advanced disease was not undertaken neither had disease recurrence while on adjuvant endocrine therapy or within 12 months of its completion, initial palbociclib dose was 100 mg or 75 mg, ECOG PS $\geq$ 2 and primary endocrine resistant according to European Society for Medical Oncology (ESMO) criteria [18]. For all sensitivity analyses, the category unknown or not evaluated was excluded. Additionally, a post-hoc bivariate analysis relating palbociclib dose reduction and ECOG PS at treatment initiation was performed using chi-square test. A multivariable proportional hazard regression was used to evaluate the association between variables of interest and rwPFS and rwOS. Covariates with more than 25% of unknown or not evaluated data were not considered for modelling. Variables included in the multivariable regression correspond to significant covariates in univariate analysis (cut-off p-value <0.20) or clinically relevant based on their prognostic value. The proportional hazard assumptions were verified.

All statistical analyses were performed using Stata software, version 13.0 [19].

3. Results

A total of 210 patients were included in this study and baseline characteristics are presented in Table 1. Almost all were women (99.05%) and median age was 58 years [interquartile range (IQR) 49–66]. The majority of the patients had a favourable ECOG PS (0–1; 89.25%), a postmenopausal status (69.71%) and metastatic disease with visceral involvement (55.29%). It is also worth mentioning that 4 patients had central nervous system metastasis (1.90%). Median follow-up time was 23.22 months and 8 patients (3.81%) were lost to follow-up.

3.1. Palbociclib-fulvestrant exposure

Treatment characteristics are detailed in Table 2. Median treatment duration was 7.48 months (IQR 3.75–15.72), the majority of patients initiated palbociclib with the recommended dose (125 mg; 84.76%) and chemotherapy was the most common systemic treatment option after palbociclib-fulvestrant. Post-hoc bivariate analysis did not find an association between palbociclib dose reduction and ECOG PS at treatment initiation (p = 0.399) and, at the time of data cut-off, 90.00% had discontinued the study treatment and the most prevalent cause was disease progression (80.42%). Moreover, haematological events were the most common AEs leading to treatment discontinuation (5 for neutropenia, 3 for pancytopenia, 3 for bicytopenia and 1 for thrombocytopenia; appendix 1).

Table 1
Baseline characteristics of included patients.

Characteristics			n = 210
Sex, n (%)	Female		208 (99.05)
	Male		2 (0.95)
Stage at diagnosis, n (%)	I-III		158 (75.96)
Unknown: n = 2	IV		50 (24.04)
Histology, n (%)	No special type invasive carcinoma		171 (81.43)
	Invasive lobular carcinoma		24 (11.43)
	Other subtypes		15 (7.14)
Age at treatment initiation, years	Median (IQR)		58 (49–66)
Stage and metastasis sites at treatment initiation, n (%)	IIIC		2 (0.95)
	IV		208 (99.05)
	Bone-only		63 (30.29)
	Visceral		115 (55.29)
	Non-visceral		30 (14.42)
ECOG PS at treatment initiation, n (%)	0–1		166 (89.25)
	≥2		20 (10.75)
Unknown: n = 24			
Menopausal status at treatment initiation, n (%)	Pre/peri-menopausal		63 (30.29)
	Post-menopausal		145 (69.71)
HR status, n (%)*	ER and/or PR positive		204 (100)
Unknown: n = 6	ER and PR negative		0
HER2 status, n (%) #	Positive		0
	Negative		201 (100)
Unknown: n = 9			
Prior endocrine therapy for advanced disease ¥	Number of patients		139 (66.19)
	Number of lines, n (%)	1	101 (72.66)
		2	27 (19.42)
		≥3	11 (7.91)
	Medicine, n (%)	Aromatase inhibitor	111 (79.86)
		Tamoxifen	22 (15.83)
		Other	6 (4.32)
	Duration of the last endocrine therapy prior to palbociclib-fulvestrant, n (%)	<6 months	33 (25.00)
		≥6 months	99 (75.00)
Unknown: n = 6			
Prior lines of chemotherapy for advanced disease, n (%)	Number of patients		98 (46.67)
	1		62 (63.27)
	2		18 (18.37)
	≥3		18 (18.37)

ECOG PS, Eastern Cooperative Oncology Group Performance Status; ER, Estrogen receptor; HER2, Human epidermal growth factor receptor 2; HR, Hormone receptor; IQR, interquartile ranges; PR, Progesterone receptor; *for 161 and 49 patients, HR status corresponds to diagnosis and treatment initiation, respectively; #for 158 and 52 patients, HER2 status corresponds to diagnosis and treatment initiation, respectively; ¥ of those 71 patients that did not receive prior endocrine therapy for advanced disease, 54 had disease recurrence while on adjuvant endocrine therapy or within 12 months of its completion.

3.2. Effectiveness

Median rwPFS was estimated to be 7.43 months (95%CI 6.28–9.05) with a 2-year rwPFS of 16.65% (95%CI 11.97–22.00) (Fig. 1A). With respect to secondary outcomes, median rwOS was estimated at 24.70 months (95%CI 21.58–29.27) (Fig. 1B), median rwTPF was estimated at 7.50 months (95%CI 6.51–9.08), with a 2-year rwTPF of 17.09% (95%CI 12.35–22.49) and median rwTTNT was estimated at 11.74 months (95% CI 10.33–14.08), with a 2-year rwTTNT of 48.01% (95%CI 39.07–56.40) (Fig. 2A and B, respectively). Sensitivity analyses showed that results were mainly consistent with those from the primary analysis, although it is worth noting that, for rwOS, higher estimates were obtained for patients with ECOG PS 0–1 [median rwOS: 28.22 months (95%CI 23.42–33,98) and for non-primary endocrine resistant patients [median rwOS: 27.34 (95%CI 21.84–33.95)] (appendix 2).

ECOG PS $\geq$ 2 and $\geq$ 3 prior lines of endocrine therapy for advanced

Table 2
Characterization of the exposure to palbociclib plus fulvestrant and subsequent treatments.

Characteristics		n = 210		
Concomitant systemic treatments to palbociclib-fulvestrant, n (%)	Bisphosphonates or anti-RANK/RANKL monoclonal antibodies	101 (48.10)		
	LHRH agonist	32 (15.24)		
Concomitant local treatments to palbociclib-fulvestrant, n (%)	Radiotherapy *	17 (8.10)		
	Surgery	4 (1.90)		
Treatment duration, months	Median (IQR)	7.48 (3.75–15.72)		
Palbociclib starting dose (mg), n (%)	125	178 (84.76)		
	100	18 (8.57)		
Unknown: n = 6	75	4 (1.90)		
Palbociclib dose reduction, n (%)	Yes	64 (43.24)		
	No	84 (56.76)		
Unknown: n = 62				
Status at cut-off date, n (%)	On-going treatment	21 (10.00)		
	Discontinued treatment	189 (90.00)		
	Reasons for treatment discontinuation			
	Disease progression	152 (80.42)		
	Death	7 (3.70)		
	Adverse event	17 (8.99)		
	Refuse	3 (1.59)		
	Other cause	3 (1.59)		
	Unknown reason	7 (3.70)		
Subsequent systemic therapies	Patients with at least one subsequent systemic therapy	141 (67.14)		
	Subsequent line	1 L (n = 141)	2 L (n = 85)	3 L+ (n = 57)
	Chemotherapy	101 (71.13)	75 (88.24)	43 (89.58)
	Endocrine therapy	14 (9.86)	2 (2.35)	10 (20.83)
	Target therapy	24 (16.90)	7 (8.24)	4 (8.33)
	mTOR inhibitors	23 (95.83)	6 (85.71)	3 (75.00)
	PI3K inhibitors	1 (4.17)	1 (14.29)	1 (25.00)
	Other CDK4/6 inhibitors	0	0	0
	Anti-HER2	0	0	1 (25.00)
	PARP inhibitors	0	0	1 (25.00)
	Clinical trial	2 (1.41)	1 (1.18)	0
	Patients with no subsequent systemic therapies[#]	48 (22.86)		
	Patients still on palbociclib-fulvestrant treatment at cut-off date	21 (10.00)		

1 L, first posterior line; 2 L second posterior line; 3 L+, third and posterior lines; CDK4/6, Cyclin-dependent kinase 4/6; IQR, Interquartile range; LHRH, Luteinizing hormone releasing hormone; mTOR, Mammalian target of rapamycin; PARP, Poly(ADP-ribose) polymerase; PI3K, Phosphatidylinositol 3-kinase; RANK/RANKL, Receptor activator of NF-κB ligand; * of those 17 patients, 8 had bone-only disease, 5 presented non-visceral involvement and 4 had visceral metastasis; [#] of those 48 patients, 39 have died after palbociclib-fulvestrant.

disease were identified by multivariable analysis as independent factors for an increased risk of disease progression, maintaining the remaining variables constant [hazard ratio (HR) 1.73 (95%CI 1.04–2.88) and 2.87 (95%CI 1.39–5.92), respectively) (Fig. 3). Moreover, patients with visceral disease and ECOG PS $\geq$ 2 had an increased risk of death comparing to bone-only metastasis and ECOG PS 0–1 patients, respectively, and adjusting also for age [HR 1.89 (95%CI 1.21–2.95) and 2.83 (95%CI 1.66–4.83), respectively) (Fig. 4).

4. Discussion

To the best of our knowledge, this is the first population-based study showing the effectiveness of palbociclib plus fulvestrant in ABC. Moreover, it is well known that cancer registries are capable of providing valuable pharmacoepidemiological and outcomes research data, which is essential in providing valuable information for patients and clinical and health technology assessment decisions.

Even though real-world utilization of medicines is usually varied and consequently real-life cohorts are heterogeneous, they might better resemble the most typical population being treated, which provide a better picture of results and outcomes. As such, we found patients initiating with a palbociclib reduced dose (100 mg and 75 mg) as well as patients that did not receive previous endocrine therapy for advanced disease neither having disease recurrence while on adjuvant treatment with tamoxifen or aromatase inhibitor or within 12 months of its completion. However, as confirmed by sensitivity analysis, their inclusion in our study did not impact the results obtained. Regarding menopausal status, it is difficult to evaluate using registry data and we recognize that limitations exist; nonetheless, we understand it is an important factor in the management of BC [20] and therefore found it relevant to consider.

We found that 84.76% of patients initiated palbociclib with a 125 mg dose, concordant with other real-world studies [21–24]. While the recommended starting dose is 125 mg, a more careful approach is given to more fragile patients and/or with relevant comorbidities. With respect to dose reduction, 43.24% of patients in our study had the initial dose reduced, in line with previous real-world studies (ranging from 31% to 50%), which could suggest that this is the prevalence of palbociclib dose reduction in real-life context in this indication [10,22,25,26]. However, these data need considering the high proportion of missing information (n = 62; 29.52%).

The fact that rwTPF was only slightly superior to rwPFS (7.50 months vs 7.43 months) suggests that the event with the greatest contribution to palbociclib failure was disease progression, as confirmed by the high number of patients discontinuing treatment for this reason (n = 152). Moreover, in our study, treatment was discontinued due to AEs in 17 patients (8.09% of the 210 patients included) and the most prevalent AEs were hematological, as could be expected by clinical trial data and by this drug's mechanism of action, which is known to potentially cause reversible bone marrow suppression [27]. It must be highlighted, however, that our study captured only AEs leading to treatment discontinuation and not AEs in general, which are reported under the National pharmacovigilance system. Nevertheless, our data suggest the medicine is well tolerated in a real-world environment.

Although some real-world studies about the effectiveness of palbociclib plus fulvestrant exist, the majority found in the literature has some limitations, particularly being single-centre studies, having limited sample sizes and/or short follow-up times [21,22,25,26,28–30]. Furthermore, other works privileged analyses per line of treatment irrespective of concomitant medicine (AI, fulvestrant or other), which may be a challenge for indirect comparisons and understanding the real benefit of this association [31–33]. Nevertheless, Taylor-Stokes et al. conducted a multicentre retrospective cohort study including 292 ABC patients, with a median follow-up time of 9.9 months. Median PFS and OS were not reached and the 1-year PFS and OS rates were estimated at 79.8% and 87.9%, respectively [34]. Varella et al. led a study that included 158 ABC patients treated with palbociclib-fulvestrant. With a median follow-up of 10.2 months, median PFS was estimated at 10.3 months (95%CI 8.16–12.3) [35]. More recently, a study conducted in Italy including 92 patients and having a median follow-up time of 24 months found a median PFS of 12.2 months (95%CI 3.0–19.0) [36]. Although our estimates [median rwPFS 7.43 months (95%CI 6.28–9.05) and median rwOS 24.70 months (95%CI 21.58–29.27)] are consistently

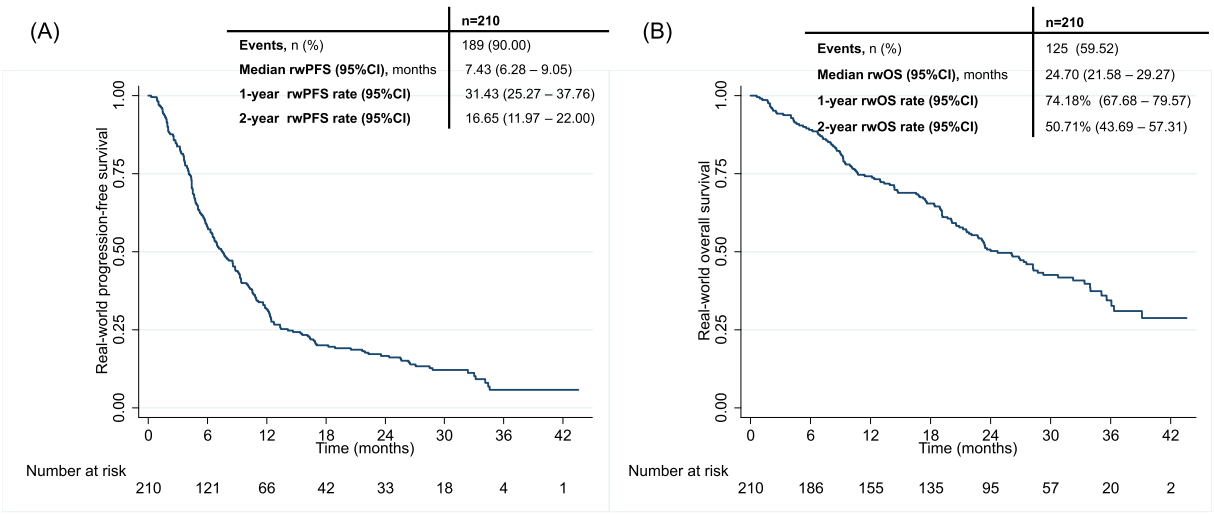

Fig. 1. Kaplan-Meier estimation on rwPFS (A) and rwOS (B) for patients exposed to palbociclib plus fulvestrant.

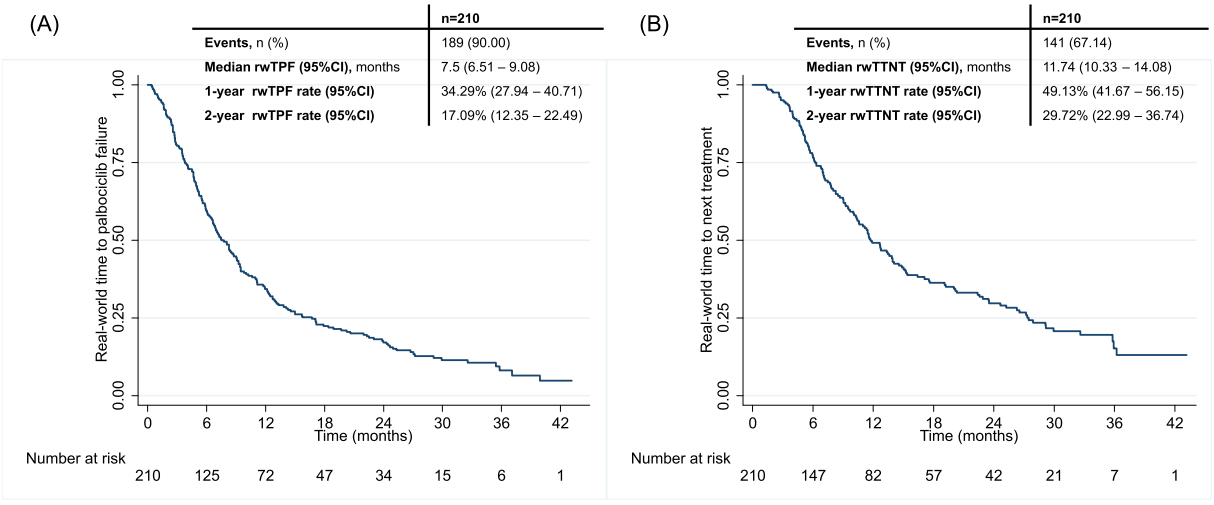

Fig. 2. Kaplan-Meier estimation on rwTPF (A) and rwTTNT (B) for patients exposed to palbociclib plus fulvestrant.

inferior to the above-mentioned studies, it should be noticed that the comparison is challenging due to the limited follow-up duration of these studies, absence of data for OS in some of them, different healthcare settings as well as imprecision of the results obtained for these studies, as exposed by the wider confidence intervals reported.

Our data suggest a lower effectiveness in a real-life context compared to the efficacy reported in the clinical trial [median rwPFS 7.43 months (95%CI 6.28–9.05) compared to median PFS 9.5 months (95%CI 9.2–11.0) [8]; median rwOS 24.70 months (95%CI 21.58–29.27) compared to 34.9 months (95%CI 28.8–40.0) [8]]. To conclude on the existence of an efficacy-effectiveness gap, it is essential to compare inclusion and exclusion criteria and baseline characteristics of patients included in this study with those included in PALOMA-3. Data suggest that patients' characteristics are similar across studies, despite the higher proportion of patients undertaking endocrine therapy for advanced disease in the clinical trial and the higher use of previous chemotherapy for advanced disease in RON's cohort. It is also worth noticing that the clinical trial only admitted patients having an ECOG PS 0–1. In fact, our sensitivity analysis showed more encouraging results when restricting the outcomes estimate to patients with a favourable ECOG PS [median rwPFS 8.59 months (95%CI 6.45–10.46) and median rwOS 28.22 months (95%CI 23.42–33.98)], which suggests the noticed efficacy-effectiveness gap may be partially explained by this difference in eligibility criteria. In addition, one could assume that different subsequent systemic therapies could have influenced rwOS estimates. However, a great similarity is observed when comparing subsequent treatments of both cohorts, prevailing the use of chemotherapy. Hence, even considering the limitations of comparing results from different studies with dissimilar designs and conducted in different populations, we consider the differences identified in rwOS likely to be clinically significant and to justify future additional research, namely comparative effectiveness studies.

Multivariable analysis demonstrated that ECOG PS ≥ 2 and ≥ 3 prior lines of endocrine therapy for advanced disease were independently associated with a higher risk of disease progression, after adjusting for age, sex, metastases' location and histology. Although these findings could be expected as they are major prognostic factors, this analysis demonstrated an increase of 73% and 187% in the risk of disease progression comparably to patients with ECOG PS 0–1 and one prior line of endocrine therapy for advanced disease, respectively, which may be valuable information for clinicians. Additionally, we found that visceral disease and ECOG PS ≥ 2 were independently associated with a higher risk of death, adjusting for age, another finding that could be expected considering these are major prognostic factors. The results obtained for patients with an ECOG PS ≥ 2 highlight the need of a multidisciplinary approach and early integration of a palliative care. It is worth

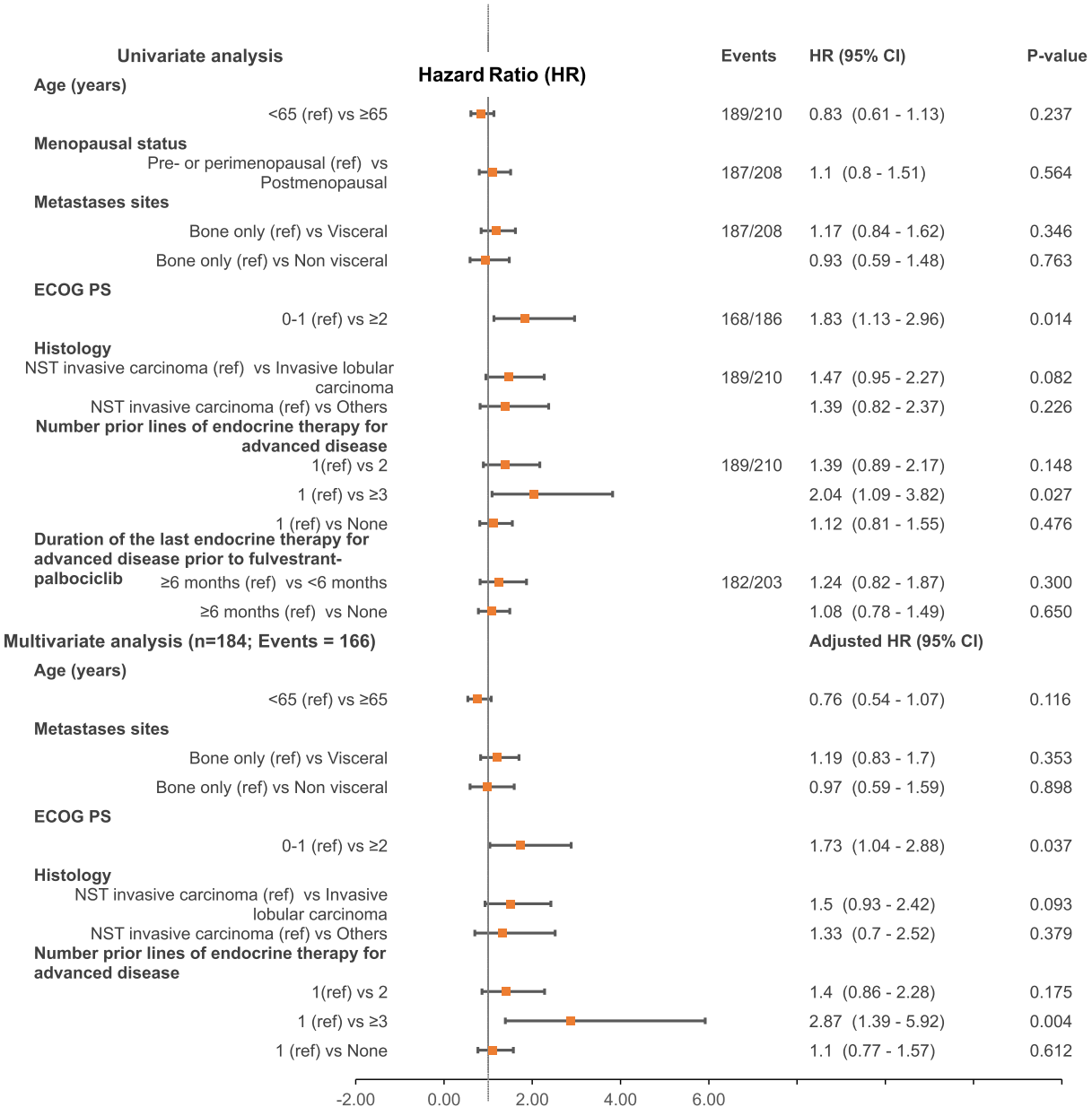

Fig. 3. Univariate and multivariable analysis for rwPFS.
CI, Confidence interval; ECOG PS, Eastern Cooperative Oncology Group Performance Status; HR, Hazard ratio; NST, No special type; Ref, Reference.

mentioning that, in our study, age was not associated with rwOS, which could suggest effectiveness of this drug in both young and elderly patients, in line with efficacy data reported in clinical trials [8].

We should recognize that this study has strengths and limitations. It included an important sample of 210 patients and adds to the body of evidence around the benefit of palbociclib in real-life context. Additional strengths include median follow-up duration (23.22 months) and having just 8 patients (3.81%) lost to follow-up. Moreover, the study was population-based and comprised individuals treated in public and private institutions in all regions of the country, thus minimizing selection bias. Resorting to different data sources to identify cases maximized exhaustiveness, contributing to the external validity of our data. It must also be recognized that effectiveness monitoring of innovative medicines in the early phase of their utilization, particularly in the timeframe of an early-access program, may contribute to underestimate the outcomes as a result of channelling bias. On the other hand, there is a possible misclassification bias in the identification of events due to retrospective nature of the study, which could affect the estimation of outcomes, particularly rwPFS. However, procedures were implemented to minimize this, namely the cross-variable validation procedures.

5. Conclusions

Palbociclib plus fulvestrant seems to be an effective treatment option for ABC in real-world context, although its effectiveness in terms of rwOS seems to be inferior to the efficacy reported in clinical trials. These dissimilarities may be partially explained by differences in ECOG PS. It would be relevant to have comparative effectiveness studies to confirm the real benefit of this association.

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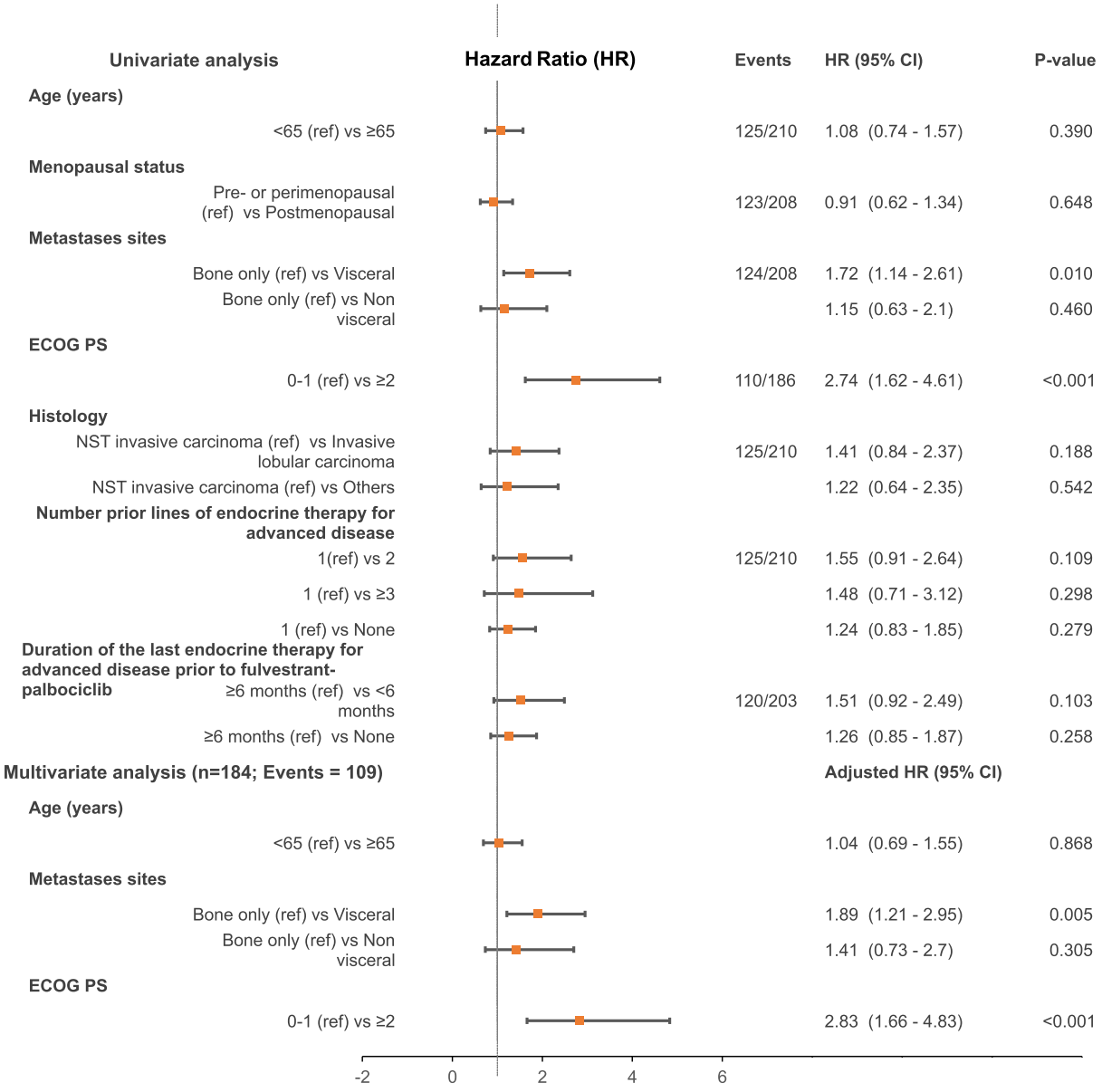

Fig. 4. Univariate and multivariable analysis for rwOS.
CI, Confidence interval; ECOG PS, Eastern Cooperative Oncology Group Performance Status; HR, Hazard ratio; NST, No special type; Ref, Reference.

Declaration of competing interest

We have read the journal's policy and the authors of this manuscript have the following competing interests: ARF reports travel grants from Roche and advisory board fees from Daiichi Sankyo, Gilead, Merck Sharp & Dohme, Novartis and Roche, outside the submitted work. DMB reports travel grants from LEO Farmacêuticos, Merck Sharp & Dohme, Ipsen, Janssen, Roche, and Novartis, advisory board fees from Janssen, Pfizer, Merck Sharp & Dohme, Angelini, AstraZeneca, and Novartis, and institutional grants from F. Hoffmann-La Roche, outside the submitted work. The other authors have declared that no competing interests exist.

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Appendix A. AEs leading to treatment discontinuation in palbociclib plus fulvestrant exposed patients

Adverse events leading to discontinuation, n (%)	n = 17 of 210 (8.99%)
Neutropenia	5 (29.41)
Bicytopenia	3 (17.65)
Pancytopenia	3 (17.65)
Upper respiratory tract infection	1 (5.88)
Neutropenia and vomiting	1 (5.88)
Urinary tract infection	1 (5.88)
Thrombocytopenia	1 (5.88)
Hepatotoxicity and neutropenia	1 (5.88)

Appendix B. Sensitivity analyses

	Number of events/n (%)	Median (95%CI)	1-year rate (95% CI)	2-year rate (95% CI)
PFS sensitivity analysis				
Excluding patients that did not receive prior endocrine therapy for advanced disease neither had had disease recurrence while on adjuvant endocrine therapy or within 12 months of its completion	175/193 (90.67)	7.17 months (5.99–9.05)	31.09% (24.70–37.68)	15.53% (10.83–21.00)
Excluding patients with an initial palbociclib dose of 100 mg or 75 mg	167/188 (88.83)	7.73 months (6.51–9.28)	32.45% (25.87–39.18)	17.54% (12.49–23.30)
Excluding patients with an ECOG PS $\geq$ 2	149/166 (89.76)	8,59 months (6.45–10.46)	34.34% (27.21–41.56)	18.05% (12.63–24.26)
Excluding primary endocrine resistant patients according to ESMO criteria	136/152 (89.47)	6.97 months (5.79–8.78)	32.89% (25.57–40.39)	18.40% (12.70–24.93)
OS sensitivity analysis				
Excluding patients that did not receive prior endocrine therapy for advanced disease neither had had disease recurrence while on adjuvant endocrine therapy or within 12 months of its completion	116/193 (60.10)	24.01 months (21.25–28.72)	74.09% (67.30–79.69)	50.23% (42.91–57.09)
Excluding patients with an initial palbociclib dose of 100 mg or 75 mg	106/188 (56.38)	27.34 months (23.13–33.95)	78.09% (71.45–83.36)	53.47% (46.00–60.37)
Excluding patients with an ECOG PS $\geq$ 2	93/166 (56.02)	28.22 months (23.42–33.98)	77.59% (70.44–83.22)	56.52% (48.54–63.74)
Excluding primary endocrine resistant patients according to ESMO criteria	88/152 (57.89)	27.34 months (21.84–33.95)	75.52% (67.85–81.61)	52.54% (44.23–44.01)

CI, Confidence interval; ECOG PS, Eastern Cooperative Oncology Group Performance Status; ESMO, European Society for Medical Oncology; HER2, Human epidermal growth factor receptor 2; HR, Hormone receptor.

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