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ABSTRACT

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INTRODUCTION

Currently, metastatic breast cancer is difficult to treat. Patients with hormone receptor (HR)-positive and HER2-negative, the most common subtype, typically undergo endocrine therapy. Therefore, new treatments can be very useful in improving quality of life, reducing toxicity, and decreasing scenarios of hormonal resistance. Medications from the group of cyclin-dependent kinase inhibitors appear as a potential improvement in the therapeutic approach to advanced breast cancer. Within this group, there are palbociclib, ribociclib, and abemaciclib. Cyclin-dependent kinases 4 and 6 (CDK4/6) are responsible for regulating the cell cycle at the transition between the G1 and S phases. In many neoplasms, this cycle is deregulated, and it promotes uncontrolled cell proliferation. It is then possible for these medications to have better effectiveness. These medications were approved by INFARMED, I.P. after an analysis of the therapeutic value they offer. For this purpose, data from clinical trials conducted with these medications were essentially used. The MONALEESA [3, 5, 7] studies were used for ribociclib, PALOMA [8, 4, 1] for palbociclib, and MONARCH [2, 6] for abemaciclib. These studies focused on testing the hypothesis of treating CDK4/6 inhibitors in combination with an aromatase inhibitor or fulvestrant as an alternative to the gold standard. In these studies, it was concluded that they brought a significant increase in effectiveness, justifying their use in clinical practice. However, this evaluation was based on clinical trials with very specific inclusion and exclusion criteria and in a highly controlled environment. It is then vital to study how these new molecules compare to current practice in terms of treatment effectiveness in a real-world setting.

MATERIALS AND METHODS

0.1 Study Design

This retrospective study was designed in 2022. The aim of the study was to evaluate the clinical benefit, side effects and long-term survival of patients with HR+/HER2− that started treatment with CDK46 inhibitors plus hormonotherapy in different lines of treatment between the 14th of March 2017 and the 31st of December 2021. The follow-up period was set until June 2022. Inclusion criteria: pre and postmenopausal women, men, Oestrogen Receptor positive % (defined by ER expression ≥ 1 % of tumour cell by immunohistochemistry, IHC) and HER2 negative (by IHC and/or amplification assay) in the primary tumour or metastatic site after biopsy. Exclusion criteria: Patients that had only ambulatory medication, and patients involved in clinical trials. The comparison group was defined by a population of patients, that were treated with hormone therapy as first-line between 2015 and 13 of match 2017.

The evaluation of effectiveness will involve overall survival and progression-free analysis. We will compare the three different cyclin-dependent kinase inhibitors in terms of efficacy in real-world patients and will also compare the effectiveness of this class of drug against traditional hormonotherapy. We will also compare them with the clinical trials when possible.

Table 1. Descriptive statistics of cyclin-dependent kinase inhibitors group

	Palbociclib	Ribociclib	Overall
	(N=247)	(N=106)	(N=353)
Age at treatment start			
Mean (SD)	59.2 (11.7)	58.2 (10.7)	58.9 (11.4)
Median [Min, Max]	60.0 [28.0, 84.0]	58.0 [32.0, 79.0]	59.0 [28.0, 84.0]
Treatment Line			
1st Line	127 (51.4%)	98 (92.5%)	225 (63.7%)
2nd+ Lines	120 (48.6%)	8 (7.5%)	128 (36.3%)
Bone metasthasis			
Não	58 (23.5%)	24 (22.6%)	82 (23.2%)
Sim	189 (76.5%)	82 (77.4%)	271 (76.8%)
PFS			
Censored	84 (34.0%)	76 (71.7%)	160 (45.3%)
Dead	163 (66.0%)	30 (28.3%)	193 (54.7%)
OS			
Censored	148 (59.9%)	88 (83.0%)	236 (66.9%)
Dead	99 (40.1%)	18 (17.0%)	117 (33.1%)
Stage			
I	22 (8.9%)	7 (6.6%)	29 (8.2%)
II	75 (30.4%)	22 (20.8%)	97 (27.5%)
III	75 (30.4%)	18 (17.0%)	93 (26.3%)
IV	65 (26.3%)	46 (43.4%)	111 (31.4%)
Missing	10 (4.0%)	13 (12.3%)	23 (6.5%)

0.2 Data collection

All data were collected from original medical records from baseline to last visit or death. The data was collected from Instituto Português de Oncologia – Porto (IPO-P). table 1 shows a comparison between the groups. Data included: demographic information, age at first diagnosis and age at the beginning of treatment with palbociclib, clinical characteristics and performance status by Eastern Cooperative Oncology Group scale (ECOG). Treatment-related data: loco-regional and neo/adjuvant systemic treatment, number and type of treatments in advance setting before palbociclib, type of treatment beyond palbociclib progression, treatment strategy in premenopausal women (ovarian suppression / ovarian ablation, OS/OA), palliative radiation therapy before or during palbociclib treatment and partner of palbociclib in different lines. Metastatic data at the beginning of palbociclib: 'de novo' metastatic disease, site of metastases (bone, soft tissue, visceral, visceral and bone, central nervous system-CNS with or without another site), and metastatic site at palbociclib progression. Patients predisposition: side effects by frequency and grade (NCI-CTCAE version 4.0), starting dose and number of patients with dose interruption, delay, reduction or treatment discontinuation

0.3 Statistical Analysis

R was used for statistical analysis. Demographic, clinical characteristics and side effects were analysed using descriptive statistics (count, percentages and median/range). Kaplan–Meier test was used to determine the median PFS and OS in the entire population and subgroups. Log-rank test was used for comparisons of PFS and OS among different subgroups. Cox Regression was used to assess feature importance and impact. All statistical tests were two-sided, and the significance level was 0.05.

RESULTS

DISCUSSION

CONCLUSIONS

AUTHOR CONTRIBUTIONS

A.O., A.T. and A.F. conceived the presented idea; A.O. wrote the main manuscript; All authors have read and agreed to the published version of the manuscript.

Table 2. Descriptive statistics of palbociclib and ribociclib group vs hormonotherapy

	CDK4/6	Chemo	Overall
	(N=225)	(N=43)	(N=268)
Age at treatment start			
Mean (SD)	59.1 (11.5)	60.1 (12.4)	59.3 (11.6)
Median [Min, Max]	59.0 [28.0, 84.0]	62.0 [34.0, 85.0]	60.0 [28.0, 85.0]
PFS			
Censored	123 (54.7%)	2 (4.7%)	125 (46.6%)
Dead	102 (45.3%)	41 (95.3%)	143 (53.4%)
OS			
Censored	168 (74.7%)	8 (18.6%)	176 (65.7%)
Dead	57 (25.3%)	35 (81.4%)	92 (34.3%)
Estrogen Receptor			
+	225 (100%)	42 (97.7%)	267 (99.6%)
-	0 (0%)	1 (2.3%)	1 (0.4%)
Progesterone Receptor			
+	168 (74.7%)	27 (62.8%)	195 (72.8%)
-	57 (25.3%)	16 (37.2%)	73 (27.2%)
Stage			
I	16 (7.1%)	3 (7.0%)	19 (7.1%)
II	55 (24.4%)	20 (46.5%)	75 (28.0%)
III	62 (27.6%)	11 (25.6%)	73 (27.2%)
IV	75 (33.3%)	2 (4.7%)	77 (28.7%)
Missing	17 (7.6%)	7 (16.3%)	24 (9.0%)

INSTITUTIONAL REVIEW

This work was approved by the ... Ethics Committee...

DATA AVAILABILITY

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FUNDING

This work was supported ... For the purpose of open access, the author has applied a CC BY public copyright licence to any Author Accepted Manuscript version arising from this submission.

ACKNOWLEDGMENTS

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CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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Figure 1. Clustering for 3 variables with 3 silos - (A) categorical variables with proportion with K-Means and (B) Categorical with K-modes

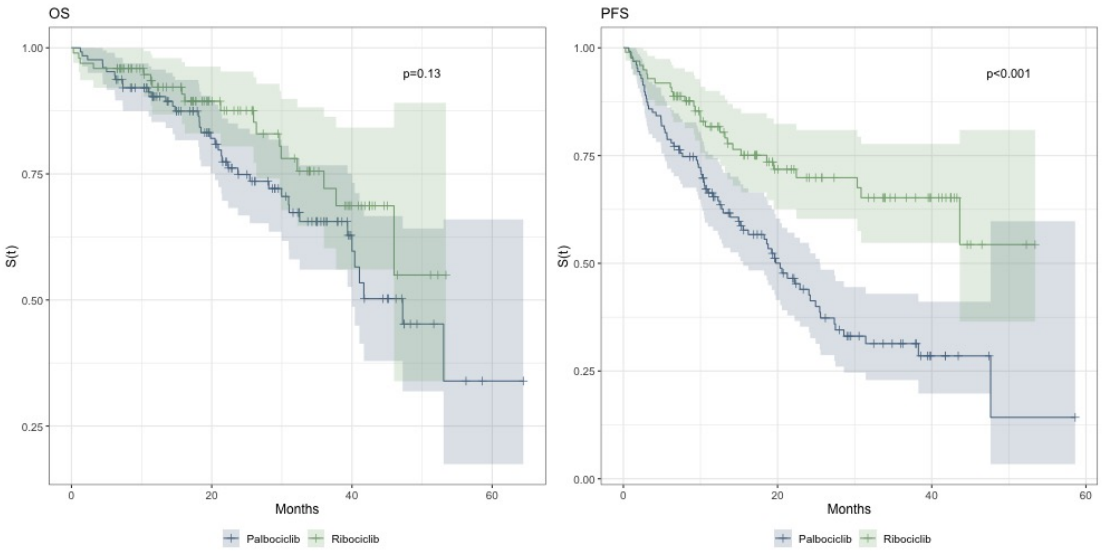

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FIGURE

TABLE

Figure 2. Clustering for 3 variables with 3 silos - (A) categorical variables with proportion with K-Means and (B) Categorical with K-modes

	OS			PFS		
Characteristic	**HR**[1]	**95% CI**[1]	**p-value**	**HR**[1]	**95% CI**[1]	**p-value**
Drug						
Palbociclib	—	—		—	—	
Ribociclib	0.69	0.38, 1.26	0.2	0.44	0.28, 0.71	<0.001
Stage						
I	—	—		—	—	
II	4.78	0.63, 36.2	0.13	2.07	0.79, 5.40	0.14
III	5.69	0.76, 42.8	0.091	2.09	0.80, 5.43	0.13
IV	3.57	0.46, 27.6	0.2	1.65	0.63, 4.36	0.3
Visceral Metastasis						
No	—	—		—	—	
Yes	1.93	1.10, 3.36	0.021	1.24	0.82, 1.86	0.3
Age at treatment start	1.02	0.99, 1.05	0.2	1.00	0.98, 1.02	0.7
ECOG at treatment start						
0	—	—		—	—	
1	1.60	0.86, 2.95	0.13	1.23	0.79, 1.92	0.4
2	2.86	1.17, 7.02	0.021	0.94	0.43, 2.06	0.9
3	8.33	1.77, 39.2	0.007	0.68	0.09, 5.17	0.7

[1] HR = Hazard Ratio, CI = Confidence Interval

Figure 3. Clustering for 3 variables with 3 silos - (A) categorical variables with proportion with K-Means and (B) Categorical with K-modes

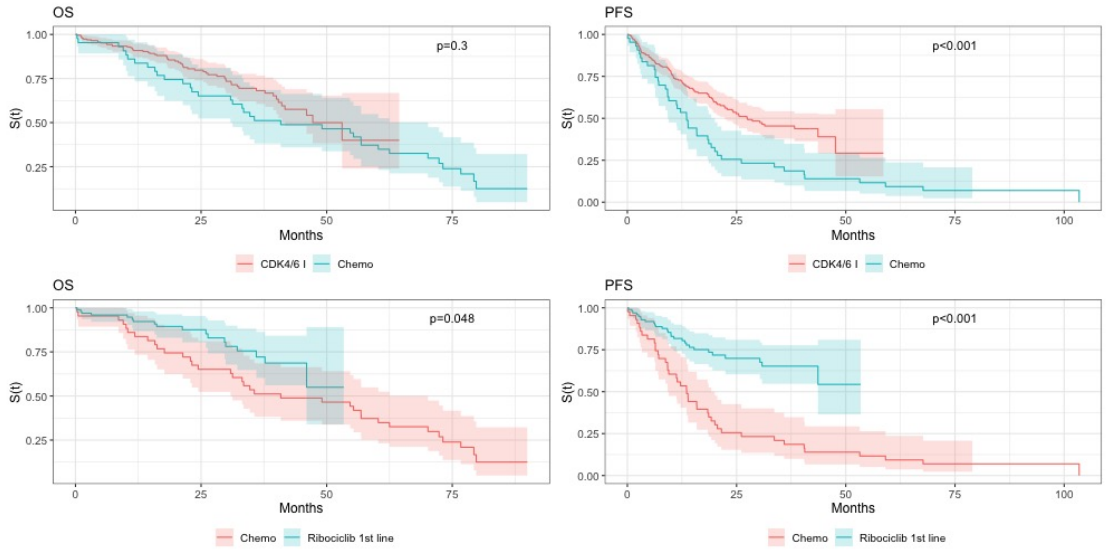
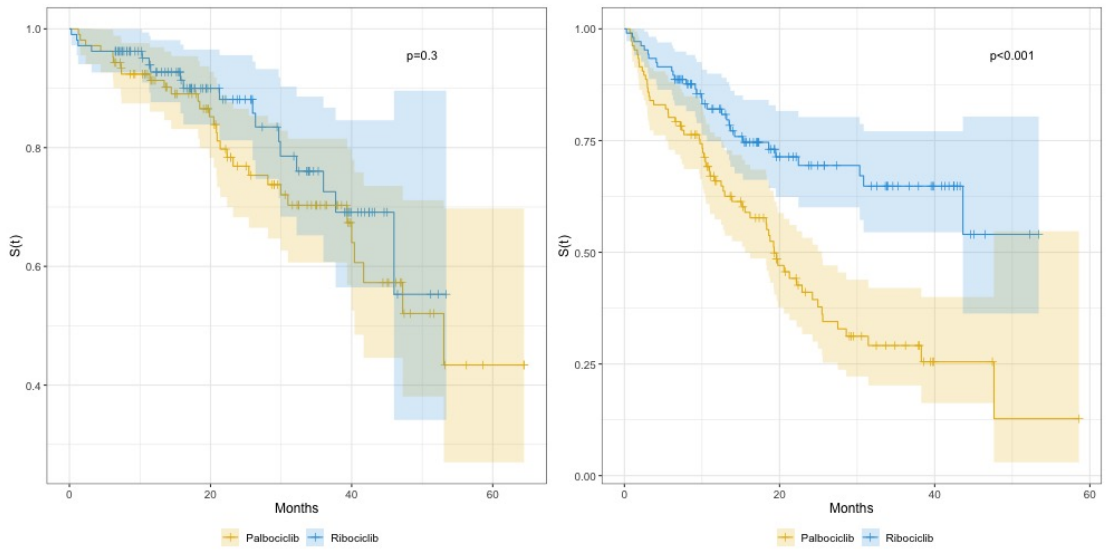


Figure 4. Clustering for 3 variables with 3 silos - (A) categorical variables with proportion with K-Means and (B) Categorical with K-modes



SUPPLEMENTARY MATERIAL