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ABSTRACT

Keywords: Keyword1; Keyword2; Keyword3

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 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: 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, diagnosed with other neoplasms or with active treatment during the study period. The comparison group was defined by a population of patients, that were treated with hormone therapy as first-line (due to bone metastases) 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.

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]
Combination			
Exemestane	1 (0.4%)	0 (0%)	1 (0.3%)
Fulvestrant	180 (72.9%)	10 (9.4%)	190 (53.8%)
Letrozol	66 (26.7%)	96 (90.6%)	162 (45.9%)
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 metastasis			
No	58 (23.5%)	24 (22.6%)	82 (23.2%)
Yes	189 (76.5%)	82 (77.4%)	271 (76.8%)
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 for population treated with CDK46 inhibitors plus hormonotherapy : demographic information, age at first diagnosis and age at the beginning of treatment, clinical characteristics and performance status by Eastern Cooperative Oncology Group scale (ECOG), treatment line and treatment schema - CDK46 inhibitor and hormonotherapy, stage of the cancer, site of metastases (bone, soft tissue, visceral, visceral and bone, central nervous system-CNS with or without another site). Data included for population treated with hormonotherapy as first-line: demographic information, age at first diagnosis and age at the beginning of treatment, clinical characteristics and performance status by Eastern Cooperative Oncology Group scale (ECOG), stage of the cancer.

For comparasion purposes, we used palbociclib and ribociclib since we had a small number of patients treated with abemaciclib (12). We also filtered by 1st line to assess the best treatment option.

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

Median OS in the entire population treated with CDK46 inhibitors was 46 months (95%CI 39.4–55.6). Median PFS was 20.3 months (95%CI 18.3–24.2). The median OS in the entire population after removing abemaciclib changed very little. When comparing Ribociclib and palbociclib with each other, we see that regarding OS, there is not significant difference, but ribociclib is significantly better in terms of PFS (p-value ≤ 0.001) (figure 1).

We then compared both with a cox-regression, checking that this trends continues where OS shows no significant difference between palbociclib and ribociclib but a significantly better PFS for ribociclib (figure 2). When adjusted to Stage, visceral metastases, Age and ECOG, ribociclib is associated to an HR of 0.44, implying that ribociclib as a first line treatment reduces the risk of the disease progression by 60% compared to palbociclib as first line treatment.

Table 2. Descriptive statistics of palbociclib and ribociclib (1st line) 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]
Medicamento			
Palbociclib	127 (56.4%)	0 (0%)	127 (47.4%)
Ribociclib	98 (43.6%)	0 (0%)	98 (36.6%)
Anastrozol	0 (0%)	3 (7.0%)	3 (1.1%)
Exemestano	0 (0%)	4 (9.3%)	4 (1.5%)
Fulvestrant	0 (0%)	5 (11.6%)	5 (1.9%)
Letrozol	0 (0%)	31 (72.1%)	31 (11.6%)
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%)

When comparing the traditional hormonotherapy with CDK4/6 inhibitors, we see that CDK4/6 inhibitors are significantly better in terms of PFS (p-value ≤ 0.001) but not OS. When comparing ribociclib first line, we see significant difference both in terms of PFS and OS (figure 3).

When comparing palbociclib and ribociclib adjusted for propensity scores, we see that the trend continues, with no significant difference between the two in terms of OS but significant in terms of PFS (figure 4). We matched for number of metastases, treatment line, combination drug, ECOG, age at beginning of treatment, bone metastases and visceral metastases.

DISCUSSION

The aim of this prospective study was to evaluate the real-world use of palbociclib and ribociclib in combination with ET for HR+/HER2− and comparing this drug class with traditional hormonotherapy. Few real-world evidence studies of palbociclib and ribociclib used in daily clinical practice have been published identifying clinical benefit, patient profile and sequencing of treatment, with even less evidence of use of palbociclib in Portugal.

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.

INSTITUTIONAL REVIEW

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

DATA AVAILABILITY

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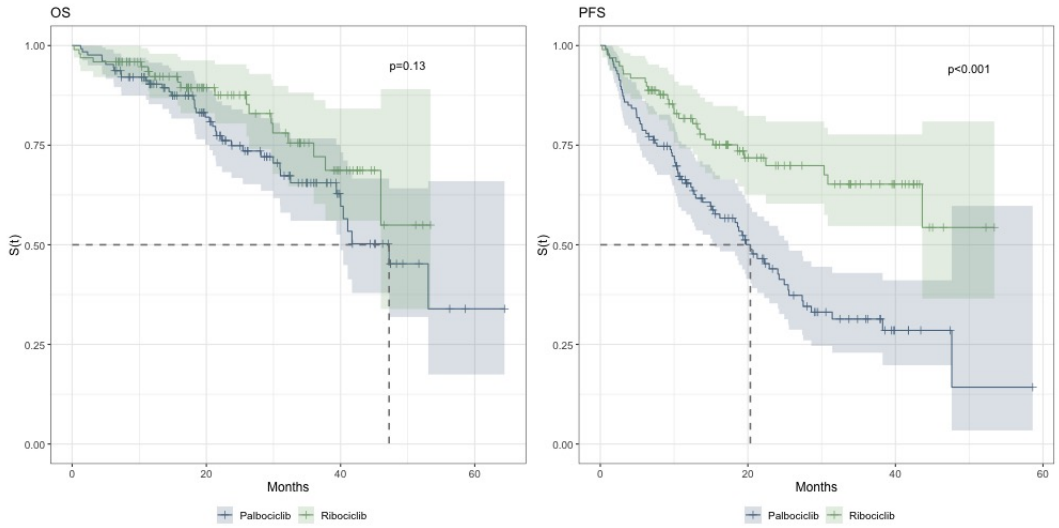
Figure 1. Survival curves for Palbociclib and Ribociclib - Progression Free Survival and Overall Survival



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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.

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CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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Figure 2. Cox Regression with palbociclib and Ribociclib - Progression Free Survival and Overall Survival

	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

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Figure 3. Comparision of traditional hormonotherapy and CDK4/6 inhibitors

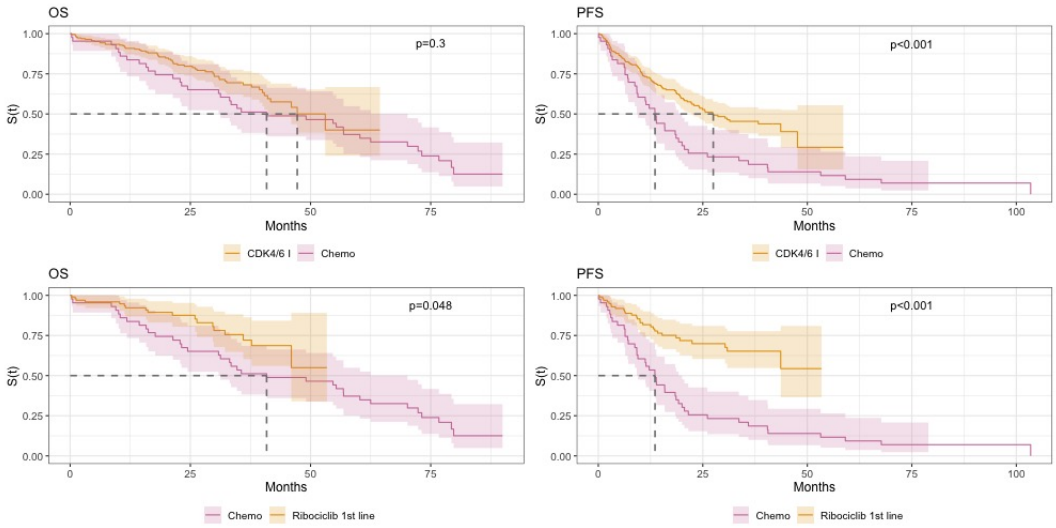
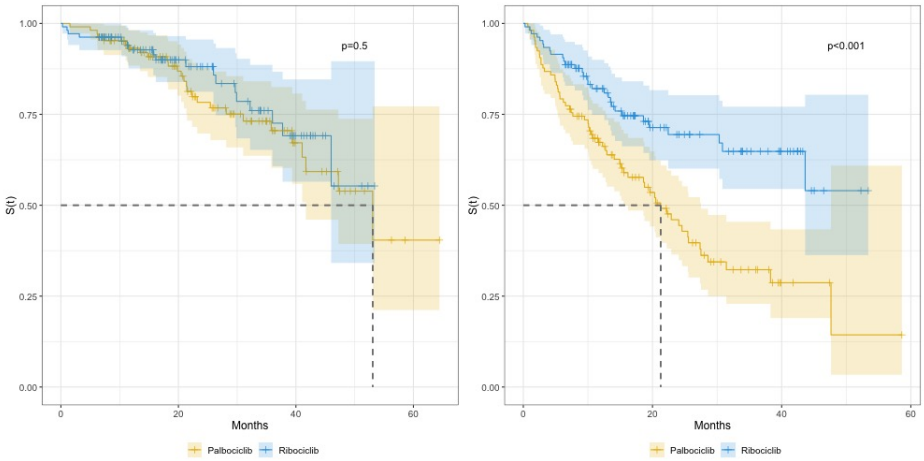


Figure 4. Comparasion of palbociclib and ribociclib adjusted for propensity scores



154 **FIGURE**

155 **TABLE**

SUPPLEMENTARY MATERIAL