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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 [5, 7, 9] studies were used for ribociclib, PALOMA [10, 6, 2] for palbociclib, and MONARCH [3, 8] 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]
Bone Only metastases			
No	161 (65.2%)	74 (69.8%)	235 (66.6%)
Yes	86 (34.8%)	32 (30.2%)	118 (33.4%)
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%)
Visceral metastasis			
No	122 (49.4%)	49 (46.2%)	171 (48.4%)
Yes	125 (50.6%)	57 (53.8%)	182 (51.6%)
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 comparison purposes, we used palbociclib and ribociclib since we had a small number of patients treated with abemaciclib (12).

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. The evaluation of the proportional hazards assumptions was done by Schoenfeld residues analysis. We applied propensity scores weights for achieving a more robust comparison between the two groups of CDK46i. We used the existence of visceral metastases, treatment line, age at treatment start and stage. We used the WeightIt package for R. We applied the weights to the Kaplan-Meier curves and to the Cox Regression. We applied the weigths to get the ATE which is $E[Y_i(1) - Y_i(0)]$, the average effect of moving an entire population from untreated to treated, or from one drug to the other. We used weigths instead of matching since it is more suited for calculating ATE and the need to preserve the sample size, since it is already small from the start. The formula for calculating the weights was through propensity score weighting with GLM.

Table 2. Descriptive statistics of palbociclib and ribociclib (1st line) group vs hormonotherapy

	CDK4/6i	HT	Overall
	(N=228)	(N=43)	(N=271)
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]
Drug			
Anastrozol	0 (0%)	3 (7.0%)	3 (1.1%)
Exemestane	0 (0%)	4 (9.3%)	4 (1.5%)
Fulvestrant	0 (0%)	5 (11.6%)	5 (1.8%)
Letrozol	0 (0%)	31 (72.1%)	31 (11.4%)
Palbociclib	127 (55.7%)	0 (0%)	127 (46.9%)
Ribociclib	98 (43.0%)	0 (0%)	98 (36.2%)
Missing	3 (1.3%)	0 (0%)	3 (1.1%)
Estrogen Receptor			
+	228 (100%)	42 (97.7%)	270 (99.6%)
-	0 (0%)	1 (2.3%)	1 (0.4%)
Progesterone Receptor			
+	171 (75.0%)	27 (62.8%)	198 (73.1%)
-	57 (25.0%)	16 (37.2%)	73 (26.9%)
Stage			
I	17 (7.5%)	3 (7.0%)	20 (7.4%)
II	55 (24.1%)	20 (46.5%)	75 (27.7%)
III	63 (27.6%)	11 (25.6%)	74 (27.3%)
IV	76 (33.3%)	2 (4.7%)	78 (28.8%)
Missing	17 (7.5%)	7 (16.3%)	24 (8.9%)

RESULTS

Median OS in the entire population treated with CDK4/6 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. Following this, we compared Palbociclib and riboclib as first line treatment. We found that regarding OS, there is not significant difference among the two, but ribociclib is significantly better in terms of PFS (p-value ≤ 0.001) (figure 1). We did

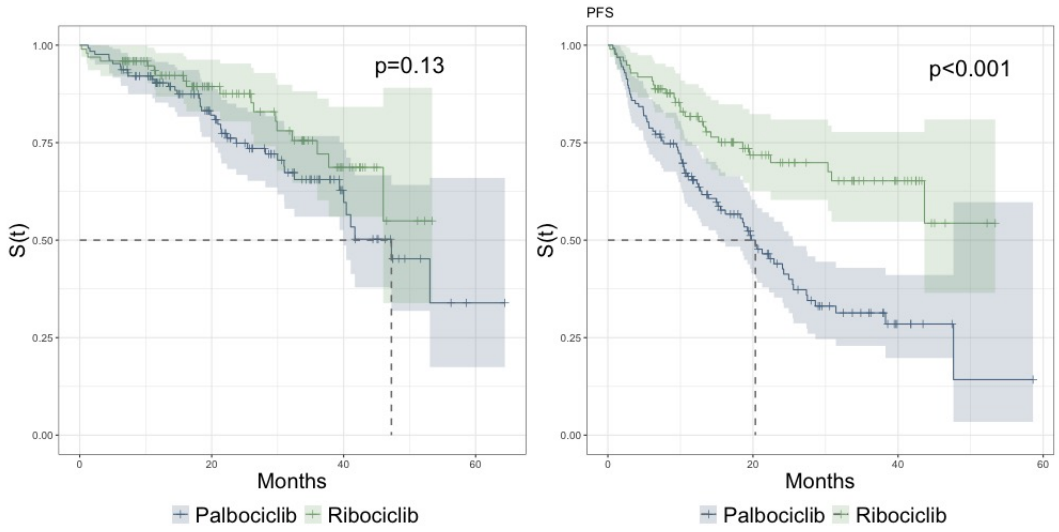
We then compared both with a cox regression, checking that the trend seen in figure 1 continues where OS shows no significant difference between palbociclib and ribociclib but a significantly better PFS for ribociclib (figure 2). When adjusted to Stage, visceral metastases, Age and ECOG, ribociclib is 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. The proportional hazards assumption was confirmed with p values all over 0.10.

When comparing hormonotherapy with CDK4/6 inhibitors as first line treatment, we see that only Ribociclib is significantly better in terms of PFS and OS (p-value ≤ 0.001). When comparing palbociclib as first line, we see that there is no significant difference both in terms of PFS and OS (p=0.08 and 0.6) (figure 3).

When comparing palbociclib and ribociclib adjusted for ATE weights, we found a different scenario from previous assessments. There is a significant difference between the two in terms of OS and PFS (figure 4). We calculated the weights taken into account stage, age at treatment start, treatment line and ECOG.

The Cox regression adjusted for weigths shows that ribociclib is associated to an HR of 0.47 [0-26-0.87], implying that ribociclib reduces the risk of the death by $\sim$50% compared to palbociclib. The HR for PFS is 0.44 [0.26-0.62], implying that ribociclib reduces the risk of the disease progression by $\sim$60% compared to palbociclib, which also indicates the adjustment caused little to no effect on the results (figure 2). Proportional hazards assumptions confirmed as well.

Figure 1. Survival curves for Palbociclib and Ribociclib (1st line) - Progression Free Survival and Overall Survival



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.

When comparing with clinical trials, regarding patient profile, in our study, 51% had visceral metastasis and 35% bone only disease comparing with 49% and 38% in PALOMA-2, and 60% and 25% in PALOMA-3, respectively [6, 1]. As for ribociclib, MONALEESA-7 [9] has 24% and MONALEESA-2 has 40% [5] and our study has 30%.

Of note, the range of median PFS for first-line palbociclib was 15.5–25.5 months, which is shorter than 27.6 months observed in a post hoc analysis of the PALOMA-2 clinical trial with extended follow-up [6], but in line with RWE studies (13.3–20.2 months) [4]. As for ribociclib, median survival time was not reached wether in OS and PFS. So we can at least say that the median PFS is longer than 50 months. This is longer that the median progression-free survival of 23.8 months (95% CI 19.2–not reached) reported in the MONALEESA-7 trial [9] and longer than 25.3 months (95% CI 23.0–30.3) in the MONALEESA-2 trial [5]. However, the HT group has a median PFS of 13.6 months, which is in tune with the reported values in the literature.

Regarding the comparison between HT and CDK4/6i first line, we found out that neither OS and PFS have significant changes when compared HT and Palbociclib 1st line. This is an unexpected result, since we would expect that the addition of palbociclib would increase at least the PFS significantly. However, the difference is significant for Ribociclib. We also made a cox regression, adjusted for drug (inside HT) which was not significant with p values over 0.2.

0.4 propensity Scores

The importance of quality data in observational studies cannot be overstated. Unlike randomized controlled trials (RCTs), where randomization helps to balance both observed and unobserved covariates between the treatment and control groups, observational studies are often fraught with selection biases, confounding variables, and imbalances in baseline characteristics. Researchers typically have no control over the assignment of subjects to treatment or control groups, leading to potential biases that can significantly skew results. Well-structured and rich datasets can provide a wealth of information that allows for more accurate control of these confounding factors. By including a variety of variables that might influence the outcome, data richness enables the use of statistical techniques like matching, stratification, or weighting to create comparable treatment and control groups, thereby mimicking the conditions of an RCT to some extent.

One of the critical ways to partially mitigate the issues inherent in observational studies is through the use of propensity score methods, such as Average Treatment Effect (ATE) and Average Treatment effect on the Treated (ATT) weighted Kaplan-Meier curves. These methods seek to balance the distribution of observed covariates between treatment and control groups, thereby reducing selection bias. Once balanced,

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	0.66	0.37, 1.17	0.2	0.44	0.28, 0.69	<0.001
Treatment Line						
1 linha	—	—		—	—	
2 ou mais linhas	1.67	1.10, 2.54	0.016	1.84	1.33, 2.55	<0.001
Stage						
I	—	—		—	—	
II	5.96	1.43, 24.9	0.014	1.92	1.00, 3.68	0.048
III	7.93	1.89, 33.3	0.005	2.99	1.55, 5.75	0.001
IV	6.52	1.55, 27.4	0.010	1.90	0.98, 3.67	0.056
Visceral Metastasis						
No	—	—		—	—	
Yes	1.69	1.16, 2.46	0.007	1.30	0.97, 1.75	0.082
Age at treatment start	1.00	0.98, 1.02	0.8	0.99	0.98, 1.00	0.2
ECOG at treatment start						
0	—	—		—	—	
1	1.49	0.98, 2.29	0.065	1.10	0.80, 1.52	0.5
2	3.65	1.93, 6.93	<0.001	1.41	0.79, 2.53	0.2
3	9.23	2.70, 31.5	<0.001	0.41	0.06, 2.97	0.4

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

the survival curves can more accurately reflect the true impact of the treatment, providing results that are closer to what might be observed in a randomized study. In essence, propensity score methods help to level the playing field by reweighting or resampling the original data based on the probability of receiving treatment, allowing for a more fair comparison between the treatment and control groups.

That being said, it's crucial to remember that even the most sophisticated statistical techniques can only control for observed confounders; hidden biases due to unmeasured or unknown variables can still persist. Additionally, the quality of the propensity score model is heavily reliant on the data available, underlining the need for comprehensive data collection and thorough exploratory data analysis. The application of methods like ATE and ATT weighted Kaplan-Meier curves is not a substitute for good data but a complement to it. In sum, while quality data and sophisticated statistical methods can't fully replicate the conditions of a randomized trial, they can substantially improve the validity and reliability of findings from observational data.

CONCLUSIONS

For conclusions and next steps, we feel we have demonstrated that the ribociclib is a good alternative to palbociclib. We still dot not have sufficient evidence to state that palbociclib is actually better than hormonotherapty regarding Overall Survival. However, it is sufficient to state that CDK4/6i have impact on PFS. Further information about the population could be interesting, as well as providing information about safety, economic impact and quality of life. Especially the characterization of the population in terms of biomarkers could be very useful. We aim to address those issues in sequencing papers. Finally, since all of this data was collected from a single institution, we can not generalize the results to the entire

Figure 3. Survival curves (OS and PFS) comparing hormonotherapy (HT) to CDK4/6 inhibitors as 1st line. p values shown as pairwise vs HT.

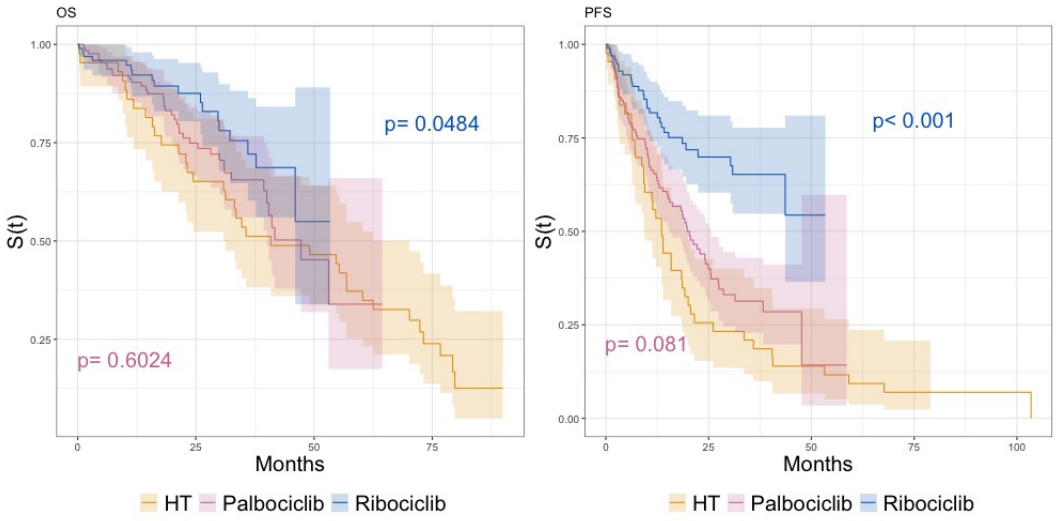
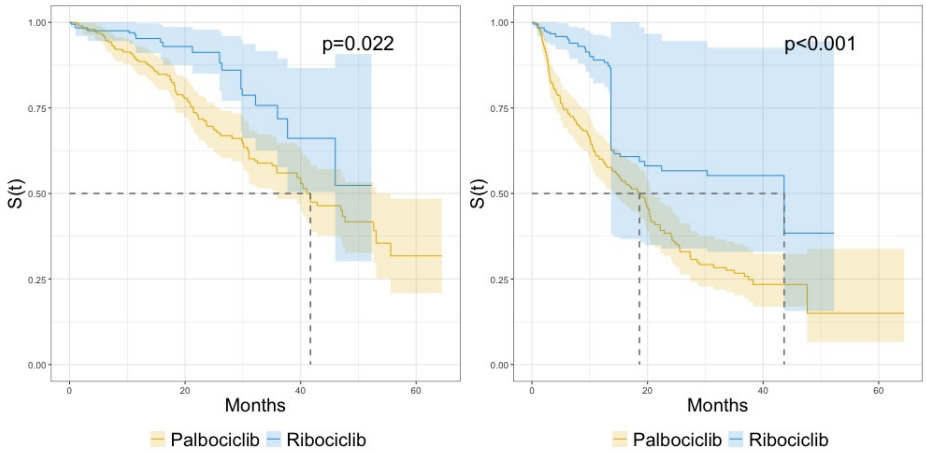


Figure 4. Comparison of palbociclib and ribociclib survival curves adjusted for propensity scores



population. However, we believe that this study can be used as a starting point for further research in this area. Additionally, this evidence was generated from observational data. Although we adjusted for confounding factors, we cannot exclude the possibility of residual confounding. However, the propensity scores matching allows for a more robust comparison between the two groups, there is still the possibility of unmeasured confounders.

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

...

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.

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CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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FIGURE

TABLE

SUPPLEMENTARY MATERIAL