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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

	Abemaciclib	Palbociclib	Ribociclib	Overall
	(N=12)	(N=247)	(N=106)	(N=365)
Age at treatment start				
Mean (SD)	58.8 (11.5)	59.2 (11.7)	58.2 (10.7)	58.9 (11.4)
Median [Min, Max]	58.5 [39.0, 74.0]	60.0 [28.0, 84.0]	58.0 [32.0, 79.0]	59.0 [28.0, 84.0]
Treatment Line				
1st Line	3 (25.0%)	127 (51.4%)	98 (92.5%)	228 (62.5%)
2nd+ Lines	9 (75.0%)	120 (48.6%)	8 (7.5%)	137 (37.5%)
PFS				
Censored	9 (75.0%)	84 (34.0%)	76 (71.7%)	169 (46.3%)
Dead	3 (25.0%)	163 (66.0%)	30 (28.3%)	196 (53.7%)
OS				
Censored	10 (83.3%)	148 (59.9%)	88 (83.0%)	246 (67.4%)
Dead	2 (16.7%)	99 (40.1%)	18 (17.0%)	119 (32.6%)
Stage				
I	1 (8.3%)	22 (8.9%)	7 (6.6%)	30 (8.2%)
II	4 (33.3%)	75 (30.4%)	22 (20.8%)	101 (27.7%)
III	3 (25.0%)	75 (30.4%)	18 (17.0%)	96 (26.3%)
IV	2 (16.7%)	65 (26.3%)	46 (43.4%)	113 (31.0%)
Missing	2 (16.7%)	10 (4.0%)	13 (12.3%)	25 (6.8%)

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.

INSTITUTIONAL REVIEW

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

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%)

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

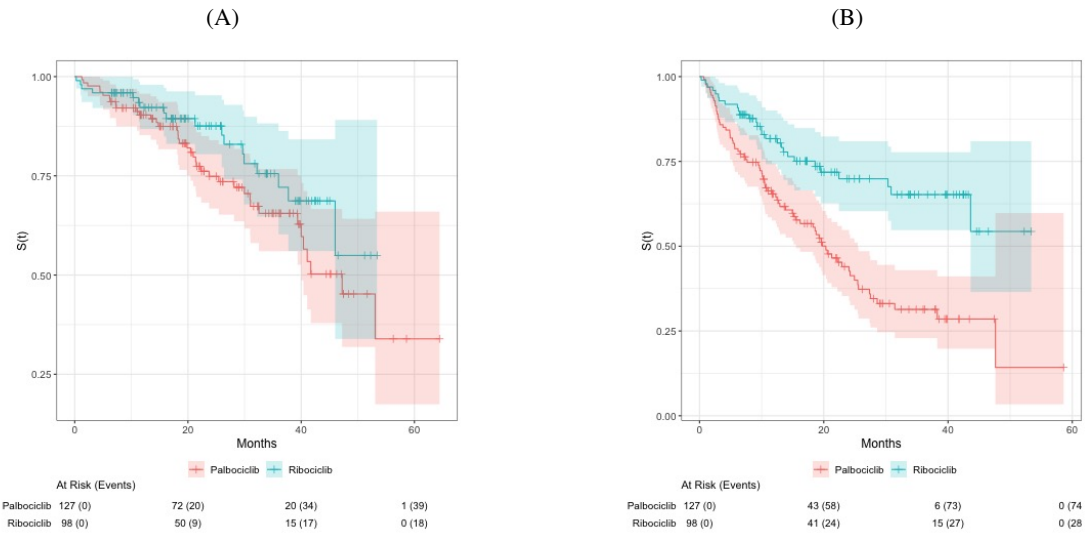
The authors declare no conflict of interest.

REFERENCES

[1] Richard S Finn, John P Crown, Istvan Lang, Katalin Boer, Igor M Bondarenko, Sergey O Kulyk, Johannes Ettl, Ravindranath Patel, Tamas Pinter, Marcus Schmidt, Yaroslav Shparyk, Anu R Thummala, Nataliya L Voytko, Camilla Fowst, Xin Huang, Sindy T Kim, Sophia Randolph, and Dennis J Slamon. The cyclin-dependent kinase 4/6 inhibitor palbociclib in combination with letrozole versus letrozole alone as first-line treatment of oestrogen receptor-positive, HER2-negative, advanced breast cancer (PALOMA-1/TRIO-18): A randomised phase 2 study. *The Lancet Oncology*, 16(1):25–35, January 2015. https://linkinghub.elsevier.com/retrieve/pii/S1470204514711593.

[2] Matthew P. Goetz, Masakazu Toi, Mario Campone, Joohyuk Sohn, Shani Paluch-Shimon, Jens Huober, In Hae Park, Olivier Trédan, Shin-Cheh Chen, Luis Manso, Orit C. Freedman, Georgina Garnica Jaliffe, Tammy Forrester, Martin Frenzel, Susana Barriga, Ian C. Smith, Nawel Bourayou, and Angelo Di Leo. MONARCH 3: Abemaciclib As Initial Therapy for Advanced Breast Cancer. *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology*, 35(32):3638–3646, November 2017.

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



[3] G. Hortobagyi, S. Stemmer, H. Burris, Y. Yap, G. Sonke, S. Paluch-Shimon, M. Campone, K. Petráková, K. Blackwell, E. Winer, W. Janni, S. Verma, P. Conte, C. Arteaga, D. Cameron, S. Mondal, F. Su, M. Miller, M. Elmeliegy, C. Germa, and J. O'Shaughnessy. Updated results from MONALEESA-2, a phase III trial of first-line ribociclib plus letrozole versus placebo plus letrozole in hormone receptor-positive, HER2-negative advanced breast cancer. *Annals of oncology : official journal of the European Society for Medical Oncology*, 2018.

[4] H. S. Rugo, V. Diéras, K. A. Gelmon, R. S. Finn, D. J. Slamon, M. Martin, P. Neven, Y. Shparyk, A. Mori, D. R. Lu, H. Bhattacharyya, C. H. U. a. N. G. Bartlett, S. Iyer, S. Johnston, J. Ettl, and N. Harbeck. Impact of palbociclib plus letrozole on patient-reported health-related quality of life: Results from the PALOMA-2 trial. *Annals of Oncology: Official Journal of the European Society for Medical Oncology*, 29(4):888–894, April 2018.

[5] Dennis J. Slamon, Patrick Neven, Stephen Chia, Peter A. Fasching, Michelino De Laurentiis, Seock-Ah Im, Katarina Petrakova, Giulia Val Bianchi, Francisco J. Esteva, Miguel Martín, Arnd Nusch, Gabe S. Sonke, Luis De la Cruz-Merino, J. Thaddeus Beck, Xavier Pivot, Gena Vidam, Yingbo Wang, Karen Rodriguez Lorenc, Michelle Miller, Tetiana Taran, and Guy Jerusalem. Phase III Randomized Study of Ribociclib and Fulvestrant in Hormone Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative Advanced Breast Cancer: MONALEESA-3. *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology*, 36(24):2465–2472, August 2018.

[6] George W. Sledge, Masakazu Toi, Patrick Neven, Joohyuk Sohn, Kenichi Inoue, Xavier Pivot, Olga Burdaeva, Meena Okera, Norikazu Masuda, Peter A. Kaufman, Han Koh, Eva-Maria Grischke, Martin Frenzel, Yong Lin, Susana Barriga, Ian C. Smith, Nawel Bourayou, and Antonio Llombart-Cussac. MONARCH 2: Abemaciclib in Combination With Fulvestrant in Women With HR+/HER2- Advanced Breast Cancer Who Had Progressed While Receiving Endocrine Therapy. *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology*, 35(25):2875–2884, September 2017.

[7] Debu Tripathy, Seock-Ah Im, Marco Colleoni, Fabio Franke, Aditya Bardia, Nadia Harbeck, Sara A. Hurvitz, Louis Chow, Joohyuk Sohn, Keun Seok Lee, Saul Campos-Gomez, Rafael Villanueva Vazquez, Kyung Hae Jung, K. Govind Babu, Paul Wheatley-Price, Michelino De Laurentiis, Young-Hyuck Im, Sherko Kuemmel, Nagi El-Saghir, Mei-Ching Liu, Gary Carlson, Gareth Hughes, Ivan Diaz-Padilla, Caroline Germa, Samit Hirawat, and Yen-Shen Lu. Ribociclib plus endocrine therapy for premenopausal women with hormone-receptor-positive, advanced breast cancer (MONALEESA-7): A randomised phase 3 trial. *The Lancet. Oncology*, 19(7):904–915, July 2018.

[8] Sunil Verma, Cynthia Huang Bartlett, Patrick Schnell, Angela M. DeMichele, Sherene Loi, Jungsil Ro, Marco Colleoni, Hiroji Iwata, Nadia Harbeck, Massimo Cristofanilli, Ke Zhang, Alexandra Thiele, Nicholas C. Turner, and Hope S. Rugo. Palbociclib in Combination With Fulvestrant in Women With Hormone Receptor-Positive/HER2-Negative Advanced Metastatic Breast Cancer: Detailed Safety Analysis From a Multicenter, Randomized, Placebo-Controlled, Phase III Study (PALOMA-3). *The Oncologist*, 21(10):1165–1175, October 2016.

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

(A)

Characteristic	HR[1]	95% CI[1]	p-value
Drug			
Palbociclib	—	—	
Ribociclib	0.69	0.38, 1.26	0.2
Stage			
I	—	—	
II	4.78	0.63, 36.2	0.13
III	5.69	0.76, 42.8	0.091
IV	3.57	0.46, 27.6	0.2
Visceral Metastasis			
No	—	—	
Yes	1.93	1.10, 3.36	0.021
Age at treatment start	1.02	0.99, 1.05	0.2
ECOG at treatment start			
0	—	—	
1	1.60	0.86, 2.95	0.13
2	2.86	1.17, 7.02	0.021
3	8.33	1.77, 39.2	0.007

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

(B)

Characteristic	HR[1]	95% CI[1]	p-value
Drug			
Palbociclib	—	—	
Ribociclib	0.44	0.28, 0.71	<0.001
Stage			
I	—	—	
II	2.07	0.79, 5.40	0.14
III	2.09	0.80, 5.43	0.13
IV	1.65	0.63, 4.36	0.3
Visceral Metastasis			
No	—	—	
Yes	1.24	0.82, 1.86	0.3
Age at treatment start	1.00	0.98, 1.02	0.7
ECOG at treatment start			
0	—	—	
1	1.23	0.79, 1.92	0.4
2	0.94	0.43, 2.06	0.9
3	0.68	0.09, 5.17	0.7

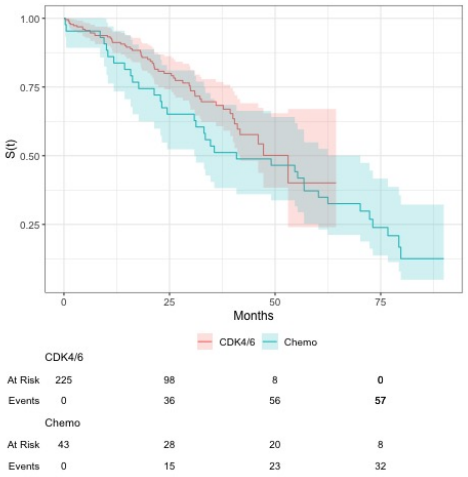
[1] HR = Hazard Ratio, CI = Confidence Interval

133 **FIGURE**

134 **TABLE**

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

(A)



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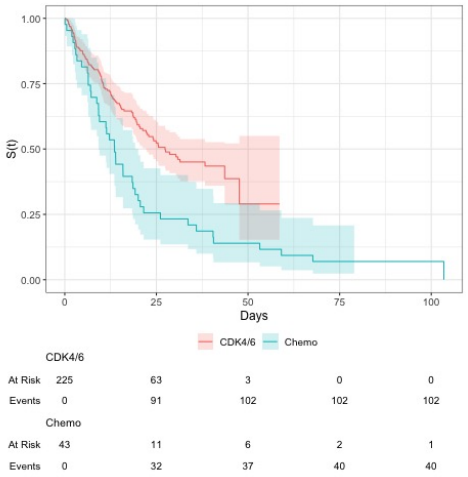
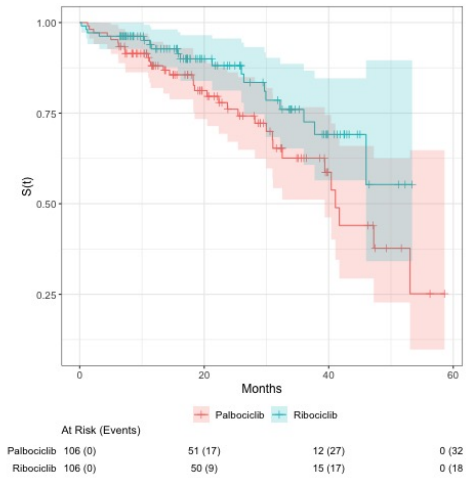
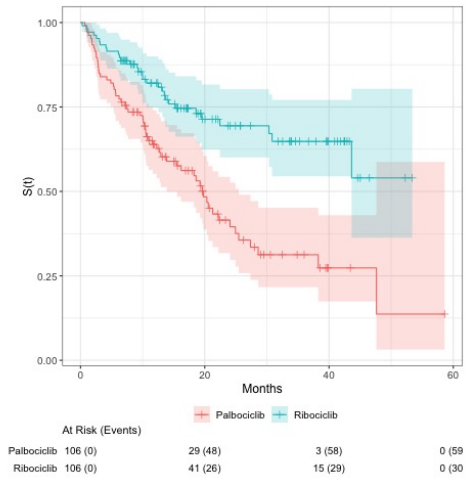


Figure 4. Clustering for 3 variables with 3 silos - (A) categorical variables with proportion with K-Means and (B) Categorical with K-modes

(A)



(B)



SUPPLEMENTARY MATERIAL