CDK4/6 inhibitors and endocrine therapy in the treatment of metastatic cancer: A real-world and Propensity Score-Adjusted comparison

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ABSTRACT

Keywords: Palbociclib; Ribociclib; Breast cancer; propensity score; real-world data; CDK4/6

INTRODUCTION

Currently, metastatic breast cancer is difficult to treat. Patients with Hormone Receptor-positive (HR+) and Human Epidermal Growth Factor Receptor 2-negative (HER2-) breast cancer, 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. This decision was made based on data provided by clinical trials done with these medications. The MONALEESA [8, 10, 12] studies were used for ribociclib, PALOMA [13, 9, 4] for palbociclib, and MONARCH [5, 11] 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 research findings, it was determined that there was a notable enhancement in effectiveness, supporting their application 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 endocrine therapy only in terms of treatment effectiveness in a real-world setting. In the meticulously controlled setting of clinical trials, patient selection often skews towards relatively healthier individuals with fewer comorbidities. However, in real-world clinical practice, patients present a diverse range of health profiles, co-existing illnesses, and medication histories that may influence drug efficacy and safety. Real-world data, drawn from electronic health records, insurance claims databases, and patient registries, offers the advantage of reflecting a more heterogeneous patient population, thus potentially uncovering insights not readily apparent in clinical trial settings. Understanding the effectiveness and safety of CDK4/6 inhibitors in real-world conditions is crucial for tailoring more individualized treatment regimens, optimizing outcomes, and enhancing the quality of life for patients with HR+, HER2- breast cancer [7]. Nevertheless, observational studies have inherent limitations, such as confounding by indication,

which can lead to biased estimates of treatment effects. To tackle this, there are causality-based assessments that can be employed in order to better estimate the causal effects of treatments. Incorporating statistical techniques like Inverse Probability of Treatment Weighting (IPTW) can play an essential role in enhancing the quality of real-world evidence by accounting for treatment selection bias and balancing observed covariates between treatment groups. IPTW, grounded in the framework of causal inference, allows for the mimicking of a randomized control trial-like setting within observational studies. By assigning weights to individual patients based on their propensity scores—the likelihood of receiving a particular treatment given a set of observed characteristics—analyses can achieve a balance between different treatment arms, thereby reducing bias and confounding factors. Establishing causality, rather than mere association, is vital for the robust interpretation of real-world data. As we strive to understand the long-term impact, efficacy, and safety of CDK4/6 inhibitors in HR+, HER2- breast cancer, the rigorous application of IPTW and causal inference methods can substantially augment the validity of real-world findings, making them a more reliable basis for clinical decision-making [1, 2] So in this paper, we propose:

- To compare the effectiveness of the CDK4/6 inhibitors drug class in terms of progression-free survival (PFS) and overall survival (OS);
- To assess the Hazard Ratio of using the CDK4/6 inhibitors drug class in terms of PFS and OS.
- To compare the effectiveness of CDK4/6 inhibitors in combination with an aromatase inhibitor or fulvestrant with the previous standard of care in terms of PFS and OS in patients with HR+, HER2- advanced breast cancer with bone only metastasis.
- To assess the differences in effectiveness between the three CDK4/6 inhibitors in combination with an aromatase inhibitor or fulvestrant in terms of PFS and OS with causality principles in mind, especially the counterfactual theory and IPTW.

MATERIALS AND METHODS

0.1 Study Design

This retrospective study was designed in 2022. The study aimed to evaluate the clinical benefit and long-term survival of patients with HR+/HER2- that started treatment with CDK4/6 inhibitors plus endocrine therapy 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: women and men, Hormone receptor-positive and HER2 negative in the primary tumor or metastatic site after biopsy. Exclusion criteria: Patients that had only one ambulatory medication, and patients involved in clinical trials, diagnosed with other neoplasms or with active treatment during the study period. The control 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 two different cyclin-dependent kinase inhibitors in terms of effectiveness in real-world patients and will also compare the effectiveness of this class combined with endocrine therapy against traditional endocrine therapy.

0.2 Data collection

All data were collected from medical and administrative 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 CDK4/6 inhibitors plus endocrine therapy: 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 - CDK4/6 inhibitor and endocrine therapy, stage of cancer, site of metastases (bone, soft tissue, visceral, central nervous system-CNS with or without another site). Data included for the population treated with endocrine therapy 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 analyzed 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

Table 1. Descriptive statistics of cyclin-dependent kinase inhibitors group and endocrine therapy group. The Drug/combination refers to the actual drug or the combination for CDK4/6

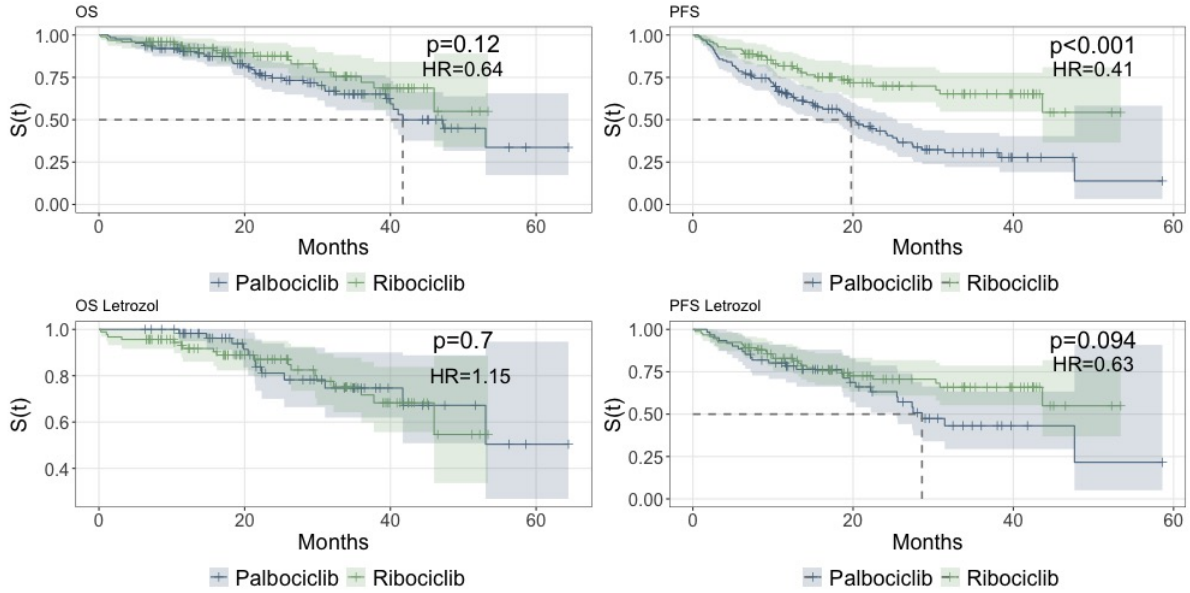
	ET	Palbociclib	Ribociclib
	(N=44)	(N=246)	(N=106)
Age at treatment start			
Mean (SD)	59.7 (12.7)	59.2 (11.7)	58.2 (10.7)
Median [Min, Max]	61.5 [34.0, 85.0]	60.0 [28.0, 84.0]	58.0 [32.0, 79.0]
Menopausal status			
Post-menopause	36 (82 %)	201 (82 %)	83 (78 %)
Pre-menopause	8 (18 %)	42 (17 %)	21 (20 %)
Missing	0 (0%)	3 (1.2%)	2 (1.9%)
Bone Only metastases			
Yes	44 (100 %)	85 (35 %)	32 (30 %)
No	NA	161 (65 %)	74 (70 %)
Visceral metastasis			
No	NA	121 (49 %)	49 (46 %)
Yes	NA	125 (51 %)	57 (54 %)
Missing	44 (100%)	0 (0%)	0 (0%)
Stage			
I	3 (7 %)	22 (9 %)	7 (7 %)
II	21 (48 %)	75 (30 %)	22 (21 %)
III	11 (25 %)	74 (30 %)	18 (17 %)
IV	2 (5 %)	65 (26 %)	46 (43 %)
Missing	7 (15.9%)	10 (4.1%)	13 (12.3%)
Drug/Combination			
Anastrozol	3 (7 %)	NA	NA
Exemestane	4 (9 %)	NA	NA
Fulvestrant	5 (11 %)	180 (73 %)	10 (9 %)
Letrozol	32 (73 %)	66 (27 %)	96 (91 %)

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 score weights to achieve a more robust comparison between the two groups of CDK46i. We used the existence of visceral metastases, menopausal status, combination, treatment line, age at treatment start, ECOG, and stage. Likewise, we used the WeightIt package for R [6]. Furthermore, we applied the weights 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. Weights were used 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. Multiple comparisons were done with the Benjamini-Hochberg (BH) method.

RESULTS

The median OS in the entire population treated with CDK4/6 inhibitors was 46 months (95%CI 39.4–55.6). Median PFS was 20.1 months (95%CI 18.3–24.2). Following this, we compared Palbociclib and riboclib as first-line treatments. We found that regarding OS, there is no significant difference between the two, but ribociclib is significantly better in terms of PFS (p-value ≤ 0.001) (figure 1). Additionally, we compared the same CDK4/6 inhibitors with letrozole as a combination only. Regarding this scenario, we found out that both were similar in terms of OS and PFS.

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



We then compared both with a cox regression, where OS shows no significant difference between palbociclib and ribociclib when adjusted to the stage, visceral metastases, age, treatment line, combination and ECOG. The proportional hazards' assumption was confirmed with p values all over 0.10 (Table 2)

When comparing endocrine therapy with CDK4/6 inhibitors as first-line treatment (figure 2), we see that only Ribociclib is significantly better (PFS p-value ≤ 0.001). For this study we only compared patients with bone only metastasis. When comparing palbociclib as the first line, we see that there is no significant difference in terms of PFS and OS (p=0.57 and 0.51). We also applied the same analysis but comparing only the letrozole combination with letrozole alone. We found that both ribociclib and palbociclib are significantly better in terms of PFS (HR 0.65 for palbociclib and 0.27 for ribociclib) but not OS.

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 (figure 3). The weights were calculated as stated in the methods section.

The Cox regression adjusted for the variables and with the weights applied to render an HR=0.55 [95% CI 0.28-1.09;p=0.086] for OS. The HR for PFS is 0.56 [95% CI 0.32-1;p=0.05].

Table 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	1.08	0.55, 2.12	0.8	0.65	0.39, 1.07	0.090
Menopausal Status						
Post-menopause	—	—		—	—	
Pre-menopause	1.04	0.58, 1.85	>0.9	1.12	0.72, 1.74	0.6
Combination						
Fulvestrant	—	—		—	—	
Letrozol	0.33	0.17, 0.64	0.001	0.39	0.24, 0.63	<0.001
Treatment Line						
1st Line	—	—		—	—	
2nd+ Lines	0.97	0.60, 1.59	>0.9	1.17	0.80, 1.72	0.4
Stage						
I	—	—		—	—	
II	5.67	1.36, 23.7	0.017	1.87	0.97, 3.59	0.062
III	8.17	1.95, 34.3	0.004	3.00	1.56, 5.79	0.001
IV	7.99	1.89, 33.8	0.005	2.27	1.16, 4.43	0.016
Visceral Metastasis						
No	—	—		—	—	
Yes	1.72	1.17, 2.52	0.005	1.37	1.01, 1.85	0.042
Age at treatment start	1.00	0.98, 1.02	>0.9	0.99	0.97, 1.00	0.082
ECOG at treatment start						
0	—	—		—	—	
1	1.60	1.04, 2.48	0.034	1.23	0.88, 1.72	0.2
2	3.93	2.06, 7.51	<0.001	1.64	0.91, 2.95	0.10
3	12.5	3.57, 43.6	<0.001	0.41	0.06, 3.01	0.4

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

DISCUSSION

This study aimed to evaluate the real-world use of palbociclib and ribociclib in combination with ET for HR+/HER2- and compare this drug class with traditional endocrine therapy. Few real-world evidence studies of palbociclib and ribociclib used in daily clinical practice have been published identifying clinical benefits, patient profiles, and sequencing of treatment, with even less evidence for the Portuguese population.

When comparing with clinical trials, regarding patient profile, in our study, 51% had visceral metastasis and 35% had bone-only metastases compared with 49% and 38% in PALOMA-2, and 60% and 25% in PALOMA-3, respectively [9, 3]. As for ribociclib and bone-only metastases, MONALEESA-7 [12] has 24% and MONALEESA-2 has 40% [8] and our study has 30%. Regarding menopausal status, our study has 20% premenopausal and 80% postmenopausal.

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 [9], but in line with RWE studies (13.3–20.2 months) [7]. When assessed with only letrozoleas a combination, the median PFS increased to 28.6 months [95% CI 25.5-not reached]. Additionally, analyzing the postmenopausal women subgroup, palbociclib showed a median PFS of 16.3 months [95% CI 12.9 -20]. Furthering analysis of the postmenopausal and with letrozole, the median was 47.6 months [95% 25.6-2–not reached].

As for ribociclib, median survival time was not reached whether in OS and PFS. So we can at least say that the median PFS is longer than 50 months. This is longer than the median progression-free survival of 23.8 months (95% CI 19.2–not reached) reported in the MONALEESA-7 trial [12] and longer than

Figure 2. Survival curves (OS and PFS) comparing endocrine therapy (ET) to CDK4/6 inhibitors as 1st line. p values shown as pairwise vs. ET.

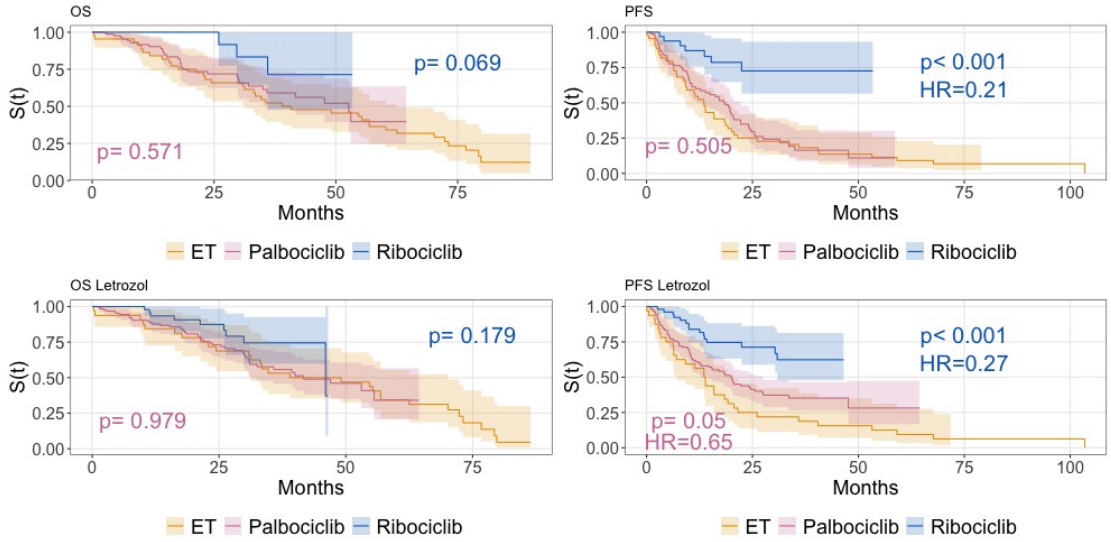
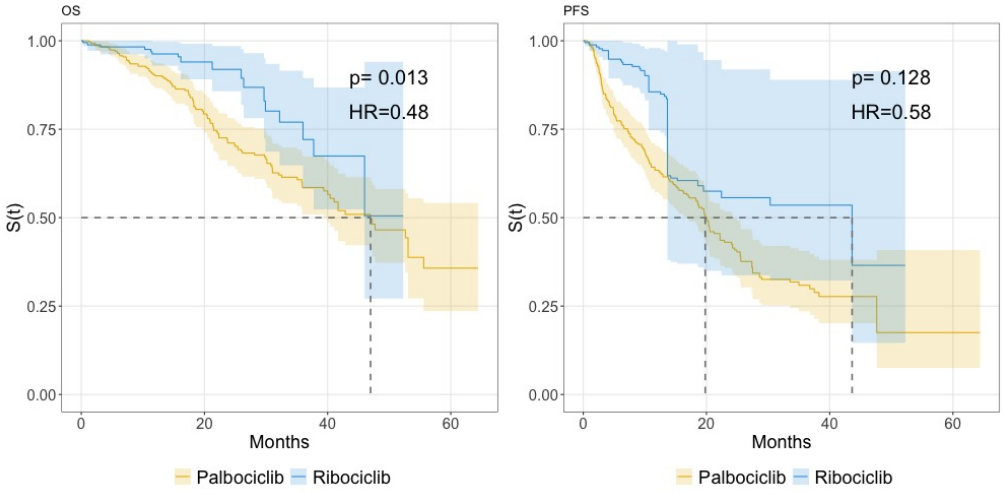


Figure 3. Comparison of palbociclib and ribociclib survival curves adjusted for propensity scores



25.3 months (95% CI 23.0–30.3) in the MONALEESA-2 trial [8]. Regarding the subgroup analysis of postmenopausal women and postmenopausal women treated ribociclib in combination with letrozole, the median was not reached.

When directly comparing ribociclib and palbociclib without any adjustments, one might deduce that ribociclib is superior to palbociclib. However, after adjusting for confounding variables, there is no significant difference between the two inhibitors in terms of Progression-Free Survival (PFS) or Overall Survival (OS) as indicated in 2. This observation is further corroborated by the lower plots in 1, where even a subgroup analysis of CDK4/6i combined solely with letrozole reveals a trend towards nonsignificance.

In the first-line comparison between Endocrine Therapy (ET) and CDK4/6 inhibitors (CDK4/6i), there is no significant impact on Overall Survival (OS) by either treatment, whether the CDK4/6i is combined with both agents or solely with letrozole. With respect to Progression-Free Survival (PFS), ribociclib demonstrates superior efficacy in both combination therapies (HR=0.29) as well as when paired only with letrozole (HR=0.28). Additionally, palbociclib exhibits significant improvement in PFS when combined with letrozole (HR=0.50).

In the first-line comparison, the analysis of overall survival outcomes reveals no substantial difference between endocrine therapy alone and the combination of CDK4/6 inhibitors with endocrine therapy, irrespective of whether the CDK4/6 inhibitors are administered concomitantly with both fulvestrant and letrozole or exclusively with letrozole (figure 2 left). With respect to PFS, ribociclib demonstrates superior efficacy in both combination therapies (HR=0.21) as well as when paired only with letrozole (HR=0.27).

Additionally, palbociclib exhibits significant improvement in PFS when combined with letrozole (HR=0.65) (figure 2 right).

When comparing with propensity scores weighting, we found out that ribociclib is significantly better than palbociclib for PFS and OS, providing a median OS of over 40 months and median PFS of around 42 months. Adjusted for the weighted variables, Ribociclib is not significantly better for PFS, but has a p-value of 0.013 for OS with an HR of 0.48. However, the Cox regression adjusted for variables and weights are not significant, even when the p-value for PFS is 0.05. This suggests that a more in depth analysis may be necessary.

CONCLUSIONS

In conclusion, our findings underscore the efficacy of CDK4/6 inhibitors in real-world settings. While we cannot definitively assert that palbociclib surpasses endocrine therapy in terms of Overall Survival—a facet not extensively explored in prominent clinical trials—we can confidently affirm the impact of CDK4/6i on Progression-Free Survival. This assertion aligns with clinical trial outcomes and real-world data further substantiates these findings. Delving deeper into the characteristics of the patient population, including safety profiles, economic implications, and quality of life metrics, would be insightful. Additionally, a thorough examination of biomarkers within the population could offer invaluable insights. We intend to explore these facets in subsequent publications. It's imperative to note that our data is sourced from a singular institution, limiting the capability of generalization of our results to a broader population. Nonetheless, we posit that this study lays a foundational groundwork for future research in this domain. While our evidence is rooted in observational data, and we've made adjustments for known confounders, the potential for residual confounding remains. Although the use of propensity score matching enhances the comparative robustness between the groups, the presence of unmeasured confounders cannot be entirely ruled out. Furthermore, the small sample size of our study limits the statistical power of our findings. We hope that our study will serve as a springboard for future research in this domain, and we look forward to furthering our research in this area.

DECLARATIONS

Authors' contributions

J.A., A.S., P.R. and A.F. conceived the idea; P.R. contributed to the experimental design and was in charge of overall direction and planning; All authors contributed to discussion and data analysis; J.A. wrote the main manuscript; All authors read and agreed to the published version of the manuscript.

Availability of data and materials

The data is not publicly available due to privacy or ethical restrictions. The code is available at .

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Ethics approval and consent to participate

This project was approved by the hospital ethics committee and privacy officers with the reference number CES 193/022. The need for informed consent was waived by the ethics committee.

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Competing interests

Not applicable

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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

TABLE

SUPPLEMENTARY MATERIAL