Journal of Cancer Therapy, 2022, 13, 266-274
https://www.scirp.org/journal/jct
ISSN Online: 2151-1942
ISSN Print: 2151-1934

Impact of Drug-Drug Interaction between CDK4/6 Inhibitors and Proton Pump Inhibitors on Survival Outcomes in the Treatment of Metastatic Breast Cancer—Real World Data from a Portuguese Center

Joana Reis*, Inês Costa, Mariana Costa, Ana Valente, Catarina Almeida, Marta Freitas, Cláudia Caeiro, Catarina Fernandes, Nuno Tavares, Miguel Barbosa

Centro Hospitalar SÃO JOÃO E.P.E., Porto, Portugal
Email: *joana11silvareis@gmail.com

How to cite this paper: Reis, J., Costa, I., Costa, M., Valente, A., Almeida, C., Freitas, M., Caeiro, C., Fernandes, C., Tavares, N. and Barbosa, M. (2022) Impact of Drug-Drug Interaction between CDK4/6 Inhibitors and Proton Pump Inhibitors on Survival Outcomes in the Treatment of Metastatic Breast Cancer—Real World Data from a Portuguese Center. *Journal of Cancer Therapy*, **13**, 266-274.
https://doi.org/10.4236/jct.2022.135022

Received: April 11, 2022
Accepted: May 27, 2022
Published: May 30, 2022

Abstract

Introduction: Proton pump inhibitors (PPi) are widely prescribed, including in patients undergoing treatment for advanced breast cancer (ABC). Due to the pharmacokinetic characteristics of the CDK4/6 inhibitor (Ci) palbociclib a drug interaction with PPi was hypothesized. It was shown in a retrospective study that this association was an independent predictive factor for worse progression-free survival (PFS). Objective: To verify the impact of concomitant administration of PPi with Ci on overall survival (OS) and PFS. Material and Methods: This is a retrospective cohort study of patients treated with Ci for HR+HER2-ABC in the period from Feb/2017 to Aug/2020. SPSS software was used for data processing. Univariate analysis was done by the Kaplan-Meier method and log-rank test, and multivariate analysis by COX regression. P-value < 0.05 was considered significant. Results: 80 patients were included. The median age at diagnosis of ABC was 56 years (25 - 75). Treatment with Ci was 1st line for ABC in 68.8%. Choice of Ci was palbociclib in 73.8% (n = 59) and ribociclib in 26.3% (n = 21). The hormone partner was a nonsteroidal aromatase inhibitor in 45.0%, and fulvestrant in 55.0% of cases. 37.5% of patients were on PPi, and 70.0% of them were during the entire treatment (23.3% omeprazole, 73.4% pantoprazole, 3.3% others). Patients taking concomitant PPi and Ci had lower OS (OS-3 years 42.6% vs. 63.4%, p = 0.254) and PFS (PFS med 15 m. vs. 21 m., p = 0.733), although with no statistically significant difference. Discussion: In the sample, there was a numerical difference, without the statistical significance in the use of PPi in the survival of patients under Ci. This difference could be more evident with a longer follow-up and a

larger sample size. This study intends to alert to the growing importance of checking for drug interactions. Polymedication, advanced age and the presence of several comorbidities are real problems in patients with ABC. Conclusion: Real-world data from this center demonstrate a negative, non-statistically significant impact of PPi treatment on survival outcomes, in patients treated with Ci for HR+HER2-ABC.

Keywords

Drug Interaction, Survival Impact, Advanced Breast Cancer, CDK4/6 Inhibitors, Proton Pump Inhibitors

1. Introduction

The benefit demonstrated by the use of CDK4/6 inhibitors (Ci) associated with hormone therapy (HT) in the first or more lines of treatment of hormone receptor-positive and HER2-negative (HR+HER2-) advanced breast cancer (ABC) is unequivocal [1] [2] [3] [4].

With the progressive "chronification" of ABC, the drug interactions of antineoplastic therapies with other "chronic" drugs are an increasingly pertinent issue.

Proton pump inhibitors (PPi) are widely used, with no exception for patients on ABC treatment. Considering the pharmacokinetic characteristics of Ci palbociclib, it has been hypothesized that drug interaction with PPi may account for worse survival outcomes. It is advocated that palbociclib, as a weak base, has its optimal absorption, and hence maximum plasma concentration, dependent on gastric acid pH, ideally below pH 4.5. Thus, PPi-induced inhibition of acid secretion may warrant plasma concentrations of palbociclib and therefore compromise its efficacy in HR+HER2-ABC. The effect of taking palbociclib fasting versus with food has already been studied, with no impact in patients with normal intestinal absorption [5] [6].

A recent retrospective study [7] tested the hypothesis of taking PPi concomitant with palbociclib as a factor impacting progression-free survival (PFS). This study included 112 patients, with two cohorts, one taking PPi (mostly lansoprazole) concomitantly with palbociclib and HT, and the other without PPi. A statistically significant difference in PFS was presented, with detriment to the cohort administrating PPi (14.0 versus 37.9 months, $p < 0.0001$). In multivariate analysis, they presented taking concomitant PPi with palbociclib and HT as an independent predictive factor for lower PFS.

In our center, the use of Ci has been subject to retrospective analysis since its systematic use began in 2017.

2. Objectives

To verify the impact on survival outcomes (OS and PFS) of taking concomitant

PPi with Ci in the context of HR+HER2-ABC.

3. Material and Methods

We conducted a retrospective analysis of clinical data of patients who started treatment with Ci for HR+HER2-ABC from February 2017 to August 2020, with data updated until September 2021. SPSS software was used as a data processing tool. Univariate analysis was performed by the Kaplan-Meier method and log-rank test, and multivariate analysis by COX regression. A $p < 0.05$ was considered significant. Hormonal resistance was defined as progression before completing 12 months of prior HT. Partial treatment with PPi was considered when it started later than the start of ABC treatment. The group of patients who underwent palbociclib and the group who underwent ribociclib were subanalyzed.

4. Results

Eighty patients were included. The median age at diagnosis of breast cancer was 51 years (22 - 85) and the median age at diagnosis of ABC was 56 years (25 - 75). 31.3% of cases were ABC at diagnosis.

Prior to treatment with Ci, in an adjuvant or palliative context, 27.5% were treated with chemotherapy, 77.0% of these with anthracyclines and 53.7% with taxanes.

Hormonal resistance was identified in 55% of cases.

Treatment with Ci was the 1st line in 68.8%. The choice of Ci was palbociclib in 73.8% and ribociclib in 26.3%. The hormone partner was a nonsteroidal aromatase inhibitor in 45.0%, and fulvestrant in 55.0% of cases. As for Ci treatment-related toxicity, in 71.3% of patients there was a need for deferrals, and in 31.3% for dose reduction.

Of the 80 patients included, 37.5% were taking PPi concomitantly (Cohort A, n = 30), while 62.5% were not taking both drugs concomitantly (Cohort B, n = 50). In Cohort A, concomitant PPi was maintained throughout the entire Ci treatment time in 70.0%, as part of the patients' prior chronic medication. The remaining 30.0% started PPI after starting Ci for various indications. The PPi used was omeprazole 20 mg in 23.3%, pantoprazole (20 or 40 mg) in 73.4%, or another PPi in 3.3% of cases.

The characteristics of the sample are summarized in the following **Table 1**.

Univariate analysis revealed that the median OS was not reached for Cohort B, and the median OS of 35 months for Cohort A. The Log-rank statistical calculation resulted in a p-value of 0.254. OS at 36 months was 63.4% in Cohort B and 42.6% in Cohort A.

Univariate analysis of PFS revealed a median of 21 months for Cohort B, and a median of 15 months for Cohort A. The p-value was 0.254. 63.0% of patients in Cohort B were progression-free at 24 months and 38.4% in Cohort A (**Figure 1** & **Figure 2**, **Table 2**).

Survival analysis of patients on palbociclib, n = 59, showed that the median

Table 1. Sample characteristics.

N = 80		
Median age ABC	56 years (25 - 75)	
Menopausal status	Pre/peri	Post
	50.0%	50.0%
ABC at diagnosis	yes	no
	31.3%	68.7%
Metastatic sites	<3	≥3
	33.8%	66.2%
Ovarian suppression with goserelin	yes	no
	28.7%	71.3%
Prior Chemotherapy	yes	no
	27.5%	72.5%
Hormonal resistance	yes	no
	55.0%	45.0%
Ci	1st line	>1st line
	68.8%	31.2%
1˚ Ci	Palbociclib	Ribociclib
	73.8%	26.2%
Hormonal partner	Non Steroidal aromatase inhibitor	Fulvestrant
	45.0%	55.0%
Non Steroidal aromatase inhibitor	Anastrozol	Letrozol
	44.4%	55.5%
Ci toxicity	Deferrals	Dose reduction
	71.3%	31.3%
Concomitant PPi	**yes**	**no**
	37.5%	**62.5%**
Concomitant PPi time	all	parcial
	70.0%	30.0%
Which PPi	Omeprazol	Pantoprazol
	23.3%	73.4%
Progression of disease under Ci	yes	no
	57.5%	42.5%

Table 2. Global sample OS and PFS results.

Endpoint	**Cohort A**	**Cohort B**	**p value**
Median OS	35 months	NR	p = 0.254
Alive at 24 months	59.6%	73.4%	
Alive at 36 months	42.6%	63.4%	

Continued

Median PFS	15 months	21 months	p = 0.773
no disease progression at 24 months	38.4%	63.0%	
no disease progression at 36 months	19.2%	46.9%	

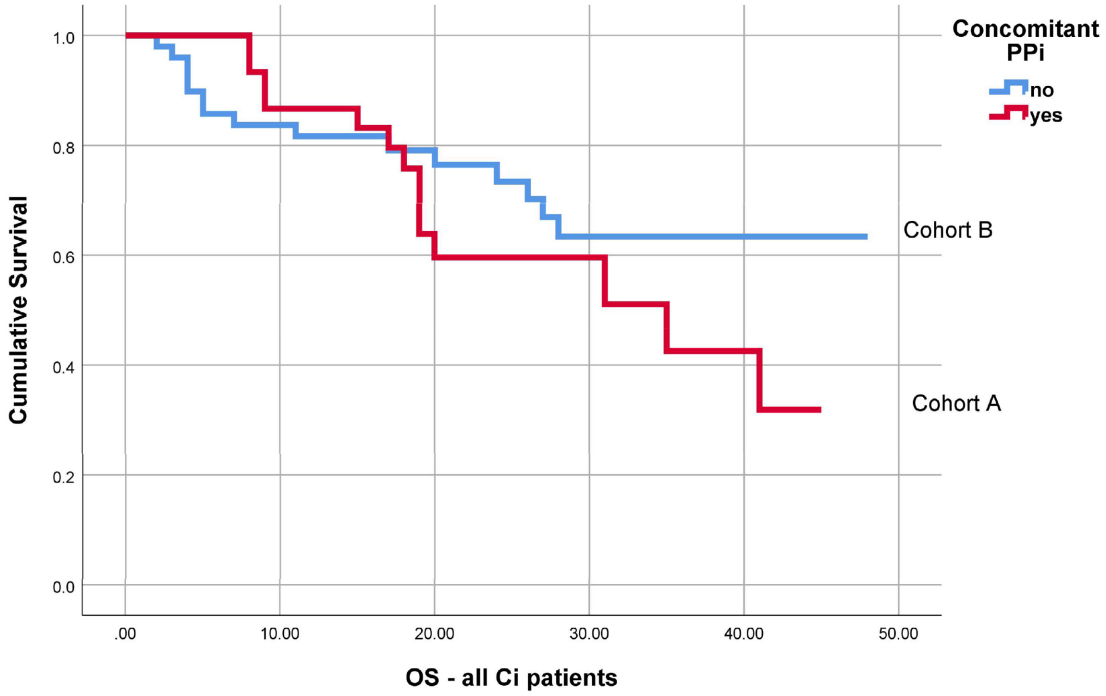

Figure 1. Global sample OS.

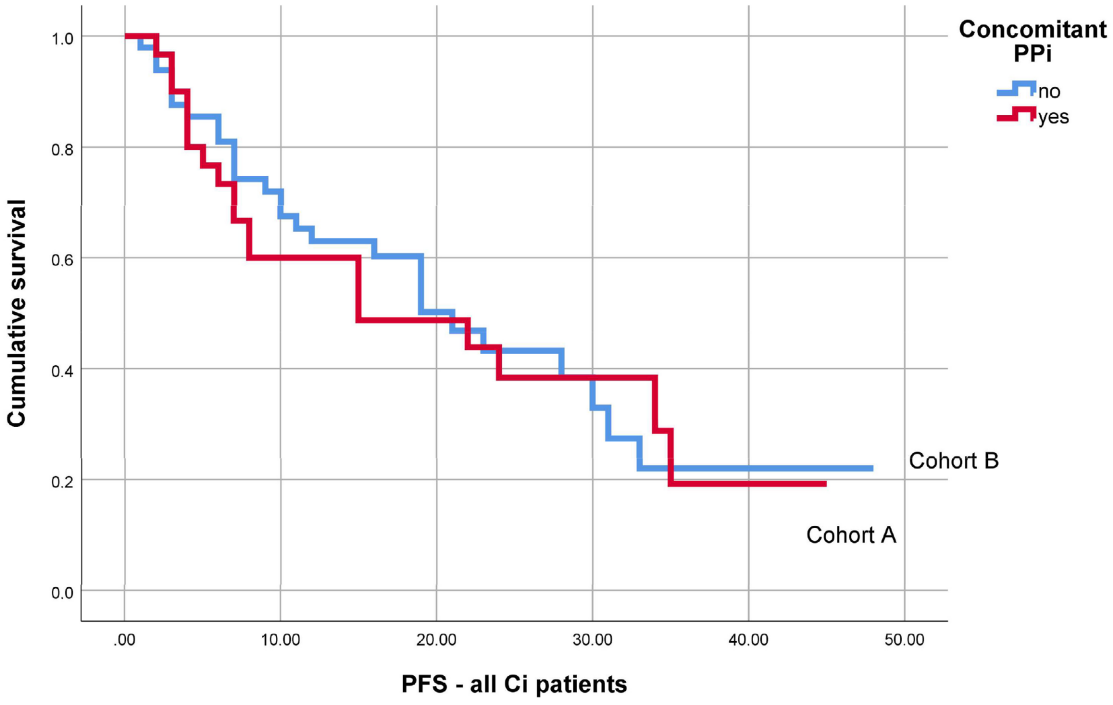

Figure 2. Global sample PFS.

OS was not reached for Cohort B and a median OS of 31 months for Cohort A (p-value was 0.363). OS at 36 months was 59.0% for Cohort B and 38.3% in Cohort A. PFS showed a median of 16 months in Cohort B and a median of 8 months in Cohort A (p-value was 0.368). 22.4% of patients in Cohort B and zero patients in Cohort A were free of disease progression at 24 months (Figure 3 & Figure 4, Table 3).

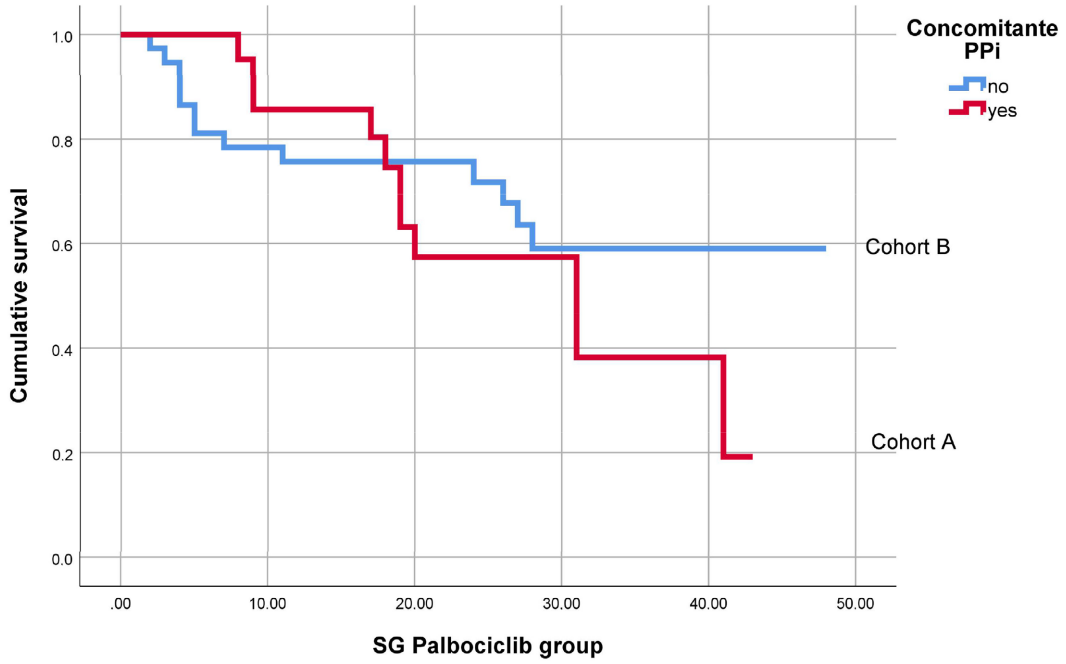

Figure 3. Palbociclib group OS.

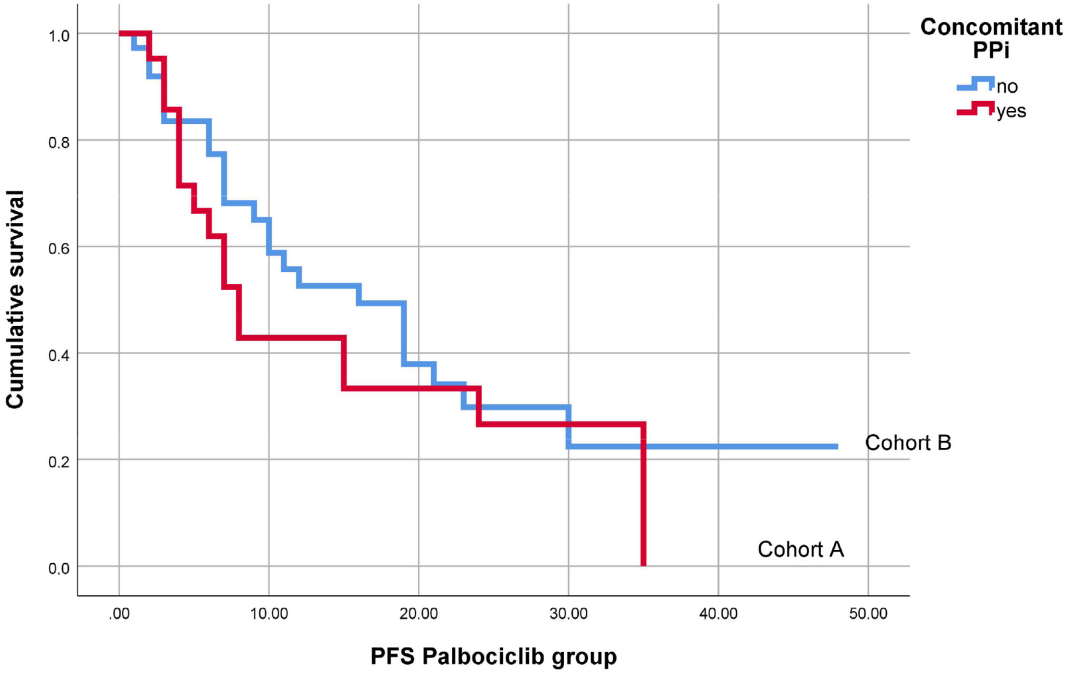

Figure 4. Palbociclib group PFS.

Table 3. Palbociclib sample OS and PFS results.

Endpoint	Cohort A	Cohort B	p value
Median OS	31 months	NR	p = 0.363
Alive at 24 months	57.4%	63.5%	
Alive at 36 months	38.3%	59.0%	
Median PFS	8 months	16 months	p = 0.368
no disease progression at 24 months	0	49.3%	
no disease progression at 36 months	0	22.4%	

Regarding the outcomes of patients on ribociclib, n = 21, the median OS was not reached for Cohort B and a median OS of 35 months for Cohort A (p-value was 0.481). PFS showed a median of 31 months in Cohort B and a median of 34 months in Cohort A (p-value was 0.481) (Table 4).

Table 4. Ribociclib sample OS and PFS results.

Endpoint	Cohort A	Cohort B	p value
Median OS	35 months	NR	p = 0.481
Alive at 24 months	64.8%	75.0%	
Alive at 36 months	48.6%	75.0%	
Median PFS	31 months	34 months	p = 0.368
no disease progression at 24 months	64.3%	91.7%	
no disease progression at 36 months	42.9%	22.9%	

5. Discussion

In the sample, there are numerical differences in OS and PFS between the group of patients medicated with PPi concomitantly with Ci versus the group of patients not medicated with PPi. The p-value is not statistically significant in any of the analyses, but the numerical expression of the differences is not negligible. Analysis according to the Ci used, palbociclib or ribociclib, showed a sustained numerical difference in OS and PFS values in the group of patients under palbociclib but not in the group under ribobiclib. More mature data and a larger sample size may enhance conclusions with greater statistical power. The class effect of ribociclib should be considered despite the small number of patients under this Ci in the total sample.

Notwithstanding the lack of statistical significance of this study, we intend to draw attention to the importance of drug interactions in obtaining optimal responses to anti-neoplastic treatments.

Theoretically, the interaction of PPi with palbociclib may compromise its efficacy. Published data have already demonstrated this effect in PFS, and our sample, although without statistically significant p-values, showed expressive differences in OS and PFS with detriment to the concomitant taking of PPi and

Ci.

We denoted the extreme importance of systematically reviewing each patient's chronic medication in order to fully contemplate possible drug interactions. Simple questions such as: why the patient is medicated with PPi; if there are any symptoms; if the indication for its use is still there; if discontinuation is optional; can be asked at each clinical evaluation. Other questions were suggested after this study: should we discontinue PPi in all patients who do not maintain the indication for its use? In a scenario where PPi cannot be suspended, will this be limited in the choice of Ci? What outcomes will be obtained by including patients on abemaciclib?

In addition to the interaction analyzed in this study, many others may not yet be known.

If survival gains underpin constant updates in the standard of care for patients with ABC, deleterious effects induced by simple and often avoidable drug interactions should also be a focus of attention.

6. Conclusions

Real-life data from this center showed a negative impact on OS and PFS of PPi treatment concomitantly with Ci treatment in HR+HER2-ABC, although without statistically significant results.

Polymedication, advanced age, and the presence of various comorbidities are real issues for ABC patients, in addition drug interactions become increasingly pertinent.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] Finn, R.S., Crown, J.P., Lang, I., Boer, K., Bondarenko, I.M., Kulyk, S.O., Ettl, J., Patel, R., Pinter, T., Schmidt, M., Shparyk, Y., Thummala, A.R., Voytko, N.L., Fowst, C., Huang, X., Kim, S.T., Randolph, S. and Slamon, D.J. (2015) 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**, 25-35. https://doi.org/10.1016/S1470-2045(14)71159-3

[2] Cristofanilli, M., Turner, N.C., Bondarenko, I., Ro, J., Im, S.A., Masuda, N., Colleoni, M., DeMichele, A., Loi, S., Verma, S., Iwata, H., Harbeck, N., Zhang, K., Theall, K.P., Jiang, Y., Bartlett, C.H., Koehler, M. and Slamon, D. (2016) Fulvestrant plus Palbociclib versus Fulvestrant plus Placebo for Treatment of Hormone-Receptor-Positive, HER2-Negative Metastatic Breast Cancer That Progressed on Previous Endocrine Therapy (PALOMA-3): Final Analysis of the Multicentre, Double-Blind, Phase 3 Randomised Controlled Trial. *The Lancet Oncology*, **17**, 425-439. https://doi.org/10.1016/S1470-2045(15)00613-0

[3] Tripathy, D., Im, S.A., Colleoni, M., Franke, F., Bardia, A., Harbeck, N., Hurvitz,

S.A., Chow, L., Sohn, J., Lee, K.S., Campos-Gomez, S., Villanueva Vazquez, R., Jung, K.H., Babu, K.G., Wheatley-Price, P., De Laurentiis, M., Im, Y.H., Kuemmel, S., El-Saghir, N., Liu, M.C., Carlson, G., Hughes, G., Diaz-Padilla, I., Germa, C., Hirawat, S. and Lu, Y.S. (2018) 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**, 904-915. https://doi.org/10.1016/S1470-2045(18)30292-4

[4] Sledge Jr, G.W., Toi, M., Neven, P., Sohn, J., Inoue, K., Pivot, X., Burdaeva, O., Okera, M., Masuda, N., Kaufman, P.A., Koh, H., Grischke, E.M., Frenzel, M., Lin, Y., Barriga, S., Smith, I.C., Bourayou, N. and Llombart-Cussac, A. (2017) 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*, **35**, 2875-2884. https://doi.org/10.1200/JCO.2017.73.7585

[5] Ruiz-Garcia, A., Plotka, A., O'Gorman, M. and Wang, D.D. (2017) Effect of Food on the Bioavailability of Palbociclib. *Cancer Chemotherapy and Pharmacology*, **79**, 527-533. https://doi.org/10.1007/s00280-017-3246-4

[6] Xu, B., Li, H., Zhang, Q., Sun, W., Yu, Y., Li, W., Wang, S., Liao, N., Shen, P., Liu, Y., Huang, Y., Linn, C., Zhao, H., Jiang, J. and Wang, D. (2021) Pharmacokinetics, Safety, Activity, and Biomarker Analysis of Palbociclib plus Letrozole as First-Line Treatment for ER+/HER2—Advanced Breast Cancer in Chinese Women. *Cancer Chemotherapy and Pharmacology*, **88**, 131-141. https://doi.org/10.1007/s00280-021-04263-9

[7] Del Re, M,, Omarini, C., Diodati, L., Palleschi, M., Meattini, I., Crucitta, S., Lorenzini, G., Isca, C., Fontana, A., Livi, L., Piacentini, F., Fogli, S., De Giorgi, U. and Danesi, R. (2021) Drug-Drug Interactions between Palbociclib and Proton Pump Inhibitors May Significantly Affect Clinical Outcome of Metastatic Breast Cancer Patients. *ESMO Open*, **6**, Article ID: 100231. https://doi.org/10.1016/j.esmoop.2021.100231