



Concomitant administration of proton pump inhibitors does not significantly affect clinical outcomes in metastatic breast cancer patients treated with ribociclib

Marzia Del Re^a, Stefania Crucitta^a, Claudia Omarini^b, Irene Bargagna^c, Marta Mongillo^d, Michela Palleschi^e, Stefania Stucci^f, Icro Meattini^{g,h}, Raffaella D'Onofrio^b, Giulia Lorenzini^c, Pamela Biondani^d, Ugo De Giorgi^e, Camillo Porta^f, Lorenzo Livi^{g,h}, Salvatore Natalizio^b, Andrea Fontana^c, Elena Giontella^d, Lucia Angelini^{g,h}, Stefano Fogli^{a,*}, Romano Danesi^a

^a Unit of Clinical Pharmacology and Pharmacogenetics, Department of Clinical and Experimental Medicine, University of Pisa, Italy

^b Division of Medical Oncology, University of Modena, Italy

^c Unit of Medical Oncology, Department of Translational Research and New Technologies in Medicine, University of Pisa, Italy

^d Section of Oncology, Department of Medicine, University of Verona and University and Hospital Trust of Verona, Italy

^e Unit of Medical Oncology, IRCCS-Istituto Romagnolo per lo Studio dei Tumori (IRST) 'Dino Amadori', Meldola, Italy

^f Division of Oncology, Department of Biomedical Sciences and Human Oncology, University of Bari, Italy

^g Department of Experimental and Clinical Biomedical Sciences 'M. Serio', University of Florence, Italy

^h Radiation Oncology Unit e Oncology Department, Azienda Ospedaliero Universitaria Careggi, Florence, Italy

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ABSTRACT

Background: Gastric pH changes by proton-pump-inhibitors (PPIs) were found to affect progression-free survival (PFS) in metastatic breast cancer (mBC) patients treated with palbociclib. The current study was aimed at investigating whether the same effect could occur in patients treated with ribociclib.

Patients and methods: Patients with hormone-positive/HER-2-negative mBC candidates for first-line treatment with ribociclib were enrolled in this retrospective-cohort study. Patients were classified as “no concomitant PPIs” or “concomitant PPIs”; PPI administration covered the entire or not less than 2/3 of treatment with ribociclib. All clinical interventions were made according to clinical practice.

Results: A total of 128 patients were consecutively enrolled in the study; 78 belonged to the “no concomitant PPIs” group and 50 to the “concomitant PPIs” group. One hundred and six patients were endocrine-sensitive and received ribociclib and letrozole, while 22 were endocrine-resistant and were treated with ribociclib and fulvestrant. The most prescribed PPI was lansoprazole. According to PFS, patients taking PPIs had a PFS almost superimposable to those assuming ribociclib and endocrine therapy alone (35.3 vs. 49.2 months, $p = 0.594$). No difference in PFS was observed in estrogen-sensitive or estrogen-resistant mBC in the presence or absence of concomitant PPI treatment ($p = 0.852$). No correlation with adverse events was found including grade>2 hematological toxicities.

Conclusions: The present study supports the hypothesis that the concomitant use of PPIs does not compromise the efficacy of ribociclib in a real-life setting.

1. Introduction

CDK4/6 inhibitors, including abemaciclib, palbociclib, and ribociclib, represent the standard of care in the I/II-line treatment of hormone receptor (HR)-positive/HER2-negative metastatic breast cancer (mBC) [1–11]. Gastric pH changes by proton pump inhibitors (PPIs) may alter

the oral bioavailability of targeted agents that exhibit pH-dependent solubility [3,4]; however, the clinical impact of such interaction remains a controversial topic that is currently debated [12]. In line with findings showing that co-administration of rabeprazole reduced palbociclib bioavailability [13], we recently demonstrated that concomitant PPIs substantially decreased progression-free survival (PFS) in

* Corresponding author. Department of Clinical and Experimental Medicine, Via Roma, 55, 56126, Pisa, Italy.

E-mail address: stefano.fogli@unipi.it (S. Fogli).

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metastatic breast cancer patients treated with palbociclib [13].

Nonetheless, the effect of acid-reducing agents may depend on the anticancer drug used. According to this, ribociclib exhibit different dissolution properties from palbociclib, and its absorption is unlikely to be affected by changes in gastric pH by PPIs [14,15].

In the current study, we retrospectively evaluated the impact of PPI use on PFS of breast cancer patients treated with ribociclib in the clinical practice.

2. Patients and methods

This is a retrospective-cohort study carried out by reviewing medical charts on HR-positive/HER2-negative mBC patients treated with ribociclib as first-line treatment in the presence or absence of concomitant PPI therapy. The primary endpoint was to assess possible differences in progression-free survival (PFS) between PPI users and non-users. A list of potential study patients was obtained from the Divisions of Medical Oncology at the University of Modena and the University of Bari (Italy), the Units of Medical Oncology at the University of Pisa (Italy), the University of Verona and IRCCS-Istituto Romagnolo per lo Studio dei Tumori (IRST) ‘Dino Amadori’ (Italy), the Department of Experimental and Clinical Biomedical Sciences ‘M. Serio’ at the University of Florence (Italy), and the Radiation Oncology Unit from Azienda Ospedaliero Universitaria Careggi (Italy). Hormone status was defined as tumors with estrogen and/or progesterone receptor expression >1% and HER2-negative (score 0 or 1+ to immuno-histochemistry). Treatment groups were defined as “no concomitant PPIs” if no PPIs were administered during ribociclib treatment, or “concomitant PPIs” if the administration of PPIs covered the entire or not less than 2/3 of treatment with ribociclib. We only included patients who were previous users of PPIs and excluded those given these treatments after initiating ribociclib. According to the duration of previous endocrine response, endocrine sensitive patients were those who relapsed ≥ 12 months after the completion of adjuvant endocrine therapy or with de novo advanced breast cancer, whereas endocrine-resistant patients were those who relapsed <12 months after ending adjuvant endocrine therapy [14]. Pharmacological and clinical interventions were carried out according to clinical practice. In particular, ribociclib was administered orally at a dose of 600 mg, once daily for 21 days on/7 days off in 28-day cycles, plus endocrine therapy (ET, fulvestrant, or letrozole), according to clinical practice. Ribociclib reduction to 400 or 200 mg was made according to the toxicity profile. Patients took the dose of lansoprazole (15 mg), esomeprazole (20 mg), omeprazole (10 mg), or pantoprazole (20 mg) in the morning at breakfast. Ribociclib was taken at lunchtime and patients were advised not to take strong inhibitors or inducers of cytochrome P450 3A4 (CYP3A4). The prescribing physician monitored the patient’s compliance with the recommendations. Toxicity was graded according to Common Terminology Criteria for Adverse Events (CTCAE v5). The study was approved by the local Ethics Committee and conducted following the Helsinki Declaration. All patients released written informed consent.

3. Statistical analysis

This cohort study set out to collect data from at least one hundred HR-positive/HER2-negative mBC patients treated with ribociclib in the presence or absence of concomitant PPI therapy. Categorical variables including Eastern Cooperative Oncology Group (ECOG) performance status, hormone sensitivity, pre/peri-menopausal status, visceral/bone disease, and the number of tumor sites were described by absolute and relative frequencies, while quantitative parameters were described by median values and range. Baseline characteristics of patients who received ribociclib with or without PPIs were assessed by the Wilcoxon rank-sum test and chi-squared test. PFS was defined as the time from treatment start to the disease progression. Survival curves were obtained by Kaplan–Meier method, and differences between curves were assessed

Table 1

Clinical characteristics of patients and distribution across PPI treatment groups.

	Total of patients (n = 128)	Concomitant use of PPIs		p- value
		No (n = 78)	Yes (n = 50)	
Age at the diagnosis of metastasis, median (range)	59 (35–85)	58	64	–
Pre/Postmenopause, n (%)				
Premenopause	31 (24.2)	18 (23.1)	13 (26)	0.87
Postmenopause	97 (75.8)	60 (76.9)	37 (74)	
ECOG PS, n (%)				
0	94 (73.4)	62 (79.5)	32 (64)	0.09
1	26 (20.3)	11 (14.1)	15 (30)	
2	8 (6.3)	5 (6.4)	3 (6)	
Disease site, n (%)				
Visceral	67 (52.3)	41 (52.6)	26 (52)	0.91
Non-visceral	61 (47.7)	37 (47.4)	24 (48)	
Type of ET associated to ribociclib, n (%)				
Fulvestrant	19 (14.8)	13 (16.7)	6 (12)	
Letrozole	109 (85.2)	65 (83.3)	44 (88)	0.64
Endocrine sensitive or resistant disease, n (%)				
Sensitive	106 (82.8)	62 (79.5)	44 (88)	
Resistant	22 (17.2)	16 (20.5)	6 (12)	0.31
Dose reduction of ribociclib, n (%)				
600 mg	77 (60.1)	48 (61.5)	29 (58)	0.06
400 mg	36 (28.1)	23 (29.5)	13 (26)	
200 mg	7 (5.5)	1 (1.3)	6 (12)	
Unknown	8 (6.3)	6 (7.7)	2 (4)	
PPI used, n (%)				
Lansoprazole			34 (68)	
Omeprazole			6 (12)	
Pantoprazole			7 (14)	
Esomeprazole			3 (6)	

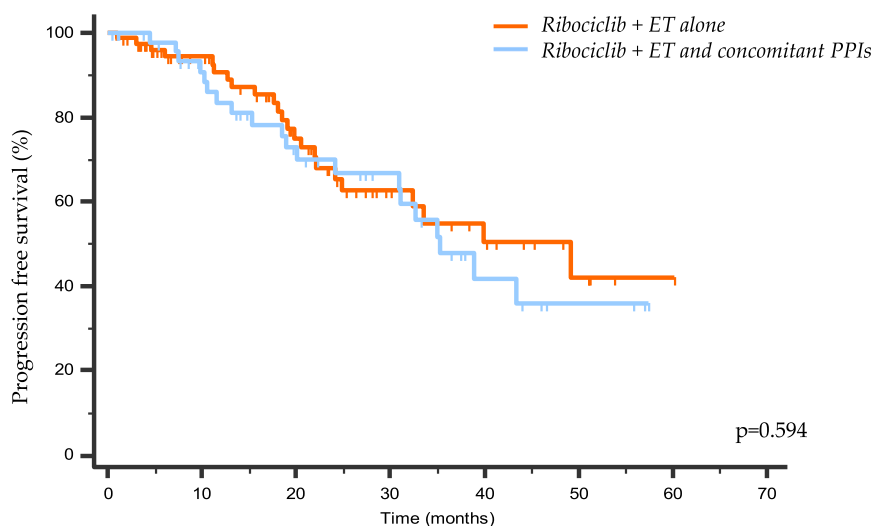
ECOG PS, Eastern Cooperative Oncology Group (ECOG) performance status; ET, endocrine therapy; PPIs, proton pump inhibitors.

using the log-rank test. The evaluation of independent risk factors for PFS was performed by Cox hazard regression model. At least 84 PFS events were expected to be sufficient to detect the treatment effect with 90% statistical power (5% type I error rate) with a hazard ratio (HR) set at 1.8. Differences were considered significant at $p < 0.05$. All statistical analyses were carried out using MedCalc Statistical Software version 14.8.1 (MedCalc Software, bvba, Ostend, Belgium).

4. Results

A total of 128 patients were included in the present study. Fifty patients received concomitant PPI during ribociclib treatment, while 78 patients were treated with the association of ribociclib plus ET. One hundred and six patients were endocrine-sensitive and were administered a combination of ribociclib and letrozole, and 22 were defined as endocrine-resistant and were treated with the combination of ribociclib and fulvestrant. Seventy-seven patients received ribociclib at a dose of 600 mg (60.1%), 36 patients (28.1%) reduced the dose to 400 mg, and 7 (5.5%) needed the 200 mg dose.

There were no significant differences between “concomitant PPIs” and “no concomitant PPIs” groups in terms of baseline characteristics



N	Number of patients at risk:							
78	55	34	17	11	5	1	0	Ribociclib + ET alone
50	37	25	18	7	3	0	0	Ribociclib + ET and concomitant PPIs

Fig. 1. Overall population treated with ribociclib plus endocrine therapy and stratified according to progression-free survival and the use of concomitant PPIs. ET, endocrine therapy; PPIs, proton pump inhibitors.

Table 2
Univariate analysis for PFS.

Variables	HR (95% CI)	p-value
Age (years)		
≤ 59	Reference	
> 59	0.74 (0.40–1.38)	0.36
Number of metastatic sites		
1	Reference	
> 1	1.27 (0.94–1.70)	0.12
Endocrine sensitive or resistant disease		
Sensitive	Reference	
Resistant	1.32 (0.62–2.83)	0.48
ECOG PS		
0	Reference	
1–2	1.81 (0.92–3.55)	0.09
Pre-/Post-menopause		
Pre-menopause	Reference	
Post-menopause	0.88 (0.45–1.71)	0.70
Visceral or non-visceral disease		
Non-visceral	Reference	
Visceral	1.35 (0.73–2.49)	0.34
Dose reduction		
No	Reference	
Yes	0.72 (0.43–1.20)	0.21
Concomitant use of PPIs		
No	Reference	
Yes	1.17 (0.65–2.14)	0.59

CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group (ECOG) performance status; PPIs, proton pump inhibitors; HR, hazard ratio.

(Table 1). Furthermore, the Kaplan-Meier curves were almost superimposable between the two groups with no statistically significant difference in PFS (35.3 vs. 49.2 months in PPI users vs. non-users, respectively; HR 1.18, 95% CI 0.64–2.15, p = 0.594; Fig. 1).

The univariate analysis on age, number of metastatic sites at ribociclib baseline, endocrine sensitivity or resistance, ECOG, menopausal status, visceral disease, and ribociclib dose reduction showed that these variables were not significantly associated with PFS (Table 2).

To further evaluate the role of PPIs over endocrine sensitivity in PFS determination, patients were stratified into endocrine-sensitive patients

(with or without concomitant PPIs) and endocrine-resistant patients (with or without concomitant PPIs). There was no statistically significant difference among endocrine-sensitive or resistant patients in the presence or absence of concomitant PPIs (HR 1.22, 95%CI 0.63–2.39; HR 1.37, 95% CI 0.30–6.16; Fig. 2A and B). No correlation with adverse events was found, particularly with grade >2 hematological toxicities since neutropenia, anemia, and thrombocytopenia were equally distributed across the two groups of patients and the majority of them developed toxicity during the first and/or second cycle of therapy (p = 0.493).

5. Discussion

Evidence from the present study suggests that the concomitant use of PPIs and ribociclib in metastatic breast cancer patients does not affect PFS. This appears to be a drug-specific property rather than a class effect since PPIs were found to substantially reduce PFS in metastatic breast cancer patients treated with palbociclib [13].

The different chemical behavior of the two CDK4/6 inhibitors in the gastric microenvironment may be due to dissolution properties rather than their acid-base properties. Structurally, ribociclib is a 2-amino-pyrrolo [2,3-d]pyrimidine derivative, whereas palbociclib is a pyrido[2,3-d]pyrimidine analogue [15]. Although they are both weak bases, ribociclib solubility is higher than 2.4 mg/ml at pH 4.5 (i.e. gastric pH values typically achieved by PPIs) [16], while that of palbociclib decreases to less than 0.5 mg/ml at pH > 4.5 [17]. To support this notion, an integrated approach, including noncompartmental analysis of clinical trial data and population pharmacokinetic analysis, indicated no effect of gastric pH changes on ribociclib pharmacokinetics [16]. Consistent with the findings of the current study, sensitivity analyses based on physiologically-based pharmacokinetic modeling showed that ribociclib exposure was independent of gastric pH in the physiologic range (1.0–8.0) [18]. Furthermore, short-term treatment with rabeprazole substantially reduced palbociclib Cmax [17], while no change in ribociclib bioavailability and/or steady-state pharmacokinetic parameters were observed in patients taking gastric pH-modifying agents [16,19].

It has also been reported that the free average steady-state

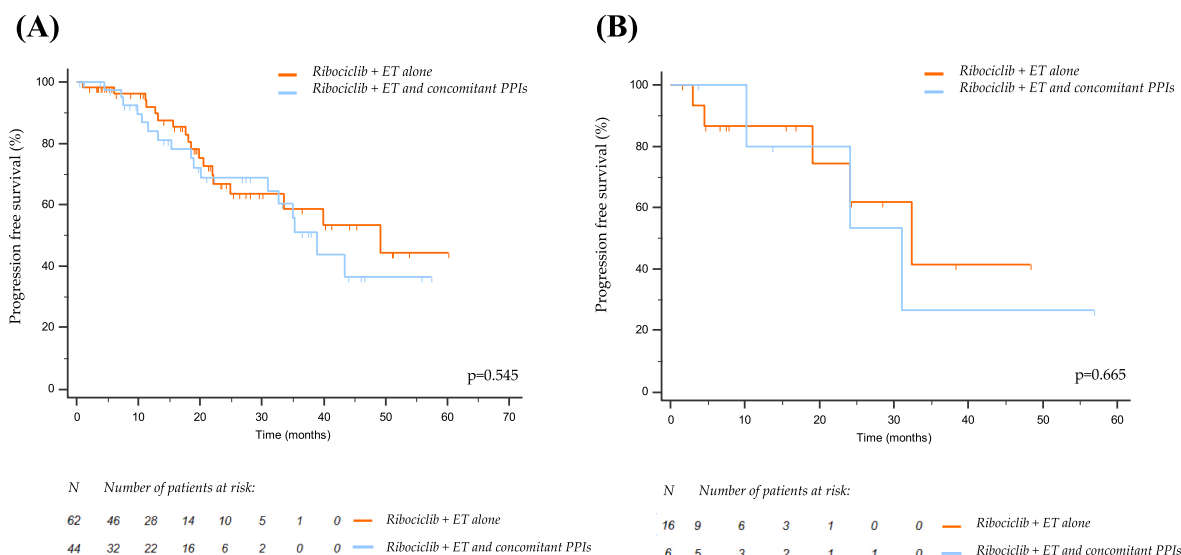


Fig. 2. Effect of concomitant PPIs on progression-free survival over endocrine sensitivity in patients treated with ribociclib. Patients were stratified into four groups: **(A)** endocrine-sensitive patients and no concomitant PPIs vs. concomitant PPIs; **(B)** endocrine-resistant patients and no concomitant PPIs vs. concomitant PPIs. ET, endocrine therapy; PPIs, proton pump inhibitors.

concentration (C_{ss}) for palbociclib was similar to the in vitro cell potency (IC₅₀), with a C_{ss}/IC₅₀ ratio of 0.94 [20], whereas ribociclib has an average free C_{ss} that largely exceeds the in vitro cell potency (C_{ss}/IC₅₀ ratio >25) [20]. Therefore, any interindividual variability caused in drug absorption may have a different clinical significance depending on the CDK4/6 inhibitor used, with no anticipated clinical relevance for ribociclib due to its broad therapeutic index [16]. This appears to be of particular clinical relevance when a dose reduction of ribociclib may be required because of toxicity. Noteworthy, the results from a recently published observational study suggest the opposite conclusion that PPIs may reduce the efficacy of ribociclib in metastatic breast cancer patients [21]. However, the higher doses of PPIs (twice the drug doses administered in our work) and heterogeneity of drugs used in that work, compared to our study, might partially account for such a difference.

Determining PFS retrospectively from patient charts is challenging and typically less reliable than in clinical trials or prospective observational studies, and some limitations need to be acknowledged. For example, PFS in our cohort was longer than that observed in pivotal studies [1,22]. Nonetheless, the difference in PFS between PPI users and non-users was not statistically significant since the Kaplan-Meier curves were almost superimposable for 2/3 of the graphs; however, it is difficult to predict whether such a difference will become significant in a larger sample. In contrast to randomized clinical trials, our population mirrors real-life practice, and the present study focused on evaluating possible changes in PFS between PPI users and non-users treated with ribociclib rather than measuring absolute PFS. Furthermore, our findings agree with the pharmacological and pharmaceutical properties of ribociclib and with most of the current literature even though few data have been published to date.

Subgroup analysis carried out in our cohort suggests that PPIs do not affect PFS, regardless of the endocrine resistance or sensitivity. Although a two-way classification (PPI yes/no, endocrine resistance yes/no) may have reduced sample size, such an approach has also been applied in previously published works [13,21]. Other unknown factors that could influence clinical outcomes were a different lifestyle in PPI users compared to non-users, e.g., alimentary disorders or unhealthy conditions associated with worse outcomes in breast cancer, and the lack of information about fed or fasting conditions during PPI administration. Regarding the latter, ribociclib absorption is unlikely to be affected by changes in gastric pH following food intake, and the bioequivalence of

ribociclib exposure with or without a high-fat meal has been demonstrated in a clinical trial [16].

Overall, our results support the hypothesis that long-term treatment with PPIs does not compromise the efficacy of ribociclib. Although we were unable to evaluate ribociclib pharmacokinetics, the lack of impact of PPIs on PFS in patients treated with this CDK4/6 inhibitor can be likely due to its greater tolerance to pH changes along with the broad therapeutic index that allowed to maintain plasma levels well above the minimum effective concentration. Such evidence may be relevant for clinical decision-making about the coadministration of PPIs in patients treated with ribociclib in a real-life setting.

Authors contribution statement

MDR, RD: conceptualization, methodology, investigation, data curation; SF, SC, MDR: writing – original draft preparation; CO, IB, MM, MP, SS, IM, RDO, GL, PB, UDG, CP, LL, SN, AF, EG, LA: collection of clinical data. SC, MDR: data Formal analysis; All: supervision, writing-reviewing and editing, conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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