Clinical outcomes of concomitant use of proton pump inhibitors and regorafenib in patients with metastatic colorectal cancer: a multicenter study

Emre Yekedüz1,2 · Mehmet Fatih Özbay3 · Dilek Çağlayan4 · Atila Yıldırım5 · Cihan Erol6 · Hasan Çağrı Yıldırım7 · Sezai Tunç8 · Neslihan Ozyurt9 · Feyyaz Özdemir5 · Mehmet Ali Nahit Şendur6 · Abdurrahman Işıkdoğan8 · Saadettin Kılıçkap7,10 · Yüksel Ürün1,2 · Şuayib Yalçın7 · Mehmet Artaç4 · Hasan Şenol Coşkun3 · Güngör Utkan1,2

Received: 4 August 2022 / Accepted: 10 October 2022 / Published online: 21 October 2022
© The Author(s), under exclusive licence to Springer-Verlag GmbH Germany, part of Springer Nature 2022

Abstract
Aim To compare survival outcomes, response rates, and adverse events (AEs) in proton pump inhibitor (PPI) user and non-user patients with metastatic colorectal cancer (mCRC) treated with regorafenib.
Methods We included 272 patients with mCRC treated with regorafenib in this study. Patients were divided into two categories according to their status of PPI use. The primary endpoint was overall survival (OS). The secondary endpoints were time to treatment failure (TTF), response rates, and safety. To exclude immortal time bias in survival analyses, we compared PPI non-user patients and all patients.
Results There were 141 and 131 patients in the PPI non-user and user groups. Baseline characteristics were similar in each group. Pantoprazole was the most used PPI. At the median 35.2 (95% confidence interval (CI): 32.6–37.9) months follow-up, the median OS was similar in PPI non-user and all patients (6.9 months (95% CI: 5.3–8.5) and 7.7 months (95% CI: 6.6–8.8), \( p = 0.913 \)). TTF was also similar in PPI non-user and all patients (3.3 months (95% CI: 2.7–3.9) and 3.5 months (95% CI: 3.0–4.0), \( p = 0.661 \)). In multivariable analysis, no statistically significant difference was observed between PPI user and non-user groups in OS and TTF (hazard ratio (HR), 0.99; 95% CI, 0.77–1.28; \( p = 0.963 \) for OS; HR, 0.93; 0.77–1.20, \( p = 0.598 \) for TTF). The objective response rates (ORR) were similar in the PPI non-user and user groups (19.8% and 16.8%, \( p = 0.455 \)). The rates of any grade AEs were also similar in each group.
Conclusion This study found no worse outcome in the combined use of PPI and regorafenib among patients with mCRC.

Keywords Drug-drug interactions · Acid suppression · Regorafenib

Abbreviations
AEs Adverse events
ATP Adenosine triphosphate
CI Confidence interval
CYP Cytochrome P450

Emre Yekedüz
emre.yekeduz@gmail.com

1 Department of Medical Oncology, Faculty of Medicine, Ankara University, 06590 Ankara, Turkey
2 Cancer Research Institute, Ankara University, Ankara, Turkey
3 Department of Medical Oncology, Faculty of Medicine, Akdeniz University, Antalya, Turkey
4 Department of Medical Oncology, Meram Faculty of Medicine, Necmettin Erbakan University, Konya, Turkey
5 Department of Medical Oncology, Faculty of Medicine, Karadeniz Technical University, Trabzon, Turkey
6 Department of Medical Oncology, University Faculty of Medicine, Faculty of Medicine Ankara, Ankara Yıldırım Beyazıt University, Ankara, Turkey
7 Department of Medical Oncology, Faculty of Medicine, Hacettepe University, Ankara, Turkey
8 Department of Medical Oncology, Faculty of Medicine, Dicle University, Diyarbakir, Turkey
9 Medical Oncology Clinic, Prof. Dr. İlhan Özdemir State Hospital, Giresun, Turkey
10 Faculty of Medicine, Liv Hospital Medical Oncology Clinic, İstinye University, Ankara, Turkey
Introduction

Regorafenib is one of the oral multi-target tyrosine kinase inhibitors (TKIs) used in the treatment of metastatic colorectal cancer (mCRC), hepatocellular cancer (HCC), and gastrointestinal stromal tumor (GIST) [1–3]. For all TKIs, drug-drug interactions due to their oral route administration are substantial for their effectiveness. In addition, the bioavailability of oral TKIs may change with drugs affecting gastric pH [4]. In this regard, one of the main concerns about the bioavailability of TKIs was the combined use of these agents with acid suppression therapies, such as proton pump inhibitors (PPIs) and anti-acids [5, 6].

PPIs are usually prescribed to cancer patients for various reasons, such as treating dyspeptic symptoms, gastric bleeding prophylaxis, and preventing gastric damage from chemotherapy and radiotherapy [7, 8]. However, acid suppression with PPIs may affect the solubility and bioavailability of TKIs [9–11]. Indeed, the proportion of ionized forms of TKIs changes as per gastric pH. Usually, they need an acid environment for more ionization that can be absorbed easier than the non-ionized form [10, 11].

However, there were conflicting results regarding the effect of PPI and TKI combinations on the clinical outcomes. For instance, in a study that assessed the impact of combined use of pazopanib and PPIs on survival outcomes and adverse event (AE) profile, no difference was observed between the PPI user and non-user groups [12]. Conversely, a study including patients with HCC treated with TKIs showed increased mortality in the PPI user group [13]. To date, one study evaluated the effect of esomeprazole on the bioavailability of regorafenib and concluded that the bioavailability of regorafenib was similar in PPI non-user and user groups. However, this study did not compare the survival outcomes between the groups [14]. Unfortunately, there is no data on whether regorafenib combined with PPI affects survival and safety outcomes in patients with mCRC.

This study aimed to assess the effect of PPIs on the survival outcomes, response rates, and AE profile in patients with mCRC treated with regorafenib.

Methods

The local ethical committee approved this study in compliance with the “Declaration of Helsinki” and local guidelines.

Patients’ cohort and data extraction

Patients with mCRC treated with regorafenib from eight cancer centers in Turkey between January 2015 and December 2021 were included in this multicenter retrospective cohort study. Patients were divided into groups according to their status of PPI use as PPI non-user and user groups. Demographic and clinical data were extracted from the electronic medical record systems and patients’ files. Patients who were prescribed PPI at any time after initiation of regorafenib were categorized in the PPI user group.

Endpoints

The primary endpoint was overall survival (OS), calculated from the initiation of regorafenib to the exitus. The secondary endpoints were time to treatment failure (TTF), calculated from the initiation of regorafenib to discontinuation for any reason, response rates, and safety. Response rates were assessed according to “Response evaluation criteria in solid tumors” (RECIST) 1.1. “Common Terminology Criteria for Adverse Events” (CTCAE version 4.03) was used to evaluate AEs.

Statistical analysis

For descriptive analyses, median with interquartile range (IQR) for non-normally distributed continuous variables, mean ± standard deviation for normally distributed continuous variables, and percentages for categorical variables were used. Mann–Whitney U and independent samples t-tests were used to compare two groups for non-normally and normally distributed continuous variables, respectively. Chi-square or Fisher’s exact test was used to compare categorical variables. Kaplan–Meier estimates were used to calculate OS and PFS. To exclude immortal time bias, we compared PPI non-user patients with all patients. A log-rank test was used to compare survival curves. Cox’s proportional hazard regression model was constructed by using variables with a p value of less than 0.2 in univariable analysis. A p value of less than 0.05 was considered statistically significant. SPSS 27.0 for Mac (IBM Corp., Armonk, NY) and RStudio were used for all statistical analyses.
|                                | PPI Non-user (n = 141) | PPI User (n = 131) | p     |
|--------------------------------|------------------------|-------------------|-------|
| **Age at starting regorafenib** |                        |                   | 0.101 |
| Years median (IQR)             | (52–67)                | (48–65)           |       |
| **Sex**                        |                        |                   | 0.063 |
| Male                           | 77                     | 86                |       |
| Female                         | 64                     | 45                |       |
| **ECOG performance status**    |                        |                   | 0.805 |
| 0–1                            | 102                    | 93                |       |
| 2                              | 39                     | 38                |       |
| **Tumor location**             |                        |                   | 0.389 |
| Right colon                    | 24                     | 25                |       |
| Left colon                     | 50                     | 53                |       |
| Rectum                         | 63                     | 47                |       |
| Missing                        | 4                      | 6                 |       |
| **Histological subtype**       |                        |                   | 0.085 |
| Non-mucinous                   | 121                    | 121               |       |
| Mucinous                       | 20                     | 10                |       |
| **KRAS or NRAS or BRAF status**|                        |                   | 0.609 |
| Mutant type                    | 73                     | 67                |       |
| Wild type                      | 51                     | 43                |       |
| Missing                        | 17                     | 21                |       |
| **First site of metastasis**   |                        |                   | 0.195 |
| Liver                          | 66                     | 70                |       |
| Lung                           | 19                     | 12                |       |
| Peritoneal                     | 13                     | 9                 |       |
| Intra-abdominal lymph node     | 9                      | 4                 |       |
| Other                          | 3                      | 0                 |       |
| Multiple                       | 31                     | 36                |       |
| **PPI Subtypes**               |                        |                   |       |
| Pantoprazole                   | N/A                    | 53                |       |
| Esomeprazole                   | 28                     | 21.4              |       |
| Lansoprazole                   | 19                     | 14.5              |       |
| Rabeprazole                    | 3                      | 2.3               |       |
| **Initial dose of regorafenib**|                        |                   | 0.574 |
| 80 mg                          | 29                     | 23                |       |
| 120 mg                         | 45                     | 51                |       |
| 160 mg                         | 60                     | 57                |       |
| Missing                        | 7                      | 0                 |       |
| **Presence of dose reduction** |                        |                   | 0.142 |
| No                             | 93                     | 102               |       |
| Yes                            | 40                     | 29                |       |
| Missing                        | 8                      | 0                 |       |
| **Treatment line of regorafenib**|                      |                   | 0.106 |
| 3                              | 71                     | 82                |       |
| 4                              | 60                     | 40                |       |
| 5–6                            | 10                     | 9                 |       |

ECOG Eastern Cooperative Oncology Group, IQR Interquartile range, N/A Not applicable, PPI Proton pump inhibitor
Results

Baseline characteristics

A total of 272 patients were included in this study. There were 141 and 131 patients in the PPI non-user and user groups, respectively. The median age at starting regorafenib was 61 (IQR: 52–67) and 57 (IQR: 48–65) in the PPI non-user and user groups. Most patients had an Eastern Cooperative Oncology Group (ECOG) 0 or 1 performance status and had left-sided colon or rectum tumors in each group. A full dose of regorafenib was started in approximately half of the patients, and dose reduction was required in about one out of four patients in the PPI non-user and user groups. Most patients received regorafenib in the third line in each group. All baseline characteristics were similar in the PPI non-user and user groups (Table 1).

Survival outcomes and response rates

At the median 35.2 (95% confidence interval (CI): 32.6–37.9) months follow-up, the median OS was similar in PPI non-user and all patients (6.9 months (95% CI: 5.3–8.5) and 7.7 months (95% CI: 6.6–8.8), p = 0.913). TTF was also similar in PPI non-user and all patients (3.3 months (95% CI: 2.7–3.9) and 3.5 months (95% CI: 3.0–4.0), p = 0.661). Kaplan-Meier estimates for OS and TTF are shown in Figs. 1 and 2. In multivariable analysis, no statistically significant difference was observed between PPI user and non-user groups in OS and TTF (hazard ratio (HR) 0.99, 95% CI 0.77–1.28, p = 0.963) for OS; HR 0.93, 0.77–1.20, p = 0.598 for TTF), after adjusting for confounding variables (i.e., ECOG performance score for OS and initial dose of regorafenib for OS and TTF).

Safety

The objective response rates (ORR) were similar in the PPI non-user and user groups (19.8% and 16.8%, p = 0.455). The best responses with regorafenib in each group are shown in Table 2.

Discussion

To the best of our knowledge, this was the first study that assessed the effect of PPI use on survival and safety outcomes in patients with mCRC treated with regorafenib. This study revealed no worse impact of PPIs in those patients. In a study assessing the bioavailability of regorafenib combined with omeprazole, de Man et al. showed no impact of esomeprazole on the bioavailability of regorafenib. This study also established that neither concomitant use nor 3-h interval time between esomeprazole and regorafenib did not affect the bioavailability of regorafenib [14]. However, it should be noticed that the study of de Man et al. did not evaluate the survival outcomes. Drug-drug interactions (DDIs) due to cytochrome P450 (CYP) may also affect the outcomes in patients with cancer treated with anti-cancer therapy [15]. Regorafenib is an inhibitor of various CYP isoenzymes, such as CYP2C8, CYP2C9, and CYP2B6. Generally, PPIs are metabolized by CYP2C19 and CYP3A4 isoenzymes. A clinical probe substrate study showed no drug-drug interactions (DDIs) between regorafenib and omeprazole, a substrate of CYP2C19 [16–18]. Our findings were consistent with pharmacokinetic studies assessing the combined use of regorafenib and PPIs.

P-glycoprotein is an adenosine triphosphate (ATP) dependent-efflux transporter, which plays a role in multidrug resistance. PPIs decrease the activity of P-glycoprotein by inhibiting ATPase activity. Combined use of PPIs and substrates of P-glycoprotein may result in increased activity of P-glycoprotein substrates [18, 19]. A pre-clinical study demonstrated the effect of inhibitors and inducers of P-glycoprotein in the active metabolites of regorafenib. However, the clinical importance of this effect is not clear [16, 20]. At that point, our study is important because it evaluated the clinical outcomes of the combined use of PPIs and regorafenib.

Abdominal symptoms and dyspepsia are common in advanced cancer patients, and the rate of PPI use in those patients is high [21]. In addition to symptom control, PPIs protect gastric damage from steroids, radiation, and...
chemotherapeutics [8]. However, the results for interaction between the PPIs and TKIs are usually extrapolated from the studies, including patients with non-CRC treated with regorafenib. In this regard, a study by Wu et al. compared the PPI non-user and user groups in patients with HCC treated with TKIs, such as sorafenib, regorafenib, lenvatinib, and cabozantinib. This study showed that the mortality rate was higher in the PPI user group than in the PPI non-user group [22]. Of note, this study was critical as it demonstrated the effect of TKIs and PPIs interaction on the survival outcomes. However, we did not show the impact of PPIs on the survival outcomes of regorafenib. Patients receiving various TKIs and PPIs were included in the study of Wu et al. It might explain the difference between the results [22].

PPIs may also have an impact on anti-cancer therapies based on the changes in the gut microbiome. The gut microbiome has an essential role in the immune system. Decreasing bacterial diversity may negatively affect immunity, thus response to anti-cancer therapies. However, this interaction is usually observed in patients with cancer treated with immune checkpoint inhibitors [23].

It is well known that PPIs may cause diarrhea [24]. Several mechanisms, such as microscopic colitis and Clostridium difficile infection, may play a role in PPI-related diarrhea [25, 26]. However, the rate of patients who reported diarrhea among PPI non-user and PPI user groups were similar in our study. Furthermore, the rates of all AEs were similar in PPI non-user and user groups.

A study by Xie et al. concluded that chronic PPI use increases mortality in the general population [27]. However, our results did not confirm this data. Indeed, our patients did not receive PPIs for the time required to see the chronic effects of those drugs.

Our study has several limitations, mainly based on its retrospective nature. We did not have data regarding antacids received without a prescription. Furthermore, we did not know the PPI indications of included patients. We did not assess the duration of PPI use and patients’ daily receiving time. It should be noted that the interval time of regorafenib and PPI receiving may affect the bioavailability of regorafenib. Despite the retrospective and observational nature of our study, we had more than one endpoint.

### Table 2: Best Response with regorafenib

|                    | PPI non-user  | PPI user  | \( P \) |
|--------------------|--------------|-----------|--------|
| \( n = 141 \) (%) | \( n = 131 \) (%) |           |        |
| Complete remission (CR) | 1 (0.7)      | 0 (0)     | 0.243  |
| Partial remission (PR)  | 27 (19.1)     | 22 (16.8) |         |
| Stable disease (SD)     | 46 (32.6)     | 35 (26.7) |         |
| Progressive disease (PD)| 40 (28.4)     | 51 (38.9) |         |
| Objective response rate (CR + PR) | 28 (19.8) | 22 (16.8) | 0.455  |
| Disease control rate (CR + PR + SD) | 74 (52.4) | 57 (43.5) | 0.066  |

*PPI* proton pump inhibitor
It might have affected the power of our results. Of note, we compared PPI non-user patients with all patients to exclude immortal time bias. It was a substantial strength of our study.

In conclusion, this study found no worse outcome in the combined use of PPI and regorafenib among patients with mCRC. Although it is hard to suggest that PPIs are entirely safe in those patients with the results of this retrospective study, they can be used in special conditions where they must be used.

Author contribution Emre Yekedüz: Conceptualization, data curation, methodology, visualization, formal analysis, writing–original draft. Mehmet Fatih Özbay: Data curation, writing–review and editing. Dilek Çağlayan: Data curation, writing–review and editing. Atilla Yıldırım: Data curation, writing–review and editing. Cihan Erol: Data curation, writing–review and editing. Hasan Çağrı Yıldırım: Data curation, writing–review and editing. Sezai Tunç: Data curation, writing–review and editing. Neslihan Özyurt: Data curation, writing–review and editing. Feyyaz Özdemir: Writing–review and editing, Supervision. Mehmet Ali Nahit Şendur: Writing, review and editing; supervision. Güngör Utkan: Conceptualization, data curation, writing–review and editing; supervision. Mehmet Artaç: Writing, review and editing; supervision. Şuayib Abdurrahman Işıkdoğan: Writing, review and editing; supervision. Mehmet Ali Nahit Şendur: Writing, review and editing; supervision. Feyyaz Özdemir: Writing–review and editing, Supervision. Mehmet Ali Nahit Şendur: Writing, review and editing; supervision. Abdurrahman İşikdoğan: Writing, review and editing; supervision. Saadettin Kılıçkap: Writing, review and editing; supervision. Yüksel Ürüm: Methodology, Writing, review and editing; supervision. Şüayib Yalçın: Writing, review and editing; supervision. Mehmet Artaç: Writing, review and editing; supervision. Hasan Şenol Coşkun: Writing, review and editing; supervision. Güngör Utkan: Conceptualization, methodology, data curation, writing (review and editing), supervision.

Data availability All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

Declarations

Competing interests The authors declare no competing interests.

Ethics approval This study was approved by the Ankara University Faculty of Medicine Human Research Ethics Committee, approval number İ9-601-21.

Consent to participate Waiver of informed consent was obtained from the Research Ethics Board due to the minimal risk to study subjects as well as the retrospective nature of this study.

Consent for publication Not applicable.

Conflict of interest The authors declare no competing interests.

References

1. Kudo M (2020) Recent advances in systemic therapy for hepatocellular carcinoma in an aging society: 2020 Update. Liver Cancer 9(6):640–662. https://doi.org/10.1159/000511001
2. Crona DJ, Keisler MD, Walko CM (2013) Regorafenib: a novel multitargeted tyrosine kinase inhibitor for colorectal cancer and gastrointestinal stromal tumors. Ann Pharmacother 47(12):1685–1696. https://doi.org/10.1177/1060028013509792
3. Shirley M, Keating GM (2015) Regorafenib: a review of its use in patients with advanced gastrointestinal stromal tumours. Drugs 75(9):1009–1017. https://doi.org/10.1007/s40265-015-0406-x
4. Gay C, Toullet D, Le Corre P (2017) Pharmacokinetic drug-drug interactions of tyrosine kinase inhibitors: a focus on cytochrome P450, transporters, and acid suppression therapy. Hematol Oncol 35(3):259–280. https://doi.org/10.1002/hon.2335
5. Yin OQ, Gallagher N, Fischer D, Demirtah A, Zhou W, Goler G, Schran H (2010) Effect of the proton pump inhibitor esomeprazole on the oral absorption and pharmacokinetics of nilotinib. J Clin Pharmacol 50(8):960–967. https://doi.org/10.1177/00223359103797961
6. van Leeuwen RWF, Jansman FGA, Hunfeld NG, Peric R, Reynolds AKL, Imholz ALT, Brouwers J, Aerts JG, van Gelder T, Mathijsen RHJ (2017) Tyrosine kinase inhibitors and proton pump inhibitors: an evaluation of treatment options. Clin Pharmacokinet 56(7):683–688. https://doi.org/10.1007/s40262-016-0503-3
7. Triadafilopoulos G, Roorda AK, Akiyama J (2013) Indications and safety of proton pump inhibitor drug use in patients with cancer. Expert Opin Drug Saf 12(5):659–672. https://doi.org/10.1517/14740338.2013.797961
8. Numico G, Fusco V, Franco P, Roila F (2017) Proton pump inhibitors in cancer patients: how useful are they? A review of the most common indications for their use. Crit Rev Oncol Hematol 111:144–151. https://doi.org/10.1016/j.critrevonc.2017.01.014
9. Herbrink M, Nuijen B, Schellens JH, Beijnen JH (2015) Variability in bioavailability of small molecular tyrosine kinase inhibitors. Cancer Treat Rev 41(5):412–422. https://doi.org/10.1016/j.ctrv.2015.03.005
10. Ohgami M, Kaburagi T, Kurosawa A, Doki K, Shiozawa T, Hizawa N, Homma M (2018) Effects of proton pump inhibitor coadministration on the plasma concentration of erlotinib in patients with non-small cell lung cancer. Ther Drug Monit 40(6):699–704. https://doi.org/10.1097/FTD.0000000000000552
11. van Leeuwen RW, van Gelder T, Mathijsen RH, Jansman FG (2014) Drug-drug interactions with tyrosine-kinase inhibitors: a clinical perspective. Lancet Oncol 15(8):e315–326. https://doi.org/10.1016/S1470-2045(13)70579-5
12. McAlister RK, Aston J, Pollack M, Du L, Koyama T, Chism DD (2018) Effect of Concomitant pH-elevating medications with pazopanib on progression-free survival and overall survival in patients with metastatic renal cell carcinoma. Oncologist 23(6):686–692. https://doi.org/10.1634/theoncologist.2017-0578

13. Wu CY, Ho HJ, Wu CY, Chen YJ, Lee TY, Hsu YC, Lin JT (2020) Association between proton pump inhibitor use and mortality in patients with hepatocellular carcinoma receiving tyrosine kinase inhibitor. Gut (Online ahead of print, 2020/09/11). https://doi.org/10.1136/gutjnl-2020-321932

14. de Man FM, Huussaarts K, de With M, Oomen-de Hoop E, de Bruijn P, van Halteren HK, van der Burg-de GN, Eskens F, van Gelder T, van Leeuwen RWF, Mathijsen RHJ (2019) Influence of the proton pump inhibitor esomeprazole on the bioavailability of regorafenib: a randomized crossover pharmacokinetic study. Clin Pharmacol Ther 105(6):1456–1461. https://doi.org/10.1002/cpt.1331

15. Wisinski KB, Cantu CA, Eickhoff J, Osterby K, Tavaarwerk AJ, Heideman J, Liu G, Wilding G, Johnston S, Kolesar JM (2015) Potential cytochrome P-450 drug-drug interactions in adults with metastatic solid tumors and effect on eligibility for Phase I clinical trials. Am J Health Syst Pharm 72(11):958–965. https://doi.org/10.2146/ajhp140591

16. (2013) Summary of Product Characteristics. In: Regorafenib, INN, 1 ed. European Medicines Agency

17. El Rouby N, Lima JJ, Johnson JA (2018) Proton pump inhibitors: from CYP2C19 pharmacogenetics to precision medicine. Expert Opin Drug Metab Toxicol 14(4):447–460. https://doi.org/10.1080/17425255.2018.1461835

18. Pauli-Magnus C, Rekersbrink S, Klotz U, Fromm MF (2001) Interaction of omeprazole, lansoprazole and pantoprazole with P-glycoprotein. Naunyn Schmiedebergs Arch Pharmacol 364(6):551–557. https://doi.org/10.1007/s00221-001-0489-7

19. Luciani F, Spada M, De Milito A, Molinari A, Rivoltini L, Montinaro A, Marra M, Lugini L, Logozzi M, Lozupone F, Federici C, Iessi E, Parmiani G, Arancia G, Belardelli F, Fais S (2004) Effect of proton pump inhibitor pretreatment on resistance of solid tumors to cytotoxic drugs. J Natl Cancer Inst 96(22):1702–1713. https://doi.org/10.1093/jnci/djh305

20. Fujita KI, Masuo Y, Yamazaki E, Shibutani T, Kubota Y, Nakamichi N, Sasaki Y, Kato Y (2017) Involvement of the transporters p-glycoprotein and breast cancer resistance protein in dermal distribution of the multikinase inhibitor regorafenib and its active metabolites. J Pharm Sci 106(9):2632–2641. https://doi.org/10.1016/j.xphs.2017.04.064

21. Koo MM, von Wagner C, Abel GA, McPhail S, Hamilton W, Rubin GP, Lyratzopoulos G (2018) The nature and frequency of abdominal symptoms in cancer patients and their associations with time to help-seeking: evidence from a national audit of cancer diagnosis. J Public Health (Oxf) 40(3):e388–e395. https://doi.org/10.1093/heapro/dfx188

22. Wu CY, Ho HJ, Wu CY, Chen YJ, Lee TY, Hsu YC, Lin JT (2020) Association between proton pump inhibitor use and mortality in patients with hepatocellular carcinoma receiving tyrosine kinase inhibitor. Gut. https://doi.org/10.1136/gutjnl-2020-321932

23. Raouf JL, Edeline J, Simmet V, Moreau-Bachelard C, Gilabert M, Frenel JS (2022) Long-term use of proton pump inhibitors in cancer patients: an opinion paper. Cancers (Basel) 14(5). https://doi.org/10.3390/cancers14051156

24. Shimura S, Hamamoto N, Yoshino N, Kushiyama Y, Fujishiro H, Komazawa Y, Furuta K, Ishihara S, Adachi K, Kinoshita Y (2012) Diarrhea caused by proton pump inhibitor administration: comparisons among lansoprazole, rabeprazole, and omeprazole. Curr Ther Res Clin Exp 73(3):112–120. https://doi.org/10.1016/jCURtheres.2012.03.002

25. Law EH, Badowski M, Hung YT, Weens K, Sanchez A, Lee TA (2017) Association Between proton pump inhibitors and microscopical colitis. Ann Pharmacother 51(3):253–263. https://doi.org/10.1177/1060028016673859

26. Trifan A, Stanciu C, Girelueanu I, Stoica OC, Singeap AM, Maxim R, Chiriac SA, Ciobica A, Boiculescu L (2017) Proton pump inhibitors therapy and risk of Clostridium difficile infection: systematic review and meta-analysis. World J Gastroenterol 23(35):6500–6515. https://doi.org/10.3748/wjg.v23.i35.6500

27. Xie Y, Bower B, Yan Y (2019) Estimates of all cause mortality and cause specific mortality associated with proton pump inhibitors among US veterans: cohort study. BMJ 365:i1580. https://doi.org/10.1136/bmj.i1580

Publisher’s Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Springer Nature or its licensor (e.g. society or other partner) holds exclusive rights to this article under a publishing agreement with the author(s) or other rightsholder(s); author self-archiving of the accepted manuscript version of this article is solely governed by the terms of such publishing agreement and applicable law.