Proton Pump Inhibitors and Survival in Patients With Colorectal Cancer Receiving Fluoropyrimidine-Based Chemotherapy

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ABSTRACT

Background: Concomitant use of proton pump inhibitors (PPIs) may negatively affect the efficacy of anticancer drugs such as fluoropyrimidines in patients with colorectal cancer (CRC). The primary objective of this study was to assess whether there is an association between concomitant PPI use and survival outcomes in patients with CRC treated with a fluoropyrimidine-based chemotherapy. **Patients and Methods:** A secondary analysis of 6 randomized controlled clinical trials in patients with advanced CRC was conducted using individual patient data through data-sharing platforms. The outcome measures were progression-free survival and overall survival in PPI users and nonusers. Subgroup analysis included the type of chemotherapy, capecitabine versus 5-FU, line of therapy, and addition of a vascular endothelial growth factor receptor inhibitor. Overall pooled hazard ratios (HRs) with 95% confidence intervals were calculated using a random effects model. **Results:** A total of 5,594 patients with advanced CRC across 6 trials and 11 trial arms were included; 902 patients were receiving a PPI at trial entry and initiation of chemotherapy. PPI use was significantly associated with worse overall survival (pooled HR, 1.20; 95% CI, 1.03–1.40; $P=.02$; I^2 for heterogeneity = 69%) and progression-free survival (overall pooled HR, 1.20; 95% CI, 1.05–1.37; $P=.009$; I^2 = 65%) after adjusting for clinical covariates. Furthermore, the association between concomitant PPI use and survival outcomes was similar across most treatment subgroups. **Conclusions:** We speculate that alterations in the gut microbiome, altered immune milieu within the tumor, and interactions through transporters are potential mechanisms behind this association between PPI use and chemotherapy in patients with CRC, which warrant further study. Concomitant use of PPIs is associated with worse survival outcomes in patients with CRC treated with fluoropyrimidine-based chemotherapy. Clinicians should cautiously consider the concomitant use of PPIs in such patients.

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Background

Proton pump inhibitors (PPIs) are one of the most commonly used drugs in patients with cancer, especially those with gastrointestinal malignancies.¹ In observational studies in noncancer populations, the long-term use of PPIs was associated with several adverse outcomes, including increased all-cause mortality, cardiovascular and renal diseases, dementia, infections, fractures, hypomagnesemia, and cancers.^{2,3} In contrast, in preclinical in vitro studies, PPIs were initially reported to improve the efficacy of some anticancer agents through direct anticancer effects and altered acidity within the tumor microenvironment.^{4–7} More recently, studies have described the potential for PPIs to adversely affect cancer outcomes when administered concomitantly with oral anticancer drugs such as kinase inhibitors.^{8–11} An increased intragastric pH from PPI use, with consequent reduced absorption of kinase inhibitors, was considered the mechanism responsible for this interaction.⁹ Changes in the gastrointestinal microbiome are another mechanism through which PPIs may affect cancer outcomes and the metabolism of drugs.¹²

Observational studies and retrospective analyses of trial data have also shown, albeit not consistently, that PPIs may decrease the efficacy of capecitabine, an oral fluoropyrimidine. As a result, patients with colorectal cancer (CRC), breast cancer, and other malignancies treated with capecitabine might have an increased risk of cancer recurrence and/or shorter survival.^{13–18} However, pharmacokinetic and in vitro studies have failed to identify the mechanisms of the interaction between PPIs and capecitabine.¹⁹ Furthermore, it is unclear whether the potentially negative effects of PPIs might also involve intravenously administered cytotoxic agents.

We sought to address these issues by assessing the association between concomitant PPI use and survival

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outcomes in patients with advanced CRC treated with a fluoropyrimidine-based chemotherapy regimens using data from 6 completed CRC clinical trials. Furthermore, we assessed whether this association differed between oral and systemically administered fluoropyrimidines and between other agents combined with the fluoropyrimidines.

Patients and Methods

Study Population

We performed a retrospective post hoc analysis using anonymized individual patient data from 6 clinical trials in patients with advanced CRC obtained through the data-sharing platforms Project Data Sphere²⁰ and Clinical Study Data Request²¹: the AVF2107g trial (ClinicalTrials.gov identifier: NCT00109070),²² the trial reported by Carrato et al²³ (NCT00457691), the HORIZON III trial (NCT00384176),²⁴ the VELOUR trial (NCT00561470),²⁵ the N016966 trial (NCT00069095),²⁶ and the RAISE trial (NCT01183780).²⁷ Sponsors of the Carrato et al, HORIZON III, and VELOUR trials released data from their respective control arms only, whereas sponsors for the other 3 trials provided data for both control and intervention arms. The Southern Adelaide Clinical Health Research ethics committee exempted review for this analysis.

Study Definitions

A fluoropyrimidine-based regimen was defined as combination anticancer therapy including at least one of the fluoropyrimidines 5-FU or capecitabine. Fluoropyrimidine-based chemotherapy, given as either first-line or second-line therapy, included either irinotecan or oxaliplatin as part of multiagent combination therapy with fluoropyrimidines and leucovorin. Concomitant vascular endothelial growth factor receptor inhibitor (VEGFi) therapies administered were bevacizumab (BEV) or ramucirumab (RAM), depending on the trial. Concomitant PPIs used were esomeprazole, lansoprazole, omeprazole, pantoprazole, or rabeprazole. PPI use was defined as treatment with any PPI at the time of initiation of the respective trial intervention, for a minimum of 7 days.

Data Collection and Outcomes

Data extracted were age at trial enrollment, sex, race, tumor response, time to progression, and survival time. The outcome measures were progression-free survival (PFS) and overall survival (OS) among PPI users and nonusers. PFS and tumor response were assessed using RECIST or RECIST version 1.1. Best overall response was defined as combined complete

and partial responses. Subgroup analysis for the association between PPI use and OS included the type of chemotherapy (oxaliplatin vs irinotecan), oral versus intravenous fluoropyrimidine administration, addition of VEGFi, and line of therapy.

Statistical Analysis

Analysis was conducted using cohorts with fluoropyrimidine-treated patients. Hazard ratios (HRs) with 95% confidence intervals for the association between PPI use and survival outcomes were estimated individually for each trial arm using Cox proportional hazards regression. HRs were adjusted for age, sex, race, ECOG performance status (PS), and serum CEA and lactate dehydrogenase (LDH) levels. Patients for whom all these covariates were available were included for adjusted analysis. Estimates were then pooled across all trials and arms using random-effects meta-analysis methods. A fixed-effect meta-analysis model was applied as a sensitivity analysis. Trial and summary HRs were visually displayed using forest plots, and statistical heterogeneity was described using the I^2 statistic. Adjustment for other contemporary confounding factors that affect survival, such as *RAS* mutations, right-side versus left-side primary, and liver versus other sites of metastases, were performed only for the RAISE trial data and not for other trials because of either the lack of collected data or data not being released by the sponsors. Analysis was performed using R version 3.4.3 (R Foundation for Statistical Computing). A P value $<.05$ was considered statistically significant.

Results

Data from 11 arms across 6 trials were available for analysis (supplemental eTable 1, available with this article at JNCCN.org). The N016966 trial had 4 arms, 2 trials had 2 arms, and the remainder had 1 arm. 5-FU with leucovorin and irinotecan (folinic acid/5-FU/irinotecan [FOLFIRI] or irinotecan/5-FU/leucovorin [IFL]) was the chemotherapy in all trials except N016966 and HORIZON III, in which a fluoropyrimidine was combined with oxaliplatin. Among the VEGFi therapies, BEV was combined with chemotherapy (BEV + IFL, BEV + folinic acid/5-FU/oxaliplatin [FOLFOX], or BEV + capecitabine/oxaliplatin [CAPOX]) in the AVF2107g, HORIZON III, and N016966 trials, whereas ramucirumab (RAM) was combined with chemotherapy (RAM + FOLFIRI) in the RAISE trial. Data on sunitinib or aflibercept treatment arms were not available for analysis. Most of the included trials were first-line interventions, whereas VELOUR and RAISE involved second-line therapies. From a total of 5,633 patients initially identified as intention to treat, data from 5,594 were available for further analysis as

Table 1. Demographics and Outcomes

Variable	Proton Pump Inhibitor Use, n (%)											
	AVF2107g ²²				N016966 ²⁶				Carrato et al ²³			
	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
Cohort size	159 (19.5)	654 (80.5)	327 (15.4)	1,792 (84.6)	43 (11.3)	336 (82.7)	111 (18.3)	494 (81.7)	258 (24.1)	814 (75.9)	88 (12.7)	602 (87.3)
Age, median (IQR), y	59 (52–65)	60 (52–69)	62 (54–69)	61 (53–67)	59 (52–66)	58 (51–65)	61 (55–70)	61 (54–68)	63 (54–69)	61 (53–67)	NA	NA
Sex												
Female	61 (38)	267 (41)	98 (40)	729 (41)	18 (42)	160 (48)	54 (48)	206 (41)	117 (45)	340 (42)	41 (47)	249 (41)
Male	98 (62)	387 (59)	145 (60)	1,062 (59)	25 (58)	176 (52)	59 (52)	291 (59)	141 (55)	474 (58)	47 (53)	353 (53)
Race												
White	125 (79)	520 (80)	225 (91)	1,485 (83)	29 (67)	216 (64)	104 (92)	416 (84)	206 (80)	609 (75)	85 (97)	559 (93)
Asian					10 (23)	103 (31)			42 (16)	172 (21)		
Black	18 (11)	77 (12)	18 (2)	32 (2)	3 (7)	5 (1)	8 (7)	19 (4)	7 (3)	23 (3)	2 (2)	38 (6)
Other/Missing	16 (10) ^a	57 (9) ^a	0 (0) ^a	275 (15) ^a	1 (2)	14 (4)	1 (1)	62 (12) ^a	3 (1)	10 (1)	1 (1)	5 (1)
ECOG PS												
0	84 (54)	376 (57)	122 (50)	1,023 (57)	21 (49)	126 (38)	57 (51)	291 (59)	105 (41)	433 (53)	48 (55)	343 (57)
1 or ≥1	75 (47)	277 (42)	121 (50)	762 (43)	13 (30)	162 (48)	54 (49)	203 (41)	152 (59)	378 (46)	40 (45)	257 (43)
Missing	0 (0)	1 (1)	0 (0)	7 (0.2)	0 (0)	2 (1)	0 (0)	0 (0)	19 (0.2)	3 (0.2)	0 (0)	0 (0)
CEA levels, median (IQR), ng/mL	NA	NA	37 (8–264)	31 (7–162)	31 (7–155)	59 (15–225)	NA	NA	46 (10–242)	30 (8–147)	NA	NA
LDH levels, median (IQR), U/L	225 (170–424)	219 (170–368)	342 (227–624)	346 (208–536)	324 (216–524)	412 (242–671)	392 (250–693)	307 (208–488)	High LDH, 122 (47%)	High LDH, 318 (39%)	High LDH, 17 (19%)	High LDH, 21 (3%)
Response												
CR	8 (5)	29 (4)	0 (0)	34 (2)	1 (2)	6 (2)	0 (0)	2 (<1)	0 (0)	2 (0.2)	0 (0)	11 (2)
PR	78 (49)	281 (43)	102 (42)	828 (46)	10 (23)	128 (38)	8 (7)	48 (10)	24 (9)	113 (14)	30 (34)	292 (49)
SD	58 (36)	227 (35)	74 (30)	578 (32)	20 (47)	159 (47)	62 (55)	320 (64)	151 (59)	476 (58)	16 (18)	61 (10)
PD	12 (8)	49 (7)	32 (13)	147 (8)	6 (14)	29 (9)	28 (25)	99 (20)	66 (26)	155 (19)	40 (45)	219 (36)
Missing/NE	3 (2)	68 (10)	35 (14)	205 (11)	6 (14)	14 (4)	15 (14)	28 (6)	17 (7)	68 (8)	2 (2)	19 (3)
PFS, median (95% CI), mo	9.7 (8.3–10.8)	8.0 (7.7–8.3)	7.6 (6.9–8.3)	8.4 (8.2–8.7)	7.4 (6.5–8.7)	9.3 (8.6–10.6)	3.1 (2.8–4.5)	5.5 (5.1–6.2)	4.2 (3.7–5.8)	5.5 (5.4–5.7)	8.4 (7.6–10.3)	10.9 (10.0–11.0)
OS, median (95% CI), mo	19.8 (17.2–25.3)	16.9 (15.8–18.1)	18.4 (16.6–19.8)	19.9 (19.1–20.8)	14.7 (10.1–NA)	21 (19.2–NA)	9.3 (7.7–11.8)	12.5 (11.8–13.9)	10.6 (9.6–11.6)	13.4 (12.6–14.6)	18.4 (13.1–NA)	21.3 (19.6–25.7)

Abbreviations: CEA, carcinoembryonic antigen; CR, complete response; IQR, interquartile range; LDH, lactate dehydrogenase; NA, not available; NE, not evaluable; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; PS, performance status; SD, stable disease.

^aIncludes Asian individuals.

per-protocol treatment population. Their baseline characteristics are shown in Table 1. Most (58.8%) were men, and the median age was 60 years.

PPI Use

A total of 902 patients were receiving a PPI at the start of the trial chemotherapy intervention. The proportion of PPI users ranged between 11.3% and 25.8% across the trial cohorts (supplemental eTable 2). PPI users had a similar median age and were more likely to be White compared with the non-PPI users. Omeprazole was the most frequently used PPI (39%).

Pooled Association of PPI Use and Survival Outcomes

Pooled analysis of the crude association between PPI use and survival outcomes indicated that PPI use was associated with statistically significant worse OS (random effects pooled HR, 1.23; 95% CI, 1.07–1.43) (supplemental eFigure 1) and PFS (HR, 1.22; 95% CI, 1.07–1.38) (supplemental eFigure 2). The association between PPI use and survival outcomes was then adjusted for age, sex, race, ECOG PS, and baseline CEA and LDH levels, when available, in 5,262 participants with complete data for the adjustment variables. Figure 1 shows the pooled estimates of adjusted HRs for OS between PPI users and nonusers during fluoropyrimidine-based chemotherapy. There was a statistically significant association between PPI use and worse OS outcomes with fluoropyrimidine-based chemotherapy (random-effects adjusted HR, 1.20; 95% CI, 1.03–1.40; $P=.02$) with substantial heterogeneity in effect size between studies ($I^2 = 69\%$). A sensitivity analysis using a fixed-effect model estimated a similar effect size (pooled HR, 1.20; 95% CI, 1.10–1.30). Based on pooled analysis, a significant effect of PPI use on PFS with fluoropyrimidine-based chemotherapy (overall

pooled HR, 1.20; 95% CI, 1.05–1.37; $P=.009$; $I^2 = 65\%$) was observed (Figure 2).

Subgroup Analyses

Subgroup analyses were performed to assess whether the adjusted association between concomitant PPI use and survival outcomes differed across key subgroups. Generally, estimates of association between PPI use and survival outcomes were relatively consistent across treatment subgroups for both OS and PFS (Figure 3). There was little evidence to support heterogeneity of effect size based on the chemotherapy agent (irinotecan vs oxaliplatin) combined with the fluoropyrimidine (supplemental eFigure 3A), the addition of a VEGFi to chemotherapy (supplemental eFigure 3B), or the line of therapy (supplemental eFigure 3C).

However, the comparison of subgroups treated with capecitabine versus intravenous 5-FU indicated a trend toward statistically significant heterogeneity of PPI effect size ($P_{\text{heterogeneity}} = .08$) (supplemental eFigure 3D). This exploratory analysis highlights that, for patients treated with capecitabine, the concomitant use of PPI may not be associated with inferior OS and PFS and that further study is warranted with respect to effects of PPI use in these subgroups.

PPI Use and Response Rates

Complete response to the treatment intervention was uncommon (<5%). Wide variations across trials were observed in partial response, stable disease, and progressive disease with ranges of 7% to 49%, 10% to 64%, and 7% to 45%, respectively (Table 1). Although the odds ratios (ORs) for objective response rates with concomitant PPI use were low in most cohorts, there was no statistically significant difference in response rates between PPI users and non-PPI users, except in the HORIZON III trial (OR, 0.51; 95% CI, 0.32–0.82) (supplemental eTable 3). No significant effect of

Figure 1. Pooled adjusted analysis of the association between PPI use and OS.

Abbreviations: BEV, bevacizumab; CAPOX, capecitabine/oxaliplatin; FOLFIRI, 5-FU/folinic acid/irinotecan; FOLFOX, 5-FU/folinic acid/oxaliplatin; HR, hazard ratio; IFL, irinotecan/leucovorin/5-FU; OS, overall survival; PPI, proton pump inhibitor; RAM, ramucirumab; Tx, treatment.

Figure 2. Pooled adjusted analysis of the association between concomitant PPI use and PFS.

Abbreviations: BEV, bevacizumab; CAPOX, capecitabine/oxaliplatin; FOLFIRI, 5-FU/folinic acid/irinotecan; FOLFOX, 5-FU/leucovorin/oxaliplatin; HR, hazard ratio; IFL, irinotecan/leucovorin/5-FU; PFS, progression-free survival; PPI, proton pump inhibitor; RAM, ramucirumab; Tx, treatment.

concomitant use of PPI on adjusted overall response rates was observed (OR, 0.83; 95% CI, 0.66–1.05; $P=.05$; $P = 45\%$) (supplemental eFigure 4).

Additional Exploratory Analyses

To explore whether the association arose from acid suppression or was specifically related to the use of a PPI, the effect of concomitant use of histamine H₂-receptor antagonists (H₂RAs) with fluoropyrimidine-based chemotherapy was evaluated in the same cohort of patients. A total of 362 patients (6.8%) who received a concomitant H₂RA were identified. There was no significant association between concomitant H₂RA use and OS (adjusted HR, 0.98; 95% CI, 0.86–1.12), PFS (adjusted HR, 0.97; 95% CI, 0.85–1.11), and response rates (adjusted OR, 1.18; 95% CI, 0.91–1.52) (supplemental eFigures 5, 6, and 7; supplemental eTable 4).

Additional contemporary prognostic factors, such as right-side versus left-side primary, *KRAS* mutation, and liver metastases, were available only for the RAISE trial. Hence, an exploratory analysis was performed by adding these variables to the other confounding factors just in these arms. After adjusting for multiple factors, the concomitant use of PPI had significantly worse OS and PFS, but not in the FOLFIRI + RAM arm (supplemental eTable 5).

Discussion

Results of this pooled analysis of 6 clinical trials in patients with advanced CRC receiving fluoropyrimidine-based combination chemotherapy indicate that concomitant PPI use is associated with significantly worse survival outcomes. This association was not seen with concomitant use of other acid-suppressing agents, such as H₂RAs, indicating some degree of specificity with PPI use.

Figure 3. Association between concomitant PPI use and survival outcomes, by subgroup.

Abbreviations: HR, hazard ratio; OS, overall survival; PFS, progression-free survival; PPI, proton pump inhibitor; VEGFi, vascular endothelial growth factor receptor inhibitor.

Substantial controversy remains regarding the potential negative effect of concomitant PPI use on cancer outcomes in patients undergoing fluoropyrimidine-based (especially capecitabine-based) chemotherapy.^{13,18,19,28,29} A retrospective series of 671 patients with CRC (474 receiving concomitant PPI) reported improved survival in the FOLFOX-treated cohort but not in the CAPOX-treated cohort.²⁹ However, using data from a prospective trial in patients with gastroesophageal cancers, Chu et al¹⁴ reported worse outcomes when PPIs were used concomitantly with CAPOX. Worse outcomes when PPIs were administered with capecitabine were also reported by other authors.^{16,17} In contrast, subgroup analyses in the present study did not find a significant negative association with survival (crude or adjusted) for concomitant PPI use across 980 patients treated with CAPOX (with and without BEV). However, there was a negative association with survival in the remaining patients treated with a range of 5-FU-based therapies. Our study did not include a cohort with monotherapy interventions with fluoropyrimidines, which prevents us from drawing any conclusions on the effect of PPIs on monotherapy. Moreover, the conflicting results between studies regarding an interaction between PPI use and add-on chemotherapy drugs indicate that the interaction is complex and may be context-specific. Prospective studies with complete data on PPI use, including duration of PPI use and treatment adherence, will help improve understanding of the association between PPI use of treatment outcomes. Similarly, the association between concomitant PPI use on the efficacy of other CRC drugs, such as anti-epidermal growth factor receptor (EGFR) inhibitors and trifluridine/tipiracil, warrants further evaluation.

Previous studies have identified that PPIs may have direct anticancer effects and also improve chemosensitivity of cancer cells by increasing extracellular pH.^{5,6,29} However, the concentration required to induce CRC cell death may not be reached in vivo.³⁰ On the contrary, as we have observed in this study, concomitant PPI use may be associated with negative effects on survival across the spectrum of combination chemotherapy with 5-FU. Although the lack of association observed with oral capecitabine (CAPOX or CAPOX + BEV) is intriguing, this association was based on data from a single study only (N016966), and the result of the test for heterogeneity did not reach statistical significance.

The mechanistic basis for the negative effect of concomitant PPI use is unclear. We speculate that PPIs may inhibit uptake transporters in tumor cells as one possible mechanism. It is well established that the chemotherapy drugs evaluated in this study are substrates for various uptake transporters, some of which

are expressed in CRC cells. PPIs, especially omeprazole, have been reported to inhibit several transporters at therapeutic concentrations. For example, PPIs inhibit oxaliplatin uptake transporters such as organic anion transporters (OATs 1 and 3) and copper transporters,³¹ whereas irinotecan and its active form, SN-38, inhibit transporters such as organic anion-transporting polypeptides (OATP1A/1B).³² However, PPIs may increase the expression of human equilibrative nucleoside transporter 1 (hENT1), potentially associated with poor response to fluoropyrimidines.^{33,34} It is also unclear whether there is a differential effect of PPIs on the intracellular uptake of oral versus intravenous fluoropyrimidines. In addition, the pH-dependent uptake of chemotherapy drugs is well recognized.³⁵ It is possible that PPIs reduce the intratumoral concentration of cytotoxic drugs through the inhibition of uptake transporters and altered pH in the tumor microenvironment. This hypothesis requires further testing in preclinical studies.

Although chronic PPI use is associated with increased all-cause mortality in the general population,³ our study shows that both PFS and OS are negatively affected by concomitant PPI use with chemotherapy in patients with CRC. The negative association between PFS and PPI use during FOLFIRI chemotherapy, especially in the second-line setting, but not with IFL, indicates a possible interaction between irinotecan scheduling and antitumor response. A previous drug-drug interaction trial with short-term omeprazole and single-agent irinotecan did not show any significant changes in pharmacokinetic parameters and toxicities of irinotecan.³⁶ Hence, it is likely that other mechanisms, such as alteration in gut microbiome, changes in tumor microenvironment and immune milieu by the PPIs, and their subsequent effects on irinotecan pharmacokinetics and pharmacodynamics, may play a role.^{4,7,37} Furthermore, the doses of 5-FU used in the IFL regimen versus FOLFIRI were different: a 500-mg/m² bolus dose weekly for 4 out of 6 weeks was used in the IFL regimen, whereas both a bolus dose and an infusional dose of 5-FU were administered in the FOLFIRI regimen. The negative association was seen in the regimen with the infusion but not with the bolus schedule. The potential interaction between the dose and schedule of 5-FU and concomitant PPI should also be explored in future studies. Moreover, PPI-related microbiome changes can alter cancer outcomes through immunosuppression, increased drug metabolism, altered autophagy, or immunosuppression, thereby increasing resistance to 5-FU and oxaliplatin.^{38–40} Further in vitro and in vivo studies will be required to confirm these findings.

This study assessed the effect of PPI use in patients with CRC undergoing fluoropyrimidine-based chemotherapy.

It is unclear whether the negative effects of PPI use occur in other cancers and/or with other drugs, such as immunotherapies, and other targeted agents, such as EGFR inhibitors. Moreover, the use of PPIs may reflect the presence of other coexisting confounders, such as symptomatic advanced cancer with liver metastases, that may increase the need for PPIs. Future studies should consider addressing these gaps by exploring PPI use in early-stage CRC, non-CRC types, and other treatment settings.

Our study has significant strengths, including a relatively large cohort size, comprehensive prospective clinical trial data from individual patients, analysis using individual participant data, and pooled data from trials that included a variety of treatment regimens. However, it also has several limitations, including lack of analysis of the effect of comorbidities on OS and the impact of chemotherapy dose modifications; lack of information on the duration of PPI use before the start of the trial, dose/adherence to PPIs during the trial, initiation of PPIs after chemotherapy initiation, and the influence of other acid-suppressing drugs; lack of access to data from other trials with anti-EGFR inhibitors; and technical issues with data merging from various sharing platforms. None of the included trials had no-chemotherapy or no-fluoropyrimidine arms for evaluation, thus precluding direct comparison and exploration of the prognostic relationship of concomitant PPI use. Further studies including an analysis of PPI use and survival outcomes in patients with metastatic CRC who are not receiving fluoropyrimidine-based chemotherapy are warranted. Such relationships could also be explored in other cancer types. Furthermore, most patients included in the trials were White individuals from the United States and Europe. Previous studies have reported regional differences in the safety of fluoropyrimidines, with East Asian individuals having the lowest incidence of adverse effects when compared with the US population, highlighting the need to evaluate the effects of concomitant PPI use among patients with different racial backgrounds and countries of origin.⁴¹

Although we adjusted for 6 clinically significant covariates in the calculation of pooled estimates, other contemporary prognostic factors such as right-sided versus left-sided location of the primary and molecular

biomarkers such as *RAS* mutations and microsatellite instability were not uniformly available for inclusion. Moreover, we did not evaluate the association between PPI use and adverse effects during fluoropyrimidine-based chemotherapy or the actual cause of death to assess competing risk-based outcomes. Although future studies should consider these issues, accessing data derived from real-world use of PPIs during chemotherapy treatment may also provide further insights into this association.

Conclusions

Using data from 6 clinical trials including >5,000 patients with advanced CRC treated with fluoropyrimidine-based combination chemotherapy, we showed that concomitant use of PPIs was associated with worse OS and PFS. This association was significant after adjusting for age, sex, race, ECOG PS, and baseline CEA and LDH levels. The effect size of the association between PPI use and survival was similar across treatment subgroups, with the possible exception of capecitabine-based therapies, which require further evaluation. Pending identification of the mechanisms involved in this interaction and further confirmation in future studies, clinicians should cautiously consider the concomitant use of PPIs in patients with advanced CRC treated with fluoropyrimidine-based combination chemotherapy.

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Supplemental online content for:

Proton Pump Inhibitors and Survival in Patients With Colorectal Cancer Receiving Fluoropyrimidine-Based Chemotherapy

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eFigure 1: Pooled OS Using Unadjusted Hazard Ratios

eFigure 2: Pooled PFS Using Unadjusted Hazard Ratios

eFigure 3: Subgroup Analysis for OS Using Adjusted Hazard Ratios

eFigure 4: Pooled Response Rates and Concomitant PPI Use

eFigure 5: Pooled Adjusted OS and Concomitant H2RA Use

eFigure 6: Pooled Adjusted PFS and Concomitant H2RA Use

eFigure 7: Pooled Adjusted OR for Response Rates and Concomitant H2RA Use

eTable 1: Included Trials of PPIs and Fluoropyrimidines

eTable 2: Proton Pump Inhibitor Use

eTable 3: Proton Pump Inhibitor Use and Outcomes

eTable 4: H2RA Use and Outcomes

eTable 5: PPI Use and Survival Outcomes in the RAISE Trial With Contemporary Prognostic Factors

eFigure 1. Pooled OS using unadjusted HRs.

Abbreviations: BEV, bevacizumab; CAPOX, capecitabine/oxaliplatin; FOLFIRI, 5-FU/folinic acid/irinotecan; FOLFOX, 5-FU/leucovorin/oxaliplatin; HR, hazard ratio; IFL, irinotecan/leucovorin/5-FU; OS, overall survival; PPI, proton pump inhibitor; RAM, ramucirumab; Tx, treatment.

eFigure 2. Pooled PFS using unadjusted HRs.

Abbreviations: BEV, bevacizumab; CAPOX, capecitabine/oxaliplatin; FOLFIRI, 5-FU/folinic acid/irinotecan; FOLFOX, 5-FU/leucovorin/oxaliplatin; HR, hazard ratio; IFL, irinotecan/leucovorin/5-FU; PFS, progression-free survival; PPI, proton pump inhibitor; RAM, ramucirumab; Tx, treatment.

A **B**

eFigure 3. Subgroup analysis of OS using aHRs: (A) concomitant chemotherapy, (B) concomitant VEGFRi use, (C) by line of use, and (D) capecitabine vs 5-FU.

Abbreviations: aHR, adjusted hazard ratio; BEV, bevacizumab; CAPOX, capecitabine/oxaliplatin; FOLFIRI, 5-FU/folinic acid/irinotecan; FOLFOX, 5-FU/leucovorin/oxaliplatin; HR, hazard ratio; IFL, irinotecan/leucovorin/5-FU; OS, overall survival; PPI, proton pump inhibitor; RAM, ramucirumab; Tx, treatment; VEGFRi, vascular endothelial growth factor receptor inhibitor.

(continued on next page)

C

D

eFigure 3 (continued). Subgroup analysis of OS using aHRs: (A) concomitant chemotherapy, (B) concomitant VEGFRi use, (C) by line of use, and (D) capecitabine vs 5-FU.

Abbreviations: aHR, adjusted hazard ratio; BEV, bevacizumab; CAPOX, capecitabine/oxaliplatin; FOLFIRI, 5-FU/folinic acid/irinotecan; FOLFOX, 5-FU/leucovorin/oxaliplatin; HR, hazard ratio; IFL, irinotecan/leucovorin/5-FU; OS, overall survival; PPI, proton pump inhibitor; RAM, ramucirumab; Tx, treatment; VEGFRi, vascular endothelial growth factor receptor inhibitor.

eFigure 4. Pooled response rates and concomitant PPI use.
Abbreviations: aRR, adjusted response rate; BEV, bevacizumab; CAPOX, capecitabine/oxaliplatin; FOLFIRI, 5-FU/folinic acid/irinotecan; FOLFOX, 5-FU/leucovorin/oxaliplatin; IFL, irinotecan/leucovorin/5-FU; OR, odds ratio; PPI, proton pump inhibitor; RAM, ramucirumab; Tx, treatment.

eFigure 5. Pooled adjusted OS and concomitant H2RA use.
Abbreviation: BEV, bevacizumab; CAPOX, capecitabine/oxaliplatin; FOLFIRI, 5-FU/folinic acid/irinotecan; FOLFOX, 5-FU/leucovorin/oxaliplatin; H2RA, histamine H2-receptor antagonists; HR, hazard ratio; IFL, irinotecan/leucovorin/5-FU; RAM, ramucirumab; Tx, treatment.

eFigure 6. Pooled adjusted PFS and concomitant H2RA use.

Abbreviation: BEV, bevacizumab; CAPOX, capecitabine/oxaliplatin; FOLFIRI, 5-FU/folinic acid/irinotecan; FOLFOX, 5-FU/leucovorin/oxaliplatin; H2RA, histamine H2-receptor antagonists; HR, hazard ratio; IFL, irinotecan/leucovorin/5-FU; PFS, progression-free survival; RAM, ramucirumab; Tx, treatment.

eFigure 7. Pooled adjusted OR for response rates and concomitant H2RA use.

Abbreviation: BEV, bevacizumab; CAPOX, capecitabine/oxaliplatin; FOLFIRI, 5-FU/folinic acid/irinotecan; FOLFOX, 5-FU/leucovorin/oxaliplatin; H2RA, histamine H2-receptor antagonists; HR, hazard ratio; IFL, irinotecan/leucovorin/5-FU; OR, odds ratio; RAM, ramucirumab; Tx, treatment.

eTable 1. Included Trials of PPIs and Fluoropyrimidines

Trial	Population	Treatment Intervention	Cohort Size n	PPI Use n (%)	Comments
First-line trials					
AVF2107g ¹	Advanced CRC, treatment-naïve	IFL+ placebo IFL + BEV	411 402	69 (16.7) 89 (22.1)	All arms included
N016966 ²	Advanced CRC, treatment-naïve	FOLFOX-4 ± placebo CAPOX ± placebo FOLFOX-4 + BEV CAPOX + BEV	668 667 350 350	123 (18.4) 99 (14.8) 47 (13.4) 53 (15.1)	All arms included
Carrato et al ³	Advanced CRC, treatment-naïve	FOLFIRI	386	43 (11.1)	Control arm only
HORIZON III ⁴	Advanced CRC, treatment-naïve	FOLFOX-4 + BEV	713	88 (12.3)	Control arm only
Second-line trials					
VELOUR ⁵	Prior oxaliplatin chemotherapy	FOLFIRI	614	113 (18.4)	Control arm only
RAISE ⁶	Prior oxaliplatin chemotherapy	FOLFIRI + placebo FOLFIRI + RAM	536 536	136 (25.3) 122 (22.7)	All arms included

Abbreviations: BEV, bevacizumab; CAPOX, capecitabine/oxaliplatin; CRC, colorectal cancer; FOLFIRI, 5-FU/folinic acid/irinotecan; FOLFOX, 5-FU/leucovorin/oxaliplatin; IFL, irinotecan/leucovorin/5-FU; PPI, proton pump inhibitor; RAM, ramucirumab.

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eTable 2. Proton Pump Inhibitor Use

Proton Pump Inhibitor	AVF2107g ¹ n (%)	N016966 ² n (%)	Carrato et al ³ n (%)	HORIZON III ⁴ n (%)	VELOUR ⁵ n (%)	RAISE ⁶ n (%)
Total, N	159	327	43	88	113	258
Esomeprazole	29 (18.2)	34 (10.3)	6 (13.9)	10 (11.4)	13 (11.5)	18 (6.9)
Lansoprazole	60 (37.7)	48 (14.6)	3 (6.9)	15 (17.0)	17 (15.0)	47 (18.2)
Omeprazole	46 (28.9)	115 (35.1)	22 (51.1)	36 (40.9)	59 (52.2)	119 (46.1)
Pantoprazole	31 (19.4)	38 (11.6)	12 (2.9)	22 (24.9)	21 (18.5)	56 (21.7)
Rabeprazole	10 (6.2)	8 (2.4)	0 (0)	5 (5.7)	3 (2.6)	18 (6.9)

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eTable 3. Proton Pump Inhibitor Use and Outcomes

Trial	Unadjusted OS HR (95% CI)	Unadjusted PFS HR (95% CI)	Unadjusted Objective RR OR (95% CI)
AVF2107g ¹			
IFL	1.09 (0.82–1.46)	0.86 (0.63–1.16)	1.26 (0.74–2.15)
IFL + BEV	0.81 (0.60–1.09)	0.96 (0.73–1.27)	1.59 (0.98–2.55)
N016966 ²			
CAPOX	0.95 (0.75–1.22)	0.94 (0.75–1.17)	0.80 (0.52–1.23)
FOLFOX	1.18 (0.96–1.46)	1.17 (0.96–1.43)	0.79 (0.54–1.18)
CAPOX + BEV	1.02 (0.73–1.43)	1.15 (0.85–1.55)	1.01 (0.56–1.81)
FOLFOX + BEV	1.37 (0.98–1.91)	1.58 (1.15–2.17)	0.73 (0.39–1.35)
Carrato et al ³			
FOLFIRI	1.82 (1.18–2.82)	1.96 (1.38–2.78)	0.52 (0.25–1.06)
VELOUR ⁴			
FOLFIRI	1.32 (1.05–1.67)	1.22 (0.97–1.54)	0.66 (0.30–1.45)
RAISE ⁵			
FOLFIRI	1.79 (1.43–2.23)	1.41 (1.15–1.72)	0.66 (0.35–1.25)
FOLFIRI + RAM	1.24 (0.97–1.59)	1.22 (0.98–1.51)	0.56 (0.28–1.11)
HORIZON III ⁶			
FOLFOX + BEV	1.49 (1.07–2.09)	1.44 (1.10–1.88)	0.51 (0.32–0.82)

Abbreviations: BEV, bevacizumab; CAPOX, capecitabine/oxaliplatin; FOLFIRI, 5-FU/folinic acid/irinotecan; FOLFOX, 5-FU/leucovorin/oxaliplatin; HR, hazard ratio; IFL, irinotecan/leucovorin/5-FU; OS, overall survival; PFS, progression-free survival; RAM, ramucirumab; RR, response rate.

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eTable 4. H2RA Use and Outcomes

Trial	Adjusted OS HR (95% CI)	Adjusted PFS HR (95% CI)	Adjusted Objective RR OR (95% CI)
AVF2107g ¹ (n=129; 5.9%)			
IFL	0.87 (0.64–1.18)	0.74 (0.55–1.02)	1.45 (0.84–2.50)
IFL + BEV	0.86 (0.62–1.20)	0.81 (0.59–1.12)	1.53 (0.87–2.67)
N016966 ² (n=120; 5.9%)			
CAPOX	0.95 (0.66–1.38)	0.83 (0.59–1.16)	1.53 (0.79–2.98)
FOLFOX	1.19 (0.83–1.71)	1.19 (0.86–1.66)	1.48 (0.73–2.97)
CAPOX + BEV	0.77 (0.47–1.26)	1.07 (0.70–1.65)	0.92 (0.39–2.16)
FOLFOX + BEV	0.94 (0.54–1.64)	0.99 (0.60–1.65)	0.81 (0.30–2.16)
Carrato et al ³ (n=16; 4.2%)			
FOLFIRI	1.39 (0.56–3.48)	1.70 (0.88–3.27)	0.56 (0.16–1.92)
VELOUR ⁴ (n=17; 2.8%)			
FOLFIRI	1.02 (0.59–1.75)	1.14 (0.64–2.03)	0.62 (0.08–4.95)
RAISE ⁵ (n=65; 6.1%)			
FOLFIRI	0.84 (0.47–1.51)	0.91 (0.55–1.52)	0.37 (0.05–2.88)
FOLFIRI + RAM	1.42 (0.85–2.38)	1.32 (0.84–2.07)	0.30 (0.04–2.30)
HORIZON III ⁶ (n=15; 2.2%)			
FOLFOX + BEV	1.06 (0.43–2.63)	1.17 (0.60–2.29)	0.51 (0.16–1.69)

Abbreviations: BEV, bevacizumab; CAPOX, capecitabine/oxaliplatin; FOLFIRI, 5-FU/folinic acid/irinotecan; FOLFOX, 5-FU/leucovorin/oxaliplatin; H2RA, histamine H2-receptor antagonists; HR, hazard ratio; IFL, irinotecan/leucovorin/5-FU; OS, overall survival; PFS, progression-free survival; RAM, ramucirumab; RR, response rate.

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eTable 5. PPI Use and Survival Outcomes in the RAISE Trial¹ With Contemporary Prognostic Factors

RAISE Trial Cohorts	Adjusted OS		Adjusted PFS	
	HR (95% CI)	P Value	HR (95% CI)	P Value
FOLFIRI alone				
PPI use	1.63 (1.27–2.09)	.0001	1.35 (1.07–1.69)	.01
Age	0.99 (0.98–1.00)	.30	0.99 (0.80–0.99)	.02
Female	1.07 (0.85–1.34)	.57	1.05 (0.85–1.28)	.67
White race	1.30 (1.01–1.67)	.04	0.87 (0.70–1.10)	.23
ECOG PS	1.33 (1.06–1.67)	.01	1.18 (0.96–1.45)	.11
Right-sided primary	1.07 (0.84–1.35)	.60	1.02 (0.83–1.26)	.84
Liver metastases	0.82 (0.60–1.13)	.23	1.11 (0.84–1.45)	.46
KRAS wild-type	0.89 (0.71–1.11)	.29	0.97 (0.80–1.12)	.79
LDH >ULN	1.37 (1.07–1.76)	.01	1.16 (0.93–1.46)	.18
ALP >ULN	1.35 (1.06–1.73)	.01	1.28 (1.02–1.60)	.03
CEA ≥200 µg/L	1.52 (1.16–2.01)	.002	1.34 (1.03–1.75)	.03
FOLFIRI + RAM				
PPI use	1.16 (0.88–1.53)	.29	1.22 (0.96–1.55)	.11
Age	0.99 (0.98–1.00)	.08	0.99 (0.98–1.00)	.45
Female	0.79 (0.62–1.00)	.05	0.84 (0.68–1.03)	.87
White race	1.25 (0.96–1.63)	.10	0.92 (0.73–1.16)	.49
ECOG PS	1.23 (0.97–1.50)	.08	1.17 (0.96–1.44)	.12
Right-sided primary	1.40 (1.08–1.80)	.009	1.18 (0.94–1.48)	.15
Liver metastases	0.75 (0.53–1.03)	.08	0.91 (0.69–1.12)	.54
KRAS wild-type	0.72 (0.57–0.91)	.006	0.87 (0.71–1.06)	.16
LDH >ULN	2.47 (1.90–3.20)	<.0001	1.58 (1.27–1.97)	<.0001
ALP >ULN	1.55 (1.19–2.01)	.001	1.13 (0.89–1.42)	.31
CEA ≥200 µg/L	1.43 (1.09–1.89)	.01	1.35 (1.05–1.73)	.02

Abbreviations: ALP, alkaline phosphatase; FOLFIRI, 5-FU/folinic acid/irinotecan; HR, hazard ratio; LDH, lactate dehydrogenase; OS, overall survival; PFS, progression-free survival; PPI, proton pump inhibitor; PS, performance status; RAM, ramucirumab; ULN, upper limit of normal.

References

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