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

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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 showed that PPI was not associated with worse survival outcomes and safety profile in patients with mCRC treated with regorafenib.

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, 6, 12] 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.[3] 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.[16, 19]

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.[9, 13] However, acid suppression with PPIs may affect the solubility and bioavailability of TKIs.[4, 10, 15] 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, 15]

However, there were conflicting results regarding the effect of PPIs and TKIs 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 events (AEs) profile, no difference was observed between the PPI user and non-user groups.[8] Conversely, a study including patients with HCC treated with TKIs showed increased mortality in the PPI user group. 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.[2] 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 AEs 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 Ev*ents” (CTCAE version 4.03) was used to evaluate AEs.

Statistical Analysis

For descriptive analyses, median with interquartile range (IQR) for normally distributed continuous variables, mean standard deviation for non-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. 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.

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 **Figures 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).

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.**

Table 1. Baseline Characteristics					
	PPI Non-user		**PPI User**		***p***
	n=141	***(%)***	**n=131**	***(%)***	
Age at Starting Regorafenib years median (IQR)	61 (52-67)		57 (48-65)		0.101
Sex					0.063
Male	77	*(54.6)*	86	*(65.6)*	
Female	64	*(45.4)*	45	*(34.4)*	
ECOG Performance Status					0.805
0-1	102	*(72.3)*	93	*(71.0)*	
2	39	*(27.7)*	38	*(29.0)*	
Tumor Location					0.389
Right Colon	24	*(17.0)*	25	*(19.1)*	
Left Colon	50	*(35.5)*	53	*(40.5)*	
Rectum	63	*(44.7)*	47	*(35.9)*	
Missing	4	*(2.8)*	6	*(4.6)*	
Histological Subtype					*0.085*
Non-mucinous	121	*(85.8)*	121	*(92.4)*	
Mucinous	20	*(14.2)*	10	*(7.6)*	
KRAS or NRAS or BRAF Status					*0.609*
Mutant Type	73	*(51.8)*	67	*(51.1)*	
Wilde Type	51	*(36.2)*	43	*(32.8)*	
Missing	17	*(12.0)*	21	*(16.0)*	
First Site of Metastasis					*0.195*
Liver	66	*(46.8)*	70	*(53.4)*	
Lung	19	*(13.5)*	12	*(9.2)*	
Peritoneal	13	*(9.2)*	9	*(6.8)*	
Intraabdominal Lymph Node	9	*(6.4)*	4	*(3.1)*	
Other	3	*(2.1)*	0	*(0)*	

Multiple	31	*(22.0)*	36	*(27.5)*	
PPI Subtypes	*N/A*				*N/A*
Pantoprazole			53	*(40.5)*	
Esomeprazole			28	*(21.4)*	
Lansoprazole			19	*(14.5)*	
Rabeprazole			3	*(2.3)*	
Initial Dose of Regorafenib					*0.574*
80 mg	29	*(20.6)*	23	*(17.6)*	
120 mg	45	*(31.8)*	51	*(38.9)*	
160 mg	60	*(42.6)*	57	*(43.5)*	
Missing	7	*(5.0)*	0	*(0)*	
Presence of Dose Reduction					*0.142*
No	93	*(66.0)*	102	*(77.9)*	
Yes	40	*(28.3)*	29	*(22.1)*	
Missing	8	*(5.7)*	0	*(0.0)*	
Treatment Line of Regorafenib					*0.106*
3	71	*(50.4)*	82	*(62.6)*	
4	60	*(42.6)*	40	*(30.5)*	
5-6	10	*(7.0)*	9	*(6.9)*	

Abbreviations: ECOG: Eastern Cooperative Oncology Group, IQR=Interquartile Range, N/A=Not applicable, PPI=Proton Pump Inhibitor

Table 2. Best Response with Regorafenib

	PPI Non-user (n=141) (%)	PPI User (n=131) (%)	P
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

Abbreviations: PPI=Proton Pump Inhibitor

Safety

The rates of any AEs were similar in PPI non-user and user groups (37.6% vs. 38.9%, p=0.820 for grade 1-2, 21.3% vs. 22.1%, p=0.863). All subtypes of AEs were also similar in each group. All AEs are shown in **Table 3.**

Table 3. Adverse Events

	PPI Non-user n=141 *(%)*		PPI User n=131 *(%)*		*p*	
	Grade 1-2	**Grade 3**	**Grade 1-2**	**Grade 3**	**Grade 1-2**	**Grade 3**
Any	53 *(37.6)*	30 *(21.3)*	51 *(38.9)*	29 *(22.1)*	0.820	0.863
Hand-Foot Syndrome	35 *(24.8)*	5 *(3.5)*	33 *(25.2)*	6 *(4.6)*	0.944	0.665
Fatigue	45 *(31.9)*	18 *(12.8)*	52 *(39.7)*	13 *(9.9)*	0.181	0.461
Hypertension	15 *(10.6)*	7 *(5.0)*	14 *(10.7)*	9 *(6.9)*	0.990	0.505
Diarrhea	24 *(17.0)*	3 *(2.1)*	22 *(16.8)*	2 *(1.5)*	0.960	1.000
Skin Rash	26 *(18.4)*	2 *(1.4)*	21 *(16.0)*	3 *(2.3)*	0.599	0.674

Abbreviations: PPI=Proton Pump Inhibitor

Discussion

To the best of our knowledge, this was the first study that assessed the effect of PPI use on the survival and safety outcomes in patients with mCRC treated with regorafenib. This study revealed no impact of PPIs on the survival outcomes, response rates, and safety profile of regorafenib 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-hour interval time between esomeprazole and regorafenib did not affect the bioavailability of regorafenib.[2] Our results were consistent with this bioavailability study. However, it should be noticed that the study of de Man et al. did not evaluate the survival outcomes.

Abdominal symptoms and dyspepsia are common in advanced cancer patients, and the rate of PPI use in those patients is high.[5] In addition to symptom control, PPIs protect gastric damage from steroids, radiation, and chemotherapeutics.[9] 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.[17] 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.[17]

It is well known that PPIs may cause diarrhea.[11] Several mechanisms, such as microscopic colitis and Clostridium difficile infection, may play a role in PPI-related diarrhea.[7, 14] 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.[18] 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 anti-acids 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. 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, concomitant use of PPIs was not associated with worse survival outcomes and safety profile in patients with mCRC treated with regorafenib. 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.

Abbreviations

AEs
Adverse Events
CI
Confidence Interval
CTCAE
Common Terminology Criteria for Adverse Events
ECOG
Eastern Cooperative Oncology Group
GIST
Gastrointestinal Stromal Tumor
HCC
Hepatocellular Cancer
IQR
Interquartile Range
mCRC
Metastatic Colorectal Cancer
ORR
Objective Response Rates
OS
Overall Survival
PPI(s)
Proton Pump Inhibitor(s)
RECIST
Response Evaluation Criteria in Solid Tumors
TKIs
Tyrosine Kinase Inhibitors
TTF
Time to Treatment Failure

Declarations

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Conflicts of Interest

All authors disclose no financial interests or conflicts of interest.

Authors' Contributions

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. **Atila 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. **Abdurrahman Işıkdoğan:** Writing – review and editing, Supervision. **Saadettin Kılıçkap:** Writing – review and editing, Supervision. **Yüksel Ürün:** Methodology, Writing – review and editing, Supervision. **Şuayib 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

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

Data Availability Statement

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

Acknowledgment

Not applicable

References

1. Crona DJ, Keisler MD, Walko CM (2013) Regorafenib: a novel multitargeted tyrosine kinase inhibitor for colorectal cancer and gastrointestinal stromal tumors Ann Pharmacother 47: 1685–1696
2. de Man FM, Hussaarts K, de With M, Oomen-de Hoop E, de Bruijn P, van Halteren HK, van der Burg-de Graauw N, Eskens F, van Gelder T, van Leeuwen RWF, Mathijssen RHJ (2019) Influence of the Proton

Pump Inhibitor Esomeprazole on the Bioavailability of Regorafenib: A Randomized Crossover Pharmacokinetic Study Clin Pharmacol Ther 105: 1456–1461

3. Gay C, Toulet 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: 259–280
4. Herbrink M, Nuijen B, Schellens JH, Beijnen JH (2015) Variability in bioavailability of small molecular tyrosine kinase inhibitors Cancer Treat Rev 41: 412–422
5. 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: e388-e395
6. Kudo M (2020) Recent Advances in Systemic Therapy for Hepatocellular Carcinoma in an Aging Society: 2020 Update Liver Cancer 9: 640–662
7. Law EH, Badowski M, Hung YT, Weems K, Sanchez A, Lee TA (2017) Association Between Proton Pump Inhibitors and Microscopic Colitis Ann Pharmacother 51: 253–263
8. 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: 686–692
9. Numico G, Fusco V, Franco P, Roila F (2017) Proton Pump Inhibitors in cancer patients: How useful they are? A review of the most common indications for their use Crit Rev Oncol Hematol 111: 144–151
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: 699–704
11. 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: 112–120
12. Shirley M, Keating GM (2015) Regorafenib: A Review of Its Use in Patients with Advanced Gastrointestinal Stromal Tumours Drugs 75: 1009–1017
13. 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: 659–672
14. Trifan A, Stanciu C, Girleanu I, Stoica OC, Singeap AM, Maxim R, Chiriac SA, Ciobica A, Boiculese L (2017) Proton pump inhibitors therapy and risk of Clostridium difficile infection: Systematic review and meta-analysis World J Gastroenterol 23: 6500–6515
15. van Leeuwen RW, van Gelder T, Mathijssen RH, Jansman FG (2014) Drug-drug interactions with tyrosine-kinase inhibitors: a clinical perspective Lancet Oncol 15: e315-326
16. van Leeuwen RWF, Jansman FGA, Hunfeld NG, Peric R, Reyners AKL, Imholz ALT, Brouwers J, Aerts JG, van Gelder T, Mathijssen RHJ (2017) Tyrosine Kinase Inhibitors and Proton Pump Inhibitors: An Evaluation of Treatment Options Clin Pharmacokinet 56: 683–688

17. 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
18. Xie Y, Bowe 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: l1580
19. Yin OQ, Gallagher N, Fischer D, Demirhan E, Zhou W, Golor G, Schran H (2010) Effect of the proton pump inhibitor esomeprazole on the oral absorption and pharmacokinetics of nilotinib J Clin Pharmacol 50: 960–967

Figures

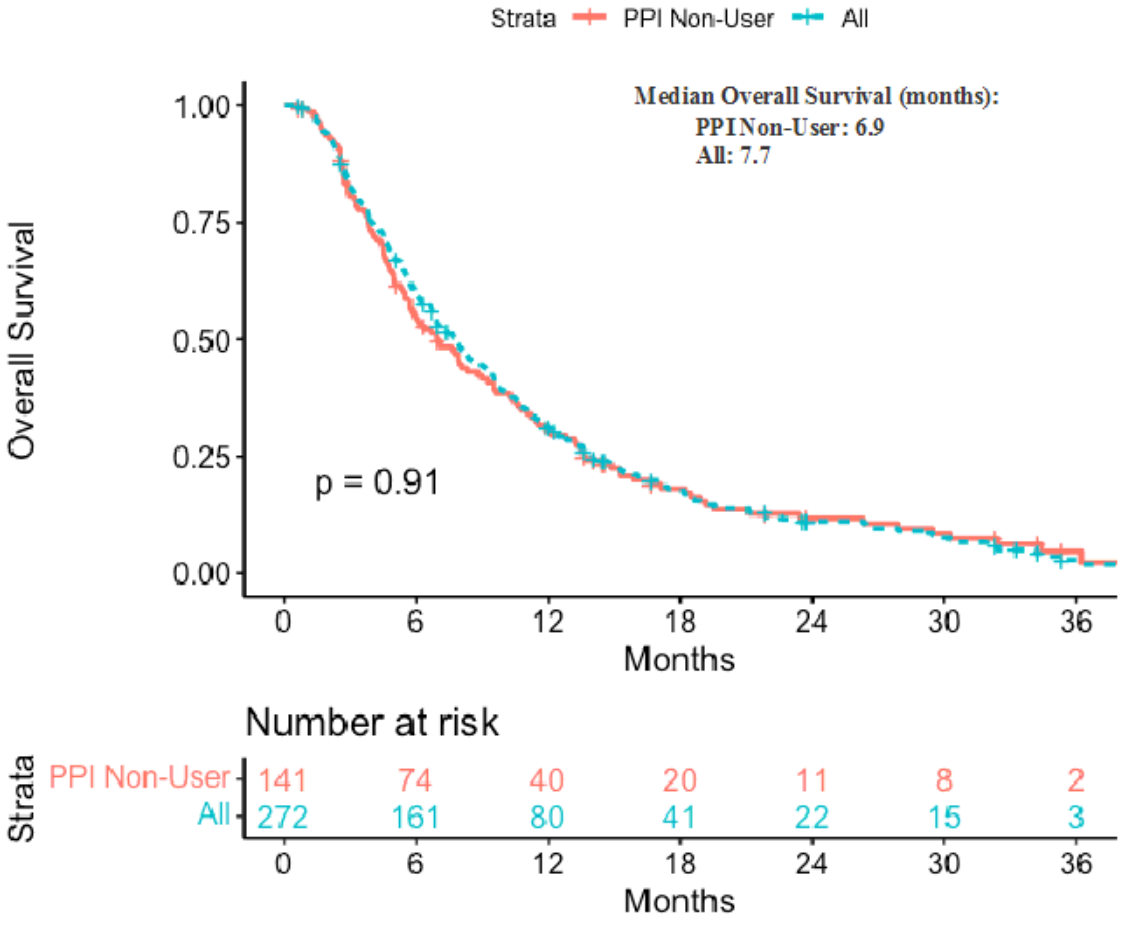


Figure 1

Kaplan-Meier Estimates for Overall Survival

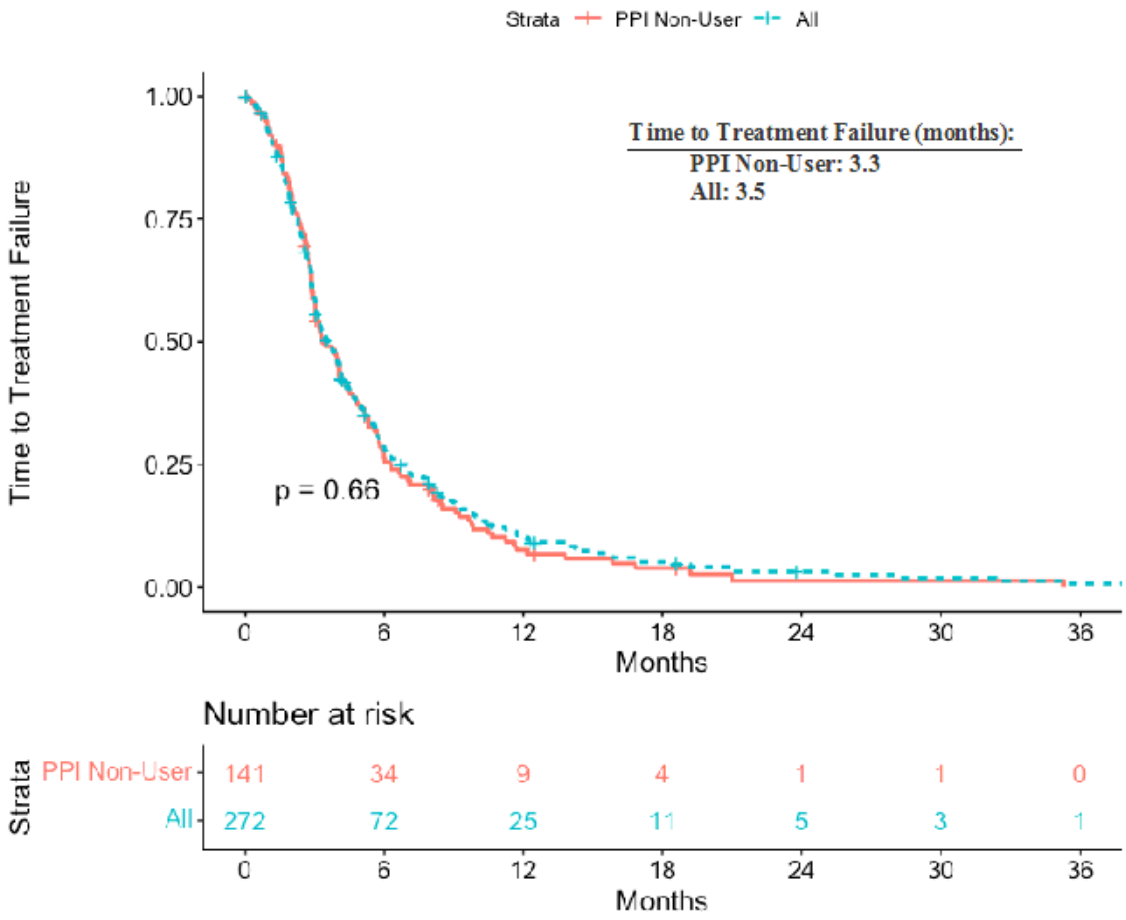


Figure 2

Kaplan-Meier Estimates for Time to Treatment Failure