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ORIGINAL RESEARCH ARTICLE

Concomitant Proton Pump Inhibitors and Outcome of Patients Treated with Nivolumab Alone or Plus Ipilimumab for Advanced Renal Cell Carcinoma

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Abstract

Background Immune checkpoint inhibitors (ICIs) represent the standard of care as first- or second-line treatment in patients with renal cell carcinoma (RCC). Proton pump inhibitors (PPIs) are among the most prescribed drugs worldwide and are known to affect gut microbiota, which is gaining interest in its association with outcomes for patients on ICIs.

Objective The aim of this study was to evaluate the impact of PPIs on outcomes in RCC patients receiving immunotherapy.

Patients and Methods We retrospectively collected data from patients with metastatic RCC who received the combination of ipilimumab and nivolumab for first-line treatment (Cohort 1) or single-agent nivolumab for second-line or third-line treatment (Cohort 2) from five international centers with expertise in the treatment of RCC. Data about clinicopathological characteristics, PPI use, and outcome on ICIs were collected. Endpoints of the study were objective response rate (ORR), progression-free survival (PFS), and overall survival (OS).

Results Two hundred and eighteen patients (71% male, median age 61 years) were included in the analysis, 62 in Cohort 1 (including 25 patients receiving PPIs) and 156 in Cohort 2 (including 88 patients receiving PPIs), and were followed up for a median of 42 months. In Cohort 1, no difference was observed in ORR (48% vs 57%; $p = 0.203$), PFS (12.2 vs 8.5 months; $p = 0.928$), or OS (not reached [NR] vs 27.3 months; $p = 0.84$). In Cohort 2, no difference was observed in ORR (32% vs 28%; $p = 0.538$), PFS (6.7 vs 9.0 months; $p = 0.799$), or OS (16.0 vs 26.0 months; $p = 0.324$).

Conclusions In patients with RCC, concomitant PPI use did not seem to affect survival outcomes on ICIs, either as combination therapy or monotherapy.

Key Points

We investigated the impact of proton pump inhibitors (PPIs) on the clinical outcome of renal cell carcinoma (RCC) patients receiving immunotherapy.

According to our results, PPIs do not seem to influence immune checkpoint inhibitor activity in RCC patients, which is consistent with some of the previously available data.

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1 Introduction

Renal cell carcinoma (RCC) incidence is increasing, with about 76,000 new cases estimated in 2021 in the United States (US) [1, 2]. Immune checkpoint inhibitors (ICIs) are the new standard of care in the treatment of metastatic RCC, either as monotherapy or combination treatment, and the rapidly changing landscape of systemic therapy in RCC has prompted clinicians to consider the expansion of immunotherapy to the earlier stages of the disease (for example, in the adjuvant setting). Several immune-based combinations, including dual checkpoint blockade (nivolumab plus ipilimumab) or ICI plus tyrosine kinase inhibitors (TKIs) (pembrolizumab plus axitinib, avelumab plus axitinib, nivolumab plus cabozantinib, pembrolizumab plus lenvatinib) have been found to be associated with favorable outcomes in first-line treatment [3–7]. Following the results of these combination approaches, the first-line treatment of metastatic RCC was revolutionized, but comparisons among these therapeutic options are not available; thus, the decision-making process takes into account several prognostic and clinical factors [8–10]. In later lines of therapy, nivolumab monotherapy was superior to everolimus, thus becoming one of the main treatment strategies for pretreated patients [11].

The gut microbiota is composed of a wide spectrum of bacteria and microorganisms that physiologically reside in the gastrointestinal tract and regulate several functions, including drug metabolism, as well as activity and toxicity of antitumoral compounds [12]. Preclinical and clinical evidence indicated that ICI activity can be modified by gastrointestinal microbiota. In fact, several retrospective and a few prospective studies demonstrated that antibiotic treatment can influence ICI efficacy by altering the normal bacterial microenvironment and, consequently, the immune system activity [13–15].

Proton pump inhibitors (PPIs), largely used for gastrointestinal disorders, including gastro-esophageal reflux or gastric ulcers, act by modifying gastric acidity through the inhibition of hydrogen–potassium pumps with subsequent suppression of acid production [16]. This dysregulation of the gastric pH leads to modification of the gut microbiota with a decreased alpha diversity. In particular, it has been pointed out that PPI use can lead to an increased prevalence of *Lactobacillales* (especially *Streptococcaceae), Actinobacteria* (in particular *Actinomycetales*), and *Clostridiales* (especially *Ruminococcaceae*) [17, 18]. This altered microbiota composition can lead not only to an increased risk of *Clostridium difficile* infections but also to a modified response to ICIs due to an alteration of the immune system response. Moreover, quantitative metagenomics of patient stool samples provided evidence that some bacteria species seem to be more immunogenic, eliciting a higher immune response, such as *Bifidobacterium*, *Akkermansia*, and *Bacteroides* [13, 19, 20]. In particular, the presence of *Akkermansia muciniphila* has been correlated to favorable outcomes in patients with non-small cell lung carcinoma or RCC [13].

We conducted a retrospective study to analyze the effect of PPIs on survival outcomes for patients with metastatic RCC receiving nivolumab plus ipilimumab in first-line treatment or nivolumab monotherapy in second or third-line therapy.

2 Patients and Methods

2.1 Study Population

We retrospectively analyzed data from patients aged ≥ 18 years with a histologically confirmed diagnosis of RCC and histologically or radiologically confirmed metastatic disease, treated with the combination of first-line nivolumab plus ipilimumab or nivolumab as second- or third-line therapy. This international real-world study collected data from five institutions from Italy and the US involved in the treatment of advanced RCC (Bologna—Italy; Macerata—Italy; New Orleans—USA; Padova—Italy; Meldola—Italy). Data collection included data from 1 January 2010 to 21 July 2021.We retrospectively extracted data from paper and electronic charts. For each institution, we created a database and collected patient data on histology, nephrectomy status, initial Eastern Cooperative Oncology Group (ECOG) performance status, International Metastatic RCC Database Consortium (IMDC) criteria, sites of metastases, and concomitant PPI use. Patients without sufficient data on tumor assessment or response to therapy were excluded from our analysis.

The study population was divided into two cohorts: Cohort 1 included patients receiving the combination of nivolumab plus ipilimumab as first-line therapy, and Cohort 2 was composed of patients treated by nivolumab monotherapy as second- or third-line therapy.

As first-line therapy, nivolumab (3 mg per kilogram of body weight) plus ipilimumab (1 mg/kg) were administered intravenously every 3 weeks for four doses, followed by nivolumab (3 mg/kg) every 2 weeks. A nivolumab monotherapy flat-dosing of 240 mg every 2 weeks or 480 mg monthly was administered in patients receiving second- or third-line immunotherapy. Treatment interruptions were carried out following National Comprehensive Cancer Network (NCCN) guidelines according to type and severity of adverse events. Treatment was continued until there was evidence of clinical or radiological tumor progression on computed tomography (CT) or magnetic resonance imaging (MRI) scans, unacceptable toxicities, or death. Follow-up was conducted through periodic physical and laboratory tests every

4–6 weeks. Imaging was performed following standard local procedures every 8–12 weeks.

Information regarding PPI therapy as concomitant medication was retrieved from medical records and collected at every clinical visit. PPI administration was started either before or concomitantly to ICI start; patients that started PPIs during the course of immunotherapy were excluded from the study. In case of missing or incomplete information, patients were excluded from the study.

The study was approved by the local Institution Review Boards and was conducted in accordance with the principles of the Declaration of Helsinki (6th revision, 2008).

2.2 Study Endpoints

Tumor radiological imaging was performed based on the RECIST 1.1 criteria [21]. Data on tumor response (complete or partial responses, stable or progressive disease) were collected and analyzed. Progression-free survival (PFS) was defined as the time from the start of treatment to progression or death from any cause. Patients without tumor progression or death or lost to follow-up at the time of the analysis were censored at their last follow-up date. Overall survival (OS) was defined as the time from the start of therapy to death from any cause.

2.3 Statistical Analysis

The Kaplan-Meier method with Rothman's 95% confidence intervals (CI) was used to estimate PFS and OS, while comparisons were performed using the log-rank test. Univariate analysis was carried out by Cox proportional hazards models. The chi-square test was used to compare categorical endpoints, and significance levels were set at a 0.05 value, with all p values being two-sided. The MedCalc version 19.6.4 (MedCalc Software, Broekstraat 52, 9030 Mariakerke, Belgium) was employed for the statistical analysis.

3 Results

3.1 Study Population

Two hundred and eighteen patients were included in our analysis. The median age was 61 years (range 29−83); 154 patients (71%) were males. Tumor histology was predominantly clear cell (177, 81%); tumor histology in the 41 patients with non-clear cell RCC was papillary type I and II (16 patients), clear cell RCC with sarcomatoid differentiation (11 patients), chromophobe (6 patients), XP11.3 translocation (1 patient), and unclassified (7 patients). Number of metastatic sites was two or more in 147 patients (62%). Lung (62%), lymph nodes (47%), and bone (30%) were the most common sites of metastasis. According to IMDC criteria, 22 patients (10%) were at favorable risk, 146 (67%) at intermediate risk, and 50 (23%) had poor-risk features. Patients' characteristics are summarized in Table 1.

Cohort 1 included 62 patients who had received the combination of nivolumab plus ipilimumab as first-line therapy, while Cohort 2 included 156 patients who received nivolumab monotherapy in the second (71%) or third-line setting (29%). A total of 113 patients (52%) received concomitant PPIs; of them, 25 (22%) were in Cohort 1 and 88 (78%) in Cohort 2. No significant differences were found in terms of clinico-pathological features between patients receiving concomitant PPIs in both cohorts (Table 1).

3.2 Response to Therapy

One hundred and three patients (46%) were dead at time of data cut-off. In Cohort 1, 19 patients (30%) were receiving ongoing treatment at time of data cut-off, while 22 (35%) and 5 patients (8%) received a second-line or third-line therapy, respectively (Table 1). We observed 33 partial responses (53%), 12 stable diseases (19%) and 17 progressive diseases (28%) as best tumor response, with an ORR of 53% and a disease control rate (DCR) of 72%. Partial responses to the combination of nivolumab plus ipilimumab were observed in 12 of the 25 patients receiving concomitant PPIs (48%) and in 21 of the 37 patients not receiving PPIs (57%), though it was not a statistically significant difference ($p = 0.203$).

In Cohort 2, 42 patients (30%) were continuing treatments at the time of data cut-off; 43 patients (28%) treated with nivolumab as second-line therapy received successive third-line therapies (Table 1). Overall, we registered 47 partial responses (30%), 37 (34%) of them in the second-line setting and 10 (22%) in third-line setting. Stable disease was observed in 48 patients (31%), 31 (32%) with nivolumab as second-line and 17 (37%) as third-line therapy. Progressive disease was the best tumor response in 50 patients, 31 (34%) in the second- and 19 (41%) in the third-line setting. Partial responses were reported in 28 of the 88 patients receiving concomitant PPIs (32%) and in 19 of the 68 patients not receiving PPIs (28%); this difference was not statistically significant ($p = 0.538$).

3.3 Survival Analysis

The median follow-up time from RCC diagnosis was 42.1 months (range 35.0−159.1). The median OS from the start of nivolumab plus ipilimumab treatment was 27.3 months (95% CI 17.8−28.1). No significant differences were found between patients with or without concomitant PPIs (not reached [NR], 95% CI NR−NR vs 27.3 months, 95% CI 17.3−28.1; $p = 0.842$, Fig. 1). At univariate analysis, only IMDC criteria were predictors of OS, while the

Table 1 Patient characteristics

	Overall study population	Cohort 1 (nivolumab + ipilimumab), $n = 63$			Cohort 2 (nivolumab monotherapy), $n = 156$		
	N. of patients (%)	PPIs, $n = 25$ (%)	No PPIs, $n = 38$ (%)	p	PPIs, $n = 88$ (%)	No PPIs, $n = 68$ (%)	p
Age (y)							
Median	61	60	61		60	62	
Range	29–83	31–81	38–82		29–80	41–83	
Gender				0.59			0.37
Male	154 (71)	21 (84)	29 (78)		61 (69)	43 (63)	
Female	64 (29)	4 (16)	8 (22)		27 (31)	25 (37)	
Nephrectomy				0.97			0.74
Yes	166 (76)	19 (76)	28 (76)		68 (77)	51 (75)	
No	52 (24)	6 (24)	9 (24)		20 (23)	17 (25)	
Histology				0.47			0.22
Clear cell RCC	187 (86)	22 (88)	30 (81)		73 (83)	52 (76)	
Non-clear cell RCC	31 (14)	3 (12)	7 (19)		15 (17)	16 (24)	
N. of metastatic sites				0.76			0.46
1 site	71 (33)	7 (28)	11 (30)		28 (32)	25 (37)	
≥ 2 sites	147 (67)	18 (72)	26 (70)		60 (68)	43 (63)	
Site of metastasis				0.97			0.75
Lung	136 (62)	17 (67)	24 (65)		59 (67)	36 (53)	
Lymph nodes	102 (47)	11 (44)	16 (43)		42 (48)	32 (47)	
Bone	65 (30)	7 (28)	10 (27)		27 (31)	21 (31)	
Liver	33 (15)	3 (12)	5 (14)		13 (15)	12 (17)	
IMDC risk group				0.66			0.66
Good	22 (10)	1 (4)	1 (3)		10 (11)	10 (15)	
Intermediate	146 (67)	16 (64)	26 (70)		59 (67)	45 (66)	
Poor	50 (23)	8 (32)	10 (27)		19 (22)	13 (19)	
First-line therapy							
Nivolumab + ipilimumab	62 (28)	25 (40)	37 (60)				
Sunitinib	122 (56)						
Pazopanib	34 (16)						
Second-line therapy							
Nivolumab	110 (62)				61 (55)	49 (45)	
Sunitinib	26 (15)						
Axitinib	11 (6)						
Cabozantinib	19 (11)						
Everolimus	12 (6)						
Third-line therapy							
Nivolumab	46 (49)				27 (59)	19 (41)	
Cabozantinib	46 (49)						
Sunitinib	1 (1)						
Everolimus	1 (1)						

IMDC International Metastatic RCC Database Consortium, *PPIs* proton pump inhibitors, *RCC* renal cell carcinoma

administration of concomitant PPIs was not correlated with patients' outcome ($p = 0.842$, Table 2).

In Cohort 1, the median PFS from the start of nivolumab plus ipilimumab was 10.4 months (95% CI 5.9−21.5). As for OS, no significant differences were observed between patients with or without concomitant PPIs (12.2 months, 95% CI 2.3−16.3 vs 8.5 months, 95% CI 5.8−21.5; $p = 0.928$, Fig. 1). At univariate analysis, no factors were found to be significantly correlated with PFS (Table 2).

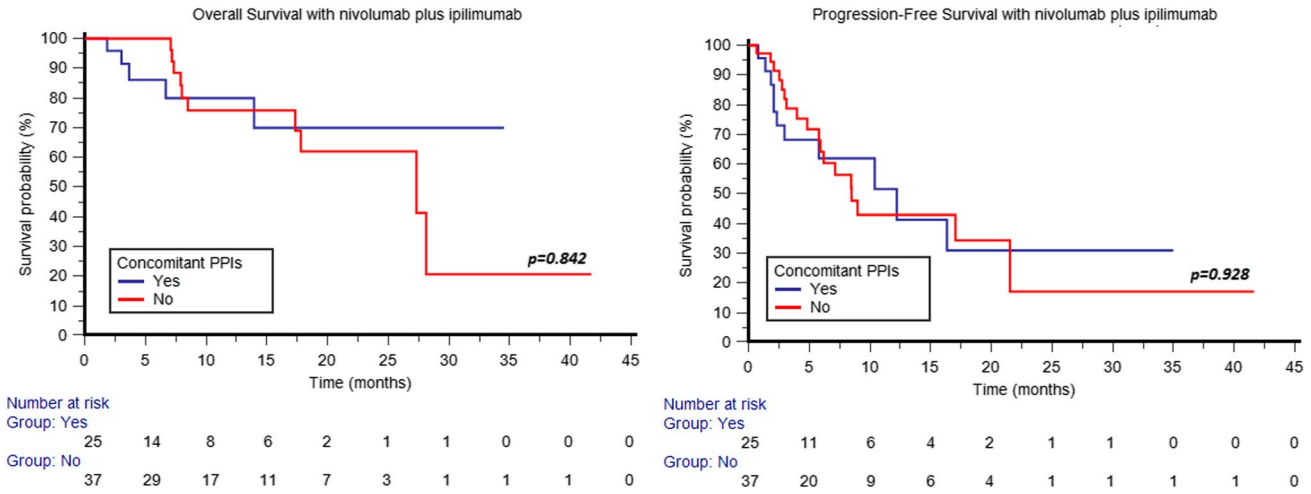

Fig. 1 Overall survival and progression-free survival of mRCC patients treated with first-line nivolumab plus ipilimumab (Cohort 1) based on the assumption of concomitant PPIs. *mRCC* metastatic renal cell carcinoma, *PPIs* proton pump inhibitors

Table 2 Univariate analysis of predictors of overall survival and progression-free survival in patients treated with nivolumab plus ipilimumab (Cohort 1)

	Univariate Cox regression	
	HR (95% CI)	*p* value
OS		
Sex (M/F)	1.84 (0.95–12.77)	0.068
Age (≥ 65 year vs < 65 year)	1.23 (0.38–3.95)	0.729
Nephrectomy (Y vs N)	2.26 (072–7.10)	0.163
Histology (clear cell vs non-clear cell)	1.00 (0.13−7.87)	0.997
Number of metastatic sites (≥ 2 vs < 2)	1.79 (0.62−5.13)	0.278
IMDC prognostic group	3.69 (1.21−11.24)	0.022
Concomitant PPIs	1.12 (0.38–3.27)	0.842
PFS		
Sex (M/F)	1.53 (0.61–3.80)	0.363
Age (≥ 65 year vs < 65 year)	0.96 (0.39–2. 37)	0.930
Nephrectomy (Y vs N)	1.27 (0.61–2.74)	0.531
Histology (clear cell vs non-clear cell)	0.42 (0.06–3.19)	0.405
Number of metastatic sites (≥ 2 vs < 2)	1.80 (0.85–3.81)	0.126
IMDC prognostic group	1.34 (0.61–2.93)	0.466
Concomitant PPIs	1.04 (0.49–2.20)	0.928

CI confidence interval, *HR* hazard ratio, *IMDC* International Metastatic RCC Database Consortium, *OS* overall survival, *PFS* progression-free survival, *PPIs* proton pump inhibitors, *RCC* renal cell carcinoma

In Cohort 2, the median OS was 20.8 months (95% CI 12.6−26.8). Furthermore, it was 16.0 months (95% CI 9.4−23.5) in patients receiving concomitant PPIs and 26.0 months (95% CI 14.5−47.0) in patients not receiving PPIs ($p = 0.324$, Fig. 2). At univariate analysis, only the correlation between IMDC criteria and OS was approaching significance ($p = 0.068$, Table 3).

The median PFS was 7.1 months (95% CI 4.6−61.1) and was significantly longer in patients with clear cell histology (8.9 months, 95% CI 6.1−61.1 vs 4.6 months, 95% CI 2.8−45.5; $p = 0.004$, Fig. S1 in the electronic supplementary material). Similar to Cohort 1, no significant differences were found between patients with or without concomitant PPI use (6.7 months, 95% CI 4.6−61.5 vs 9.0 months, 95% CI 3.7−45.5; $p = 0.799$, Fig. 2). At univariate analysis, RCC histology was significantly associated with PFS ($p = 0.004$), while concomitant PPIs and other analyzed factors were not correlated (Table 3).

4 Discussion

We assessed the effect of PPI use on ICI treatment in patients with metastatic RCC and showed that in patients treated with either ICI combination treatment or monotherapy, there was no difference in terms of OS, PFS, and ORR between patients with or without concomitant PPI use.

PPIs are widely used in clinical practice for gastrointestinal disorders and also for symptoms arising during anticancer treatment, including drug- or tumor-induced dyspepsia. PPI-induced hypochlorhydria has been shown to alter gut microbiota by reducing its alpha diversity, which in turn has been associated with reduced benefit on ICIs in multiple cancer types [17]. In everyday clinical practice, the use of antibiotics within 30 days from the start of treatment was associated with worse outcomes in patients affected by different tumor types and receiving ICIs, supporting the negative prognostic role of microbiota-altering drugs in this setting [14]. Indeed, the role of PPIs on ICI activity in patients

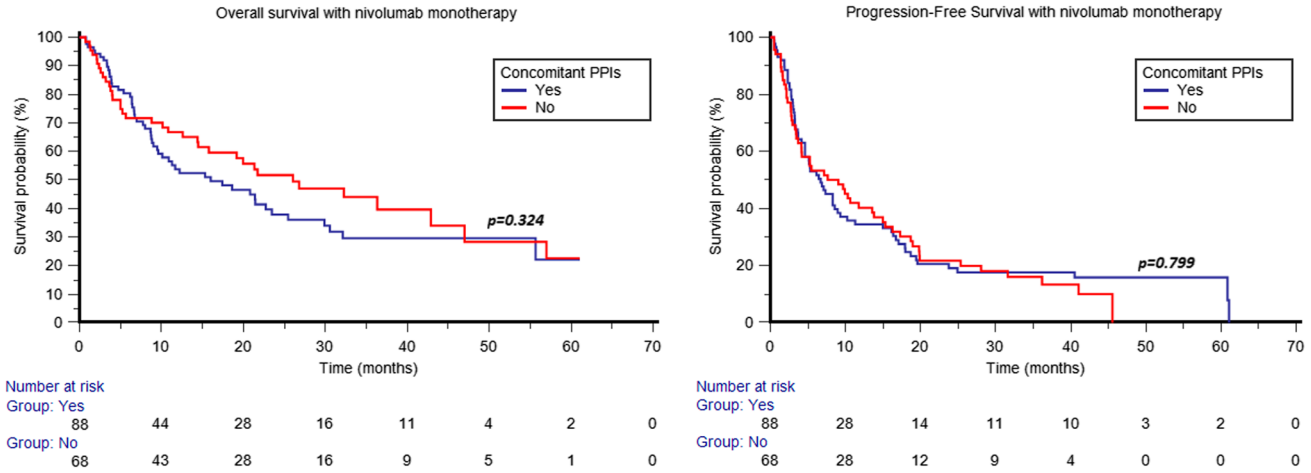

Fig. 2 Overall survival and progression-free survival of mRCC patients treated with nivolumab monotherapy as second- or third-line therapy (Cohort 2) basing on the assumption of concomitant PPIs. *mRCC* metastatic renal cell carcinoma, *PPIs* proton pump inhibitors

Table 3 Univariate analysis of predictors of overall survival and progression-free survival in patients treated with nivolumab monotherapy as second- or third-line therapy (Cohort 2)

	Univariate Cox regression	
	HR (95% CI)	*p* value
OS		
Sex (M/F)	0.93 (0.59–1.45)	0.743
Age (≥ 65 year vs < 65 year)	1.35 (0.88–2.07)	0.167
Nephrectomy (Y vs N)	1.29 (0.86–1.95)	0.223
Histology (clear cell vs non-clear cell)	1.46 (0.90–2.37)	0.126
Number of metastatic sites (≥ 2 vs < 2)	0.89 (0.59–1.34)	0.578
IMDC prognostic group	1.36 (0.98–1.89)	0.068
Concomitant PPIs	0.81 (0.53–1.24)	0.324
PFS		
Sex (M/F)	0.88 (0.60–1.30)	0.517
Age (≥ 65 year vs < 65 year)	0.73 (0.50–1.08)	0.119
Nephrectomy (Y vs N)	1.10 (0.77–1.57)	0.592
Histology (clear cell vs non-clear cell)	1.78 (1.17–2.71)	0.004
Number of metastatic sites (≥ 2 vs < 2)	1.17 (0.82–1.65)	0.385
IMDC prognostic group	1.08 (0.80–1.46)	0.609
Concomitant PPIs	1.05 (0.73–1.50)	0.799

CI confidence interval, *HR* hazard ratio, *IMDC* International Metastatic RCC Database Consortium, *OS* overall survival, *PFS* progression-free survival, *PPIs* proton pump inhibitors, *RCC* renal cell carcinoma

with different solid tumors has been widely investigated in retrospective series, although results were mixed [22–27]. Remarkably, an individual-participant data analysis from IMvigor 210 [28] and IMvigor 211 [29] trials of single-agent atezolizumab in 1360 patients with urothelial carcinoma showed that PPI use was associated with worse OS in patients receiving atezolizumab, but not in those receiving chemotherapy, suggesting a negative effect of PPIs on outcomes in ICI-treated patients with urothelial carcinoma [30].

The effect of PPIs has been previously investigated in patients with metastatic RCC treated with TKIs, which was the standard of care for many years. Also in this population, PPIs did not appear to influence treatment response, even though TKIs are oral drugs for which gastric pH plays a crucial role in the absorption process [31]. Similar to what was observed in patients with urothelial carcinoma [30], alterations in gut microbiota composition caused by TKIs and antibiotics negatively affected ICI outcomes in patients with RCC in a retrospective series [32]. Nevertheless, Kulkarni et al. investigated the role of antibiotics and PPI on the outcomes of 148 and 55 patients with non-small-cell lung cancer and RCC, respectively, who received ICI treatment [25]. While antibiotics use was found to affect PFS, PPI use did not influence outcomes. Furthermore, a recent meta-analysis conducted by Li and colleagues on the effect of PPIs on ICI outcomes, which included five studies for a total of 1167 cancer patients, demonstrated no impact of PPI use on OS or PFS [33]. The studies collected for the analysis included patients with non-small-cell lung cancer, melanoma, RCC, and other tumors, that presented contrasting results [33–38]. Despite including patients with different tumor types and only a small subset of patients with RCC, these results are concordant with those of the present study and support our findings in a larger population.

The main strengths of our study are the large sample size consisting only of patients with RCC, as well as the level of expertise on RCC malignancies through the involved oncologic centers.

Our study's limitations are mainly due to its retrospective nature. First, we did not perform a centralized review

of radiological imaging and histology; in addition, data about the concomitant use of medications other than PPIs that could influence the efficacy of immunotherapy (e.g., antibiotics) was not collected. The population of Cohort 1 was limited, including only 62 patients due to the relatively recent introduction of the nivolumab plus ipilimumab combination in clinical practice. Lastly, there was not a prior estimation of the sample size that would be needed to assess the hypothesis that PPI use could change ICI efficacy in RCC patients. Based on these premises, the lack of a significant effect may just reflect that the sample size and the statistical power were not sufficient.

Furthermore, another factor to keep in mind and that should be investigated in future specific studies is the impact of gut microbiota alteration due to PPI use on ICI activity, considering the preliminary evidence that microbiota composition seems to be a factor that influences the response to immunotherapy. In this regard, metagenomics analyses could further increase the knowledge on the bacterial composition modifications consequent to PPI use and their correlation with clinical outcomes of patients treated with immunotherapy.

5 Conclusion

While a prospective validation of our findings would be desirable, our study suggest that PPIs do not seem to influence ICI activity in RCC patients, which is consistent with some of the previously available data. Given the wide use of these drugs to treat and prevent gastrointestinal toxicities and diseases, these findings may be useful in everyday clinical practice for clinicians treating RCC patients with ICIs.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s11523-021-00861-y.

Declarations

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Conflict of interest Veronica Mollica, Matteo Santoni, Marc R. Matrana, Umberto Basso, Ugo De Giorgi, Alessandro Rizzo, Marco Maruzzo, Andrea Marchetti, Matteo Rosellini, Sara Bleve, Diana Maslov, Karine Tawagi, Ernest Philon, Zoe Blake, and Francesco Massari declare that they have no conflicts of interest that might be relevant to the contents of this manuscript.

Ethics approval and consent to participate Not required. Informed consent was not required due to the retrospective nature of the study.

Availability of data and material Data are available upon reasonable request.

Code availability Not applicable.

Author contributions Conception and design: VM, MS, and FM. Collection and assembly of data: VM, MS, and FM. Provision of study material or patients: all authors. Data analysis and interpretation: MS and FM performed the data analysis, all authors interpreted the data. Manuscript writing: VM, MS, and FM. Review of manuscript draft: all authors. Final approval of manuscript: all authors. Accountable for all aspects of the work: all authors.

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