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# Prognostic Impact of the Administration of Antibiotics and Proton Pump Inhibitors in Immune Checkpoint Inhibitor Combination Therapy for Advanced Renal Cell Carcinoma

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**Abstract.** *Background/Aim: The prognostic impact of the administration of antibiotics and proton pump inhibitors (PPIs) in immune checkpoint inhibitor (ICI) therapy for advanced cancer has recently been documented. However, how these drugs affect the outcomes of first-line ICI combination therapy for advanced renal cell carcinoma (RCC) remains unclear. Patients and Methods: We retrospectively evaluated the data of 128 patients with RCC who received first-line ICI combination therapy. The patients were grouped according to their history of antibiotics and PPIs use one month before the initiation of ICI combination therapy. Progression-free survival (PFS), overall survival (OS), and objective response rate (ORR) after ICI combination therapy were compared between patients treated with and without antibiotics or PPIs. Results: Of the 128 patients, 30 (23%) and 44 (34%) received antibiotics and PPIs, respectively. Patients treated with antibiotics exhibited shorter PFS and OS compared to those who did not receive antibiotics (median PFS: 4.9 vs. 16.1 months, p<0.0001; OS: 20.8 vs. 49.0 months, p=0.0034). Multivariate analyses showed that antibiotic administration was an independent predictor of shorter PFS (hazard ratio: 2.54: p=0.0002) and OS (hazard ratio: 2.56: p=0.0067) after adjusting for other covariates. In contrast, there were no significant differences in either PFS or OS between patients who received PPIs and those who did not. (PFS: p=0.828; OS: p=0.105). Conclusion: Antibiotics administration before ICI combination therapy was negatively associated with outcomes of first-line ICI combination therapy for advanced RCC. Therefore, careful monitoring is required for potentially high-risk patients undergoing ICI combination therapy.*

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The use of immune checkpoint inhibitors (ICIs) has markedly improved the outcomes of patients with advanced renal cell carcinoma (RCC). Pivotal phase III randomized clinical trials have shown the superior efficacy and manageable safety profile of ICI combination therapy compared with sunitinib in patients with advanced RCC (1-6). Evidence indicates that ICI combination therapy currently plays a central role in systemic therapy as the standard of care for advanced RCC (7, 8).

There are two major types of ICI combination therapy regimens: dual ICI combinations, namely immunotherapy (IO)-IO therapy, and combinations of ICIs with tyrosine kinase inhibitors (TKIs), namely IO-TKI therapy. These multiple regimens have contributed to improved outcomes; however, the lack of predictive or prognostic biomarkers that could facilitate more effective individualized treatment remains an unmet need.

It has recently been highlighted that the gut microbiota is significantly associated with the therapeutic effects of ICIs (9). The administration of antibiotics affects the gut microbiota *via*

Table I. *Patient background according to antibiotics and proton pump inhibitors (PPIs).*

| | All (n=128) | With antibiotics (n=30) | Without antibiotics (n=98) | *p*-Value | With PPIs (n=44) | Without PPIs (n=84) | *p*-Value |
|---|---|---|---|---|---|---|---|
| Age, years | | | | | | | |
| >65 (ref. ≤65) | 74 (57.8%) | 18 (60.0%) | 56 (57.1%) | 0.782 | 31 (70.5%) | 43 (51.2%) | 0.036 |
| Sex | | | | | | | |
| Male (ref. female) | 89 (69.5%) | 15 (50%) | 74 (75.5%) | 0.008 | 25 (56.8%) | 64 (76.2%) | 0.024 |
| Prior nephrectomy | | | | | | | |
| Presence (ref. absence) | 84 (65.6%) | 23 (76.7%) | 61 (62.2%) | 0.146 | 34 (77.3%) | 50 (59.5%) | 0.045 |
| Histopathology | | | | 0.232 | | | 0.841 |
| Clear-cell RCC | 85 (66.4%) | 19 (63.3%) | 66 (67.3%) | | 29 (65.9%) | 56 (66.7%) | |
| Non-clear-cell RCC | 31 (24.2%) | 10 (33.3%) | 21 (21.4%) | | 10 (22.7%) | 21 (25%) | |
| Unknown | 12 (9.4%) | 1 (3.3%) | 11 (11.2%) | | 5 (11.4%) | 7 (8.3%) | |
| IMDC risk | | | | 0.553 | | | 0.010 |
| Favorable | 10 (7.8%) | 1 (3.3%) | 9 (9.2%) | | 0 (0%) | 10 (11.9%) | |
| Intermediate | 76 (59.4%) | 18 (60%) | 58 (59.2%) | | 33 (75%) | 43 (51.2%) | |
| Poor | 42 (32.8%) | 11 (36.7%) | 31 (31.6%) | | 11 (25%) | 31 (36.9%) | |
| Metastatic sites | | | | | | | |
| Lung | 76 (59.4%) | 23 (76.7%) | 53 (54.1%) | 0.028 | 32 (72.7%) | 44 (52.4%) | 0.026 |
| Liver | 18 (14.1%) | 5 (16.7%) | 13 (13.3%) | 0.639 | 11 (25.0%) | 7 (8.3%) | 0.010 |
| Bone | 26 (20.3%) | 8 (26.7%) | 18 (18.4%) | 0.323 | 9 (20.5%) | 17 (20.2%) | 0.980 |
| Lymph node | 43 (33.6%) | 10 (33.3%) | 33 (33.6%) | 0.973 | 16 (36.4%) | 27 (32.2%) | 0.631 |
| cM status | | | | | | | |
| cM1 (ref. cM0) | 66 (51.6%) | 24 (80.0%) | 42 (42.9%) | 0.0004 | 28 (53.6%) | 38 (45.2%) | 0.048 |

modification of specific species, consequently changing metabolic capacity (10). Furthermore, proton pump inhibitors (PPIs) affect the gut microbiota by altering the gastric pH and balance of the microbiota environment (11, 12). In patients with melanoma and non-small cell lung cancer, the administration of antibiotics is significantly associated with decreased ICIs effectiveness (13). Additionally, PPIs administration was negatively associated with outcomes (14). However, the effect of these drugs on the outcomes of first-line ICIs combination therapy in patients with advanced RCC remains unclear. Given this context, we retrospectively investigated the association of the administration of antibiotics and PPIs with the outcomes of patients with RCC and who underwent first-line ICI combination therapy.

## Patients and Methods

*Patient selection and study design.* All clinical and laboratory data were obtained from our electronic databases and patient medical records. The study protocol was approved by the institutional ethics review board of Tokyo Women's Medical University (ID: 2020-0009). The study was conducted in accordance with the 1964 Declaration of Helsinki and its later amendments. The need for informed consent was waived due to the retrospective observational nature of the study.

At our department and its affiliated institutions, 133 patients with advanced RCC received ICI combination therapy, including IO-IO (nivolumab plus ipilimumab) and IO-TKI treatment (pembrolizumab plus lenvatinib, pembrolizumab plus axitinib, avelumab plus axitinib, and nivolumab plus cabozantinib) between 2018 and 2023. Among them, five patients without eligible clinical data were excluded, and the remaining 128 patients were evaluated.

The patients were classified into two groups according to their history of antibiotic or PPIs administrated one month before the initiation of ICI combination therapy. The progression-free survival (PFS) and overall survival (OS) after ICI combination therapy and the objective response rate (ORR) during therapy were compared according to the administration of antibiotics and PPIs, respectively. To assess tumor responses, posttreatment follow-up computed tomography of the chest, abdomen, and pelvis was conducted regularly at 4- to 12-week intervals, depending on the patient's condition.

Magnetic resonance imaging scans or positron emission tomography/computed tomography was performed when necessary. Brain scans were also performed when necessary. Drugs were administered until radiographic or clinical disease progression or intolerable adverse events occurred. The ORR for measurable targeted lesions was determined according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1 (15).

*Statistical analysis.* The Mann–Whitney *U*-test was used to compare continuous variables between the two groups, and Fisher's exact test was used to compare categorical variables. PFS was calculated from the initiation of ICI combination therapy until disease progression or death, whichever occurred first. OS was calculated from the initiation of ICI combination therapy until death. Survival was determined using the Kaplan–Meier method and compared using the log-rank test. Multivariate analysis using the Cox proportional hazard regression model was conducted to identify the independent factors affecting PFS and OS. Risk was expressed in terms of

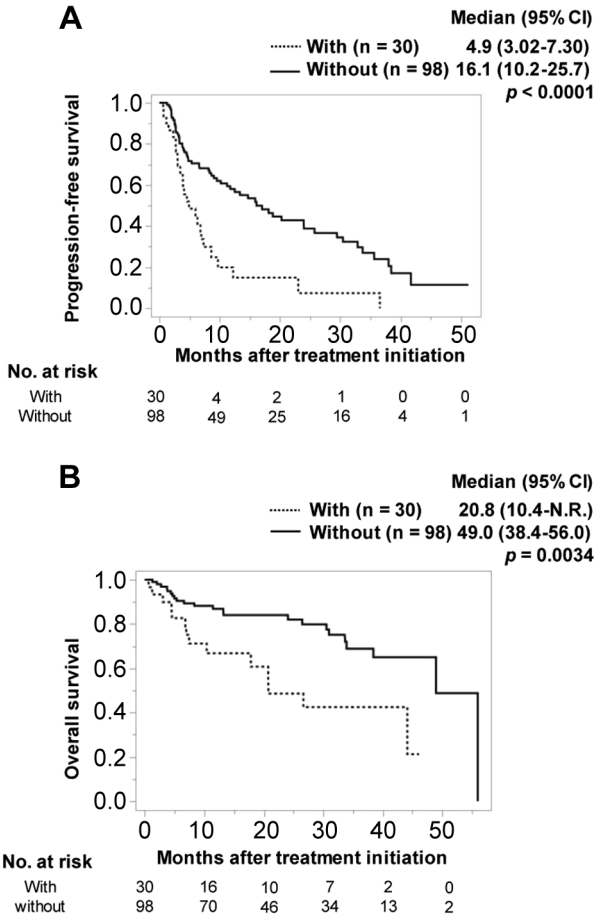


Figure 1. *Survival according to antibiotics administration. (A) Progression-free survival. (B) Overall survival. CI: Confidence interval; N.R.: not reached.*

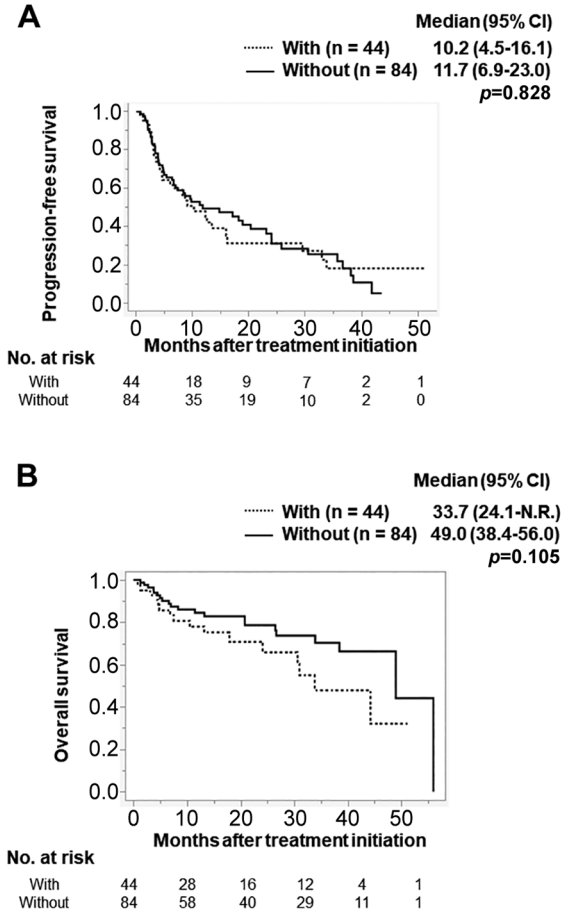


Figure 2. *Survival according to proton pump inhibitor administration. Progression-free survival. (B) Overall survival. CI: Confidence interval; N.R.: not reached.*

hazard ratios (HRs) with 95% confidence intervals (CIs). All statistical analyses were performed using soft of JMP version 17, and statistical significance was set at $p<0.05$.

## Results

*Patient characteristics*. The patient characteristics according to the administration of antibiotics and PPIs are summarized in Table I. Of the 128 patients, 30 (23%) received antibiotics. The most frequent reason for antibiotics administration was preoperative prophylaxis (n=80%), followed by urinary tract infections (n=10%) (Table I). Patients who were administered antibiotics were more frequently diagnosed with synchronous metastasis (*i.e.*, cM1) (80.0% *vs*. 42.9%, $p=0.0004$) and had lung metastasis (76.7% *vs*. 54.1%, $p=0.028$) compared with those who were not administered antibiotics. Sex, age, prior nephrectomy status, international metastatic (IMDC) risk, status of metastasis to the liver, bone, and lymph nodes, and histopathological type of RCC were not significantly different according to the antibiotics administration ($p>0.05$).

PPIs were administered to 44 (34.4%) patients. Patients who received PPIs were predominately elderly (70.5% *vs*. 51.2%, $p=0.0361$), more likely to undergo nephrectomy (77.3% *vs*. 59.5%, $p=0.046$), more frequently categorized as having intermediate risk according to the IMDC classification (75% *vs*. 51.2%, $p=0.0098$), and had a higher incidence of lung (72.7% *vs*. 52.4%, $p=0.026$) and liver metastases (25.0% *vs*. 8.3% $p=0.01$) compared with those who did not receive PPIs. The status of metastasis to the bone and lymph nodes, as well as the histopathological type, did not show significant differences according to PPIs administration (all, $p>0.05$).

*Survival based on antibiotics and PPIs administration*. During the median follow-up period of 15.4 months (interquartile range=7.50-33.2), 82 (%) patients experienced

Table II. *Univariate and multivariate analyses of progression-free survival.*

| | Univariate | | Multivariate | |
|---|---|---|---|---|
| | HR (95%CI) | *p*-Value | HR (95%CI) | *p*-Value |
| Age, years | | | | |
| >65 (ref. ≤65) | 1.04 (0.67-1.62) | 0.845 | | |
| Sex | | | | |
| Male (ref. female) | 0.79 (0.49-1.29) | 0.352 | | |
| Prior nephrectomy | | | | |
| Presence (ref. absence) | 1.02 (0.64-1.62) | 0.933 | | |
| Histopathology | | | | |
| Clear-cell RCC (ref. non-clear-cell RCC/unknown) | 0.75 (0.47-1.19) | 0.222 | | |
| IMDC risk | | | | |
| Favorable | 0.56 (0.24-1.31) | 0.187 | | |
| Intermediate | Reference | - | | |
| Poor | 0.97 (0.60-1.55) | 0.884 | | |
| Lung metastasis status | | | | |
| Presence (ref. absence) | 0.87 (0.56-1.37) | 0.554 | | |
| Bone metastasis status | | | | |
| Presence (ref. absence) | 0.80 (0.45-1.40) | 0.427 | | |
| Liver metastasis status | | | | |
| Presence (ref. absence) | 1.83 (1.00-3.32) | 0.049 | 1.70 (0.93-3.10) | 0.086 |
| Lymph node metastasis status | | | | |
| Presence (ref. absence) | 1.36 (0.86-2.14) | 0.192 | | |
| cM status | | | | |
| cM1 (ref. cM0) | 1.17 (0.76-1.81) | 0.468 | | |
| Antibiotics | | | | |
| With (ref. without) | 2.61 (1.61-4.25) | 0.0001 | 2.54 (1.56-4.2) | 0.0002 |
| PPIs | | | | |
| With (ref. without) | 1.05 (0.67-1.65) | 0.828 | | |

disease progression and 37 (%) died. PFS was shorter in patients who received antibiotics than in those who did not [median: 4.9 (95%Cl=3.02-7.30) *vs*. 16.1 (95%Cl=10.2-25.7) months, $p<0.0001$]. OS was also shorter in patients who received antibiotics compared to those who did not [median: 20.8 (95%Cl=10.4-not reached) *vs*. 49.0 (95%Cl=38.4-56.0) months, $p=0.0034$] (Figure 1).

To further analyze whether antibiotics administration was independently associated with shorter survival, we conducted univariate and multivariate analyses of PFS and OS. Univariate analysis of PFS showed that liver metastasis status (HR=1.83, $p=0.049$) and antibiotics administration (HR=2.61, $p<0.0001$) were significantly associated with survival (Table II). Multivariate analysis using two factors further showed that antibiotics administration (HR=2.54, $p=0.0002$) was an independent factor influencing shorter PFS. Univariate analysis of OS showed that antibiotics administration (HR=2.65; $p=0.0048$) was significantly associated with survival. In contrast, histopathological type ($p=0.071$) and age ($p=0.069$) appeared to be potentially relevant factors, although the differences were not significant (Table III). Multivariate analysis using three factors further showed that antibiotics administration (HR=2.56, $p=0.0067$) was an independent factor for shorter OS (Table III).

Regarding PPIs administration, PFS was not significantly different between patients who received PPIs and those who did not [median: 10.2 (95%Cl=4.5-16.1 *vs*. 11.7 (95%Cl=6.9-23.0)] months, $p=0.828$). OS was not significantly different between patients who received PPIs and those who did not [median: 33.7 (95%Cl=24.1-not reached) *vs*. 49.0 (95%Cl=38.4-56) months, $p=0.105$] (Figure 2).

*Tumor response based on antibiotics and PPIs administration.* Next, we assessed the tumor responses based on the administration of antibiotics. Regarding best overall response, among patients who received antibiotics, complete response, partial response, stable disease, and progressive disease were observed in 0, 14 (47%), eight (27%), and five (17%), respectively. The corresponding numbers for those who did not receive antibiotics were 10 (10%), 39 (40%), 28 (29%), and 16 (16%); eight patients were ineligible for the analysis of tumor response. ORR did not differ significantly according to antibiotics administration (47% *vs*. 50%, $p=0.749$).

Table III. *Univariate and multivariate analyses of overall survival.*

| | Univariate | | Multivariate | |
|---|---|---|---|---|
| | HR (95%CI) | *p*-Value | HR (95%CI) | *p*-Value |
| Age, years | | | | |
| >65 (ref. ≤65) | 1.91 (0.95-3.83) | 0.069 | 2.09 (1.02-4.26) | 0.043 |
| Sex | | | | |
| Male (ref. female) | 1.05 (0.51-2.19) | 0.891 | | |
| Prior nephrectomy | | | | |
| Presence (ref. absence) | 0.88 (0.44-1.78) | 0.720 | | |
| Histopathology | | | | |
| Clear-cell RCC (ref. non-clear-cell RCC/unknown) | 0.54 (0.27-1.05) | 0.071 | 0.50 (0.25-1.01) | 0.055 |
| IMDC risk | | | | |
| Favorable | 0.37 (0.05-2.78) | 0.335 | | |
| Intermediate | Reference | - | | |
| Poor | 1.60 (0.82-3.16) | 0.168 | | |
| Lung metastasis status | | | | |
| Presence (ref. absence) | 1.27 (0.64-2.51) | 0.494 | | |
| Bone metastasis status | | | | |
| Presence (ref. absence) | 1.22 (0.56-2.69) | 0.615 | | |
| Liver metastasis status | | | | |
| Presence (ref. absence) | 0.79 (0.28-2.25) | 0.660 | | |
| Lymph node metastasis status | | | | |
| Presence (ref. absence) | 1.44 (0.73-2.79) | 0.288 | | |
| cM status | | | | |
| cM1 (ref. cM0) | 1.67 (0.85-3.27) | 0.136 | | |
| Antibiotics | | | | |
| With (ref. without) | 2.65 (1.35-5.23) | 0.0048 | 2.56 (1.30-5.05) | 0.0067 |
| PPIs | | | | |
| With (ref. without) | 1.72 (0.89-3.32) | 0.109 | | |

When compared according to the administration of PPIs, complete response, partial response, stable disease, and progressive disease were, respectively, observed in four (9%), 16 (36%), 13 (30%), and eight (18%) patients who received PPIs. The corresponding numbers in those who did not receive PPIs were six (7%), 37 (44%), 23 (27%), and 13 (15%). The ORR did not significantly differ according to PPIs administration (45% *vs*. 50%, $p$=0.538).

## Discussion

This retrospective study, using real-world data from multiple institutions, showed that antibiotics administration before the initiation of ICI combination therapy was significantly associated with shorter PFS and OS in patients with advanced RCC. Multivariate analyses, adjusted for covariates, showed that antibiotics administration was an independent factor of shorter survival. In contrast, PPIs administration was not significantly associated with the outcomes.

Several studies have recently indicated a significant association between antibiotics administration and outcomes of ICIs for RCC. Derosa *et al*. reported that patients with RCC who received antibiotics had a significantly shorter PFS than those who did not receive nivolumab monotherapy as a subsequent therapy (16). Ueda *et al*. also reported a negative association between antibiotics administration and PFS in a cohort receiving nivolumab monotherapy or nivolumab plus ipilimumab combination therapy (17). However, in that study, patients treated with nivolumab plus ipilimumab comprised only a fraction of the entire cohort (9.7%). Therefore, to the best of our knowledge, this is the first study to indicate the prognostic impact of antibiotic administration in a cohort exclusively comprising patients treated with first-line ICI combination therapy, including IO-IO and IO-TKI therapies.

The mechanisms underlying the association between the gut microbiome and tumor immunity, as well as the efficacy of ICIs, have been intensively investigated. Some metabolites produced by intestinal bacteria, such as inosine and short-chain fatty acids, potentially enhance the therapeutic effects of ICIs by activating CD8+ T cells (18-20). In addition, the intestinal microbiota, impaired by ICIs, migrated out of the intestinal wall. Subsequently, the bacteria directly infiltrate the tumors, inducing the mobilization of immune cells (21, 22). Also, commensal Bifidobacterium has been reported to be

associated with the antitumor effects of PD-L1 blockade, while the intestinal Bacteroides fragilis plays an important role in the antitumor effects of CTLA-4 blockade (23). Thus, the administration of antibiotics potentially eliminates these intestinal bacteria, resulting in the reduction of the effectiveness of ICIs (23). Interestingly, it takes 4-6 weeks for the intestinal microflora to recover from the modifications caused by antibiotics (24). Collectively, our findings suggest that antibiotics administered one month before ICI initiation are associated with decreased effectiveness.

We did not find a significant association between PPIs administration and the outcomes of ICI combination therapy, which is inconsistent with the results of previous studies. Giordan *et al*. reported that patients who received PPIs had significantly shorter PFS and OS than those who did not for various types of cancers, including RCC (25). However, in that study, the association between PPI administration and outcomes was not analyzed in a cohort exclusively comprising patients with RCC. Taken together, our findings indicate that further studies are needed to determine the prognostic impact of PPIs administration in ICI treatment, particularly in the first-line setting.

*Study limitations*. First, this was a retrospective study with a small sample size, potentially inducing bias. Second, the dosage or treatment duration of antibiotics and PPIs was not assessed because of the lack of such data; these factors might also be associated with the outcomes. Third, patients requiring antibiotics might inherently have a poor prognosis owing to their impaired general condition, high number of comorbidities, or aggressive RCC, factors that also potentially affect survival.

## Conclusion

Real-world, multi-institutional data showed that the administration of antibiotics prior to the initiation of ICI combination therapy was significantly associated with poor survival in patients with advanced RCC. Therefore, careful and intensive monitoring of these patients is required.

## Conflicts of Interest

Toshio Takagi received honoraria from Bristol-Myers Squibb and Ono Pharmaceutical. Tsunenori Kondo received honoraria from Pfizer, Novartis, and Bristol-Myers Squibb and Ono Pharmaceutical.

## Authors' Contributions

Hiroki Ishihara conceived the study. Nanaka Katsurayama designed and analyzed the data. Nanaka Katsurayama and Hiroki Ishihara drafted the manuscript. All Authors revised the article for important intellectual content, reviewed the data and their analysis, and approved this article.

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