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Correlation Between First-line Immunotherapy and Second-line TKI Outcomes in Metastatic Renal Cell Carcinoma

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Abstract

Background/Aim: Immune checkpoint inhibitors (ICIs) have improved survival in metastatic renal cell carcinoma (mRCC), with nivolumab (NIVO) plus ipilimumab (IPI) showing benefits in intermediate- and poor-risk patients. Despite first-line efficacy, progression is common, requiring second-line therapies. Tyrosine kinase inhibitors (TKIs) are commonly administered after ICIs; however, the relationship between progression-free survival (PFS) in first- and second-line settings is not well defined. This study examined the correlation of PFS in patients with mRCC treated with ICIs followed by TKIs.

Patients and Methods: This retrospective multicenter study analyzed 66 patients with mRCC who received NIVO + IPI as first-line therapy and subsequent TKIs between September 2018 and February 2023. Patients were stratified according to the International Metastatic RCC Database Consortium (IMDC) risk classification.

Results: Median PFS for second-line TKIs was 6.9 months, and overall survival was 17.7 months. While no significant correlation was observed between first- and second-line PFS in the overall cohort or the IMDC intermediate-risk subgroup, a significant positive correlation was found in the poor-risk group (Spearman's rho=0.677, p=0.002).

Conclusion: Treatment outcomes in poor-risk patients may exhibit a predictable response pattern across therapy lines, potentially informing personalized treatment strategies.

Keywords: mRCC, ipilimumab, nivolumab, tyrosine kinase inhibitors, correlation analysis.

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Introduction

The combination of ipilimumab (IPI) and nivolumab (NIVO) is an established first-line immunotherapy for metastatic renal cell carcinoma (mRCC). This regimen has demonstrated a significant overall survival benefit in patients classified as intermediate- or poor-risk according to the International Metastatic RCC Database Consortium (IMDC). However, the objective response rate to IPI + NIVO is approximately 42%, and disease progression occurs in nearly 60% of patients within two years (1, 2).

Following progression, these patients commonly receive tyrosine kinase inhibitors (TKIs), such as cabozantinib, axitinib, pazopanib, or sunitinib, as second-line therapy (3). Importantly, unlike patients treated with other immune-oncology (IO)-based combination therapies (*e.g.*, NIVO + cabozantinib or pembrolizumab + lenvatinib), those progressing after IPI + NIVO are TKI-naïve. This distinction suggests the potential for favorable responses to subsequent TKI therapy. Nonetheless, predicting the efficacy of second-line treatment in this setting remains challenging.

This retrospective multicenter study aimed to assess the therapeutic efficacy of second-line TKIs in patients who received IPI + NIVO as first-line treatment for mRCC.

Patients and Methods

We retrospectively analyzed clinical data from 193 patients with mRCC who received NIVO and IPI as first-line therapy. Among these, 84 patients who underwent second-line treatment following NIVO + IPI between September 2018 and February 2023 at six institutions were identified: Jikei University School of Medicine (Tokyo), Kindai University Faculty of Medicine (Osaka), Fujita Health University School of Medicine (Aichi), Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences (Okayama), Osaka Medical and Pharmaceutical University (Osaka), and Tokyo Medical University (Tokyo), Japan. Patients with incomplete medical records or missing key data on treatment efficacy, such as imaging results or follow-up information, were excluded from the analysis. After applying these criteria, 66 patients were deemed eligible for inclusion. This study was conducted in accordance with ethical guidelines, and all patient data were anonymized to ensure confidentiality. The study protocol was approved by the Institutional Review Board of the lead institution, Osaka Medical and Pharmaceutical University (approval number: RIN750-2571).

All patients were categorized as intermediate- or poor-risk groups based on the IMDC criteria. Progression-free survival (PFS) was defined as the time from the start of combination therapy to either disease progression or death, whichever occurred first. Treatment efficacy was assessed based on RECIST v1.1 criteria.

To examine the potential association between PFS in first- and second-line treatments, Spearman's rank correlation coefficient was calculated. All statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). A p-value of <0.05 was considered statistically significant.

Results

A total of 66 patients with mRCC were included in this study. The median age at the initiation of second-line therapy was 66 years (range=25-86 years). Patient characteristics are summarized in Table I. Of the 66 patients, 86.4% (n=57) were male and 13.6% (n=9) were female. Based on the IMDC criteria, 63.6% (n=42) were classified as intermediate-risk and 36.4% (n=24) as poor-risk. The majority of tumors were histologically classified as clear cell carcinoma (70.0%, n=46), while 3.0% (n=2) were unclassified. The most common sites of metastasis included the lungs (68.2%, n=45), lymph nodes (54.5%, n=36), bones (36.4%, n=26), and liver (24.2%, n=16). Discontinuation of first-line therapy was primarily due to disease progression (90.9%, n=60), with fewer cases attributed to adverse events (6.1%, n=4) or other reasons

Table I. *Patients' characteristics.*

Number of patients (N)	66
Median age (range)	66 (25-86)
Sex, n (%)	
Male	57 (86.4)
Female	9 (13.6)
IMDC risk score at first line, n (%)	
Intermediate	42 (63.6)
Poor	24 (36.4)
Histology, n (%)	
Clear cell	46 (70)
Papillary	2 (3)
Unclassified	2 (3)
HD-related	2 (3)
Others	14 (21)
Metastatic site, n (%)	
Lung	45 (68.2)
Liver	16 (24.2)
Bone	26 (39.4)
Brain	3 (4.5)
Lymph node	36 (54.5)
Reasons for switching to second-line treatment, n (%)	
Progressive disease	60 (90.9)
Adverse event	4 (6.1)
Others	2 (3)
2nd line treatment, n (%)	
Cabozantinib	31 (47)
Axitinib	24 (36.4)
Pazopanib	10 (15.2)
Sunitinib	1 (1.5)

IMDC: International Metastatic Renal Cell Carcinoma Database Consortium; HD: hemodialysis.

(3.0%, n=2). Cabozantinib was the most frequently administered second-line TKI (47.0%, n=31), followed by axitinib (36.4%, n=24), pazopanib (15.2%, n=10), and sunitinib (1.5%, n=1). The median follow-up duration from the start of second-line therapy was 10.4 months (range=0.5-52.6 months). Median PFS and overall survival (OS) were 6.9 months [95% confidence interval (CI)=4.8-10.3] and 17.7 months (95%CI=9.4-28.3), respectively.

The objective response rate (ORR) for second-line therapy was 28.8%, and the disease control rate (DCR) was 62.1%. One patient achieved a complete response (CR), 18 patients (27.3%) achieved a partial response (PR), and 22 patients (33.3%) had stable disease (SD). The ORR and DCR for each second-line TKI were as follows: cabozantinib demonstrated an ORR of 25.8% and a DCR of 64.5%; axitinib showed an ORR of 29.2% and a DCR of 54.2%; pazopanib achieved the highest ORR at 40.0% and a DCR of 70.0%; while sunitinib, although associated with a DCR of 100%, yielded no objective responses.

Spearman's rank correlation analysis revealed no significant association between first-line (NIVO + IPI) PFS and second-line TKI PFS in the overall cohort of IMDC intermediate- and poor-risk patients (n=40; r=0.164, p=0.311; Figure 1A) or within the intermediate-risk group alone (n=22; r=–0.128, p=0.571; Figure 1B). However, in the poor-risk group, a strong positive correlation was observed (n=18; r=0.677, p=0.002; Figure 1C).

Among individual second-line TKIs, cabozantinib (n=21) demonstrated a significant positive correlation between first- and second-line PFS (r=0.479, p=0.028; Figure 1D), while axitinib (n=15) did not show a significant correlation (r=–0.0667, p=0.813; Figure 1E).

We further investigated factors associated with second-line PFS. Variables assessed included age (continuous), IMDC risk (poor *vs.* intermediate), histology (non-clear cell *vs.* clear cell RCC), treatment regimen (cabozantinib *vs.* others), presence of liver metastasis (yes *vs.* no), bone metastasis (yes *vs.* no), and neutrophil-to-lymphocyte ratio (≥3 *vs.* <3). In univariate analysis, IMDC poor-risk classification was significantly associated with shorter second-line PFS. In multivariate analysis, both IMDC risk [hazard ratio (HR)=2.984; 95% CI=1.272-7.000; p=0.012] and liver metastasis (HR=2.698; 95%CI=1.108-6.567; p=0.029) were independently associated with poor second-line PFS.

Discussion

Following disease progression after first-line IO–IO combination therapy, various TKIs are commonly employed as second-line treatments. However, clinical data regarding the efficacy of second-line TKIs in mRCC patients previously treated with IO combination therapies remain limited. In our analysis, prolonged PFS during first-line IO–IO therapy was associated with extended PFS during second-line treatment, specifically within the IMDC poor-risk subgroup.

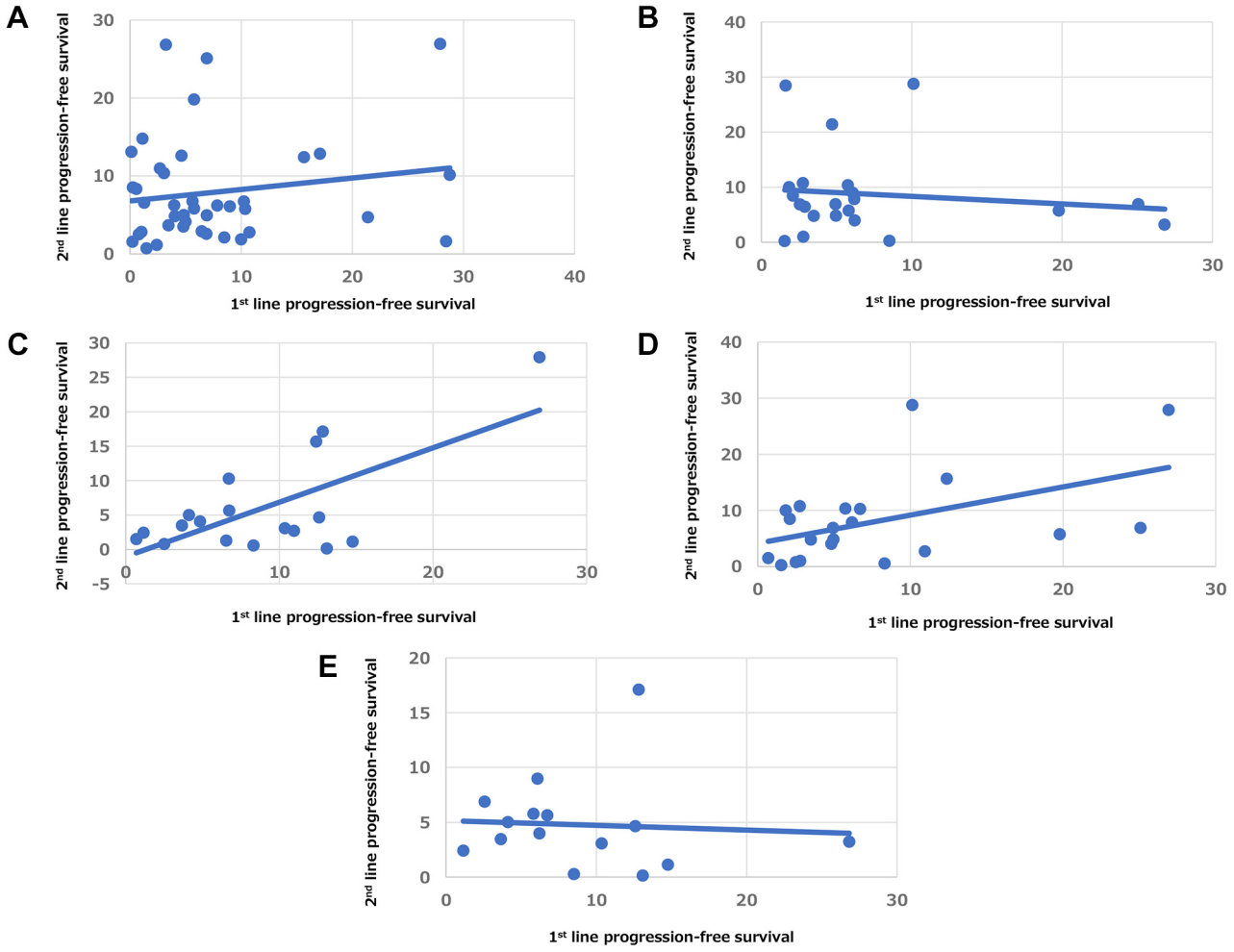

Figure 1. *Correlation between first-line progression-free survival (PFS) and second-line PFS. A) No significant correlation was observed between first-line PFS with nivolumab and ipilimumab and second-line PFS under tyrosine kinase inhibitor treatment when the IMDC intermediate- and poor-risk groups were analyzed together (Spearman's r=0.164, p=0.311; n=40). B) Similarly, no significant relationship was found for the IMDC intermediate-risk group alone (Spearman's r=-0.128, p=0.571; n=22). C) A significant correlation was observed in the IMDC poor-risk group (Spearman's r=0.677, p=0.002; n=18). D) Cabozantinib demonstrated a notable correlation between 1st and 2nd line PFS (Spearman's r=0.479, p=0.028; n=21). E) Axitinib exhibited no significant correlation between 1st and 2nd line PFS (Spearman's r=–0.0667, p=0.813; n=15).*

Several previous studies have explored the outcomes of second-line TKIs following IO-based therapies, particularly in the Japanese population. Matsushita *et al.* analyzed 189 patients who received first-line IO combination therapy and evaluated the efficacy of subsequent TKI treatment. They reported an ORR of 34.4%, a DCR of 68.8%, a median PFS of 9.7 months, and an OS of 23.1 months (4). Similarly, Fitzgerald *et al.* examined patients with metastatic clear cell RCC treated initially with IO combinations and reported a median PFS of 19 months after IO–IO therapy and 33 months after IO–TKI therapy in patients with IMDC intermediate- and poor-risk classifications (5). In contrast, Fujita *et al.* investigated the efficacy of second-line TKIs in patients with metastatic non-clear cell RCC and reported a shorter median PFS of 5 months following second-line therapy (6),

suggesting that histological subtype may significantly influence treatment efficacy.

Despite these findings, the relationship between first-line and second-line PFS remains unclear. In our study, no significant correlation was observed in the overall cohort. However, a distinct trend was evident in the IMDC poor-risk group, where outcomes in first-line therapy appeared to predict those in second-line treatment. Specifically, patients who experienced early progression during first-line IO–IO therapy tended to have poorer outcomes with second-line TKI treatment, whereas those with prolonged first-line PFS demonstrated more favorable second-line responses. This correlation suggests that treatment responsiveness may persist across therapeutic lines in certain patients and highlights the need for personalized treatment strategies. This observation is further supported by previous findings demonstrating the efficacy of IO–TKI combination therapy in IMDC poor-risk patients, where significantly longer PFS and OS were observed compared to TKI monotherapy. Such data reinforce the hypothesis that first-line treatment responsiveness may influence outcomes in subsequent lines of therapy, particularly in high-risk subgroups (7).

Among second-line TKIs, cabozantinib showed a particularly strong association between first- and second-line PFS, suggesting its potential utility in outcome prediction and risk-adapted treatment sequencing. While these findings are promising – especially for IMDC poor-risk patients – they do not establish causality and require prospective validation. Nonetheless, such data may inform future treatment algorithms or clinical guidelines for high-risk mRCC patients progressing after immunotherapy. Notably, patients with longer first-line PFS may derive greater benefit from subsequent therapies, underscoring the potential of first-line treatment response as a biomarker for individualized treatment planning.

Future studies should aim to identify clinical and biological factors underlying this correlation. Such insights may lead to improved risk stratification and more effective treatment selection for high-risk mRCC populations.

Study limitations. The relatively small sample size may have limited the statistical power and could explain the lack of correlation observed in the overall cohort. Additionally, our focus on PFS alone, without including OS, restricts the ability to fully assess long-term treatment effectiveness. Incorporating OS analyses in future research may provide a more comprehensive evaluation of therapeutic impact.

Conclusion

Our findings highlight a notable correlation between first- and second-line treatment outcomes in IMDC poor-risk mRCC patients. Early progression on first-line IO–IO therapy may indicate resistance to subsequent TKI treatment, emphasizing the need for tailored strategies for this high-risk subgroup.

Conflicts of Interest

KF received honoraria from Ono Pharmaceutical, Bristl-Meyers, Astellas, Takeda, Eisai, Pfizer, Janssen, AstraZeneca and Merck. The other Authors have no conflicts of interest to declare in relation to this study.

Authors' Contributions

KS and KF conceived and designed the study, conducted data collection and analysis, and drafted the manuscript. TM, TN, RM, TT, KM, TY, TY and SN contributed to study execution and data collection. KT was involved in drafting or critically revising manuscript.

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Artificial Intelligence (AI) Disclosure

During the preparation of this manuscript, a large language model (ChatGPT,) was used solely for language editing and stylistic improvements in select paragraphs. No sections involving the generation, analysis, or interpretation of research data were produced by generative AI.

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