ANTICANCER RESEARCH *41*: 5811-5816 (2021)
doi:10.21873/anticanres.15398

Real-world Outcomes of Tyrosine Kinase Inhibitors Immediately After Immune Checkpoint Inhibitors in Renal Cell Carcinoma

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Abstract. *Background/Aim: Immune checkpoint inhibitors (ICIs) have demonstrated a survival benefit for patients with cancer. However, the clinical outcomes of subsequent tyrosine kinase inhibitors (TKIs) after ICI failure in patients with metastatic renal cell carcinoma (mRCC) remain unclear. Patients and Methods: We retrospectively examined 38 patients with mRCC who started TKIs immediately after nivolumab with (combination group) or without ipilimumab (nivolumab group) between September 2016 and July 2019. Results: Of the 38 patients, 16 and 11 achieved partial response and stable disease, respectively, resulting in a 42.1% objective response rate and 71.1% disease control rate. The median progression-free survival (PFS) from TKI initiation was 8.8 and 12.9 months in the nivolumab and combination groups, respectively. PFS and overall survival were significantly longer in patients with long-term responses to previous ICI treatment (p=0.0152 and p=0.0155, respectively). Conclusion: TKIs demonstrate adequate anti-tumour activity after treatment with ICIs in real-world settings.*

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Key Words: Renal cell carcinoma, tyrosine kinase inhibitor, immune checkpoint inhibitor, nivolumab, ipilimumab.

Renal cell carcinoma (RCC) is the seventh most common cancer and accounts for 2.4% of all adult malignancies worldwide (1). The 5-year specific survival rate is reported to be approximately 71%, although 30% of RCC patients present with evidence of distant metastasis at initial diagnosis, which is associated with poor prognosis for patients in the advanced stage (1). To date, several molecular targeted therapies, including tyrosine kinase inhibitors (TKIs), such as sunitinib, sorafenib, pazopanib, cabozantinib, and axitinib, have been approved and have extended clinical prognosis in metastatic RCC (mRCC) patients (1).

Recently, immune checkpoint inhibitors (ICIs) have revolutionized the cancer field and have remarkably improved the prognosis of several types of cancer (1). In 2016, nivolumab emerged as a new target therapy for mRCC in Japan based on the results of the clinical trial Checkmate 025 (2, 3). Moreover, the combination of cytotoxic T-lymphocyte antigen 4 (CTLA-4) and programmed cell death 1 (PD-1) inhibitors, ipilimumab and nivolumab, became the preferred first-line therapy for mRCC patients with International Metastatic RCC Database Consortium (IMDC) intermediate or poor risk in 2018 (4, 5). However, as ICIs have been used over the years, only a subset of patients achieved a durable response, and the majority of patients developed progressive disease requiring subsequent molecular targeted therapy (6, 7). Given these circumstances, we need to optimize sequential treatments for mRCC patients who discontinued ICIs since real-world evidence is still limited regarding the treatment sequences for mRCC patients who discontinued ICIs, and no prospective clinical trial

evaluating the efficacy of molecular targeted therapy following ICIs has been reported.

In the present study, we aimed to report the real-world efficacy and safety of TKI therapy immediately after discontinuation of ICIs in patients with mRCC. In particular, we focused on mRCC patients treated with second-line nivolumab and first-line nivolumab plus ipilimumab to evaluate the efficacy of TKI therapy after ICI discontinuation.

Patients and Methods

Patients. We conducted a retrospective study aimed to investigate the clinical outcome of TKIs as a third-line therapy after second-line nivolumab monotherapy (nivolumab group) and as a second-line therapy after first-line nivolumab plus ipilimumab therapy (combination group). A total of 38 patients with mRCC were identified between September 2016 and July 2019 (nivolumab group, n=24; combination group, n=14). For each patient, we collected demographic data and disease characteristics including age, sex, Karnofsky Performance Status, IMDC risk group, tumour histology, and sites of metastasis.

Evaluation of response was performed by computed tomography, according to Response Evaluation Criteria in Solid Tumors version 1.1, every 2-3 months. For each patient, we measured the best response during treatment including the complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD). Progression-free survival (PFS) was defined as the time from the start of TKI therapy to the documented progression or death from any cause. Overall survival (OS) was defined as the time from the start of TKI therapy to the documented death from any cause or last contact. We also collected data on the adverse events (AEs) during TKI treatment using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) ver 5.0.

The study was approved by the Institutional Review Board of each institution (approval number 018-0003 at the Osaka University Hospital) and was conducted in accordance with the Declaration of Helsinki.

Treatment schedule. Nivolumab monotherapy was administered by intravenous infusion at a dose of 3 mg/kg or 240 mg/kg every 2 weeks, while nivolumab plus ipilimumab was administered every 3 weeks for the first four cycles, followed by nivolumab every 2 weeks until disease progression, clinical deterioration, unacceptable toxicity, or patient's refusal. TKI therapy was initially administered to all included patients at the standard dose and subsequently reduced depending on the level of AEs.

Statistical analysis. PFS and OS in the nivolumab and combination groups were estimated using the Kaplan–Meier method and compared using the log-rank test. Differences were considered significant at $p<0.05$. All statistical analyses were conducted using JMP software (version 14.0; SAS Institute, Cary, NC, USA).

Results

Patient characteristics. The clinical characteristics of all patients at baseline are summarized in Table I. The median age of patients in the nivolumab and combination group was 61 years (range=42-80 years) and 67.5 years (range=52-83 years), respectively. The most prevalent histological type was clear cell carcinoma, which was present in 19 (79.2%) patients in the nivolumab group and 12 (76.2%) in the combination group. The nivolumab group consisted mostly of patients with IMDC intermediate risk (75.0%), especially IMDC risk score 1 (70.8%). For the combination group, 57.1% and 42.9% of patients were classified as intermediate and poor risk, respectively.

The median duration of TKI therapy was 7.3 months (range=0.3-23.9 months). As shown in Table II, the most common treatment immediately after discontinuation of nivolumab and combination therapy was axitinib (91.7% and 71.4%, respectively).

Clinical outcomes of patients with TKI after ICI discontinuation. In the nivolumab group, the best overall responses were PR in 12 patients and SD in 7 patients, resulting in an ORR of 50.0% and DCR of 79.2% (Table III). Among the 14 patients in the combination group, PR was achieved in 4 patients, and SD was observed in 4 patients, resulting in an ORR of 28.6% and DCR of 57.2% (Table III). Overall, the median PFS was 8.8 months and 12.9 months in the nivolumab and combination groups, respectively (Figure 1). The median OS was 23.4 months and 12.9 months in the nivolumab and combination groups, respectively (Figure 2).

We further investigated whether the duration of response to previous ICI treatment affects the clinical efficacy of TKI therapy in mRCC patients. In the present study, considering the median PFS in the clinical trial of nivolumab (Checkmate 025) (2) and nivolumab plus ipilimumab (Checkmate 214) (4), we defined long-term response (LTR) and short-term response (STR) as patients with a PFS of ≥6 and <6 months to previous ICI therapy, respectively. As result, the number of patients with LTR was 21 (12 and 9 patients for nivolumab and combination group, respectively), whereas those with STR was 17 (12 and 5 patients for nivolumab and combination group, respectively). Interestingly, patients with LTR in previous ICI treatment showed significantly longer durations of response to subsequent TKI than those with STR in previous ICI treatment ($p=0.0152$, Figure 3A). In addition, OS from subsequent TKI treatment was significantly longer in patients with LTR in the previous ICI treatment ($p=0.0155$, Figure 3B).

Safety analysis. Specific details regarding the AEs reported in our study are shown in Table IV. Grade 3-4 AEs occurred in 27 (71.1%) and 4 (10.5%) patients in both groups, respectively. No treatment-related deaths were reported. Hypertension (n=11) and diarrhea (n=11) were the most common AEs. All AEs were generally manageable with a dose reduction of the treatment. Only 3 (7.9%) patients discontinued TKI because of grade 3 AEs, including liver dysfunction (n=1), anemia (n=1), and hypertension (n=1).

Table I. *Characteristics of patients in nivolumab and combination groups.*

	Nivolumab monotherapy	Combination therapy	Total
Number of patients	24	14	38
Gender			
Male	17 (70.8)	12 (83.3)	29 (76.3)
Female	7 (29.2)	2 (16.7)	9 (23.7)
Age, median	61 (42-80)	67.5 (52-83)	
<65	15 (62.5)	4 (33.3)	19 (50.0)
≥65	9 (37.5)	10 (66.7)	19 (50.0)
Karnofsky performance status			
80-100	23 (95.8)	12 (88.1)	35 (92.1)
<80	1 (4.2)	2 (11.9)	3 (7.9)
Number of metastatic sites			
Single	11 (45.8)	5 (26.2)	16 (42.1)
Multiple	13 (54.2)	9 (73.8)	22 (57.9)
Tissue type			
Clear	19 (79.2)	12 (76.2)	31 (81.6)
Non-clear	5 (20.8)	2 (23.8)	7 (18.4)
International metastatic RCC database consortium risk			
Favorable	4 (16.7)		
Inter (score 1)	17 (70.8)	1 (7.1)	18 (47.4)
Inter (score 2)	1 (4.2)	7 (50.0)	8 (21.1)
Poor (score 3)	2 (8.3)	3 (21.4)	5 (13.2)
Poor (score >3)	0 (0)	3 (21.4)	3 (13.2)
Completeion of ipilimumab		9 (64.3)	
Neutrophil-lyphocyte ratio			
Low (<4)	20 (83.3)	10 (76.2)	30 (78.9)
High (≥4)	4 (16.7)	4 (23.8)	8 (21.1)
C-reactive protein			
Low (<1.0)	17 (70.8)	10 (26.2)	27 (71.1)
High (≥1.0)	7 (29.2)	4 (73.8)	11 (28.9)

Table II. *TKI regimens immediately after ICI discontinuation.*

	Nivolumab monotherapy n=24	Combination therapy n=14	Total n=38
n (%)			
Axitinib	22 (91.7)	10 (71.4)	32 (84.2)
Pazopanib	0 (0)	2 (14.3)	2 (5.3)
Cabozantinib	1 (4.2)	1 (7.1)	2 (5.3)
Sunitinib	1 (4.2)	1 (7.1)	2 (5.3)

Table III. *Clinical outcomes with TKI therapy after ICI discontinuation.*

	Nivolumab monotherapy n=24	Combination therapy n=14	Total n=38
Best response, n (%)			
PR	12 (50.0)	4 (28.6)	16 (42.1)
SD	7 (29.2)	4 (28.6)	11 (28.9)
PD	5 (20.8)	6 (42.8)	11 (28.9)
ORR			
n (%)	12 (50.0)	4 (28.6)	16 (42.1)
DCR			
n (%)	19 (79.2)	8 (57.1)	27 (71.1)

DCR: Disease control rate; ORR: objective response rate; SD: stable disease; PD: progressive disease; PR: partial response.

Discussion

The treatment of mRCC has been dramatically changed twice in the past two decades, with the introduction of targeted therapies and subsequent introduction of ICIs (8). Recently, ICI therapy was moving upfront in mRCC treatments, as seen in the approval of combination therapy such as nivolumab and ipilimumab or nivolumab monotherapy as the first- or second-line therapy in mRCC patients based on the results of clinical trials (2, 4). However, there are minimal data regarding the use and efficacy of subsequent lines of treatment in real-world settings (9). Hence, in this study, we performed the data analysis of mRCC patients treated with TKI therapy who received ICI therapy, nivolumab alone or with ipilimumab as previous treatments, and provide evidence on clinical outcomes and the incidence of AEs.

First, we confirmed that the effect of TKI therapy after ICI discontinuation was promising, as evidenced by the high ORR (42.1%) and DCR (71.1%) (Table III), leading to the clinical benefit of long mPFS and OS (Figure 1 and Figure 2). Our findings partially align with those reported by Auvray *et al*. who described patients treated with TKIs after first-line nivolumab plus ipilimumab demonstrating an ORR to subsequent TKI of 36% and a median PFS of 8 months (95%CI=5.0-13.0) (10). Tomita *et al*. also reported the clinical outcomes of TKIs after nivolumab (Checkmate 025) and nivolumab plus ipilimumab (Checkmate 214) in the Japanese population, which showed ORRs of 27% and 32% (all risks) and median PFS of 8.9 and 16.3 months, respectively (11). Given that our cohort in the combination group mainly consisted of IMDC poor risk patients (42.8%), TKI after combination therapy was deemed effective even in the real world. Furthermore, third-line TKIs after first-line TKIs and second-line nivolumab achieved 50.0% ORR and 79.2% DCR, and the median PFS was 9.0 months, which is slightly better than that in previous reports of mRCC (9, 12-15). These results led to the hypothesis that nivolumab therapy may affect the response to subsequent TKI therapy by modifying the tumour microenvironment (16). Pal *et al*. characterized the mutational landscape of circulating tumor DNA (ctDNA) in mRCC patients and found that specific acquired mutations affected clonal evolution in mRCC throughout several types of TKI therapy (17). Such an analysis would help to predict the

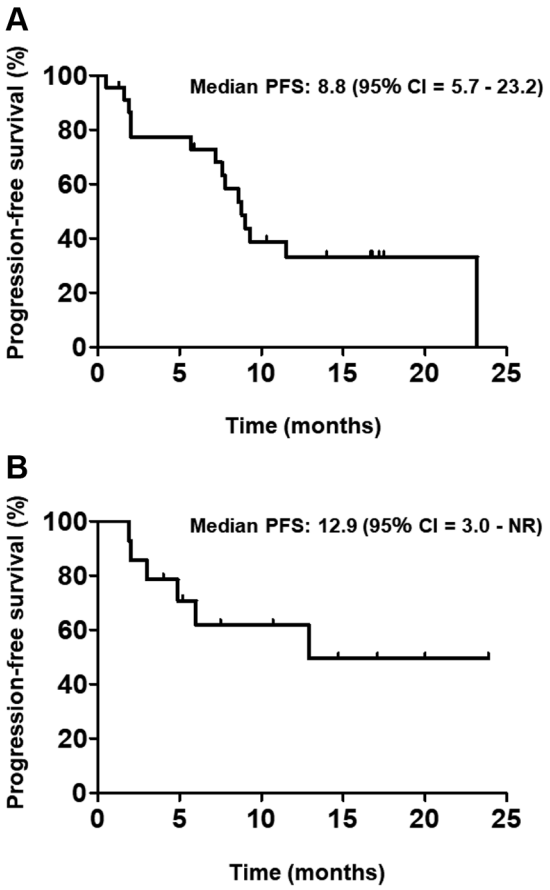

Figure 1. *Progression-free survival for all metastatic renal cell carcinoma patients treated with tyrosine kinase inhibitor (TKI) therapy immediately after immune checkpoint inhibitor (ICIs). (A) Progression-free survival (PFS) after the initiation of TKI therapy after second-line nivolumab monotherapy (nivolumab group) and (B) after second-line nivolumab plus ipilimumab (combination group). NR: Not reached.*

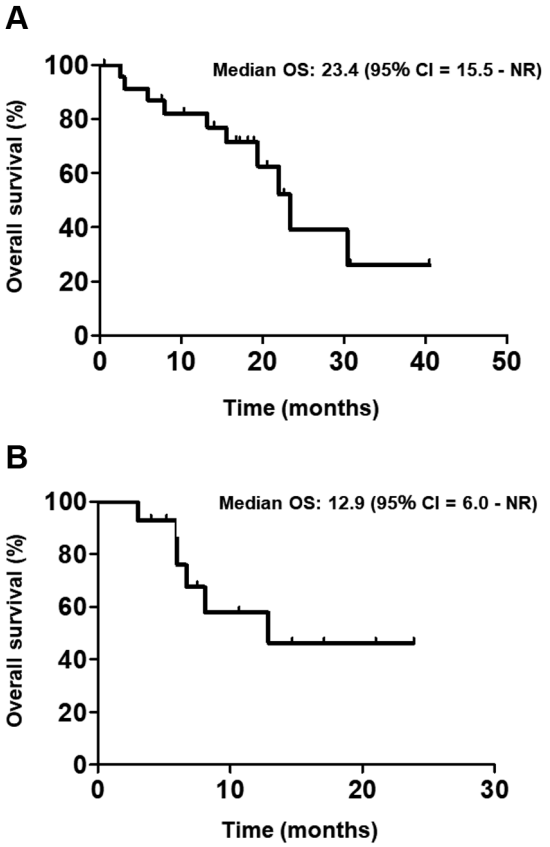

Figure 2. *Overall survival for all metastatic renal cell carcinoma patients treated with tyrosine kinase inhibitor (TKI) therapy immediately after immune checkpoint inhibitors (ICIs). (A) Overall survival (OS) after the initiation of tyrosine kinase inhibitor (TKI) therapy after second-line nivolumab monotherapy (nivolumab group) and (B) after second-line nivolumab plus ipilimumab (combination group). NR: Not reached.*

Table IV. *Summary of adverse events following TKI therapy after I-O discontinuation.*

	Nivolumab monotherapy		Combination therapy		Total	
	Any Grades, n (%)	Grade 3-4, n (%)	Any Grades, n (%)	Grade 3-4, n (%)	Any Grades, n (%)	Grade 3-4, n (%)
All event	16 (66.7)	3 (12.5)	11 (78.6)		27 (71.1)	4 (10.5)
Hypertension	6 (25.0)	1 (4.2)	4 (28.6)		11 (28.9)	1 (2.6)
Hoarseness	3 (12.5)		2 (14.3)		5 (13.2)	
Oral ulcer	2 (8.3)		1 (4.2)		3 (7.9)	
Dysgeusia	1 (4.2)				1 (2.6)	
Proteinuria			2 (14.3)		2 (5.3)	
Hypothyroidism	2 (8.3)		4 28.6)		6 (15.8)	
Diarrhea	6 (25.0)	1 (4.2)	4 28.6)		11 (28.9)	1 (2.6)
Fatigue	1 (4.2)		3 (12.5)		4 (10.5)	
Anemia		1 (4.2)			1 (2.6)	1 (2.6)
Liver dysfunction	1 (4.2)			1 (4.2)	2 (5.3)	1 (2.6)
Hand foot syndrome	4 (16.7)		2 (14.3)		6 (15.8)	

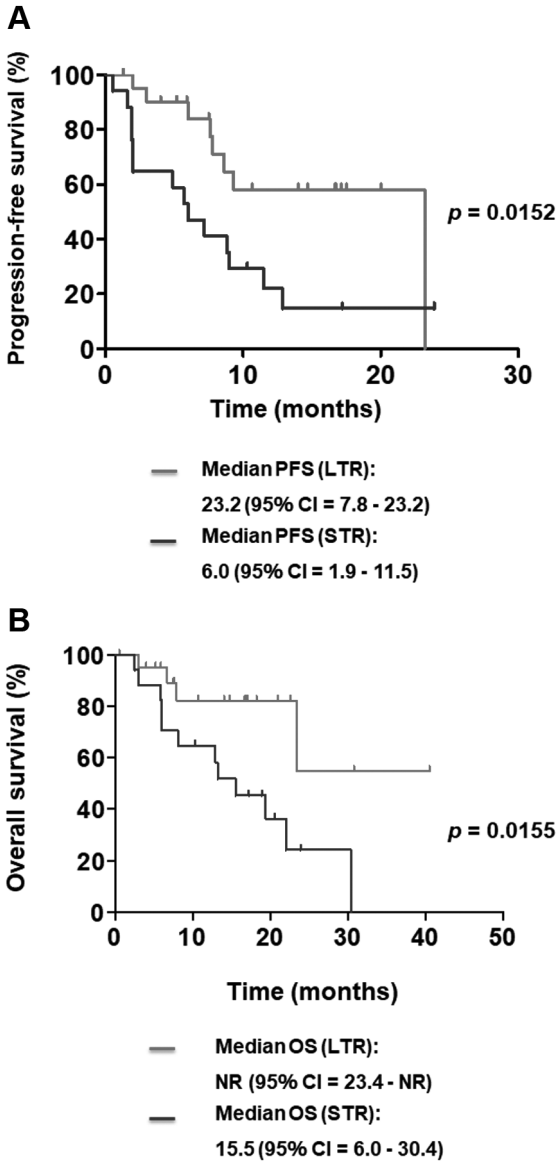

Figure 3. *Survival analysis for patients who received tyrosine kinase inhibitor (TKI) therapy after long-term and short-time response to previous immune checkpoint inhibitor (ICI) treatments. (A) Progression-free survival (PFS) and (B) overall survival (OS) of patients who received TKI therapy after long-term (n=21, LTR) and short-term response (n=17, STR) to previous ICI treatments. NR: Not reached.*

clinical response to TKI therapy in mRCC patients after discontinuation of ICIs.

Second, we found that PFS from the start of TKI therapy (PFS2) was significantly longer in patients with a durable response from the start of ICI therapy (PFS1) for more than 6 months (LTR). Our results align with the data published by Auvray *et al*., who reported that long-term responders receiving nivolumab plus ipilimumab therapies (patients with ≥6 months PFS) exhibited better prognosis after TKI initiation than short-term survivors (patients with <6 months PFS) among mRCC patients (10). Indeed, prolonged nivolumab binding to CD8 T cells was detected more than 20 weeks after the last infusion, regardless of the total number of nivolumab infusions in patients with non-small cell lung cancer (18). These findings suggest that TKI may have additive anti-tumor effects in combination with residual activated nivolumab-bound T cells, which may contribute to better prognosis of patients with mRCC.

Third, 71.1% of patients characterized the toxicity profile as acceptable and AEs as manageable. Severe AEs (grade 3-4 AEs) occurred in only four patients (10.5%). None of the patients had previously discontinued ICI therapy due to toxicity. A previous report also showed that only 9.1% of mRCC patients discontinued TKI therapy due to intolerable AEs after first-line ICI therapy (10). Based on these data, we suggest that TKI therapy could be safely applied with an AE profile similar to historical data for first-line TKIs.

This study has some limitations. First, this was a retrospective and observational study with a small sample size and was therefore subject to possible selection bias. Second, only the data entered into the medical records were available for analysis, which may lead to underestimation of disease and AE frequency. Further multi-institutional studies are needed to validate our results in larger numbers of patients.

In conclusion, the current analysis reveals the clinical effectiveness of TKI therapy following ICI therapy and demonstrates that mRCC patients benefit from targeted therapy after progression with ICI therapy. In a real-world setting, this study also validated that TKI immediately after ICI therapy is safe and effective for mRCC patients, assuring clinicians in deciding the treatment process following failure of ICI therapy.

Conflicts of Interest

The Authors declare that they have no conflicts of interest in relation to this study.

Authors' Contributions

T. K. was responsible for the study conception and design, conducted the study, collected and analyzed data, and drafted the manuscript. A. N., N. K., W. N., T.S, K.M, K.H, A.K, T.U, R.I, K.N, S.Y, T.T, M.T, S.T, M.N, K.N, N.N, and M.U conducted the study, collected and analyzed data, drafted the manuscript, and revised the manuscript. All Authors read and approved the final manuscript for submission.

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Received August 29, 2021
Revised September 26, 2021
Accepted September 27, 2021