CANCER DIAGNOSIS & PROGNOSIS *6*: 125-134 (2026)
doi: 10.21873/cdp.10513

Comparison of IO-IO and IO-TKI Treatment Outcomes in Metastatic Renal Cell Carcinoma: Influence of Metastatic Site Count

HIROSHI KIKUCHI[1], TAKAHIRO OSAWA[1], SEI NAITO[2], KAZUYUKI NUMAKURA[3], OJIRO TOKAIRIN[1], YUKI TAKAI[2], YUYA SEKINE[3], HARUKA MIYATA[1], RYUJI MATSUMOTO[1], TAKASHIGE ABE[1], YOICHI ITO[4], TOMONORI HABUCHI[3], NORIHIKO TSUCHIYA[2] and NOBUO SHINOHARA[1]

[1]Department of Renal and Genitourinary Surgery, Graduate School of Medicine, Hokkaido University, Sapporo, Japan;
[2]Department of Urology, Yamagata University Faculty of Medicine, Yamagata, Japan;
[3]Department of Urology, Akita University Graduate School of Medicine, Akita, Japan;
[4]Clinical Research and Medical Innovation Center, Hokkaido University Hospital, Sapporo, Japan

Abstract

Background/Aim: The therapeutic efficacy of Immuno-Oncology combination therapy based on the number of metastatic organs in renal cancer has yet to be examined. Therefore, we herein compared the efficacy of dual immune checkpoint blockade (IO-IO) and combination of immunotherapy with tyrosine kinase inhibitors (IO-TKI) strategies in metastatic renal cell carcinoma (mRCC), with a focus on how the number of metastatic organs affects clinical outcomes.

Patients and Methods: This retrospective study included 147 patients with mRCC treated with systemic therapies between August 2015 and July 2023. A multivariable Cox proportional hazards model was used to examine the relationships between clinical parameters and survival. To examine whether the effects of the number of metastatic organs on survival varied between treatment regimens, interaction terms were evaluated.

Results: In the multivariate Cox regression analysis, IMDC poor risk [hazard ratio (HR)=1.95; 95% confidence interval (CI)=1.19-3.18] and the presence of three or more metastatic organs in the IO-TKI group (HR=3.72; 95% CI=1.35-10.23) were identified as independent predictors of progression-free survival (PFS). In the IO-TKI group, patients with <3 metastatic organs had longer PFS than those with ≥3 metastatic organs. No significant difference in PFS was observed between <3 and ≥3 metastatic organs in the IO-IO group. This differential effect of the metastatic burden was confirmed by a significant interaction between the treatment group and number of metastatic organs (*p* for interaction=0.001).

continued

Dr. Takahiro Osawa, Department of Urology, Hokkaido University, Graduate School of Medicine, N15 W7 Kita-ku, Sapporo, 060-8638 Japan. Tel: +81 117065966, Fax: +81 117067853, e-mail: taka0573@gmail.com

Received August 12, 2025 | Revised September 22, 2025 | Accepted October 1, 2025

Conclusion: The number of metastatic organs affects the efficacy of IO-TKI but has no effect on the efficacy of IO-IO treatment. We recommend considering the number of metastatic organs as an additional prognostic factor to optimize treatment selection for patients with mRCC.

Keywords: Renal cell carcinoma, dual immune checkpoint blockade, immune-oncology combination therapy, systemic treatment, tyrosine kinase inhibitors, metastasis.

Introduction

In the last decade, the treatment landscape for advanced renal cell carcinoma (RCC) has been revolutionized by recent advances in immunotherapy. Dual immune checkpoint blockade (IO-IO) and the combination of immunotherapy with tyrosine kinase inhibitors (IO-TKI) have emerged as two promising approaches in the management of metastatic RCC (mRCC) (1-4). IO-IO regimens, which typically include agents targeting complementary immune pathways, aim to synergistically enhance the anti-tumor immune response, while IO-TKI combinations not only modulate immune activity, but also target tumor angiogenesis and other oncogenic pathways that are critical for tumor growth and dissemination (5, 6).

Clinical trials showed that survival outcomes were significantly better with the IO-IO and IO-TKI combinations than with conventional therapies; however, the degree of benefit appeared to vary with the metastatic burden and disease distribution (7, 8). In IO-IO, the tumor burden has been reported to correlate with prognosis, with a higher tumor burden being associated with a poorer prognosis (7, 9). Nevertheless, the impact of the number of metastatic organs, a simple and clinically accessible variable, on the efficacy of these therapeutic strategies has not yet been characterized in detail. A deeper understanding of how metastatic patterns affect treatment responses may lead to more personalized treatment strategies.

Therefore, the present study aimed to investigate differences in treatment efficacy between IO-IO and IO-TKI combinations in mRCC patients, with a focus on the impact of the number of metastatic organs on treatment outcomes.

Patients and Methods

Study design. This was a retrospective study conducted by three institutions (Akita University Hospital, Hokkaido University Hospital, and Yamagata University Hospital). The Ethics Committee of Hokkaido University approved the present study (Approval no. 023-0105). Informed consent was waived though the use of an opt-out method.

Study population. The present study included 176 mRCC patients who were treated with IO combination therapy as the first-line treatment at three institutions between August 2015 and July 2023. Of 176 patients, International Metastatic RCC Database Consortium (IMDC) favorable risk cases (n=24) were excluded. Furthermore, after the exclusion of five patients [without a pathology (n=1), less than four weeks of treatment (n=3), and missing detailed data (n=1)], 147 were ultimately included in the present study. Data collected included age, sex, histology, the IMDC risk status, treatment regimen and outcomes, previous nephrectomy, and the number of metastatic organs.

Evaluation. Initially, we estimated overall survival (OS) and progression-free survival (PFS) for the entire cohort. The best overall response (BOR) in the first-line treatment, PFS with the first-line treatment, and OS in the IO-IO and IO-TKI groups were the primary endpoints assessed. Subsequently, a comparative analysis was conducted between the PFS and OS of the IO-IO and IO-TKI groups, with the metrics evaluated based on the number of metastatic organs. The percentage of patients exhibiting a complete or partial response was determined to be the best response, and this response was designated as BOR.

Statistical analysis. Continuous variables are presented as median (interquartile range; IQR), while categorical variables are as counts and percentages. The differences in patient characteristics were analyzed utilizing the chi-square test or Fisher's exact test (for categorical variables) or with Student's *t*-test, for continuous variables. PFS was calculated from the initiation of the immunotherapy combination to the date of first progression or death, whichever occurred first. OS was calculated from the initiation of the immunotherapy combination to death. Patients without an event were censored at the date of last follow-up. OS and PFS curves were estimated using the Kaplan-Meier method and comparisons between the groups were performed using the Log-rank test. A multivariable Cox proportional hazards model was used to investigate associations between patient characteristics and OS or PFS. We evaluated whether the effect of treatment (IO-IO *vs*. IO-TKI) on survival differed by IMDC risk group and the number of metastatic organs (<3 *vs*. ≥3) by including interaction terms in a Cox proportional hazards model. The statistical significance of these differences was set at a *p*-value of less than 0.05. The analysis of the data was conducted using JMP version 17 (SAS Institute).

Results

Patient characteristics. Patient characteristics are shown in Table I. A total of 103 patients received IO-IO and 44 received IO-TKI. The median observation time from the initiation of drug treatment was 16.0 months (IQR=6.3–31.4). The median age of the entire group was 68 years (IQR=63-73). In total, 81.0% of patients had a clear cell pathology and 45.6% underwent nephrectomy prior to the drug treatment. Overall, 67.4% of patients had less than three metastatic organs at baseline (63.1 and 77.7% in the IO-IO and IO-TKI groups, respectively). No significant difference was observed in the frequency of metastasis by organ between the IO-IO and IO-TKI groups.

Treatment outcomes in IO-IO and IO-TKI groups. BOR in the IO-IO and IO-TKI groups are shown in Table II. Objective response rates were 44.7% for IO-IO and 63.6% for IO-TKI. Median OS and PFS in the entire cohort were not reached (NR) (95% CI=40.1-NR) and 12.9 months (95% CI=8.7-17.1), respectively (Figure 1). Median OS did not differ between the IO-IO and IO-TKI groups (NR and 43.4, respectively; p=0.1497), while median PFS was lower in the IO-IO group compared to the IO-TKI group (10.1 *vs*. 24.2, p=0.0215) (Supplementary Figure 1). The clinical course from the first- to second-line treatment is shown in Figure 2. Progressive disease was observed after the first-line treatment in 67.0% and 36.3% of patients in the IO-IO and IO-TKI groups, respectively. Eighteen (17.4%) and 22 (50.0%) patients in the IO-IO and IO-TKI groups, respectively, continued the first-line treatment. Forty-five (43.7%) and 13 (29.5%) patients in the IO-IO and IO-TKI groups, respectively, moved to the second-line treatment. Cabozantinib was the most frequently used drug in the second-line treatment (Supplementary Table I).

Comparison of treatment outcomes between IO-IO and IO-TKI groups according to the number of metastatic organs. Patients were further classified according to the number of metastatic organs (<3 or ≥3). Among patients with <3 or ≥3 metastatic organs, there was no significant difference in the pattern of metastatic organ involvement between the IO-IO and IO-TKI groups (Supplementary Table II and III). Kaplan-Meier curves for PFS and OS were also calculated for each treatment group stratified by the number of metastatic organs (Figure 3A, Supplementary Figure 2A). PFS was longer in patients who were treated with IO-TKI and had <3 metastatic organs than in those who were treated with IO-TKI and had ≥3 metastatic organs (median PFS=NR, 95% CI=11.5-NR *vs.* median PFS=7.0, 95% CI=2.8-13.8, p=0.0032). On the other hand, no significant difference was noted between patients with <3 and ≥3 metastatic organs in the IO-IO group. In the multivariate Cox regression for PFS, IMDC poor risk was associated with shorter PFS compared to intermediate risk (HR=1.95, 95% CI=1.19-3.18) (Table III). Among patients with <3 metastatic organs, those treated with IO-TKI had longer PFS compared to those treated with IO-IO (HR=0.38, 95%

Table I. *Demographic and clinical-pathological characteristics of the metastatic renal cell carcinoma (mRCC) patient cohort.*

	All (N=147)	IO-IO (N=103)	IO-TKI (N=44)	*p*-Value
Follow-up duration, months, median (IQR)	16.0 (6.3-31.4)	18.8 (6.5-32.5)	9.8 (6.3-26.6)	0.14
Age, years, median (IQR)	68 (63-73)	68 (62-72)	71 (65-74)	0.08
Sex, N (%)				0.05
Male	115 (78.2)	85 (82.5)	30 (68.2)	
Female	32 (21.8)	18 (17.5)	14 (31.8)	
IMDC, N (%)				0.01
Intermediate	83 (56.5)	51 (49.5)	31 (72.7)	
Poor	64 (43.5)	52 (50.5)	12 (27.3)	
Subtype, N (%)				0.53
Clear	119 (81.0)	82 (79.6)	37 (84.1)	
non-clear/not confirmed	28 (19.0)	21 (20.4)	7 (15.9)	
1st-line treatment, N (%)				
Nivolumab + Ipilimumab	103 (70.1)	103 (100)	0	
Avelumab + Axitinib	7 (4.8)	0	7 (15.9)	
Pembrolizumab + Axitinib	12 (8.2)	0	12 (27.3)	
Nivolumab + Cabozantinib	8 (5.4)	0	8 (18.2)	
Pembrolizumab + Lenvatinib	17 (11.6)	0	17 (38.6)	
Prior nephrectomy, N (%)				0.06
Yes	67 (45.6)	41 (39.8)	26 (59.1)	
No	80 (54.4)	62 (60.2)	18 (40.9)	
Number of metastatic organs at baseline, N (%)				0.12
1	56 (38.1)	35 (34.0)	21 (47.7)	
2	43 (29.3)	30 (29.1)	13 (29.6)	
3	29 (19.7)	26 (25.2)	3 (6.8)	
4	10 (6.8)	6 (5.8)	4 (9.1)	
>5	9 (6.1)	6 (5.8)	3 (6.8)	
Metastatic organ sites at baseline				
Lung	99 (67.3)	68 (66.0)	31 (70.5)	0.60
Liver	26 (17.7)	20 (19.4)	6 (13.6)	0.40
Lymph node	56 (38.1)	40 (38.8)	16 (36.4)	0.78
Bone	49 (33.3)	39 (37.9)	10 (22.7)	0.07
Brain	16 (10.9)	11 (10.7)	5 (11.4)	0.90
Pancreas	18 (12.2)	13 (12.6)	5 (11.4)	0.83
Others	52 (35.4)	38 (36.9)	14 (31.8)	0.56
Status, N (%)				
Continued efficacy of the 1st-line treatment	58 (39.5)	31 (30.1)	27 (61.4)	
PD on the 1st line; continuation of the 1st line	6 (4.1)	4 (3.9)	2 (4.6)	
PD on the 1st line; move to the 2nd line	54 (36.7)	42 (40.8)	12 (27.3)	
PD on the 1st line; treatment interrupted	4 (2.7)	4 (3.9)	0 (0.0)	
Discontinue the 1st line without PD; move to the 2nd line	4 (2.7)	3 (2.9)	1 (2.3)	
Death without the 2nd-line treatment	21 (14.3)	19 (18.5)	2 (4.6)	
Outcome, N (%)				
Alive	102 (69.4)	66 (64.1)	36 (81.8)	
RCC-related death	39 (26.5)	31 (30.1)	8 (18.2)	
Other causes of death	6 (4.1)	6 (5.8)	0 (0.0)	

IO, Immune-oncologic drug; TKI, tyrosine kinase inhibitor; IQR, interquartile range; IMDC, international metastatic renal cell carcinoma database consortium; PD, progressive disease; RCC, renal cell carcinoma.

CI=0.18-0.81), based on multivariable Cox proportional hazards regression model analysis, adjusted for age, sex, histology, nephrectomy, and IMDC risk (Figure 3B). Interactions between treatment group (IO-IO *vs.* IO-TKI) and IMDC risk status, as well as between treatment group and the number of metastatic organs (<3 *vs.* ≥3), were tested to determine whether the survival benefit differed across these subgroups (Table IV). We found a statistically

Table II. *Best overall response to the first-line treatment.*

	All (N=147)	IO-IO (N=103)	IO-TKI (N=44)	*p*-Value
Complete response, N (%)	8 (5.4)	5 (4.9)	3 (6.8)	0.16
Partial response, N (%)	66 (44.9)	41 (39.8)	25 (56.8)	
Stable disease, N (%)	43 (29.3)	32 (31.1)	11 (25.0)	
Progression of disease, N (%)	30 (20.4)	25 (24.3)	5 (11.4)	

IO, Immune-oncologic drug; TKI, tyrosine kinase inhibitor.

significant interaction only between treatment group and number of metastatic organs (*p* for interaction=0.001). Specifically, although treatment had no significant effect on PFS in patients with ≥3 metastatic organs, IO-TKI treatment was associated with significantly longer PFS compared to IO-IO, among patients with <3 metastatic organs.

Discussion

We herein investigated how the number of metastatic organs affected the efficacy of IO combination therapy in patients with mRCC. Patients under treatment with IO-TKI and with fewer than three metastatic organs had significantly longer PFS, whereas in patients treated with IO-IO, the number of metastatic organs was not associated with PFS.

Previous studies have examined the relationship between the tumor burden and the efficacy of IO-based therapies (7, 9); however, data specifically addressing the number of metastatic organs remain limited. In the era of TKI monotherapy, the number of metastatic organs and the tumor burden have been associated with the prognosis of patients. Basappa *et al*. showed that in a group of patients treated with sunitinib, patients with a single metastatic organ had a better prognosis than those with multiple metastatic organs (10). Roviello *et al*. also reported similar findings in a group of favorable-risk patients treated with TKI (sunitinib or pazopanib) (11). In the IO era, a *post hoc* analysis of the CLEAR trial demonstrated that fewer metastatic sites were associated with longer survival in patients receiving lenvatinib plus pembrolizumab (8). The present results are consistent with these findings, supporting the prognostic relevance of the number of metastatic organs in mRCC.

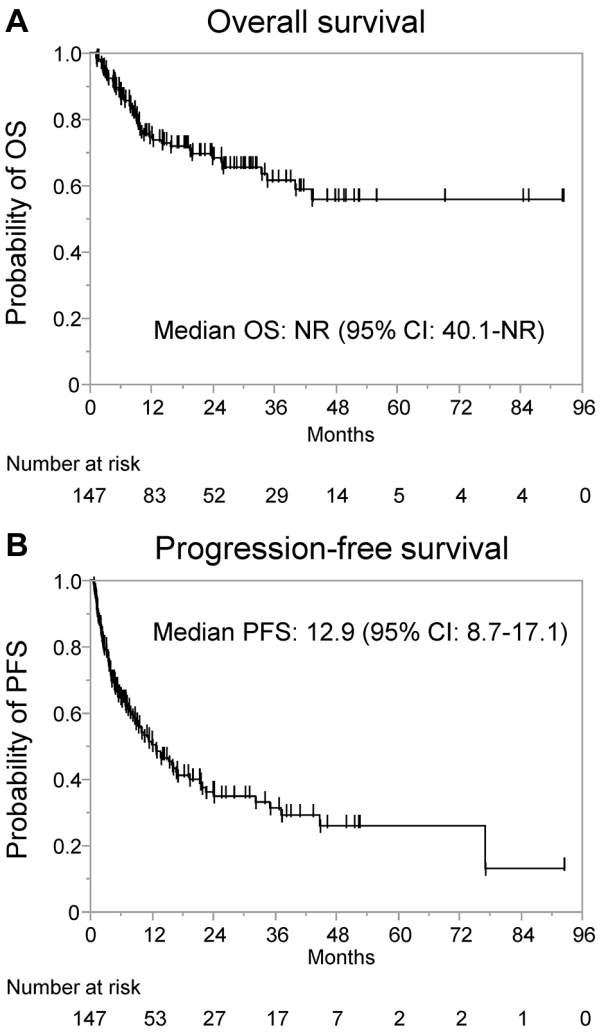

Figure 1. *Kaplan-Meier curves of overall survival (OS) (A) and progression-free survival (PFS) (B) for the 147 patients with metastatic renal cell carcinoma (mRCC). NR, Not reached.*

The number of metastatic organs may not only reflect the extent of tumor dissemination but also suggests underlying differences in cancer biology. While previous

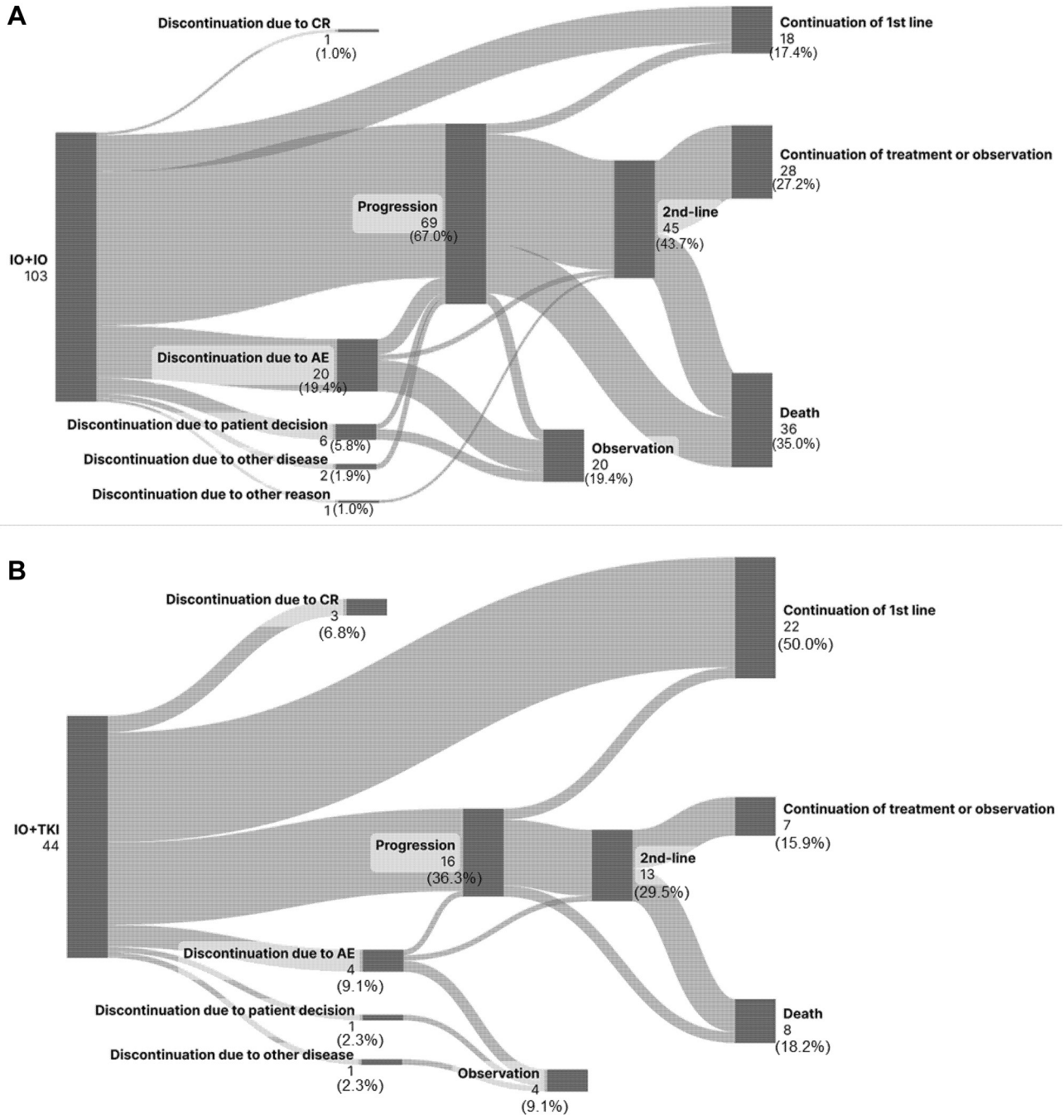

Figure 2. *Sankey diagram of metastatic renal cell carcinoma (mRCC) patients treated with dual immune checkpoint blockade (IO-IO) (A) or combination of immunotherapy with tyrosine kinase inhibitors (IO-TKI) (B).*

studies reported aggressive pathological features in metastatic lesions, such as sarcomatoid differentiation and high PD-L1 expression (12-14), patients with multiple metastatic organs may be more likely to harbor such biologically aggressive tumors. Although this relationship has not been directly demonstrated, it is plausible that the

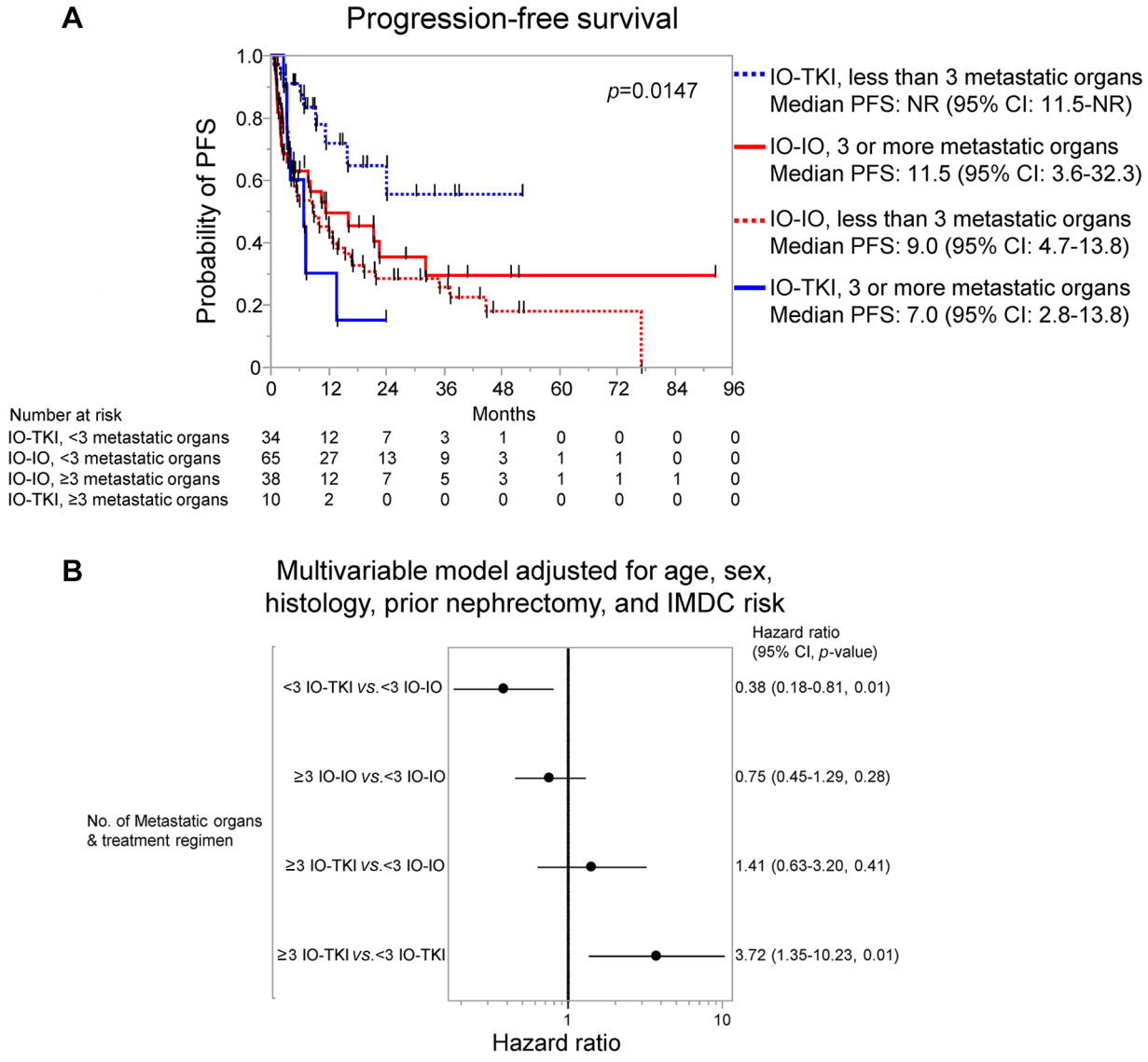

Figure 3. *Kaplan-Meier curves of progression-free survival (PFS) between metastatic renal cell carcinoma (mRCC) patients treated with dual immune checkpoint blockade (IO-IO) and combination of immunotherapy with tyrosine kinase inhibitors (IO-TKI) according to the number of metastatic organs (<3 or ≥3) (A). Forest plot showing results of multivariable Cox proportional hazards regression model analyses for progression-free survival (PFS) across four groups (IO-IO <3, IO-IO ≥3, IO-TKI <3, IO-TKI ≥3 metastatic organs), adjusted for age, sex, histology, nephrectomy, and IMDC risk (B).*

accumulation of metastatic lesions reflects the selective expansion of clones with an enhanced metastatic potential and immune evasion capabilities. Notably, tumors with multiple metastatic lesions have been associated with the increased expression of aggressive-featured genes, such as PD-L1, and were historically linked to a poor prognosis in the era of TKI monotherapy. However, the introduction of IO-based therapy has significantly improved clinical outcomes in this group.

Conversely, limited metastatic spread may reflect tumors with less aggressive clonal evolution. Indeed, patients in whom complete resection of metastatic lesions is feasible tend to have favorable outcomes (15), suggesting that such tumors progress more slowly. Genomic analyses

Table III. *Multivariate Cox proportional hazards regression model analysis of risk factors for PFS in the 147 patients with metastatic renal cell carcinoma.*

Variable	Hazard Ratio (95% CI)	*p*-Value
Sex		
Female	Reference	0.74
Male	0.90 (0.49-1.66)	
Age		
<75	Reference	0.95
≥75	1.02 (0.57-1.81)	
Prior nephrectomy		
No	Reference	0.75
Yes	1.08 (0.66-1.77)	
Histology		
nccRCC	Reference	0.12
ccRCC	0.66 (0.39-1.12)	
IMDC		
Intermediate	Reference	0.008
Poor	1.95 (1.19-3.18)	
Number of metastatic organs		
<3	Reference	0.84
≥3	1.05 (0.66-1.66)	

PFS, Progression-free survival; IO, immune-oncologic drug; TKI, tyrosine kinase inhibitor; IQR, IMDC, international metastatic renal cell carcinoma database consortium.

Table IV. *Relationships between treatment regimens and progression-free survival, stratified according to IMDC risk status and the number of metastatic organs.*

Variable	No. of events/ No. of patients	Median PFS, months	Hazard Ratio	*p*-Value	*p*-Value for interaction
IMDC					0.51
Intermediate					
IO-IO	32/51	16.8	Reference	0.13	
IO-TKI	10/32	24.2	0.57 (0.28-1.17)		
Poor					
IO-IO	38/52	4.8	Reference	0.50	
IO-TKI	6/12	11.5	0.74 (0.31-1.76)		
Number of metastatic organs at baseline					0.001
Less than 3 metastatic organs					
IO-IO	48/65	9.0	Reference	0.004	
IO-TKI	9/34	NR	0.35 (0.17-0.71)		
Three or more metastatic organs					
IO-IO	22/38	11.7	Reference	0.45	
IO-TKI	7/10	7.0	1.40 (0.59-3.33)		

PFS, Progression-free survival; IO, immune-oncologic drug; TKI, tyrosine kinase inhibitor; IQR, IMDC, international metastatic renal cell carcinoma database consortium.

have shown that early driver mutations, such as VHL and PBRM1, are associated with more indolent disease trajectories (12). These tumors may remain more dependent on angiogenic signaling pathways, which could explain their higher sensitivity to TKI-containing regimens. Notably, the prognosis of patients with IMDC favorable risk does not differ significantly between the IO and TKI eras (16). This may reflect the fact that favorable-risk cases often present with a limited metastatic burden, which may confer greater responsiveness to TKIs. This hypothesis warrants further investigation and may contribute to future biomarker development for treatment stratification in mRCC.

Study limitations. It was a retrospective analysis with a relatively small cohort and short observation period. In particular, the small sample size and short follow-up period in the IO-TKI group may have introduced bias. Although a large-scale analysis is necessary, the ability to predict the efficacy of IO combination therapy, particularly IO-TKI, based on the number of metastatic organs, may be a useful tool for guiding treatment in clinical practice. The number of metastatic organs does not require much effort and may be used immediately in clinical practice.

Conclusion

The efficacy of IO-TKI therapy was affected significantly more than that of IO-IO by the number of metastatic organs. The present results suggest the potential of the number of metastatic organs as an additional prognostic variable to optimize treatment selection for patients with mRCC.

Supplementary Material

Available at: https://github.com/hiroshikikuchi16/Manuscript-No-233-K/tree/f84460971ab681f8d7d80b7cf358234ebe54260c

Conflicts of Interest

Takahiro Osawa has received honoraria from MSD and Eisai. Tomonori Habuchi has received honoraria from Ono Pharmaceutical Co., Merck Biopharma Co., MSD and research fundings from Novartis Pharmaceuticals Co, LTD., Chugai Pharm. Nobuo Shinohara has received honoraria from Pfizer, MSD, ONO, Bristol-Meyers Squibb, Eisai, Bayer, Takeda. Norihiko Tsuchiya has received honoraria from Pfizer, Astellas Pharma Inc. None of the other authors have any conflicts of interest.

Authors' Contributions

Hiroshi Kikuchi: Data curation, Formal analysis, Investigation, Methodology, Writing – original draft. Takahiro Osawa: Conceptualization, Formal analysis, Methodology, Project administration, Supervision, Validation, Writing – review & editing. Sei Naito: Investigation, Project administration. Kazuyuki Numakura: Investigation, Project administration. Ojiro Tokairin: Investigation. Yuki Takai: Investigation. Yuya Sekine: Investigation. Haruka Miyata: Investigation. Ryuji Matsumoto: Investigation. Takashige Abe: Supervision, Writing – review & editing; Yoichi Ito: Formal analysis. Tomonori Habuchi: Conceptualization, Supervision. Norihiko Tsuchiya: Conceptualization, Supervision. Nobuo Shinohara: Supervision.

Acknowledgements

We express our gratitude to Editage (www.editage.com) for their assistance with English language editing.

Artificial Intelligence (AI) Disclosure

No artificial intelligence (AI) tools, including large language models or machine learning software, were used in the preparation, analysis, or presentation of this manuscript.

References

1 Motzer RJ, Tannir NM, McDermott DF, Arén Frontera O, Melichar B, Choueiri TK, Plimack ER, Barthélémy P, Porta C, George S, Powles T, Donskov F, Neiman V, Kollmannsberger CK, Salman P, Gurney H, Hawkins R, Ravaud A, Grimm MO, Bracarda S, Barrios CH, Tomita Y, Castellano D, Rini BI, Chen AC, Mekan S, McHenry MB, Wind-Rotolo M, Doan J, Sharma P, Hammers HJ, Escudier B, CheckMate 214 Investigators: Nivolumab plus ipilimumab *versus* sunitinib in advanced renal-cell carcinoma. N Engl J Med 378(14): 1277-1290, 2018. DOI: 10.1056/NEJMoa1712126

2 Rini BI, Plimack ER, Stus V, Gafanov R, Hawkins R, Nosov D, Pouliot F, Alekseev B, Soulières D, Melichar B, Vynnychenko I, Kryzhanivska A, Bondarenko I, Azevedo SJ, Borchiellini D, Szczylik C, Markus M, McDermott RS, Bedke J, Tartas S, Chang YH, Tamada S, Shou Q, Perini RF, Chen M, Atkins MB, Powles T, KEYNOTE-426 Investigators: Pembrolizumab plus axitinib versus sunitinib for advanced renal-cell carcinoma. N Engl J Med 380(12): 1116-1127, 2019. DOI: 10.1056/NEJMoa1816714

3 Choueiri TK, Powles T, Burotto M, Escudier B, Bourlon MT, Zurawski B, Oyervides Juárez VM, Hsieh JJ, Basso U, Shah AY, Suárez C, Hamzaj A, Goh JC, Barrios C, Richardet M, Porta C, Kowalyszyn R, Feregrino JP, Żołnierek J, Pook D, Kessler ER, Tomita Y, Mizuno R, Bedke J, Zhang J, Maurer MA, Simsek B, Ejzykowicz F, Schwab GM, Apolo AB, Motzer RJ, CheckMate 9ER Investigators: Nivolumab plus cabozantinib versus sunitinib for advanced renal-cell carcinoma. N Engl J Med 384(9): 829-841, 2021. DOI: 10.1056/NEJMoa2026982

4 Motzer R, Alekseev B, Rha SY, Porta C, Eto M, Powles T, Grünwald V, Hutson TE, Kopyltsov E, Méndez-Vidal MJ, Kozlov V, Alyasova A, Hong SH, Kapoor A, Alonso Gordoa T, Merchan JR, Winquist E, Maroto P, Goh JC, Kim M, Gurney H, Patel V, Peer A, Procopio G, Takagi T, Melichar B, Rolland F, De Giorgi U, Wong S, Bedke J, Schmidinger M, Dutcus CE, Smith AD, Dutta L, Mody K, Perini RF, Xing D, Choueiri TK, CLEAR Trial Investigators: Lenvatinib plus pembrolizumab or everolimus for advanced renal cell carcinoma. N Engl J Med 384(14): 1289-1300, 2021. DOI: 10.1056/NEJMoa2035716

5 Wei SC, Duffy CR, Allison JP: Fundamental mechanisms of immune checkpoint blockade therapy. Cancer Discov 8(9): 1069-1086, 2018. DOI: 10.1158/2159-8290.cd-18-0367

6 Roberto M, Botticelli A, Panebianco M, Aschelter AM, Gelibter A, Ciccarese C, Minelli M, Nuti M, Santini D, Laghi A, Tomao S, Marchetti P: Metastatic renal cell carcinoma management: from molecular mechanism to clinical practice. Front Oncol 11: 657639, 2021. DOI: 10.3389/fonc.2021.657639

7 Ishihara H, Kondo T, Nakamura K, Nemoto Y, Tachibana H, Fukuda H, Yoshida K, Kobayashi H, Iizuka J, Shimmura H, Hashimoto Y, Tanabe K, Takagi T: Association of tumor burden with outcome in first-line therapy with nivolumab plus ipilimumab for previously untreated metastatic renal

cell carcinoma. Jpn J Clin Oncol 51(12): 1751-1756, 2021. DOI: 10.1093/jjco/hyab142
8 Grünwald V, McKay RR, Buchler T, Eto M, Park SH, Takagi T, Zanetta S, Keizman D, Suárez C, Négrier S, Lee JL, Santini D, Bedke J, Staehler M, Kollmannsberger C, Choueiri TK, Motzer RJ, Burgents JE, Xie R, Okpara CE, Powles T: Clinical outcomes by baseline metastases in patients with renal cell carcinoma treated with lenvatinib plus pembrolizumab versus sunitinib: Post hoc analysis of the CLEAR trial. Int J Cancer 156(7): 1326-1335, 2025. DOI: 10.1002/ijc.35288
9 Hara T, Ueki H, Okamura Y, Bando Y, Suzuki K, Terakawa T, Chiba K, Hyodo Y, Teishima J, Miyake H: Comparative prognostic value of tumor volume in IOIO and IOTKI treatment for metastatic renal cancer. Urol Oncol 43(1): 63.e19-63.e27, 2025. DOI: 10.1016/j.urolonc.2024.10.015
10 Basappa NS, Elson P, Golshayan AR, Wood L, Garcia JA, Dreicer R, Rini BI: The impact of tumor burden characteristics in patients with metastatic renal cell carcinoma treated with sunitinib. Cancer 117(6): 1183-1189, 2011. DOI: 10.1002/cncr.25713
11 Catalano M, De Giorgi U, Bimbatti D, Buti S, Procopio G, Sepe P, Santoni M, Galli L, Conca R, Doni L, Antonuzzo L, Roviello G: Impact of metastatic site in favorable-risk renal cell carcinoma receiving sunitinib or pazopanib. Clin Genitourin Cancer 22(2): 514-522.e1, 2024. DOI: 10.1016/j.clgc.2024.01.006
12 Turajlic S, Xu H, Litchfield K, Rowan A, Chambers T, Lopez JI, Nicol D, O'Brien T, Larkin J, Horswell S, Stares M, Au L, Jamal-Hanjani M, Challacombe B, Chandra A, Hazell S, Eichler-Jonsson C, Soultati A, Chowdhury S, Rudman S, Lynch J, Fernando A, Stamp G, Nye E, Jabbar F, Spain L, Lall S, Guarch R, Falzon M, Proctor I, Pickering L, Gore M, Watkins TBK, Ward S, Stewart A, DiNatale R, Becerra MF, Reznik E, Hsieh JJ, Richmond TA, Mayhew GF, Hill SM, McNally CD, Jones C, Rosenbaum H, Stanislaw S, Burgess DL, Alexander NR, Swanton C, PEACE, TRACERx Renal Consortium: Tracking cancer evolution reveals constrained routes to metastases: TRACERx renal. Cell 173(3): 581-594.e12, 2018. DOI: 10.1016/j.cell.2018.03.057
13 Turajlic S, Xu H, Litchfield K, Rowan A, Horswell S, Chambers T, O'Brien T, Lopez JI, Watkins TBK, Nicol D, Stares M, Challacombe B, Hazell S, Chandra A, Mitchell TJ, Au L, Eichler-Jonsson C, Jabbar F, Soultati A, Chowdhury S, Rudman S, Lynch J, Fernando A, Stamp G, Nye E, Stewart A, Xing W, Smith JC, Escudero M, Huffman A, Matthews N, Elgar G, Phillimore B, Costa M, Begum S, Ward S, Salm M, Boeing S, Fisher R, Spain L, Navas C, Grönroos E, Hobor S, Sharma S, Aurangzeb I, Lall S, Polson A, Varia M, Horsfield C, Fotiadis N, Pickering L, Schwarz RF, Silva B, Herrero J, Luscombe NM, Jamal-Hanjani M, Rosenthal R, Birkbak NJ, Wilson GA, Pipek O, Ribli D, Krzystanek M, Csabai I, Szallasi Z, Gore M, McGranahan N, Van Loo P, Campbell P, Larkin J, Swanton C, TRACERx Renal Consortium: Deterministic evolutionary trajectories influence primary tumor growth: TRACERx renal. Cell 173(3): 595-610.e11, 2018. DOI: 10.1016/j.cell.2018.03.043
14 Rizzo M, Pezzicoli G, Porta C, Povero M, Pradelli L, Sicari E, Barbiero VS, Porta C: The genomic landscape of metastatic clear-cell renal cell carcinoma and its prognostic value: a comprehensive analysis of a large real-world clinico-genomic database. ESMO Open 10(3): 104294, 2025. DOI: 10.1016/j.esmoop.2025.104294
15 Chiou JK, Chang LW, Li JR, Wang SS, Yang CK, Chen CS, Lu K, Cheng CL, Chiu KY, Hung SC: Metastasectomy improves overall survival in metastatic renal cell carcinoma: a retrospective cohort study. Anticancer Res 43(7): 3193-3201, 2023. DOI: 10.21873/anticanres.16493
16 Ishihara H, Nemoto Y, Mizoguchi S, Nishimura K, Fukuda H, Yoshida K, Shimmura H, Hashimoto Y, Iizuka J, Kondo T, Takagi T: Comparative analysis of outcomes for patients with advanced renal cell carcinoma: immuno-oncology era *versus* tyrosine kinase inhibitor era in the IMDC favorable-risk group. Anticancer Res 45(4): 1643-1652, 2025. DOI: 10.21873/anticanres.17545