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Analysis of Early Progression in Advanced Renal Cell Carcinoma Treated With Nivolumab Plus Ipilimumab

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Abstract

Background/Aim: In the CheckMate 214 trial, approximately 40% of patients with advanced renal cell carcinoma (aRCC) treated with nivolumab plus ipilimumab (NIVO + IPI) achieved long-term survival and a durable response to treatment. However, about 20% of patients experienced early disease progression (EDP). This retrospective study aimed to identify predictive factors for EDP among patients with aRCC treated with NIVO + IPI.

Patients and Methods: We retrospectively analyzed clinical information from patients with aRCC, 19 patients in the EDP group and 40 patients in the control disease group, all of whom were treated with NIVO + IPI at Kurume University Hospital between September 2018 and February 2024.

Results: The EDP group exhibited significantly worse progression-free survival and overall survival compared to the control disease group. Multivariate analyses revealed that a performance states (PS) ≥2 (p=0.0312) and the presence of bone metastases (p=0.0374) were independent predictors of EDP.

Conclusion: Treatment with NIVO + IPI in patients with aRCC who have a poor PS or bone metastases may be linked to a high risk of EDP.

Keywords: Renal cell carcinoma, bone metastasis, nivolumab, ipilimumab, immune checkpoint inhibitor, early disease progression.

Introduction

Renal cell carcinoma (RCC) is a prevalent malignancy, with over 300,000 new cases diagnosed annually worldwide (1). Approximately 15% of patients with RCC present with concurrent lymph node or multiorgan metastases at diagnosis, most often to the lungs or bones (2). In the era dominated by interferons and tyrosine kinase inhibitors (TKIs), securing long-term survival for patients with advanced RCC (aRCC) was challenging. However, the introduction of immune checkpoint inhibitors (ICIs) has transformed the prognosis for RCC, offering the potential

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for extended survival (3). Notably, the CheckMate 214 study highlighted the benefits of combing nivolumab and ipilimumab (NIVO + IPI)-a programmed death-1 (PD-1) inhibitor and a cytotoxic T-lymphocyte-associated protein-4 (CTLA-4) inhibitor for patients classified as intermediate- and high-risk per the International Metastatic RCC Database Consortium (IMDC) criteria (4). Long-term follow-up from this study showed a median overall survival of 52.7 months (5). Approximately 40% of patients treated with NIVO + IPI experience a durable response, although 20% face early disease progression (EDP) (5). Numakura *et al.* have indicated that primary resistance in patients treated with NIVO + IPI for metastatic RCC correlates with poor survival outcomes (6). Identifying patients prone to EDP could offer advantages by guiding the selection of initial treatment strategies. This study aimed to analyze the clinical data of 59 patients undergoing NIVO + IPI therapy, seeking to identify the clinical predictors of EDP.

Patients and Methods

Study design and patients. We retrospectively analyzed the clinical date of 59 patients with locally advanced and metastatic RCC who were treated with NIVO + IPI at Kurume University Hospital from September 2018 to February 2024. In the induction phase, NIVO + IPI was administered intravenously at a dose of 240 mg/body and 1 mg/kg, respectively, every three weeks for four cycles. During the maintenance phase, NIVO monotherapy was given at a dose of 240 mg/body every two weeks or 480 mg/body every four weeks until the patient developed intolerable immune-related adverse events (irAEs) or disease progression was observed. Treatment discontinuation due to persistent disease was based on the individual physician's discretion. EDP was defined as progressive disease identified on initial imaging evaluations or clinical progression within three months of starting treatment. The severity of irAEs was assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Radiological assessments were conducted using computed tomography (CT), and tumor responses were evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.

Statistical analysis. Progression-free survival (PFS) and overall survival (OS) were analyzed using Kaplan-Meier curves, with between group comparisons made via the log-rank test. The relationships between groups were examined using the chi-square test, Fisher's exact test, and Student's *t*-test. Univariate and multivariate analysis were conducted using Cox proportional hazards models, from which hazard ratios (HR) and 95% confidence intervals (95%CI) were derived. Variables with p-values <0.05 in the univariate analysis were included in the multivariate analysis. All statistical analyses were conducted using JMP 16 software (SAS Institute Inc., Cary, NC, USA), with all p-values being two-sided and the significance level set at $p<0.05$.

Ethical approval. This study was conducted in accordance with the World Medical Association Declaration of Helsinki and received approval from the Ethics Review Committee at Kurume University School of Medicine (approval number: 22112). Informed consent was obtained through an opt-out mechanism on the Kurume University website. All patient information was anonymized and de-identified before analysis.

Results

Patient characteristics. Table I shows the clinicopathological characteristics of patients prior to initiating NIVO + IPI therapy. The median age of the cohort was 68 years; 47 patients (79.7%) were male, and 49 patients (83.1%) had histologically confirmed clear cell RCC. Ten patients (17.0%) had a poor performance status (PS), and 23 patients (39.0%) had undergone nephrectomy. The number of target lesions was one, two, three, and four or more, which were 16 (27.1%), 14 (23.7%), 17 (28.8%), and 12 (20.3%), respectively. The primary metastatic sites included the lungs (33 patients, 55.9%), lymph nodes (25 patients, 42.4%), bones (15 patients, 25.4%), and liver (6 patients, 10.2%).

Table I. *Clinicopathological characteristics of patients with advanced renal cell carcinoma treated with nivolumab plus ipilimumab.*

Patient's characteristics		All (n=59)	EDP group (n=19)	Control group (n=40)	*p*-Value
Age median, years (range)		68 (42-80)	67.0 (46-76)	68.5 (42-80)	0.1684
Sex, n (%)	Male	47 (79.7)	14 (73.7)	33 (82.5)	0.4318
	Female	12 (20.3)	5(26.3)	7 (17.5)	
ECOG Performance status, n (%)	0,1	49 (83.0)	12 (63.2)	37 (92.5)	0.005
	≥2	10 (17.0)	7 (36.8)	3 (7.5)	
Prior nephrectomy, n (%)	Yes	23 (39.0)	4 (21.1)	19 (47.5)	0.0516
IMDC risk classification, n (%)	Intermediate	30 (50.9)	9 (47.4)	21 (52.5)	0.7126
	Poor	29 (49.1)	10 (52.6)	19 (47.5)	
Histology of primary tumor, n (%)	CCRCC	49 (83.1)	14 (73.7)	35 (87.5)	0.0998
	Non-CCRCC	8 (13.5)	5 (26.3)	3 (7.5)	
	Unknown	2 (3.4)	0 (0.0)	2 (5.0)	
Sarcomatoid variant, n (%)		9 (15.3)	1 (5.3)	8 (20.0)	0.1413
Metastatic organs, n (%)	Lymph node	25 (42.4)	10 (52.6)	15 (37.5)	0.2718
	Lung	33 (55.9)	9 (47.4)	24 (60.0)	0.3612
	Bone	15 (25.4)	9 (47.4)	6 (15.0)	0.0076
	Liver	6 (10.2)	2 (10.5)	4 (10.0)	0.9502
Number of target lesions, n (%)	1	16 (27.1)	4 (21.1)	12 (30.0)	0.0411
	2	14 (23.7)	5 (26.3)	9 (22.5)	
	3	17 (28.8)	6 (31.6)	11 (27.5)	
	≧4	12 (20.3)	4 (21.1)	8 (20.0)	
CRP median, (mg/dl) (range)		1.32 (0.04-20.42)	1.77 (0.04-16.47)	1.13 (0.08-20.42)	0.6592
NLR median, (range)		3.42 (1.03-11.5)	3.74 (1.03-11.5)	3.43 (1.10-6.72)	0.0101

EDP: Early disease progression; ECOG: Easten Cooperative Oncology Group; IMDC: International Metastatic RCC Database Consortium; CCRCC: advanced clear cell renal cell carcinoma; CRP: C-reactive protein; NLR: neutrophil-to-lymphocyte ratio.

Best overall response of NIVO + IPI therapy. Table II outlines the best overall response (BOR) rates during NIVO + IPI treatment. The BOR included a complete response (CR) in 9 patients (15.2%) and a partial response (PR) in 20 patients (33.9%), resulting in an overall response rate (ORR) of 49.1%. However, EDP was observed in 19 patients (32.2%).

Clinical course according to NIVO + IPI therapy. Figure 1 presents the estimated PFS and OS curves for all patients treated with NIVO + IPI. The median PFS was 12.4 months, and the median OS was not reached. Figure 2 compares the PFS and OS for the EDP group with the control disease group; the median PFS was 1.7 months for the EDP group and 25.0 months for the control disease group (HR=15.26, 95%CI=6.40-36.38, $p<0.0001$). The median OS was 17.1 months in the EDP group and not reached in the control group (HR=6.18, 95%CI=2.61-14.65, $p<0.0001$). The two-year survival rate was 32.8% in the EDP group and 74.0% in the control group.

Table II. *Best overall response of patients with advanced renal cell carcinoma treated with nivolumab plus ipilimumab.*

	n=59 (%)
Complete response	9 (15.2)
Partial response	20 (33.9)
Stable disease	11 (18.6)
Progressive disease	19 (32.2)

Univariate and multivariate Cox proportional hazards models identified performance status (PS) ≥2 [odds ratio (OR)=7.194, 95%CI=1.604-32.278, $p=0.0100$] and bone metastasis (OR=5.100, 95%CI=1.460-17.813, $p=0.0107$) as factors associated with EDP. Multivariate analysis further confirmed PS ≥2 (OR=5.644, 95%CI=1.169-27.257, $p=0.0312$) and bone metastasis (OR=4.086, 95%CI=1.086-15.378, $p=0.0374$) as independent risk factors for EDP (Table III).

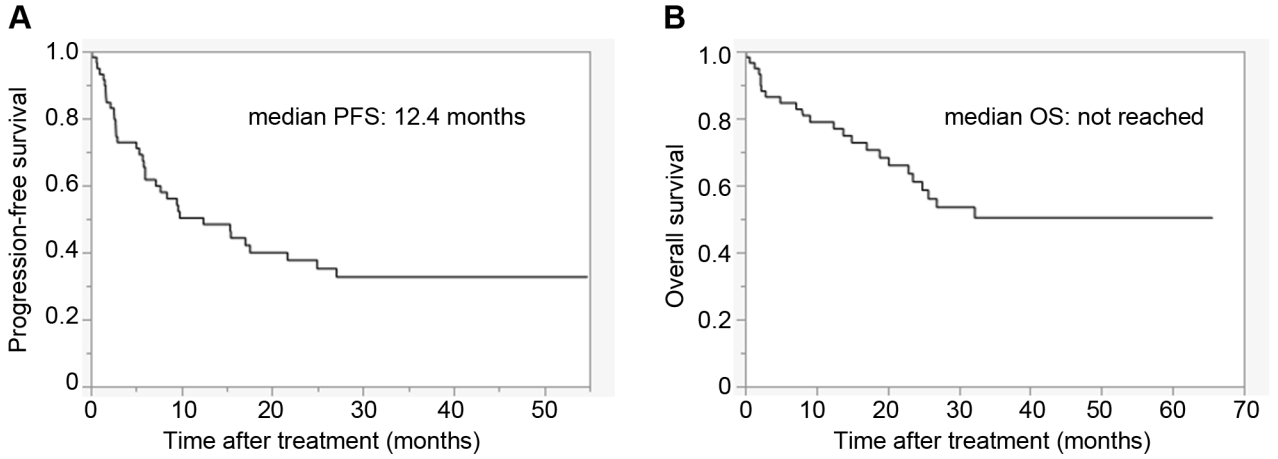

Figure 1. *Progression-free survival (PFS) (A) and overall survival (OS) (B) in all patients with advanced renal cell carcinoma who were treated with nivolumab plus ipilimumab.*

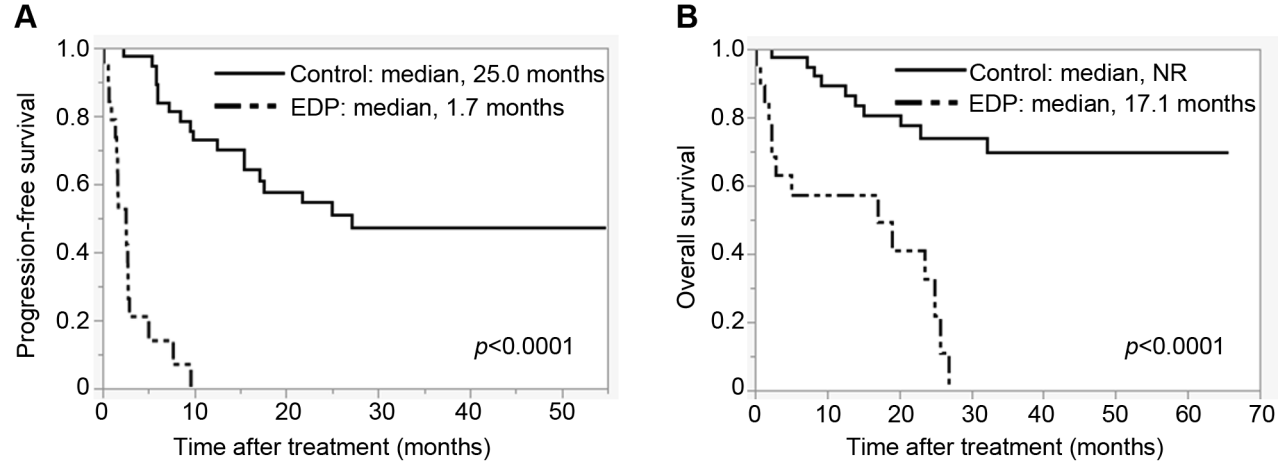

Figure 2. *Comparison of progression-free survival (PFS) and overall survival (OS) between the early disease progression (EDP) and control group in patients with advanced renal cell carcinoma who were treated with nivolumab plus ipilimumab.*

irAEs of NIVO + IPI therapy. Table IV details the irAEs observed with NIVO + IPI therapy in patients with aRCC. Out of all participants, 34 patients (57.6%) experienced irAEs. Grade 3 or higher irAEs were reported in 16 patients (27.1%). Corticosteroids were administered to 18 patients (30.5%), with nine of these patients (15.3%) required high doses. The control group experienced significantly higher rates of irAEs compared to the EDP group, including higher incidences of Grade 3 or higher irAEs and more frequent steroid use. Additionally, skin reactions, endocrine disturbances, and adrenal dysfunction were more prevalent in the control disease group.

Discussion

In this retrospective study, 32.2% of patients with aRCC treated with NIVO+IPI experienced EDP. This rate was higher than that observed in the CheckMate 214 trial. Our

Table III. *Univariate and multivariate analysis in EDP of patients with advanced renal cell carcinoma treated with nivolumab plus ipilimumab.*

Risk factor	Risk category	Univariate		Multivariate	
		Odds risk (95%CI)	*p*-Value	Odds risk (95%CI)	*p*-Value
Age	≧68	0.533 (0.166-1.709)	0.29		
Sex	Male	0.594 (0.161-2.194)	0.5939		
Performance states	≧2	7.194 (1.604-32.278)	0.01	5.644 (1.169-27.257)	0.0312
Prior nephrectomy	Yes	0.295 (0.083-1.045)	0.0585		
RCC histology	Non-clear cell	4.167 (0.876-19.824)	0.0729		
Sarcomatoid variant	Yes	0.222 (0.026-1.922)	0.1718		
Location of metastases	Lymph node	1.851 (0.613-5.590)	0.2744		
	Lung	0.600 (0.200-1.803)	0.363		
	Bone	5.100 (1.460-17.813)	0.0107	4.086 (1.086-15.378)	0.0374
	Liver	1.059 (0.176-6.359)	0.9502		
	Brain	1.451 (0.222-9.500)	0.6978		
Number of target lesions	≧3	2.308 (0.755-7.055)	0.1425		
IMDC risk	Poor	1.228 (0.411-3.666)	0.7127		
Number of IMDC risk factors	≧4	1.067 (0.278-4.106)	0.6252		
CRP median	≥1.32	1.228 (0.411-3.666)	0.7127		
NLR median	≧3.42	1.111 (0.372-3.315)	0.8502		

EDP: Early disease progression; RCC: renal cell carcinoma; IMDC: International Metastatic RCC Database Consortium; CRP: C-reactive protein; NLR: neutrophil-to-lymphocyte ratio.

Table IV. *Treatment-related immune-related adverse events.*

	All patients (n=59)	EDP group (n=19)	Control group (n=40)	*p*-Value
All events	34 (57.6)	4 (21.1)	30 (75.0)	<0.0001
Skin	24 (41.3)	2 (10.1)	22 (56.4)	0.0004
Endocrine disorder	15 (25.9)	1 (5.3)	14 (35.9)	0.006
Adrenal dysfunction	12 (20.7)	1 (5.3)	11 (28.2)	0.0268
Thyroid dysfunction	8 (13.8)	1 (5.3)	7 (18.0)	0.1578
Colitis	7 (12.1)	1 (5.3)	6 (15.4)	0.2367
Hepatitis	4 (6.9)	0 (0.0)	4 (10.3)	0.0685
≥Grade 3	16 (27.1)	2 (10.5)	14 (35.0)	0.0363
Steroids	18 (30.5)	2 (10.5)	16 (40.0)	0.0147
High dose steroids	9 (15.3)	2 (10.5)	7 (17.5)	0.4742

EDP: Early disease progression.

cohort included patients with poor PS, non-clear cell RCC, and those without prior nephrectomy, which may explain the higher incidence of EDP. The EDP group had significantly shorter PFS and OS compared to the control disease group. Poor PS and bone metastases were independently associated with EDP.

The advent of ICIs has significantly transformed the prognosis for patients with metastatic or unresectable RCC, offering the prospect of extended survival compared to the era dominated by interferon and TKIs (7-9). In particular, long-term follow-up data from CheckMate 214 demonstrated the durable efficacy of NIVO + IPI. However, approximately 20% of patients exhibited progressive disease as their BOR to NIVO + IPI (4, 5). Studies have linked inflammatory markers with prognosis in NIVO + IPI-treated metastatic RCC (mRCC). Numakura *et al.* found

a significant association between the lymphocyte-to-monocyte ratio and prognosis (10), while Nakayama *et al.* reported that high neutrophil-to-lymphocyte ratio and C-reactive protein levels were significantly correlated with poor prognosis (11). There are various regimens for the primary treatment of metastatic RCC, including ICI-ICI and ICI-TKI combinations, yet there are no definitive criteria for regimen selection. Thus, understanding the prognostic factors and outcomes of patients with EDP under NIVO + IPI therapy can aid in selecting appropriate treatment. Poor PS, identified as a negative prognostic factor in the TKI era's International Metastatic RCC Database Consortium (IMDC) risk classification, continues to be relevant in the immuno-oncology (IO) era (12, 13). Although poor PS was an independent factor associated with EDP in this study, previous reports suggest that while it is a poor prognostic factor across different therapies (ICI+TKI, TKI alone), it does not predict the response to NIVO + IPI specifically and thus is not a determinant for first-line treatment selection. Bone metastasis, the second most frequent site after lung metastasis and occurring in one-third of cases (14), remains a significant poor prognostic factor in RCC (15). Numakura reported that positive lymph nodes in metastatic RCC were independently associated with primary resistant disease (6). Although bone metastasis was not identified as a significant factor leading to EDP, a trend was noted. Bone metastases are known to reduce the effectiveness of immunotherapy not only in RCC but also in other cancers (16). This is largely due to the unique immunosuppressed microenvironment formed within the bone marrow, an important secondary lymphoid organ. For instance, bone metastatic sites in non-small cell lung cancer (NSCLC) have been described as immunologically "cold" with fewer tumor-infiltrating lymphocytes present (17), and lower PD-L1 expression observed in patients with bone metastases (18). Similarly, a lower rate of PD-L1 positivity has been noted in bone metastases in breast cancer compared to the primary tumor or other metastatic sites (19). Kähkönen *et al.* outlined factors contributing to the formation of an immunosuppressed bone metastasis microenvironment, including the ability of cancer cells to evade immune elimination during metastasis formation, a naturally lower concentration of cytotoxic cells in the bone marrow, immunomodulation of the pre -metastatic niche to facilitate cancer cell seeding, and modulation of the microenvironment through interactions with stromal cells (20). Thus, immunotherapy might be less effective in patients with bone metastases, a phenomenon observed in RCC as well. While NIVO + IPI showed superior outcomes compared to sunitinib in patients with RCC with bone metastases in the CheckMate 214 trial (4, 21), real-world data suggest that NIVO + IPI is relatively ineffective in these patients (22). Additionally, a relationship has been suggested between T lymphocytes and mature osteoclasts/osteoclast progenitors in bone remodeling (23). In this study, the use of bone-modifying agents such as denosumab and bisphosphonates, as well as local treatments like radiation therapy to bone lesions, was left to the discretion of the treating physician. Current treatment guidelines for metastatic clear cell RCC do not provide specific recommendations for optimal systemic therapy in patients with bone metastases (24). It has been suggested that c-mesenchymal-epithelial transition (c-MET) may be associated with bone metastasis of RCC, but the mechanism is unknown (25). However, c-MET has been associated with progression of RCC, with 86% of bone marrow cells showing high expression of c-MET, and high expression of c-MET in bone marrow cells is associated with poor prognosis (26). Several malignancies with bone metastases have increased expression of fibroblast growth factor-2 (FGF-2) (27). Therapies combining ICIs and TKIs, such as nivolumab plus cabozantinib or lenvatinib plus pembrolizumab, which inhibit MET and FGF-2, respectively, have shown relative effectiveness even in patients with bone metastases (28, 29). Comparing ICI+ICI and ICI+TKI treatments for renal cancer with bone metastases directly is challenging, but patients may benefit more from the latter as described above. The mechanism of irAEs is not clear, but the bystander effect of activated T cells may be involved (30). In this study, the reason why irAEs were less in the EDP

group may be that immune activation did not occur. Another reason may be that the EDP group had a shorter survival and treatment period than the target group, and some patients died before the onset of irAEs.

This report has some limitations, including potential selection bias due to its retrospective nature. Additionally, the sample size is limited, and decisions regarding bone remodeling agents and local treatments for bone metastases were subject to individual physician judgment.

Conclusion

Treatment with NIVO + IPI in patients with aRCC who have poor PS or bone metastases is likely to result in EDP. This outcome can be detrimental to patients and may necessitate a reevaluation of their treatment options.

Conflicts of Interest

The Authors declare that there are no conflicts of interest regarding this study.

Authors' Contributions

Conceptualization: N.I., K.U. (Kosuke Ueda), S.S. and T.I.; methodology: N.I, K.U. (Kosuke Ueda), S.O., H.S., T.H. and T.I.; validation: N.I., K.W. K.C., K.U. (Keiichiro Uemura), S.S. and T.I.; formal analysis: N.I., K.U. (Keiichiro Uemura), K.N., M.N., and S.S.; investigation: N.I. K.U. (Kosuke Ueda), S.O., H.S., S.S., and T.I.; resources: N.I., K.U. (Kosuke Ueda), S.O., T.H., K.W., K.N., M.N., S.S., and T.I.; data curation: N.I., K.U. (Kosuke Ueda), S.O., H.S., and K.C.; writing—original draft preparation: N.I. and K.U. (Kosuke Ueda); writing—review and editing: M.N., S.S. and T.I.; visualization: K.N. and M.N.; supervision: S.S and T.I. All Authors have read and agreed to the published version of the manuscript.

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