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Comparative Efficacy of Combination Therapy of Ipilimumab Plus Nivolumab for Non-clear Cell Renal Cell Carcinoma

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Abstract. *Background/Aim: The survival benefit of immune checkpoint inhibitors for non-clear cell renal cell carcinoma (nccRCC) is unclear. Our purpose was to evaluate the real-world survival benefit of ipilimumab plus nivolumab retrospectively. Patients and Methods: We retrospectively reviewed medical records of 33 patients with metastatic nccRCC who received combination therapy with ipilimumab plus nivolumab or monotherapy with a molecular targeted agent as initial systemic therapy. Progression-free survival (PFS), overall survival (OS) and objective response rate were compared between the two groups. Results: Median PFS of each therapy was 3.5 and 4.7 months (p=0.61) and median OS was 19.6 and 10.6 months (p=0.23), respectively. Three patients treated with ipilimumab and nivolumab had a complete response, resulting in an objective response rate of 30.0%, while that for molecular targeted therapy was 4.5% (p=0.04). Conclusion: Ipilimumab plus nivolumab achieved statistically non-significant, but longer overall survival and significantly higher objective response rate.*

During the last decade, phase III clinical trials of immune checkpoint inhibitors (ICIs) have yielded significantly improved treatment outcomes of patients with renal cell carcinoma (1-4). Consequently, several combination therapies including ICIs have been widely adopted for renal cell carcinoma (5, 6). After the CheckMate 214 trial, combination therapy with nivolumab plus ipilimumab became a mainstay of treatment of intermediate- or poor-risk renal cell carcinoma because overall survival (OS) benefit was maintained after >4 years' follow-up (7).

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Key Words: Non-clear cell renal cell carcinoma, immune checkpoint inhibitor.

However, patients with non-clear cell renal cell carcinoma (nccRCC) were excluded from most clinical trials that included ICIs (8). Therefore, the benefit of ICIs compared to molecular targeted therapy in nccRCC remains uncertain. Consequently, molecular targeted therapy remains the leading recommendation for initial treatment of nccRCC (5, 6). Several retrospective studies have indicated efficacy of combination therapy with ipilimumab and nivolumab in nccRCC (9-11).

The aim of this study was to evaluate the survival benefit of combination therapy with ipilimumab plus nivolumab compared to molecular targeted therapy in patients with nccRCC.

Patients and Methods

This study was conducted under Institutional Review Board approval of the Kobe University Hospital (approval No. B210089). We retrospectively reviewed the medical records of 33 patients with metastatic nccRCC at Kobe University Hospital between April 2008 and December 2020. Patients who received nivolumab monotherapy as subsequent systemic therapy during follow-up were also included in the patient group of molecular targeted therapy. Baseline clinical data including age, gender, body mass index, ethnic origin, Karnofsky performance status, prior nephrectomy status, primary histology, metastatic sites, and laboratory data were collected by reviewing patient medical records. Treatment outcomes, including best response [assessed by RECIST 1.1 (12)], time to treatment failure, progression-free survival (PFS), OS, and adverse effects retrieved from medical records were evaluated according to the nature of initial systemic therapy.

All statistical analyses were performed with JMP 12.0 (SAS Institute Inc, Cary, NC, USA), using $p<0.05$ to indicate significant results. PFS and OS were estimated with Kaplan–Meier curves, and differences were analysed by log-rank test.

Results

The clinicopathological characteristics of eligible patients are listed in Table I. The median age of eligible patients was 65 years, and there were 24 men (72.7%) and 9 women (27.3%). Prior definitive surgical therapy had been performed in 26

Table I. *Characteristics of eligible patients*.

	IN (N=10)	MTT (N=23)	Total (N=33)	*p*-Value
Age (median, IQR)	60 (44-70)	67 (60-71)	65 (58-71)	0.07
Male/Female (%)	8 (80.0%)/2 (20.0%)	16 (69.6%)/7 (30.4%)	24 (72.7%)/9 (27.3%)	0.53
Karnofsky performance status				
≥80%	7 (70.0%)	21 (91.3%)	28 (84.8%)	0.13
<80%	3 (30.0%)	2 (8.7%)	5 (15.2%)	
Prior nephrectomy				
Yes	6 (60.0%)	20 (87.0%)	26 (78.8%)	0.09
Histological type				
Papillary	3 (30.0%)	11 (47.8%)	14 (42.4%)	
Unclassified	3 (30.0%)	4 (17.4%)	7 (21.2%)	
Collecting duct	0 (0%)	4 (17.4%)	4 (12.1%)	
Translocation associated	2 (20.0%)	2 (8.7%)	4 (12.1%)	
Spindle cell	1 (10.0%)	2 (8.7%)	3 (9.1%)	
Chromophobe	1 (10.0%)	0 (0%)	1 (3.0%)	
Existence of sarcomatoid differentiation	2 (20.0%)	3 (13.0%)	5 (15.2%)	0.62
Number of metastatic sites				
1	5 (50.0%)	15 (65.2%)	20 (60.6%)	0.17
2	4 (40.0%)	5 (21.7%)	9 (27.3%)	
≥3	1 (10.0%)	3 (13.0%)	4 (12.1%)	
Sites of metastases				
Lymph node	3 (30.0%)	7 (30.4%)	10 (30.3%)	
Lung	6 (60.0%)	11 (47.8%)	17 (51.5%)	
Bone	5 (50.0%)	3 (13.0%)	8 (24.2%)	
Liver	0 (0%)	4 (17.4%)	4 (12.1%)	
IMDC risk classification				
Favorable	0 (0%)	3 (13.0%)	3 (9.1%)	0.18
Intermediate	3 (30.0%)	10 (43.5%)	13 (39.4%)	
Poor	7 (70.0%)	10 (43.5%)	17 (51.5%)	
Laboratory data				
Hemoglobin (g/dl) (median, IQR)	11.4 (9.2-12.6)	10.8 (9.5-13.1)	10.9 (9.5-13.1)	0.81
Platelet count (10^4/ml) (median, IQR)	35.0 (27.2-45.4)	25.3 (18.3-35.6)	27.4 (19.5-41.0)	0.06
Neutrophil-lymphocyte ratio (median, IQR)	4.6 (2.1-8.1)	2.8 (2.3-6.4)	3.6 (2.2-7.5)	0.58
Corrected Ca (mg/dl) (median, IQR)	9.5 (9.1-9.9)	9.5 (9.2-10.0)	9.4 (9.2-10.0)	0.35
CRP (mg/dl) (median, IQR)	3.8 (0.1-7.9)	0.61 (0.1-4.3)	1.6 (0.1-4.4)	0.31

IQR, Interquartile range; IMDC, International Metastatic RCC Database Consortium; CRP, C-reactive protein; IN, ipilimumab and nivolumab; MTT, molecular targeted therapy.

patients (78.8%). Regarding histological subtypes, 14 (42.4%) patients were diagnosed as papillary, 7 (21.2%) as unclassified, 4 (12.1%) as collecting duct, 4 (12.1%) as translocation associated, 3 (9.1%) as spindle cell, and 1 (3.0%) as chromophobe renal cell carcinoma. Five patients (15.2%) were diagnosed as having sarcomatoid differentiation. Common sites of metastases were lymph nodes (10 patients, 30.3%), lung (17, 51.5%), bone (8, 24.2%) and liver (4, 12.1%). Three patients (9.1%) were classified into the favourable-risk group, 13 (39.4%) were in the intermediate-risk group, and 17 (51.5%) were in the poor-risk group according to International Metastatic RCC Database Consortium prognostic assessments.

Treatment outcomes are summarized in Table II. Ten patients were administered ipilimumab plus nivolumab as initial systemic therapy. Twenty-three patients were administered a molecular targeted agent as initial systemic therapy: 11 (47.8%) received sunitinib, 2 (8.7%) sorafenib, 1 (4.3%) pazopanib and 9 (39.1%) temsirolimus. The median time to treatment failure with ICIs and molecular targeted therapy was 2.4 and 5.0 months, respectively (p=0.16). Median PFS for treatment with ICIs and molecular targeted agent was 3.5 and 4.7 months, respectively (p=0.61) (Figure 1). Median OS of patients with initial systemic therapy of ICIs and molecular targeted agent was 19.6 and 10.6 months, respectively (p=0.23) (Figure 2).

The best treatment responses for each histological type according to initial systemic therapy are shown in Table III. Among 10 patients with initial systemic therapy with ICIs, complete response was confirmed in 3 (30.0%), stable disease in 3 (30.0%), and progressive disease in 4 (40.0%). Two patients with papillary renal cell carcinoma and one with spindle cell renal cell carcinoma experienced complete

Table II. *Treatment outcomes of initial systemic therapy.*

Regimen of initial systemic therapy	IN (N=10)	MTT (N=23)	Total (N=33)	*p*-Value
Ipilimumab plus nivolumab	10 (100%)	-	10 (30.3%)	
Sunitinib		11 (47.8%)	11 (33.3%)	
Sorafenib		2 (8.7%)	2 (6.1%)	
Pazopanib		1 (4.3%)	1 (3.0%)	
Temsirolimus		9 (39.1%)	9 (2.7%)	
Treatment outcomes				
Follow-up period (months, range)	13 (1.3-35.3)	10.6 (1.1-78.9)	11.7	
Median overall survival (months)	19.6	10.6	12.6	0.23
Median time to treatment failure (months)	2.4	5.0	4.3	0.16
Median progression-free survival (months)	3.5	4.7	4.5	0.61
Reason of discontinuation of initial systemic therapy				
Progression disease	5 (50.0%)	18 (78.3%)	23 (69.7%)	
Adverse event	3 (30.0%)	4 (17.4%)	7 (21.2%)	
Ongoing	2 (20.0%)	0 (0%)	2 (6.1%)	
Others	0 (0%)	1 (4.3%)	1 (3.0%)	
Completion of 4 cycles of ipilimumab plus nivolumab (%)				
Yes	4 (40.0%)	-		

IN, Ipilimumab and nivolumab; MTT, molecular targeted therapy.

response. Among 23 patients with initial systemic therapy with a molecular targeted agent, partial response was confirmed in 1 (4.3%), stable disease in 16 (69.5%), and progressive disease in 5 (21.7%). One patient who experienced a partial response was diagnosed as renal cell carcinoma, unclassified. The objective response rates for ICIs and molecular targeted therapy were 30.0% and 4.5%, respectively (p=0.04).

All adverse events of initial systemic therapy are listed in Table IV. Six patients (60.0%) who were administered ICIs and 21 (91.3%) administered a molecular targeted agent experienced adverse events. Three patients (30.0%) administered ICIs and two patients (8.7%) who were administered a molecular targeted agent experienced grade 3/4 adverse events. Five patients (50%) who received ICIs experienced immune-related adverse events, and three of those (60.0%) received systemic treatment with steroid.

Discussion

In this study, we retrospectively evaluated the efficacy of combination therapy with ipilimumab plus nivolumab as initial systemic treatment for nccRCC in comparison with molecular targeted therapy. Combination therapy with ipilimumab plus nivolumab achieved nonsignificant but longer OS and significantly higher objective response rate than molecular targeted therapy.

Several phase III clinical trials of first-line combination therapy including ICIs for renal cell carcinoma excluded patients with non-clear cell histological type, although most trials yielded an excellent treatment outcome (1-4). Clinical trials of combination therapy including ICIs targeting non-clear cell renal cell carcinoma are ongoing in phase II and promising interim results have been reported (13-15). Previous small retrospective studies have shown efficacy of combination therapy with ipilimumab and nivolumab for nccRCC (9-11). However, there are limited clinical data to evaluate whether combination of ipilimumab plus nivolumab is the optimal systemic treatment for nccRCC because all these studies were single-arm and did not measure OS (9-11). Our study showed that combination therapy using ICIs, compared to molecular targeted therapy, prolonged OS and improved objective response rate, although there was no significant difference in OS.

There are some hypotheses on the efficacy of ICIs for nccRCC. One hypothesis for the variable response is the difference in expression of programmed death ligand-1 (PD-L1) in the different types of nccRCC. The extent to which PD-L1 is expressed on tumour cells is reported to be one predictor of efficacy of programmed death-1 (PD-1) blockade (16, 17). Some authors have reported that some patients with nccRCC have high levels of PD-L1 expression. One study examining 26 patients with renal cell carcinoma with sarcomatoid differentiation identified PD-1þ tumour-infiltrating lymphocytes in 96% of cases and PD-L1þ sarcomatoid cells in 54% of cases, with co-expression identified in 13 cases (18). However, there were limitations related to the assessment method and to the tumour heterogeneity. The variety of available tests and different methodologies for determining positivity of PD-L1 expression result in different positive rates (19). Furthermore, the expression of PD-L1 can change during

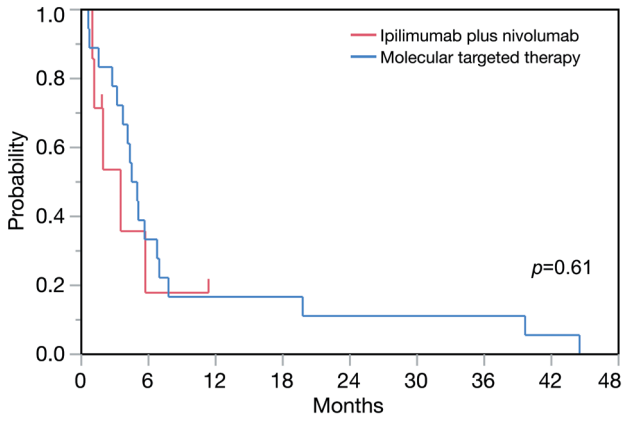

Figure 1. *Progression-free survival according to initial systemic therapy (comparison between Ipilimumab plus nivolumab and molecular targeted therapy).*

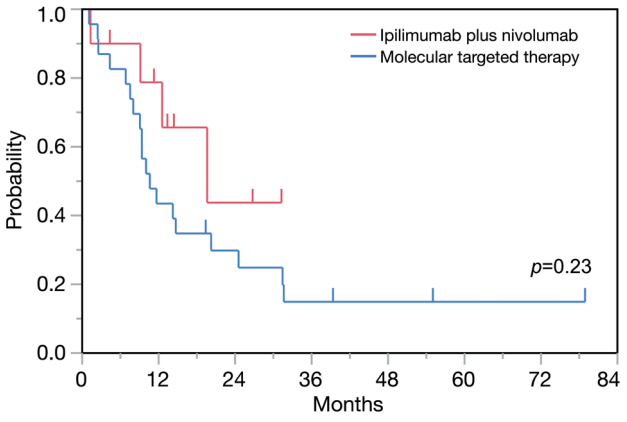

Figure 2. *Overall survival according to initial systemic therapy (comparison between Ipilimumab plus nivolumab and molecular targeted therapy).*

Table III. *Best response of initial therapy.*

	No.	Best response				
		CR (%)	PR (%)	SD (%)	PD (%)	N/A(%)
All	33	3 (9.1%)	1 (3.0%)	19 (57.6%)	9 (27.3%)	1 (3.0%)
Ipilimumab and nivolumab	10	3 (30.0%)	0 (0%)	3 (30.0%)	4 (40.0%)	0 (0%)
Papillary	3	2 (66.7%)	0 (0%)	0 (0%)	1 (33.3%)	0 (0%)
Unclassified	3	0 (0%)	0 (0%)	1 (33.3%)	2 (66.7%)	0 (0%)
Translocation associated	2	0 (0%)	0 (0%)	1 (50.0%)	1 (50.0%)	0 (0%)
Spindle cell	1	1 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Chromophobe	1	0 (0%)	0 (0%)	1 (100%)	0 (0%)	0 (0%)
Molecular targeted therapy	23	0 (0%)	1 (4.3%)	16 (69.5%)	5 (21.7%)	1 (4.3%)
Papillary	11	0 (0%)	0 (0%)	9 (81.8%)	1 (9.1%)	1 (9.1%)
Unclassified	4	0 (0%)	1 (25.0%)	2 (50.0%)	1 (25.0%)	0 (0%)
Collecting duct	4	0 (0%)	0 (0%)	3 (75.0%)	1 (25.0%)	0 (0%)
Translocation associated	2	0 (0%)	0 (0%)	1 (50.0%)	1 (50.0%)	0 (0%)
Spindle cell	2	0 (0%)	0 (0%)	1 (50.0%)	1 (50.0%)	0 (0%)

	Ipilimumab+nivolumab	Molecular targeted therapy	*p*-Value
Objective response rate	30.0%	4.5%	**0.04**
Disease control rate	60.0%	77.3%	0.32

CR, Complete response; PR, partial response; SD, stable disease; PD, progressive disease; N/A, not applicable. Statistically significant *p*-values are shown in bold.

tumour natural history or as a consequence of antineoplastic treatments. PD-L1 expression shows increased heterogeneity both intratumorally and between the primary tumour and distant metastases (20, 21). The second hypothesis comes from the immune microenvironment. ICIs activate immune pathways to induce T-cell-mediated tumour cell death (22). Accordingly, inflamed tumours that are highly infiltrated by tumour-reactive T cells, such as cytotoxic T lymphocytes, are more likely to respond to ICIs than are non-inflamed tumours (23). According to a meta-analysis, papillary renal cell carcinoma had a higher objective response rate to immune-checkpoint-based therapies (18.9%) than chromophobe renal cell carcinoma did because the latter had a low number of immune infiltrates (23).

However, neither hypothesis can fully explain the efficacy of ICIs for treatment of nccRCC, and expression of PD-L1

Table IV. *Summary of adverse events.*

	Ipilimumab and nivolumab (N=10)		Molecular targeted therapy (N=23)	
	All grades	Grade 3-4	All grades	Grade 3-4
Any event	6 (60.0%)	3 (30.0%)	21 (91.3%)	2 (8.7%)
Anemia			2 (8.7%)	1 (4.3%)
Neutropenia			2 (8.7%)	0 (0%)
Thrombocytopenia			7 (30.4%)	0 (0%)
Hepatic failure	2 (20.0%)	1 (10.0%)	1 (4.3%)	0 (0%)
Acute kidney injury			2 (8.7%)	0 (0%)
Malaise			2 (8.7%)	0 (0%)
Skin rash	1 (10.0%)	0 (0%)	2 (8.7%)	0 (0%)
Mucositis oral			4 (17.4%)	0 (0%)
Appetite loss			1 (4.3%)	0 (0%)
Hand-foot syndrome			3 (13.0%)	0 (0%)
Anaphylaxis			1 (4.3%)	1 (4.3%)
Pneumonitis	1 (10.0%)	1 (10.0%)	1 (4.3%)	0 (0%)
Hypopituitarism	1 (10.0%)	1 (10.0%)		
Adrenal insufficiency	1 (10.0%)	1 (10.0%)		
Hypothyroidism	1 (10.0%)	0 (0%)	1 (4.3%)	0 (0%)
Any irAE	5 (50.0%)	3 (30.0%)		
Usage of steroid for irAE	3 (30.0%)	3 (30.0%)		

irAE, Immune-related adverse event.

in eligible patients was not evaluated in our study. Further molecular studies are required to understand the oncogenic mechanisms of this heterogeneous group of tumours.

We reported several adverse events, including those requiring steroid treatment, after combination therapy with ipilimumab plus nivolumab. The frequency of grade 3/4 adverse events was higher than that for molecular targeted therapy. However, it is equivalent or lower than that reported in the CheckMate 214 trial (1).

The present study had several limitations, including its retrospective nature and small sample size, resulting in differences between the two treatment groups. The percentage of patients with each histological subtype between the two treatment groups differed because nccRCC is a rare malignancy. The small sample size might have affected the outcome of this study because each tumour subtype harbours a distinct cell of origin and exhibits a distinct clinical behaviour that is expected to differentially affect responses to ICIs (24). The median follow-up of patients treated with combination of ipilimumab plus nivolumab was shorter than that of those treated with a molecular targeted agent. To evaluate the treatment outcome without these limitations, the results of prospective clinical trials, including SUNIFORECAST, of ipilimumab plus nivolumab are awaited (13). Furthermore, regarding subsequent therapy after initial therapy of immune checkpoint inhibitors, optimal second-line treatment strategy for nccRCC still remains unclear. There are limited clinical data though Japanese authors demonstrated anticancer activity of tyrosine kinase inhibitors after treatment of immune checkpoint inhibitors for nccRCC (25). In order to optimize the treatment strategy including second-line treatment for nccRCC, randomized clinical trial are awaited.

In conclusion, we confirmed that combination of ipilimumab plus nivolumab demonstrated better OS and objective response rate than a molecular targeted agent as initial systemic treatment of nccRCC. In the absence of available prospective data, this analysis aids selection of the initial systemic therapy for patients with nccRCC.

Conflicts of Interest

The Authors declare no conflicts of interest.

Authors' Contributions

Yukari Bando: Data curation, Writing and Original draft preparation. Junya Furukawa: Conceptualization, Methodology and Creation of research design. Yasuyoshi Okamura, Takuto Hara and Tomoaki Terakawa: Methodology and Investigation. Yuzo Nakano and Masato Fujisawa: Supervision.

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