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ORIGINAL ARTICLE

Efficacy and safety profile of nivolumab for Japanese patients with metastatic renal cell cancer

Ryo Fujiwara[1] · Kentaro Inamura[2] · Takeshi Yuasa[1] · Noboru Numao[1] · Shinya Yamamoto[1] · Hitoshi Masuda[1] · Akihiro Kawauchi[3] · Kengo Takeuchi[2] · Junji Yonese[1]

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Abstract

Background Nivolumab, which has a promising anti-tumor efficacy and a manageable safety profile, has being rapidly introduced in metastatic renal cell cancer therapy in Japan. We evaluated the efficacy and adverse events of nivolumab in real world clinical practice in Japan.

Methods The medical records of 45 consecutive patients who started treatment with nivolumab, up to September 2018, were reviewed and statistically analyzed.

Results The median follow-up period was 22.3 months. The best responses were a complete response in three patients (8%), a partial response in 14 patients (36%), stable disease in 14 patients (36%), and progressive disease in eight patients (20%). The median progression-free survival period and 1 year progression-free survival rate were 14.9 months and 54.5%, respectively. The estimated overall survival period and 1-year and 2-year overall survival rates from initiation of nivolumab were not reached, and 91.1%, and 86.2%, respectively. Twenty-seven patients (60%) experienced adverse events including four (10%) severe adverse events (Grade 3 or 4). The most common adverse event was rash ($n=9$, 20%). Five patients discontinued nivolumab therapy, because of an adverse event (Grade 3 diarrhea, one patient; Grade 2 fatigue, one patient; Grade 3 uveitis, two patients; and Grade 3 adrenal insufficiency, one patient).

Conclusions Nivolumab has a relatively favorable efficacy and safety profile for Japanese metastatic renal cell cancer patients in clinical practice.

Keywords Clinical outcome · Safety profile · Nivolumab · Metastatic renal cell cancer · PD-L1 expression

Introduction

A better understanding of molecular biology has led to major breakthrough in medical treatment for patients with metastatic renal cell cancer (mRCC). Various targeted agents have been approved for the treatment of mRCC, since 2008 in Japan. Vascular endothelial growth factor (VEGF) pathway inhibitors, including sorafenib (Nexaval®, Beyer), sunitinib (Sutent®, Pfizer), pazopanib (Votorient®, Novartis pharma), and axitinib (Inlyta®, Pfizer) and mechanistic target agents of rapamycin (mTOR) inhibitors, including temsirolimus (Torisel®, Pfizer) and everolimus (Affinitor®, Novartis pharma) have played a role as the main treatment for mRCC [1].

Nivolumab (Optivo, Ono/Bristol-Myers Squibb), which is a fully human IgG4 programmed death 1 (PD-1) antibody, is a novel targeted agent that has been available in clinical practice for the treatment of mRCC since 2016 [2]. Its promising anti-tumor efficacy and manageable safety profile were demonstrated in the phase III CheckMate 025 trial [2] and nivolumab therapy is being rapidly introduced in mRCC clinical practice in Japan. Currently, information on the efficacy and adverse events (AEs) is limited to these results from clinical trials and results from clinical practice are lacking [3, 4]. The present study retrospectively examined the therapeutic outcomes and safety profiles of nivolumab

✉ Ryo Fujiwara
ryo.fujiwara@jfcr.or.jp

[1] Department of Urology, Cancer Institute Hospital, Japanese Foundation for Cancer Research, Ariake, Tokyo, Japan

[2] Department of Pathology, Cancer Institute Hospital, Japanese Foundation for Cancer Research, 3-8-31, Ariake, Tokyo 135-8550, Japan

[3] Department of Urology, Shiga University of Medical Science, Seta-Tsukinowa, Otsu, Japan

for Japanese patients with mRCC, after targeted therapy in real world clinical practice.

Patients and methods

Study population

The clinical and laboratory data from 45 consecutive patients with mRCC who were previously treated with VEGF-targeted therapy and who started treatment with nivolumab, up to September 2018 at our institution, were retrospectively investigated. Two patients of this cohort were enrolled in clinical trial. Thirty nine patients had target lesions among these patients. This study was approved by the institutional review board at the Cancer Institute Hospital, Japanese Foundation for Cancer Research. Before the initial treatment, all patients provided written informed consent for nivolumab treatment. Patients who showed disease progression underwent nivolumab therapy when a potential clinical benefit with tolerable toxicity was expected.

Treatment and follow-up examination

Nivolumab was administered every 2 weeks as previously described [3, 4]. In Japan, the dose of nivolumab was 3 mg/kg until September 2018 and thereafter it was changed to 240 mg in October 2018. We recorded the medical history, including physical examination, Karnofsky performance status (KPS), laboratory findings, and chest radiography before starting treatment and during nivolumab therapy, based on the attending physician's decision. We evaluated the objective response by computed tomography (CT) every 2 or 3 months using the Response Evaluation Criteria in Solid Tumors (RECIST) guidelines version 1.1 [5]. Toxicity was assessed by the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 [6].

Pathological evaluation of PD-L1 and CD8 + TILs

Formalin-fixed paraffin-embedded specimens were available from 21 patients with mRCC. The source of the tissue for immunohistochemical study was the primary kidney tumors in 20 patients and the metastatic tumor (pleura) in 1 patient. Tumor programmed death-ligand 1 (PD-L1) membrane expression and cluster of differentiation 8 (CD8) + tumor-infiltrating lymphocytes (TILs) in pathological slides were stained with the PD-L1 (Abcam 28–8) immunohistochemistry assay (Abcam plc, Cambridge, UK) and CD8 antibody (Nichirei Biosciences Inc., Tokyo, Japan). Quantitative evaluations of PD-L1 membrane expression and CD8 + TILs were performed by examining five non-overlapping high-power fields (40 × objective and 10 × eyepiece) in each stained section. PD-L1 membrane expression was considered to be positive if distinct membranous staining in ≥ 5% of tumor cells was observed. PD-L1 expression was not examined in the immune cells in this study. CD8 + TILs were counted in the cancer cell nest and in the tumor stroma. PD-L1 membrane expression was assessed as ≥ 5% vs. < 5% and the mean number of CD8 + TILs per field were calculated by two experienced pathologists who were blinded to clinicopathologic information [7].

Statistical analysis

Descriptive statistics for continuous variables were presented as the median and interquartile range (IQR) and categorical variables were reported as frequencies and percentages. Best overall response was defined as the best response based on the target lesions with CT during nivolumab therapy. Progression-free survival (PFS) and overall survival (OS) periods were defined as the time from initiation of nivolumab to the date of progression and death from any cause, respectively, and these survival curves were estimated using the Kaplan–Meier method. In addition, we investigated the following variables as candidate predictors of efficacy, including age, KPS, duration from diagnosis to treatment, blood hemoglobin concentration, platelet count, neutrophil count, lymphocyte count, neutrophil/lymphocyte ratio (NLR), C-reactive protein (CRP), serum calcium, serum lactate dehydrogenase (LDH), number of treatment line (2nd line versus 3rd or following line), histology (clear cell versus non-clear cell cancer), International Metastatic Renal cell cancer Database Consortium (IMDC) risk classification, number of metastatic lesion, and duration of the first-line therapy. A Chi-squared test was used to compare between objective response rate (ORR) and the categorical covariates as the univariate analysis. Using a multivariate logistic regression analysis, the significant association between ORR and clinical factors was investigated. The hazard ratio (HR) and 95% confidence interval (CI) were calculated as the predictors for an objective response. All of the statistical analyses were performed using JMP software version 14.0 (SAS Institute Inc., Cary, NC, USA) and P values < 0.05 were considered statistically significant.

Results

Patient characteristics

The median follow-up period was 22.3 (IQR 14.1–26.2) months, after initiation of nivolumab. Patient characteristics are described in Table 1. Six patients (13%) died as a result of disease progression and the remaining 39 patients (87%) were alive; among these patients, 36 (80%) were alive

Table 1 Patient characteristics

Clinical factors	
Median age, years (inter-quartile range)	62 (55–69)
KPS (%)	
< 80	8 (18)
≥ 80	37 (82)
Histology (%)	
Clear cell	39 (88)
Papillary	
Type 1	1 (2)
Type 2	2 (4)
Unknown	1 (2)
Unclassified	2 (4)
Duration of the 1st-line therapy, months (%)	
< 6	13 (29)
≥ 6	32 (71)
Number of metastatic lesion (%)	
< 2	16 (36)
≥ 2	29 (64)
Number of treatment line (%)	
< 2	30 (67)
≥ 2	15 (33)
IMDC risk classification (%)	
Favorable	10 (22)
Intermediate	25 (56)
Poor	10 (22)
PD-L1 expression (%)	
< 5%	13 (62)
≥ 5%	8 (38)
Median CD8 + TILs (cells/hpf)	42

KPS Karnofsky performance status, *IMDC* International Metastatic Renal Cell Carcinoma Database Consortium, *PD-L1* programmed death-1 ligand 1, *CD8* cluster of differentiation 8, *TILs* tumor-infiltrating lymphocytes

at least 1 year after initiation of nivolumab. Thirty-one, 11, and three patients were administered nivolumab as second-line, third-line, and fourth-line therapy, respectively. Overall, the sites of metastases at initiation of nivolumab included 19 lung (42.2%), 19 lymph node (42.2%), 12 bone (26.7%), seven liver (15.6%), six pancreas (13.3%), five adrenal gland (11.1%), three pleura (6.7%), two bilateral/multifocal kidney (4.4%), one stomach (2.2%), one spleen (2.2%), and one soft tissue (2.2%). According to the IMDC risk classification [2], the number of patients with favorable, intermediate, and poor risk was 10 (22.2%), 25 (55.6%), and 10 (22.2%), respectively.

Efficacy of nivolumab therapy

Overall, 39 patients were evaluated for response. The other six patients had non-target lesions based on the RECIST guidelines. The ORR was 44% [complete response (CR), three patients (8%); partial response (PR), fourteen patients (36%)]. Stable disease (SD) was present in 36% (14/39) and progressive disease (PD) was present in 20% (8/39) of the patients as the best response to nivolumab (Fig. 1a). The ORR was 42% (11/26) and 46% (6/13) in the patients with nivolumab as second-line and third- or following line, 38% (13/34) and 80% (4/5) in those with clear cell and non-clear cell cancer and 11% (1/9), 52% (12/23), and 57% (4/7) in those with favorable, intermediate, and poor risk in IMDC risk classification, respectively (Table 2). From the initiation of nivolumab, the median PFS period and 1year PFS rate were 14.9 months and 54.5%, respectively (Fig. 1b). The median OS period and 1-year and 2-year OS rates were not reached, and 91.1%, and 86.2%, respectively (Fig. 1c). During the study period, 22 patients discontinued nivolumab therapy; 16 among these patients underwent axitinib therapy after nivolumab. From the initiation of axitinib subsequent

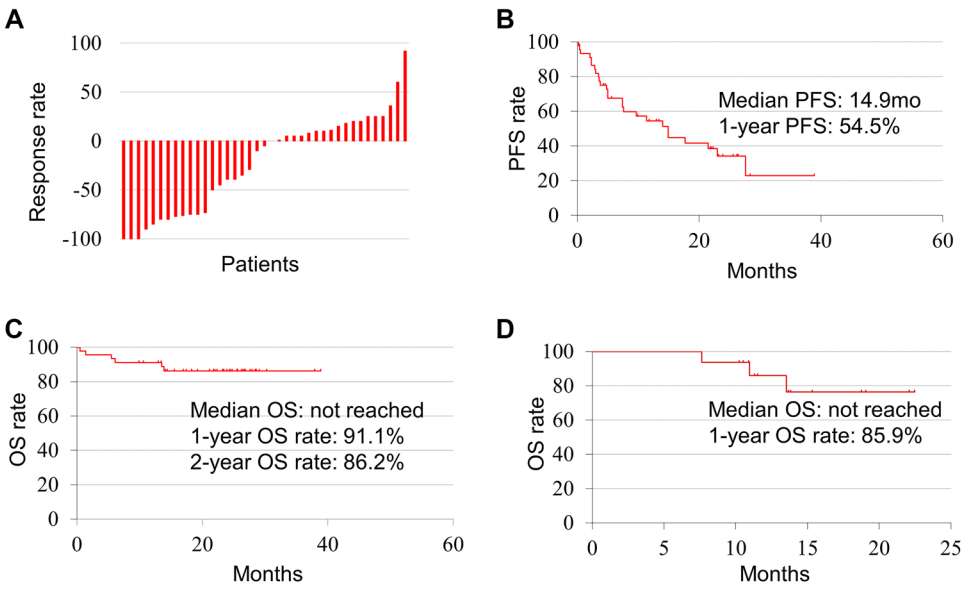

Fig. 1 Efficacy of nivolumab for the patients with metastatic renal cell cancer. Waterfall plots of the response to nivolumab (**a**, $n = 39$). Progression-free survival and overall survival curves (**b**, **c**, $n = 45$). Overall survival curve from the initiation of axitinib subsequent to nivolumab (**d**, $n = 16$)

Table 2 Comparison of objective response rate (ORR) in the risk factors for nivolumab

Variables	ORR[a] (%) (numbers)	Hazard ratio (95% CI)	Univariate
Age (year)			
< 65	55 (6/11)	2.52	0.186
≥ 65	39 (11/28)	(0.64, 10.6)	
KPS			
< 80	50 (3/6)	1.43	0.688
≥ 80	42 (14/33)	(0.25, 8.14)	
Duration from diagnosis to treatment (year)			
< 1	53 (9/17)	1.46	0.554
≥ 1	36 (8/22)	(0.42, 5.15)	
Hemoglobin			
< LLN	48 (10/21)	1.31	0.676
≥ LLN	39 (7/18)	(0.37, 4.76)	
Serum calcium (mg/dl)			
< 11	45 (17/38)	3.1×10^{6}	0.289
≥ 11	0 (0/1)	(0, ∞)	
Platelet (cell count/μl)			
$< 400 \times 10^{3}$	42 (16/38)	6.9×10^{-9}	0.186
$\geq 400 \times 10^{3}$	100 (1/1)	(∞, 4.24)	
LDH (U/l)			
< 230	50 (15/30)	4.0	0.086
≥ 230	22 (2/9)	(0.83, 29.5)	
Neutrophil (cell count/μl)			
< 4000	30 (9/30)	0.386	0.198
≥ 4000	67 (6/9)	(0.08, 1.64)	
Lymphocyte (cell count/μl)			
< 1000	0 (0/3)	9.6×10^{-9}	0.06
≥ 1000	47 (17/36)	(∞, 0)	
NLR			
< 2	35 (6/17)	0.54	0.370
≥ 2	50 (11/22)	(0.14, 2.10)	
CRP (mg/dL)			
< 0.3	45 (9/20)	1.13	0.855
≥ 0.3	42 (8/19)	(0.31, 4.06)	
Number of treatment line			
2nd-line	42 (11/26)	0.86	0.820
3rd-or following line	46 (6/13)	(0.22, 3.34)	
Histology			
Clear cell	38 (13/34)	0.15	0.074
Non-clear cell	80 (4/5)	(0.007, 1.18)	
IMDC risk classification			
Favorable	11 (1/9)		
Intermediate	52 (12/23)		
Poor	57 (4/7)		
Intermediate vs. favorable		8.7 (1.29, 175)	0.023
Poor vs. favorable		10.7 (1.06, 262)	0.045
Number of metastatic lesion			
< 2	46 (6/13)	1.25	0.746
≥ 2	42 (11/26)	(0.32, 4.79)	
Duration of the 1st-line therapy (months)			
< 6	36 (5/14)	0.54	0.361
≥ 6	48 (12/25)	(0.13, 2.00)	
PD-L1 expression (%)			
< 5	67 (8/12)	4.0	0.178
≥ 5	40 (2/5)	(0.5, 32.0)	
CD8 + TILs (cells/hpf)			
≤ 42	67 (6/9)	2.0	0.488
> 42	50 (4/8)	(0.28–14.2)	

KPS Karnofsky performance status, *LDH* lactate dehydrogenase, *NLR* neutrophil-to-lymphocyte ratio, *CRP* C-reactive protein, *IMDC risk classification* the International Metastatic Renal cell cancer Database Consortium risk classification, *ORR* objective response rate, *HR* hazard ratio, *CI* confidence interval, *PD-L1* programed death-ligand 1, *CD8* cluster of differentiation 8, *TIL* tumor infiltrating lymphocyte, *hpf* high-power field

[a]Non-target lesions were excluded

to nivolumab, the median OS period and 1-year OS rate were not reached, and 85.9%, respectively (Fig. 1d).

Next, we investigated the response predictors among the pre-treatment variables. In the univariate analysis, there was a significant difference of ORR between intermediate and favorable risk ($P = 0.023$) and between poor and favorable risk ($P = 0.045$) in IMDC risk classification. In multivariate analysis, however, there was no significant predictor of ORR for nivolumab therapy (Table 2). Among the factors, the patients with low blood lymphocyte count ($P = 0.06$) tended to have a poor response. In addition, there was significant poor predictor neither of PFS nor of OS in this study.

Association of ORR with PD-L1 and CD8 + TILs

Overall, formalin-fixed paraffin-embedded specimens from 21 patients were available for the immunohistochemical study. All but one specimen was gained before VEGF-targeted therapy. Four patients, who had only non-target lesions, were excluded from evaluation of PD-L1 expression and CD8 + TILs for ORR of nivolumab. Membranous PD-L1 expression ≥ 5% in tumor cells was detected in five (29.4%) of 17 patients. Median CD8 + TILs in 17 patients were 42 cells/high-power field (hpf). We analyzed the association between the treatment efficacy of nivolumab and PD-L1 expression and the number of CD8 + TILs. There was no significant association of ORR with PD-L1 expression ($P = 0.178$) or with the number of CD8 + TILs ($P = 0.488$). However, one patient who had achieved CR with nivolumab had showed PD-L1 expression in 90% of cells and 200

cells/hpf showed CD8 + TILs (Fig. 2a, b). The patient with advanced papillary type 2 RCC (cT3aN2M0) had previously undergone nephrectomy followed by recurrence of lymph node metastases. Subsequently, the patient underwent pazopanib therapy as a first-line treatment for 12 months and axitinib therapy as the second-line treatment for 8 months. After the disease progressed, while on these VEGF-targeted therapies, the patient was switched to nivolumab treatment as a third-line therapy and he maintained CR for 20 months (Fig. 2c, d). Tumor tissues from the other two patients, who demonstrated CR with nivolumab, could not be obtained.

Toxicity

Twenty-seven patients (60%) experienced AEs, including four (10%) severe AEs (Grade 3 or 4), which are described in Table 3. The most common AE was rash ($n = 9$, 20%), but none had a severe grade. Five patients (11.1%) discontinued nivolumab therapy because of the AEs (Grade 3 diarrhea, one patient; Grade 2 fatigue, one patient; Grade 3

Table 3 Treatment-related adverse events

Events	*n* (%)	
	Any grade	Grade 3–4
Diarrhea	7 (16)	1 (2)
Uveitis	2 (4)	2 (4)
Adrenal insufficiency	2 (4)	1 (2)
Rash	9 (20)	0
Fatigue	7 (16)	0
Constipation	6 (13)	0
Stomatitis	5 (11)	0
Neutropenia	4 (8)	0
Peripheral neuropathy	3 (7)	0
Edema	2 (4)	0
Arthritis	1 (2)	0
Cystitis	1 (2)	0
Pneumonitis	1 (2)	0
Nausea	1 (2)	0
Hypertension	1 (2)	0

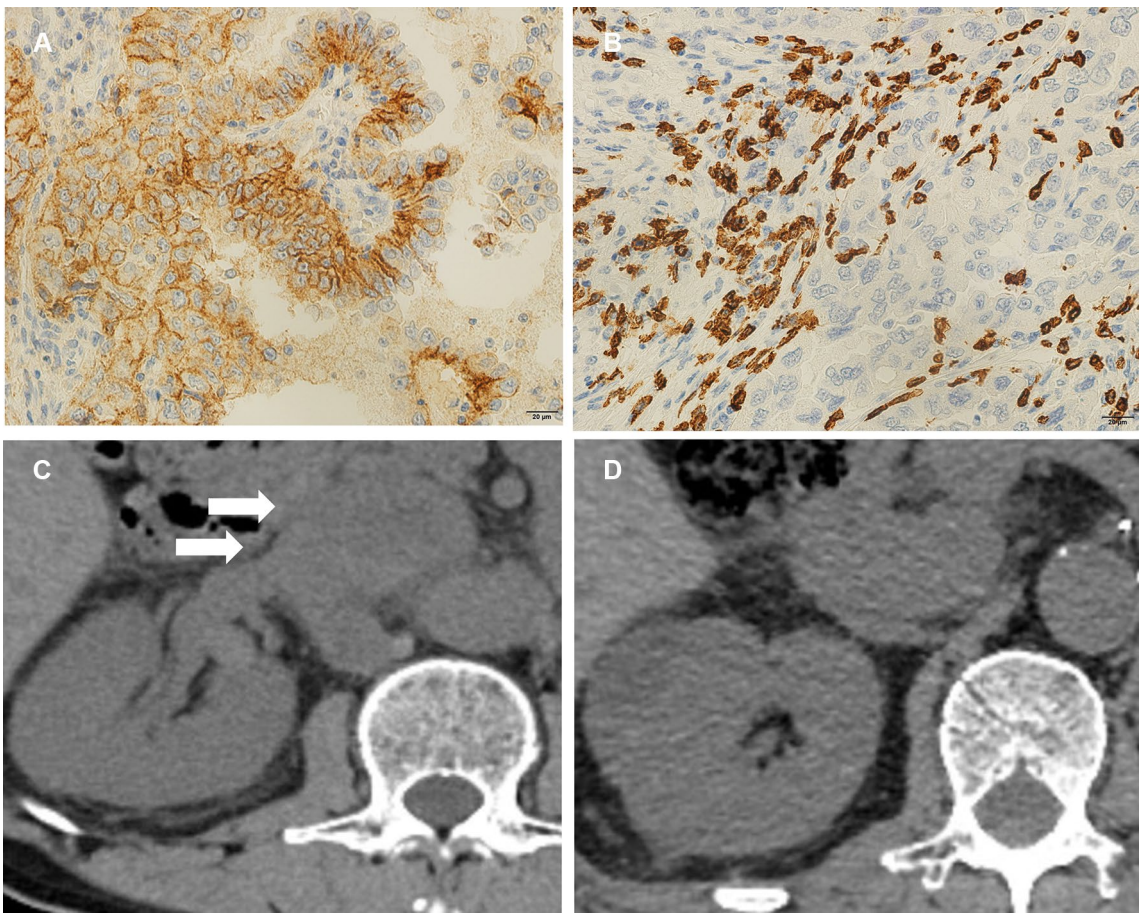

Fig. 2 A patient with a complete response whose primary tumor tissues demonstrated remarkable programed death-ligand 1 (PD-L1) expression and an increased number of CD8 + tumor infiltrating lymphocytes (TILs). High PD-L1 expression (90%) in the primary lesion (**a**). Increased number of CD8 + TILs (200/hpf: high power field) in the primary lesion (**b**). Computed tomography appearance of the recurrence of lymph-node metastasis before (**c**) and during nivolumab therapy (**d**). The patient maintained a complete response for 20 months

uveitis, two patients; and Grade 3 adrenal insufficiency, one patient). Sixteen patients (36%) were considered to experience immune-related AEs (irAEs), including diarrhea, uveitis, adrenal insufficiency, and rash.

Discussion

We demonstrated the therapeutic outcomes and safety profiles in Japanese patients with mRCC after targeted therapy in real world clinical practice. The therapeutic outcomes of nivolumab in our study were similar to the Japanese subgroup investigation of the CheckMate 025 study. In our study, the ORR was 44% (CR, 8%; PR, 36%) and the median PFS and OS period were 14.9 months and not reached, respectively. One-year and 2-year OS rates were 91.1% and 86.2%, respectively. In the Japanese subgroup analysis of the CheckMate 025 study, ORR, median PFS, and median OS with nivolumab were 43%, 5.6 months, and not reached, respectively [8]. In real world clinical practice, efficacy of nivolumab for Japanese patients also seems to be relatively good. Additionally, the safety profile of nivolumab in our study was similar to that of the CheckMate 025 study. Twenty-seven patients (60%) experienced AEs and the most common AE was rash in our study. The incidence of severe AEs (Grade 3 or 4) in the CheckMate 025 study, Japanese subgroup analysis, and our study was 20%, 19%, and 10%, respectively [8, 9].

Biomarkers to predict the response to nivolumab need to be identified to achieve a better efficacy and safety profile for nivolumab therapy that is used to treat mRCC [10]. In this study, the ORR was significantly higher in patients with intermediate and poor risk than favorable risk in the univariate analysis. The ORR of the combination of iplimumab and nivolumab was reported higher than sunitinib (42% vs. 27%) in patients with intermediate and poor risk. On the other hand, the ORR of this combination was lower than sunitinib (29% vs. 52%) in patients with favorable risk in the CheckMate 214 study [11]. The efficacy of nivolumab-monotherapy may be higher in intermediate and poor risks than in favorable risk. The patients with a low blood lymphocyte count ($P=0.06$) tended to have a poor response. Previously, higher baseline or increased absolute lymphocyte count with treatment was also reported to be associated with improved response to immunotherapy and OS in melanoma [12, 13]. These results suggest that a higher lymphocytes peripheral blood cell count may be associated with more PD-L1-positive lymphocytes in the tumor, and thus better anti-tumor effects with immunotherapy [14, 15].

High PD-L1 levels within the tumors were associated with a significantly worse prognosis in RCC patients in the pre-immune checkpoint inhibitor therapy era [16, 17]. However, the association between PD-L1 and the nivolumab treatment effect remains controversial. Motzer et al. reported that the PFS and OS were longer and ORR was better in the PD-L1 ≥ 5% subgroup compared with those of the PD-L1 < 5% subgroup in the phase II study [4]. However, in the phase III CheckMate 025 study, Motzer et al. also reported that there was no difference in OS between the PD-L1 ≥ 5% and PD-L1 < 5% subgroups (21.9 and 24.6 months, respectively) [9]. Assay clone used for PD-L1 staining was reported to affect the evaluation of PD-L1 expression. PD-L1 immunohistochemistry assay for lung cancer revealed that 22C3, 28–8, and SP263 assays were closely aligned on tumor cell staining, whereas SP142 assay in which fewer tumor cells stained than the other assays [18]. Because this study used 28-8 immune staining, we consider that PD-L1 immunohistochemistry assay system did not affect these results in this study. The correlation between the efficacy of nivolumab and TILs in RCC is also unclear. Ueda et al. reported that PD-1 and PD-L1 expression was associated with high CD4 and CD8 infiltration into RCC [19]. They demonstrated that CD4 + and CD8 + TILs in tumor tissues were associated with an unfavorable prognosis in mRCC in the pre-immune checkpoint inhibitor era [20]. Recently, McDermott et al. showed no association between CD8 + T cell and a clinical benefit, when atezolizumab was used to treat RCC [21]. Although there was no significant difference of ORR between the PD-L1 ≥ 5% subgroup and the PD-L1 < 5% subgroup or between CD8 + TILs and ORR in our study, PD-L1 and CD8 + TILs may still be associated with the effect of nivolumab treatment, because a patient in our study with a PD-L1 of 90% and strong TILs infiltration had achieved CR with nivolumab for 20 months. Further investigation is required to clarify this issue.

We conducted this retrospective study to clarify the characteristics of nivolumab for Japanese patients. The major limitations of our study are its retrospective study design and small study cohort size. However, for nivolumab therapy for RCC, no large, multi-institutional, and prospective or retrospective study has been published from Japan. These results described here reflect the characteristics of nivolumab therapy for mRCC patients in current clinical practice in Japan.

In conclusion, for the first time, we demonstrated a relatively favorable efficacy and safety profile of nivolumab therapy for Japanese patients with mRCC in real-world clinical practice in this study. Further investigation is necessary to clarify a biomarker for this novel therapy.

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Compliance with ethical standards

Conflict of interest T. Yuasa received remuneration for a lecture from Astellas (Tokyo, Japan), Sanofi Japan (Tokyo, Japan), Pfizer Japan (Tokyo, Japan), Novartis Pharma Japan (Tokyo, Japan), Ono Pharma (Osaka, Japan), Bristol-Myers Squibb Japan (Tokyo, Japan), Janssen Pharmaceutical K.K Japan (Tokyo, Japan), MSD Japan (Tokyo, Japan), and Daiichi Sankyo (Tokyo, Japan). The other authors have declared no conflicts of interest.

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