Clinical-Kidney cancer

Association between immune-related adverse events and prognosis in patients with metastatic renal cell carcinoma treated with nivolumab

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Abstract

Objectives: Immune-related adverse events (irAEs) develop in a subset of patients with metastatic renal cell carcinoma (mRCC) treated with immune checkpoint inhibitors. The relationship between presence of irAEs and prognosis in these patients remains unknown. Thus, we evaluated the prognostic impact of irAEs caused by nivolumab therapy in mRCC patients who had received prior molecular-targeted therapies.

Methods: We retrospectively evaluated 47 patients with mRCC who were treated with nivolumab after receiving at least 1 molecular-targeted therapy. The irAEs assessed in this study included cutaneous, gastrointestinal, endocrine, pulmonary, hepatobiliary, renal, and other (rheumatic disease and pancreatitis) manifestations. The grade of irAEs was defined based on the Common Terminology Criteria for Adverse Events version 4.0.

Results: In total, 23/47 patients (48.9%) experienced 29 irAEs. The most frequent irAE was rash/pruritus (12/23, 52.2%). The median progression-free survival (PFS) and overall survival after the initiation of nivolumab therapy were significantly longer in patients with irAEs than in those without irAEs (PFS: 13.1 vs. 4.87 months, $P < 0.0001$; overall survival: 26.0 vs. not reached, $P = 0.0072$). The multivariate analysis of PFS showed that irAE development was an independent prognostic factor (hazard ratio: 0.25, $P = 0.0009$). Additionally, the 2-cycle landmark analysis showed that PFS was significantly longer in patients with irAEs than in those without irAEs (median: not reached vs. 6.28 months, $P = 0.0279$).

Conclusions: This retrospective study revealed a significant association between nivolumab-associated irAEs and prognosis in previously treated mRCC. Further prospective studies are necessary to confirm our findings. © 2019 Elsevier Inc. All rights reserved.

1. Introduction

Nivolumab is a human immunoglobulin G4 (IgG4) monoclonal antibody that acts as an immune checkpoint inhibitor (ICI), selectively blocking the interaction between programmed cell death-1 and programmed cell death ligand-1. It has been shown recently that nivolumab had superior therapeutic efficacy and caused less drug-induced toxicity than everolimus in previously treated metastatic renal cell carcinoma (mRCC) [1]. Furthermore, patients treated with a combination therapy of nivolumab and ipilimumab, a monoclonal antibody targeting cytotoxic T-lymphocyte antigen 4, showed prolonged survival and higher objective response than those treated with sunitinib in the first-line setting [2]. Moreover, several other combination therapies involving ICIs are currently being tested in phase III trials [3]. Thus, ICIs are significantly changing the clinical management of mRCC [3,4], and this paradigm

shift will likely continue in the future systematic therapy strategies.

Fewer adverse events (AEs) have been observed after the treatment with nivolumab than with everolimus [1]. However, a fraction of nivolumab-treated patients experienced severe AEs, including autoimmune disease requiring immunosuppression by steroid replacement therapy [5−8]. Immune-related AEs (irAEs) are different in both the mechanism and management from the AEs commonly observed in cytotoxic chemotherapy and molecular-targeted therapy [8].

Correlative relationships between irAEs on the one hand and patient survival and tumor response on the other hand have been described in melanoma [9−12] and nonsmall cell lung cancer [13,14]. Furthermore, a prognostic association between irAEs and mRCC has been recently reported [15,16]. However, mRCC patients represented only a minor population in those studies. Thus, reliable data regarding the relationship between irAEs and the prognosis of mRCC patients treated with nivolumab are currently lacking.

In the present study, we therefore investigated the incidence, grade, and patterns, as well as the prognostic impact of irAEs during nivolumab therapy of previously treated mRCC patients.

2. Patients and methods

2.1. Study design

In our department and its affiliated institution, 55 patients with previously treated mRCC received nivolumab at least once between June 2013 and November 2018. We excluded 6 patients whose treatment was discontinued after 2 initial cycles owing to immediate disease progression. In addition, we excluded another 2 patients because their detailed data were lacking. The remaining 47 patients were evaluated in this retrospective study.

The Internal Ethics Review Boards of the Tokyo Women's Medical University and Tokyo Women's Medical University Medical Center East approved this study (ID: 4941), which was performed within the tenets of the Declaration of Helsinki. All clinical and laboratory data were extracted from the electronic database and patient medical records.

2.2. Protocol for nivolumab therapy

Nivolumab (3 mg/kg) was intravenously administered every 2 weeks. Dose modifications were not permitted for any reason. However, the interval between administrations could be modified according to the patient condition or irAE development. In this study, all patients received nivolumab after 1 or more molecular-targeted therapies had failed. Other ICI therapies, such as ipilimumab, were not administered. The protocols for molecular-targeted therapies adopted in our departments have been described in previous studies [17−19].

Post-treatment follow-up scans were obtained using plane or contrast computed tomography or magnetic resonance imaging of the chest, abdomen, and pelvis at regular 4- to 12-week intervals, depending on the patient conditions. Nivolumab was administered until radiographic or clinical disease progression, or intolerable irAEs were observed. Radiographic evaluation of the treatment response was defined based on the Response Evaluation Criteria in Solid Tumors version 1.1 [20].

2.3. The irAEs of nivolumab therapy

The irAEs evaluated in this study included cutaneous, gastrointestinal, endocrine, pulmonary, hepatobiliary, and renal AEs according to previous studies [9,13,21,22]. In addition, autoimmune conditions, such as rheumatic disease [7,23] and pancreatitis, (elevated pancreatic enzymes) were included [9,24]. The grade of irAEs was defined based on the Common Terminology Criteria for Adverse Events version 4.0. The irAEs were checked by medical staff, including physicians, nurses, and pharmacists, when patients came to outpatient clinics.

2.4. Statistical analysis

Continuous variables were analyzed using the Mann-Whitney U test, and categorical variables were analyzed using the Fisher's exact test or $\chi 2$ test. Progression-free survival (PFS) was calculated from the start of nivolumab therapy until progressive disease or death, whichever came first. Alive patients without progressive disease were censored at the time of the last follow-up. In this study, we determined the overall survival (OS) at 2 time points: OS was calculated from the start of nivolumab therapy and irAE diagnosis until death from any cause. Patients lost to follow-up were censored at the time of the last contact. Survival was calculated using the Kaplan-Meier method and compared using the log-rank test. Univariate and multivariate analyses were used to identify risk factors for survival. The risk was expressed as hazard ratios (HRs) and 95% confidence intervals (CIs). All statistical analyses were conducted using JMP software (version 14; SAS Institute Inc., Cary, NC) with a significance level of $\alpha = 0.05$ ($P < 0.05$).

3. Results

3.1. Patient characteristics

During nivolumab therapy, 23/47 patients (48.9%) experienced 29 irAEs of any grade. Of those, 10/47 patients (21.3%) experienced 10 irAEs with grade ≥3. The development of irAEs was significantly more frequent in patients with clear-cell carcinoma than in those with nonclear cell carcinoma ($P = 0.0116$) (Table 1). Meanwhile, other baseline patient characteristics, including age, sex, the Memorial Sloan Kettering Cancer Center (MSKCC) risk based on

Table 1
Baseline characteristics of patients

	With irAEs (n = 23)	Without irAEs (n = 24)	P
Age, years			
≥65	17 (73.9%)	12 (50.0%)	0.0918
Sex			
Female	4 (17.4%)	6 (25.0%)	0.524
Histopathology			
Clear-cell carcinoma	22 (95.7%)	16 (66.7%)	0.0116
MSKCC risk at the initiation of nivolumab therapy[a]			0.580
Favorable	1 (4.35%)	1 (4.17%)	
Intermediate	19 (82.6%)	17 (70.8%)	
Poor	3 (13.0%)	6 (25.0%)	
Cytokine therapy			
With	4 (17.4%)	1 (4.17%)	0.142
First-line molecular-targeted therapy			
Sunitinib	11 (47.8%)	10 (41.7%)	0.671
Number of previous molecular-targeted therapies			
≥2	11 (47.8%)	10 (41.7%)	0.671
Number of metastatic sites		18 (75.0%)	
≥2	13 (56,5%)		0.181
Liver metastasis			
Present	2 (8.70%)	6 (25.0%)	0.137
Serum CRP level, mg/dl			
≥1	12 (52.2%)	16 (66.7%)	0.312
Follow-up, months[b]	16.3 (11.0−23.5)	9.42 (6.24−13.8)	0.0078

CRP = C-reactive protein; irAEs = immune-related adverse events; MSKCC = Memorial Sloan Kettering Cancer Center.
[a] Median (interquartile range).
[b] Based on the Motzer's risk classification [25].

Motzer's risk classification [25], presence of cytokine therapy, first-line molecular-targeted therapy, number of previous molecular-targeted therapies, number of metastatic sites, presence of liver metastasis, or serum C-reactive protein level did not significantly affect irAE emergence (all, $P >$ 0.05). Follow-up duration was significantly longer in patients with irAEs ($P = 0.0078$).

3.2. Profile of irAEs

Table 2 summarizes the profile of irAEs. The median time from nivolumab therapy initiation to irAE onset was 1.38 months (interquartile range: 0.46−3.91). Cutaneous AEs were the most frequent (12/23 patients, 52.2%), followed by endocrine and hepatobiliary AEs (both, 4/23 patients, 17.4%). The most common grade ≥3 irAEs were endocrine and hepatobiliary AEs (both, 3/10 patients, 30.0%).

3.3. Survival after the initiation of nivolumab therapy according to irAEs

During the observational period, 32/47 (68.1%) and 13/47 (27.7%) patients, respectively, had disease progression and died. Median PFS and OS after the initiation of nivolumab therapy were significantly longer in patients with irAEs than in those without irAEs (PFS: 13.1 [95% CI: 8.05−not reached (NR)] vs. 4.87 [3.39−7.30] months, $P <$ 0.0001; OS: 26.0 [21.4−NR] vs. NR [8.02−NR] months, $P = 0.0072$; Fig. 1). The 2-year OS rate after irAE development was 50.2%.

We further analyzed PFS and OS based on severity of irAEs (i.e., "grade ≥3" vs. "<3"). As shown in Fig. 2, longer PFS was observed in patients with irAEs regardless of the severity (grade ≥3 vs. without irAEs: $P = 0.0023$; grade <3 vs. without irAEs: $P = 0.0024$). Furthermore, longer OS in patients with irAEs was associated with grade <3 irAEs rather than with grade ≥3 (grade <3 vs. without: $P = 0.0124$; grade ≥3 vs. without irAEs: $P = 0.136$). Next, we analyzed PFS and OS based on the location of manifested irAEs (i.e., cutaneous vs. noncutaneous). As shown in Fig. 3, longer PFS was observed in patients with irAEs regardless of the location of irAEs (cutaneous vs. without irAEs: $P = 0.0003$; noncutaneous vs. without irAEs: $P = 0.0181$). In addition, longer PFS was associated with cutaneous irAEs (cutaneous vs. noncutaneous: $P = 0.0242$). Similarly, longer OS in patients with irAEs was associated with cutaneous irAEs rather than noncutaneous irAEs (cutaneous vs. without irAEs: $P = 0.0110$; noncutaneous vs. without irAEs: $P = 0.160$).

3.4. Objective response rate according to irAEs

Fig. 4 shows a patient ratio regarding the best overall response during nivolumab therapy. The objective response

Table 2
Profile of irAEs

| irAEs	Any grade $n = 23$	Grade ≥ 3 $n = 10$	Developed within the initial 2 cycles $n = 11$
Cutaneous			
Rash/pruritus	12 (52.2%)	0	7 (63.6%)
Gastrointestinal			
Colitis/diarrhea	3 (13.0%)	1 (10.0%)	1 (9.10%)
Endocrine	4 (17.4%)	3 (30.0%)	1 (9.10%)
Hypothyroidism	2 (8.70%)	1 (10.0%)	1 (9.10%)
Thyroiditis/hypophysitis	1 (4.35%)	1 (10.0%)	0
Diabetes mellitus type 1	1 (4.35%)	1 (10.0%)	0
Pulmonary			
Interstitial pneumonia	1 (4.35%)	1 (10.0%)	0
Hepatobiliary			
Elevated hepatic enzymes	4 (17.4%)	3 (30.0%)	3 (27.3%)
Renal			
Elevated creatinine	3 (13.0%)	0	0
Other	2 (8.70%)	2 (20.0%)	0
Elevated pancreatic enzymes	1 (4.35%)	1 (10.0%)	0
Polymyalgia rheumatica	1 (4.35%)	1 (10.0%)	0

irAEs = immune-related adverse events.
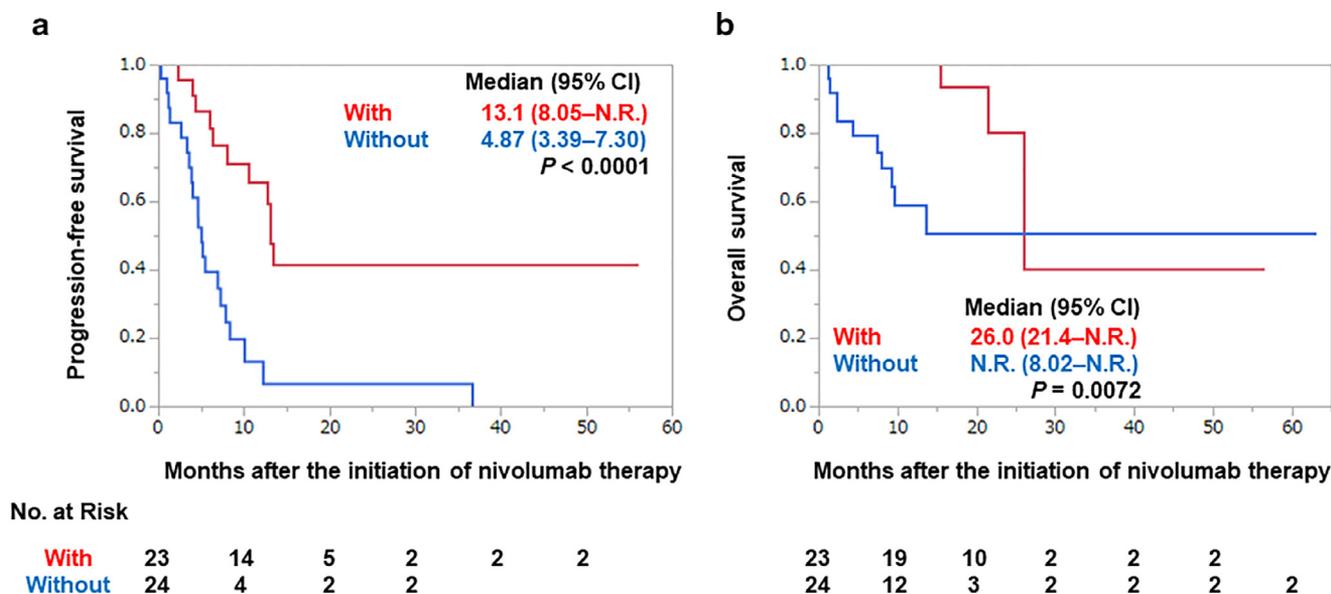
Fig. 1. Progression-free and overall survival after the initiation of nivolumab therapy depending on the presence of immune-related adverse events. (a) Progression-free survival and (b) overall survival after the initiation of nivolumab therapy in the presence or absence of immune-related adverse events. CI = confidence interval; NR = not reached.

rate (ORR) was significantly higher in patients with irAEs than in those without irAEs (60.9% vs. 12.5%, $P = 0.0006$).

3.5. Prognostic factors of PFS

The univariate analysis showed that sex, MSKCC risk, and the presence of irAEs were significant factors affecting PFS (all, $P < 0.05$; Table 3). Moreover, although the difference was not significant, histopathology showed a tendency to be associated with PFS ($P = 0.115$). The multivariate analysis of PFS showed that the presence of irAEs was an

independent factor (HR: 0.25 [95% CI: 0.11−0.56], $P = 0.0009$), along with sex (HR: 2.67, 95% CI: 1.04−6.54, $P = 0.0416$) and MSKCC risk (HR: 1.45×10^{-9}, 95% CI: 1.44×10^{-9}−0.95, $P = 0.0452$).

3.6. Landmark analysis for survival

Next, we conducted the 2-cycle landmark analysis because patients with longer PFS might have a higher chance of irAE development that could lead to a bias in the
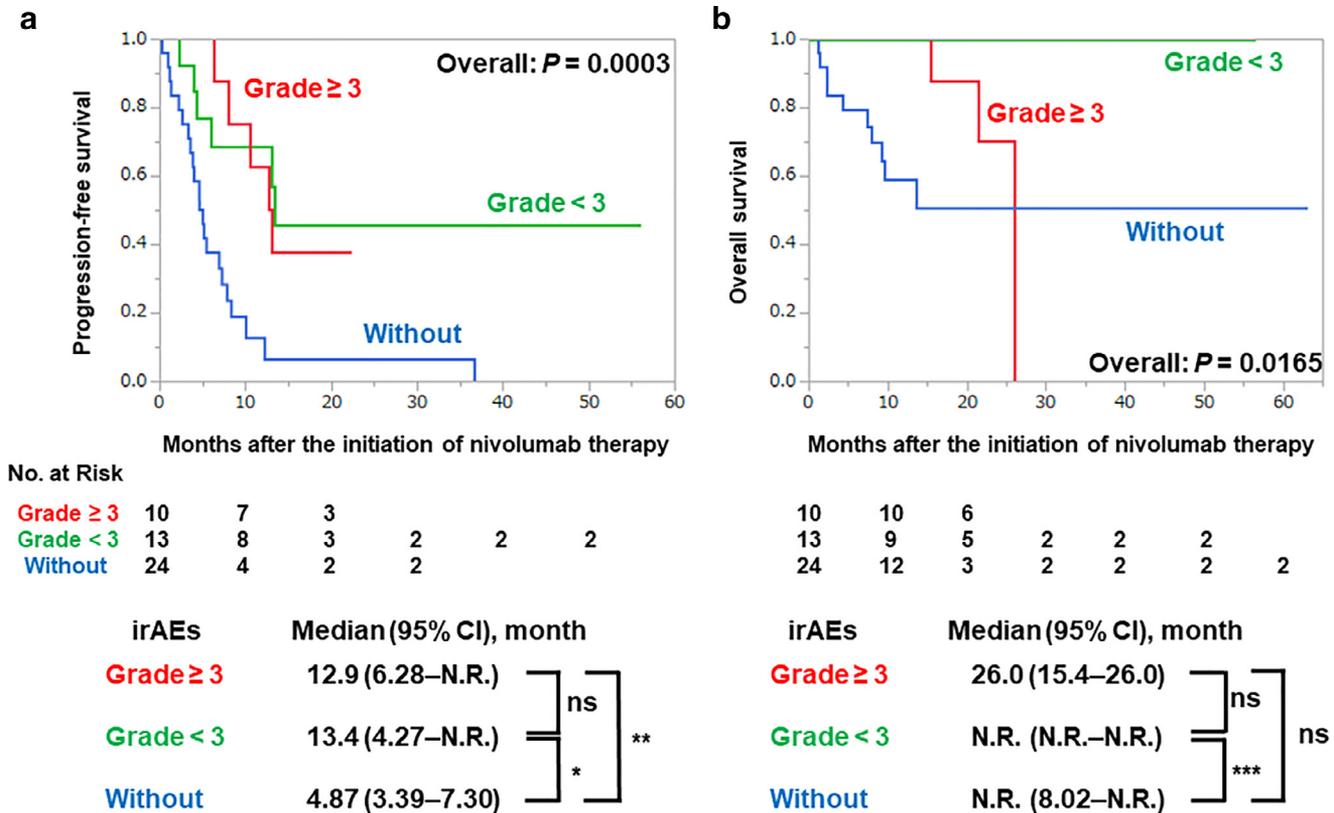
Fig. 2. Progression-free and overall survival after the initiation of nivolumab therapy depending on the severity of immune-related adverse events. (a) Progression-free survival and (b) overall survival after the initiation of nivolumab therapy in the severity of immune-related adverse events: grade ≥3 ($n = 10$); grade <3 ($n = 13$); without ($n = 24$). *$P = 0.0024$; **$P = 0.0023$; ***$P = 0.0124$. CI = confidence interval; NR = not reached; ns = not significant.

survival analysis. As shown in Table 2, 12 irAEs developed in 11/47 patients (23.4%) within the initial 2 cycles. The 2-cycle landmark analysis showed that median PFS but not OS was significantly longer in patients with irAEs than those without irAEs (PFS: NR [4.27−NR] vs. 6.28 [4.64−10.1] months, $P = 0.0279$; OS: NR [21.4−NR] vs. 26.0 [13.6−NR] months, $P = 0.193$; Fig. 5).

3.7. Prognosis in patients with irAEs that required cessation of nivolumab therapy

We focused on 9/47 patients (19.1%) who had to stop nivolumab therapy due to intolerable irAEs (Table 4). Most patients had clear-cell histology (8/9 patients) and were considered to be at intermediate risk (8/9 patients). During the observational period, 2 patients died from cancer (Fig. 6). Median OS after cessation of nivolumab therapy was 20.7 months (interquartile range: 10.5−NR). Overall, 4 patients, including 3 previously reported ones [26], presented a durable response for at least 6 months, even off treatment. Steroid replacement therapy was administered to 5 patients for colitis, elevated liver enzymes, thyroiditis/ hypophysitis, interstitial pneumonia, or polymyalgia rheumatica.

4. Discussion

This retrospective study showed that PFS and OS after the initiation of nivolumab therapy were significantly longer in patients with irAEs than in those without irAEs. Multivariate analysis indicated that the presence of irAEs was an independent factor of longer PFS. Moreover, a higher ORR was observed in patients with irAEs. Furthermore, the 2-cycle landmark analysis showed a significant association between irAEs and PFS.

The number of studies of the association between prognosis or tumor response with irAEs in ICI therapies is increasing, especially in skin and lung cancers [15,16]. The mRCC was included as a minor population in several previous studies (19.1% in the Shafqat study [15]; 11.4% in the Fujii study [16]), but the amount of data was limited. Therefore, to improve our knowledge, in this study, we evaluated for the first time the relationship between irAEs and oncological outcomes, such as survival and ORR, during nivolumab therapy exclusively in mRCC patients.

In our analysis, PFS and OS were significantly associated with all irAEs developed during the nivolumab therapy. This finding suggested that irAE development could be used as a surrogate marker of patient survival. The
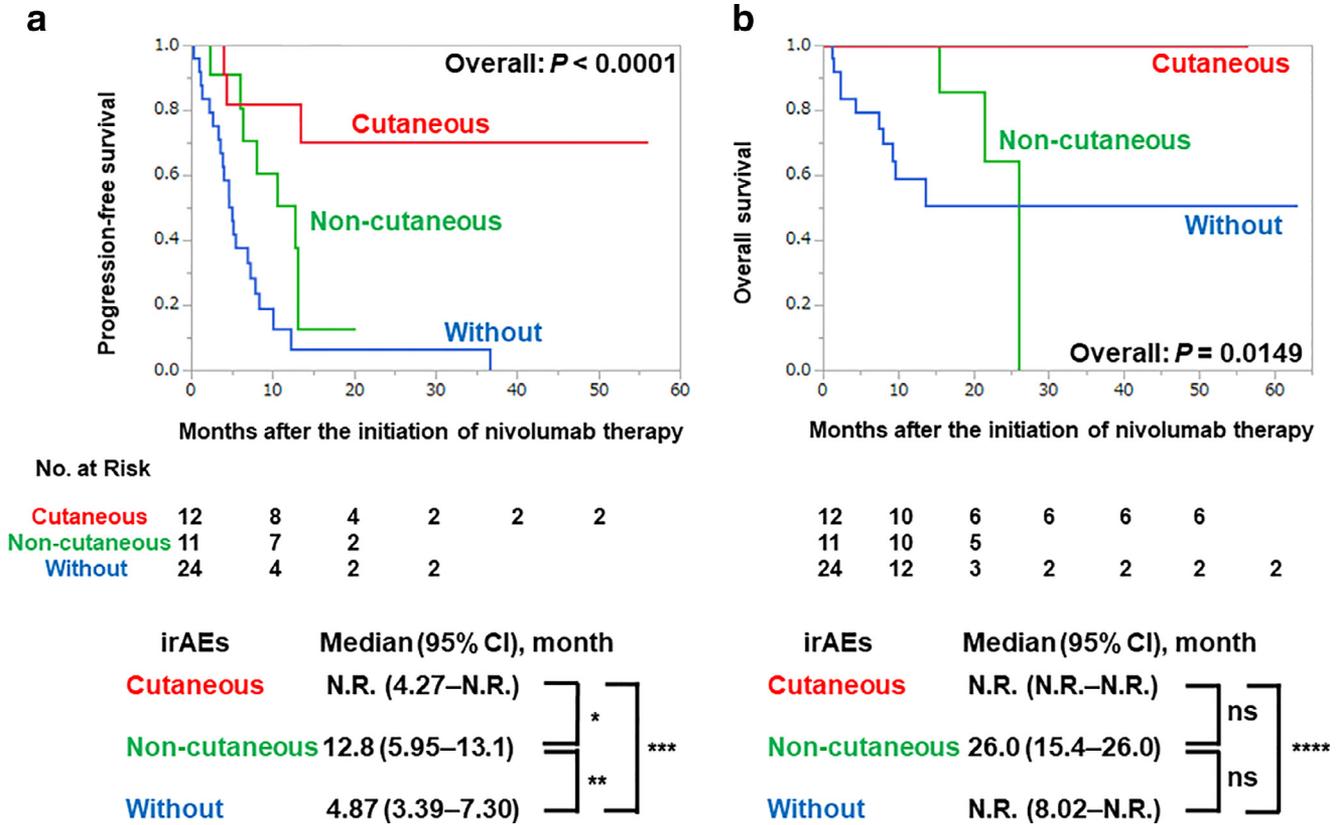
Fig. 3. Progression-free and overall survival after the initiation of nivolumab therapy depending on the site of immune-related adverse event manifestation. (a) Progression-free survival and (b) overall survival after the initiation of nivolumab therapy in the site of immune-related adverse event manifestation: cutaneous ($n = 12$); noncutaneous ($n = 11$); without ($n = 24$). *$P = 0.0242$; **$P = 0.0181$; ***$P = 0.0003$; ****$P = 0.0110$. CI = confidence interval; NR = not reached; ns = not significant.

landmark analysis also indicated that irAEs developed during the early phases of therapy could be used as a predictive marker. The landmark analysis did not find a significant improvement in OS; however, the sample size was small,
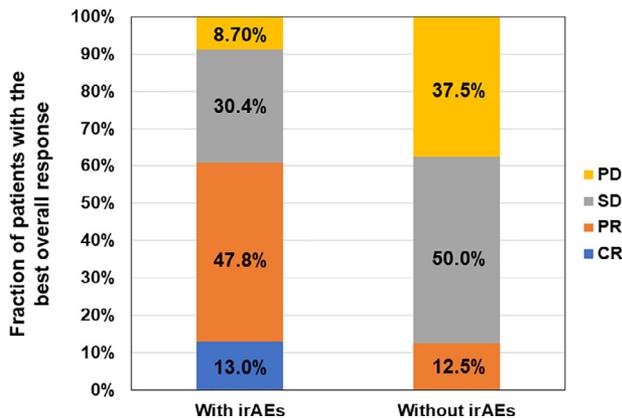

Fig. 4. Objective response rate depending on the presence of immune-related adverse events. The fraction of patients with the best overall response during nivolumab therapy depending on the presence of immune-related adverse events. Progressive disease (PD), stable disease (SD), partial response (PR), and complete response (CR) were observed in 2/23 (8.70%), 7/23 (30.4%), 11/23 (47.8%), and 3/23 (13.0%) patients with immune-related adverse events (irAEs); and 9/24 (37.5%), 12/24 (50.0%), 3/24 (12.5%), 0 patients without irAEs, respectively.

making it hard to interpret the result statistically. Indeed, the fraction of the patients who were alive at the time of the last follow-up was higher in patients with irAEs than in those without irAEs (10/11 [90.9%] vs. 24/36 [66.7%]), suggesting that OS might have a potential association with irAEs.

We also evaluated the prognosis in the patients who had to stop nivolumab therapy due to intolerable irAEs. Durable responses even in the absence of active treatment have been reported in ICI therapy [22,27,28]. Martini et al. reported that 68.4% of mRCC patients experienced at least 6 months of time to progression during the cessation of treatment with ICIs due to irAEs [27]. We also reported 3 cases obtaining a clinical response benefit at least 6 months after cessation of nivolumab therapy [26]. Collectively, these data indicated that a predictive marker for a durable response after the cessation of therapy should be identified in future investigations.

Interestingly, our analysis also showed that moderate or cutaneous irAEs were associated with favorable prognosis. Similarly, in melanoma and nonsmall cell lung cancer, significant associations between cutaneous irAEs and improved survival after nivolumab therapy have been reported [9,13,29]. In our cases, severe cutaneous irAEs were hardly observed, enabling continuous treatment

Table 3
Univariate and multivariate analysis of progression-free survival

	Univariate HR (95% CI)	P	Multivariate HR (95% CI)	P
Age, years				
≥65 (ref. <65)	0.84 (0.42−1.71)	0.618		
Sex				
Female (ref. male)	3.51 (1.47−7.86)	0.0059	2.67 (1.04−6.54)	0.0416
Histopathology				
Clear-cell carcinoma (ref. nonclear cell carcinoma)	0.50 (0.23−1.20)	0.115	1.01 (0.38−2.82)	0.992
MSKCC risk at initiation of nivolumab therapy				
Favorable (ref. intermediate and poor)	1.82×10^{-9} (0.83−0.83)	0.0317	1.45×10^{-9} (1.44×10^{-9}−0.95)	0.0452
First-line molecular-targeted therapy				
Sunitinib (ref. others)	1.02 (0.50−2.05)	0.949		
Number of previous molecular-targeted therapies				
≥2 (ref. 1)	0.76 (0.37−1.51)	0.430		
Number of metastatic organ sites				
≥2 (ref. 1)	1.47 (0.72−3.23)	0.303		
Liver metastasis				
Present (ref. absent)	2.02 (0.74−4.72)	0.157		
Serum CRP level, mg/dl				
≥ 1 (ref. <1)	1.46 (0.72−3.14)	0.305		
irAEs				
Present (ref. absent)	0.23 (0.10 − 0.48)	<0.0001	0.25 (0.11−0.56)	0.0009

HR = hazard ratio; CI = confidence interval; MSKCC = Memorial Sloan Kettering Cancer Center; CRP = C-reactive protein; irAEs = immune-related adverse events.

without cessation in the majority of patients. Even though some patients may show durable response after severe irAEs requiring cessation of treatment as described above, continuous treatment with careful irAE monitoring may provide a more significant clinical benefit. Importantly, a tendency of higher prevalence of severe irAEs was observed in patients who had undergone multiple rounds of molecular-targeted therapies than in those with single

therapy (Supplementary Table 1). Thus, patients receiving nivolumab therapy at a later phase of sequential therapy may be at a higher risk of developing severe irAEs and compromised treatment efficacy.

This study has several limitations. First, this was a retrospective study conducted in only 2 institutions with a fairly small sample size. Thus, unavoidable biases in patient selection or any other findings obtained from the analyses
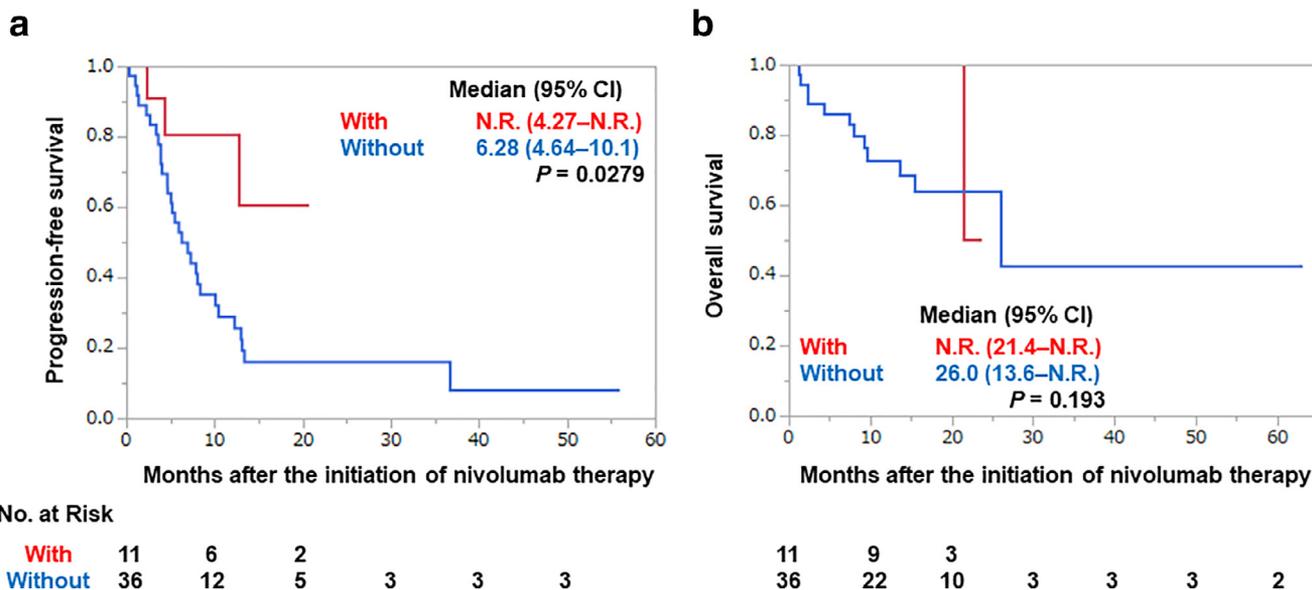

Fig. 5. Landmark analysis of progression-free and overall survival after the initiation of nivolumab therapy depending on the presence of immune-related adverse events that developed within the initial 2 cycles. (a) Progression-free survival and (b) overall survival after the initiation of nivolumab therapy in the presence or absence of immune-related adverse events shown by the 2-cycle landmark analysis. CI = confidence interval; NR = not reached.

Table 4
Individual profile in patients with irAEs requiring cessation of nivolumab therapy

Pt.	Age/sex	Histopathology	MSKCC risk	Number of previous molecular-targeted therapies	irAEs	Grade of irAEs	Steroid replacement therapy
1	71 y/female	Clear-cell carcinoma	Intermediate	1	Colitis/diarrhea	3	Presence
2	73 y/male	Clear-cell carcinoma	Intermediate	1	Elevated hepatic enzymes	4	Presence
3[a]	72 y/male	Clear-cell carcinoma	Intermediate	4	Diabetes mellitus type I	3	Absence
4	69 y/male	Clear-cell carcinoma	Intermediate	1	Thyroiditis/hypophysitis	3	Presence
5	53 y/male	Clear-cell carcinoma	Intermediate	2	Elevated pancreatic enzymes	3	Absence
6[a]	65 y/male	Clear-cell carcinoma	Intermediate	5	Interstitial pneumonia	3	Presence
7[a]	55 y/male	Papillary renal cell carcinoma type II	Favorable	2	Elevated hepatic enzymes	3	Absence
8	76 y/male	Clear-cell carcinoma	Intermediate	4	Polymyalgia rheumatica	3	Presence
9	51 y/male	Clear-cell carcinoma	Intermediate	1	Elevated hepatic enzymes	3	Absence

irAEs = immune-related adverse events; MSKCC = Memorial Sloan Kettering Cancer Center.
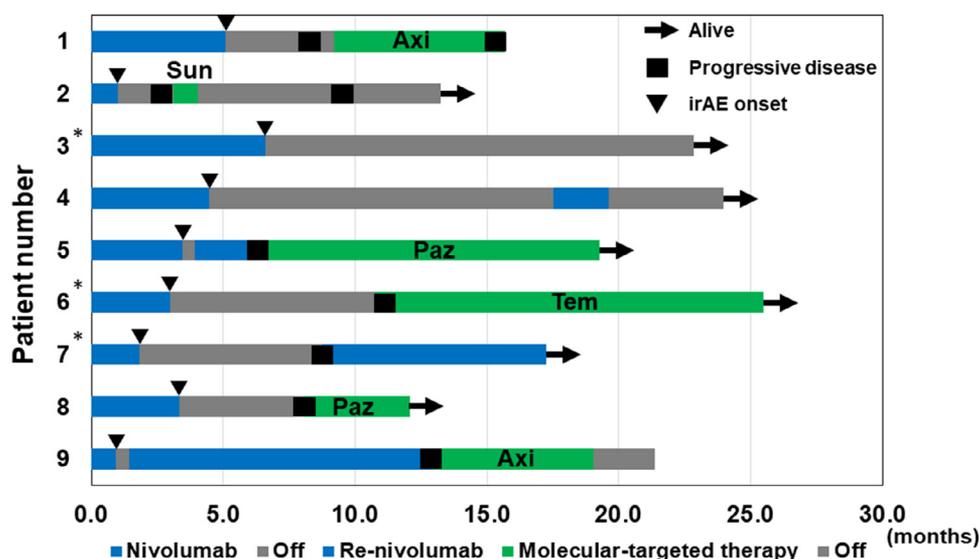[a] Previously reported in our study [26].

Fig. 6. Prognosis of patients with immune-related adverse events that required cessation of nivolumab therapy. The swimmer plot shows the prognosis of 9 patients who developed immune-related adverse events that required cessation of nivolumab therapy. *Reported in our previous study [26]. irAE = immune-related adverse event; Axi = axitinib; Sun = sunitinib; Paz = pazopanib; Tem = temsirolimus.

exist. In some analyses, especially for OS, results are hard to interpret statistically, and we could not conduct the multivariate analysis for identifying factors. Moreover, due to its retrospective nature and the system of irAE identification, not all irAEs might have been recognized (especially mild or transient irAEs), and any unrecorded irAEs could have affected our analyses. Third, an irregular interval of radiographic examination can induce a bias in the survival analysis. Finally, in this study, nivolumab was administered as the second- or later line therapy after the failure of prior molecular-targeted therapies in all patients, although this protocol is not recommended in the current guideline [4]. However, overall, many significant results were observed despite the small sample size. Furthermore, considering these limitations, we believe that the present results further the current understanding of this field and warrants further confirmation in future prospective studies with larger cohorts.

5. Conclusions

In this retrospective study, we showed that irAE development was positively and significantly associated with oncological outcomes, including survival and tumor response during nivolumab therapy for previously treated mRCC. Additionally, the landmark analysis showed a prognostic impact of irAEs developed within the early phase of therapy. We believe that presence of irAE has the potential to be an effective surrogate and predictive marker of survival in nivolumab therapy of mRCC; however, further prospective studies are necessary to confirm our findings.

Conflicts of interest

Acknowledgments

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.1016/j.urolonc.2019.03.003.

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