Original

Efficacy and safety of nivolumab for metastatic renal cell carcinoma: A Japanese single institutional retrospective study

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【Purpose】 The phase III CheckMate 025 trial showed that nivolumab improved clinical benefit in advanced renal cell carcinoma. Herein, we report the efficacy and safety of nivolumab for metastatic renal cell carcinoma (mRCC) patients in a Japanese single institution.

【Material and Methods】 Twenty-eight mRCC patients who had failed prior molecular targeted therapy (MTT) were treated with nivolumab between December 2016 and December 2017. Our cohort included heterogeneous cases with non-clear cell carcinoma, three or more prior lines of MTT, and a higher proportion in the poor risk group.

【Results】 Median overall survival and progression-free survival were 11.7 and 6.1 months, respectively. The objective response rate and clinical benefit rate were 8.3 and 75.0%, respectively; one case achieved complete response. Any-grade and severe nivolumab-related adverse events in our cohort accounted for 50.0 and 3.6%, respectively.

【Conclusion】 The current results showed the usefulness of nivolumab treatment for mRCC patients, regardless of the small cohort with heterogeneous characteristics studied.

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Key words: renal cell carcinoma, nivolumab, outcome

Introduction

Advanced or metastatic renal cell carcinoma (mRCC) is currently treated with molecular targeted therapy (MTT) agents as a first-line treatment[1)]. Nivolumab is a highly selective anti-programmed death 1 (PD-1) human monoclonal IgG4 antibody that potentiates T-cell responses by blocking the binding of PD-1 on activated T cells with its ligands, PD-L1 and PD-L2, expressed on antigen-presenting cells and on some tumor cells[2)]. Clinical trials (known as the CheckMate 025 trial[3)]) with nivolumab showed an overall survival (OS) benefit compared with everolimus in patients who had failed prior MTT for clear cell RCC.

Based on the subgroup analysis of Japanese patients treated with nivolumab or everolimus in the CheckMate 025 trial, Tomita et al.[4)] showed that the objective response rate (ORR) was higher for nivolumab in the Japanese cohort than for the Global cohort, and that a favorable safety profile in the Japanese cohort was generally consistent with the Global one. However, we infer that the above results were different from those in the real world because of the strict selection criteria of candidates in the phase III trial. We aimed to retrospectively investigate the efficacy and safety of nivolumab treatment for mRCC patients based on our primary clinical experience.

Materials and Methods

This retrospective study received approval from the Institutional Review Board of Saitama Medical University Interna-

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tional Medical Center (SIMC, approval #: 14-049). We reviewed the clinical and pathological data of 28 patients treated with nivolumab for mRCC who had failed prior MTT between December 2016 and December 2017. (Patients' characteristics are summarized in Table 1.)

Patients received nivolumab 3 mg/kg intravenously every two weeks. Radiographic evaluations using computed tomography (CT) and/or magnetic resonance imaging (MRI) were performed every two to three months. In order to predict the outcomes of mRCC patients after MTT treatment, we stratified them into three groups based on the Memorial Sloan-Kettering Cancer Center (MSKCC) model[5].

The purpose of the study was to evaluate overall survival (OS), progression-free survival (PFS), and response rates (objective response rate [ORR] and clinical benefit rate [CBR]) based on the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1[6]. ORR was defined as the proportion of patients achieving complete response (CR) and partial response (PR). CBR was defined as the proportion of patients with CR, PR, and stable disease (SD). In a fair and equitable manner, three urologists (HK, TH, and TM [see Acknowledgements]) blindly re-measured the lengths of metastatic lesions in each case. Survival curves were constructed using the Kaplan-Meier method. Based on the NCI Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.0, adverse events were comprehensively managed by physicians and pharmacists, e.g. patient education and pharmacist guidance.

Table 1. Patient characteristics and objective response

Patient characteristics		n	%
Age at initiation of nivolumab			
	median (range, years old)	70	(44 - 84)
Gender			
	male	23	82.1%
	female	5	17.9%
Pathology			
	clear cell component	26	92.9%
	papillary	1	3.6%
	unknown	1	3.6%
Prior nephrectomy			
	yes	26	92.9%
	no	2	7.1%
mRCC risk classification			
	favorable	6	21.4%
	intermediate	17	60.7%
	poor	4	14.3%
	unknown	1	3.6%
Number of prior MTTs lines			
	1	11	39.3%
	2	9	32.1%
	≥3	8	28.6%
Metastatic sites at initiation of nivolumab			
	≥2 sites of metastases	19	67.9%
	lung	21	75.0%
	bone	7	25.0%
	liver	4	14.3%
Objective response †			
	ORR	2	8.3%
	CBR	18	75.0%
	Complete response	1	4.2%
	Partial response	1	4.2%
	Stable disease	16	66.7%
	Progressive disease	6	25.0%

MTT: molecular targeted therapy, ORR: objective response rate, CBR: clinical benefit rate
†: 24 cases who could be evaluated for tumor response in the present study

Results

Patient characteristics (Table 1)

Twenty-eight cases (23 males, 5 females) were treated with nivolumab for mRCC in our institution. Twenty-seven cases were pathologically diagnosed with RCC (pure clear cell carcinoma; n = 25, clear cell carcinoma with a papillary carcinoma component; n = 1, and papillary carcinoma; n = 1). Regarding the MSKCC criteria, 6 (21.4%), 17 (60.7%), and 4 (14.3%) cases were stratified into the favorable-, intermediate-, and poor-risk groups, respectively, at the time of mRCC diagnosis. The candidates in the CheckMate 025 trial excluded patients treated with three or more prior systemic therapies; however, the number of MTT lines in our cohort were one for 11 (39.3%), two for 9 (32.1%), and three or more for 8 (28.6%) cases.

The reason for changing from MTT to nivolumab was disease progression in all cases. The median follow-up of the cohort was 7.1 months (interquartile range [IQR], 3.8–10.3) following nivolumab induction. The reasons for discontinuation of nivolumab in 15 cases were disease progression (n = 11, 73.3%), poor performance status (n = 3, 20.0%), and adverse events (AEs) related to nivolumab (n = 1, 6.7%; proteinuria and anemia).

Efficacy (Figure 1, Table 1)

Median OS was 11.7 months (95% CI: 10.0–13.4, Figure 1A). Four cases died during the short follow-up: 3 cases due to disease progression and one case due to another cause (chronic renal failure). Median PFS was 6.1 months (95% CI: 2.6–9.6, Figure 1B), and was similar to the results of the CheckMate 025 trial (Global: 4.6 months, Japanese: 5.6 months). Median PFS in groups in terms of the number of prior MTT lines was not significantly different; 4.2 for one line, 6.1 for two lines, and 6.7 months for three or more lines ($p = 0.530$, Figure 1C). According to the MSKCC risk classification, the median PFS times of the favorable, intermediate, and poor groups were 4.2, 6.7, and 1.5 months, respectively ($p = 0.120$, Figure 1D); however, that of the non-poor group was significantly longer than the poor group (6.7 and 1.5 months, $p = 0.046$, data not shown). The Karnofsky performance status (KPS, Figure 1E) and the number of metastatic sites (data not shown) at nivolumab initiation were not significantly associated with PFS. Interestingly, the median PFS of patients with lung metastasis was significantly longer than without lung metastasis (not reach vs 1.8 months, $p = 0.010$, Figure 1F); however, there was no significant difference in those with other metastatic sites including liver, bone, and lymph nodes (data not shown). Twenty-four cases were evaluable for change in tumor size based on RECIST criteria, and the change in the tumor response rate is shown in Figure 1G. The median response rate of tumor size was +6.7% (IQR: −5.7 to +23.4, range: −65.4 to +84.0). (Best overall responses (CR, PR, SD, and PD) are summarized in Table 1.)

Adverse events (Table 2)

All cases could be consistently evaluated for nivolumab-related AEs based on NCI-CTCAE criteria. The common AEs are shown in Table 2. Any-grade and severe (≥ grade 3) nivolumab-related AEs accounted for 50.0 and 3.6%, respectively. The major nivolumab-related AEs were pruritus (25.0%) and rash (21.4%), while a few patients in our cohort had malaise (7.1%) and diarrhea (3.6%), AEs that commonly occurred in the CheckMate 025 cohort. In one case in our cohort, the nivolumab-related AEs led to discontinuation of nivolumab administration. To date, most cases have been safely treated with nivolumab at our institution.

Discussion

In approximately one year since the approval of nivolumab for mRCC patients following failed MTT in Japan, we administered nivolumab treatment to 28 cases with mRCC. Our cohort included more cases with a non-clear cell component, those in the poor risk group, and with a higher number of lines of prior MTT compared to the CheckMate 025 cohort[3, 4]. The small sample size with heterogenous characteristics (e.g. histology and prior systemic therapies), and short duration of follow-up were major limitations in this small-scale retrospective study.

In the CheckMate 025 trial, the median OS was longer in the Japanese cohort than in the Global one treated with nivolumab (26.0 months vs not reached), and ORR with nivolumab was also higher for the Japanese cohort than the Global one (43% vs 26%). Tomita et al. considered the reasons for these differences to be as follows: The higher PS, differences in prior as well as subsequent systemic therapies, and smaller sample size in the Japanese cohort compared with the Global one[4]. In our cohort, some patients had a non-clear cell component, many prior systemic therapies, and poor risk factors including lower PS. Our results showed that the poor risk group had significantly shorter PFS than the non-poor risk group, which could help explain the difference in clinical benefit between the Global and Japanese cohorts (16% and 8% of patients with poor risk, respectively) in the CheckMate 025 trial. Another notable result was that the median PFS in groups with three or more prior MTT lines was similar to groups with two or fewer prior MTT lines. This may contribute to clinical benefit, including the anti-tumor response and the release from MTT-related AEs, for patients treated with several prior MTTs. In the CheckMate 214 trial, subgroup analysis of OS according to metastatic sites showed that the nivolumab plus ipilimumab group had a better OS than the sunitinib group for

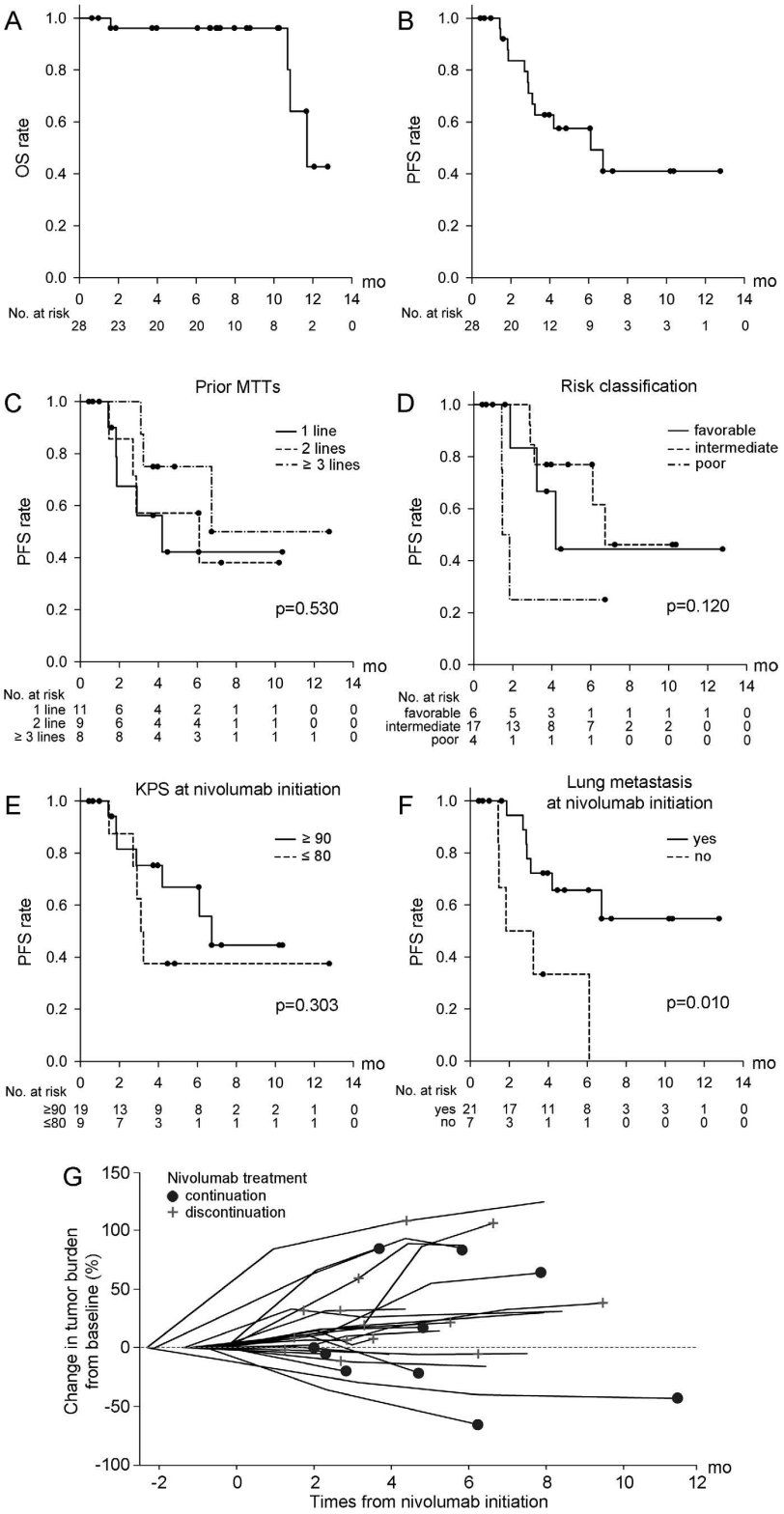

Fig. 1. Kaplan-Meier curves show overall survival (OS, A) and progression free survival (PFS, B) in all cases. In sub-group analysis, Kaplan-Meier curves show PFS according to the number of prior MTT lines (C), risk classification (D), KPS at nivolumab initiation (E), and lung metastasis at nivolumab initiation (F). Change in tumor burden from baseline in patients treated with nivolumab (n = 24, G).

patients with lung metastases, but not for those without lung metastases[7]. This may support our finding of a longer PFS in patients with lung metastases at nivolumab initiation than those without.

Some cases in this current study, as well as in the Check-Mate 025 trial[3], had durable responses with nivolumab irre-

Table 2. Nivolumab related adverse events (>5%)

	any grade		grade ≥3	
Total adverse events	14	50.0%	1	3.6%
pruritus	7	25.0%	0	0%
rash	6	21.4%	0	0%
arthritis	2	7.1%	1	3.6%
fever	2	7.1%	0	0%
malaise	2	7.1%	0	0%
anorexia	2	7.1%	0	0%
hypothyroidism	2	7.1%	0	0%

spective of the prognostic risk score or number of prior therapies. A relationship between PD-L1 expression and improved outcomes with nivolumab has been observed for melanoma and lung cancer[8, 9]; however, a clinical benefit was observed with nivolumab irrespective of PD-L1 expression in RCC[3]. Bilen et al. retrospectively reported an association between the neutrophil-to-lymphocyte ratio (NLR) at baseline and clinical outcome of mRCC patients receiving nivolumab[10]. Serum inflammatory biomarkers including NLR and CRP may contribute to predicting the clinical outcomes for mRCC patients treated with nivolumab. Therefore, further large-scale clinical or molecular biological studies are required.

At our institution, comprehensive management in collaboration with physicians and pharmacists who are oncology specialists is performed for most patients with malignancies, including mRCC, in the outpatient department. During nivolumab treatment, any cause-related AEs were detected in all cases; e.g. hyperglycemia (78.6%), malaise (64.3%), proteinuria (57.1%), and hypothyroidism (53.6%). Most cases had prior MTT-related AEs, and there were few cases with nivolumab-related AEs. Malaise related to nivolumab commonly occurred in the CheckMate 025 cohort (Global: 33.0%, Japanese: 16.2%), but not in our cohort (7.1%) because the malaise in our cases was caused by prior MTT or disease progression. Arakawa et al. reported that treatment adherence improved due to patients' increased knowledge and awareness as a result of pharmacist guidance regarding the management of AEs[11]. As previously reported regarding mRCC patients treated with MTT[12], we also believe that a better relationship between the attending physician, the pharmacist and the patient makes it possible to maintain nivolumab treatment, and this in turn may greatly contribute to clinical benefit.

In conclusion, despites a small cohort with heterogeneous characteristics, our results showed the usefulness of nivolumab treatment for mRCC patients. Further studies are necessary to identify potential predictive factors for selection of eligible patients in the real world.

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Conflict of Interest Disclosure

We have read and understood the *Saitama Medical University*'s policy on disclosing conflicts of interest and declare that we have none.

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当院における転移性腎細胞癌に対するニボルマブの初期使用経験

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【緒言】CheckMate025 第 III 相試験において，転移性腎細胞癌（metastatic renal cell carcinoma: mRCC）に対する二次治療としてのニボルマブの臨床効果の改善が示された．今回我々は，当院における mRCC に対するニボルマブの短期的な効果と安全性について後方視的検討を行った．
【対象と方法】2016 年 12 月から 2017 年 12 月の間，28 例の mRCC に対してニボルマブを投与した．CheckMate025 試験と異なり，非淡明細胞成分を有する症例や 3 種類以上の分子標的薬が投与された症例が含まれていた．RECIST version1.1 に基づき，3 名の測定者によって腫瘍縮小効果を検討した．
【結果】経過観察期間の中央値は 7.1 カ月（四分位範囲：3.8 – 10.3）であった．全生存期間および無増悪生存期間の中央値は 11.7 カ月と 6.1 カ月であった．客観的奏効率（ORR: 完全完解率 + 部分寛解率）は 8.3% であり，臨床的有用率（ORR+ 安定率）は 75.0%であった．ニボルマブ関連有害事象は 50.0%，とくに Grade3 以上は 3.6%の症例に認められた．
【結論】本検討は，少数のコホートであるが，mRCC に対するニボルマブ療法の有用性と安全性が示された．

