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ORIGINAL ARTICLE

Comparable efficacy and safety between second-line and later-line nivolumab therapy for metastatic renal cell carcinoma

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Abstract

Background The aim of this study was to compare the efficacy and safety of nivolumab as second-line and later-line (third-line or thereafter) therapy in metastatic renal cell carcinoma (mRCC).

Methods Sixty-seven patients who received nivolumab after the failure of at least one molecular-targeted therapy were evaluated. The patients were divided into two groups based on the line of nivolumab: second-line and later-line groups. Efficacy was assessed using progression-free survival and overall survival (OS) after nivolumab initiation, and objective response rate. Safety was assessed using the incidence of immune-related adverse events. These outcomes were compared between the second-line and later-line groups.

Results Forty-two patients (62.7%) received nivolumab as second-line therapy. There was no significant difference in the progression-free survival (median: 5.06 vs. 6.28 months, $p=0.691$) or objective response rate (35.7% vs. 32.0%, $p=0.757$) between the second-line and later-line groups. The OS tended to be longer in the second-line group (not reached vs. 26.0 months, $p=0.118$), and the rate of patients who received subsequent therapy after nivolumab failure was significantly higher in the second-line group (90.9% vs. 55.0%, $p=0.0025$). There was no difference in the incidences of immune-related adverse events between the second-line and later-line groups (any grade: 54.8% vs. 48.0%, $p=0.592$; grade ≥ 3: 19.1% vs. 20.0%, $p=0.924$).

Conclusions The efficacy of nivolumab did not deteriorate and the tolerability was also maintained even in later-line therapy. However, a tendency of longer OS and a higher chance of subsequent therapy after nivolumab failure were observed with nivolumab as second-line therapy.

Keywords RCC · Immune checkpoint inhibitor · irAE · PD-1 · Sequential therapy · ORR · Systemic therapy

Introduction

Nivolumab, a fully human IgG4 PD-1 immune checkpoint inhibitor (ICI) antibody that selectively blocks the PD-1/PD-L1 interaction, plays a central role in the systemic therapy for metastatic renal cell carcinoma (mRCC) [1]. Following the introduction of nivolumab, other novel ICIs targeting other molecules, such as PD-L1 or CTLA4, have been intensively developed and tested in clinical trials as monotherapy or combinative therapy [2–5]. The strategy of systemic therapy for mRCC is dramatically changing and this paradigm shift is ongoing.

The European Association of Urology guideline indicates that nivolumab monotherapy is now recommended as second-line or later-line therapy in patients who fail first-line molecular-targeted therapy [1]. This is based on

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evidence from a previous pivotal trial, CheckMate 025, that demonstrated the effectiveness and safety of nivolumab over everolimus in second-line and third-line settings [6]. Since then, several real-world outcome data on nivolumab therapy have been reported [7–9]; however, there is limited information on the direct comparison of the efficacy and safety of nivolumab between second-line and later-line therapy. In clinical practice, we encounter patients who are not treated with first-line ICI combination therapy recommended by the guideline (i.e., pembrolizumab/axitinib or ipilimumab/nivolumab) for some reason. Thus, it is necessary to understand the possible differences in outcome between second-line and later-line nivolumab therapy to provide effective treatment for mRCC.

In this context, we compared the oncological outcomes, including efficacy and safety of nivolumab between second-line and later-line (third-line or thereafter) therapy among mRCC patients who received prior targeted therapy.

Materials and methods

Study design

At our department and its affiliated institution, a total of 78 patients received nivolumab therapy after the failure of at least one targeted therapy for mRCC between June 2013 and July 2019. We excluded patients with missing clinical data before and after nivolumab therapy ($n=7$) or missing data regarding imaging examinations ($n=4$). Finally, the remaining 67 patients were evaluated in this retrospective study. We further divided the patients into two groups based on the line of nivolumab: second-line and later-line (third-line or thereafter) groups. The presence of prior cytokine therapy was not counted as a line of therapy in this study.

All clinical and laboratory data were obtained from the electronic database and patient medical records. The study protocol was approved by the Institutional Ethics Review Board of the Tokyo Women's Medical University. The present study was performed in accordance with the principles outlined in the Declaration of Helsinki of 1964 and its later amendments. Due to the retrospective observational nature of this study, the need for informed consent was waived.

Protocol of nivolumab therapy

Nivolumab (3 mg/kg) was administered intravenously every 2 weeks based on a protocol used in the CheckMate 025 study [6]. Dose modifications were not allowed in any cases. Otherwise, the interval between administrations could be modified according to the patient's condition or in cases of immune-related adverse events (irAEs). In this study, all patients received nivolumab after the failure of prior targeted therapy and did not receive any other ICI therapies during sequential therapy. The regimen of sequential targeted therapy adopted at our departments was described in our previous studies [10, 11]. Post-treatment follow-up computed tomography or magnetic resonance imaging scans of the chest, abdomen, and pelvis were obtained at regular 4–12-week intervals depending on the condition of the patient. Nivolumab was administered until radiographic or clinical disease progression or intolerable irAE was observed.

Outcomes and assessment in nivolumab therapy

The efficacy was assessed using the progression-free survival (PFS) and overall survival (OS) after nivolumab initiation, and objective response rate (ORR) during nivolumab therapy. Furthermore, we evaluated the OS after nivolumab failure among patients who were diagnosed with disease progression. Safety was assessed using the incidence of irAEs. These outcomes were compared between the second-line and later-line groups. The tumor response and ORR were determined according to the Response Evaluation Criteria in Solid Tumors version 1.1 [12]. The irAEs were graded according to the Common Terminology Criteria for Adverse Events version 4.0.

Statistical analysis

Continuous variables were analyzed using the Mann–Whitney U test, and categorical variables were analyzed using the χ^2 test or Fisher's exact test, as appropriate. The PFS was calculated from nivolumab initiation until disease progression or death, whichever occurred first. Living patients without disease progression were censored at the time of last follow-up. The OS was mainly determined at two timepoints: (1) from nivolumab initiation and (2) from nivolumab failure (i.e., disease progression) until death from any cause. In addition, OS was calculated from initial nephrectomy, from the diagnosis of metastases, and from the initiation of first-line targeted therapy. Patients lost to follow-up were censored at the time of last contact. Survival was assessed using the Kaplan–Meier method and compared using the log-rank test. Univariate and multivariate analyses were used to identify risk factors for survival. Risks were expressed as hazard ratios (HRs) and their 95% confidence intervals (CIs). All statistical analyses were performed using JMP version 14 (SAS Institute Inc., Cary, NC, USA), and $p<0.05$ indicated statistical significance.

Results

Patient characteristics

In this study, 42 patients (62.7%) received nivolumab as second-line therapy. The comparison of patient characteristics

between the second-line and later-line groups is shown in Table 1. Although there was no significant difference in patient characteristics, the rate of clear-cell carcinoma histotype tended to be lower in the second-line group [$n=31$ (73.8%) vs. $n=23$ (92.0%), $p=0.0686$]. In the later-line group, nivolumab was administered as third-, fourth-, fifth-, and sixth-line therapy in 17 (68.0%), 3 (12.0%), 4 (16.0%), and 1 (4.00%) patients, respectively.

Survival after nivolumab initiation according to the line of nivolumab

During the follow-up period, 53 (79.1%) and 21 (31.3%) patients had disease progression and died of any cause, respectively. There was no significant difference in PFS between the second-line and later-line groups [median: 5.06 (95% CI 2.93–8.05) vs. 6.28 (95% CI 3.39–8.38) months, $p=0.691$] (Fig. 1a). The OS after nivolumab initiation tended to be longer in the second-line group, although the difference was not statistically significant [not reached (N.R.) (21.4–N.R.) vs. 26.0 (7.36–N.R.) months, $p=0.118$] (Fig. 1b).

Factors associated with survival after nivolumab initiation

Table 2 shows the results of the univariate and multivariate analyses of PFS. Univariate analysis showed that the line of nivolumab was not significantly associated with survival (HR: 0.89, 95% CI 0.51–1.59, $p=0.693$). In the multivariate analysis, the line of nivolumab was not an independent factor for the PFS (HR: 0.79, 95% CI 0.43–1.48; $p=0.461$) after adjusting other factors including histopathological diagnosis and the International Metastatic RCC Database Consortium (IMDC) risk score [13]. Similarly, Table 3 shows the results of the univariate and multivariate analyses for OS after nivolumab initiation. Both the univariate and multivariate analyses showed that the line of nivolumab was not an independent factor for the OS (HR 0.69, 95% CI 0.27–1.73;

Table 1 Patient characteristics according to the line of nivolumab

Variable	Second-line ($n=42$)	Later-line ($n=25$)	p
Age, years			0.726
≥65 (ref. <65)	27 (64.3%)	15 (60.0%)	
Sex			0.842
Male (ref. female)	31 (73.8%)	19 (76.0%)	
Histopathology			0.0686
Clear-cell carcinoma (ref. non-clear-cell carcinoma)	31 (73.8%)	23 (92.0%)	
IMDC risk at nivolumab initiation[a]			0.252
Favorable	4 (9.52%)	0	
Intermediate	25 (59.5%)	14 (56.0%)	
Poor	13 (31.0%)	11 (44.0%)	
Number of metastatic organ sites			0.615
Multiple (ref. single)	26 (61.9%)	17 (68.0%)	
Liver metastasis			0170
Presence (ref. absence)	6 (14.3%)	7 (28.0%)	
First-line molecular-targeted therapy			0.544
Sunitinib (ref. other than sunitinib)	20 (47.6%)	10 (40.0%)	
Line of nivolumab			<0.0001
Second-line	42 (100%)	0	
Third-line	0	17 (68.0%)	
Fourth-line	0	3 (12.0%)	
Fifth-line	0	4 (16.0%)	
Sixth-line	0	1 (4.00%)	
Follow-up period, months[b]	13.3 (7.13–21.4)	13.6 (5.28–25.8)	0.645

IMDC International Metastatic Renal Cell Carcinoma Database Consortium

[a]The IMDC prognostic risk groups are based on the presence of 0 (favorable), 1–2 (intermediate), or ≥3 (poor) of the following prognostic factors: anemia, thrombocytosis, neutrophilia, Karnofsky performance status <80, <1 year from diagnosis to first-line targeted therapy, and hypercalcemia

[b]Shown as median (range)

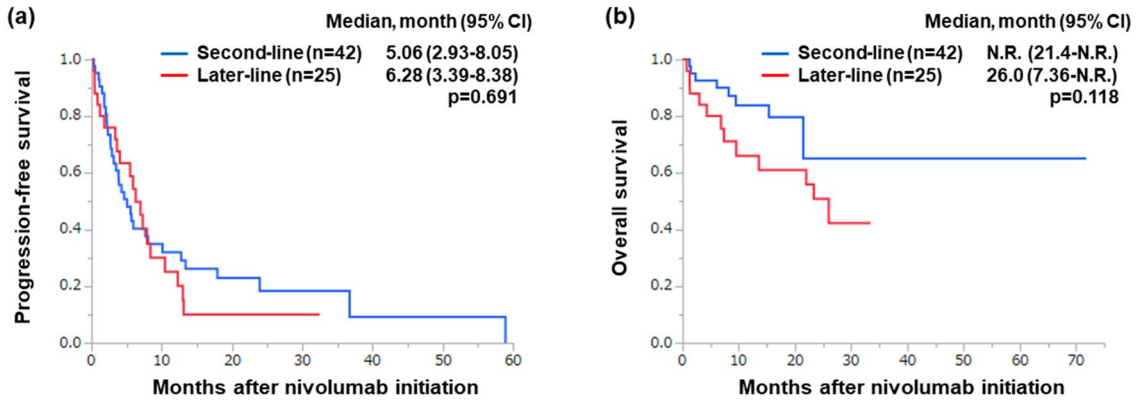

Fig. 1 Progression-free survival and overall survival after nivolumab initiation according to the line of nivolumab. **a** Progression-free survival and **b** overall survival after nivolumab initiation. CI, confidence interval; *N.R.* not reached

Table 2 Univariate and multivariate analyses of progression-free survival after nivolumab initiation

Variable	Univariate HR (95% CI)	*p*	Multivariate HR (95% CI)	*p*
Age, years		0.183		
≥65 (ref. <65)	0.68 (0.40–1.20)			
Sex		0.0750		
Male (ref. female)	0.53 (0.28–1.07)			
Histopathology		0.0182		0.0897
Clear-cell carcinoma (ref. non-clear-cell carcinoma)	0.42 (0.22–0.85)		0.50 (0.24–1.12)	
IMDC risk at initiation of nivolumab		0.0033		0.0236
Poor (ref. favorable and intermediate)	2.54 (1.38–4.63)		2.11 (1.11–3.98)	
Number of metastatic organ sites		0.543		
Multiple (ref. single)	1.20 (0.68–2.19)			
Liver metastasis		0.232		
Presence (ref. absence)	1.53 (0.75–2.89)			
First-line molecular-targeted therapy		0.952		
Sunitinib (ref. other than sunitinib)	1.02 (0.58–1.76)			
Line of nivolumab		0.693		0.461
Second-line (ref. later-line)	0.89 (0.51–1.59)		0.79 (0.43–1.48)	

HR hazard ratio, *CI* confidence interval, *IMDC* International Metastatic Renal Cell Carcinoma Database Consortium

$p = 0.430$) after adjusting other factors including the IMDC risk score and status of liver metastasis.

Objective response rate in nivolumab therapy according to the line of nivolumab

As the best overall response, complete response, partial response, stable disease, and progressive disease were observed in 2 (4.76%), 13 (31.0%), 13 (31.0%), and 14 (33.3%) patients in the second-line group and in 2 (8.00%), 6 (24.0%), 9 (36.0%), and 8 (32.0%) patients in the later-line group, respectively (Fig. 2). There was no significant difference in the ORR between the two groups (35.7% vs. 32.0%, $p = 0.757$).

Subsequent therapy and prognosis after nivolumab failure according to the line of nivolumab

We further evaluated the prognosis after nivolumab failure according to the line of nivolumab (Fig. 3). Of 33 patients who had disease progression in the second-line group, 30 patients (90.9%) received subsequent therapy [$n = 17$ (51.5%), subsequent targeted therapy; $n = 8$ (24.2%), nivolumab treatment beyond progression; and $n = 5$ (15.2%), nivolumab treatment beyond progression and subsequent

Table 3 Univariate and multivariate analyses of overall survival after nivolumab initiation

Variable	Univariate HR (95% CI)	*p*	Multivariate HR (95% CI)	*p*
Age, years		0.724		
≥65 (ref. <65)	0.85 (0.36–2.10)			
Sex		0.570		
Male (ref. female)	0.74 (0.29–2.28)			
Histopathology		0.163		
Clear-cell carcinoma (ref. non-clear-cell carcinoma)	0.49 (0.19–1.38)			
IMDC risk at initiation of nivolumab		0.0058		0.0055
Poor (ref. favorable and intermediate)	3.50 (1.45–8.54)		3.69 (1.48–9.39)	
Number of metastatic organ sites		0.359		
Multiple (ref. single)	1.54 (0.62–4.32)			
Liver metastasis		0.0018		0.0027
Presence (ref. absence)	4.89 (1.87–12.1)		4.90 (1.78–13.1)	
First-line molecular-targeted therapy		0.927		
Sunitinib (ref. other than sunitinib)	1.04 (0.43–2.48)			
Line of nivolumab		0.123		0.430
Second-line (ref. later-line)	0.50 (0.20–1.21)		0.69 (0.27–1.73)	

HR, hazard ratio; CI, confidence interval; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium

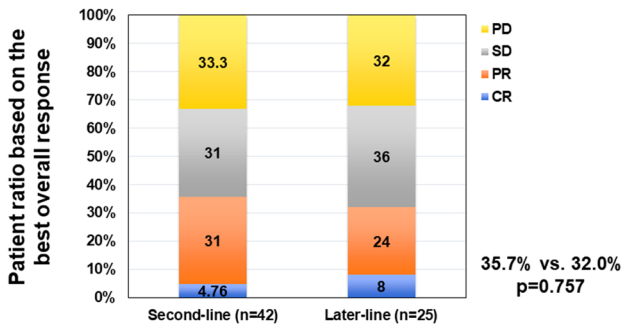

Fig. 2 Objective response rate in nivolumab therapy according to the line of nivolumab. *PD* progressive disease; *SD* stable disease; *PR* partial response; *CR* complete response

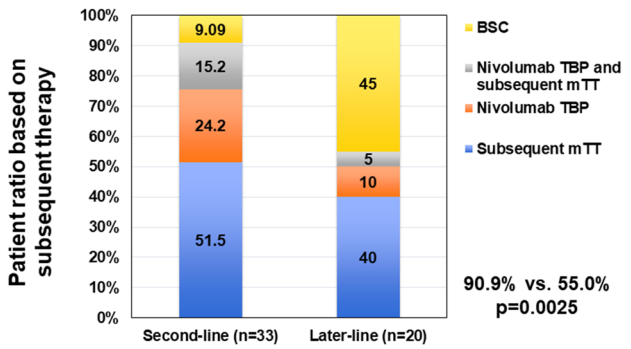

Fig. 3 Subsequent therapy after nivolumab failure according to the line of nivolumab. BSC, best supportive care; TBP, treatment beyond progression; mTT, molecular-targeted therapy

targeted therapy]. Of 20 patients who had disease progression in the later-line group, 11 patients (55.0%) received subsequent therapy [$n=8$ (40.0%), $n=2$ (10.0%), and $n=1$ (5.00%) in each of the aforementioned categories]. The rate of subsequent therapy was significantly higher in the second-line group than in the later-line group (90.9% vs. 55.0%, $p=0.0025$).

Furthermore, the OS duration after nivolumab failure tended to be longer in the second-line group than in the later-line group [median: N.R. (8.68–N.R.) vs. 9.18 (1.25–N.R.) months, p = 0.0827) (Fig. 4a). In both the second-line and later-line groups, the OS after nivolumab failure was significantly longer among patients who received subsequent therapy [second-line group: N.R.[8.68–N.R.] vs. 0.39 (0–0.95) months, $p<0.0001$; later-line group: N.R. (9.18–N.R.) vs. 1.09 (0.26–3.16) months, $p<0.0001$] (Fig. 4b, c).

Survival after initial nephrectomy, the diagnosis of metastases, and the initiation of first-line targeted therapy according to the line of nivolumab

We further performed OS analyses with respect to several timepoints prior to nivolumab initiation: after initial nephrectomy, diagnosis of metastases, and initiation of first-line targeted therapy in patients with eligible data ($n=62$, 65, and 65, respectively). Between the second-line and later-line groups, there were no significant differences in OS after initial surgery [median: 237.6 (237.6–N.R.) vs. 145.7 (62.8–254.1) months, $p=0.227$], after the diagnosis

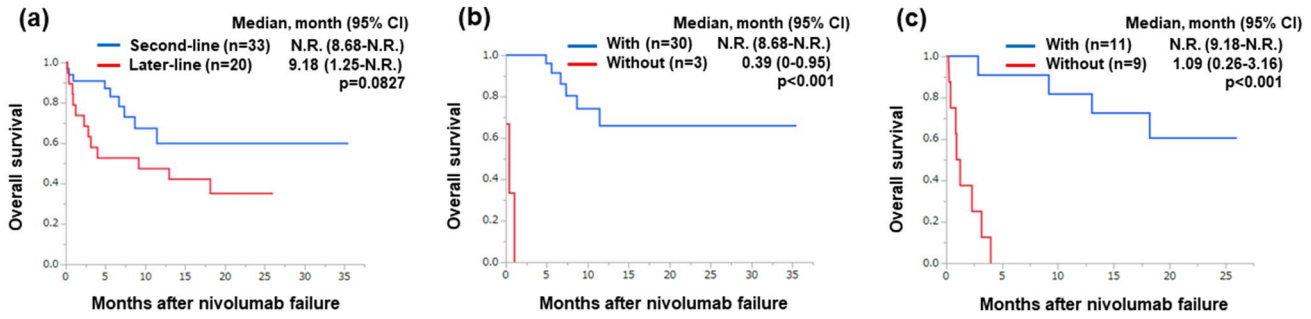

Fig. 4 Overall survival after nivolumab failure according to the line of nivolumab and presence of subsequent therapy. **a** Overall survival after nivolumab failure according to the line of nivolumab. **b** Overall survival after nivolumab failure according to the presence of subsequent therapy in the second-line group and **c** later-line group. *CI* confidence interval; *N.R.* not reached

of metastases [106.1 (106.1–N.R.) vs. 74.4 (41.9–N.R.) months, $p=0.551$], and after the initiation of first-line therapy [N.R. (39.6–N.R.) vs. 77.0 (40.7–N.R.) months, $p=0.796$] (Supplementary Fig. 1).

Immune-related adverse events according to the line of nivolumab

Table 4 shows a comparative profile of irAEs in the second-line and later-line groups. irAEs of any grade were observed in 23 (54.8%) and 12 (48.0%) patients in the second-line and later-line groups, respectively. Also, grade ≥ 3 irAEs were observed in 8 (19.1%) and 5 (20.0%) patients in the second-line and later-line groups, respectively. There was no significant difference in the irAE incidences between the two groups (any grade: $p=0.592$; grade ≥ 3: $p=0.924$).

Discussion

This retrospective study showed that there was no difference in PFS or ORR between second-line and later-line nivolumab therapy for previously-treated mRCC. Meanwhile, the OS after nivolumab initiation tended to be longer and the rate of subsequent therapy after nivolumab failure was significantly higher in second-line therapy. In addition, the OS after nivolumab failure tended to be longer with second-line therapy. Regarding safety, there was no difference in the incidences of irAEs between the second-line and later-line therapy.

Recent data from the IMDC showed the equivalent duration of treatment and ORR among second-, third-, and fourth-line nivolumab therapy in mRCC [14].

Table 4 Profile of immune-related adverse events according to the line of nivolumab

Event	Any grade		*p*	Grade ≥ 3		*p*
	Second-line (*n* = 42)	Later-line (*n* = 25)		Second-line (*n* = 42)	Later-line (*n* = 25)	
All events	23 (54.8%)	12 (48.0%)	0.592	8 (19.1%)	5 (20.0%)	0.924
Rash/ pruritus	11 (26.2%)	7 (28.0%)		0	0	
Alanine/aspartate aminotransferase increased	5 (11.9%)	1 (4.00%)		3 (7.14%)	1 (4.00%)	
Creatinine increased	3 (7.14%)	0		0	0	
Fever	3 (7.14%)	0		0	0	
Colitis/ diarrhea	2 (4.76%)	1 (4.00%)		1 (2.38%)	0	
Hypothyroidism	1 (2.38%)	1 (4.00%)		0	1 (4.00%)	
Thyroiditis/ hypophysitis	1 (2.38%)	0		1 (2.38%)	0	
Fatigue	1 (2.38%)	0		1 (2.38%)	0	
Uveitis	1 (2.38%)	0		1 (2.38%)	0	
Polymyalgia rheumatica	1 (2.38%)	0		1 (2.38%)	0	
Diabetes mellitus type 1	0	1 (4.00%)		0	1 (4.00%)	
Pancreatitis	0	1 (4.00%)		0	1 (4.00%)	
Nausea/ vomiting	0	1 (4.00%)		0	0	
Interstitial pneumonia	0	1 (4.00%)		0	1 (4.00%)	

Furthermore, an Italian group reported that there was no significant difference in the ORR between second-line and later-line nivolumab [8]. Thus, our findings are consistent with these previous reports in terms of the PFS and ORR. This non-deterioration of PFS and ORR of nivolumab even in the later-line setting is interesting because, in targeted therapy, several studies indicated that the PFS and ORR tended to decline according to the line of therapy [11, 15–17]. This difference between nivolumab and targeted therapy may be due to the differences in mode of action [18]. Importantly, we also found that second-line and later-line therapy had similar safety profiles. Collectively, these data suggested that nivolumab would be beneficial and safe even in patients who undergo prior multiple targeted therapy.

The Italian group also showed that second-line nivolumab was associated with a longer OS by multivariate analysis [8]. In our analysis, a tendency for longer OS and significantly higher chance of subsequent therapy after nivolumab failure were observed with second-line therapy. Indeed, the efficacy of subsequent targeted therapy after ICI failure was reported in several studies [19–21]. Also, nivolumab can be effective in the treatment of beyond disease progression [22]. In addition to these reports, we identified the therapeutic effect of subsequent therapy regardless of the line of nivolumab therapy. These data suggest that nivolumab would be recommended as second-line rather than later-line therapy because a longer OS may be expected with a higher chance of subsequent therapy after nivolumab failure.

We found no significant differences in OS between the second-line and later-line nivolumab therapy groups according to timepoints prior to nivolumab initiation. However, this finding may have been observed because the later-line group might have an inherent prognosis (e.g., slow growth of tumor). In other words, these patients could have received multiple therapies prior to nivolumab. Thus, it may be difficult to directly compare the OS according to timepoints prior to nivolumab initiation owing to strong biases in the patient background.

This study has several limitations. First, this study was retrospectively conducted using a small sample size. Thus, any findings could be affected by the unavoidable selection biases. Second, the relatively short duration of follow-up and the small number of patients who died could statistically affect the analyses, particularly the OS. Third, the patients in the later-line group might inherently have less aggressive disease because they could receive multiple lines of therapy. Thus, this possible bias might mask the difference of OS between the second-line and later-line therapy, resulting in a non-significant difference statistically. Nevertheless, our analysis showed the possibility of superior efficacy of second-line nivolumab therapy, consolidating our conclusions.

In conclusion, this retrospective study showed equivalent efficacy and safety profiles between second-line and later-line therapies with nivolumab. The anti-tumor effect of nivolumab did not deteriorate, and the tolerability was maintained even in later-line therapy. Meanwhile, a tendency of longer OS and a higher chance of subsequent therapy after nivolumab failure were observed with nivolumab as second-line therapy. Further studies are warranted to validate our findings.

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Compliance with ethical standards

Conflict of interest Tsunenori Kondo received honoraria from Ono Pharmaceutical. All other authors have no conflicts of interest to declare.

Ethical approval The study protocol was approved by the Institutional Ethics Review Board of the Tokyo Women's Medical University. The present study was performed in accordance with the principles outlined in the Declaration of Helsinki of 1964 and its later amendments.

Informed consent Due to the retrospective observational nature of this study, the need for informed consent was waived.

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