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ORIGINAL PAPER

Correlation between the magnitude of best tumor response and patient survival in nivolumab therapy for metastatic renal cell carcinoma

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Abstract

The correlation between the magnitudes of best tumor response (bTR) and patient survival in immune checkpoint inhibitor therapy for metastatic renal cell carcinoma (mRCC) remains unclear. In this article, we retrospectively investigated the prognostic association of the magnitude of bTR in nivolumab therapy for mRCC. Fifty-five patients treated with nivolumab after failure of at least one molecular-targeted therapy were evaluated. Assessment of the magnitude of bTR was based on the Response Evaluation Criteria in Solid Tumors (RECIST) v.1.1. Endpoints were progression-free survival (PFS) and overall survival (OS) after the initiation of nivolumab therapy. In regard to the magnitude of bTR, complete response, partial response, stable disease, and progressive disease were observed in three (5.46%), 15 (27.3%), 19 (34.5%), and 18 (32.7%) patients, respectively. PFS and OS were significantly correlated with the magnitude of bTR (median PFS: not reached (N.R.) [95% confidence interval (CI) 16.8–N.R.] vs. 13.0 [8.38–56.0] vs. 5.95 [4.27–7.30] vs. 1.92 [0.53–3.91] months, $p < 0.0001$; OS: N.R. [N.R.–N.R.] vs. N.R. [21.4–N.R.] vs. 23.3 [23.3–N.R.] vs. 7.36 [1.41–N.R.] months, $p < 0.0001$). In addition, multivariate analyses show that the magnitude of bTR was an independent factor for PFS ($p < 0.0001$) and OS ($p = 0.0010$). In conclusion, this retrospective study shows the significant correlation between the magnitude of bTR and patient survival in nivolumab therapy for mRCC. The magnitude of bTR can be an effective surrogate marker for survival.

Keywords RCC · Tumor shrinkage · PD-1 · RECIST · Objective response rate · Best overall response

Introduction

The appearance of immune checkpoint inhibitors (ICIs) has dramatically changed the treatment strategy for metastatic renal cell carcinoma (mRCC). A pivotal phase III trial, "CheckMate 025," demonstrated that nivolumab, an anti-PD-1 monoclonal antibody, conferred a prolonged overall survival (OS) and a more favorable safety profile than everolimus in previously treated advanced clear-cell RCC [1]. In an additional pivotal trial, "CheckMate 214," combination therapy with nivolumab and ipilimumab—an anti-CTLA4 monoclonal antibody with a different mode of action from nivolumab—was shown to have a superior therapeutic efficacy over sunitinib in nontreated advanced clear-cell RCC [2]. Several additional combination regimens with dual ICIs or ICIs and molecular-targeted agents are currently being tested in clinical trials [3].

Although ICIs including nivolumab have provided a paradigm shift in the treatment of mRCC, only a subset of patients benefit from the therapy [1]. In the CheckMate 025 trial, objective response rates (ORRs) were 25% in the nivolumab arm, and more importantly, the rate of patients with progressive disease (PD) as the best tumor response (bTR) was 35% [1]. Also, in real-world data, similar or worse ORRs and rates of patients with PD as bTR were

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recently reported [4, 5]. Thus, effective predictive or prognostic factors are emergently needed to provide appropriate selection of patients and treatment options.

In targeted therapy, several studies indicated that the magnitude of bTR was significantly associated with patient survival [6–8]; the high magnitude of bTR reflected the prolonged progression-free survival (PFS) and OS both in first- and second-line therapy. The findings indicated that this factor could be an effective surrogate marker for prognosis in mRCC patients. However, the prognostic impact of the magnitude of bTR in ICI therapy remains unclear.

In this context, we evaluated the prognostic impact of the magnitude of bTR in nivolumab therapy for mRCC in this retrospective study.

Patients and methods

Study design

The Internal Ethics Review Board of the Tokyo Women's Medical University approved this retrospective study (ID: 4998), which was performed in accordance with the principals outlined in the Declaration of Helsinki. Because this was a retrospective study, no formal consent was required.

In our department and its affiliated institution, 68 patients received nivolumab therapy after at least one targeted therapy for mRCC between June 2013 and February 2019. Patients who did not receive any imaging evaluation for therapeutic effect ($n=6$) and whose follow-up duration was less than two months ($n=7$) were excluded. Finally, the remaining 55 patients were evaluated. All clinical and laboratory data were obtained from the electronic database and patient medical records.

Protocol of nivolumab therapy

Nivolumab 3 mg/kg was intravenously administered every 2 weeks based on a protocol used in the CheckMate 025 study [1]. 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 nivolumab-induced adverse events. In this study, all patients received nivolumab after failure of prior targeted therapy. The regimen of sequential targeted therapy adopted in our departments was previously described [9, 10]. Posttreatment follow-up scans obtained using computed tomography or magnetic resonance imaging of the chest, abdomen, and pelvis were taken at regular 4- to 12-week intervals, depending on the condition of the patient. Nivolumab was administered until radiographic or clinical disease progression or intolerable adverse events were observed. Radiographic evaluation of treatment efficacy was defined based on the Response Evaluation Criteria in Solid Tumors (RECIST) v. 1.1 [11].

Statistical analysis

The PFS was calculated from the initiation of nivolumab therapy until disease progression or death, whichever came first. Alive patients without disease progression were censored at the time of last follow-up. In this study, we determined two time points of OS; OS was calculated (i) from the initiation of nivolumab therapy and (ii) from a diagnosis of PD until death for any cause. Patients lost to follow-up were censored at the time of 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 PFS and OS. 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, USA), and $p<0.05$ indicated statistical significance.

Results

Patient characteristics

Patient characteristics are shown in Table 1. Thirty-four (61.8%) patients were more than 65 years old, and 12 (21.8%) patients were female. Forty-five (81.8%) patients had clear-cell RCC. Based on the Memorial Sloan Kettering Cancer Center (MSKCC) risk [12], two (3.64%), 40 (72.7%), and 13 (23.6%) patients were categorized into favorable, intermediate, and poor risk, respectively. Six (10.9%) patients had received prior cytokine therapy. Twenty-five (45.5%) patients had more than two prior targeted agents, and sunitinib was most commonly administered as first-line therapy ($n=25$, 45.5%). Thirty-seven (67.3%) patients had multiple metastatic organ sites, and liver metastasis was observed in 13 (23.6%) patients. In regard to the magnitude of bTR, complete response (CR), partial response (PR), stable disease (SD), and PD was observed in three (5.46%), 15 (27.3%), 19 (34.5%), and 18 (32.7%) patients, respectively. Thus, ORRs in this study were 32.7%. A waterfall plot shows the magnitude of bTR in individual patients (Fig. 1). The median change from baseline was − 6.45% (interquartile range: − 44.9% to 17.4%). In six (10.9%) patients, nontarget lesion growth or new lesion appearance developed in spite of nonprogression of target lesion, resulting in a PD diagnosis as the bTR (Tables 2, 3).

Table 1 Patient characteristics

	n (%)
Age	
More than 65 years-old	34 (61.8%)
Sex	
Female	12 (21.8%)
Histopathology	
Clear-cell carcinoma	45 (81.8%)
MSKCC risk at initiation of nivolumab	
Favorable	2 (3.64%)
Intermediate	40 (72.7%)
Poor	13 (23.6%)
Prior cytokine therapy	
Presence	6 (10.9%)
Number of prior molecular-targeted therapies	
More than 2	25 (45.5%)
Number of metastatic organ sites	
Multiple site	37 (67.3%)
Liver metastasis	
Presence	13 (23.6%)
First-line molecular-targeted therapy	
Sunitinib	25 (45.5%)
Magnitude of best tumor response	
Complete response	3 (5.46%)
Partial response	15 (27.3%)
Stable disease	19 (34.5%)
Progressive disease	18 (32.7%)
[a]Duration of follow-up, months	14.4 (7.36–22.0)

MSKCC Memorial Sloan Kettering Cancer Center

[a]Shown as median (interquartile range)

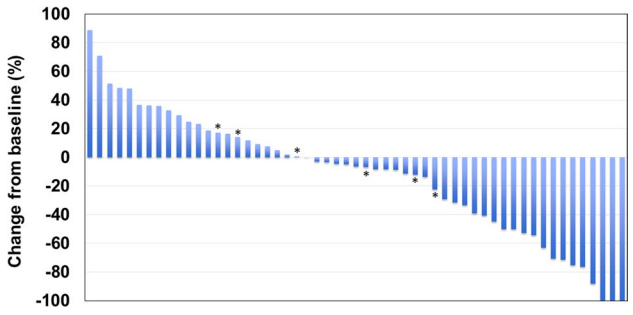

Fig. 1 Waterfall plot showing the magnitudes of best tumor response. Maximum change in tumor burden from baseline for individual patients is shown by waterfall plot. A patient with an asterisk indicates that the best tumor response is PD due to either nontarget lesion growth or new lesion appearance in spite of nongrowth of the target lesion. PD, progressive disease

Survival according to the magnitude of best tumor response

During the follow-up, 41 (74.5%) patients had disease progression and 21 (38.2%) died for any cause. As shown in Fig. 2, PFS and OS after the initiation of nivolumab therapy were significantly associated with the magnitude of bTR (median PFS: N.R. [95% CI 16.8–N.R.] vs. 13.0 [8.38–56.0] vs. 5.95 [4.27–7.30] vs. 1.92 [0.53–3.91] months, $p<0.0001$; OS: N.R. [N.R.–N.R.] vs. N.R. [21.4–N.R.] vs. 23.3 [23.3–N.R.] vs. 7.36 [1.41–N.R.] months, $p<0.0001$). We further analyzed the association between the magnitude of bTR and survivals (PFS and OS) in 45 patients with clear-cell RCC (CR, $n=3$; PR, 14; SD, 14; PD, 14) (Fig. 3). PFS and OS after the initiation of nivolumab therapy were significantly associated with the magnitude of bTR (median PFS: N.R. [95% CI 16.8–N.R.] vs. 13.1 [8.38–56.0] vs. 6.97 [4.27–7.89] vs. 1.36 [0.43–3.39] months, $p<0.0001$; OS: N.R. [N.R.–N.R.] vs. N.R. [21.4–N.R.] vs. N.R. [N.R.–N.R.] vs. 4.31 [1.25–N.R.] months, $p<0.0001$).

Factors for survival

Univariate analysis for PFS shows that sex, MSKCC risk, and magnitude of bTR were significant factors (all, $p<0.05$). Multivariate analysis shows that the magnitude of bTR ($p<0.0001$) was an independent factor for PFS, together with sex (HR 2.59 [1.03–6.37], $p=0.0443$) and MSKCC risk ($p<0.0001$). Also, univariate analysis for OS shows that liver metastasis and magnitude of bTR were significant factors (both, $p<0.05$). Multivariate analysis shows that the magnitude of bTR was an independent factor for OS ($p=0.0010$), together with liver metastasis (HR 3.92 [1.38–11.2], $p=0.0110$).

Survival after disease progression diagnosis according to the presence of subsequent therapy in patients with progressive disease as the best tumor response

We further evaluated OS after a PD diagnosis according to the presence of subsequent therapy in the 18 patients with PD as the bTR (Supplementary Fig. 1). Among them, 11 patients (61.1%) received subsequent therapy after failure of nivolumab. OS after the PD diagnosis was significantly longer in patients with subsequent therapy than those without subsequent therapy (median: 5.59 [2.8–N.R.] vs. 0.92 [0.26–1.25] months, $p=0.0002$).

Discussion

This retrospective study conducted in two academic centers shows that the magnitude of bTR was significantly associated with PFS and OS in nivolumab therapy for

Table 2 Univariate and multivariate analyses for progression-free survival

	Univariate HR (95% CI)	*p*	Multivariate HR (95% CI)	*p*
Age		0.667		
More than 65 years-old (ref. less than 65)	0.87 (0.46–1.67)			
Sex		0.0290		0.0443
Female (ref. male)	2.46 (1.10–5.11)		2.59 (1.03–6.37)	
Histopathology		0.146		
Clear-cell carcinoma (ref. non-clear-cell carcinoma)	0.55 (0.27–1.25)			
MSKCC risk at initiation of nivolumab		0.0007		< 0.0001
Favorable	1.86E−09 (0–0.86)	0.0351	3.65E−10 (0–0.14)	< 0.0001
Intermediate	Ref	–	Ref	–
Poor	3.37 (1.57–6.94)	0.0024	2.46 (1.02–5.85)	0.0458
Number of prior molecular-targeted therapies		0.957		
More than 2 (ref. 1)	1.02 (0.54–1.90)			
Number of metastatic organ sites		0.707		
Multiple site (ref. single site)	1.13 (0.60–2.24)			
Liver metastasis		0.0518		
Presence (ref. absence)	2.19 (0.99–4.48)			
First-line molecular-targeted therapy		0.529		
Sunitinib (ref. other than sunitinib)	1.22 (0.65–2.28)			
Magnitude of best tumor response		< 0.0001		< 0.0001
Complete and partial response	0.21 (0.079–0.53)	0.0007	0.16 (0.056–0.41)	0.0001
Stable disease	Ref	–	Ref	–
Progressive disease	2.22 (1.08–4.58)	0.0294	4.49 (2.07–9.96)	0.0002

HR hazard ratio, *CI* confidence interval, *Ref* reference

previously treated mRCC. Multivariate analyses further show that the magnitude of bTR was an independent factor for PFS and OS. In clinical practice, the magnitude of bTR is difficult to predict in a subset of patients during the therapy. Therefore, the magnitude of bTR can be an effective surrogate marker rather than a predictive marker for survival in nivolumab therapy.

The prognostic impact of magnitude of bTR has already been recognized in targeted therapy [6–8]; Grünwald et al. reported the significant correlation between the depth of remission and survival in first- and second-line targeted therapy using a database with a large cohort from a clinical trial [7]. We also reported the association between the magnitude of bTR and survival in second-line targeted therapy using real world data [8]. In contrast, clinical information regarding the association between the magnitude of bTR and prognosis in ICI therapy is limited as yet.

Interestingly, our analysis found a similar OS in patients categorized into PR and SD groups. This finding was also reported in targeted therapy settings [6, 8, 13]. It is difficult to explain the underlying reasons for this due to multiple heterogeneous factors in these patients. Collectively, the appropriate prediction of OS remains difficult, and further effective prognostic factors should be identified in these heterogeneous populations.

During ICI therapy, several unique patterns of tumor response have been reported. One of them is "pseudoprogression"; T cell recruitment and infiltration in tumors induced by the activation of the immune system may apparently increase tumor volume before leading to tumor shrinkage [14]. In the CheckMate 025 trial, clinical benefit and tumor response beyond radiographic disease progression were observed in a subset of patients [15]. This unique pattern was also observed in other types of ICI therapy for other cancers [14]. Thus, initially, we had hypothesized that the correlation between the magnitude of bTR and prognosis might be unclear in nivolumab therapy, but our analysis indicated a significant correlation. It may be that the incidence of pseudoprogression was too low to affect the correlation in the overall population.

Recently, several studies reported data regarding ORRs and the rates of bTR in nivolumab therapy in real world settings. De Giorgi et al. reported that ORRs were 23.1% and the rates of PD as bTR was 36.2% using data from the Italian Nivolumab Renal Cell Cancer Expanded Access Program [4]. Also, Zahoor et al. reported that ORRs were 15% and

Table 3 Univariate and multivariate analyses for overall survival

	Univariate HR (95% CI)	*p*	Multivariate HR (95% CI)	*p*
Age		0.725		
More than 65 years-old (ref. less than 65)	0.86 (0.36–2.10)			
Sex		0.339		
Female (ref. male)	1.69 (0.54–4.45)			
Histopathology		0.133		
Clear-cell carcinoma (ref. non-clear-cell carcinoma)	0.46 (0.18–1.30)			
MSKCC risk at initiation of nivolumab		0.0580		
Favorable	5.62E−9 (0–3.75)	0.295		
Intermediate	Ref	–		
Poor	2.87 (1.05–7.23)	0.0397		
Number of prior molecular-targeted therapies		0.431		
More than 2 (ref. 1)	1.42 (0.59–3.51)			
Number of metastatic organ sites		0.384		
Multiple site (ref. single site)	1.51 (0.61–4.26)			
Liver metastasis		0.0014		0.0110
Presence (ref. absence)	5.58 (2.01–15.6)		3.92 (1.38–11.2)	
First-line molecular-targeted therapy		0.886		
Sunitinib (ref. other than sunitinib)	1.07 (0.44–2.54)			
Magnitude of best tumor response		0.0002		0.0010
Complete and partial responses	0.44 (0.10–1.73)	0.235	0.48 (0.11–1.90)	0.288
Stable disease	Ref	–	Ref	–
Progressive disease	5.87 (1.95–21.1)	0.0014	5.10 (1.67–18.5)	0.0037

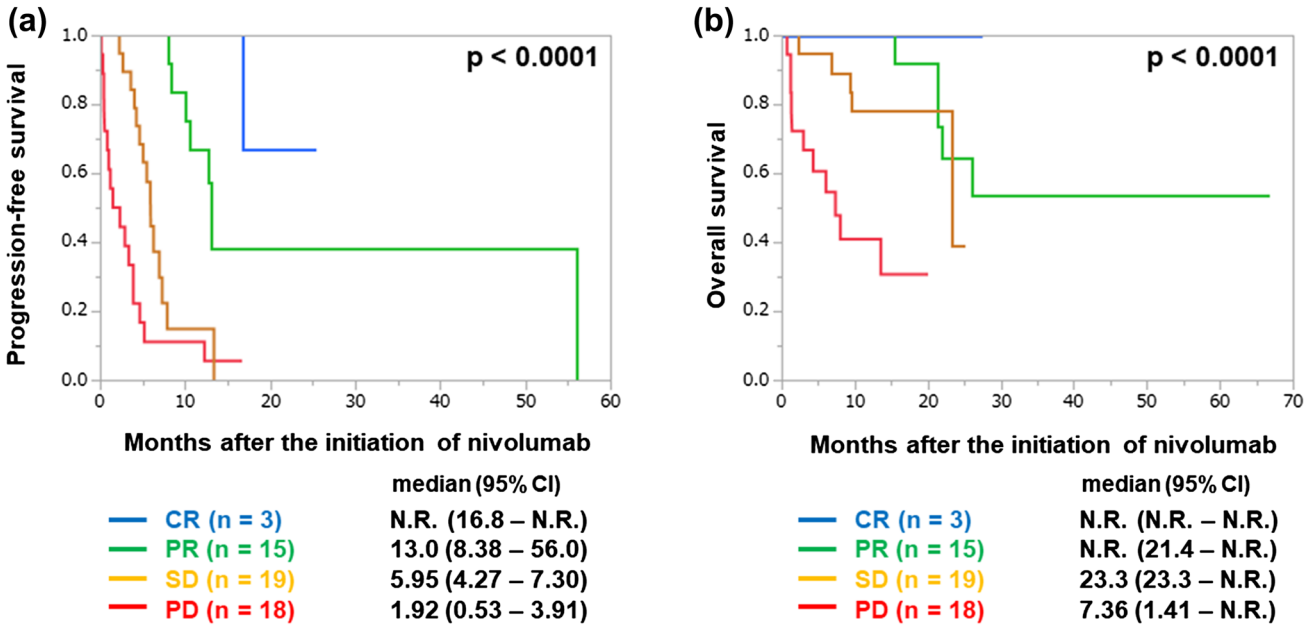

Fig. 2 PFS and OS after the initiation of nivolumab therapy, according to the magnitude of best tumor response. The magnitude of best tumor response had a significant correlation with **a** PFS and **b** OS (both, $p < 0.0001$) in all 55 mRCC patients. *CR* complete response, *PR* partial response, *SD* stable disease, *CI* confidence interval, *NR* not reached, *PFS* progression-free survival, *OS* overall survival, *mRCC* metastatic renal cell carcinoma

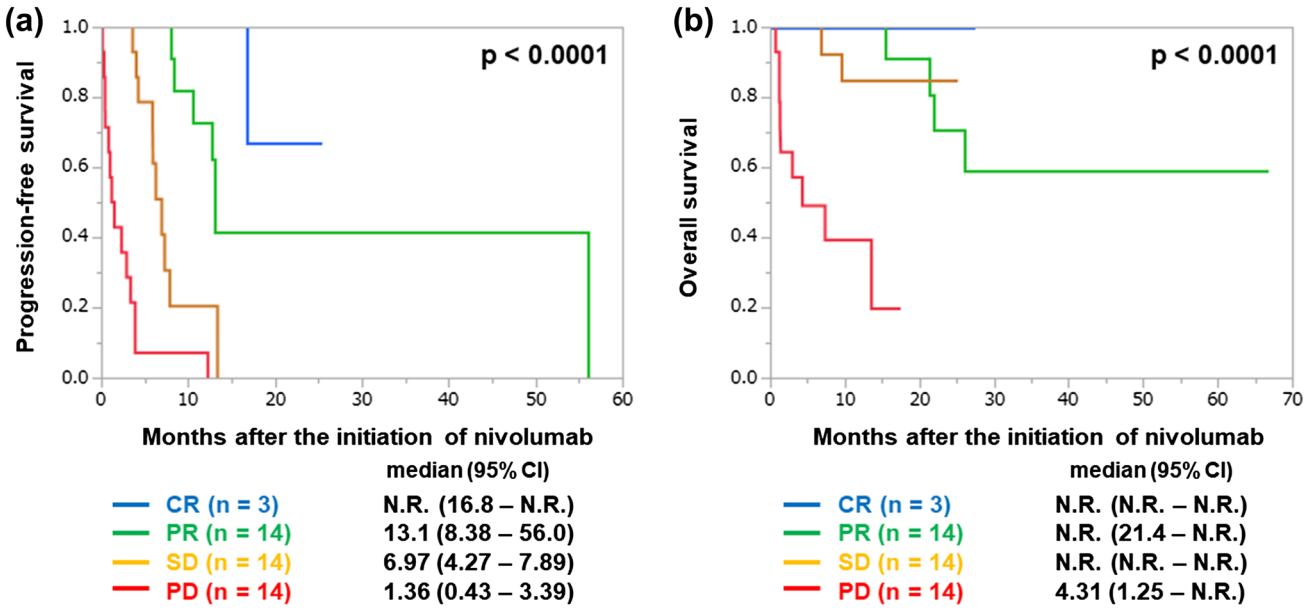

Fig. 3 PFS and OS after the initiation of nivolumab therapy, according to the magnitude of best tumor response in clear cell renal cell carcinoma. The magnitude of best tumor response had a significant correlation with **a** PFS and **b** OS (both, $p < 0.0001$) in 45 metastatic clear-cell RCC patients

the rates of PD as bTR was 47% using a cohort from the Cleveland Clinic [5]. Thus, the degree of tumor response in this analysis appears to be similar to or better than those from western countries. This may be supported by a previous report of Japanese subgroup analysis from the CheckMate 025 study, indicating a higher tumor response in the Japanese patients than in the general population (43% of ORRs and 16% of PD as bTR in Japanese population) [16].

Importantly, our data show that 32.7% of patients do not benefit from nivolumab therapy (i.e., PD as the bTR). Among these patients, 61.1% received subsequent therapy, and they had longer OS from the PD diagnosis than those without subsequent therapy. These data suggest that one of reasons for deteriorated prognosis in patients with PD as the bTR is the absence of subsequent therapy, and that if possible, subsequent therapy can provide a favorable therapeutic efficacy for survival even in these patients.

This study had several limitations. First, this was a retrospective study conducted in a small patient cohort. Thus, any findings could be affected by unavoidable selection bias. Second, due to the relatively short duration of follow-up, the OS data appeared to be immature. Because nivolumab therapy can provide prolonged OS [1, 16], longer observations are required to confirm our findings. Third, the evaluation of tumor response was based on RECIST v.1.1. rather than newer criteria used in the evaluation of immune-related response, such as the immune-related RECIST (irRECIST) [17–20] or iRECIST [21]. Newer criteria could not be used because most of the patients did not receive radiographic examinations for PD confirmation after the first PD evaluation [20]. Forth, the irregular interval of radiographic examinations could have induced bias in the survival analysis. Finally, in this study, nivolumab was administered as second- or later line therapy after failure of prior targeted therapies, although this regimen has not been recommended in the current guideline [22].

In conclusion, this retrospective study shows that the magnitude of bTR was significantly associated with patient survival in nivolumab therapy for previously treated mRCC. This factor can be an effective surrogate marker for survival in nivolumab therapy.

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Compliance with ethical standards

Conflict of interest Tsunenori Kondo received honoraria from Ono Pharmaceutical but did not have any nonfinancial conflict of interest to declare. All other authors have no conflicts of interest.

Ethical approval The Internal Ethics Review Board of the Tokyo Women's Medical University approved this retrospective study (ID: 4998), which was performed in accordance with the principals outlined in the Declaration of Helsinki. Because this was a retrospective study, no formal consent was required.

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