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Site-specific Response to Nivolumab in Renal Cell Carcinoma

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Abstract. *Background/Aim: Nivolumab monotherapy for advanced/metastatic renal cell carcinoma (RCC) shows a survival benefit. The purpose of this study was to evaluate tumor responses to nivolumab in various metastatic and primary sites in patients with RCC. Patients and Methods: We retrospectively reviewed 68 patients who underwent nivolumab monotherapy after one or more regimens of targeted therapy for advanced/metastatic RCC. The site-specific response was evaluated and progression-free survival was estimated. Results: The site-specific overall response rates (ORRs) were as follows: lung (36%), bone (5%), lymph node (33%), liver (50%), adrenal gland (29%), pancreas (33%), and brain (0%). The ORR of bone metastasis was significantly worse in comparison to lung and liver metastases (p=0.017, 0.008). The site-specific median progression-free survival times were as follows: lung (5.1 months), bone (not reached), lymph node (not reached), and liver (17.5 months). Conclusion: Responses to nivolumab may vary depending on metastasized organs.*

In 2018, more than 400,000 new cases of renal cell carcinoma (RCC) are diagnosed and 175,000 patients die from the disease worldwide (1). It is reported that 30% of newly diagnosed RCC cases present with metastases, and up to 30% of patients with locally limited RCC relapse after curative treatment (1). For the treatment of unresectable advanced/metastatic RCC, systemic therapies including targeted therapies and immune checkpoint inhibitors (ICIs) are administered. Since the development of targeted therapies in the 2000s, the prognosis of advanced/metastatic RCC has improved significantly (2). Recently, nivolumab [an anti-programmed death 1 (PD-1) antibody] after treatment with targeted therapies, and first-line therapy with nivolumab plus ipilimumab [an anti-cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) antibody] were reported to achieve superior overall survival (OS) in comparison to targeted therapy (3, 4).

Although ICIs achieve a good response and long-term survival benefit, the overall response rate (ORR) to nivolumab monotherapy is only 25% (3). It is necessary to clarify the characteristics of patients in whom ICIs can be expected to be effective, as <50% of patients benefit from ICIs. Some predictors [*e.g.*, the International Metastatic RCC Database Consortium (IMDC) criteria (5)], of the effects of targeted therapy have been reported; however, their applicability to ICIs is unknown.

In melanoma, non-small cell lung cancer, and hepatocellular carcinoma, responses to ICIs are reported to vary depending on the tumor site (6-8). The impact on the response to ICIs was mainly attributed to the tumor microenvironment (9), which includes tissue-resident immune cells, fibroblasts, endothelial cells and neurons, together with blood-derived cells that are recruited to the tumor site upon cancer progression (10). The tumor microenvironment differs between the primary organ and sites of metastasis, and there are differences among sites of metastasis (9, 11). These differences are expected to lead to the varied responses to ICIs.

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In RCC, tumor responses in different organs have not been reported; however, this would help for selecting treatment or predicting the effectiveness of ICIs. We herein evaluated the tumor response to nivolumab in various organs and primary sites in patients with advanced/metastatic RCC.

Patients and Methods

Enrollment of patients. We retrospectively reviewed 68 patients who received nivolumab monotherapy with the standard dose of 240 mg/body every 2 weeks as a beyond first-line regimen following ≥1 targeted therapy regimens for advanced/metastatic RCC in 7 hospitals between October 2016 and June 2020. The key inclusion criteria were histologically diagnosed RCC and a measurable metastatic or primary site on computed tomography (CT) or magnetic resonance imaging (MRI) (defined below) at the initiation of nivolumab. The key exclusion criteria were prior immune checkpoint therapy before nivolumab and no radiographic examination after the initiation of nivolumab treatment. This study was approved by the institutional review board of National Hospital Organization Kyushu Cancer Center (approval no. 2020-4) and respective institutions. Obtaining additional informed consent from patients was not required by the Institutional Review Board of National Hospital Organization Kyushu Cancer Center for this retrospective study.

Radiography. Radiographic examinations, including CT/MRI, were performed every 4-12 weeks. The response of the entire cohort was evaluated according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 (12). Site-specific responses were evaluated according to modified RECIST 1.1 (12) and immune-related RECIST (13), which were previously reported (7). In each organ system, including the primary site, measurable lesions were defined as lesions of ≥1.0 cm (longest diameter) and lymph nodes of ≥1.5 cm (short axis diameter). At baseline, a maximum of 5 lesions were identified as target lesions in each organ. Tumor burden was defined as the sum of the long axis for all non-lymph nodes target lesions plus the short axis of all lymph nodes target lesions measured. The site-specific response was determined for each site. Responses were classified as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD) according to the rate of change in the organ size. The cut-off values for the rate of change used to classify the response were in accordance with RECIST1.1 (12). A new lesion did not define PD; measurements were included in the sum of measurements (7, 13). The ORR was defined as the sum of the CR and PR rates, and disease control rate (DCR) was defined as the sum of the CR, PR, and SD rates.

Statistical analysis. The ORR and DCR were compared between tumor sites using Fisher's exact test. OS was calculated using Kaplan–Meier method from the initiation of nivolumab to death. Patients who were lost to follow-up or no death was experienced were censored at the last date known to be alive. Progression-free survival (PFS) was calculated using Kaplan–Meier method from the initiation of nivolumab until tumor progression according to the above-mentioned criteria or death due to any reason, whichever occurred first. Patients were still alive and having no progression were censored at the last follow-up date. Waterfall plots were used to evaluate the best percentage changes in the tumor burden of each patient relative to baseline in each site. *p*-Values of <0.05 were considered to indicate statistical significance. All analyses were performed using the JMP® Pro software package (version 15.1.0; SAS Institute, Cary, NC, USA, Inc.).

Table I. *Characteristics of the patients*.

Median age at initiation of nivolumab, years	67	(42-85)
Gender		
Male	46	(68)
Female	22	(32)
Histology		
Clear cell carcinoma	53	(78)
Non-clear cell carcinoma	15	(22)
IMDC risk classification		
Favorable	13	(19)
Intermediate	36	(53)
Poor	17	(25)
Unknown	2	(3)
Previous nephrectomy	60	(88)
Treatment line of nivolumab		
Second	36	(53)
Third or later	32	(47)
Metastasis sites		
Lung	32	(47)
Bone	21	(30)
Lymph node	15	(22)
Liver	10	(15)
Adrenal gland	7	(10)
Pancreas	3	(4)
Brain	2	(3)

Data are presented as n (%) or median (range).

Results

Patient characteristics. The patient characteristics are presented in Table I. The median follow-up period after the initiation of nivolumab was 13.4 months (range=1.0-42.7 month). Fifteen of the 68 patients (22%) patients with non-clear cell carcinoma were included. Thirteen (19%), 36 (53%) and 17 (25%) patients had favorable, intermediate, and poor-risk IMDC classifications, respectively. Sixty (88%) patients underwent nephrectomy. Thirty-six (53%) and 32 (47%) patients received nivolumab as second-line and beyond first-line therapy, respectively. The sites of metastasis at the initiation of nivolumab were as follows: lung (n=32; 47%), bone (n=21; 30%), lymph node (n=15; 22%), liver (n=10; 15%), adrenal gland (n=7; 10%), pancreas (n=4; 6%) and brain metastasis (n=2; 3%).

Treatment efficacy in the entire cohort. The CR, PR, SD, and PD rates in the entire cohort were 2%, 26%, 38%, and 34% respectively. Kaplan–Meier curves for PFS and OS are shown in Figure 1. The median PFS was 7.5 months and the median OS was 31.9 months.

Table II. *Average change in target lesions and site-specific responses.*

	Lung (n=32)	Bone (n=21)	Lymph node (n=15)	Liver (n=10)	Adrenal gland (n=7)	Pancreas (n=3)	Brain (n=2)	Primary site (n=8)
Average change in target lesions from baseline, % (range)	29 (–88-226)	27 (–30-188)	7 (–72-162)	20 (–72-60)	2 (–70-41)	–46 (–100- –6)	–5 (–5-0)	–14 (–44-13)
Overall response rate, %	34	5	33	50	29	33	0	13
Disease control rate, %	50	67	60	60	59	66	100	100
Complete response, n (%)	0	0	0	0	0	1 (33)		0
Partial response, n (%)	11 (34)	1 (5)	5 (33)	5 (50)	2 (29)	1 (33)		1 (13)
Stable disease, n (%)	5 (16)	13 (62)	4 (27)	1 (10)	2 (29)	1 (33)	2 (100)	7 (87)
Progressive disease, n (%)	16 (50)	7 (33)	6 (40)	4 (40)	3 (42)	0		0

Table III. *Comparison of overall response rate between tumor sites using Fisher's exact test.*

	Bone	Liver	Lymph node	Adrenal gland	Primary site
Lung	0.017	0.465	1.000	1.000	0.396
Bone	-	0.008	0.063	0.145	0.483
Liver	-	-	0.442	0.622	0.152
Lymph node	-	-	-	1.000	0.369
Adrenal gland	-	-	-	-	0.569

Site-specific overall response. The overall responses for each metastatic site were as follows lung (36%), bone (5%), lymph node (33%), liver (50%), adrenal gland (29%), pancreas (33%), and brain (0%) (Table II). The ORR for bone metastasis was significantly worse in comparison to those for lung and liver metastases (p=0.017, 0.008. Table III). The ORR varied among tumor sites, however the DCR was comparatively consistent, ranging from 49% in the lung to 100% in the brain. The primary site ORR was only 13%, whereas the DCR was 100%. Only one pancreatic lesion showed a CR.

Change in tumor burden. The best percentage changes in the tumor burden of each patient relative to baseline in the lung, bone, lymph node, liver, and primary site are shown in Figure 2, which shows the analysis of primary tumor sites that were present in >10 patients. The average change in each metastasis site was as follows: lung (29%), bone (26%), lymph node (7%), liver (20%), adrenal gland (2%), pancreas (-46%), and brain (-5%) (Table II). In 2 patients with lung metastasis, tumors enlarged >200% in the 8 weeks after the initiation of nivolumab. They met the definition for hyperprogressive disease (HPD) (14). In addition to lung metastasis, one of these patients had bone metastasis; the other had liver metastasis. The patient with bone metastasis achieved SD; the patient with liver metastasis achieved PD after the initiation of nivolumab. At the primary site, the change in tumor size was not large and there was no great variation among patients.

Site-specific progression-free survival. Kaplan–Meier curves for PFS in each tumor site are shown in Figure 3; the analysis of tumor sites included >10 patients. The median PFS was as follows: lung (5.1 months), bone (not reached), lymph node (not reached), and liver (17.5 months). The Kaplan–Meier curves for liver, bone, and lymph node metastasis stopped falling approximately 5 months after the initiation of nivolumab, whereas the curves for lung metastasis continued to fall consistently. Regarding the primary site, PFS was 21.5 months. The Kaplan–Meier curves flattened at 5 months after the initiation of nivolumab and continued for 16 months.

Discussion

Although a low response rate requires predictive factors to determine patients who should be treated with nivolumab, there are currently no such predictors for RCC In melanoma, non-small cell lung cancer, and hepatocellular carcinoma, the responses to ICIs were reported to vary depending on the site of metastasis (6-8). The impact on the response to ICIs was mainly attributed to the tumor microenvironment (9), which

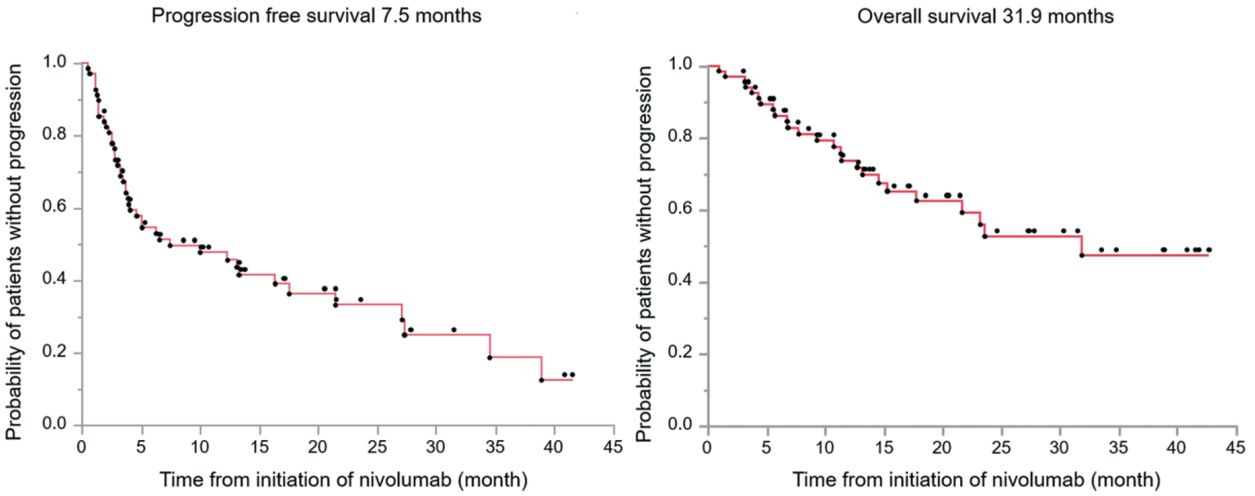

Figure 1. *Progression-free survival and overall survival in the entire cohort.*

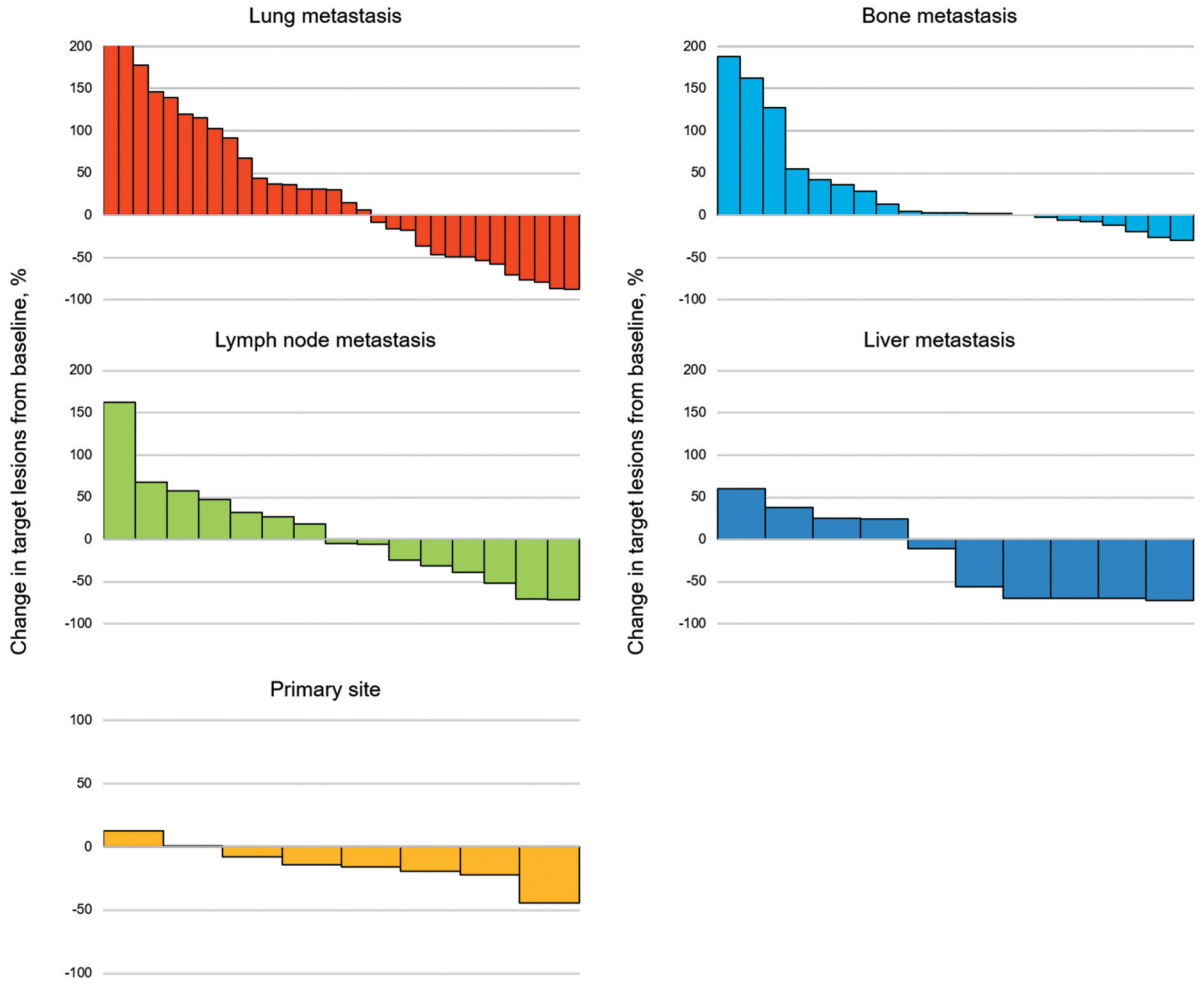

Figure 2. *Best percentage change over time (from baseline) in tumor burden in various tumor sites.*

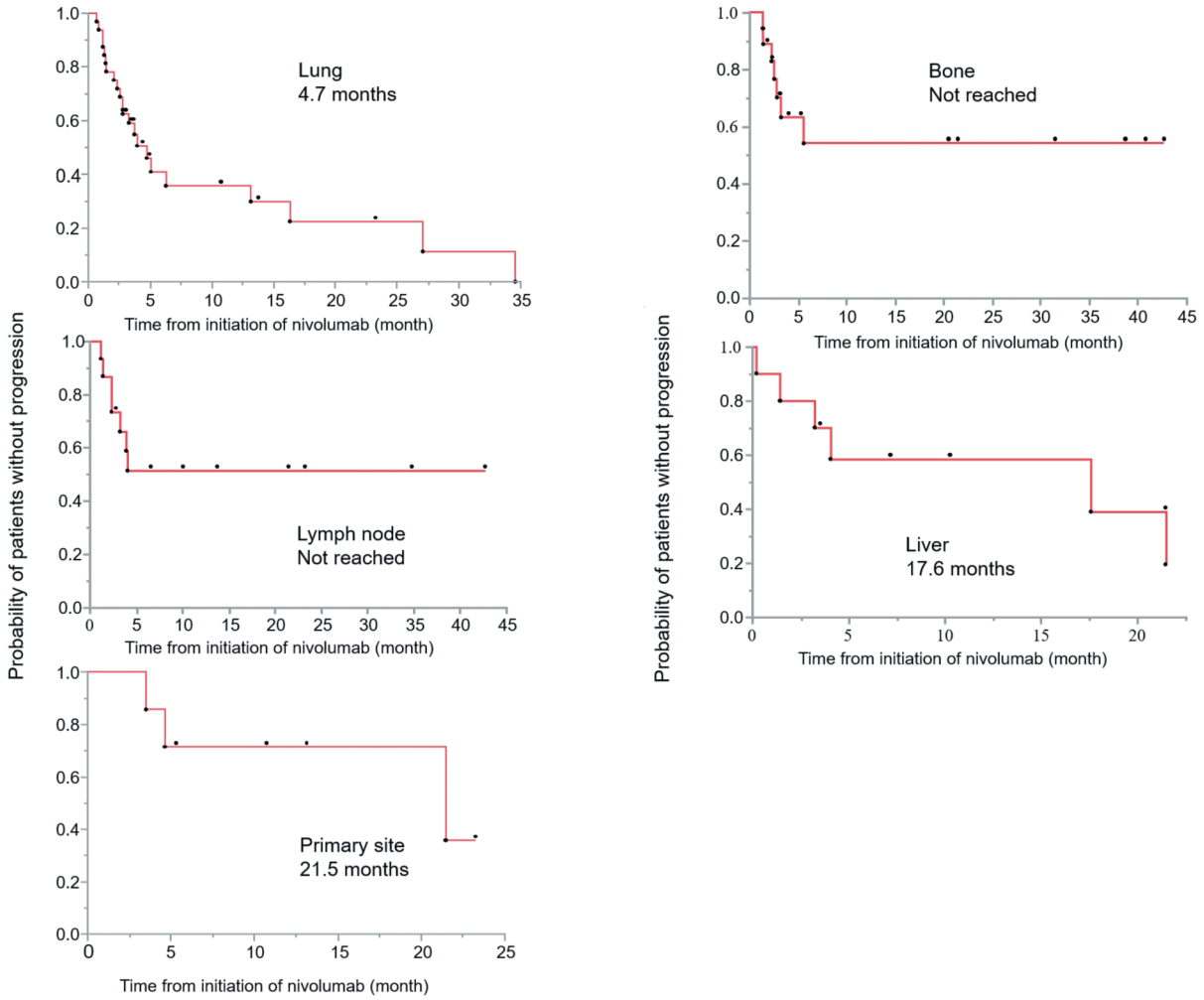

Figure 3. *Progression-free survival in various tumor sites.*

differs between the primary organ and sites of metastasis, and there are differences among sites of metastasis (9, 11). These differences are expected to lead to the varied responses to ICIs.

The site-specific ORR of bone metastasis was significantly worse in comparison to lung and liver metastases. Bone tissue provides a good environment for metastatic tumor cells, is rich in hematopoietic cells, bone cells, and growth factors (15), and is an active and fertile ground for the development of bone metastasis. Thus, targeted therapy or immune checkpoint inhibitor monotherapy had limited effects on bone metastasis (15, 16). Combined therapy should be considered to improve the efficacy of nivolumab in such cases. The concomitant use of denosumab (a monoclonal antibody against receptor activator for nuclear factor-kappa B ligand) and an PD-1 antibody, showed promising efficacy for bone metastasis from melanoma (17). Moreover, radiotherapy with systemic therapy including TKI or ICIs achieved a superior radiographic response to systemic therapy without radiotherapy (16). These modalities should be used with nivolumab for bone metastasis from RCC.

The ORR of lung metastasis was comparable to that of other tumor sites; however, PFS was shorter in comparison to other organs. Lung metastasis is reported to have a more immunogenic environment with higher lymphocytic infiltration and myeloid dendritic cells than brain, bone, and liver metastases, regardless of tumor origin, whereas lung metastasis showed high PD-L1 and CTLA-4 gene expression levels (18), implying that nivolumab monotherapy is inadequate for lung metastasis and that combination with an anti-CTLA-4 antibody is more suitable. Moreover, anti-CTLA-4 antibodies, which are reported to enhance CD8+ T-cell memory formation (19), possibly prolong the duration of response and improve PFS.

There were two cases with lung metastasis in which the tumor size increased >200% in 2 months (14), satisfying the definition of HPD [clinically defined by the unexpected acceleration of cancer evolution on initiation of immunotherapy, and more accurately defined by a >200% increase in tumor growth kinetics with <2 months to treatment failure (14)]. These cases had no reported risk factors for HPD (*i.e.*, age>65 years; >2 metastatic sites) (20). The biological mechanism underlying the development of HPD is unknown (14), and it is not clear whether the tumor site is associated with HPD.

The present study was associated with several limitations. RCC after ICI treatment sometimes shows a histological CR after resection, even when a tumor is visible on CT (21). We only evaluated responses on images using the combined RECIST and immune-related RECIST according to a previous report (7), because it is not possible to remove or histologically evaluate all metastasis. RECIST and immune-related RECIST were properly validated (12, 13), and are reasonable methods for evaluating tumor response. Furthermore, the population was relatively small. The sample sizes of studies investigating site-specific responses to ICIs in melanoma, non-small cell lung cancer, and liver cancer (6-8) were 52, 75, and 140, respectively. Although the populations of the latter 2 studies were larger than this study, they included patients treated with various ICIs including anti-PD-1, anti-PD-L1, and anti-CTLA-4 antibodies. Our study population is the largest to evaluate patients treated by nivolumab monotherapy.

The response to nivolumab differed according to tumor site, which was attributed to the microenvironment (7, 8). Improving the microenvironment, which may be achieved by combination therapy with an additional ICI, targeted therapy (22), or radiotherapy (23), is therefore necessary to overcome resistance. These modalities combined with PD-1 blockade exerted better cancer control than PD-1 blockade monotherapy (4, 24, 25). Clinical trials of various combination therapies are ongoing (26) and further improvement is expected.

Conclusion

Responses to nivolumab may vary depending on metastasized organs. Efficacy of nivolumab has a risk of limiting when treating RCC metastasis in specific sites. The mechanism underlying the differing responses among tumor sites remains to be elucidated. More evidence and the development of basic research will provide clues to clarify the phenomenon.

Conflicts of Interest

T Nakagawa has received research support from Ono Pharmaceutical. H Kitamura has received a speaker honorarium from Bristol-Myers Squibb. The other Authors declare that they have no competing interests.

Authors' Contributions

T Negishi: Protocol/project development, Data collection and management, Data analysis, Manuscript writing; N Furubayashi: Data collection; T Nakagawa: Data collection, Manuscript revision; N Nishiyama: Data collection, Manuscript revision; H Kitamura: Data collection, Manuscript revision; Y Hori: Data collection; K Kuroiwa: Data collection; Y Son: Data collection; N Seki: Data collection; Tomoda: Data collection; E Okajima: Data collection, Manuscript revision; M Nakamura: Data management; All Authors read and approved the final manuscript.

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