Immediate Progressive Disease in Patients with Metastatic Renal Cell Carcinoma Treated with Nivolumab: a Multi-Institution Retrospective Study

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Immediate progressive disease after nivolumab therapy in patients with metastatic renal cell carcinoma: a multi-institution retrospective study

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Abstract

Background: Investigation on the rapid disease progression after immune checkpoint inhibitor therapy in urologic malignancies is lacking.

Objective: The objective was to evaluate the immediate progressive disease (PD) after nivolumab therapy for pretreated metastatic renal cell carcinoma.

Patients and Methods: Forty patients were retrospectively evaluated. Immediate PD was clinically or objectively diagnosed. Clinical diagnosis was defined as an acceleration of symptoms directly caused by tumor growth or systematic worsening of the general condition such as cachexia. Objective diagnosis was based on imaging evaluation using Response Evaluation Criteria in Solid Tumors version 1.1 and development within the initial two cycles of nivolumab therapy.

Results: Seven patients (17.5%) experienced immediate PD; thereafter, all patients died of cancer. The median time from therapy initiation to development was 14 days. Progression-free and overall survival after nivolumab therapy were significantly shorter in patients with immediate PD compared with those without immediate PD (progression-free survival: 0.66 vs. 10.5 months, $p<0.0001$; overall survival: 1.41 months vs. not reached, $p<0.0001$). Furthermore, female sex ($p=0.0434$), poor MSKCC risk ($p=0.0263$), and shorter duration of prior-line time to progression ($p=0.0218$) were associated with immediate PD.

Conclusions: The development of immediate PD in a subset of patients could deteriorate patient prognosis. Sex, MSKCC risk, and duration of prior-line time to progression might be involved in the development. Although these findings had limited evidence due to the study design, the data have the potential to improve treatment strategy. Therefore, prospective studies should further assess these findings.

Key points

1. Rapid disease progression after immune checkpoint inhibitor therapy has been discussed in various types of cancer.

2. Immediate progressive disease developed in 17.5% of metastatic renal cell carcinoma patients after nivolumab therapy and deteriorated patient prognoses.

3. Female sex, poor risk, and shorter duration of prior-line time to progression were potential predictive factors of development of immediate progressive disease.

1. Introduction

The immune checkpoint inhibitor (ICI) nivolumab has been approved for previously treated patients with metastatic renal cell carcinoma (mRCC) based on a pivotal phase III trial [1]. The CheckMate 025 study demonstrated that nivolumab had an overall survival (OS) benefit and more favorable tolerability compared with everolimus [1-4]; therefore, the treatment strategy for mRCC has dramatically changed [5, 6].

As experience with the use of nivolumab increases, a unique phenomenon specific to ICIs has come to light. Rapid disease progression after therapy initiation, namely "hyperprogression," has been recently discussed because ICIs can have a deleterious effect of accelerating the disease in a subpopulation [7-9]. It is suggested that this undesired phenomenon can develop regardless of cancer type or prior corresponding therapies [7, 9, 10]. A recent study showed preliminary data regarding hyperprogression in patients with advanced head and neck squamous cell carcinoma during anti-programmed cell death 1 (PD-1)/PD-ligand 1 (PD-L1) therapy [8].

For now, hyperprogression is defined as the tumor growth rate incorporating the time of the event, allowing for a quantitative and dynamic evaluation of the tumor burden along the treatment sequence [8, 7, 9]. This definition is highly objective and reproducible; however, some patients can be excluded from analyses because rapid clinical disease progression does not allow imaging evaluation [7]; thus, the detection of "clinical hyperprogression" may be missed. Most importantly, such cases always exist in a real-world setting. However, the number of studies regarding the phenomenon is limited in urologic malignancies, including cases involving mRCC.

Herein, we evaluated mRCC patients with rapid disease progression clinically or objectively diagnosed using imaging evaluation with immediate progressive disease

(immediate PD), which is defined as an acceleration of cancer-related symptoms, after nivolumab therapy initiation. The prognostic impact and risk factors of immediate PD were analyzed.

2. Materials and methods

2.1. Study design

In our department and its affiliated institution, 42 patients received nivolumab administration at least once for previously treated mRCC between June 2013 and October 2017. After exclusion of two patients whose clinical data were lacking, the remaining 40 patients were evaluated in this study.

The Internal Ethics Review Boards of the Tokyo Women's Medical University and Tokyo Women's Medical University Medical Center East approved this multi-institutional retrospective study (ID: 4717), which was performed in accordance with the principles of the Declaration of Helsinki. All clinical and laboratory data were extracted from the electronic database and patient medical records.

2.2. Protocol of nivolumab therapy

The protocol of nivolumab therapy is based on that used in the previous pivotal study [1]. Briefly, nivolumab was intravenously administered every two weeks. Dose modifications were not permitted in any cases. Otherwise, an interval of administration could be modified according to patients' conditions or cases with onset of drug-induced adverse events. In all cases, nivolumab was administered in patients with previously treated mRCC based on the consensus guidelines [5]. A detailed regimen of sequential molecular-targeted therapy is described in our previous studies [11-13].

Post-treatment 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 patients' conditions. Drugs were administered until disease progression or intolerable adverse events were observed.

2.3. Definition of immediate PD and evaluation of objective response during nivolumab therapy

We defined immediate PD as progressive disease that was clinically or objectively diagnosed using imaging examination with an acceleration of cancer-related symptoms. In addition, immediate PD was defined as a disease that developed within the initial two cycles of nivolumab therapy and required the permanent termination of nivolumab therapy.

Specifically, the clinical definition of immediate PD was based on the cancer-related symptoms. Cancer-related symptom was defined as a symptom that was physically or directly caused by tumor growth or infiltration of surrounding tissues. For example, when a patient had back pain caused by a spinal metastatic tumor growth, this pain was defined as a cancer-related symptom. Meanwhile, worsening of the general condition such as cancer cachexia that was indirectly or systematically caused by disease progression was considered as clinical immediate PD.

The definition of objective immediate PD was assessed using imaging evaluation based on the standard Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 [14]. We evaluated the tumor response of target lesions, non-target lesions, and new lesions, with each classification defined as follows: target lesion growth was defined as an increase of ≥20% in the sum of diameters of the target lesions, taking the smallest sum observed in the study as reference. In addition to a relative increase of 20%, the sum had to demonstrate an absolute increase of at least 5 mm. The unequivocal progression of existing non-target lesions and the appearance of new malignant lesions were defined as disease progression.

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. Time to progression (TTP) and progression-free survival (PFS) were defined as the time from prior therapy initiation to the date of progression and from nivolumab therapy initiation to the date of progression, respectively. OS was defined as the time from nivolumab therapy initiation to the date of death from any cause. Survival was calculated using the Kaplan-Meier method and compared using the log-rank test. Univariate logistic regression analysis was used to identify risk factors for immediate PD development. Risk was expressed as odds ratio (ORs) and 95% confidence intervals (CIs). All statistical analyses were conducted using JMP software (version 11; SAS Institute Inc., Cary, NC, USA), and $p<0.05$ indicated statistical significance.

3. Results

3.1. Patient background

In total, immediate PD developed in seven patients (17.5%). The median time from nivolumab therapy initiation to immediate PD onset was 14 days (interquartile range: 12-16 days). Table 1 shows the baseline patient characteristics. At the time of nivolumab therapy initiation, 30 patients (75.0%) were classified into the intermediate MSKCC risk group (based on the Motzer's risk classification [15]). Nivolumab was administered as a second-line agent in 16 patients (40.0%), and tyrosine kinase inhibitors were frequently used as the first-line targeted therapy (n=39, 97.5%). The patients were divided into two groups based on immediate PD development; poor performance status (≥2) (57.1% vs. 6.1%, p=0.0006), poor MSKCC risk (57.1% vs. 15.2%, p=0.0337), and shorter duration of TTP prior to nivolumab (<6 months) (85.7% vs. 30.3%, p=0.0109) were frequently observed in patients with immediate PD compared to those without immediate PD. Furthermore, the percentage of female patients tended to be higher in the immediate PD group (57.1% vs. 18.2%, p=0.052). There were no significant differences in any other clinicopathological factors between the two groups (all p>0.05). As expected, the follow-up duration was significantly shorter in patients with immediate PD (median: 1.41 vs. 10.0 months, p=0.0002).

3.2. Patient survival after immediate PD development

During the follow-up, 25 (62.5%) and 12 (30.0%) patients among the total number of patients experienced disease progression and death due to any cause. Figure 1 shows PFS and OS after nivolumab therapy initiation according to immediate PD development. Patients with immediate PD had a significantly shorter duration of PFS and OS compared

to those without immediate PD (median PFS: 0.66 [95% CI: 0.13-1.38] vs. 10.5 [95% CI: 7.30-36.6] months, p<0.0001; OS: 1.41 months [95% CI: 0.72-2.99] vs. not reached [95% CI: 21.4-not reached], p<0.0001).

3.3. Risk factors for immediate PD development

Table 2 shows the results of the univariate analysis for risk factors of immediate PD development. The univariate analysis showed that female sex (OR: 6.00, 95% CI: 1.05-34.1, p=0.0434), poor MSKCC risk (OR: 7.47, 95% CI: 1.27-44.0, p=0.0263), and shorter duration of prior TTP (OR: 13.8, 95% CI: 1.46-130.1, p=0.0218) were associated with immediate PD development.

3.4. Individual clinical profiles in patients with immediate PD

Table 3 shows individual clinical profiles in the seven patients with immediate PD development. In four patients, performance status was poor and the corresponding risk was classified into poor risk. Acute respiratory failure due to rapid lung metastasis was observed in three patients. Only one patient (patient 6) received sequential targeted therapy after immediate PD and happened to have longer survival compared to the other patients (Figure 2). As for components of immediate PD, target lesion growth with/without appearance of new lesions was observed in three patients (patients 2, 6, and 7) (Supplementary Figure 1), whereas the appearance of new lesions with/without non-target lesion growth was found in three patients (patients 1, 4 and 5) (Figure 3). In patient 3, although imaging evaluation of immediate PD was not conducted, the cancer-related cachexia was rapidly accelerated, and we determined that the patient could be included in this study based on the definition of immediate PD.

4. Discussion

In this study, seven (17.5%) of 40 patients experienced immediate PD after nivolumab therapy for mRCC. Immediate PD developed with substantial incidence and seriously deteriorated patient prognoses. Female sex, poor risk, and shorter duration of prior TTP were indicated to be associated with immediate PD. To the best of our knowledge, this is the first study to evaluate the prognostic impact and predictive factors for rapid disease progression after ICI therapy for mRCC. Because immediate PD was defined as rapid disease progression diagnosed clinically or objectively in this study, we believe that the present data can reflect the situation in real-world clinical practice.

Champiat et al. [7] reported that 9% of patients were considered to have hyperprogression with various types of cancers after corresponding prior therapies. In their cohort, however, hyperprogression was not observed in patients with mRCC (0/9 patients). In another study, a higher proportion (29%) of patients underwent hyperprogression after anti-PD-1/PD-L1 therapy for advanced head and neck squamous cell carcinoma [8]. In this context, we focused on clinical disease progression additional to the imaging evaluation, and the findings were believed to reflect the real-world clinical situations.

Patient prognosis after immediate PD appeared to be extremely poor, which was consistent with the findings of previous studies [8, 16]. Only one patient (patient 6) received sequential targeted therapy, and the prognosis appeared to be relatively favorable. This might indicate that, even after immediate PD, sequential therapy was a feasible option in this patient [13, 17, 18]. However, the possible benefit of sequential therapy should be assessed via further prospective controlled studies with a larger sample.

We found that female sex, poor risk, and shorter prior TTP might be used to predict

the immediate PD development. Thus, upon further validation of data, consideration of these factors has the potential to avoid immediate PD and contribute to the improvement of treatment strategies. Male sex was previously indicated as a preferable factor for OS [1], and a recent systematic review and meta-analysis study also showed that therapeutic efficacy of ICI therapy was sex-dependent [19]. In addition, sex-related differences of immune response in cancer microenvironment have been indicated [20, 21]. A shorter prior TTP might reflect a high aggressiveness of the disease. Thus, possibly, the rapidly growing tumor cannot be suppressed even by nivolumab, which has a higher objective response rate than molecular-targeted therapies [1, 22].

Interestingly, patient 5 of the present study developed a cerebral hemorrhage from a new brain metastasis (Table 3). In this case, the brain metastasis could have existed before nivolumab was started, albeit undetected because of the lack of neurological symptoms. It may suggest that an untreated metastatic brain disease can be a factor in the critically deteriorating patient prognosis, as reported in a previous study regarding non–small-cell lung cancer [23].

It is difficult to identify whether the rapid disease progression, namely hyperprogression or immediate PD, is caused by nivolumab or just reflected the nature of aggressive disease. The disease treated with nivolumab may have already hovered inherent aggressiveness or resistance to any therapies. Another concern is that the withdrawal of prior targeted therapy after a long-term response may reflect the rapid disease progression [24, 25]. The immune microenvironment plays a dual role: both anti-tumor and cancer-promoting effects [26-29]. Furthermore, changes in immune-modifying factors encoding genomic or epigenetic alterations can affect the variability in the tumor response [9, 30-32]. Once we can determine whether the immune microenvironment is

unexpectedly altered and becomes “tolerant to cancer” after nivolumab therapy, we can demonstrate that immediate PD is caused by nivolumab. However, it is merely a conjecture at this point, and further basic research investigating the immune microenvironment alterations during nivolumab therapy is needed to elucidate the mechanism of immediate PD.

In addition, ICI therapy has been approved in first-line setting for untreated advanced renal cancer according to a result from a phase III trial “CheckMate 214” [22]. Thus, we should monitor whether the same phenomenon develops even in the first-line setting where there is no influence of prior therapies.

This study has several limitations. First, this was a retrospective study conducted using limited sample with heterogeneous patient background such as regimens of prior therapies in only two institutions. Therefore, the findings could be affected by unrevealed factors or biases. In addition, only univariate analysis was carried out due to the limited sample size and few incidences of immediate PD development. Second, we did not evaluate the possibilities for pseudoprogression in the seven patients because subsequent imaging evaluation, which were needed for diagnosis of pseudoprogression [16, 33], was not performed because of the patients’ clinical course. However, we considered possibility of pseudoprogression to be low because the distinctive worsening of symptoms was concomitant with the progression of the disease in all the patients. Third, there was some time lag between time at baseline imaging and time at therapy initiation, as shown in Table 3. Thus, the disease might have already progressed before nivolumab therapy, and this could raise one interpretation that the nature of disease was in part involved in immediate PD. Taken together, the present finding should be assessed in future prospective studies with homogeneous treatment profiles.

5. Conclusions

This study showed that immediate PD developed in a subset of mRCC patients after nivolumab therapy and could significantly deteriorate patient prognoses. Furthermore, female sex, poor risk, and shorter prior TTP might be effective predictive factors for immediate PD development. Although these findings have limited evidence due to the nature of study design, the data have potential to improve treatment strategy of mRCC in ICI treatment era. Therefore, further prospective studies are required to assess these findings.

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Compliance with Ethical Standards

Disclosure of Conflict of Interest

Tsunenori Kondo received honoraria from Pfizer, Bayer, and Novartis. No external funding was used in the preparation of this manuscript. All other authors have no conflicts of interest to declare.

Research

The Internal Ethics Review Board of Tokyo Women's Medical University approved this retrospective study (ID: 4717). For this type of study, formal consent is not required.

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Figure legends

Figure 1. Progression-free and overall survival after nivolumab therapy initiation according to immediate PD development

Progression-free and overall survival were significantly shorter in patients with immediate PD (n=7) compared to those without immediate PD (n=33) (median progression-free survival: 0.66 vs. 10.5 months, p<0.0001; overall survival: 1.41 months vs. not reached, p<0.0001).

PD, progressive disease; CI, confidence interval; N.A., not applicable

Figure 2. Time to immediate PD onset and subsequent patient prognosis shown by a swimmer plot

All patients died of cancer.

Figure 3. Changes in the sum of the diameters of the target lesions and the objective response rate from baseline to initial evaluation

Patient 4 was excluded due to a lack of imaging evaluation after immediate PD. Initial imaging evaluation was performed at the time of immediate PD development in six patients.

Table 1. Baseline patient characteristics according to the presence of immediate PD development

Variable	All (n=40)	With immediate PD (n=7)	Without immediate PD (n=33)	p
Sex				0.052
Female (reference: male)	10 (25.0%)	4 (57.1%)	6 (18.2%)	
Age, years				0.432
≥65 (reference: <65)	23 (57.5%)	3 (42.9%)	20 (60.6%)	
Histology				1[a]
Clear-cell carcinoma	33 (82.5%)	6 (85.7%)	27 (81.8%)	
Papillary renal cell carcinoma type II	2 (5.0%)	0	2 (6.1%)	
Xp 11.2 translocation renal cell carcinoma	2 (5.0%)	0	2 (6.1%)	
Mucinous tubular and spindle cell carcinoma	1 (2.5%)	1 (14.3%)	0	
Others/unknown	2 (5.0%)	0	2 (6.1%)	
Performance status at nivolumab therapy initiation				0.0006[b]
0	27 (67.5%)	1 (14.3%)	26 (78.8%)	
1	7 (17.5%)	2 (28.6%)	5 (15.2%)	
≥2	6 (15.0%)	4 (57.1%)	3 (6.1%)	
MSKCC risk at nivolumab therapy initiation				0.0337[c]
Favorable	1 (2.50%)	0	1 (3.03%)	
Intermediate	30 (75.0%)	3 (42.9%)	27 (81.8%)	
Poor	9 (22.5%)	4 (57.1%)	5 (15.2%)	

Number of prior therapies				1
1 (reference: ≥ 2)	16 (40.0%)	3 (42.9%)	13 (39.4%)	
Prior cytokine therapy				1
With	7 (17.5%)	1 (14.3%)	6 (18.2%)	
First-line targeted therapy				1[d]
TKI	39 (97.5%)	7 (100%)	32 (97.0%)	
Sorafenib	14 (35.0%)	1 (14.3%)	13 (39.4%)	
Sunitinib	18 (45.0%)	4 (57.1%)	14 (42.4%)	
Axitinib	2 (5.00%)	0	2 (6.06%)	
Pazopanib	5 (12.5%)	2 (28.6%)	3 (9.09%)	
mTORi	1 (2.50%)	0	1 (3.03%)	
Temsirolimus	1 (2.50%)	0	1 (3.03%)	
Everolimus	0	0	0	
Serum CRP level, mg/dL				0.387
≥1.0 (reference: < 1.0)	26 (65.0%)	6 (85.7%)	20 (60.6%)	
First-line TTP, months				0.679
<6 (reference: ≥6)	14 (35.0%)	3 (42.9%)	11 (33.3%)	
Prior-line TTP, months				0.0109
<6 (reference: ≥6)	16 (40.0%)	6 (85.7%)	10 (30.3%)	
Number of metastatic sites				0.681
Multiple (reference: single)	24 (60.0%)	5 (71.4%)	19 (57.6%)	
Liver metastasis				0.0878

Presence (reference: absence)	7 (17.5%)	3 (42.9%)	4 (12.1%)	
Follow-up period, months[e]	9.14 (4.43-12.1)	1.41 (1.25-2.99)	10.0 (7.27-14.3)	0.0002

[a] Clear-cell carcinoma vs. non-clear-cell carcinoma. [b] ≤1 vs. ≥2. [c] Favorable/intermediate vs. poor. [d] TKI vs. mTORi. [e] Median (interquartile range).

PD, progressive disease; MSKCC, Memorial Sloan Kettering Cancer Center; TKI, tyrosine kinase inhibitor; mTORi, mammalian target of rapamycin inhibitor; CRP, C-reactive protein; TTP, time to progression.

Table 2. Univariate analysis for risk factors of immediate PD development

Variable	Univariate OR (95% CI)	p
Sex		
Female (reference: male)	6 (1.05-34.1)	0.0434
Age, years		
≥65 (reference: <65)	0.49 (0.09-2.54)	0.394
Histology		
Clear-cell carcinoma (reference: non-clear-cell carcinoma)	1.33 (0.134-13.2)	0.806
MSKCC risk at nivolumab therapy initiation		
Poor (reference: favorable/intermediate)	7.47 (1.27-44.0)	0.0263
Number of prior therapies		
1 (reference: ≥2)	1.15 (0.22-6.02)	0.865
Prior cytokine therapy		
With	0.75 (0.076-7.44)	0.806
First-line targeted therapy		
mTORi (reference: TKI)	1.14E-06	0.995
Serum CRP level, mg/dL		
≥1.0 (reference: <1.0)	3.9 (0.42-36.2)	0.232
First-line TTP, months		
<6 (reference: ≥6)	1.50 (0.28-7.91)	0.633
Prior-line TTP, months		

<6 (reference: ≥6)	13.8 (1.46-130.1)	0.0218
Number of metastatic sites		
Multiple (reference: single)	1.84 (0.31-10.9)	0.501
Liver metastasis		
Presence (reference: absence)	5.44 (0.88-33.8)	0.0691

OR, odds ratio; CI, confidence interval.

Table 3. Individual clinical profiles in patients with immediate PD

Patient	Age (years)/sex	Prior therapy to nivolumab	Line of nivolumab	Comorbidity	Metastatic sites	MSKCC	PS	TTP of prior therapy, months	Days from therapy initiation to event (TTP of nivolumab)	Days from baseline imaging to event	Events as immediate PD	Patterns of PD according to the RECIST
1	63/M	Cytokines, pazopanib, axitinib	Fourth-line	Dyslipidemia	Lung, liver, adrenal, kidney	Intermediate	0	3.65	13	16	Carcinomatous lymphangiosis due to rapid lung metastasis	Non-target lesion growth and appearance of new lesions
2	66/F	Pazopanib, sorafenib, axitinib	Fourth-line	Hypertension	Bone, liver, lymph node	Poor	2	15.8	12	16	Acute paralysis due to rapid tumor growth of spinal metastasis	Target lesion growth
3	63/F	Sunirinib	Second-line	None	Lymph node	Poor	2	5.92	16	65	Rapid cancer-related	Not evaluated

											cachexic acceleratio n	
4	71/F	Sunitinib , axitinib	Third-line	Colon cancer[a]	Lung, kidney, lymph node	Poor	2	4.54	2	14	Acute respiratory failure due to rapid lung metastasis	Non-target lesion growth and appearance of new lesions
5	64/M	Sunitinib , axitinib, everolimus	Fourth-line	None	Lung, liver, renal pelvis, lymph node	Poor	2	1.12	14	42	Cerebral hemorrhage from brain metastasis	Appearance of new lesions
6	41/M	Sunitinib	Second-line	None	Lymph node	Intermediate	1	2.47	14	28	Back pain due to rapid tumor growth of retroperitoneal lymph node	Target lesion growth and appearance of new lesions

											metastasis	
7	75/F	Sorafenib	Second-line	None	Lung, lymph node	Intermediate	1	3.06	28	47	Acute respiratory failure due to rapid lung metastasis	Target lesion growth and appearance of new lesions
Median (interquartile range)	64 (63-71)						2 (1-2)	3.65 (2.47-5.92)	14 (12-16)	28 (16-47)		

[a] Treated 10 years ago for an early-stage cancer, and the disease appeared to be in remission.

PS, performance status; RECIST, Response Evaluation Criteria in Solid Tumors.

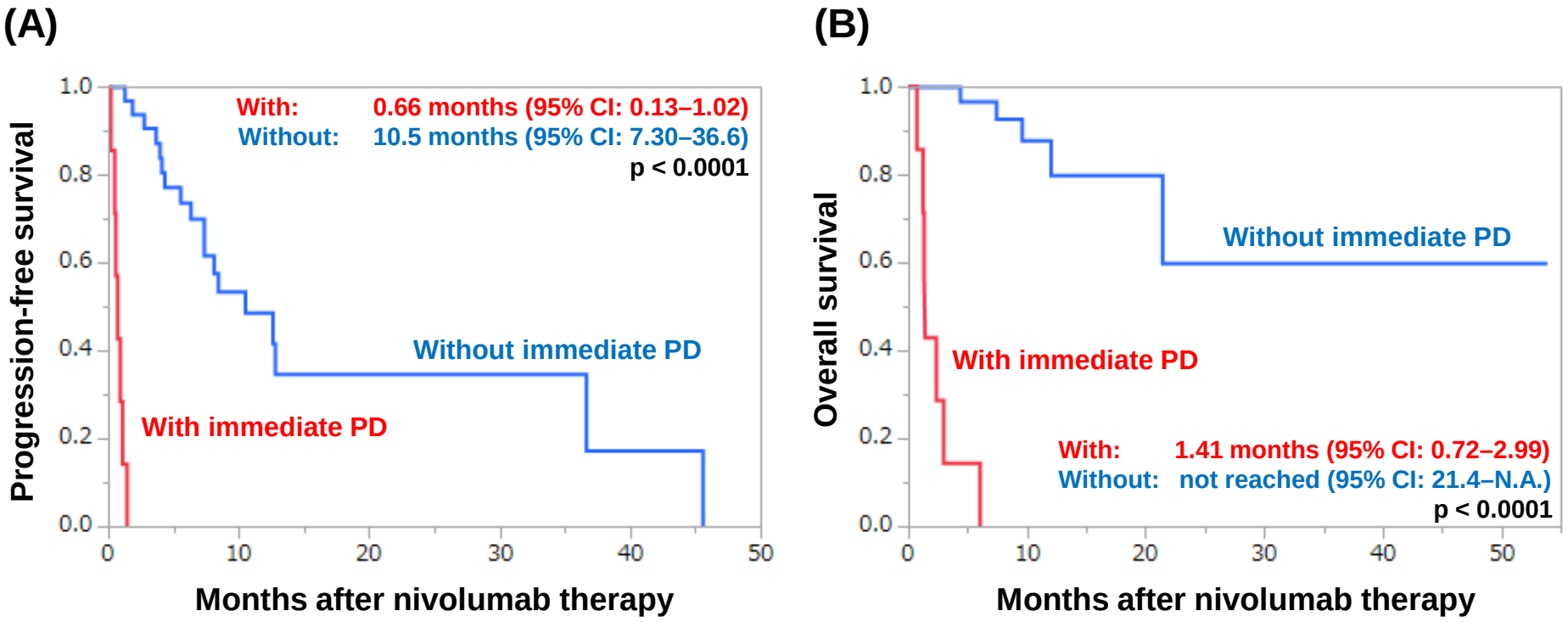

(A)
Progression-free survival
1.0
0.8
0.6
0.4
0.2
0.0
0
10
20
30
40
50
With: 0.66 months (95% CI: 0.13–1.02)
Without: 10.5 months (95% CI: 7.30–36.6)
p < 0.0001
Without immediate PD
With immediate PD
Months after nivolumab therapy
(B)
Overall survival
1.0
0.8
0.6
0.4
0.2
0.0
0
10
20
30
40
50
Without immediate PD
With immediate PD
With: 1.41 months (95% CI: 0.72–2.99)
Without: not reached (95% CI: 21.4–N.A.)
p < 0.0001
Months after nivolumab therapy

Figure 1

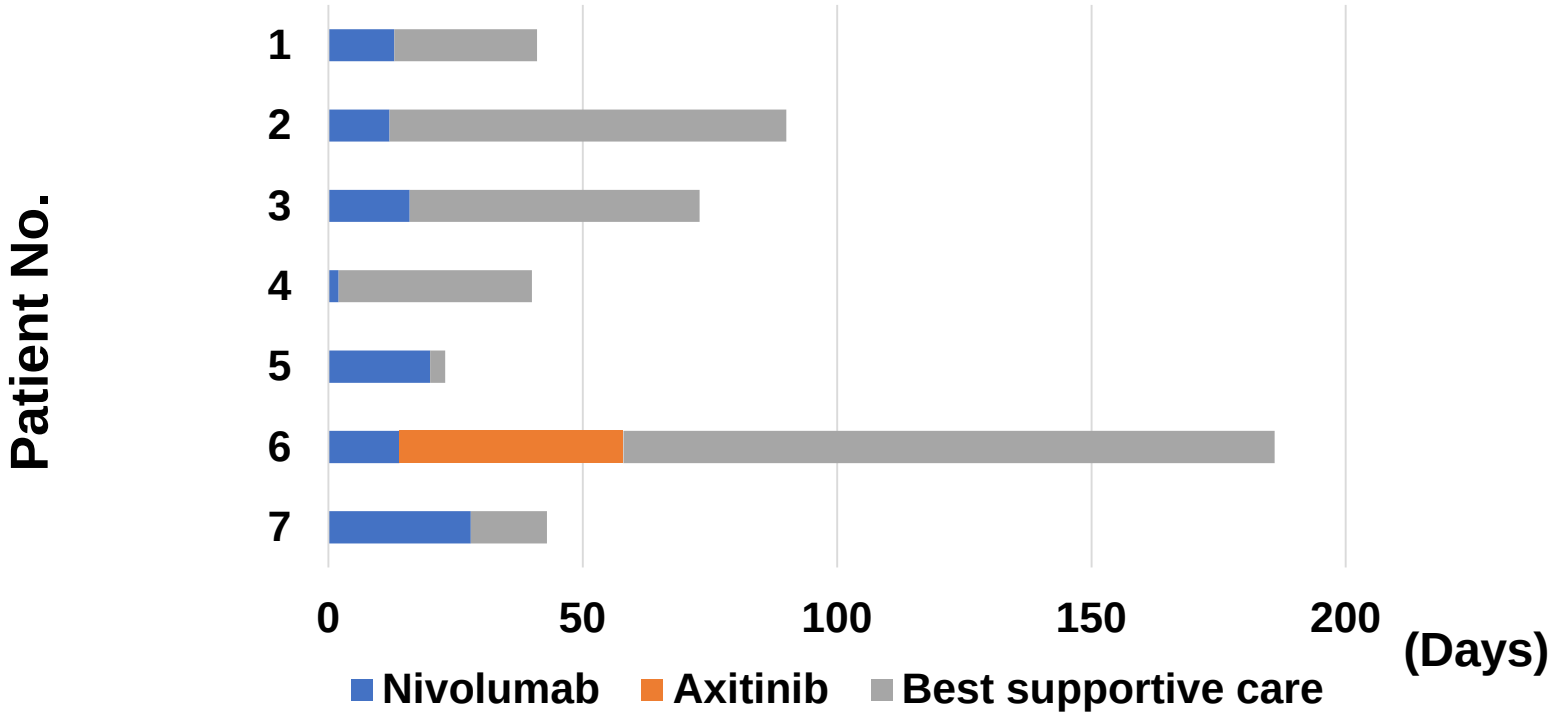

Patient No.
1
2
3
4
5
6
7
0
50
100
150
200
(Days)
Nivolumab
Axitinib
Best supportive care

Figure 2

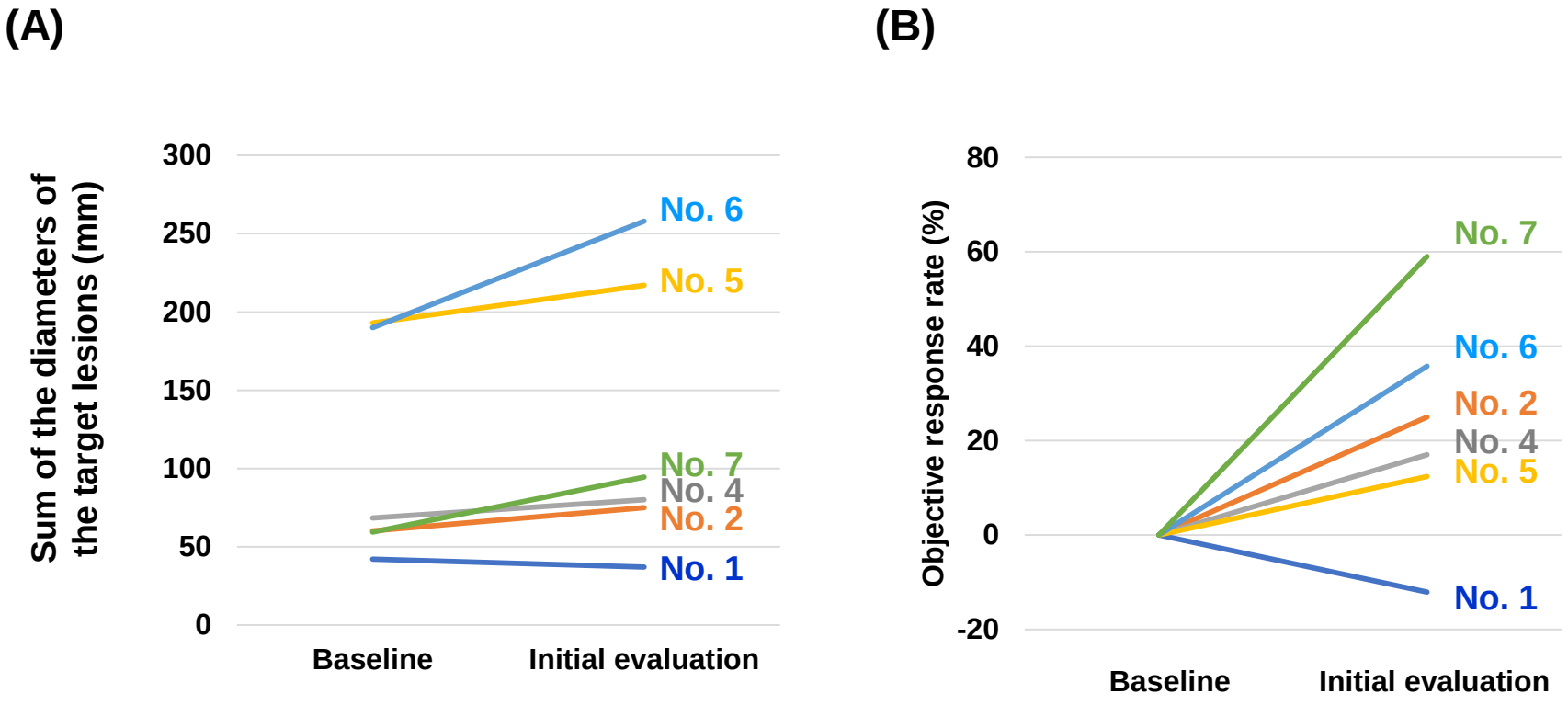
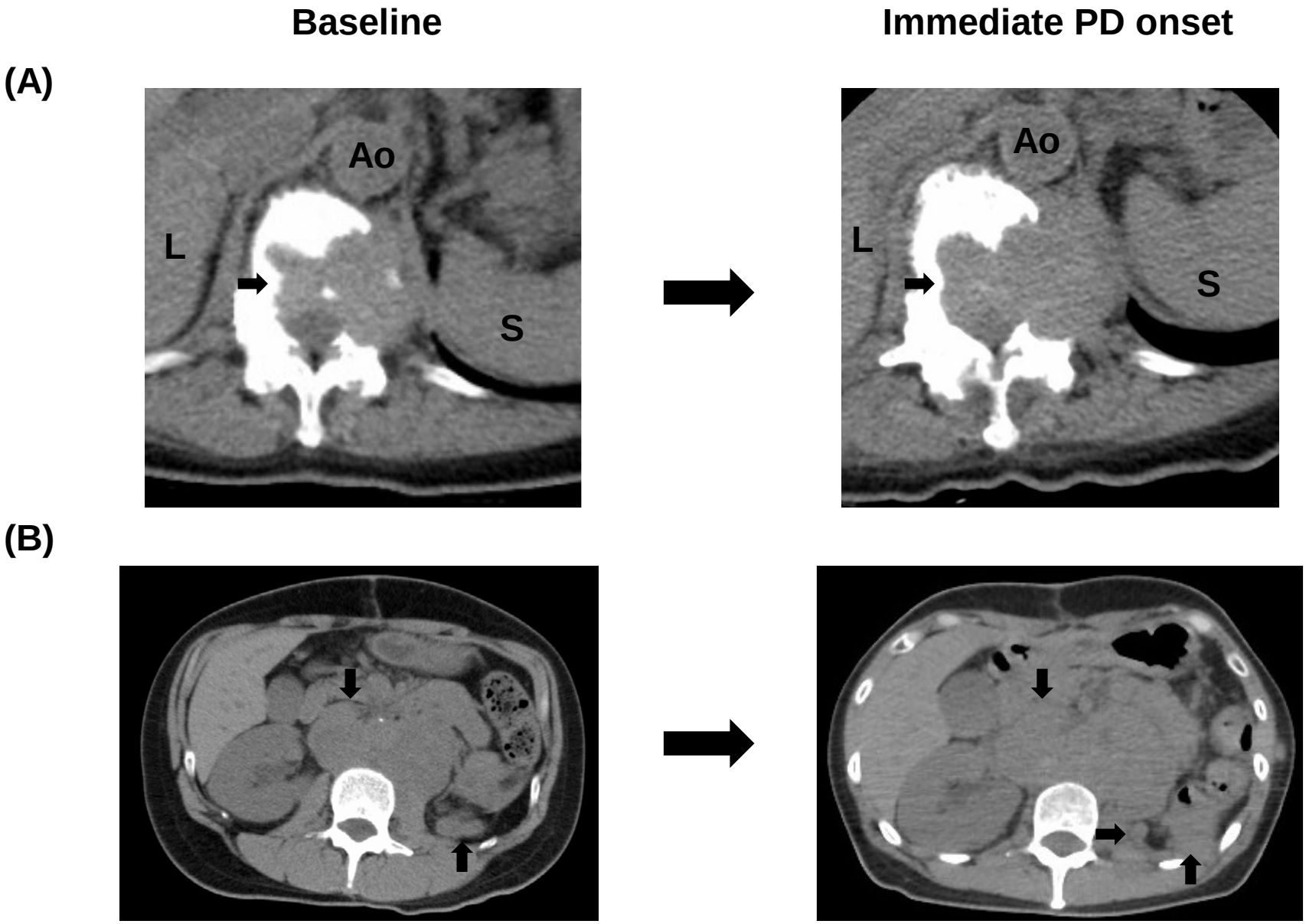

(A)
Sum of the diameters of the target lesions (mm)
300
250
200
150
100
50
0
No. 6
No. 5
No. 7
No. 4
No. 2
No. 1
Baseline
Initial evaluation
(B)
Objective response rate (%)
80
60
40
20
0
-20
No. 7
No. 6
No. 2
No. 4
No. 5
No. 1
Baseline
Initial evaluation

Figure 3



Supplementary Figure 1

Immediate progressive disease after nivolumab therapy in patients with metastatic renal cell carcinoma: a multi-institution study

Targeted Oncology

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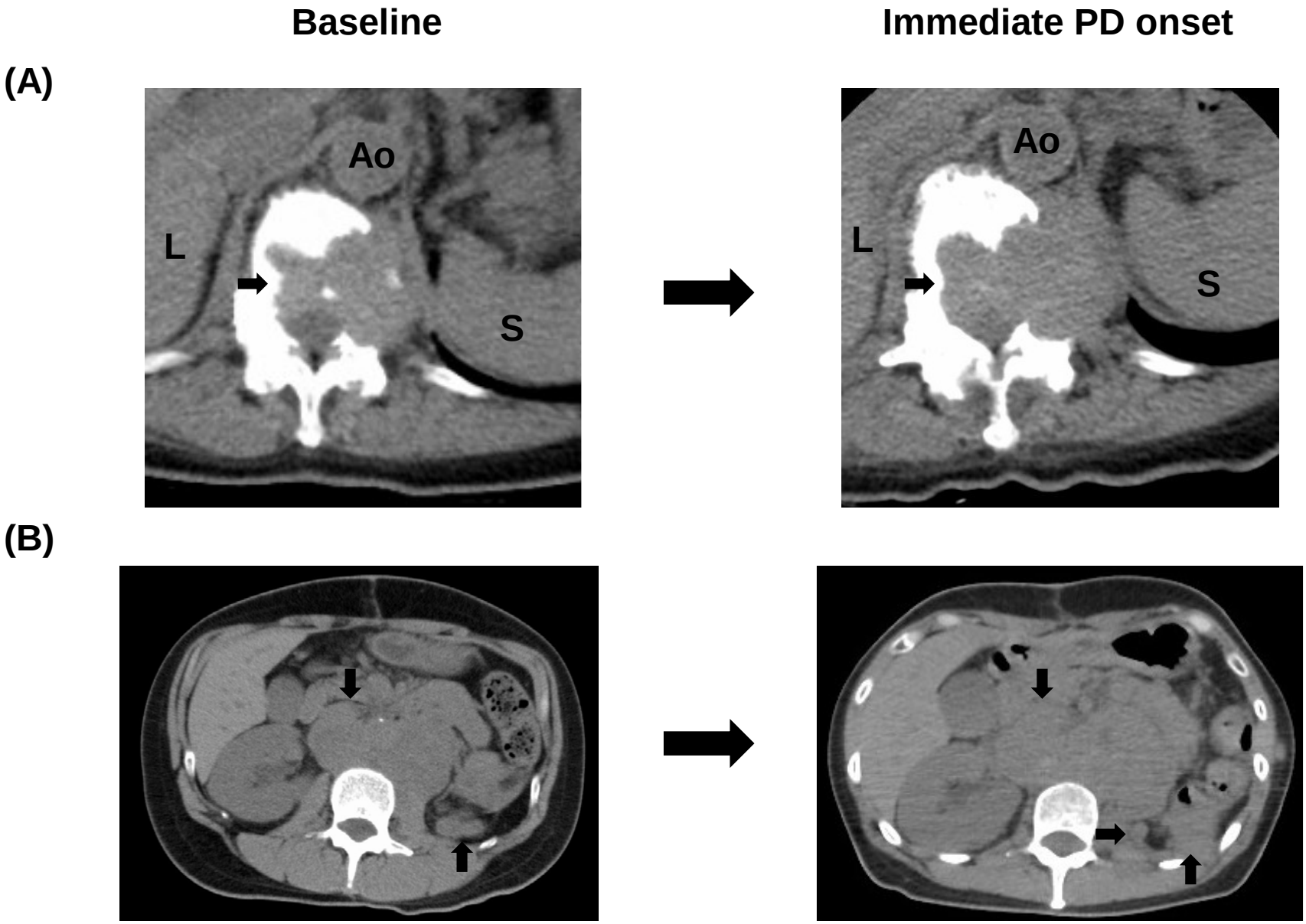

Supplementary Figure 1

Supplementary Figure 1. Representative imaging showing immediate PD in two cases

(A) In patient 2, a spinal metastasis at the first lumbar vertebra grew.

(B) In patient 6, retroperitoneal metastases grew and spread.

Ao, aorta; L, liver; S, spleen.