Oncological outcomes of a multicenter cohort treated with axitinib for metastatic renal cell carcinoma

Takahiro Osawa1 | Takahiro Kojima2 | Tomohiko Hara3 | Mikio Sugimoto4 |
Masatoshi Eto5 | Ario Takeuchi5 | Keita Minami6 | Yasutomo Nakai7 | Kosuke Ueda8 |
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Hiroyuki Nishiyama2 | Nobuo Shinozuka1 | on behalf of the Japanese Urological Oncology Group

1Department of Urology, Hokkaido University Hospital, Sapporo, Japan
2Department of Urology, University of Tsukuba Hospital, Tsukuba, Japan
3Office of Pharmacovigilance II, Pharmaceuticals and Medical Devices Agency, Tokyo, Japan
4Department of Urology, Kagawa University, Takamatsu, Japan
5Department of Urology, Kyushu University, Fukuoka, Japan
6Department of Urology, Sapporo City General Hospital, Sapporo, Japan
7Department of Urology, Osaka International Cancer Institute, Osaka, Japan
8Department of Urology, Kurume University Hospital, Kurume, Japan
9Department of Urology, Faculty of Medicine, Yamagata University, Yamagata, Japan
10Department of Urology, Osaka University Hospital, Suita, Japan
11Department of Urology, Nagasaki University Hospital, Nagasaki, Japan
12Department of Urology, Shinshu University Hospital, Matsumoto, Japan
13Department of Urology, Nara Medical University, Kashihara, Japan
14Department of Urology, Sapporo Medical University, Sapporo, Japan
15Department of Urology, Obihiro Kosei Hospital, Obihiro, Japan
16Department of Urology, Hamamatsu University School of Medicine, Hamamatsu, Japan
17Urology Division, National Cancer Center Hospital, Chuo-ku, Japan
18Department of Urology, Kyoto University, Kyoto, Japan
19Department of Urology, Harasanshin Hospital, Fukuoka, Japan
20Department of Urology, Shizuoka General Hospital, Shizuoka, Japan

Abbreviations: AE, adverse event; ATP, axitinib treatment prediction; AUC, area under the curve; CI, confidence interval; CR, complete response; CRP, C-reactive protein; CT, computerized tomography; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; IO, immune-oncology; IQR, interquartile range; LDH, lactate dehydrogenase; LLN, lower limit of normal; MSKCC, Memorial Sloan-Kettering Cancer Center; NCCN, National Comprehensive Cancer Network; NR, not reached; ORR, objective response rate; OS, overall survival; PD, progression of disease; PFS, progression-free survival; PR, partial response; PS, performance status; SD, stable disease; TKI, tyrosine kinase inhibitor; TRIPOD, transparent reporting of a multivariable prediction model for individual prognosis or diagnosis; ULN, upper limit of normal; VEGFR, vascular endothelial growth factor receptor.

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Abstract
The present study aimed to evaluate the efficacy of the real-world use of axitinib and to develop a prognostic model for stratifying patients who could derive long-term benefit from axitinib. This was a retrospective, descriptive study evaluating the efficacy of axitinib in patients with metastatic renal cell carcinoma that had been treated with 1 or 2 systemic antiangiogenic therapy regimens at 1 of 36 hospitals belonging to the Japan Urologic Oncology Group between January 2012 and February 2019. The primary outcome was overall survival (OS). Using a split-sample method, candidate variables that exhibited significant relationships with OS were chosen to create a model. The new model was validated using the rest of the cohort. In total, 485 patients were enrolled. The median OS was 34 months in the entire study population, whereas it was not reached, 27 months, and 14 months in the favorable, intermediate, and poor risk groups, respectively, according to the new risk classification model. The following 4 variables were included in the final risk model: the disease stage at diagnosis, number of metastatic sites at the start of axitinib therapy, serum albumin level, and neutrophil:lymphocyte ratio. The adjusted area under the curve values of the new model at 12, 36, and 60 months were 0.77, 0.82, and 0.82, respectively. The efficacy of axitinib in routine practice is comparable or even superior to that reported previously. The patients in the new model’s favorable risk group might derive a long-term survival benefit from axitinib treatment.

KEYWORDS
axitinib, metastatic, prognostic factor, renal cell carcinoma, risk model

INTRODUCTION
The NCCN recommends sunitinib, pazopanib, cabozantinib, nivolumab plus ipilimumab, or axitinib plus pembrolizumab as first-line treatments for advanced or metastatic renal cell carcinoma. However, almost all patients eventually become resistant to these drugs and show progression during first-line treatment. The recommended postprogression treatment options include axitinib, nivolumab, and more recently, cabozantinib, and lenvatinib plus...
everolimus. Although there are several subsequent therapy options, the information regarding their comparative effectiveness is limited due to a lack of head-to-head comparisons of the efficacy of these drugs against advanced or metastatic kidney cancer after the failure of first-line therapy.

Axitinib, a selective TKI of VEGFR-1, -2, and -3, has been accepted as one of the subsequent treatment options for patients with advanced renal cell carcinoma that have previously been treated with systemic therapy since the pivotal phase III study AXIS trial. The AXIS trial showed that axitinib was more effective than sorafenib against metastatic renal cell carcinoma in the second-line setting (PFS, 6.7 vs 4.7 months; hazard ratio, 0.67; P < .001). Although the AXIS trial and other registration studies established the efficacy and safety of axitinib as a subsequent therapy for metastatic renal cell carcinoma, data regarding its real-world use in the second- or third-line treatment setting are still limited. Recently, immune checkpoint inhibitors, such as programmed cell death-1 Ab, have become promising treatment options. Although this immunotherapy drug induces a durable response in some patients, it is sometimes associated with severe irreversible immune-related AEs. Therefore, the safety of axitinib and its ability to achieve prolonged PFS as a subsequent treatment for metastatic renal cell carcinoma suggest that it could be an important drug, especially if it was given to appropriately selected patients who could expect to achieve long survival. In these circumstances, we could save other effective treatment options, such as immune checkpoint inhibitors, for subsequent, and possibly extended, phases of treatment. From this point of view, there are still unmet needs with regard to the data available about the post-VEGFR-TKI monotherapy treatment outcomes of kidney cancer patients from outside of clinical trials, which would help clinicians to choose appropriate patients who could expect to derive benefit from axitinib therapy.

Until now, IMDC models have been used to allocate patients who were scheduled to receive second-line treatment into favorable, intermediate, and poor risk groups in randomized clinical trials. However, there are several weaknesses with the risk classification system. As for the IMDC model, it was originally developed for patients that were treated with first-line therapy, although it was recently validated for those receiving second-line treatment. Due to the lack of effective predictive markers for choosing appropriate subsequent treatments for kidney cancer, physicians need other clinical guides so that they can ensure that patients will really benefit from the selected therapy.

The first aim of the present study was to evaluate the efficacy of the real-world use of axitinib as a second- or third-line therapy in a Japanese multicenter cohort. Second, we sought to identify pretreatment clinical factors that could affect the prognosis of previously treated metastatic renal cell carcinoma patients. Finally, we aimed to develop and validate a prognostic model that could be used to stratify such patients into appropriate risk groups and identify those patients who could derive a long-term benefit from axitinib therapy.

2 | MATERIALS AND METHODS

2.1 | Patients

We undertook a retrospective, descriptive study to evaluate the efficacy of axitinib in patients with metastatic renal cell carcinoma that had previously been treated with 1 or 2 VEGFR-TKI regimens at 1 of 36 university, public, or private hospitals belonging to the Japan Urologic Oncology Group between January 2012 and February 2019. This study was approved by the institutional review board of each hospital. The approval number was 018-0003 for Hokkaido University Hospital. The patients' background and survival data were retrospectively obtained from medical charts. All patients (n = 590) were aged 20 years or older, had no history of immune checkpoint inhibitor treatment, and started receiving axitinib between January 2012 and December 2016. In addition, we excluded cases without a pathological diagnosis (n = 43) or in which the axitinib treatment period was less than 4 weeks (n = 49). The detailed reasons for discontinuation and any subsequent treatments are shown in Table S1. Of the remaining 498 patients, 13 patients for whom detailed data were missing were also excluded. In total, 485 patients were analyzed in the final cohort. The patient flow is described in Figure 1.

Axitinib was prescribed as recommended, with a starting dose of 5 mg twice daily (10 mg/d). Dose titration was allowed if a patient tolerated the standard dose without suffering AEs. When a patient suffered from an intolerable AE, dose reduction was considered based on the severity of the AE. The severity of AEs was defined based on the Common Terminology Criteria for Adverse Events version 5.0. Among the AEs related to axitinib, those that led to dose reduction or treatment interruption were retrieved during the medical chart review.

As a baseline assessment, patient performance and laboratory data that were obtained just before the start of the axitinib therapy were collected. Laboratory data related to the IMDC system were standardized according to the institutional ULN and LLN. The patients were generally followed up with physical examinations and routine blood tests every 2-4 weeks. Radiographic CT assessments were generally carried out every 3 months, whereas bone scans were not routinely scheduled, but were carried out when clinically indicated. The tumor response was recorded as the percentage of cases that showed a PR or CR during the treatment, according to RECIST version 1.1. The ORR was defined as the percentage of cases that showed a PR or CR during the treatment assessment.

The primary outcome was the OS of metastatic renal cell carcinoma patients that were treated with axitinib after 1 or 2 VEGFR-TKI regimens before the immunotherapy era, which is consistent with the Checkmate 025 study. In addition, we also investigated potential prognostic factors for predicting OS in this cohort (sex, age, disease stage at diagnosis, prior nephrectomy, histology, sarcomatoid features, the number of metastatic sites at the start of axitinib therapy, time interval from initial diagnosis, the number of previous lines of
TKI treatment received before axitinib, the total duration of prior TKI treatment, Karnofsky PS, the neutrophil : lymphocyte ratio, a low hemoglobin level [less than LLN], a high platelet count [greater than ULN], the serum albumin level, a high serum calcium level, a high serum LDH level [>1.5× ULN], and the CRP level). The cut-off value for the neutrophil : lymphocyte ratio, the serum albumin level, and the CRP level were set as their median values. Overall survival was defined as the time from the start of the axitinib therapy to death from any cause. Regarding the calculation of OS, patients that were treated with nivolumab as a subsequent therapy were censored at the time when nivolumab was administered. The reason for this is that we intended to focus on the clinical outcomes of the patients who received molecular targeted therapy before the introduction of IO drugs. Progression-free survival was defined as the time from the start of the axitinib therapy to the first documentation of progression or death. For each outcome, patients with no events of interest were also censored at the date of their last outpatient visit.

2.2 | Statistical analysis

The details of the patients’ baseline characteristics, responses to treatment, and AEs were analyzed. Categorical variables are shown as percentages. Continuous variables are presented as median and interquartile range values. Overall survival and PFS were estimated using the Kaplan-Meier method. We used 4-week landmark survival analysis to remove the bias introduced by patients whose treatment periods were too short. In the exploratory analyses, we evaluated the associations between the patients’ characteristics before administration of axitinib therapy (IMDC risk group [poor, intermediate, or favorable]) and OS.

A total of 485 patients were randomly assigned to the model-development set (n = 242) or the validation set (n = 243) at a 1:1 ratio using a random number generator. First, we undertook univariate analyses of each variable using Cox’s model. Then we chose variables that showed P values of less than .10 in the univariate analyses as candidates for the multivariate model. We undertook a multivariate analysis with the candidate variables, and the variables that displayed P values of less than .05 were selected as independent predictors of OS. Risk scores for the selected variables were then calculated for the patients in the model-development set, who were categorized based on their total scores as favorable, intermediate, or poor risk. Kaplan-Meier survival curves were then calculated for each risk category. Finally, the patients in the validation set were categorized into risk groups based on our new risk model. Comparisons of our model with the IMDC risk model and MSKCC risk model for second-line treatment, respectively, were undertaken using the same steps as were used in our validation process. The ability of our model to predict OS was compared with that of the IMDC model by evaluating the AUC values of time-dependent ROC curves of the prognostic abilities of the predictive models. The AUC values were calculated using SAS version 9.4 (SAS Institute). Other statistical analyses were undertaken using JMP version 14 (SAS Institute), and P values of less than .05 were considered to indicate a statistically significant difference.

The study design and reporting were carried out based on the TRIPOD statement, and the findings of this study were reported according to the TRIPOD guidelines throughout the study period (Table S2).

3 | RESULTS

3.1 | Patients’ characteristics

The patients’ characteristics are shown in Table 1. Four hundred and eighty-five metastatic renal cell carcinoma patients (median follow-up time, 18.0 months [range, 1-72 months]) received axitinib as a second-line (86.8%) or third-line (13.2%) treatment. As shown in Table 1, 76.7% of the patients were male, and 48.7% presented with metastatic disease at diagnosis. In total, 12.2%, 64.3%, and 19.6% were classified as favorable, intermediate, and poor risk, respectively, according to the IMDC risk model. The most prevalent histological type...
| Baseline characteristics | Entire cohort (n = 485) |
|--------------------------|------------------------|
| Age, median (IQR)        | 67 (61-74)             |
| Gender, n (%)            |                        |
| Male                     | 372 (76.7)             |
| Female                   | 113 (23.3)             |
| Stage at diagnosis, n (%)|                        |
| Localized                | 249 (51.3)             |
| Metastatic               | 236 (48.7)             |
| Risk group (IMDC), n (%) |                        |
| Favorable                | 59 (12.2)              |
| Intermediate             | 312 (64.3)             |
| Poor                     | 95 (19.6)              |
| NA                       | 19 (3.9)               |
| Prior nephrectomy, n (%) | 440 (90.7)             |
| Metastasectomy, n (%)    | 100 (22.2)             |
| Histology, n (%)         |                        |
| Clear cell adenocarcinoma| 429 (88.5)             |
| Papillary carcinoma (type 1) | 7 (1.4)           |
| Papillary carcinoma (type 2) | 19 (3.9)           |
| Chromophobe carcinoma    | 10 (2.1)               |
| Others                   | 20 (4.1)               |
| Sarcomatoid feature, n (%) | 43 (8.9)           |
| Number of metastatic sites, n (%) |                  |
| 1                        | 216 (44.5)             |
| 2                        | 139 (28.7)             |
| 3 or more (range, 3-6)   | 130 (26.8)             |
| Site of metastases, n (%)|                        |
| Lung                     | 339 (69.9)             |
| Liver                    | 75 (15.5)              |
| Bone                     | 147 (30.3)             |
| Brain                    | 23 (4.7)               |
| Lymph node               | 137 (28.3)             |
| Adrenal gland            | 27 (5.6)               |
| Pancreas                 | 39 (8.0)               |
| Others                   | 93 (19.2)              |
| Less than 1 y from initial diagnosis | 29 (6.0)   |
| Number of previous lines of TKI treatment before axitinib, n (%) |                 |
| 1 line                   | 421 (86.8)             |
| 2 lines                  | 64 (13.2)              |
| First-line treatment, n (%)|                     |
| Sorafenib                | 115 (23.7)             |
| Sunitinib                | 335 (69.1)             |
| Pazopanib                | 35 (7.2)               |
| Second-line treatment, n (%)|                   |
| Sorafenib                | 21 (32.8)              |
| Sunitinib                | 34 (53.1)              |

(Continues)
3.2 | Outcomes of patients treated with axitinib

The median duration of axitinib therapy was 8 months (Table 2). Initially, 5 mg axitinib was given twice daily to 399 (82.2%) patients. Eighty-three (17.1%) patients started receiving axitinib at a dose that was lower than this recommended dose, and 3 (<1%) patients started receiving axitinib at a dose that was higher than the recommended dose. Dose escalation and reduction were carried out in 65 (13.4%) and 103 (21.2%) patients, respectively, resulting in a mean relative dose intensity of 85.2% throughout this series. At the time of the analysis, 44 patients (9.1%) were still being treated. The main reasons for treatment interruption were PD (67.6%), toxicities (26.8%), CR (2.8%), and other (2.8%). The best response was CR, PR, SD, and PD in 2.3% (n = 11), 19.8% (n = 96), 56.1% (n = 272), and 20.6% (n = 100) of cases, respectively. The median OS was 34 (95% CI, 28-43) months, and the median PFS was 13 (95% CI, 11-16) months (Figure 2). The median OS of the patients treated with axitinib after 1 and 2 VEGFR-TKI regimens was 34 (95% CI, 28-44) months and 31 (95% CI, 17-50) months, respectively (P = .434). Table S3 summarizes the previously reported clinical outcomes of the patients that were treated in the subsequent treatment setting with axitinib and other promising drugs.

The treatment-related AEs that led to dose reduction or treatment interruption are summarized in Table S4. Toxicities of grade 2 or higher occurred in 227 (46.8%) patients, and toxicities of grade 3 or higher occurred in 123 (25.3%) patients. Diarrhea and fatigue were AEs that occurred in more than 10% of the 485 patients. Diarrhea (17.1%) was the most common AE grade 2 or lower. The only other common AE grade 2 or lower was fatigue (13.0%). Similarly, diarrhea (5.4%) was the most common AE grade 3 or higher. The only other common AEs grade 3 or higher was decreased appetite (4.5%).

3.3 | Development of the new ATP model

Table S5 shows the baseline characteristics of all patients, the model-development cohort, and the validation cohort. The following 9 variables showed significance in the univariate analyses (Table 3) and were included in the multivariate model: disease stage at diagnosis, the number of metastatic sites at the start of axitinib therapy, a high calcium level, the CRP level, a low hemoglobin level (<LLN), the serum albumin level, the neutrophil : lymphocyte ratio, prior nephrectomy, and a Karnofsky PS of 80% or lower. Based on the multivariate analysis, 4 adverse variables (disease stage at diagnosis, number of metastatic sites at the start of axitinib therapy, serum albumin level, and neutrophil : lymphocyte ratio) were included in the
model (Table 3). Using these 4 prognostic factors, the model-development cohort (n = 242) was separated into 3 risk groups. Patients with 0-1 adverse factors were included in the favorable risk group (n = 74; 35.4%), in which the median OS was NR (95% CI, 50–NR). Patients with 2 adverse factors were included in the intermediate risk group (n = 62; 29.7%), in which the median OS was 29 (95% CI, 19-50) months. Finally, the patients with 3-4 adverse factors were included in the poor risk group (n = 73; 34.9%), in which the median OS was 11 (95% CI, 9-15) months. The Kaplan-Meier curves for these 3 risk groups are shown in Figure 3. Significant differences in OS (P < .01) were detected among the 3 risk groups.

In the validation cohort (n = 243), 79 (36.7%), 60 (27.9%), and 76 (35.7%) patients were assigned to the favorable, intermediate, and poor risk groups, respectively. Figure 4 shows the Kaplan-Meier curves for these 3 risk groups in the validation cohort. The median OS of the favorable, intermediate, and poor risk groups were NR (95% CI, 50–NR), 27 (95% CI, 19-45) months, and 14 (95% CI, 12-21) months, respectively (P < .001).

Figure 5 shows the Kaplan-Meier curves of OS for all subjects stratified according to the ATP model and IMDC model, respectively. In addition, the median OS values according to the 2 systems are shown in Figure 5. The application of the ATP risk system to the patients that had been stratified according to the IMDC model led to the reclassification of 126 (54.1%) patients. The intermediate risk group accounted for 28.8% and 67.0% of all patients in the ATP model and IMDC model, respectively.

To analyze the accuracy of the OS predictions after the initiation of axitinib treatment, AUC values were calculated for each model (Figure 6). The adjusted AUC values at 12, 36, and 60 months after the initiation of axitinib were 0.77, 0.82, and 0.82, respectively, for the ATP model, and 0.69, 0.67, and 0.56, respectively, for the IMDC model. Thus, the longer the follow-up period was, the more precisely the ATP model predicted prognosis when it was compared with IMDC risk model. In addition, this risk model can also be used to stratify patients into favorable, intermediate, and poor prognosis groups for estimating PFS. The median PFS of the patients with favorable, intermediate, and poor prognoses were 25, 15, and 8 months, respectively (Figure S1). The therapies the patients received following axitinib are shown in Table S6.

4 | DISCUSSION

This study focused on patients that were treated with axitinib after 1 or 2 VEGFR-TKI regimens. The clinical outcomes of these patients were reported, and a new prognostic model for these patients was developed. The median OS of all patients was 34 months, which was comparable with the findings of previous reports (Table S3). In addition, we identified potential prognostic factors for OS, that is, the neutrophil : lymphocyte ratio, serum albumin level, the number of metastases at diagnosis, and the disease stage at diagnosis. Patients that did not show any of these adverse prognostic factors experienced a long-term benefit from axitinib as a second-line or subsequent treatment and showed favorable OS. These findings indicate that axitinib is still active and well tolerated as a second-line or subsequent treatment among metastatic renal cell carcinoma patients that were previously treated with VEGFR-TKI monotherapy.

The results of the present study were comparable with those of the large-cohort AXIS trial. In the current study and the AXIS trial, the median OS of the study population was 34.0 and 20.1 months, respectively, and the median PFS was 13 (95% CI, 11-16) months.
Interestingly, the median OS and PFS values reported in Asian countries were longer than those reported in Europe and North America, despite both groups showing similar ORR (Table S3).

Some of the possible reasons for this include racial differences and differences in health insurance systems.

As reported elsewhere, the clinical response to axitinib therapy was not dependent on the type of first-line VEGFR-TKI therapy given for metastatic renal cell carcinoma. In addition, no significant differences in the effects of treatment were observed between the second-line or third-line settings. This could be due to the low statistical power of this study cohort.

Although direct comparison might be difficult, the target cohort of this retrospective study is similar to that of the median OS, our result was comparable with those of other retrospective cohort studies (median OS, 15.5-29.5 months). Interestingly, the median OS and PFS values reported in Asian countries were longer than those reported in Europe and North America, despite both groups showing similar ORR (Table S3).

Some of the possible reasons for this include racial differences and differences in health insurance systems. As reported elsewhere, the clinical response to axitinib therapy was not dependent on the type of first-line VEGFR-TKI therapy given for metastatic renal cell carcinoma. In addition, no significant differences in the effects of treatment were observed between the second-line or third-line settings. This could be due to the low statistical power of this study cohort.

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**TABLE 3** Univariate and multivariate analyses of overall survival 1-mo landmark analysis with model-development cohort of patients with metastatic renal cell carcinoma treated with axitinib (n = 242)

|                      | Univariate analysis |          | Multivariate analysis |          |
|----------------------|---------------------|----------|-----------------------|----------|
|                      | HR (95% CI)         | P-value  | HR (95% CI)           | P-value  |
| Age (y)              |                     |          |                       |          |
| <67                  | 1.00                | .93      |                       |          |
| ≥67                  | 0.98 (0.68-1.43)    |          |                       |          |
| Gender               |                     |          |                       |          |
| Male                 | 1.00                | .67      |                       |          |
| Female               | 1.10 (0.69-1.69)    |          |                       |          |
| Stage at diagnosis   |                     |          |                       |          |
| Localized            | 1.00 < .01          |          | 1.00 < .01            |          |
| Metastasized         | 2.68 (1.84-3.97)    |          | 2.60 (1.61-4.26)      |          |
| Less than 1 y from initial diagnosis | | | | |
| No                   | 1.00 .06            |          |                       |          |
| Yes                  | 2.17 (0.98-6.17)    |          |                       |          |
| Prior nephrectomy    |                     |          |                       |          |
| Yes                  | 1.00 < .01          |          | 1.00 .12              |          |
| No                   | 3.96 (2.26-6.53)    |          | 1.71 (0.87-3.23)      |          |
| Histology            |                     |          |                       |          |
| Other                | 1.00 .50            |          |                       |          |
| Clear cell carcinoma | 1.27 (0.66-2.84)    |          |                       |          |
| Sarcomatoid feature  |                     |          |                       |          |
| No                   | 1.00 .50            |          |                       |          |
| Yes                  | 1.27 (0.60-2.39)    |          |                       |          |
| No. of metastatic sites at the time of axitinib therapy | | | | |
| 1                    | 1.00 < .01          |          | 1.00 .01              |          |
| 2 or more            | 2.26 (1.53-3.42)    |          | 1.82 (1.11-3.05)      |          |
| Number of previous lines of TKI treatment before axitinib | | | | |
| 1 line               | 1.00 .16            |          |                       |          |
| 2 lines              | 1.45 (0.86-2.32)    |          |                       |          |
| Total duration of prior TKI treatment |          |          |                       |          |
| >7                   | 1.00 .26            |          |                       |          |
| <7                   | 1.24 (0.85-1.79)    |          |                       |          |
| Karnofsky PS         |                     |          |                       |          |
| >80                  | 1.00 < .01          |          | 1.00 .78              |          |
| ≤80                  | 2.26 (1.55-3.32)    |          | 1.07 (0.66-1.75)      |          |

(Continues)
Checkmate 025 trial, in which nivolumab was compared with everolimus. The proportions of the patients that were treated with axitinib after 1 and 2 VEGFR-TKIs in the present study were 87% and 13%, respectively. These values are similar to those seen in the Checkmate 025 study (83% and 17%, respectively). Even though patients who received subsequent immune checkpoint inhibitor treatment were censored in this trial, the patients that were assigned to the favorable and intermediate risk groups displayed better OS (favorable, 64 [44–NR] months; intermediate, 34 [28-50] months) (Figure 5) compared with the patients in the Checkmate 025 trial (favorable, NR; intermediate, 21.8 [18.3–NR] months). Our findings support the idea that selected metastatic renal cell carcinoma patients with favorable prognoses can benefit from axitinib, as the patients with favorable and intermediate risk disease showed comparable OS to the patients that were treated with nivolumab in the Checkmate 025 study.

The most common AEs of grade 3 or higher, or that led to dose reduction or treatment interruption, were diarrhea, fatigue, proteinuria, a decreased appetite, and hand-foot syndrome. Although the most common AE (any grade) in the AXIS trial was hypertension, hypertension was the seventh most common AE in the present study. One of the reasons for this was that blood pressure was appropriately managed, and axitinib was not interrupted or discontinued due to hypertension in the current study. The other reason was that the initial dose of axitinib was carefully reduced in 17% of patients in this real-world setting. The fact that axitinib has a short half-life, which allows patients to easily recover from AEs if the drug is discontinued, and an acceptable toxicity profile support the selection of axitinib as a subsequent therapy for metastatic renal cell carcinoma after VEGFR-TKI therapy.

All 4 of the prognostic factors identified in the present study, the neutrophil : lymphocyte ratio,19,20 the serum albumin level,21 the disease stage at diagnosis,22 and the number of metastatic sites,23 have already been reported in the first-line treatment setting. In particular, the neutrophil : lymphocyte ratio and serum albumin level are both recognized as inflammatory markers. As reported previously, the serum albumin level was one of the Glasgow prognostic factors.24 Recently, the neutrophil : lymphocyte ratio was reported to be associated with the prognosis of metastatic renal cell carcinoma patients that were treated with VEGFR-TKI or immune checkpoint inhibitors.25-27 Regarding the prognostic factors for subsequent therapy for metastatic renal cell carcinoma, the neutrophil : lymphocyte ratio,28 serum albumin level,29 serum LDH level,29 serum CRP level,28-30 and platelet : lymphocyte ratio28 have been identified as prognostic markers. However, the model-development cohorts for these studies consisted of heterogenous populations, which included patients that had received a variety of treatments, including VEGFR-TKIs and mTOR inhibitors. Some previous studies that focused on the subsequent treatment of metastatic renal cell carcinoma with axitinib identified the serum CRP level,8 prior nephrectomy,6 age at the time of diagnosis, clear cell histology, and the number of metastatic sites7 as significant predictors of OS.

One of the advantages of the present risk model is its objectivity. Unlike other conventional risk models, such as the IMDC risk model,11 the present risk model does not include subjective PS variables. Another advantage is that almost equal proportions of the study population were assigned to the favorable, intermediate, and poor risk groups by the present ATP risk model. As previously reported, it was pointed out by some of the authors that the conventional risk models assign more than half of patients to the
intermediate risk group. Therefore, they tried to optimize the conventional risk models so that they would assign patients to the intermediate risk group more precisely, according to their actual prognoses. As far as we are aware, this is the first risk model developed using a study population that had all received axitinib after 1 or 2 VEGFR-TKI regimens.

**FIGURE 5** Kaplan-Meier curves of overall survival (OS) for the entire study population of patients with metastatic renal cell carcinoma treated with axitinib, stratified using (A) axitinib treatment prediction (ATP) model and (B) International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) model. The median OS of the favorable, intermediate, and poor risk groups were not reached (NR) (95% confidence interval [CI], 58–NR), 27 (95% CI, 21-42) months, and 13 (95% CI, 11-15) months by ATP risk stratification. The median OS of the favorable, intermediate, and poor risk groups were 64 (95% CI, 44–NR), 35 (95% CI, 28-50) months, and 13 (95% CI, 9-15) months by IMDC risk stratification.

**FIGURE 6** Comparison of trends in the area under the curve (AUC) values of time-dependent receiver operating characteristic (ROC) curves (prognostic performance) among the axitinib treatment prediction (ATP) model (disease stage at diagnosis, number of metastatic sites at the start of axitinib therapy, serum albumin level, and neutrophil : lymphocyte ratio) and International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) model. The adjusted AUC values at 12, 36, and 60 mo after the initiation of axitinib were 0.77, 0.82, and 0.82, respectively, for the ATP model, and 0.69, 0.67, and 0.56, respectively, for the IMDC model.
Our study is limited by its retrospective design, selection bias, unmeasured confounding factors, changes in clinical practice patterns over time, and the fact that the cohort was previously treated with VEGFR-TKI monotherapy before the immunotherapy era. Currently, all patients are candidates for first-line immunotherapy including axitinib plus avelumab, axitinib plus pembrolizumab, and nivolumab plus ipilimumab. Although CR rates of the IO drug/VEGFR-TKI combination therapy or IO/IO combination therapy are higher than that of VEGFR-TKI monotherapy, they are still approximately 10%. Accordingly, sequential therapy still plays an important role in improving OS for patients with metastatic renal cell carcinoma. In this viewpoint, this study provides additional data that will help clinicians to identify patients with metastatic renal cell carcinoma who would obtain a long-term benefit from axitinib. Although further studies with a cohort that was treated with IO therapy and longer follow-up times will be needed to validate our model, we expect that the ATP model will be a clinically valuable tool for the risk stratification of first-line or further-line treatment. In the future, analysis of gene expression signatures and further refinement of prognostic biomarkers will enable us to precisely decide optimal treatment regimens for patients.

The results of the present study suggest that 4 factors, the neutrophil : lymphocyte ratio, the serum albumin level, the disease stage at diagnosis, and the number of metastatic sites at the start of axitinib treatment, were identified as potential prognostic factors for OS among metastatic renal cell carcinoma patients that are treated with axitinib in the subsequent treatment setting. Patients without any of these prognostic factors would be assigned to the favorable risk group and would be expected to show favorable OS when treated with axitinib.

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ORCID
Takahiro Osawa https://orcid.org/0000-0003-4444-7958

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SUPPORTING INFORMATION
Additional supporting information may be found online in the Supporting Information section.

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