



Prognostic outcomes in patients with metastatic renal cell carcinoma receiving second-line treatment with tyrosine kinase inhibitor following first-line immune-oncology combination therapy

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Title page

Title: Prognostic outcomes in patients with metastatic renal cell carcinoma receiving second-line treatment with tyrosine kinase inhibitor following first-line immunotherapy combination therapy

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Running title: Second-line TKI following IO combination

Objectives: This study aimed to assess the prognostic outcomes in mRCC patients receiving second-line TKI following first-line IO combination therapy.

Methods: This study retrospectively included 243 mRCC patients receiving second-line TKI after first-line IO combination therapy: nivolumab plus ipilimumab (n = 189, IO-IO group) and either pembrolizumab plus axitinib or avelumab plus axitinib (n = 54, IO-TKI group). Oncological outcomes between the 2 groups were compared, and prognostication systems were developed for these patients.

Results: In the IO-IO and IO-TKI groups, the objective response rates to second-line TKI were 34.4% and 25.9% ($P = 0.26$), the median PFS periods were 9.7 and 7.1 months ($P = 0.79$), and the median OS periods after the introduction of second-line TKI were 23.1 and 33.5 months ($P = 0.93$), respectively. Among the several factors examined, non-CCRCC, high CRP and low albumin levels were identified as independent predictors of both poor PFS and OS by multivariate analyses. It was possible to precisely classify the patients into 3 risk groups regarding both PFS and OS according to the positive numbers of the independent prognostic factors. Furthermore, the c-indices of this study were superior to those of previous systems as follows: 0.75, 0.64, and 0.61 for PFS prediction and 0.76, 0.70, and 0.65 for OS prediction by the present, IMDC and MSKCC systems, respectively.

Conclusions: There were no significant differences in the prognostic outcomes after introducing second-line TKI between the IO-IO and IO-TKI groups, and the histopathology, CRP and albumin levels had independent impacts on the prognosis in mRCC patients receiving second-line TKI, irrespective of first-line IO combination therapies.

Keywords: first-line IO combination therapy, second-line TKI, PFS, OS, risk classification

Introduction

Several first-line systemic therapies remain available for patients with mRCC; however, IO combination therapies, either by IO-IO combination or IO-TKI combinations, have been strongly recommended as the optimal first-line therapy according to major clinical guidelines,^{1, 2} based on the promising outcomes observed in pivotal RCTs, including CheckMate 214 (nivolumab plus ipilimumab),³ KEYNOTE-426 (axitinib plus pembrolizumab),⁴ JAVELIN Renal 101 (axitinib plus avelumab),⁵ CHECKMATE-9ER (cabozantinib plus nivolumab),⁶ and CLEAR (lenvatinib plus pembrolizumab).⁷ In recent years, IO combination therapies have also been widely accepted in routine clinical practice, and several studies have obtained findings similar to the RCTs. For example, a multicenter retrospective study conducted in Japan revealed the favorable outcomes in mRCC patients treated with first-line nivolumab plus ipilimumab: ORR, 38.5%; median PFS, 17 months; and median OS, not reached.⁸ We also reported on mRCC patients receiving axitinib plus pembrolizumab: ORR, 59.6%; median PFS, 18 months; and median OS, not reached.⁹

Although IO combination therapies have been established as the standard first-line therapy for mRCC patients, TKI therapy has recently been introduced to the majority of mRCC patients as a second-line agent, and there is a lack of information regarding the

prognostic outcomes and safety profiles of second-line TKI therapy.¹⁰⁻¹⁴ Considering this limitation, we conducted a retrospective multicenter study including a total of 243 mRCC patients who were treated with first-line IO combination therapy followed by second-line TKI to compare prognostic outcomes of second-line TKI between patients receiving first-line IO-IO and IO-TKI combination therapies and to develop systems to predict prognostic outcomes in these patients.

Methods

Study design

This retrospective multicenter study was conducted under the JUOG framework and approved by the Ethics Committee at Hamamatsu University School of Medicine (No. 22-008), followed by those of all 34 participating institutions in Japan. The need to obtain informed consent was waived because of the retrospective design; however, the ability to opt-out was provided through the websites of all participating institutions.

Patients

This study included a total of 243 Japanese patients who were diagnosed with mRCC and treated with first-line IO combination therapy, followed by second-line TKI therapy, between August 2018 and January 2022, from 34 institutions belonging to the JUOG. Of the 243 patients, 189 received nivolumab plus ipilimumab therapy as a first-line treatment

(IO-IO group), whereas the remaining 54 received either first-line combination therapy with pembrolizumab plus axitinib or avelumab plus axitinib (IO-TKI group).

Evaluation

All of the data examined in this study were obtained from the medical records of each patient. The following clinicopathological characteristics were collected: age, sex, histology, sarcomatoid component, KPS < 80, time to systemic therapy after diagnosis, hemoglobin, corrected calcium, neutrophils, platelets, albumin, CRP, and metastatic organs. In addition, follow-up data on the prognostic and safety outcomes of these patients were also investigated. Considering the baseline data prior to the introduction of second-line TKI, risk classification was performed for each patient using the IMDC system considering anemia, hypercalcemia, neutrophilia, thrombocytosis, KPS < 80, and < 1 year from diagnosis to first-line therapy¹⁵ and MSKCC systems considering anemia, hypercalcemia, and poor performance.¹⁶

Statistical analyses

Statistical analyses were performed using SPSS v28.0 (IBM Corp. Chicago, IL, USA), EZR v1.52 (Saitama Medical Center, Jichi Medical University), and R v4.1.3 (R Foundation for Statistical Computing, <https://www.r-project.org/>), and *P*-values < 0.05 were considered significant. Differences in clinicopathological characteristics between

the IO-IO and IO-TKI groups were compared using Fischer's test. The best response was defined using RECIST v1.1, and the response rate between the 2 groups was compared using Fischer's test. We calculated OS and PFS using the Kaplan–Meier method, and the differences between the 2 groups were compared using the log-rank test. The prognostic impact of clinicopathological factors was assessed by uni and multivariate analyses using the Cox proportional hazards regression model. The c-index was calculated, and the decision curve analyses were performed to compare the accuracy and feasibility of the risk prediction models, as previously described.

Results

The clinicopathological characteristics are shown in Table 1. In the IO-IO group, nivolumab plus ipilimumab therapy was performed in all 189 patients, but 42 received combined treatment with axitinib plus pembrolizumab and 12 received combined treatment with axitinib plus avelumab. The ORR of first-line therapy was higher in the IO-TKI group than in the IO-IO group; however, there were no significant differences in TTF or PF between the two groups. As for the second-line therapy with TKI, the distributions of administered agents between the 2 groups were significantly different; that is, the proportion of patients receiving cabozantinib was markedly higher in the IO-TKI group, and the proportion of patients receiving axitinib was higher in the IO-IO group.

Furthermore, the incidences of time to systemic therapy < 1 year, anemia, hypercalcemia, and thrombocytosis, which are factors considered in the IMDC system, were higher in the IO-IO group than those in the IO-TKI group; therefore, the risk classification using the IMDC system tends to be significantly poorer in the IO-IO group than in the IO-TKI group.

Table 2 summarizes the response status of the second-line TKI therapies according to the first-line IO combination therapies. In the whole cohort, the ORR and DCR were 32.5% and 69.5%, respectively. The ORRs in the IO-IO and IO-TKI groups were 34.4% and 25.9%, and the DCRs were 68.8% and 72.2%, respectively. No significant difference was noted in either the ORRs or DCRs between the 2 groups.

During the observation period after initiation of the second-line TKI therapy (median, 12.2 months), disease progression and overall death occurred in 147 (60.5%) and 94 (38.7%) patients in the whole cohort, 127 (67.2%) and 75 (40.0%) patients in the IO-IO group, and 31 (57.4%) and 19 (35.2%) patients in the IO-TKI group, respectively. In the whole cohort, the median PFS and OS after introducing second-line TKI therapy were 9.3 and 28.2 months, respectively. As shown in Figure 1, there were no significant differences in the PFS (median, 9.7 and 7.1 months in the IO-IO and IO-TKI groups,

respectively) or OS (median, 23.1 and 33.5 months in the IO-IO and IO-TKI groups, respectively) between the 2 groups.

We then examined the impacts of several clinicopathological factors on PFS and OS using uni and multivariate Cox regression hazard analyses (Tables 3 and 4). Univariate analysis identified the following significant prognostic factors: histopathological type, resection of primary lesion, albumin, CRP, IMDC classification, and MSKCC classification for PFS, and histopathological type, presence of sarcomatoid component, resection of primary lesion, albumin, CRP, liver metastasis, bone metastasis, IMDC classification, and MSKCC classification for OS. Of these significant factors, only histopathological type, albumin and CRP were shown to be independently associated with both PFS and OS by multivariate analyses.

To characterize the prognostic features more precisely in this cohort, we divided the patients into the following 3 groups based on the positive number of independent risk factors (histopathological type, albumin and CRP): 70 without risk factors (28.8%, favorable risk group), 80 positive for a single risk factor (32.9%, intermediate risk group), and 93 positive for 2 or 3 risk factors (38.3%, poor risk group). As shown in Figure 2, the median periods of PFS times in the favorable, intermediate, and poor risk groups were 19.5, 9.3, and 4.7 months, and the median periods of OS were not reached, 21.9, and 11.6

months, respectively. There were significant differences in the PFS and OS among these 3 groups. To compare the accuracy of this stratification system with the IMDC and MSKCC prognostication systems for previously treated patients,^{15, 16} we calculated the c-indices of these models at 1 year. For PFS, the c-indices of this study, IMDC, and MSKCC were 0.75, 0.64, and 0.61, and those for OS were 0.76, 0.70, and 0.65, respectively. Moreover, the decision curve analyses showed that the present risk stratification model exhibited a superior net benefit compared with the other models, for both the PFS and OS (Figure 3).

Table 5 shows the profiles of adverse events occurred in $\geq 5\%$ of patients in each group. There were no significant differences in the incidences of AE in any grade or those \geq Grade 3 between the two groups ($P = 0.62$ and 0.86 , respectively). In addition, 36 (19%) and 10 patients (19%) in the IO-IO and IO-TKI groups, respectively, discontinued second-line therapy because of AEs ($P = 1.00$).

Discussions

In recent years, IO combination therapy, either by IO-IO or IO-TKI combination, has been established as a standard first-line treatment for mRCC patients and is widely performed in clinical practice. In addition, detailed characteristics of each IO combination therapy have been clarified based on the findings on RCTs, as well as retrospective

studies.³⁻⁹ Although IO combination therapies have been shown to result in favorable disease control in mRCC patients, the majority of these patients, except for those achieving long-term CR using these combinations, are subsequently treated with TKIs as a second-line therapy. To date, however, limited information is available regarding the clinical outcomes of second-line TKI therapy in mRCC patients receiving first-line IO combination therapy.¹⁰⁻¹⁴ Therefore, this multicenter retrospective study was conducted, including a total of 243 mRCC patients receiving second-line TKI after first-line IO combination therapy. This study aimed to assess the prognostic findings in these patients according to the type of first-line IO combination therapy and to develop a reliable prognostication system after the introduction of second-line TKI therapy.

In this series, more than 75% of the 243 patients received IO-IO combination therapy, and the remaining patients were treated with IO-TKI combination, either using axitinib plus pembrolizumab or axitinib plus avelumab. This distribution of first-line IO combination therapy may reflect the status of the Japanese insurance system regarding IO combination therapy for mRCC during the interval of the present study. However, second-line therapy with TKI appears to be similar to that in current clinical practice; that is, most of the patients in the IO-IO group received axitinib or cabozantinib, whereas those in the IO-TKI group received cabozantinib. These findings suggest the suitability of the current

cohort for investigating prognostic issues associated with second-line TKI therapy following IO-IO combination therapy.

In this study, there were no significant differences in several prognostic indicators, including ORR, DCR, PFS, and OS, between the IO-IO and IO-TKI groups. Despite the lack of previous reports, several studies have revealed various findings on this point. For example, based on the IMDC dataset, Dudani et al. showed that ORR to second-line VEGF-based therapy in mRCC patients receiving IO-IO combination was significantly higher than that in those receiving IO-TKI combination; however, no significant difference in time to treatment failure for second-line VEGF-based therapy was noted between the 2 groups.¹⁷ Barata et al. retrospectively analyzed the efficacies of second-line TKI therapy and reported that there was no significant difference in the ORR or PFS between mRCC patients receiving first-line IO-IO combination and those receiving IO-VEGFR TKI combination therapies.¹⁰ Conflicting findings concerning the differences in the ORR to second-line TKI therapy between the IO-IO and IO-TKI groups may be explained, at least in part, by the recent introduction of cabozantinib into clinical practice, characterized by the ability to inhibit multi-kinases, which may help overcome resistance to previously used TKIs. Considering these findings, currently available second-line TKIs may provide similar disease control in patients receiving first-line IO

combination therapy, irrespective of the regimen. In addition, we compared PFS and OS between the cohorts with and without the introduction of cabozantinib as second-line treatment, and no significant difference in PFS or OS between these two cohorts (data not shown).

It is necessary to determine whether previously established prognostication systems, such as the IMDC and MSKCC systems,^{15, 16} can be applied to mRCC patients receiving second-line TKI therapy after first-line IO combination therapy. To address this problem, we initially attempted to identify factors closely associated with the prognostic outcomes and found that histopathological type, CRP and albumin levels, but not the classification by the IMDC or MSKCC systems, had independent impacts on both PFS and OS in patients receiving second-line TKIs. To date, there have been several studies showing the effectiveness of the IMDC and MSKCC systems as prognostic predictors of mRCC patients receiving systemic therapies in the era of IO drugs, including IO combination therapy.^{18, 19} For example, the IMDC system was shown to continue to stratify the risk of mRCC patients treated with first-line IO combination therapy using the IMDC database.¹⁸ Despite the lack of independent impact, the classifications of the IMDC and MSKCC systems were also significantly correlated with both the PFS and OS in the present series; however, as described above, histopathological type, the CRP and albumin

levels were more strongly correlated with the PFS and OS in this study. Prognostication systems based on the positive numbers of independent risk factors, namely non-CCRCC, high CRP and low albumin levels, were shown to predict the PFS and OS in mRCC patients receiving second-line TKI therapy more accurately than the conventional IMDC and MSKCC systems. In fact, the prediction system for both PFS and OS developed in this study could be regarded as acceptable in both PFS and OS according to the previously reported criteria.²⁰

Incidences of AEs in the present study were comparatively low compared with those in previous prospective studies, such as AXIS trial²¹ and METEOR trial,²² because retrospective study is likely to have a limited ability to accurately capture AEs. However, discontinuation rate due to AEs in this study was not different from that of a previous retrospective report by Shah et al.¹³ Accordingly, second-line TKIs could be continued under acceptable risk of AEs in Japanese real-world practice.

Notably, there were several limitations in the present study. First, this was a retrospective study that included an insufficient number of patients, particularly those treated with first-line IO-TKI combination therapy. In addition, owing to the study period, patients who received combined therapy with cabozantinib plus nivolumab and with lenvatinib plus pembrolizumab were not included. Second, there were no strict criteria

for several issues related to systemic therapies, such as the selection of agents in each line of therapy or the schedule of follow-up examinations. Third, there were significant imbalances in several baseline features between the IO-IO and IO-TKI groups when interpreting the outcomes of this study. Fourth, the selection bias exists in this study; that is, this series consisted of only patients who received second-line TKI therapy, indicating that patients who could not receive second-line therapy because of rapid progression on first-line therapy or who showed long-term response to first-line therapy were not included. Finally, the findings presented in this study have not been validated using data from other cohorts.

In conclusion, we conducted a retrospective multicenter study including a total of 243 Japanese patients with mRCC who received first-line IO combination therapy followed by second-line TKI therapy, and we analyzed the prognostic outcomes in these patients after the introduction of TKIs. There were no significant differences in several prognostic factors, including ORR, DCR, PFS, and OS, between the IO-IO and IO-TKI groups. In the entire cohort, only histopathological type, high CRP and low albumin levels were identified as independent predictors of poor PFS and OS. Furthermore, we developed prognostication systems by classifying the patients into 3 groups according to the positive numbers of these 3 independent risk factors, which provided a simple and

acceptable system that was superior to the conventional IMDC and MSKCC systems in predicting both PFS and OS.

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Author contributions

Yuto Matsushita, Takahiro Kojima, Hideaki Miyake, and Hiroshi Kitamura contributed to the study conception and design. Data collection and analysis were performed by Yuto Matsushita, Takahiro Kojima, Takahiro Osawa, Tomokazu Sazuka, Shingo Hatakeyama, Keisuke Goto, Kazuyuki Numakura, Kazutoshi Yamana, Shuya Kandori, Kazutoshi

Fujita, Kosuke Ueda, Hajime Tanaka, Masayuki Takahashi, Toshifumi Kurahashi, Yukari Bando, Naotaka Nishiyama, Takahiro Kimura, and Shimpei Yamashita. The first draft of the manuscript was written by Yuto Matsushita and Hideaki Miyake, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Disclosure

Conflict of interest

Takahiro Osawa received honoraria from Takeda and Ono. Tomokazu Sazuka received honoraria from Takeda and BMS. Shingo Hatakeyama received honoraria from MSD.

Kazutoshi Fujita received honoraria from Ono, Bristol, MSD, Pfizer, Merck, and Takeda and grant from Pfizer. Hajime Tanaka received honoraria from MSD. Hiroshi Kitamura received honoraria from Bristol, Merck, MSD, and Takeda. Hideaki Miyake received honoraria from Takeda and MSD. The other authors declare no conflicts of interest.

Approval of the research protocol by an Institutional Reviewer Board

This study was approved by the Ethics Committee at Hamamatsu University School of Medicine (No. 22-008).

Informed Consent

The need to obtain informed consent was waived because of the retrospective design; however, the ability to opt-out was provided through the websites of all participating institutions.

Registry and the Registration No. of the study

N/A.

Animal Studies

N/A.

Data Availability Statement

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Abbreviations & Acronyms

mRCC = metastatic renal cell carcinoma

IO = immuno-oncology

TKI = tyrosine kinase inhibitor

RCT = randomized controlled trial

ORR = objective response rate

OS = overall survival

PFS = progression-free survival

JUOG = Japanese Urological Oncology Group

KPS = Karnofsky performance status

CRP = C-reactive protein

IMDC = International Metastatic Renal Cell Carcinoma Database Consortium

MSKCC = Memorial Sloan Kettering Cancer Center

c-index = concordance index

DCR = disease control rate

TTF = time to treatment failure

AE = adverse event

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Figure legends

Figure 1 Kaplan–Meier curves in the IO-IO and IO-TKI groups and the *P*-values calculated using the log-rank test between the 2 groups. **a** PFS: the time from initiation of second-line TKI therapy to disease progression or overall death. **b** OS: the time from initiation of second-line TKI therapy to overall death.

Figure 2 Risk stratification according to CRP and albumin levels. Kaplan–Meier curves and the *P*-values calculated using the log-rank test to compare the risk groups. The number of patients in each risk group is indicated. **a** PFS. **b** OS.

Figure 3 The decision curve analysis of PFS and OS, comparing the risk model proposed in this study with the IMDC and MSKCC models. **a** PFS. **b** OS.

Table 1 The characteristics at the time of second-line TKI therapy initiation

Variables		IO-IO group N = 189	IO-TKI group N = 54	P-value
First-line therapy	Ipilimumab + Nivolumab	189	-	
	Pembrolizumab + Axitinib	-	42 (78%)	
	Avelumab + Axitinib	-	12 (22%)	
ORR of first-line therapy		22.8%	42.3%	0.008 [†]
Median TTF of first-line therapy		4.96 months	4.86 months	0.72 ^{††}
Median PFS of first -line therapy		6.21 months	7.20 months	0.50 ^{††}
Second-line therapy	Cabozantinib	73 (38.6%)	45 (83.3%)	< 0.001 [†]
	Axitinib	92 (48.7%)	0 (0%)	
	Pazopanib	16 (8.5%)	7 (13.0%)	
	Sunitinib	8 (4.2%)	1 (1.9%)	
	Sorafenib	0 (0%)	1 (1.9%)	
Age	< 70	117 (61.9%)	35 (64.8%)	0.75 [†]
	≥ 70	71 (37.6%)	19 (35.2%)	
Sex	Male	140 (74.1%)	46 (85.2%)	0.10 [†]
	Female	49 (25.9%)	8 (14.8%)	
Resection of primary lesion	Yes	104 (55.0%)	39 (72.2%)	0.028 [†]
	No	85 (45.0%)	15 (27.8%)	
Histology	CCRCC	140 (74.1%)	42 (77.8%)	< 0.001 [†]
	non-CCRCC	47 (24.9%)	6 (11.1%)	
	unknown	2 (1.1%)	6 (11.1%)	
Sarcomatoid component	Yes	19 (10.1%)	6 (11.1%)	0.80 [†]
	No or unknown	170 (89.9%)	48 (88.9%)	
KPS	≥ 80	166 (87.8%)	50 (92.6%)	0.46 [†]
	< 80	23 (12.2%)	4 (7.4%)	
Time to systemic therapy	< 1 year	147 (77.8%)	27 (50.0%)	< 0.001 [†]
	≥ 1year	42 (22.2%)	27 (50.0%)	
Hemoglobin	≥ LLN	62 (32.8%)	27 (50.0%)	0.025 [†]
	< LLN	127 (67.2%)	27 (50.0%)	
Serum corrected calcium	> ULN	11 (5.8%)	10 (18.5%)	0.010 [†]
	≤ ULN	179 (94.7%)	44 (81.5%)	
Neutrophils	> ULN	42 (22.2%)	10 (18.5%)	0.71 [†]

	≤ ULN	147 (77.8%)	44 (81.5%)	
Platelets	> ULN	40 (21.2%)	4 (7.4%)	0.026 [†]
	≤ ULN	149 (78.8%)	50 (92.6%)	
Serum albumin (g/dl)	≥ 3.5	111 (58.7%)	37 (68.5%)	0.52 [†]
	< 3.5	78 (41.3%)	17 (31.5%)	
CRP (mg/dl)	> 0.5	116 (61.4%)	28 (51.9%)	0.21 [†]
	≤ 0.5	73 (38.6%)	26 (48.1%)	
Lung metastasis	Yes	137 (72.5%)	32 (59.3%)	0.067 [†]
	No	52 (27.5%)	22 (40.7%)	
Liver metastasis	Yes	37 (19.6%)	12 (22.2%)	0.70 [†]
	No	152 (80.4%)	42 (77.8%)	
Bone metastasis	Yes	75 (39.7%)	17 (31.5%)	0.34 [†]
	No	114 (60.3%)	37 (68.5%)	
Brain metastasis	Yes	10 (5.3%)	4 (7.4%)	0.52 [†]
	No	179 (94.7%)	50 (92.6%)	
IMDC classification at second-line treatment	Favorable	15 (7.9%)	12 (22.2%)	0.008 [†]
	Intermediate	110 (58.2%)	31 (57.4%)	
	Poor	64 (33.9%)	11 (20.4%)	
MSKCC classification at second-line treatment	Favorable	55 (29.1%)	21 (38.9%)	0.35 [†]
	Intermediate	99 (52.4%)	26 (48.1%)	
	Poor	35 (18.5%)	7 (13.0%)	

ORR, objective response rate; TTF, time to treatment failure; PFS, progression-free survival; CCRCC, clear cell renal cell carcinoma; KPS, Karnofsky performance status; LLN, lower limit of normal; ULN, upper limit of normal; CRP, c-reactive protein; IMDC, International Metastatic RCC Database Consortium; MSKCC, Memorial Sloan Kettering Cancer Center

[†] Fisher's test

^{††} Log-rank test

Table 2 The response rate of second-line therapy according to the first-line therapy

	IO-IO group N = 189	IO-TKI group N = 54	<i>P</i> -value†
Objective response rate - %	34.4%	25.9%	0.26
Disease control rate - %	68.8%	72.2%	0.74
Best overall response - no. (%)			
Complete response	4 (2.1)	1 (1.9)	
Partial response	61 (32.3)	13 (24.1)	
Stable disease	65 (34.4)	25 (46.3)	
Progressive disease	42 (22.2)	10 (18.5)	
Not available	17 (9.0)	5 (9.3)	

†Fisher's test

Table 3 Cox regression analysis of PFS

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	<i>P</i> -value	HR (95% CI)	<i>P</i> -value
Age (years) (< 70 vs. ≥ 70)	1.10 (0.80 – 1.52)	0.56	-	-
Sex (Male vs. Female)	1.25 (0.88 – 1.77)	0.22	-	-
Histopathological type (CCRCC vs. non-CCRCC)	2.07 (1.46 – 2.94)	< 0.001	2.12 (1.47 – 3.07)	< 0.001
Sarcomatoid component (Yes vs. No)	1.51 (0.91 – 2.50)	0.11	-	-
Resection of primary lesion (Yes vs. No)	0.70 (0.51 – 0.96)	0.029	0.95 (0.68 – 1.33)	0.75
First-line therapy (IO-IO vs. IO-TKI)	1.05 (0.71 – 1.56)	0.80	-	-
Albumin (g/dl) (< 3.5 vs. ≥ 3.5)	2.40 (1.74 – 3.31)	< 0.001	1.52 (1.00 – 2.31)	0.048
CRP (mg/dl) (≤ 0.5 vs. > 0.5)	2.87 (2.03 – 4.06)	< 0.001	2.29 (1.56 – 3.35)	< 0.001
Lung metastasis (Yes vs. No)	1.26 (0.89 – 1.80)	0.20	-	-
Liver metastasis (Yes vs. No)	1.43 (0.99 – 2.09)	0.060	-	-
Bone metastasis (Yes vs. No)	1.23 (0.90 – 1.70)	0.20	-	-
Brain metastasis (Yes vs. No)	0.93 (0.47 – 1.82)	0.83	-	-
IMDC classification at second-line treatment (Favorable plus Intermediate vs. Poor)	2.07 (1.48 – 2.88)	< 0.001	1.13 (0.69 – 1.83)	0.63
MSKCC classification at second-line treatment (Favorable plus Intermediate vs. Poor)	2.31 (1.57 – 3.39)	< 0.001	1.22 (0.69 – 2.14)	0.50

IO, immune-oncology; TKI, tyrosine kinase inhibitors; CCRCC, clear cell renal cell carcinoma; CRP, c-reactive protein; IMDC, International Metastatic RCC Database Consortium; MSKCC, Memorial Sloan Kettering Cancer Center

Table 4 Cox regression analysis of OS

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	<i>P</i> -value	HR (95% CI)	<i>P</i> -value
Age (years) (< 70 vs. ≥ 70)	1.26 (0.83 – 1.91)	0.28	-	-
Sex (Male vs. Female)	1.49 (0.97 – 2.29)	0.071	-	-
Histopathological type (CCRCC vs. non-CCRCC)	1.97 (1.29 – 3.03)	0.002	1.83 (1.16 – 2.89)	0.010
Sarcomatoid component (Yes vs. No)	1.83 (1.02 – 3.29)	0.044	1.62 (0.88 – 2.99)	0.12
Resection of primary lesion (Yes vs. No)	0.55 (0.36 – 0.82)	0.004	0.89 (0.57 – 1.37)	0.59
First-line therapy (IO-IO vs. IO-TKI)	1.02 (0.62 – 1.70)	0.93	-	-
Albumin (g/dl) (< 3.5 vs. ≥ 3.5)	3.10 (2.06 – 4.68)	< 0.001	1.96 (1.17 – 3.27)	0.010
CRP (mg/dl) (≤ 0.5 vs. > 0.5)	3.58 (2.19 – 5.83)	< 0.001	2.41 (1.41 – 4.14)	0.001
Lung metastasis (Yes vs. No)	1.06 (0.68 – 1.65)	0.81	-	-
Liver metastasis (Yes vs. No)	1.65 (1.03 – 2.65)	0.036	1.45 (0.88 – 2.38)	0.14
Bone metastasis (Yes vs. No)	1.50 (1.00 – 2.26)	0.049	1.30 (0.85 – 2.00)	0.22
Brain metastasis (Yes vs. No)	1.02 (0.45 – 2.35)	0.96	-	-
IMDC classification at second-line treatment (Favorable plus Intermediate vs. Poor)	2.65 (1.76 – 4.00)	< 0.001	1.26 (0.70 – 2.29)	0.44
MSKCC classification at second-line treatment (Favorable plus Intermediate vs. Poor)	2.84 (1.79 – 4.50)	< 0.001	1.02 (0.52 – 1.98)	0.96

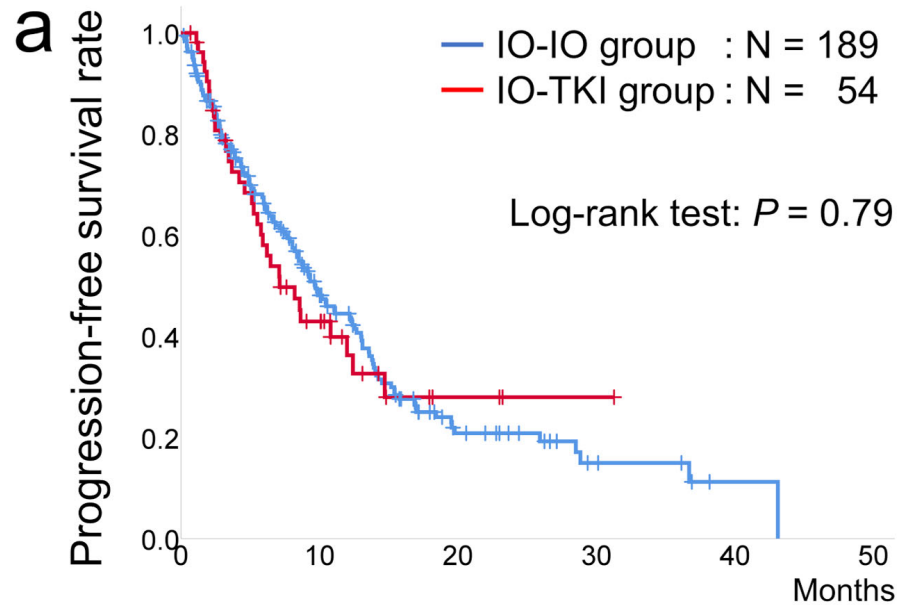
IO, immune-oncology; TKI, tyrosine kinase inhibitors; CCRCC, clear cell renal cell carcinoma; CRP, c-reactive protein; IMDC, International Metastatic RCC Database Consortium; MSKCC, Memorial Sloan Kettering Cancer Center

Table 5 The profile of adverse events according to first line therapy

Event – no. (%)	IO-IO group N = 189		IO-TKI group N=54	
	Any grade	Grade ≥ 3	Any grade	Grade ≥ 3
All events	128 (67.7)	48 (25.4)	34 (63.0)	15 (27.8)
Fatigue	28 (14.8)	6 (3.2)	3 (5.6)	1 (1.9)
Diarrhea	25 (13.2)	4 (2.1)	10 (18.5)	1 (1.9)
Hypertension	21 (11.1)	7 (3.7)	6 (11.1)	3 (5.6)
Palmar-plantar erythrodysesthesia	20 (10.6)	3 (1.6)	9 (16.7)	2 (3.7)
AST/ALT elevation	18 (9.5)	8 (4.2)	9 (16.7)	4 (7.4)
Anorexia	16 (8.5)	3 (1.6)	1 (1.9)	0 (0.0)
Hypothyroidism	14 (7.4)	2 (1.1)	0 (0.0)	0 (0.0)
Stomatitis	14 (7.4)	1 (0.5)	1 (1.9)	1 (1.9)

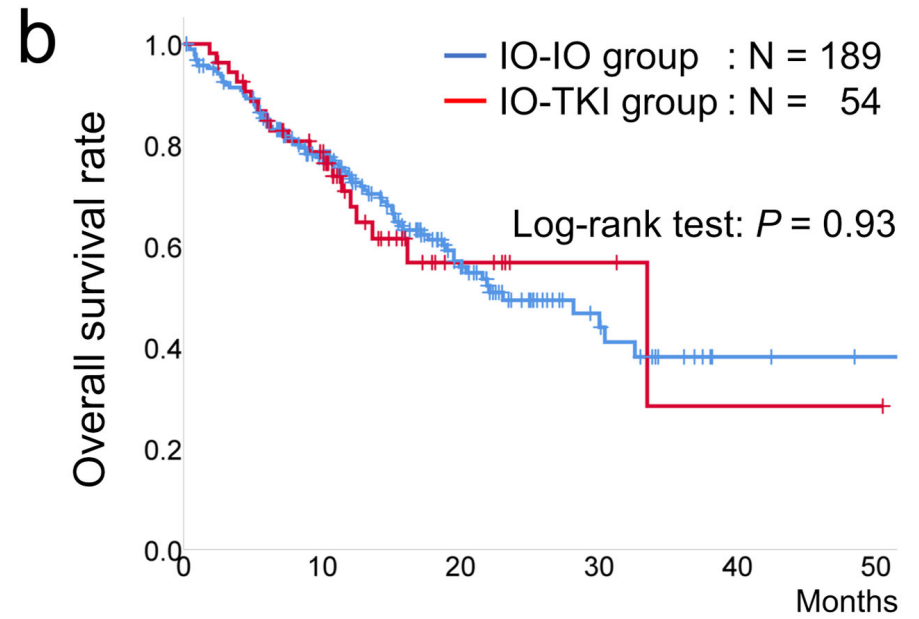
IO, immune-oncology; TKI, tyrosine kinase inhibitors

Figure 1



Number at risk

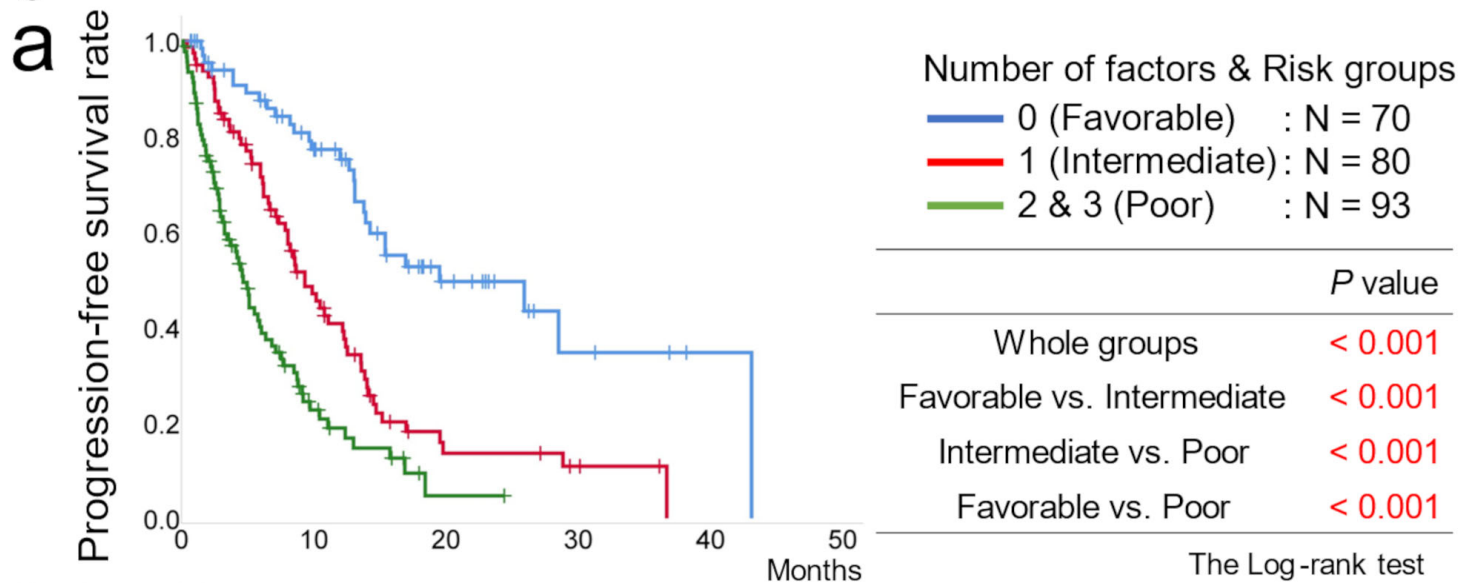
IO-IO group	189	70	19	6	1	0
IO-TKI group	54	18	3	1	0	0



Number at risk

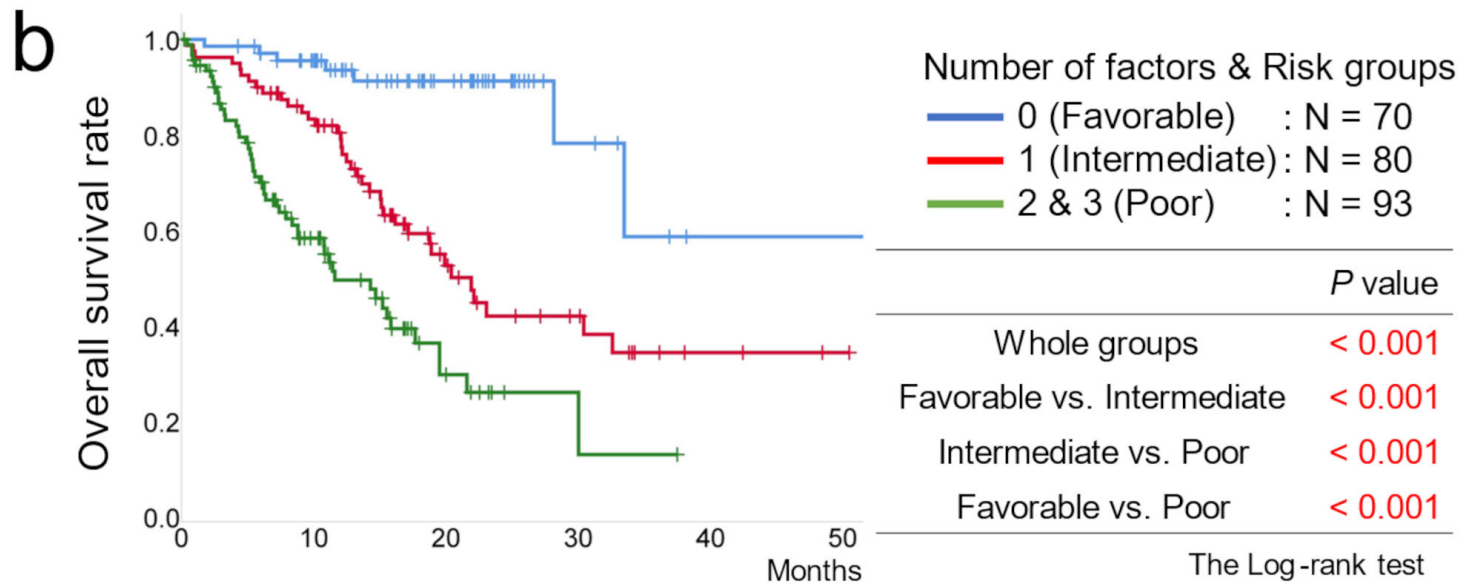
IO-IO group	189	120	50	17	3	1
IO-TKI group	54	36	8	3	1	1

Figure 2



Number at risk

	0	10	20	30	40	50
Favorable	70	44	15	4	1	0
Intermediate	80	31	6	3	0	0
Poor	93	13	1	0	0	0

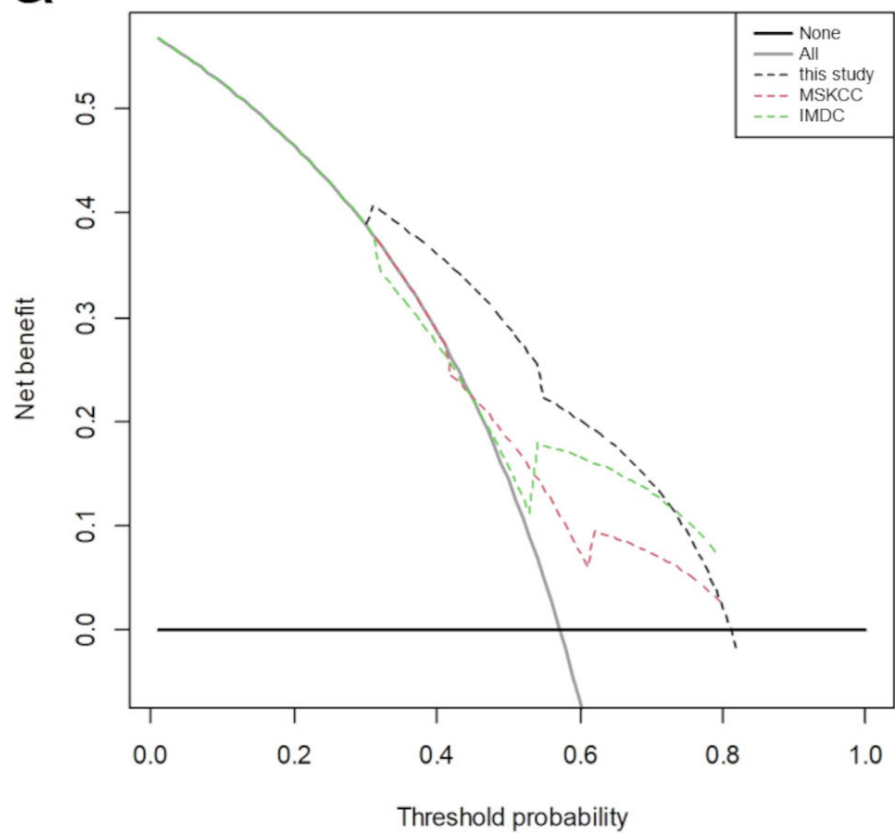


Number at risk

	0	10	20	30	40	50
Favorable	70	57	27	6	1	1
Intermediate	80	61	22	12	3	1
Poor	93	38	9	2	0	0

Figure 3

a



b

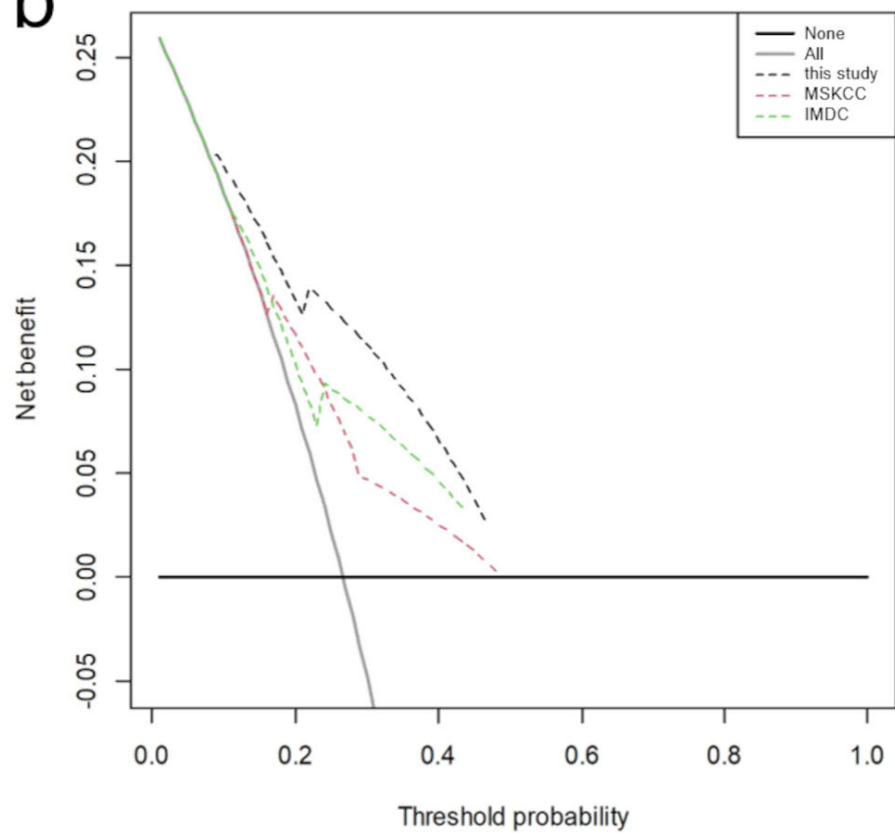
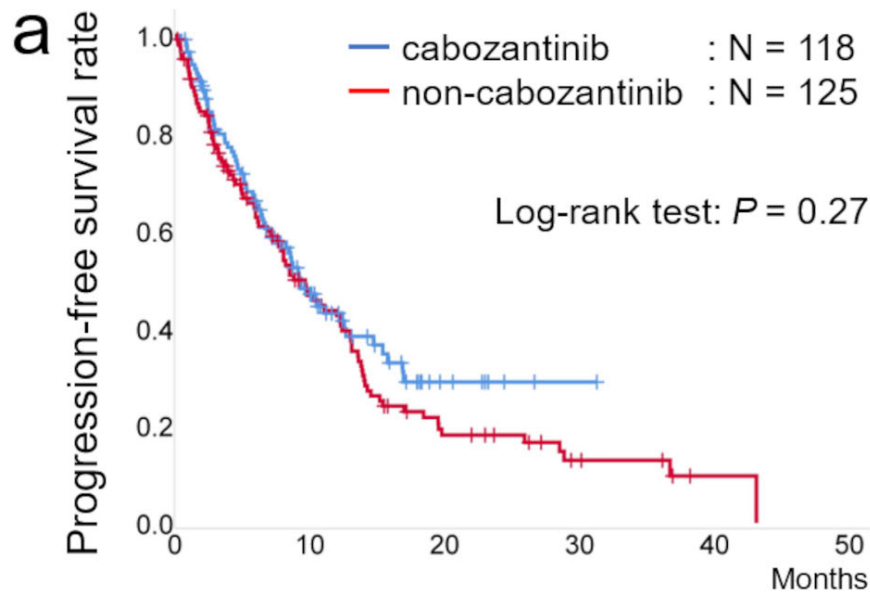
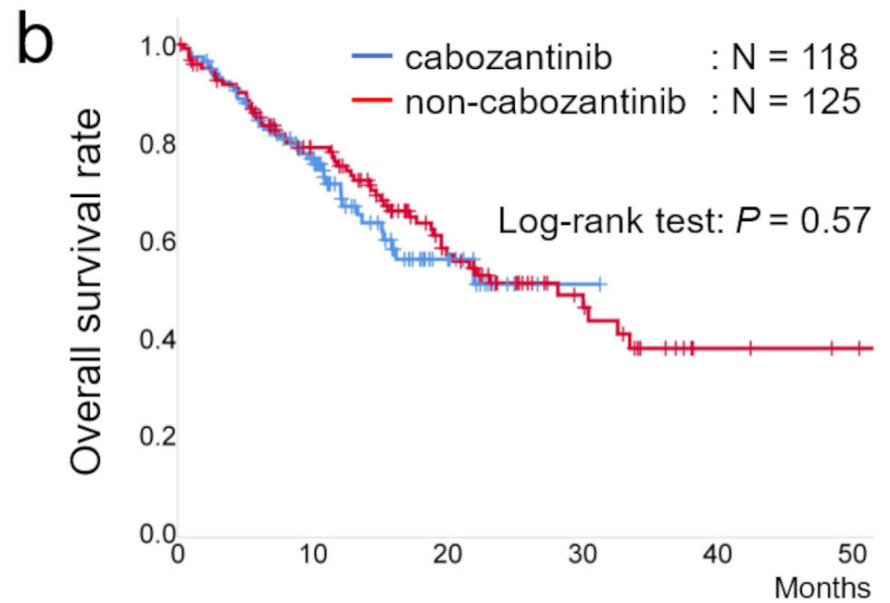


Figure 4



Number at risk

cabozantinib	118	43	7	1	0	0
non-cabozantinib	125	45	15	6	1	0



Number at risk

cabozantinib	118	72	16	1	0	0
non-cabozantinib	125	84	42	19	4	2