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Impact of high relative dose intensity on effectiveness and treatment continuity of IO-TKI therapy in Japanese advanced renal cell carcinoma

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Abstract

This study investigated the impact of relative dose intensity (RDI) on the effectiveness and safety of immuno-oncology plus tyrosine kinase inhibitor (IO-TKI) therapy in Japanese patients with renal cell carcinoma (RCC). A total of 145 patients receiving first-line treatment were analyzed: 55 received IO-TKI therapy and 90 received immuno-oncology combination (IO-IO) therapy. Patients in the IO-TKI group were divided based on an RDI threshold of 80% into high- and low-RDI groups. Median progression-free survival (mPFS) was significantly longer in the IO-TKI group compared to the IO-IO group ($P < 0.05$), while no significant difference in median overall survival (mOS) was observed ($P = 0.53$). Interestingly, the mOS tended to be shorter in the IO-TKI high-RDI group than in the IO-TKI low-RDI ($P = 0.05$) and IO-IO groups ($P = 0.13$). Moreover, treatment discontinuation due to adverse effects occurred earlier in the IO-TKI high-RDI group ($P < 0.05$). An association was found between RDI ≥80% in IO-TKI therapy, discontinuation due to adverse events, and poor prognosis. Careful dose adjustment of TKIs may be necessary to optimize outcomes in Japanese patients with RCC receiving IO-TKI combination therapy.

Keywords

relative dose intensity, immune checkpoint inhibitor, tyrosine kinase inhibitor, renal cell carcinoma, efficacy, adverse event

Introduction

Renal cell carcinoma (RCC) is among the most malignant cancers [1]; however, the situation is gradually improving, with the five-year survival rate increasing to approximately 18 owing to the development of immuno-oncology (IO) therapy [2-7]. Five regimens of IO plus tyrosine kinase inhibitor (IO-TKI) therapy and IO combination (IO-IO) therapy are strongly or weakly recommended by the National Comprehensive Cancer Network as standard first-line therapies for RCC, including pembrolizumab plus axitinib, avelumab

plus axitinib, nivolumab plus cabozantinib, pembrolizumab plus lenvatinib, and ipilimumab plus nivolumab [2-7]. However, evidence to determine whether IO-TKI or IO-IO therapy is the best treatment option is lacking. To address this gap, evidence to select optimal treatments in terms of efficacy and safety should be gathered. Although evidence for IO-IO therapy is accumulating [8-12], that for IO-TKI therapy is lacking, necessitating further studies to complement the evidence for the efficacy of IO-TKI therapy.

Relative dose intensity (RDI), calculated as the ratio of the actual dose to the maximum dose during the planned treatment period, is used to assess the amount of drug administered. RDI is a well-known a simple index associated with chemotherapy efficacy [13, 14]. The association of RDI with the efficacy of TKIs is known [15, 16]. For example, a higher RDI of TKI used as second-line therapy in patients with RCC is associated with higher efficacy [15]. In contrast, patients with a high RDI have a higher blood concentration of TKI, leading to a higher incidence of adverse events (AEs), especially the case in Japanese patients [17-21]. Therefore, it is important to investigate the appropriate RDI range in terms of efficacy and safety among Japanese patients receiving TKIs. However, no report has focused on the association between the RDI of TKI and safety in patients with RCC treated with IO-TKI therapy.

In this study, we examined whether the RDI of TKI affects the efficacy and safety of IO-TKI therapy in Japanese patients with RCC.

Results

Patient characteristics in the IO-TKI and IO-IO groups

The patient characteristics in the IO-TKI (n = 55) and IO-IO (n = 90) groups are summarized in Supplementary Table S1. Treatments administered included pembrolizumab plus axitinib (18.2%, n = 10), avelumab plus axitinib (9.1%, n = 5), nivolumab plus cabozantinib (20.0%, n = 11), and pembrolizumab plus lenvatinib (52.7%, n = 29). Age, sex ratio, body weight, histological subtype, sarcomatoid change, and metastasis site (bone, liver, lung, adrenal glands, lymph nodes) did not differ between the IO-TKI and IO-

IO groups. The ratios of International mRCC Database Consortium risk classification and metastasis site (brain) differed significantly between the IO-TKI and IO-IO groups. The number of death cases was 52 cases in the current study.

Comparison of efficacy between the IO-TKI and IO-IO groups

First, we examined the differences in efficacy between the IO-TKI and IO-IO groups. The best responses in the IO-TKI and IO-IO groups was complete response (CR) in 1.8% (n = 1) and 4.4% (n = 4), partial response (PR) in 58.2% (n = 32) and 37.8% (n = 34), stable disease (SD) in 21.8% (n = 12) and 25.6% (n = 23), and progressive disease (PD) in 3.6% (n = 2) and 27.8% (n = 25) of the patients, respectively (Table 1). The overall response rate (ORR) and disease control rate (DCR) were significantly higher in the IO-TKI group than those in the IO-IO group (ORR: 60.0% vs. 42.2%; DCR: 81.8% vs. 67.8%; $P < 0.05$; Table 1). Although median progression-free survival (mPFS) in the IO-TKI group was significantly longer than that in the IO-IO group (IO-TKI group, not reached vs. IO-IO group, 12.8 months, $P < 0.05$; Figure 1A), the median overall survival (mOS) did not differ between the IO-TKI and IO-IO groups (IO-TKI group, not reached vs. IO-IO group, 47.4 months, $P = 0.53$; Figure 1B).

Association between RDI and clinical outcomes

Next, we examined whether the RDI of TKI, which is the period from initiation to the end of IO-TKI therapy, was associated with prognosis and efficacy. The number of patients who maintained an RDI of 80–100% (n = 26) was the highest, followed by those who maintained an RDI of 40–60% (n = 16), 20–40% (n = 9), 60–80% (n = 3), and 0–20% (n = 1; Figure 2A). We defined RDI 80% as the cut-off and divided the IO-TKI group into two subgroups based on RDI 80% (IO-TKI low-RDI and IO-TKI high-RDI groups). Patient characteristics did not differ between the IO-TKI low-and high-RDI groups (Table 2).

mPFS of the IO-TKI low-RDI group was significantly longer than that of the IO-IO group (not reached

vs. 12.8 months, $P < 0.05$; Figure 2B). The mPFS of the IO-TKI high-RDI group did not differ compared with the IO-TKI low-RDI (not reached vs. not reached, $P = 0.88$; Figure 2B) and IO-IO groups (not reached vs. 12.8 months, $P = 0.81$; Figure 2B). In contrast, the mOS of the IO-TKI low-RDI group did not differ from that of the IO-IO group (not reached vs. 47.4 months, $P = 1.00$; Figure 2C). The mOS of the IO-TKI high-RDI group tended to be shorter than that of the IO-TKI low-RDI (20.0 months vs. not reached, $P = 0.05$; Figure 2C) and the IO-IO groups (20.0 vs. 47.4 months, $P = 0.13$; Figure 2C). We examined the mOS by using the median cutoff (RDI = 77%) and other cutoff (RDI = 50%, 60% and 90%) values of RDI. The mOS at each cutoff was as follows: not reached (IO-TKI RDI <50% group) vs. not reached (IO-TKI RDI 50–100% group; $P = 1.00$); not reached (IO-TKI RDI <60% group) vs. 20.3 months (IO-TKI RDI 60–100% group; $P = 0.11$); not reached (IO-TKI RDI <77% group) vs. 20.0 months (IO-TKI RDI 77–100% group; $P = 0.10$); and not reached (IO-TKI RDI <90% group) vs. 20.0 months (IO-TKI RDI 90–100% group; $P = 0.11$; Supplementary Figures 1–4). Uni- and multivariate cox regression analyses in IO-TKI low-RDI (n = 29), IO-TKI high-RDI (n = 26) or IO-IO (n = 90) groups showed that high RDI was risk factor for shorter OS (univariate cox regression analyses: hazard ratio [HR] = 2.15, 95% confidence interval [CI] = 1.11–4.15, $P < 0.05$; multivariate cox regression analyses: HR = 2.16, 95% CI = 1.04-4.49, $P < 0.05$; Table 3). Univariate cox regression analyses in IO-TKI low-RDI (n = 29) or IO-TKI high-RDI (n = 26) groups also showed that high RDI associated with poor OS (HR = 3.28, 95% CI = 1.14-9.41, $P < 0.05$; Table 4). These data suggested that RDI ≥80% may negatively affect prognosis.

Association between early discontinuation of treatment and high RDI

We examined the association between the incidence of AEs and RDI. The incidence of AEs of any grade in the IO-TKI low-RDI group was higher than that in the IO-TKI high-RDI and IO-IO groups (IO-TKI low-RDI, 96.6%; IO-TKI high-RDI, 73.1%; IO-IO group, 71.1%; Table 5). In contrast, the incidence of grade 3 AEs in the IO-IO group was higher than that in the IO-TKI low-RDI and IO-TKI high-RDI groups

(IO-TKI low-RDI: 27.6%, IO-TKI high-RDI: 19.2%, IO-IO group: 41.1%, Table 5). While the proportion of patients who experienced discontinuation due to PD was highest in the IO-IO group among the three groups (IO-TKI low-RDI, 13.8%; IO-TKI high-RDI, 11.5%; IO-IO group, 51.1%; Table 6), the proportion of patients who experienced discontinuation due to AEs was lowest in the IO-IO group among the three groups (IO-TKI low-RDI, 44.8%; IO-TKI high-RDI, 46.2%; IO-IO group, 21.1%; Table 6). The proportion of patients who discontinued treatment owing to AEs was similar between the IO-TKI low-RDI and IO-TKI high-RDI groups (Table 6).

We examined the association between time to treatment discontinuation and RDI. The median time to treatment discontinuation owing to PD in the IO-IO group was the shortest among the three groups (IO-TKI low RDI: not reached vs. IO-TKI high RDI: not reached vs. IO-IO group; 25.0 months, Figure 3). Notably, the median time to treatment discontinuation due to AEs in the IO-TKI high-RDI group was the shortest among the three groups (IO-TKI low-RDI; 13.8 months vs IO-TKI high-RDI; 8.8 months vs IO-IO group: not reached; Figure 3).

IO-TKI RDI 50–<80% group is associated with better survival

Lastly, the IO-TKI group was subdivided into three groups based on the RDI (IO-TKI RDI <50% group: n = 16; IO-TKI RDI 50–<80% group: n = 13; IO-TKI RDI ≥80% group: n = 26), and the mPFS, mOS, and time to treatment discontinuation were examined (Figure 4). mPFS of the IO-IO group was shortest (Figure 4A). mPFS was not reached in any of the IO-TKI RDI <50%, IO-TKI RDI 50–<80%, or IO-TKI RDI ≥80% groups (Figure 4A). While the mOS in the IO-TKI RDI ≥80% group was the shortest, that in the IO-TKI RDI 50–<80% group was the longest (not reached [IO-TKI RDI <50% group] vs. not reached [IO-TKI RDI 50–<80% group] vs. 20.0 months [IO-TKI RDI ≥80% group] vs. 47.4 months [IO-IO group]; Figure 4B). The median time to treatment discontinuation due to AEs in the IO-TKI RDI ≥80% group was the shortest among the four groups, while the IO-TKI RDI 50–<80% and IO-IO groups had longer times to treatment

discontinuation due to AEs (12. 4 months [IO-TKI RDI <50% group] vs. 35.4 months [IO-TKI RDI 50–<80% group] vs. 8.8 months [IO-TKI RDI ≥80% group] vs. not reached [IO-IO group]; Figure 4C). These data may indicate the importance of keeping the RDI within the 50–80% range from the perspective of efficacy and safety.

Discussion

Recently, the treatment of RCC has undergone remarkable advances, significantly improving its prognosis and efficacy [2-7]. The first-line therapies for RCC are particularly robust and are one of the factors that improve prognosis [2-7]. However, it is unclear which treatment is the best among first-line therapies. Therefore, it is important to analyze the five treatments, including IO-IO therapy, from the perspectives of efficacy and safety. This study is the first to report an association between the RDI and the efficacy and continuity of IO-TKI therapy in patients with RCC with two key findings: first, while the efficacy of IO-TKI therapy was higher than that of IO-IO therapy, the prognosis of patients with RCC treated with IO-TKI and IO-IO therapy was comparable. Second, the prognosis of the IO-TKI high-RDI group may be worse because of early treatment discontinuation owing to AEs.

Although whether IO-TKI or IO-IO therapy is the best first-line treatment option in terms of efficacy and prognosis is unclear, five studies have analyzed the comparative efficacy and prognosis of IO-TKI and IO-IO therapies in patients with RCC [22-26]. Santoni *et al.* reported better OS and PFS in the intermediate-risk IO-TKI group than in the intermediate-risk IO-IO group [26]. In contrast, two study groups reported that PFS in the IO-TKI group was better than that in the IO-IO group but OS did not differ between the IO-TKI and IO-IO therapies [22, 25]. Furthermore, the other two Japanese groups showed no differences in terms of OS and PFS between IO-TKI and IO-IO therapies [23, 24]. Consistent with the four study groups, our study showed similar OS between the IO-TKI and IO-IO groups (Figure 1B). Although the controversial results of our and previous studies are reflected in different patient characteristics, the reports

show no difference in long-term survival between IO-TKI and IO-IO therapies. Large-scale clinical studies are needed to address this discrepancy, but an important aspect of RCC treatment for long-term survival is the selection of the first-line treatment after considering multidisciplinary treatment strategies, including second- and third-line therapies and deferred cytoreductive nephrectomy.

RDI is a crucial factor associated with efficacy and safety in patients with RCC receiving TKI therapy [15, 16, 27]. Sunitinib, previously administered for RCC, was associated with better clinical outcomes and a higher RDI [28-31]. Moreover, Naoki Fukuda *et al.* reported significantly longer OS and PFS in patients who received RDI ≥60% of lenvatinib than those with thyroid cancer who received RDI <60% of lenvatinib (OS; not reached vs. 27.6 months, PFS; not reached vs. 11.0 months [16]). Shirotake reported that RDI <70% increased the risk of disease progression and poor prognosis in patients with RCC receiving TKI monotherapy [15]. Although the optimal cutoff value of the TKI-RDI in patients with RCC has not been determined, many researchers have stated that maintaining a high TKI-RDI is important for better efficacy and prognosis. However, our results differ from those of previous studies (Figure 2B and C). RDI ≥80% is associated with poor prognosis owing to early discontinuation due to AEs (Figure 2C and Figure 3). A low RDI is not sufficient. An RDI <50% may also be associated with poor prognosis (Figure 4B), suggesting that an appropriate range of RDI in terms of efficacy and safety (Figure 4C). Planned drug holidays are associated with better clinical outcomes and tolerability [32, 33]. Moreover, Noda *et al.* revealed an appropriate range of blood lenvatinib concentrations to maintain disease control and reduce severe AEs in patients with hepatocellular carcinoma [19]. Furthermore, interruption of TKI was associated with a negative effect on clinical outcomes [34]. Therefore, maintaining the RDI in an appropriate range is important, such as between 50% and 80%, depending on the patient's condition, to safely and effectively continue treatment without early discontinuation in Japanese patients with RCC receiving IO-TKI therapy.

The incidence of AEs induced by TKIs is related to the blood concentration of TKIs [17-21]. High blood concentrations of TKIs increase the incidence of AEs, such as anorexia, hypertension, and hepatotoxicity,

in patients with hepatocellular carcinoma and thyroid cancer [17-21]. Furthermore, subgroup analysis of clinical trials demonstrated increased blood concentrations of TKIs in Japanese patients with thyroid cancer compared with non-Japanese patients [20]. Increased blood concentrations of TKI are associated with treatment discontinuation due to AEs [21]. Interestingly, we found that the time to treatment discontinuation owing to AEs was significantly shorter in the IO-TKI high-RDI group than in the IO-TKI low-RDI group (Figure 3). Although the association between the blood concentration of TKIs and the incidence of AEs in patients with RCC remains unclear, several studies have explained this association. Ours and previous studies suggest that physicians should consider the dose of TKI when administering it to Japanese patients with RCC.

This study had some limitations that warrant further consideration. The number of participants was small, and because this was a retrospective study, we could not control for patient bias. Furthermore, we validated four different regimens in the IO-TKI group. We did not examine the blood concentration of TKIs or analyze the relationship between RDI and blood concentration. Therefore, we plan to confirm these findings in a large-scale prospective study.

In conclusion, an association between an IO-TKI RDI ≥80% and shorter prognosis in Japanese patients with RCC treated with IO-TKI therapy was observed. Physicians should carefully adjust the dose of TKIs such that the severity of AEs is manageable, and Japanese patients can continue to receive IO-TKI therapy for an extended period without discontinuing owing to AEs.

Methods

Patients and treatment

We retrospectively analyzed the efficacy and safety of IO-TKI therapy (IO-TKI group (n = 55); pembrolizumab (200 or 400 mg/kg every 3 or 6 weeks) plus axitinib (10 mg twice daily), avelumab (10 mg/kg every 2 weeks) plus axitinib (10 mg twice daily), nivolumab (240 or 480 mg/kg every 2 or 4 weeks)

plus cabozantinib (40 mg once daily), and pembrolizumab (200 or 400 mg/kg every 3 or 6 weeks) plus lenvatinib (20 mg once daily) or IO-IO therapy (IO-IO group (n = 90); 1 mg/kg ipilimumab and 240 mg/body nivolumab on day 1, every 3 weeks) as first-line therapy in Japanese patients with RCC between October 2015 and December 2024 at four hospitals in Japan (Nagoya City University Hospital, Kainan Hospital, Anjo Kosei Hospital, and Konan Kosei Hospital). Physicians decided on the first-line treatment from among these five regimens based on the patient's condition. The TKI dosage during treatment was adjusted by the physician based on the severity of AEs. The criteria for dose reduction or discontinuation of treatment are based on standards recommended by pharmaceutical companies and are common across four hospitals. Pathologists diagnosed RCC based on histological analyses. However, 13 cases were not diagnosed based on the histological subtype because of an insufficient amount of tissue or inability to collect tissue. Therefore, experienced radiologists and urologists diagnosed RCC by computed tomography and magnetic resonance imaging analyses. All data were obtained from the patients' medical records. This study was approved by the Ethics Committee of Nagoya City University Hospital (approval number 70-25-0001) and conducted following the tenets outlined in the Declaration of Helsinki. As the current study was a retrospective study, patient consent was deemed unnecessary by the approval committee. Patients were also allowed to opt out of the study via the authors' institutional websites.

Evaluation of efficacy

Responses were classified by experienced physicians based on radiology reports or imaging reviews using the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1: CR, PR, SD, and PD). The ORR and DCR were defined as CR + PR, CR, and PR + SD. All patients were followed up until death or loss of contact. OS was defined as the period from the initiation of IO-TKI or IO-IO therapy to death or loss of contact. PFS was defined as the period from initiation of IO-TKI or IO-IO therapy to disease progression.

Evaluation of safety

We defined the symptoms caused by immune dysregulation as irAEs and defined symptoms not involving the immune system as AEs induced by TKI. AEs were graded based on the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0.

RDI

The RDI was calculated as the ratio of the actual dose to the maximum dose during the period from initiation till the end of IO-TKI therapy.

Statistical analyses

A *P*-value<0.05 was considered statistically significant. Fisher's exact test was used to assess differences in patient characteristics. mOS and mPFS were calculated using the Kaplan–Meier method and log-rank tests, followed by the Bonferroni test. The cumulative incidence rates of treatment discontinuation due to PD and AEs were analyzed using Gray's test. Univariate and multivariate Cox regression analyses were used to evaluate risk factors for OS. Four factors were selected as variables for univariate and multivariate Cox regression analyses based on their association with OS in RCC and the number of death events. Statistical analyses were performed using EZR software (Saitama Medical Center, Jichi Medical University, Saitama, Japan) [35].

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Author Contributions

Yoshihiko Tasaki and Shuzo Hamamoto designed and directed the study. Yoshihiko Tasaki analyzd the majority of the data. Yoshihiko Tasaki, Shuzo Hamamoto, Hiroaki Ikoma, Misato Tomita, Takuya Sakata, Hiroko Suzuki, Yusuke Noda, Masayuki Usami, Yohei Tsubouchi, Toshiharu Morikawa, Yoshihisa Mimura, Yosuke Sugiyama, Takashi Nagai, Rei Unno, Toshiki Etani, Taku Naiki, Yoko Furukawa-Hibi, and Takahiro Yasui acquired the data. Yosuke Sugiyama conducted the statistical analyses. Yoshihiko Tasaki and Shuzo Hamamoto prepared the manuscript. All authors discussed the results and commented on the manuscript.

Competing Interests

The authors declare no conflict of interest.

Data availability statement

The datasets analyzed during the current study available from the first and corresponding author (Yoshihiko Tasaki and Shuzo Hamamoto) on reasonable request.

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Figure legends

Figure 1. Overall and progression-free survival in immuno-oncology plus tyrosine kinase inhibitors (n = 55) and immuno-oncology combination therapy (n = 90) groups

A–B, Kaplan–Meier survival curves for (A) progression-free survival (IO-TKI group, n = 55; IO-IO group, n = 90) and (B) overall survival (IO-TKI group, n = 55; IO-IO group, n = 90) of patients with renal cell carcinoma. (A–B) Log-rank test using the Bonferroni test. IO, immuno-oncology; TKI, tyrosine kinase inhibitor.

Figure 2. Survival outcomes by relative dose intensity in IO-TKI low-RDI (n = 29), IO-TKI high-RDI (n = 26), or IO-IO (n = 90) groups.

A: The bar graph shows the number of patients at each relative dose intensity. B–C Kaplan–Meier survival curves for (B) progression-free survival (IO-TKI low-RDI group: n = 29; IO-TKI high-RDI group: n = 26; IO-IO group: n = 90) and (C) overall survival (IO-TKI low-RDI group: n = 29; IO-TKI high-RDI group: n = 26; IO-IO group: n = 90) in patients with renal cell carcinoma. (B–C) Log-rank test using the Bonferroni test. IO, immuno-oncology; TKI, tyrosine kinase inhibitor; RDI, relative dose intensity.

Figure 3. Cumulative incidence rate of treatment discontinuation by relative dose intensity in IO-TKI low-RDI (n = 29), IO-TKI high-RDI (n = 26), or IO-IO (n = 90) groups.

Kaplan–Meier curves for the cumulative incidence of treatment discontinuation owing to disease progression and adverse events (IO-TKI low-RDI group, n = 29; IO-TKI high-RDI group, n = 26; IO-IO group, n = 90). Gray's Test. IO, immuno-oncology; TKI, tyrosine kinase inhibitor; RDI, relative dose intensity.

Figure 4. Survival outcomes and cumulative incidence rate of treatment discontinuation by relative dose intensity in IO-TKI RDI <50% (n = 16), IO-TKI RDI 50–<80% (n = 13), IO-TKI RDI ≥80% (n = 26), or IO-IO (n = 90) groups.

A–B Kaplan–Meier survival curves for (A) progression-free survival (IO-TKI RDI <50% group: n = 16; IO-TKI RDI 50–<80% group: n = 13; IO-TKI RDI ≥80% group: n = 26; IO-IO group: n = 90) and (B) overall survival (IO-TKI RDI <50% group: n = 16; IO-TKI RDI 50–<80% group: n = 13; IO-TKI RDI ≥80% group: n = 26; IO-IO group: n = 90) in patients with renal cell carcinoma. C Kaplan–Meier curves for the cumulative incidence of treatment discontinuation owing to disease progression and adverse events (IO-TKI RDI <50% group: n = 16; IO-TKI RDI 50–<80% group: n = 13; IO-TKI RDI ≥80% group: n = 26; IO-IO group: n = 90). (A–B) Log-rank test. (C) Gray's Test. IO, immuno-oncology; TKI, tyrosine kinase inhibitor; RDI, relative dose intensity.

Table 1. Efficacy data of patients with IO-TKI (n = 55) or IO-IO (n = 90) groups

Characteristics, n (%)	IO-TKI group	IO-IO group	*P* value
	55 (100)	90 (100)	
Best response to treatment, n (%)			<0.05
Complete response	1 (1.8)	4 (4.4)	
Partial response	32 (58.2)	34 (37.8)	
Stable disease	12 (21.8)	23 (25.6)	
Progression disease	2 (3.6)	25 (27.8)	
Not evaluable	8 (14.5)	4 (4.4)	
Overall response rate, n (%)	33 (60.0)	38 (42.2)	<0.05
Disease control rate, n (%)	45 (81.8)	61 (67.8)	<0.05

IO: immuno-oncology, TKI: tyrosine kinase inhibitors

Table 2. Clinical features of patients with IO-TKI low-RDI (n = 29) or IO-TKI high-RDI (n = 26) groups

	IO-TKI low-RDI group	IO-TKI high-RDI group	*P* value
Characteristics, n (%)	29 (100)	26 (100)	
Type of combination therapy, n (%)			0.08
Pembrolizumab plus axitinib	3 (10.3)	7 (26.9)	
Avelumab plus axitinib	2 (6.9)	3 (11.5)	
Nivolumab plus cabozantinib	4 (13.8)	7 (26.9)	
Pembrolizumab plus lenvatinib	20 (69.0)	9 (34.6)	
Age, n (%)			0.28
<65 years	3 (10.3)	3 (11.5)	
≥65 years	26 (89.7)	26 (76.9)	
Sex			0.18
Male	21 (72.4)	23 (88.5)	
Female	8 (27.6)	3 (11.5)	
Body Weight; ≥60kg			0.58
No	16 (55.2)	17 (65.4)	
Yes	13 (44.8)	9 (34.6)	
IMDC risk classification			0.56
Favorable	5 (17.2)	4 (15.4)	
Intermediate	18 (62.1)	13 (50.0)	
Poor	6 (20.7)	9 (34.6)	
Histological subtype			0.79
Clear cell	23 (79.3)	19 (73.1)	
Non-clear cell	5 (17.2)	5 (19.2)	
Unknown	1 (3.4)	2 (7.7)	
Sarcomatoid change			0.33
No	28 (96.6)	23 (88.5)	
Yes	1 (3.4)	3 (11.5)	
Metastasis site, Bone			0.14
No	23 (79.3)	15 (57.7)	
Yes	6 (20.7)	11 (42.3)	
Metastasis site, Liver			1.00
No	27 (93.1)	24 (92.3)	
Yes	2 (6.9)	2 (7.7)	
Metastasis site, Lung			0.26
No	11 (37.9)	6 (23.1)	
Yes	18 (62.1)	20 (76.9)	
Metastasis site, Brain			0.69
No	26 (89.7)	22 (84.6)	
Yes	3 (10.3)	4 (15.4)	
Metastasis site, Adrenal glands			0.42
No	24 (82.8)	24 (92.3)	
Yes	5 (17.2)	2 (7.7)	
Metastasis site, Lymph node			1.00
No	21 (72.4)	19 (73.1)	
Yes	8 (27.6)	7 (26.9)	
Metastasis site, Others			1.00
No	25 (86.2)	23 (88.5)	
Yes	4 (13.8)	3 (11.5)	

IMDC: International Metastatic Renal Cell Carcinoma Database Consortium

IO: immuno-oncology, TKI: tyrosine kinase inhibitors

Table 3. Univariate and multivariate cox regression analysis of risk factors for overall survival in IO-TKI low-RDI (n = 29), IO-TKI high-RDI (n = 26) or IO-IO (n = 90) groups

	Univariate				Multivariate		
	HR	95%CI	*P* value		HR	95%CI	*P* value
IMDC risk group: Poor	2.73	1.58-4.73	<0.05		2.74	1.49-5.03	<0.05
Histology: Non clear	2.54	1.06-6.09	<0.05		1.86	0.84-4.11	0.12
Metastasis site, liver: yes	1.06	0.45-2.51	0.87		0.98	0.38-2.54	0.98
Relative dose intensity: ≥80 %	2.15	1.11-4.15	<0.05		2.16	1.04-4.49	<0.05

IMDC: International Metastatic Renal Cell Carcinoma Database Consortium; HR: hazard ratio; CI: confidence interval

Table 4. Univariate cox regression analysis of risk factors for overall survival in IO-TKI low-RDI (n = 29) or IO-TKI high-RDI (n = 26) groups

	Univariate		
	HR	95%CI	*P* value
IMDC risk group: Poor	7.74	2.40-24.9	<0.05
Histology: Non clear	4.63	1.00-21.4	<0.05
Metastasis site, liver: yes	0.74	0.09-5.59	0.77
Relative dose intensity: ≥80 %	3.28	1.14-9.41	<0.05

IMDC: International Metastatic Renal Cell Carcinoma Database Consortium; HR: hazard ratio; CI: confidence interval

Table 5. The number of patients who experienced any type of AEs in IO-TKI low-RDI (n = 29), IO-TKI high-RDI (n = 26) or IO-IO (n = 90) groups

	IO-TKI low-RDI group	IO-TKI high-RDI group	IO-IO group	*P* value
Number of patients, n (%)	29 (100)	26 (100)	90 (100)	
Any grade AEs	28 (96.6)	19 (73.1)	64 (71.1)	<0.05
≥grade 3 AEs	8 (27.6)	5 (19.2)	37 (41.1)	0.08

AEs: adverse events, irAEs: immune-related adverse events, IO: immuno-oncology, TKI: tyrosine kinase inhibitors

Table 6. Reasons for discontinuing treatment of patients with IO-TKI or IO-IO groups in IO-TKI low-RDI (n = 29), IO-TKI high-RDI (n = 26) or IO-IO (n = 90) groups

	IO-TKI low-RDI group	IO-TKI high-RDI group	IO-IO group	*P* value
Number of patients, n (%)	29 (100)	26 (100)	90 (100)	
Discontinued due to progression disease	4 (13.8)	3 (11.5)	46 (51.1)	<0.05
Discontinued due to AEs	13 (44.8)	12 (46.2)	19 (21.1)	<0.05

AEs: adverse events, IO: immuno-oncology, TKI: tyrosine kinase inhibitors