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Prognostic Impact of Trial-Eligibility Criteria in Patients with Metastatic Renal Cell Carcinoma

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Keywords
Kidney cancer · Renal cell carcinoma · Advanced renal cell carcinoma · Targeted therapy · Prognosis

Abstract
Objective: The aim of the study was to evaluate the prognostic impact of trial-eligibility criteria on outcome in real-world metastatic renal cell carcinoma (mRCC) patients treated with tyrosine kinase inhibitors (TKIs). ***Patients and Methods:*** mRCC patients treated with TKIs as first-line systemic therapy were retrospectively evaluated. The patients were determined as trial-ineligible when they met at least 1 following trial-ineligible criteria; Karnofsky performance status score <70, hemoglobin <9.0 g/dL, creatinine >2.4 mg/dL (male) or >2.0 mg/dL (female), calcium >12.0 mg/dL, platelet <100,000 /μL, neutrophil <1,500 /μL, nonclear-cell histology, and brain metastasis. ***Results:*** Of 238 patients, 101 patients (42%) were determined as trial-ineligible. Progression-free survival (PFS) and overall survival (OS) after the TKI initiation were significantly shorter in the trial-ineligible patients than in the trial-eligible patients (median PFS: 5.53 vs. 15.8 months, $p < 0.0001$; OS: 13.8 vs. 43.4 months, $p < 0.0001$). Objective response rate was also significantly lower in the trial-ineligible patients (15% vs. 37%, $p = 0.0003$). Multivariate analysis further showed that the trial-eligibility was an independent factor for PFS (hazard ratio [HR]: 2.46, $p < 0.0001$) and OS (HR: 2.39, $p < 0.0001$). In addition, the number of trial-ineligible factors were negatively correlated with PFS and OS. ***Conclusions:*** In real-word, the substantial number of mRCC patients did not meet the trial-eligibility criteria, and their outcome was worse than that in the trial-eligible patients. Further studies focusing on the outcome in real-world trial-ineligible patients in the immune checkpoint inhibitor era are warranted.

Introduction

Antitumor drugs are approved based on the data from clinical trials in cancer. In metastatic renal cell carcinoma (mRCC), previous trials demonstrated efficacy and safety of molecular-targeted therapy, including tyrosine kinase inhibitors (TKIs) [1–5]. Based on these evidences, TKIs had played a central role in systemic therapy for mRCC. Currently, although the guidelines recommend immune checkpoint inhibitors (ICIs) as first-line therapy, TKIs

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still assume a therapeutic role as combination therapy with ICIs or subsequent therapy after failure of first-line ICI therapy [6, 7].

Clinical trials on TKIs generally recruit patients with strict eligibility criteria, and those with severe comorbidity, organ dysfunction, or poor general condition are excluded [1–5]. Thus, evidence on antitumor activity of TKIs in this population is missing. However, clinicians always face such patients in daily clinical practice and treat them with the drugs which efficacy was demonstrated in clinical trials, although it remains unclear whether the application of evidences from clinical trials in such patients is appropriate. Indeed, in multiple types of cancers, several studies indicated that outcome in patients who did not meet eligibility criteria of clinical trials was worse than that in patients who fulfilled these criteria [8, 9]. Furthermore, in mRCC, inferior outcome in trial-ineligible patients compared to that in trial-eligible patients was reported by using the database of International mRCC Database Consortium (IMDC) [10] or multi-center German cohort [11]. Thus, to improve the strategy of systemic therapy for real-world patients with mRCC, we need more understanding of outcome in patients who did not meet eligibility criteria of trials. In this study, we retrospectively evaluated the prognostic impact of trial-eligibility criteria on outcome in real-world mRCC patients treated with TKIs.

Patients and Methods

Study Design and Patient Selection

The institutional review board at Tokyo Women's Medical University approved the anonymous use of patient data for this study (ID: 5453). As this was a retrospective observational study, informed patient consent was waived.

At our 2 institutions (Tokyo Women's Medical University and Tokyo Women's Medical University Medical Center East), 299 mRCC patients received at least 1 administration of TKIs as first-line systemic therapy between January 2008 and December 2018. From them, we have excluded 61 patients whose posttreatment follow-up period was short (i.e., <1.0 month) or those who did not have eligible data during the therapy. The remaining 238 patients were enrolled in this study.

Criteria for Trial-Eligible and Trial-Ineligible Patients

We classified the 238 patients according to trial-eligibility criteria. The eligibility criteria were based on a previous study identifying an association between the trial-eligibility and outcome in mRCC patients by using the IMDC database [10]. Trial-ineligible factors included Karnofsky performance status (KPS) score <70, hemoglobin <9.0 g/dL, creatinine >2.4 mg/dL for male or >2.0 mg/dL for female, calcium >12.0 mg/dL, platelet <100,000 /μL, neutrophil <1,500 /μL, non-clear cell histology, or presence of brain metastasis. A patient who had at least one of these factors was classified as a trial-ineligible patient, whereas a patient who did not have any factors was classified as a trial-eligible patient. When a patient had missing datum on one or some of the factors, the patient was classified as a trial-ineligible patient if this patient had at least one of the other factors. When a patient had missing datum on one or some of the factors, the patient was classified as a trial-eligible patient if this patient did not have any other factors.

Table 1. Contents of trial-ineligible factors

Trial-ineligible factors	Trial-ineligible patients (n = 101), n (%)
Factors, n	
1	65 (64)
2	25 (25)
3	9 (9)
4	2 (2)
Karnofsky performance status score	
<70	27 (27)
Serum hemoglobin levels, g/dL	
<9.0	21 (21)
Serum creatinine levels, mg/dL	
>2.4 for male or >2.0 for female	36 (36)
Serum calcium levels, mg/dL	
>12.0	2 (2)
Platelet count, /μL	
<100,000	5 (5)
Neutrophil count, /μL	
<1,500	2 (2)
Histology	
Nonclear-cell RCC	50 (50)
Brain metastasis	
Presence	7 (7)

RCC, renal cell carcinoma.

Protocol for TKIs

In terms of the first-line TKI therapy, sorafenib was used in an early phase, and it was subsequently replaced with either sunitinib or pazopanib. Sunitinib treatment was generally administered based on a 2-weeks-on/1-week-off alternative schedule [12]. Alternatively, for patients with severe kidney dysfunction including end-stage renal disease requiring maintenance dialysis therapy, sorafenib was preferentially used [13].

For the assessment of TKI effects, computed tomography of the chest, abdomen, and pelvis were generally performed at 1- to 3-month intervals, depending on patient's condition. Magnetic resonance imaging or elective bone scan was conducted when clinically needed. TKI therapy was continued until either disease progression was radiographically or clinically observed or intolerable adverse events were developed.

Outcome for TKIs

To assess outcome of TKIs, we evaluated progression-free survival (PFS) and overall survival (OS) after the initiation of first-line TKI therapy. In addition, objective response rates (ORRs) during

Table 2. Patient characteristics according to trial-eligibility

Variable	Trial-eligible patients (n = 137)	Trial-ineligible patients (n = 101)	p value
Sex, n (%)			
Male	107 (78)	69 (68)	0.0891
Age,* years	67 (62–72)	64 (55–69)	0.0004
Histology, n (%)			
Clear-cell RCC	130 (95)	37 (37)	
Nonclear-cell RCC	0	50 (50)	
Papillary RCC	0	26 (26)	
Chromophobe RCC	0	1 (1)	
Clear-cell RCC with spindle	0	11 (11)	
Mucinous tubular spindle cell carcinoma	0	5 (5)	<0.0001
Xp11. Translocation RCC	0	2 (2)	
Acquired cystic disease-associated RCC	0	2 (2)	
Bellini duct carcinoma	0	1 (1)	
Unclassified RCC	0	2 (2)	
Unknown	7 (5)	14 (14)	
IMDC risk, n (%)			
Favorable	30 (22)	3 (3)	
Intermediate	89 (65)	57 (56)	<0.0001
Poor	18 (13)	41 (41)	
TKIs, n (%)			
Sorafenib	38 (28)	43 (43)	
Sunitinib	79 (58)	49 (49)	0.0448
Pazopanib	20 (15)	9 (9)	
Metastatic organ sites, n (%)			
Multiple	72 (53)	58 (57)	0.456
Lung metastasis, n (%)			
Presence	101 (74)	53 (52)	0.0007
Bone metastasis, n (%)			
Presence	27 (20)	24 (24)	0.451
Liver metastasis, n (%)			
Presence	12 (9)	25 (25)	0.0008
Lymph node metastasis, n (%)			
Presence	40 (29)	29 (29)	0.935
Follow-up period,* months	28.8 (15.7–57.4)	11.8 (4.72–22.4)	<0.0001

IMDC, International Metastatic Renal Cell Carcinoma database Consortium; RCC, renal cell carcinoma; TKIs, tyrosine kinase inhibitors. * Indicated as median (interquartile range).

the therapy were evaluated. The ORR was determined based on the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. [14].

Statistical Analysis

Continuous and categorical variables were analyzed using the Mann-Whitney U test and χ^2 test, respectively. The PFS was calculated from the initiation of TKI therapy to disease progression or death, whichever occurred first. The OS was calculated from the initiation of TKI therapy to death owing to any causes. Survival data were obtained until the end of June 2020. Survival was calculated using the Kaplan-Meier method and compared using the log-rank test. Multivariate analysis based on the Cox proportional hazard regression models was performed to identify risk factors of PFS and OS. Risk was expressed as hazard ratios (HRs) with 95% confidence intervals (CIs). All statistical analyses were performed using JMP version 15 (SAS Institute Inc., Cary, NC, USA), and $p < 0.05$ indicated statistically significant difference.

Results

Patient Characteristics Based on Trial-Eligibility

Of the 238 patients, 101 patients (42%) were determined as trial-ineligible (Table 1). Among them, 36 patients (36%) had multiple trial-ineligible factors. Most frequent factor was non-clear cell histology (n = 50, 50%),

followed by high serum creatinine levels (n = 36, 36%), and low KPS score (n = 27, 27%).

With regard to patient characteristics, the trial-ineligible patients were younger (p = 0.0004) and had a higher rate of poor IMDC risk (p < 0.0001), lower rate of lung metastasis (p = 0.0007), and higher rate of liver metastasis (p = 0.0008) than the trial-eligible patients had (Table 2). As expected, higher rates of nonclear cell histology (p < 0.0001) and sorafenib usage (p = 0.0448) were observed in the trial-ineligible patients. The duration of follow-up period was significantly shorter in the trial-ineligible patients (p < 0.0001).

Survival according to Trial-Eligibility

During the median follow-up of 20.2 months (interquartile range: 9.62–40.9), 184 (77%) and 148 (62%) patients had disease progression and died, respectively. Termination of first-line TKI therapy owing to adverse events occurred in 33 patients (14%), and its frequency did not significantly differ between the trial-eligible and trial-ineligible patients (n = 19 [14%] vs. n = 14 [14%], p = 0.999).

The PFS was significantly shorter in the trial-ineligible patients than that in the trial-eligible patients (median: 5.53 [95% CI: 3.75–6.91] vs. 15.8 [13.4–26.6] months, p < 0.0001) (Fig. 1a). The OS was also significantly shorter in the trial-ineligible patients than that in the trial-eligible patients (13.8 [11.4–19.1] vs. 43.4 [30.2–72.5] months, p < 0.0001) (Fig. 1b).

Because the histology was the most frequent deciding factor for trial-eligibility (Table 1), it had a potential to directly impact the prognostic association. Thus, we analyzed the association between survival and trial-eligibility exclusively among patients with clear-cell RCC (n = 167). The PFS and OS were significantly shorter in the trial-ineligible patients (n = 37) than those who were eligible (n = 130) (PFS: 6.28 [5.00–8.75] vs. 17.6 [12.2–26.6] months, p < 0.0001; OS: 18.0 [12.1–33.1] vs. 48.7 [31.3–77.0] months, p = 0.0011) (online supplementary Fig. 1, available at www.karger.com/doi/10.1159/000518162).

We further analyzed the association between the burden of trial-ineligible factors and survival. The PFS was negatively correlated with the number of trial-ineligible factors (1.89 [0.79–6.91] vs. 5.89 [2.30–6.97] vs. 6.22 [5.00–8.75] vs. 15.8 [13.4–26.6] months) in patients with 3 or 4 trial-ineligible factors, 2 factors, 1 factor, and trial-eligible patients, respectively (Fig. 2a). Furthermore, OS was negatively correlated with the number of trial-ineligible factors, except for patients with 3 or 4 trial-ineligible factors (14.2 [0.92–19.5] vs. 8.65 [4.70–15.2] vs. 18.0 [12.2–22.8] vs. 43.4 [30.2–72.5] months) (Fig. 2b).

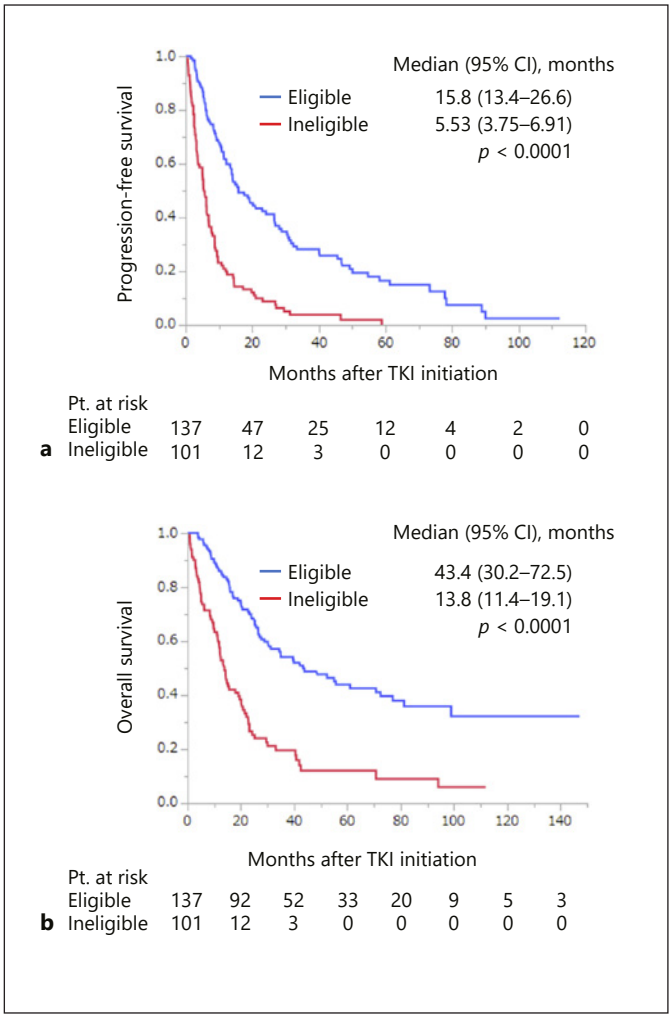

Fig. 1. PFS and OS according to trial-eligibility. PFS (**a**) and OS (**b**) after the TKI initiation were compared between trial-eligible and trial-ineligible patients. PFS, progression-free survival; OS, overall survival; CI, confidence interval; Pt., patient; TKI, tyrosine kinase inhibitor.

Factors for Survival

Univariate analysis of PFS showed that IMDC risk, number of metastatic organ sites, liver metastasis status, and trial-eligibility were significant factors (all, p < 0.05) (Table 3). Multivariate analysis using these factors showed that the trial-eligibility was an independent factor for PFS (HR: 2.46 [95% CI: 1.79–3.37], p < 0.0001), together with IMDC risk (p < 0.0001) and liver metastasis status (HR: 1.55 [1.03–2.33], p = 0.0345).

Univariate analysis of OS showed that IMDC risk, number of metastatic organ sites, liver metastasis status, lymph node metastasis status, and trial-eligibility were significant factors (all, p < 0.05) (Table 3). Multivariate analysis using

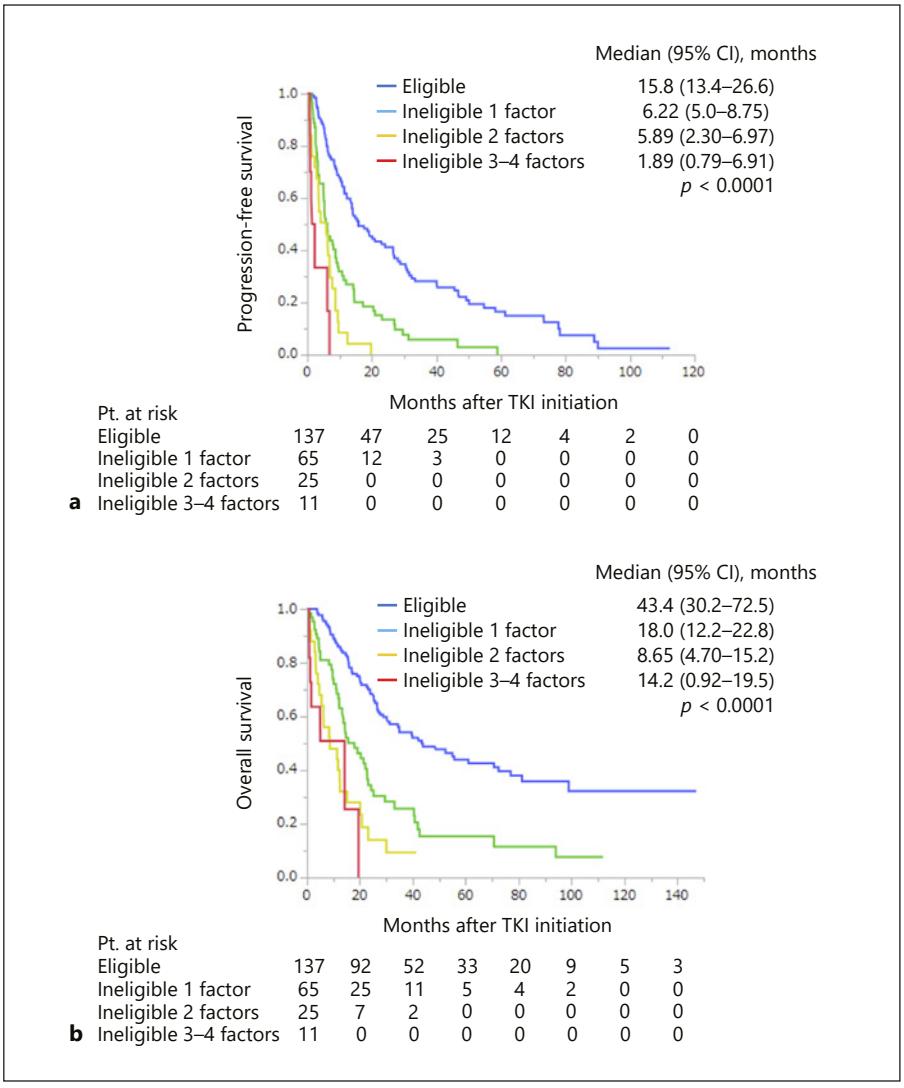

Fig. 2. PFS and OS according to the number of trial-ineligibility factors. PFS (**a**) and OS (**b**) after TKI initiation were compared according to the number of trial-ineligibility factors. PFS, progression-free survival; OS, overall survival; CI, confidence interval; Pt., patient; TKI, tyrosine kinase inhibitor.

these factors showed that the trial-eligibility was an independent factor for OS (HR: 2.39 [1.69–3.39], $p < 0.0001$), together with IMDC risk ($p < 0.0001$), liver metastasis status (HR: 1.91 [1.27–2.87], $p = 0.0020$), and lymph node metastasis status (HR: 1.56 [1.06–2.31], $p = 0.0253$).

ORR Based on Trial-Eligibility

We compared tumor response according to the trial-eligibility in 214 patients whose imaging data were available (126 trial-eligible and 88 trial-ineligible patients). In terms of the best overall response, complete response, partial response, stable disease, and progressive disease were observed in 6 (5%), 41 (33%), 69 (55%), and 10 (8%) trial-eligible patients, and in 0, 13 (15%), 50 (57%), and 25 (28%) trial-ineligible patients, respectively (Table 4). The ORR was significantly lower in the trial-ineligible patients than that in the trial-eligible patients (15% vs. 37%, $p = 0.0003$). Magnitude of the best tumor shrinkage in targeted lesions was also significantly lower in the trial-ineligible patients than that in the trial-eligible patients (median: 1.21% [interquartile range: −17.1% to 16.3%] vs. −18.7% [−43.6% to −6.18%], $p < 0.0001$).

Discussion

This retrospective study identified that the substantial number of real-world patients with mRCC did not meet trial-eligibility criteria. In addition, both survival and tumor response in first-line TKI therapy were inferior in

Table 3. Univariate and multivariate analyses of PFS and OS

Variable	PFS				OS			
	univariate HR (95% CI)	*p* value	multivariate HR (95% CI)	*p* value	univariate HR (95% CI)	*p* value	multivariate HR (95% CI)	*p* value
Sex								
Male (ref. female)	0.81 (0.58–1.13)	0.218			0.75 (0.52–1.08)	0.123		
Age (continuous variable)	0.99 (0.98–1.01)	0.472			1.01 (0.99–1.02)	0.438		
IMDC risk		<0.0001		<0.0001		<0.0001		<0.0001
Favorable	Ref.	–	Ref.	–	Ref.	–	Ref.	–
Intermediate	2.12 (1.30–3.46)	0.0027	1.77 (1.07–2.92)	0.0264	2.58 (1.38–4.83)	0.0030	2.01 (1.07–3.79)	0.0297
Poor	4.90 (2.86–8.40)	<0.0001	3.21 (1.83–5.61)	<0.0001	6.89 (3.53–13.4)	<0.0001	4.46 (2.21–8.98)	<0.0001
TKIs		0.411				0.515		
Sorafenib	Ref.	–			Ref.	–		
Sunitinib	0.81 (0.59–1.10)	0.181			0.82 (0.58–1.15)	0.248		
Pazopanib	0.85 (0.50–1.46)	0.556			0.87 (0.47–1.60)	0.651		
Metastatic organ sites, *n*								
Multiple (ref. single)	1.47 (1.09–1.97)	0.0110	1.23 (0.90–1.68)	0.203	1.91 (1.36–2.67)	0.0002	1.31 (0.89–1.92)	0.169
Lung metastasis								
Presence (ref. absence)	1.07 (0.78–1.45)	0.684			0.94 (0.67–1.32)	0.707		
Bone metastasis								
Presence (ref. absence)	1.27 (0.89–1.80)	0.191			1.43 (0.98–2.08)	0.0624		
Liver metastasis								
Presence (ref. absence)	2.65 (1.82–3.86)	<0.0001	1.55 (1.03–2.33)	0.0345	2.77 (1.88–4.10)	<0.0001	1.91 (1.27–2.87)	0.0020
Lymph node metastasis								
Presence (ref. absence)	1.12 (0.81–1.54)	0.494			1.42 (1.00–2.02)	0.0488	1.56 (1.06–2.31)	0.0253
Trial-eligibility								
Trial-ineligible patients	3.05 (2.25–4.13)	<0.0001	2.46 (1.79–3.37)	<0.0001	3.06 (2.19–4.26)	<0.0001	2.39 (1.69–3.39)	<0.0001

PFS, progression-free survival; OS, overall survival; CI, confidence interval; HR, hazard ratio; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; TKIs, tyrosine kinase inhibitors.

Table 4. Tumor response according to trial-eligibility

Tumor response	Trial-eligible patients (*n* = 126)*	Trial-ineligible patients (*n* = 88)*	*p* value
Best overall response, *n* (%)			
Complete response	6 (5)	0	
Partial response	41 (33)	13 (15)	
Stable disease	69 (55)	50 (57)	
Progressive disease	10 (8)	25 (28)	
ORR, *n* (%)	47 (37)	13 (15)	0.0003
Magnitude of best tumor shrinkage in targeted lesions, %	−18.7 (−43.6 to 6.18)	1.21 (−17.1 to 16.3)	<0.0001

ORR, objective response rate. * Analyzed in 214 patients with evaluable imaging data.

trial-ineligible patients to those in trial-eligible patients. After adjustment with other prognostic factors, trial-eligibility was an independent risk factor for survival. Furthermore, burden of trial-ineligible factors was negatively associated with the survival.

Clinical trials on mRCC generally recruit patients based on strict eligibility criteria; and the patients harboring poor prognostic factors such as comorbidity or organ dysfunction are excluded [1–5]. Thus, such patient selection can induce a gap in outcome data between clinical trial and real-world. Indeed, Heng et al. [10] indicated worse survival and response rates to TKI therapy in the trial-ineligible patients than in the trial-eligible patients based on the common trial-eligibility criteria using the IMDC database. In addition, using the German cohort database, Marschner et al. [11] reported similar findings based on loosely modified criteria from Heng's study. Our findings were generally consistent with those shown in previous research, in-

dicating that worse outcome in the trial-ineligible patients were regardless of race or country of origin.

We have also found that a non-negligible number of patients had multiple trial-ineligible factors and their survival was even worse. The trial-eligibility criteria used in this study included factors of Memorial Sloan-Kettering Cancer Center (MSKCC) or IMDC risk model. The number of risk factors in IMDC model was negatively associated with survival [15]. Thus, the negative impact of burden of trial-ineligible factors could be reasonable. Furthermore, as a sufficient efficacy of TKI therapy cannot be expected in patients harboring multiple trial-ineligible factors, ICI therapy would be an appropriate option for them.

In this study, the trial-eligible patients had favorable survival and tumor response which were similar those found in the data from Japanese subgroup analyses in previous trials [16, 17]. Specifically, a subgroup analysis of CheckMake 214 showed that in sunitinib-treated Japanese patients, the median PFS and OS were 15.2 and 33.4 months, respectively, and ORR was 31% [16]. These outcomes were better than those in the global population (median PFS: 8.3 months; OS: 26.6 months; ORR: 29%) [18]. Another subgroup analysis of JAVELIN Renal 101 showed that median PFS was 11.2 months and ORR was 17.6% in suntinib-treated Japanese patients [17]. Taken together, patients who meet the trial-eligibility criteria are expected to have equivalent outcome to that reported in clinical trials even though they are real-world patients.

The current guidelines of systemic therapy for mRCC recommend ICIs as first-line therapy [6], but the corresponding trials were conducted under the strict eligibility criteria, as it was done in the previous TKI era [19–22]. Thus, further studies focusing on the outcome in trial-ineligible patients treated with first-line ICI therapy are needed to increase understanding of its efficacy in real-world.

This study has several limitations. First, as it was a retrospective study conducted in a small cohort size from 2 medical centers, selection biases inevitably affected any findings. Especially, due to the retrospective nature, the trial-ineligible patients inherently might have had poorer prognosis owing to more aggressive disease rather than the lower efficacy of TKI therapy. However, we could not completely exclude the possible effect of this bias on the outcome analysis. Second, we did not evaluate possible effects of non-pharmacotherapy, such as metastasectomy or radiotherapy, on the outcome. Third, we excluded the 61 patients whose follow-up intervals or data were immature from the study (Patients and Methods). However, a subset of the patients might still harbor poor prognostic factors, resulting in poor prognosis. Thus, we might have underestimated the prognostic impact of trial-eligibility. Fourth, since we included patients treated with sorafenib, interpreting the findings might become difficult as sorafenib is no longer regarded as a standard therapy for mRCC.

In conclusion, this retrospective study showed that the substantial number of real-world patients with mRCC did not meet the trial-eligibility criteria. These patients had worse outcome including shorter survival and lower tumor response in first-line TKI therapy than the trial-eligible patients. Furthermore, the number of trial-ineligible factors was negatively correlated with survival. Further studies investigating the difference in outcome between the trial-eligible and trial-ineligible patients in the ICI era are warranted.

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Statement of Ethics

The Internal Ethics Review Board of the Tokyo Women's Medical University approved the anonymous use of patient data for this study (ID: 5453), which was performed in accordance with the Helsinki Declaration. As this was a retrospective observational study, informed patient consent was waived.

Conflict of Interest Statement

Toshio Takagi received honoraria from Bristol-Myers Squibb and Ono Pharmaceutical. Tsunenori Kondo received honoraria from Ono Pharmaceutical, Novartis, and Pfizer.

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The authors have no funding to declare.

Author Contributions

H.I. contributed to conception and design of the study, acquisition, analysis, interpretation of data, and drafting the manuscript; H.T., H.F., K.Y., J.I., H.I., and K.T. contributed to acquisition of data; T.T. and T.K. contributed to acquisition and interpretation of data and revising the manuscript for important intellectual content. All authors approved the final manuscript.

Data Availability Statement

Due to the nature of this research, participants of this study did not agree for their data to be shared publicly, so supporting data are not available.

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