Time to progression after first-line tyrosine kinase inhibitor predicts survival in patients with metastatic renal cell carcinoma receiving second-line molecular-targeted therapy

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Highlights

- Associations between first- and second-line survival in mRCC patients are unclear.
- Second-line treatments efficacy after tyrosine kinase inhibitor is controversial.
- Time to progression after first-line treatment predicts second-line survival.
- First-line time to progression is an independent predictor for second-line survival.

Time to progression after first-line tyrosine kinase inhibitor predicts survival in patients with metastatic renal cell carcinoma receiving second-line molecular-targeted therapy

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Abstract

Objectives: The impact of response to first-line tyrosine kinase inhibitor (TKI) therapy on second-line survival in patients with metastatic renal cell carcinoma (mRCC) who receive second-line molecular-targeted therapy (mTT) after first-line failure remains unclear.

Materials and methods: Sixty patients who developed disease progression after first-line TKI, without prior cytokine therapy, were enrolled. According to the median first-line time to progression (1L-TTP), patients were divided into two groups (i.e., short vs. long). Second-line progression-free survival (2L-PFS) and second-line overall survival (2L-OS) were defined as the time from second-line mTT initiation. Survival was calculated with the Kaplan-Meier method and compared using the log-rank test between patients with short and long 1L-PFS. Predictors for survivals were identified using Cox proportional hazards regression models.

Results: The median 1L-TTP was 8.84 months. Thirty patients (50.0%) with short 1L-TTP (<8.84 months) had significantly shorter 2L-PFS and 2L-OS compared to patients with long 1L-TTP (2L-PFS: 4.96 vs. 10.2 months, p = 0.0002; 2L-OS: 9.6 vs. 28.0 months, p = 0.0036). Multivariable analyses for 2L-PFS and 2L-OS

showed that 1L-TTP was an independent predictor both as a categorical classification (cutoff: 8.84 months) and as a continuous variable (both $p < 0.05$). The median follow-up duration was 13.1 months (interquartile range: 6.56 – 24.7). *Conclusions*: Patients who achieve a long-term response after first-line TKI therapy could have a favorable prognosis with second-line mTT.

Keywords

Renal cell carcinoma; metastasis; targeted therapy; tyrosine kinase inhibitor; survival; prognosis

1. Introduction

Molecular-targeted therapy (mTT) contributed to the improvement in prognosis for patients with metastatic renal cell carcinoma (mRCC) compared to earlier treatments with cytokine therapy [1]. After failure of first-line therapy, subsequent second-line therapy is performed to prolong overall survival (OS) [2]. According to a previous study, just 100 of 2803 patients (3.57%) achieved a complete response after first-line therapy [3]; most patients had subsequent disease progression even after mTT initiation. Therefore, effective prognosis prediction after sequential mTT is important, and numerous studies have been performed to evaluate and establish a more effective and safe treatment strategy. For example, the Memorial Sloan Kettering Cancer Center (MSKCC) and the International Metastatic Renal-Cell Carcinoma Database Consortium risk classifications include well-known predictors for first- and second-line therapies [4-7]. Imaging evaluations, including the magnitude of early or best tumor shrinkage, and tumor burden have also been identified as useful factors [8-12]. Additionally, systematic inflammatory markers including C-reactive protein or sarcopenia have been recently highlighted as significant predictors for patients with mRCC [13, 14]. In this context, several studies have investigated whether

the response to first-line therapy, such as time to progression (TTP), could predict second-line outcome in sequential mTT. However, to date, the correlation between first- and second-line survival remains controversial [2, 15-18].

Thus, in the present study, we evaluated the influence of TTP during first-line tyrosine kinase inhibitor (TKI) therapy on survival after second-line therapy in a cohort of patients with mRCC after first-line failure without prior cytokine therapy.

2. Patients and methods

Between January 2007 and March 2016, a total of 123 patients at our department received second-line mTT for mRCC. Several patients were excluded because they received prior cytokine therapy (n = 29), first-line mammalian target of rapamycin inhibitor (mTORi) therapy (n = 11), or underwent hemodialysis or kidney transplant (n = 4). Eleven patients whose reason for shifting second-line therapy was adverse events during first-line therapy were excluded. After exclusion of 8 patients whose data were missing, the remaining 60 patients were enrolled in this analysis (Figure 1).

All study procedures were approved by the Institutional Review Board of Tokyo Women's Medical University (ID: 3824), and were in accordance with the

Declaration of Helsinki.

2.1 Study design and endpoint

The endpoints of this study were progression-free survival (PFS) and OS after second-line mTT initiation (2L-PFS and 2L-OS). First-line TTP (1L-TTP) was defined as the time from first-line mTT initiation to the date of progression. We divided patients into two groups based on the median duration of 1L-TTP (i.e., long vs. short). In this study, the median 1L-TTP was 8.84 months (interquartile range 5.3 – 14.0 months). Based on this cut-off value, patients were divided into two groups, as follows: 30 patients (50.0%) with short 1L-TTP (<8.84 months) and 30 patients (50.0%) with long 1L-TTP (≥8.84 months). Clinicopathological parameters, including sex, age at the time of second-line initiation, pathology, first- and second-line MSKCC risk, the number and sites of organs involved by metastatic disease at the time of second-line initiation, first- and second-line agent, and follow-up duration were compared between patients with long and short 1L-TTP. Second-line MSKCC risk was defined according to Motzer's risk classification [6]. Moreover, adverse events (AEs) that required dose modification, including reduction and discontinuation, and reasons for second-line therapy

discontinuation were compared. AEs were graded using the Common Terminology Criteria for Adverse Events of the National Cancer Institute, version 4.0. 2L-PFS and 2L-OS were also compared according to 1L-TTP, and predictors of 2L-PFS and 2L-OS were analyzed by multivariable analyses using factors that could be evaluated at the time of second-line initiation.

2.2 Protocols of molecular-targeted therapies

Our protocols for mTT have been described previously [10, 19].

A main agent for first-line TKI therapy is sunitinib. In the sunitinib regimen, we recently used a 2-week-on/1-week-off schedule, based on findings from our previous study [19]. Sunitinib treatment was orally initiated at a dosage of 50 mg/day and was modified according to patients' conditions. When patients had a poor performance status or were elderly (>80 years), sorafenib or pazopanib is chosen. In the sorafenib regimen, 200 mg sorafenib was orally administered twice daily and was increased up to 800 mg within 2-4 weeks to reduce the acute dermatological reaction, with a continuous dosing schedule. In the pazopanib regimen, pazopanib was orally administered once daily at a dose of 800 mg, with continuous dosing. The dose was reduced to 600 mg and then to 400 mg

according to the severity of AEs. In Japan, first -line axitinib therapy was not covered by insurance; we used axitinib administration as second- and subsequent therapy. In the axitinib regimen, patients received 5 mg of axitinib orally twice daily with a continuous dosing schedule. Based on patients' tolerability, the dosage of axitinib could either increase to 7 mg twice daily or it could be reduced to 3 mg twice daily and then further to 2 mg twice daily, if needed. Patients received oral everolimus 10 mg once daily until disease progression or unacceptable toxicity. A dose reduction to 5 mg once daily was permitted. Temsirolimus was administered weekly at a fixed dose of 25 mg intravenously.

2.3 Statistical analysis

Continuous variables were analyzed using the Mann-Whitney *U*-test, and categorical variables were analyzed using the χ^2 test. PFS was defined as the time from therapy initiation to the date of progression or death from any cause, whichever came first. OS was defined as the time from therapy initiation to death from any cause. Survival was calculated with the Kaplan-Meier method and compared using the log-rank test between patients with long vs. short 1L-TTP. Univariable and multivariable analyses using Cox proportional hazards

regression models were used to identify predictors of survival. To manage larger statistical effects for categorical classification based on dichotomous values in 1L-TTP, we performed multivariable analyses using both a categorical classification (Model 1) and a continuous variable (Model 2). Survival risk was expressed as hazard ratios (HR) and 95% confidence intervals (CIs). All analyses were performed using JMP software (version 11; SAS Institute Inc., Cary, NC, USA), and *p*-values <0.05 were considered statistically significant.

3. Results

3.1 Patient and tumor characteristics

Among the patient characteristics, including sex, age, first- and second-line MSKCC risks, and agents, only first-line MSKCC risk was significantly poorer in patients with short 1L-TTP (p = 0.0288). With respect to the tumor characteristics, including pathology, number of organs with metastasis disease, and metastatic sites (i.e., lymph nodes, lung, bone and liver), there were no significant differences (all p >0.05). Neither AEs that required dose modification nor reasons for second-line therapy discontinuation significantly differed between groups (both p >0.05). Follow-up duration was significantly shorter in patients with short

1L-TTP (p = 0.0008) (Table 1).

3.2 Survival according to 1L-TTP

During the follow-up period, disease progression and death due to any cause occurred in 49 (81.7%) and 41 (68.3%) patients, respectively. As shown in Figures 2a and 2b, 2L-PFS and 2L-OS were significantly shorter in patients with short 1L-TTP compared to those with long 1L-TTP (2L-PFS: 4.96 vs. 10.2 months; p = 0.0002; 2L-OS: 9.6 vs. 28.0 months; p = 0.0036).

3.3 Survival according to 1L-TTP and second-line agent

To evaluate the influence of second-line targeted agent, we divided patients into 4 subgroups according to the combination of 1L-TTP and second-line agent: patients with long 1L-TTP and second-line mTORi (n = 7), long 1L-TTP and second-line TKI (n = 23), short 1L-TTP and second-line mTORi (n = 5), and short 1L-TTP and second-line TKI (n = 25). There were no significant differences in 2L-PFS and 2L-OS in terms of 1L-TTP and type of second-line agent (all p > 0.05) (Figures 3a and 3b).

3.4 Predictors for 2L-PFS and 2L-OS

As shown in Table 2, univariable analysis for 2L-PFS showed that pathology, second-line MSKCC risk, the number of organs with metastatic disease, and 1L-TTP were significant factors. Multivariable analysis for 2L-PFS showed that 1L-TTP was an independent predictor both as a categorical classification (Model 1: HR 2.45, p = 0.0097) and as a continuous variable (Model 2: HR 0.95, p = 0.0034). Pathology in Model 1, and the number of organs with metastatic disease in Models 1 and 2, were also independent factors for 2L-PFS (all $p<0.05$).

As shown in Table 3, the univariable analysis for 2L-OS showed that pathology, second-line MSKCC, the number of organs with metastatic disease, presence of lymph node and lung metastases, and 1L-TTP were significant factors. The multivariable analysis for 2L-OS showed that 1L-TTP was an independent predictor both as a categorical classification (Model 1: HR 2.37, p = 0.176) and as a continuous variable (Model 2: HR 0.95, p = 0.0106). Both in Models 1 and 2, second-line MSKCC risk, the number of organs with metastatic disease, and the presence of lymph node metastasis were also independent factors for 2L-OS (all $p>0.05$).

4. Discussion

The influence of clinical response to first-line TKI on outcome after sequential second-line therapy has been discussed. Al-Marrawi et al. indicated that there were no correlations between first- and second-line PFS in a cohort of 464 patients who received TKI-TKI therapy for mRCC [18]. Similarly, Miyazaki et al. suggested that no significant correlation of PFS was identified in 76 patients receiving TKI-TKI [17]. Meanwhile, a sub-analysis of the AXIS trial, the first randomized phase III trial study to compare two active TKI agents, axitinib vs. sorafenib, for second-line treatment of mRCC [20, 21], showed that longer prior treatment with sunitinib or cytokines was generally associated with longer OS with second-line axitinib or sorafenib [15]. Another retrospective study of 119 patients with mRCC showed that PFS > 6 moths with a prior TKI (sunitinib, sorafenib, or axitinib) was a prognostic factor for longer OS with a second-line TKI or mTORi [2]. Finally, a recent study of mRCC with clear-cell histology reported that 241 patients who remained on first-line TKI between 11 and 22 months benefited from second-line TKI rather than mTORi [16]. Thus, it has been suggested that the short- or long-term response to a first-line TKI therapy should guide optimal choice of the second-line agent [22]. In this context, we indicated

that longer response to first-line TKI therapy could predict favorable prognosis after second-line mTT for mRCC, supporting the findings of previous studies [15, 16]. Interestingly, we also found that tolerability for second-line therapy (i.e., AEs rate and reasons for therapy termination) was not associated with first-line response as shown in Table 1; 1L-TTP predicted second-line survival regardless of second-line tolerability.

In the present cohort, patients with prior cytokine therapy were excluded; this represents a unique aspect of this study in comparison to previous analyses [2, 15, 16]. The current treatment strategy consists of mTT, not cytokines [23, 24]. To the best of our knowledge, this was the first study demonstrating a significant association between first- and second-line outcomes in sequential mTT without prior cytokine therapy. Moreover, as described in a study of Escudier et al., patients who had been previously treated with cytokines for a long period without disease progression may have had inherently less-aggressive disease or better general condition; that is, possible bias exists [15]. Therefore, we believe that our finding in this setting provides important information for physicians.

Unfortunately, we could not identify an indication for second-line therapy (i.e., TKI vs. mTORi) due to the small number of patients receiving second-line mTORi,

although the selection of second-line agent does not appear to be associated with prognosis (Figures 3a and 3b). This finding was consisted with our previous report [25]. Several studies have been performed to clarify the superiority of sequential second-line therapy. Busch et al. compared TKI-TKI and TKI-mTORi groups and suggested that they were equally efficacious in terms of PFS and response rate, whereas the TKI-mTORi group had a tendency toward improved OS [26]. Meanwhile, in the INTORSECT trial, longer OS, but not PFS, was observed in patients with sunitinib-sorafenib vs. sunitinib-temsirolimus treatment [27]. Finally, Park et al. reported that second-line TKI seemed to be as effective as mTORi after first-line TKI failure in terms of PFS and OS [28]. Thus, there has not been strong evidence demonstrating the superiority between second-line TKI vs. mTORi, and it is possible that there is no difference in outcome between them. In this context, Elaidi et al. indicated that second-line TKI, rather than mTORi, was recommended in patients with long response to first-line TKI [16]. This finding might also be observed in the present study; as shown in Figure 3a, patients who had a long 1L-TTP had longer 2L-PFS after second-line TKI, compared to that after second-line mTORi, although this difference was not statistically significant (19.4 vs. 7.2 months, p = 0.155). Meanwhile, in OS, there was no superiority

between second-line TKI and mTORi; this might be due to equal efficacy in terms of OS for third-line therapy of TKI-TKI-mTORi vs. TKI-mTORi-TKI, as previously reported [29]. It is difficult to explain the mechanism of these findings; the response to mTT may depend on not only the power of the targeted agents in terms of tumor shrinkage or suppression, but also tumor characteristics such as sensitivity to therapy or inherent tumor aggressiveness.

The present study has several limitations. First, this study was retrospectively performed in a single-center with a small cohort; therefore, unavoidable biases in patient selection or findings obtained from the analyses exist. Secondly, regimens of mTT were heterogeneous, also potentially introducing bias. Third, dose-limiting toxicity or relative dose intensity in each agent was not evaluated. Therefore, the findings of the present study should be confirmed in a further analysis with a large and homogeneous cohort in terms of patients' characteristics and mTT regimens.

5. Conclusions

This study revealed that long 1L-TTP with first-line TKI therapy was associated with long 2L-PFS and 2L-OS after second-line mTT in a cohort of mRCC patients without prior cytokine therapy. Although the superiority of TKI over mTORi in

second-line therapy could not be confirmed, long response to first-line therapy is a useful factor for the prediction of favorable outcome after second-line mTT, regardless of second-line agent. This information is useful for physicians to establish the treatment strategy for second-line therapy after first-line TKI failure.

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Conflict of interest

Tsunenori Kondo received honoraria from Pfizer, Bayer, and Novartis. All other authors have no conflicts of interest to declare.

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Figure legends

Figure 1: Patient selection

Figure 2: Second-line progression-free and overall survivals according to first-line time to progression

(a, b) A short first-line time to progression was significantly associated with shorter second-line progression-free and overall survivals compared to that for a

long first-line time to progression (median second-line progression-free survival: 4.96 vs. 10.2 months; median overall survival: 9.6 vs. 28.0 months)

TTP, time to progression

Figure 3: Second-line progression-free and overall survivals according to first-line time to progression and second-line agents

(a, b) There were no significant differences in second-line progression-free or overall survival between second-line agents, regardless of first-line time to progression.

*Performed between mTORi vs. TKI in patients with long 1L-TTP

** Performed between mTORi vs. TKI in patients with short 1L-TTP

mTORi, mammalian target of rapamycin inhibitor; TKI, tyrosine kinase inhibitor

Table 1: Patient and tumor characteristics

Parameter	Short 1L-TTP (n = 30)	Long 1L-TTP (n = 30)	p
Sex, %			0.260
Male (ref. female)	19 (63.3)	23 (76.7)	
Age, %			0.432
≥65 years (ref. < 65)	16 (53.3)	19 (63.3)	
Pathology, %			0.0670
Clear-cell carcinoma	20 (66.7)	26 (86.7)	
Non-clear-cell carcinoma	10 (33.3)	4 (13.3)	
Papillary renal cell carcinoma type 2	4 (13.3)	1 (3.33)	
Clear-cell carcinoma with spindle cell	3 (10.0)	1 (3.33)	
Others/ Unknown	3 (10.0)	2 (6.66)	
MSKCC risk, %			0.0288
Favorable/intermediate/poor	1 (3.33)/24 (80.0)/5 (16.7)	8 (26.7)/20 (66.7)/2 (6.67)	

Second-line MSKCC risk, % Favorable/intermediate/poor	 2 (6.67)/16 (53.3)/12 (40.0)	 3 (10.0)/23 (76.7)/4 (13.3)	0.0653
Number of organs with metastatic disease, % Multiple (ref. solitary)	 21 (70.0)	 21 (70.0)	1.000
Lymph node metastasis, % With (ref. without)	 10 (33.3)	 9 (30.0%)	0.781
Lung metastasis, % With (ref. without)	 24 (80.0)	 26 (86.7%)	0.488
Bone metastasis, % With (ref. without)	 3 (10.0)	 9 (30.0%)	0.0528
Liver metastasis, % With (Without)	 6 (20.0)	 4 (13.3%)	0.488
First-line agent, % TKI Sorafenib/Sunitinib/Pazopanib	 30 (100) 10 (33.3)/19 (63.3)/1 (3.33)	 30 (100) 11 (36.7)/ 18 (60.0)/1 (3.33)	0.963

Second-line agent, %			0.519
TKI	25 (83.3)	23 (76.7)	
Sorafenib/Sunitinib/Axitinib/Pazopanib	1 (3.33)/7 (23.3)/16 (53.3)/1 (3.33)	1 (3.33)/6 (20.0)/14 (46.7)/2 (6.67)	
mTORi	5 (16.7)	7 (23.3)	
Temsirolimus/Everolimus	2 (6.67)/3 (10.0)	2 (6.67)/5 (16.7)	
Adverse events requiring dose modification, %			
Any grade			0.559
With (ref. without)	23 (76.7)	21 (70.0)	
Grade 2			1.00
With (ref. without)	11 (36.7)	11 (36.7)	
Grade 3 or more			0.598
With (ref. without)	13 (43.3)	11 (36.7%)	

*Reasons for second-line therapy discontinuation, %			0.129
Disease progression	27 (93.1)	20 (76.9)	
Adverse events	0	3 (11.5)	
Others	2 (6.90)	3 (11.5)	
**Follow-up, months	7.87 (4.84 – 17.5)	21.7 (11.1 – 28.3)	0.0008

*Evaluated in 55 patients (short 1L-TTP: 29; long 1L-TTP: 36 patients) after excluding 5 patients who were still ongoing when these analyses were performed.

**Median and interquartile range

Clinicopathological characteristics of 60 patients with metastatic renal cell carcinoma who underwent second line molecular- targeted therapy after first-line tyrosine kinase inhibitor failure

TTP, time to progression; MSKCC, Memorial Sloan Kettering Cancer Center; TKI, tyrosine kinase inhibitor; mTORi, mammalian target of rapamycin inhibitor

Table 2: Results of univariable and multivariable analyses for 2L-PFS

Parameter	Univariate OR (95%CI)	p	Model 1 Multivariate OR (95%CI)	p	Model 2 Multivariate OR (95%CI)	p
Sex Male (ref. female)	0.65 (0.36 – 1.20)	0.164				
Age, years ≥ 65 (ref. < 65)	0.77 (0.44 – 1.38)	0.377				
Pathology Clear-cell carcinoma (ref. non-clear-cell carcinoma)	0.40 (0.21 – 0.80)	0.0107	0.45 (0.23 – 0.93)	0.0330	0.51 (0.26 – 1.06)	0.0686
MSKCC risk Poor (ref. favorable/intermediate)	0.99 (0.34 – 2.30)	0.988				
Second-line MSKCC risk Poor (ref. favorable/intermediate)	3.02 (1.54 – 5.68)	0.0017	1.75 (0.84 – 3.56)	0.133	2.08 (1.02 – 4.11)	0.0448
Number of organs with metastatic disease Multiple (ref. solitary)	1.93 (1.02 – 3.91)	0.0426	2.09 (1.09 – 4.30)	0.0265	2.06 (1.07 – 4.25)	0.0309

Lymph node metastasis With (ref. without)	 1.42 (0.75 – 2.57)	0.274				
Lung metastasis With (ref. without)	 0.55 (0.28 – 1.18)	0.118				
Bone metastasis With (ref. without)	 0.82 (0.37 – 1.63)	0.597				
Liver metastasis With (Without)	 1.32 (0.54 – 2.79)	0.511				
First-line agent Sutinitinb/pazopanib (ref. sorafenib)	 1.18 (0.65 – 2.29)	0.592				
Second-line agent TKI (ref. mTORi)	 0.65 (0.35 – 1.32)	0.225				
1L-TTP, month (categorical classification) <8.84 (ref. ≥ 8.84)	 2.95 (1.62 – 5.45)	0.0004	 2.45 (1.24 – 4.82)	0.0097	-	-
1L-TTP, month (continuous variable)	0.94 (0.90 – 0.97)	0.0003	-	-	0.95 (0.91 – 0.98)	0.0034

OR, odds ratio; CI, confidence interval

Model 1: A model with 1L-TTP as a categorical classification

Model 2: A model with 1L-TTP as a continuous variable

Table 3: Results of univariable and multivariable analyses for 2L-OS

Parameter	Univariate OR (95%CI)	p	Model 1 Multivariate OR (95%CI)	p	Model 2 Multivariate OR (95%CI)	p
Sex Male (ref. female)	0.69 (0.37 – 1.33)	0.261				
Age, years ≥ 65 (ref. < 65)	0.71 (0.38 – 1.32)	0.274				
Pathology Clear-cell carcinoma (ref. non-clear cell carcinoma)	0.41 (0.21 – 0.88)	0.0230	0.61 (0.28 – 1.39)	0.232	0.64 (0.30 – 1.46)	0.279
MSKCC risk Poor (ref. favorable/intermediate)	1.20 (0.35 – 3.07)	0.742				
Second-line MSKCC risk Poor (ref. favorable/intermediate)	2.96 (1.49 – 5.69)	0.0027	2.48 (1.16 – 5.15)	0.0201	2.42 (1.14 – 4.98)	0.0218
Number of organs with metastatic disease Multiple (ref. solitary)	2.88 (1.37 – 6.86)	0.0044	2.40 (1.12 – 5.79)	0.0239	2.42 (1.12 – 5.82)	0.0243

Lymph node metastasis With (ref. without)	 2.01 (1.03 – 3.78)	0.0410	 2.56 (1.25 – 5.12)	0.0110	 3.01 (1.46 – 6.07)	0.0034
Lung metastasis With (ref. without)	 2.50 (1.10 – 5.18)	0.0307	 2.41 (0.99 – 5.44)	0.0522	 2.41 (0.99 – 5.45)	0.0530
Bone metastasis With (ref. without)	 1.11 (0.47 – 2.30)	0.798				
Liver metastasis With (Without)	 1.87 (0.75 – 4.10)	0.168				
First-line agent Sutinitinb/pazopanib (ref. sorafenib)	 1.01 (0.53 – 2.01)	0.982				
Second-line agent TKI (ref. mTORi)	 1.13 (0.56 – 2.50)	0.735				
1L-TTP, month (categorical classification) <8.84 (ref. ≥8.84)	 2.48 (1.32 – 4.73)	0.0047	 2.37 (1.16 – 4.93)	0.0176	-	-
1L-TTP, month (continuous variable)	0.95 (0.91 – 0.99)	0.0057	-	-	0.95 (0.90 – 0.99)	0.0106

Model 1: A model with 1L-TTP as a categorical classification

Model 2: A model with 1L-TTP as a continuous variable

Figure 1

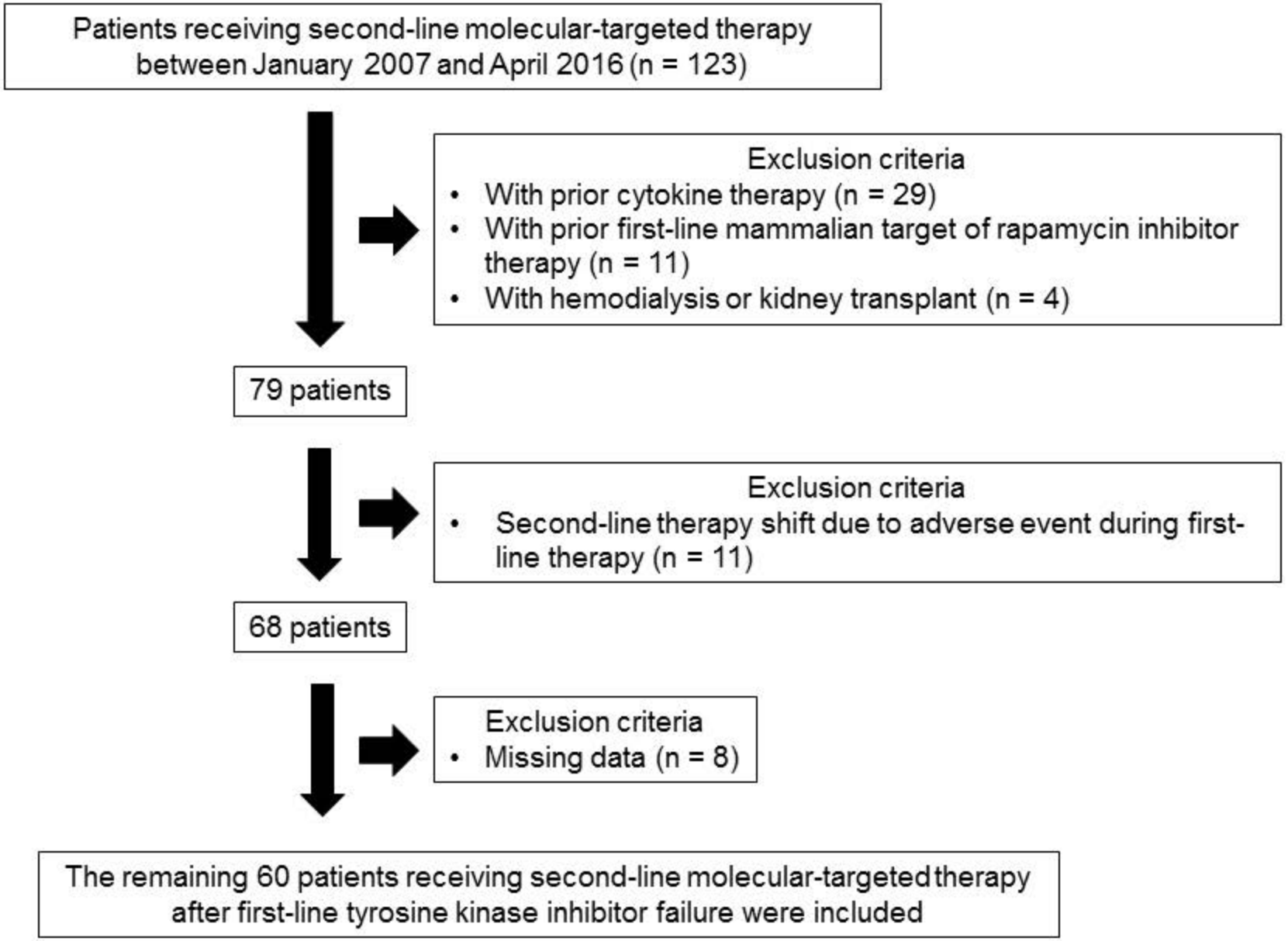

Patients receiving second-line molecular-targeted therapy between January 2007 and April 2016 (n = 123)
Exclusion criteria
• With prior cytokine therapy (n = 29)
• With prior first-line mammalian target of rapamycin inhibitor therapy (n = 11)
• With hemodialysis or kidney transplant (n = 4)
79 patients
Exclusion criteria
• Second-line therapy shift due to adverse event during first-line therapy (n = 11)
68 patients
Exclusion criteria
• Missing data (n = 8)
The remaining 60 patients receiving second-line molecular-targeted therapy after first-line tyrosine kinase inhibitor failure were included

Figure 2

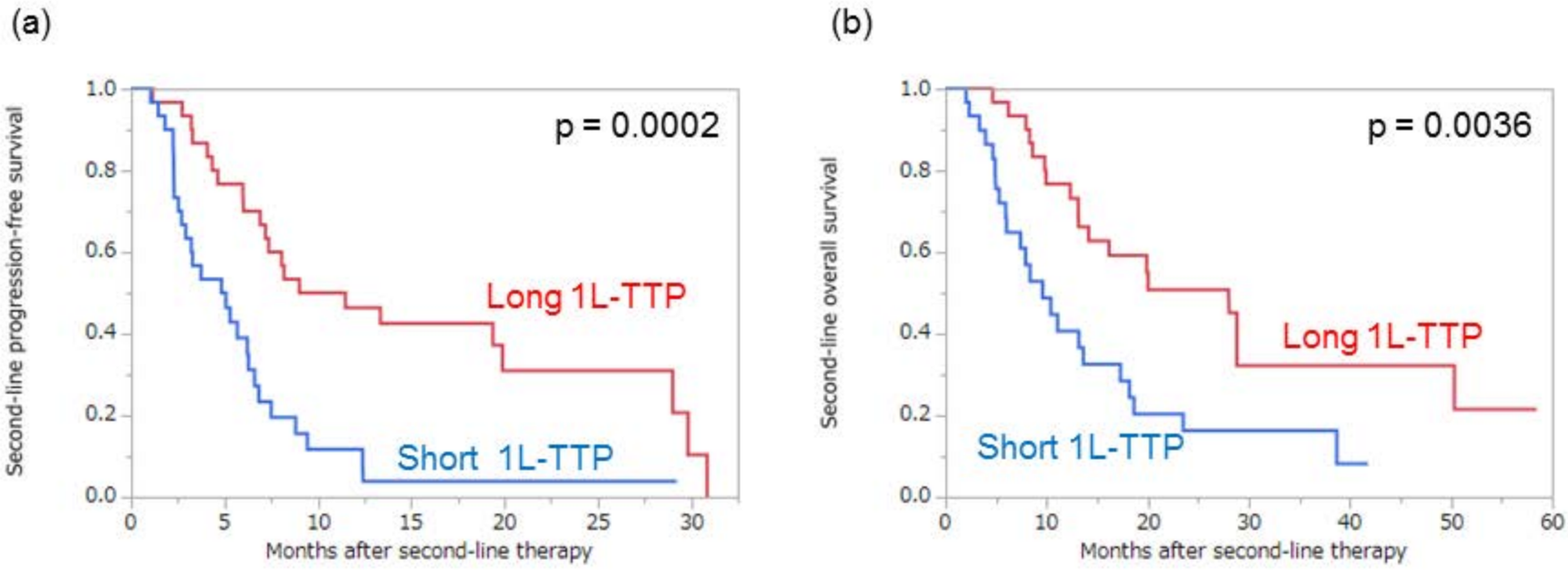
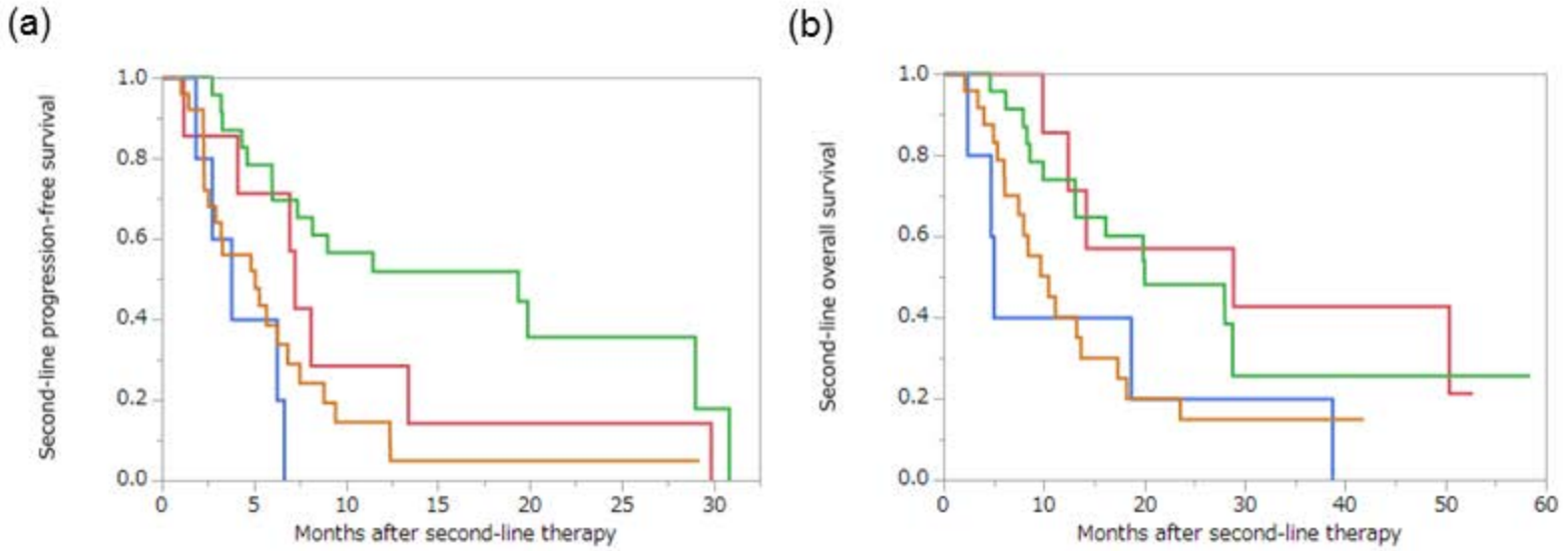

(a)
Second-line progression-free survival
1.0
0.8
0.6
0.4
0.2
0.0
0
5
10
15
20
25
30
Months after second-line therapy
p = 0.0002
Long 1L-TTP
Short 1L-TTP
(b)
Second-line overall survival
1.0
0.8
0.6
0.4
0.2
0.0
0
10
20
30
40
50
60
Months after second-line therapy
p = 0.0036
Long 1L-TTP
Short 1L-TTP

Figure 3



Subgroup	Median		Median	
1L-TTP - second-line agent				
Long - mTORi (n = 7)	7.2m	p = 0.155*	28.8m	p = 0.642*
Long - TKI (n = 23)	19.4m		20.0m	
Short - mTORi (n = 5)	3.75m	p = 0.326**	4.96m	p = 0.685**
Short - TKI (n = 25)	5.07m		10.4m	