Effect of the timing of best tumor shrinkage on survival of patients with metastatic renal cell carcinoma who received first-line tyrosine kinase inhibitor therapy

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Abstract

Background: To evaluate the association between the timing of best tumor shrinkage (bTS) and metastatic renal cell carcinoma (mRCC) patient survival after 1st-line tyrosine kinase inhibitor (TKI) therapy.

Methods: The tumors of 91 patients with mRCC showed a response to TKIs. None of the patients had received prior cytokine therapy. The magnitude of bTS was categorized according to the Response Evaluation Criteria in Solid Tumors v. 1.1. The patients were divided into two subgroups according to the timing of bTS: early responders (≤3 months) and late responders (>3 months). Overall survival (OS) and progression-free survival (PFS) after 1st-line TKI therapy were evaluated, and factors predicting survival were examined.

Results: Sunitinib, sorafenib, and pazopanib were used in 62, 25, and 4 responders, respectively. In total, 52 (57.1%) and 39 (42.9%) patients were early and late responders, respectively. Early responders had significantly lower PFS compared to late responders (median survival: 11.4 vs. 19.1 months, log-rank test: $p = 0.0263$), although there were no significant differences in the OS of early and late responders (27.0 vs. 30.1 months, $p = 0.306$). Multivariate analyses revealed that the timing of bTS was an independent predictor of PFS and OS (PFS: hazard ratio 4.09, $p < 0.0001$; OS: hazard ratio 2.32, $p = 0.0107$).

Conclusion: The timing of bTS was an independent predictor of survival in patients with mRCC who

received 1st-line TKIs.

Key words

Tumor shrinkage, timing, metastatic renal cell carcinoma, tyrosine kinase inhibitor, predictor

Abbreviation

bTS, best tumor shrinkage; mRCC, metastatic renal cell carcinoma; TKI, tyrosine kinase inhibitor, OS, overall survival; PFS, progression-free survival; RECIST, the standard Response Evaluation Criteria in Solid Tumors: AE, adverse events; HR, hazard ratios; CI, confidence intervals; MSKCC, Memorial Sloan Kettering Cancer Center

Introduction

The standard treatment strategy for metastatic renal cell carcinoma (mRCC) consists of molecular-targeted agents, and the prognosis of patients has improved, compared to that observed in the era of cytokine therapy [1]. Among molecular-targeted agents, tyrosine kinase inhibitors (TKIs), which are multi-targeted inhibitors of receptors for vascular endothelial growth factors, have powerful antitumor activities against mRCC, as demonstrated in previous randomized trials [2-4].

As the response and survival rates have improved since the introduction of targeted agents, the prognostic or predictive indicators of outcomes have been investigated. In this context, the objective response, i.e., tumor shrinkage (TS), based on the standard Response Evaluation Criteria in Solid Tumors (RECIST) [5], is a useful marker for predicting the outcomes. The best TS (bTS), which is the magnitude of maximum TS [6,7], or early TS, which is the magnitude of TS at a single cut-off time, for example 3 months after therapy initiation [8,9], is an independent predictor of survival after targeted agent therapy. However, to the best of our knowledge, studies that investigated the influence of timing of bTS on survival are limited. Moreover, in the previous studies [6-10], the cohorts consisted of patients who received prior cytokine therapy; as the current treatment strategy for mRCC includes the use of molecular-targeted agents without previous cytokine therapy [2,11,12], data are needed from patients who have not received previous cytokine therapy.

Therefore, in this study, we evaluated the influence of timing of bTS on patient survival among

patients with mRCC who received 1st-line TKI therapy without prior cytokine therapy.

Patients and methods

Patients and study design

The Internal Ethics Review Board of Tokyo Women's Medical University approved this retrospective study (ID: 3871), which was performed in accordance with the principals outlined in the Declaration of Helsinki.

In our department, a total of 242 patients received 1st-line TKIs (115 who received sunitinib; 120, sorafenib; and 7, pazopanib) between January 2008 and March 2015. Of these 242 patients, 40 patients who had received prior cytokine therapy, 21 patients who had received TKIs for less than 4 weeks, 23 patients who had received hemodialysis or kidney transplantation, and 45 patients whose detailed clinical or imaging data were missing were excluded. Furthermore, we excluded 22 patients because no tumor response was observed after therapy initiation. The remaining 91 patients (62 who received sunitinib; 25, sorafenib; and 4, pazopanib) were enrolled. These patients were divided into two subgroups according to the timing of bTS. Patients were categorized as early responders when the maximum TS was obtained within 3 months after therapy initiation and the tumors did not shrink any more after that. Similarly, late responders were defined as those who showed maximum TS after 3 months since therapy initiation (Figure 1). Clinical and laboratory data were obtained from the

electronic database and patient medical records.

Imaging methods and imaging evaluation

Baseline imaging examinations, including plain or contrast-enhanced computed tomography or magnetic resonance imaging of the chest, abdomen, and pelvis, was performed within 28 days before the start of a new therapy course. Regular scans were also performed every 8-12 weeks of therapy, according to the patients' condition.

The target lesions were selected on the basis of the baseline imaging results, and evaluated according to RECIST v. 1.1 [5]. The bTS was defined as the time point at which maximum TS was observed (percentage change in the sum diameter of all the target lesions). Sclerotic osseous lesions were excluded. Two investigators (H.I. and T.Y.), who were blinded to all other clinical parameters and the patient outcomes, performed all image analyses.

In this study, response duration was defined as the time between initial response with > 0% tumor shrinkage and disease progression.

TKI regimens

In this study, none of the patients had received prior cytokine therapy. About the strategy of targeted therapy used in this study, the first-choice agent was sorafenib until December 2008 when sunitinib

could not be used in our department because of it had not yet been approved for use. After December 2008, we used sunitinib as the 1st-line agent.

In the sunitinib regimen, we treated our patients with mRCC using a 4-week-on/2-week-off schedule or a 2-week-on/1-week-off schedule on the basis of the findings in our previous study [13]. Sunitinib treatment was initiated at a dosage of 50 mg/day, and was modified according to the following three patient factors: (1) age of >65 years, (2) serum creatinine levels of >2 mg/dL, and (3) a body weight of <50 kg. If one of these three factors was noted, the initial dose was reduced to 37.5 mg. If two of these three factors were observed, the initial dose was reduced to 25 mg. Even if all the three factors were observed, we never reduced the initial dose to <25 mg. The dose was subsequently increased by 12.5 mg until we found the highest dose that these patients could tolerate, although this dose never exceeded 50 mg.

In the sorafenib regimen, 400 mg sorafenib was administered twice daily, with a continuous dosing schedule. When severe adverse events (AEs) developed, the dose was reduced to 400 mg once daily, followed by an additional reduction to a single 400 mg dose every alternate day.

When patients had a poor performance status or were elderly (>65 years), pazopanib was chosen as the 1st-line TKI agent. In the pazopanib regimen, pazopanib was administered orally once daily at a dose of 800mg, with continuous dosing. The dose was reduced to 600 mg and then to 400 mg according to the severity of the AEs.

In all the regimens, the drugs were administered until disease progression was observed or intolerable AEs developed.

Statistical analysis

Continuous variables were analyzed using the Mann-Whitney *U*-test, and categorical variables were analyzed using the χ^2 test. Progression-free survival (PFS) and overall survival (OS) after the administration of the 1st-line TKIs were calculated using the Kaplan-Meier method, and compared using the log-rank test. PFS was defined as the time of 1st-line TKI initiation to the date of progression or death from any cause, whichever came first. OS was defined as the time of 1st-line TKI initiation to death from any cause. Univariate and multivariate analyses were used to identify factors that were associated with PFS and OS, via Cox proportional hazards regression models. Risk of survival 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 differences were considered statistically significant at *p*-values of <0.05.

Results

Patient characteristics

According to the timing of bTS, 52 and 39 patients were early and late responders, respectively. There

were no significant differences in the patient baseline characteristics (Table 1). The rate of patients with pancreatic metastasis was significant higher among late responders ($p = 0.0171$). There was no significant difference in magnitude of bTS according to categorical classification based on RECIST and continuous variable ($p > 0.05$, both). As expected, time from treatment initiation to bTS was significantly earlier in early responders ($p < 0.0001$), whereas response duration between the initial response to disease progression did not significantly differ between early and late responders ($p = 0.716$). Moreover, magnitude of tumor shrinkage within first 3 months after treatment initiation (i.e., initial evaluation) was significantly greater in early responders according to categorical classification based on RECIST and continuous variable ($p < 0.05$, both).

The magnitude of bTS of target lesions according to the 1st-line targeted agents is demonstrated by using a waterfall plot for individual patients (Figure 2).

Survival according to the timing of bTS

During the follow-up period, disease progression and death occurred in 67 and 44 patients, respectively. Figure 3 and Figure 4 show the Kaplan-Meier survival curves of PFS and OS after 1st-line TKI therapy according to the timing of bTS. Early responders had significantly shorter PFS compared to late responders (median survival: 11.4 vs. 19.1 months, $p = 0.0263$), although there was no significant difference in OS between early and late responders (27.0 vs. 30.1 months, $p = 0.306$).

Prognostic indicators for patient survival

On univariate analysis, the significant predictors of PFS were pathology, prior nephrectomy status, number of metastatic organs, baseline volume of metastasis, magnitude of bTS, response duration, and timing of bTS (all. $p < 0.05$), and the Memorial Sloan Kettering Cancer Center (MSKCC) outcome classification tended towards significance ($p = 0.0543$). On multivariate analysis for PFS, the timing of bTS was an independent predictor (HR 4.09, $p < 0.0001$), along with the MSKCC outcome classification ($p = 0.0365$) and response duration ($p < 0.0001$) (Table 2). On univariate analysis, the significant predictors of OS were prior nephrectomy status, MSKCC outcome classification, number of metastatic organs, baseline volume of metastasis, and response duration (all, $p < 0.05$). On multivariate analysis for OS, the timing of bTS was an independent predictor (HR 2.32, $p = 0.0107$), along with MSKCC outcome classification ($p = 0.0050$), number of metastatic organs ($p = 0.0214$), baseline volume of metastasis ($p = 0.0035$), and response duration ($p < 0.0001$) (Table 3).

Outcomes after 1st-line TKI failure according to the timing of bTS

We evaluated the outcomes of 67 patients who subsequently showed failure to 1st-line TKIs. There were no significant differences in the rate of shifting to 2nd-line therapy between early and late responders (68.3% vs. 57.7%, respectively; $p = 0.438$). Among 43 patients who were shifted to 2nd-

line therapy, of the early responders, 6 received sunitinib, 1 received sorafenib, 17 received axitinib, and 4 received everolimus; and of the late responders, 2 received sunitinib, 1 recieved pazopanib, 7 received axitinib, 2 received temsiroimus, and 3 received everolimus (Table 4). Among the 43 responders, the Kaplan-Meier survival curves for OS after 2nd-line therapy revealed that there were no significant differences between early (n = 28) and late responders (n = 15) (median survival: 13.2 vs. 19.9 months, $p = 0.764$) (Figure 5).

Discussion

The present study revealed that the timing of bTS was an independent predictor of PFS and OS among the patients with mRCC who received 1st-line TKIs without prior cytokine therapy. We did not observe any significant correlation between the timing of bTS and OS according to the log-rank test. However, on multivariate analysis, the timing of bTS was an independent predictive factor of PFS and OS, after adjustments of other factors. Moreover, we found no significant differences in the outcomes after 1st-line TKI failure; the rate of patients who could be shifted to 2nd-line therapy, and the OS after 2nd-line therapy did not differ between early and late responders. Hence, the timing of bTS during 1st-line TKI therapy was an independent predictor of survival, regardless of the outcomes after 1st-line TKI failure. These results indicated that evaluating imaging a second time (or more) can possibly predict patient prognosis; therefore, we believe that timing of bTS can be utilized as a new and effective predictive

marker in clinical practice because it can be evaluated while TKI treatment is ongoing.

The molecular-targeted agents such as TKIs, which inactive multiple signal transduction pathways that mediate angiogenesis, have been developed for the treatment of mRCC. These new agents contributed to improving the prognosis of patients with mRCC, compared to that observed in the cytokine era [1]. The magnitude of bTS could predict patient survival in those who received 1st-line targeted therapy [6], as well as those who received 2nd-line therapy [7,14]. According to a previous study by Grünwald et al. [7], survival was significantly correlated with the depth of remission during 1st- and 2nd-line therapy. However, in clinical practice, it is difficult to predict when we can observe bTS during treatment. Meanwhile, early TS was also identified as an effective predictor of the survival of patients with mRCC who received 1st-line targeted therapy [8,9]. Recently, Miyake et al. [9] suggested that the magnitude of early TS, identified 3 months after therapy initiation, was an independent prognostic indicator of OS among patients with mRCC who received 1st-line sunitinib and sorafenib. This method with fixed a time-point can be used to resolve a weak point of the magnitude of bTS for predicting survival.

However, it remains unclear how the timing of bTS influences patient survival after 1st-line TKI therapy. Molina et al. [10] previously reported that the timing of bTS significantly influenced PFS ($p = 0.001$) but not OS ($p = 0.144$) in a large cohort study among patients who received 1st-line sunitinib, although the Kaplan-Meier curve seemed to show a tendency towards a significant difference in OS.

However, in their study, only the Kaplan-Meier method was performed; multivariate analysis was not performed. Moreover, because their cohort consisted of patients who had participated in previous trials, the general condition of the enrolled patients might have been better than that of patients usually observed in clinical settings. Furthermore, approximately 25% of the patients in the cohort studied by Molina et al. [10] were treated with prior cytokine therapy (101/398 responders). Hence, the present study demonstrates that the timing of bTS is an independent predictor of PFS and OS of patients with mRCC after 1st-line TKIs without prior cytokine therapy in clinical settings. In this study, multivariate analysis revealed that the timing of bTS was an independent predictor of OS, although the Kaplan-Meier method did not show statistical difference. This difference might be caused by a severe confounding bias. After adjusting for other factors including prior nephrectomy status, MSKCC outcome classification, number of metastatic organs, tumor burden, and response duration [15-19], the timing of bTS was shown to be an independent predictive factor. Furthermore, MSKCC outcome classification, number of metastatic organs, baseline volume of metastasis, and response duration also remained significant predictive indicators. We believe that these results obtained on multivariate analysis should be emphasized.

Our analysis showed that late responders had superior PFS and OS compared to early responders, and among all responders, 42.9% were late responders. This rate was similar to that obtained by Molina et al. [10] (38.9%, 155/398 sunitinib-responders). This information obtained in the study by

Molina et al. [10] and in our study is important because some tumors showed slow tumor shrinkage during a relatively long treatment period. Moreover, some late responders (25.6%) had no response at initial treatment evaluation (i.e., within the first 3 months after treatment initiation), and had weaker tumor shrinkage compared to early responders, as shown in Table 1. In this context, these results indicated that even if initial tumor response was poor, some patients subsequently had a higher magnitude of tumor shrinkage, that resulting in better prognosis.

This study has several limitations. First, as this was a retrospective, single-center study with a relatively small cohort, our survival analyses may have some bias. Therefore, our results should be confirmed in a prospective, multi-institution study with a large cohort. Second, we did not consider the withdrawal period and/or dose changes of agents caused by the AEs; the true duration and/or density (i.e., relative dose intensity) of treatment were not assessed. In addition, the enrolled patients in the present study were administered various kinds of TKIs, and the schedule or density was not uniform. Third, the indications for treatment with targeted agents were not determined according to strictly established criteria, which may have affected the outcomes of this study. Forth, the present study showed that late responders had superior survival rates compared to early responders, in spite of the weaker magnitude of initial tumor shrinkage; however, this result seemed to be inconsistent with findings from previous studies [8,9]. Seidel et al. [8] and Miyake et al. [9] reported that initial/early stronger tumor shrinkage was defined as a predictor of mRCC in patients receiving TKI

treatment. However, in their studies, the influence of bTS magnitude was not evaluated. Moreover, there were differences in study cohorts and factors evaluated in the multivariate analyses. Thus, these differences might explain the discrepancy between their and our results.

In conclusion, the present study demonstrated that the timing of bTS was an independent predictive factor of PFS and OS among patients with mRCC who showed a response to 1st-line TKIs. Late responders had superior survival after 1st-line TKI therapy compared to early responders, regardless of the outcomes after 1st-line failure. This new marker may enable effective prediction of patient survival during treatment.

Conflicts of Interest

The authors have no conflicts of interest to disclose.

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Figure legends

Figure 1: Patient selection

SU, sunitinib; SO, sorafenib; PA, pazopanib; CK, cytokine; HD, hemodialysis; KTx, kidney transplantation; TKI, tyrosine kinase inhibitor; TS, tumor shrinkage

Figure 2: Waterfall plot

Waterfall plot showing the magnitude of best tumor shrinkage according to the 1st-line TKIs used in each patient, with comparisons of SU (blue bar, n = 62), SO (red, n = 25), and PA (green, n = 4). TKI, tyrosine kinase inhibitor; SU, sunitinib; SO, sorafenib; PA, pazopanib

Figure 3: Progression-free survival according to response to 1st-line tyrosine kinase inhibitor therapy

The survival rate was calculated by the Kaplan-Meier method, and statistical significance was compared using the log-rank test ($p = 0.0263$).

Figure 4: Overall survival according to response to 1st-line tyrosine kinase inhibitor therapy

The survival rate was calculated by the Kaplan-Meier method, and statistical significance was compared using the log-rank test ($p = 0.306$).

Figure 5: Overall survival after 2nd-line targeted therapy according to timing of best tumor shrinkage

after 1st-line tyrosine kinase inhibitor therapy (n = 43)

The survival rate was calculated by the Kaplan-Meier method, and statistical significance was compared using the log-rank test ($p = 0.764$).

Table 1: Patient characteristics

Variable	**Early responders (n = 52)**	**Late responders (n = 39)**	***p****
Mean age, year (median, range)	66.2 (68.0, 29.0 – 87.0)	65.1 (65.0, 41.0 – 77.0)	0.249
Sex			0.777
Male	40 (76.9%)	29 (74.4%)	
Female	12 (23.1%)	10 (25.6%)	
Pathology			0.352
CCC	44 (84.6%)	30 (76.9%)	
Non-CCC	8 (15.4%)	9 (23.1%)	
CCC with spindle	1 (1.92%)	4 (10.3%)	
MTSC	0	2 (5.13%)	
PRCC type 2	2 (3.85%)	1 (2.56%)	
Medullary carcinoma	1 (1.92%)	0	
Unknown	4 (7.69%)	2 (5.13%)	
Prior nephrectomy			0.629
With	47 (90.4%)	34 (87.2%)	
Radical nephrectomy	45 (86.5%)	30 (76.9%)	
Partial nephrectomy	2 (3.85%)	4 (10.3%)	
Without	5 (9.62%)	5 (12.8%)	
Time from diagnosis to treatment, day			0.359
≥ 365 day	14 (26.9%)	14 (35.9%)	
< 365 day	38 (73.1%)	25 (64.1%)	
MSKCC outcome classification			0.637
Favorable	8 (15.4%)	9 (23.1%)	
Intermediate	39 (75.0%)	27 (69.2%)	
Poor	5 (9.62%)	3 (7.69%)	
Targeted agent			0.915
Sunitinib	35 (67.3%)	27 (69.2%)	
Sorafenib	15 (28.9%)	10 (25.6%)	
Pazopanib	2 (3.85%)	2 (5.13%)	
Other therapy			0.137
With	8 (15.9%)	11 (28.2%)	
Radiation	4 (7.69%)	7 (17.9%)	
Metastatectomy	4 (7.69%)	5 (12.8%)	

Without	44 (84.6%)	28 (71.8%)	
Metastatic lesions			0.805
Solitary	20 (38.5%)	16 (41.0%)	
Multiple	32 (61.5%)	23 (59.0%)	
Metastatic organ			
Lungs	40 (76.9%)	26 (66.7%)	0.278
Bone	11 (21.2%)	11 (28.2%)	0.437
Liver	7 (13.5%)	4 (10.3%)	0.643
Adrenal grands	3 (5.77%)	6 (15.4%)	0.128
Pancreas	1 (1.92%)	6 (15.4%)	0.0171
Lymph nodes	17 (32.7%)	11 (28.2%)	0.646
Other	5 (9.62%)	5 (12.8%)	0.629
Mean baseline volume of metastasis, cm (median, range)	7.54 (4.70, 1.0 – 42.7)	9.06 (6.10, 1.30 – 31.5)	0.151
Magnitude of bTS (categorical classification based on RECIST)			0.568
-100% (CR)	3 (5.77%)	3 (7.69%)	
- 30% to -100% (PR)	14 (26.9%)	14 (35.9%)	
0% to -30%	35 (67.3%)	22 (56.4%)	
Magnitude of bTS (continuous variable), %	-27.6 (-18.1, -100 - -1.3)	-32.2 (-23.0, - 100 - -1.1)	0.365
Time to bTS, month	2.42 (2.5, 0.53 – 3.71)	8.68 (6.64, 4.27 – 39.4)	< 0.0001
Response duration			0.543
≥ 6 months	30 (57.7%)	20 (51.3%)	
< 6 months	22 (42.3%)	19 (48.7%)	
Magnitude of tumor shrinkage within first 3 months (categorical classification based on RECIST)			0.0005
-100% (CR)	3 (5.77%)	0	
- 30% to -100% (PR)	14 (26.9%)	12 (30.8%)	
0% to - 30%	35 (67.3%)	17 (43.6%)	
> 0%	0	10 (25.6%)	
Magnitude of tumor shrinkage within first 3 months (continuous variable)	-27.6 (-18.1, -100 − -1.3)	-14.4 (-10.1, -86.5 – 21.9)	0.0096
Mean follow-up period, months (median, range)	23.3 (19.9, 4.31 – 67.7)	29.0 (21.4, 5.95 – 87.2)	0.106

*p-value is analyzed between early and late responders.

CCC, clear cell carcinoma; MTSC, mucinous tubular and spindle cell carcinoma; PRCC, papillary renal cell carcinoma; MSKCC, Memorial Sloan Kettering Cancer Center; bTS, best tumor shrinkage; RECIST, Response Evaluation Criteria in Solid Tumors; CR, complete response; PR, partial response; SD, stable disease

Table 2: Univariate and multivariate analyses for progression-free survival

Variable	**Univariate** **HR (95% CI)**	**p**	**Multivariate** **HR (95% CI)**	**p**
Age	0.99 (0.96 – 1.02)	0.557		
Sex				
Male	Ref.	-		
Female	1.15 (0.62 – 2.00)	0.641		
Pathology				
CCC	Ref.	-	Ref.	-
Non-CCC/ Unknown	2.17 (1.17 – 3.80)	0.0159	1.09 (0.55 – 2.05)	0.798
Prior nephrectomy				
With	Ref.	-	Ref.	-
Without	3.38 (1.52 – 6.76)	0.0042	1.19 (0.49 – 1.83)	0.692
Time from diagnosis to treatment				
≥ 365 day	Ref.	-		
< 365 day	1.55 (0.92 – 2.73)	0.104		
MSKCC outcome classification				
Favorable/ Intermediate	Ref.	-	Ref.	-
Poor	2.59 (0.98 – 5.69)	0.0543	3.12 (1.08 – 7.87)	0.0365
Targeted agent				
Sunitinib	Ref.	-		
Sorafenib/ Pazopanib	1.07 (0.64 – 1.75)	0.780		
Metastatic lesions				
Solitary	Ref.	-	Ref.	-
Multiple	2.70 (1.57 – 4.73)	0.0002	1.57 (0.82 – 3.07)	0.176
Baseline volume of metastasis	1.06 (1.03 – 1.08)	0.0003	1.02 (0.99 – 1.05)	0.219
Magnitude of bTS				
-30% to -100%	Ref.	-	Ref.	-
0% to -30%	1.75 (1.05 – 2.99)	0.0304	1.24 (0.69 – 2.27)	0.472
Response duration				
≥ 6 months	Ref.	-	Ref.	-
< 6 months	8.70 (4.76 – 16.3)	< 0.0001	13.8 (6.32 – 31.0)	< 0.0001
Timing of bTS				
Early responder	1.75 (1.07 – 2.93)	0.0258	4.09 (2.24 – 7.81)	< 0.0001

Late responder	Ref.	-	Ref.	-

HR, hazard ratio; CI, confidence intervals; CCC, clear cell carcinoma; ; MSKCC, Memorial Sloan Kettering Cancer Center; bTS, best tumor shrinkage; CR, complete response; PR, partial response; SD, stable disease

Table 3: Univariate and multivariate analyses for overall survival

Variable	**Univariate** **HR (95% CI)**	**p**	**Multivariate** **HR (95% CI)**	**p**
Age	0.99 (0.96 – 1.02)	0.487		
Sex				
Male	Ref.	-		
Female	1.32 (0.63 – 2.55)	0.446		
Pathology				
CCC	Ref.	-		
Non-CCC/ Unknown	1.64 (0.76 – 3.22)	0.196		
Prior nephrectomy				
With	Ref.	-	Ref.	-
Without	5.48 (2.23 – 12.4)	0.0005	1.83 (0.71 – 4.37)	0.200
Time from diagnosis to treatment				
≥ 365 day	Ref.	-		
< 365 day	1.64 (0.85 – 3.42)	0.141		
MSKCC outcome classification				
Favorable/ Intermediate	Ref.	-	Ref.	-
Poor	4.42 (1.47 – 10.8)	0.0109	5.90 (1.81 – 16.5)	0.0050
Targeted agent				
Sunitinib	Ref.	-		
Sorafenib/ Pazopanib	1.11 (0.59 – 2.04)	0.733		
Metastatic lesions				
Solitary	Ref.	-	Ref.	-
Multiple	3.55 (1.80 – 7.68)	0.0002	2.51 (1.14 – 5.90)	0.0214
Baseline volume of metastasis	1.08 (1.05 – 1.11)	<0.0001	1.05 (1.02 – 1.09)	0.0035
Magnitude of bTS				
-30% to -100%	Ref.	-		
0% to -30%	1.66 (0.88 – 3.30)	0.119		
Response duration				
≥ 6 months	Ref.	-	Ref.	-
< 6 months	6.05 (3.19 – 11.8)	< 0.0001	6.70 (3.11 – 14.7)	< 0.0001

Timing of bTS				
Early responder	1.37 (0.75 – 2.58)	0.304	2.32 (1.21 – 4.60)	0.0107
Late responder	Ref.	-	Ref.	-

HR, hazard ratio; CI, confidence intervals; CCC, clear cell carcinoma; ; MSKCC, Memorial Sloan Kettering Cancer Center; bTS, best tumor shrinkage; CR, complete response; PR, partial response; SD, stable disease

Table 4: Comparison of 2nd-line targeted therapy according to timing of tumor shrinkage (24 patients without progression disease during 1st-line therapy were excluded).

2nd-line therapy	**All (n = 67)**	**Early responders (n = 41)**	**Late responders (n = 26)**	***p***
2nd-line targeted therapy status				0.438
With	43 (64.2%)	28 (68.3%)	15 (57.7%)	
Without	24 (35.8%)	13 (31.7%)	11 (42.3%)	
Agents				
Sunitinib	8 (18.6%)	6 (21.4%)	2 (13.3%)	
Sorafenib	1 (2.33%)	1 (3.57%)	0	
Pazopanib	1 (2.33%)	0	1 (6.67%)	
Axitinib	24 (55.8%)	17 (60.7%)	7 (46.7%)	
Temsirolimus	2 (4.65%)	0	2 (13.3%)	
Everolimus	7 (16.3%)	4 (14.3%)	3 (20.0%)	

Figure 1

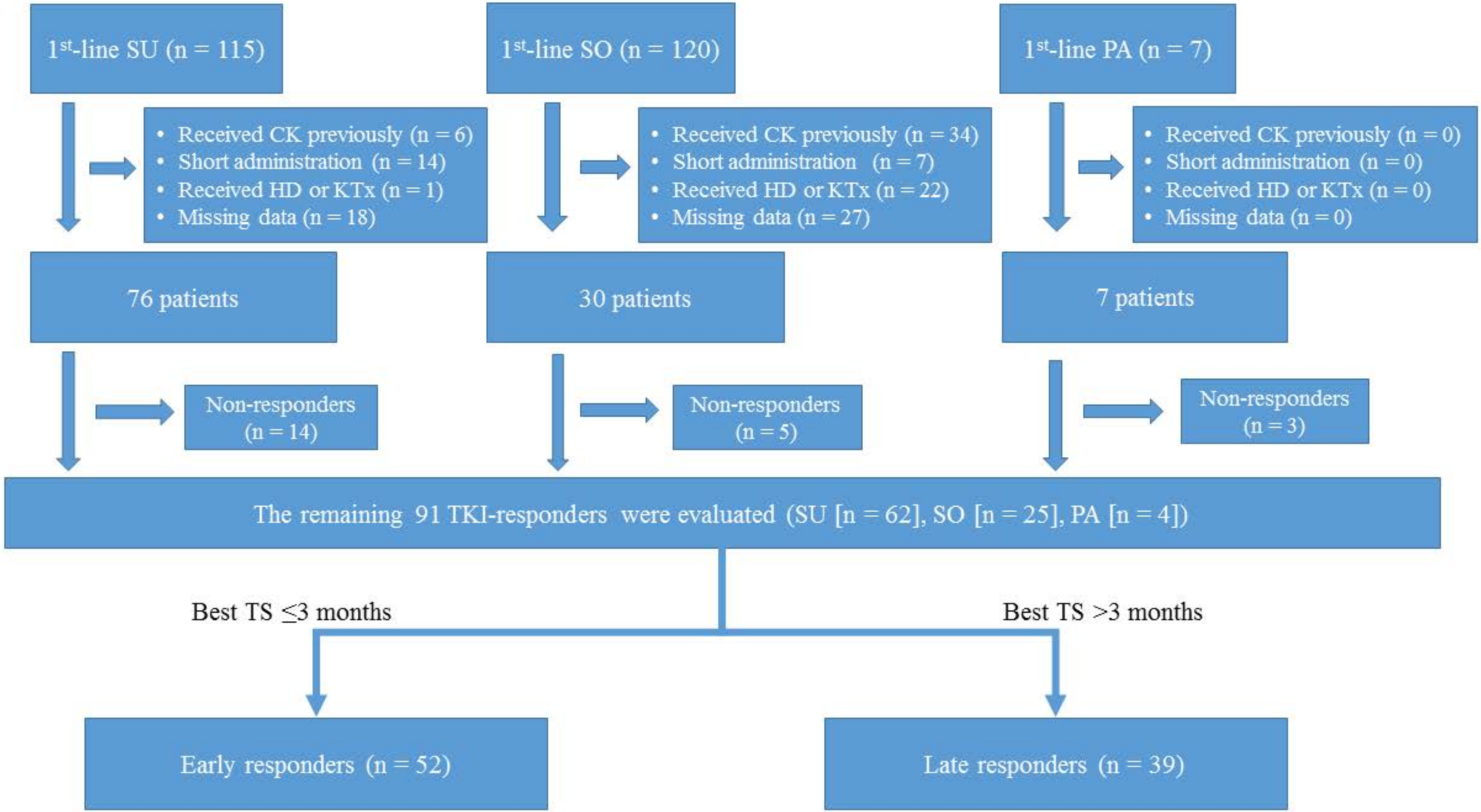

1st-line SU (n = 115)
1st-line SO (n = 120)
1st-line PA (n = 7)
• Received CK previously (n = 6)
• Short administration (n = 14)
• Received HD or KTx (n = 1)
• Missing data (n = 18)
• Received CK previously (n = 34)
• Short administration (n = 7)
• Received HD or KTx (n = 22)
• Missing data (n = 27)
• Received CK previously (n = 0)
• Short administration (n = 0)
• Received HD or KTx (n = 0)
• Missing data (n = 0)
76 patients
30 patients
7 patients
Non-responders (n = 14)
Non-responders (n = 5)
Non-responders (n = 3)
The remaining 91 TKI-responders were evaluated (SU [n = 62], SO [n = 25], PA [n = 4])
Best TS ≤3 months
Best TS >3 months
Early responders (n = 52)
Late responders (n = 39)

Figure 2

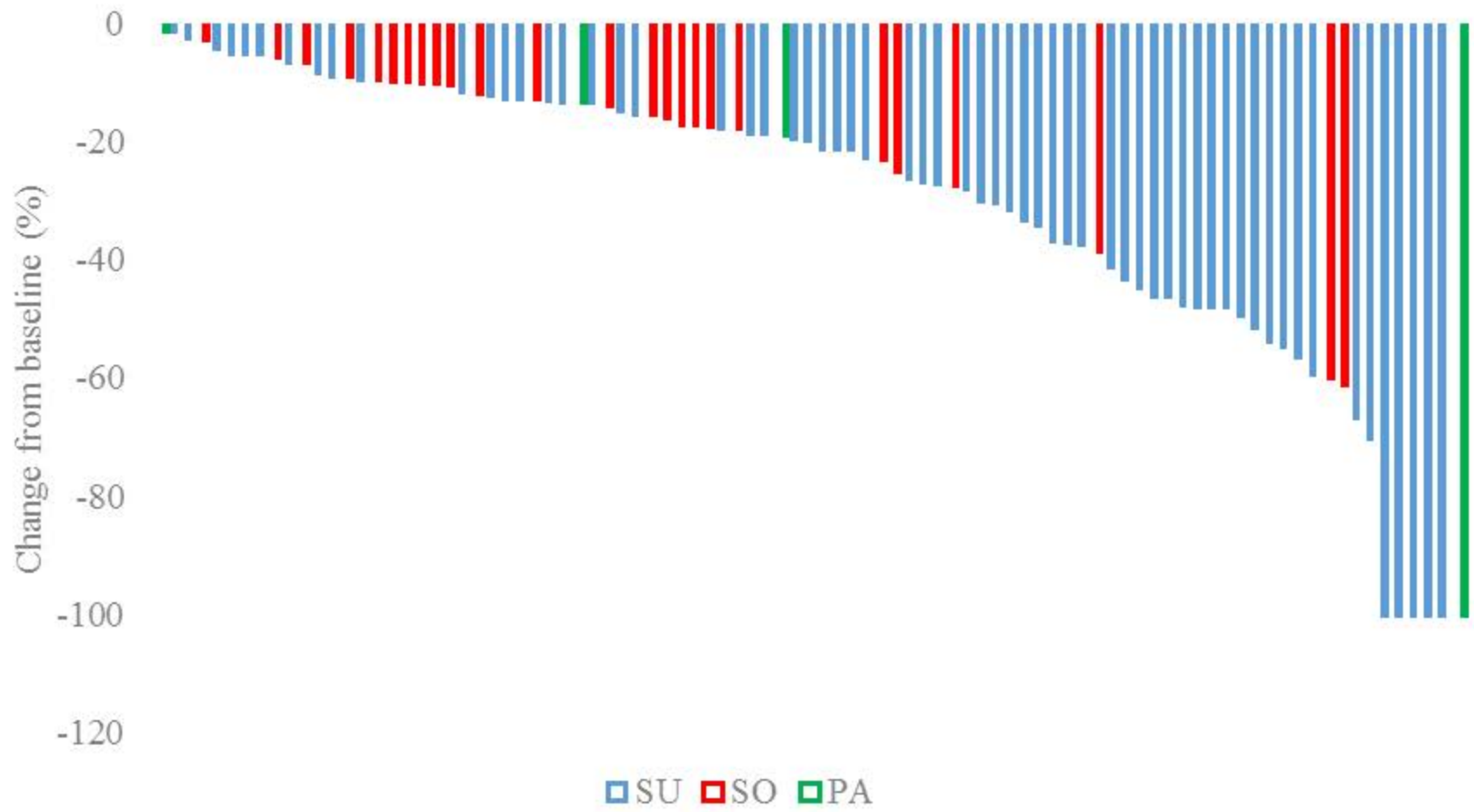
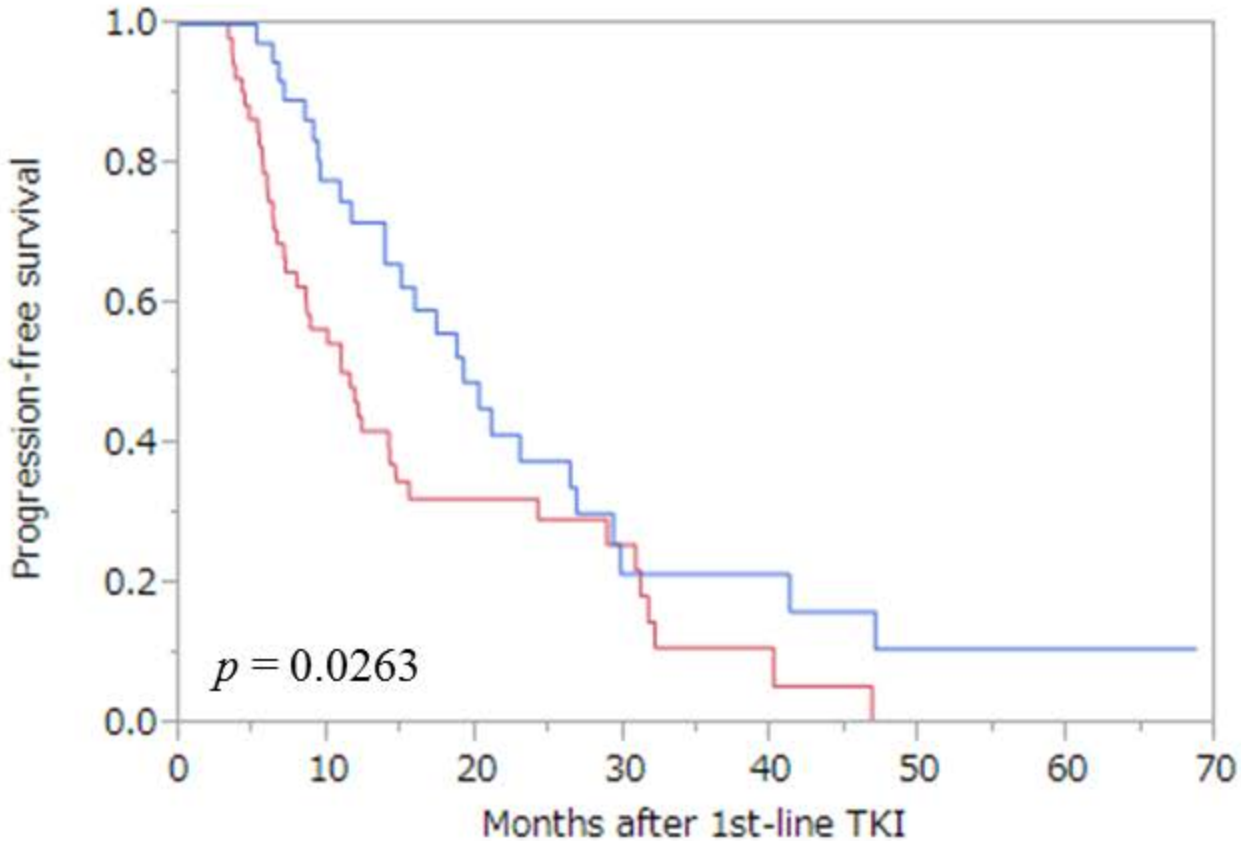
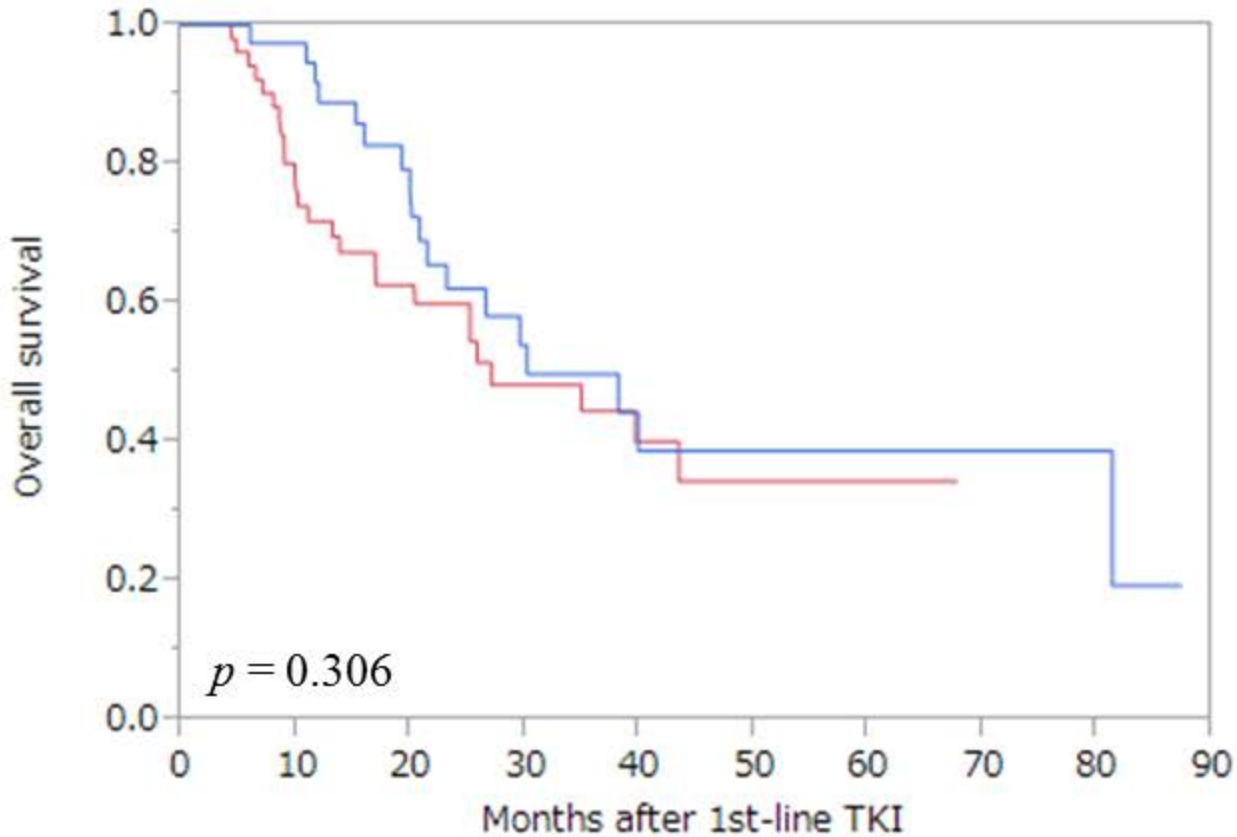


Figure 3



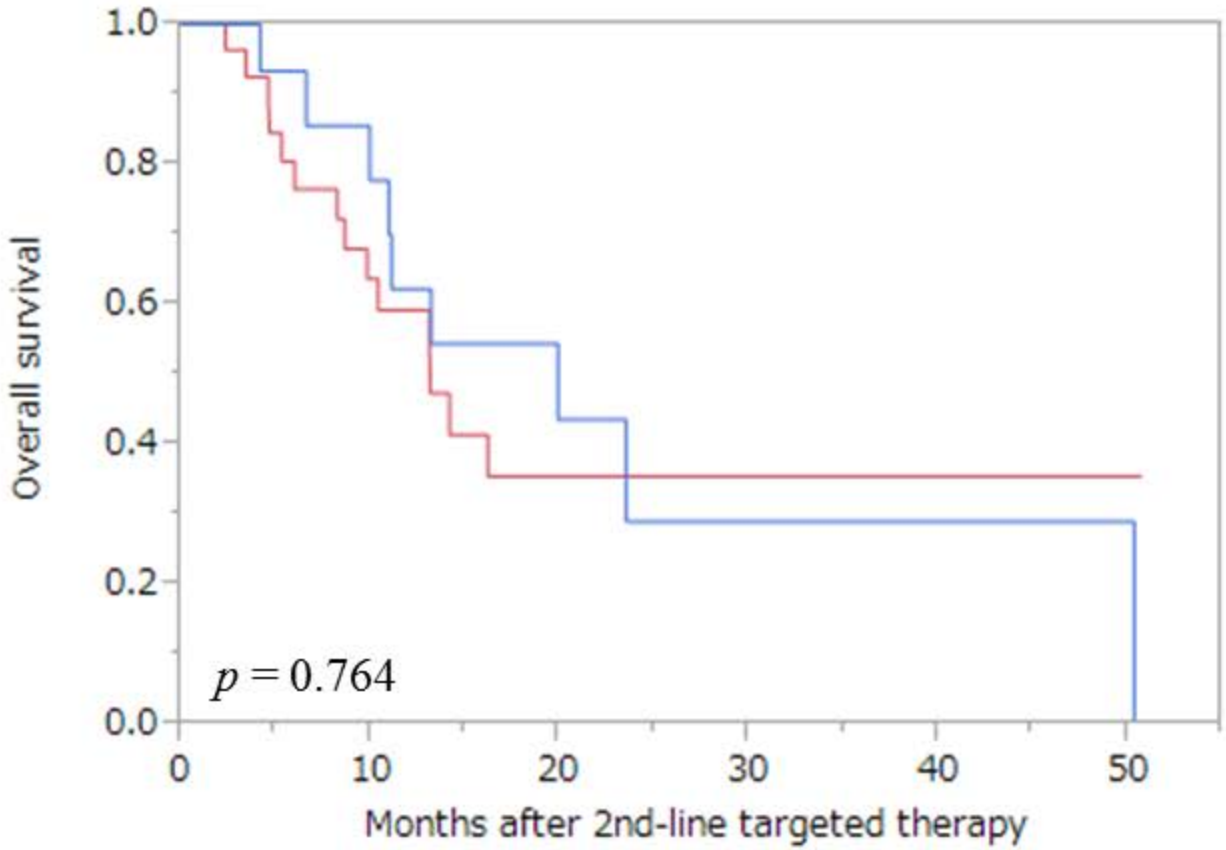
Timing	Median (months)
Late responders (n = 39)	19.1
Early responders (n = 52)	11.4

Figure 4



Timing	Median (months)
Late responders (n = 39)	30.1
Early responders (n = 52)	27.0

Figure 5



Timing	Median (months)
Late responders (n = 15)	19.9
Early responders (n = 28)	13.2