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Efficacy and safety of third-line molecular-targeted therapy in metastatic renal cell carcinoma resistant to first-line vascular endothelial growth factor receptor tyrosine kinase inhibitor and second-line therapy

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Running title

Third-line targeted therapy for mRCC

Abstract

Background: The number of studies evaluating the efficacy and safety of third-line molecular-targeted therapy for metastatic renal cell carcinoma (mRCC) are limited.

Methods: The data of 48 patients with disease progression after first-line vascular endothelial growth factor receptor tyrosine kinase inhibitor (TKI) and second-line targeted therapy, were evaluated. Patients with prior cytokine therapy were excluded. Overall survival (OS) after first- and second-line therapy initiation was compared according to the use of third-line therapy. In addition, dose-limiting toxicities (DLTs) were evaluated.

Results: Twenty-two of 48 patients (45.8%) received third-line therapy, and TKI and mammalian target of rapamycin inhibitor were administered, each, in 11 patients (50%). Patients with third-line therapy had significantly longer median OS after first-line (26.6 vs. 14.6 months, $p = 0.0010$) and second-line therapy (18.2 vs. 7.4 months, $p < 0.0001$), compared to those without third-line therapy. Multivariable analysis showed that the use of third-line therapy following second-line therapy was an independent prognosticator for longer OS (hazard ratio: 0.29, 95% confidence interval: 0.14 – 0.58, $p = 0.0005$). The median progression-free survival and OS after third-line therapy was 2.76 and 8.71 months, respectively. Although a high frequency of DLTs was observed (n = 10, 45.5%), the frequencies were similar among the sequential therapies.

Conclusions: Third-line therapy exhibits a beneficial therapeutic effect in patients with mRCC that is resistant to previous therapies. However, there is a need to evaluate in detail the high frequency of adverse events, including DLTs.

Key Words

renal cell carcinoma; targeted therapy; third-line therapy; tyrosine kinase inhibitor; mTORi; metastasis

Introduction

Following the discovery of molecular-targeted therapies, the treatment strategies for metastatic renal cell carcinoma (mRCC) have been dramatically changed, and patient prognosis has improved compared to that in the cytokine therapy era [1,2]. Unfortunately, even after the introduction of targeted therapy, only a limited number of patients can achieve complete remission because of the intrinsic or eventual resistance to targeted agents [3]. In this context, previous studies have suggested that subsequent therapy, including second-, third-line or later, following first-line therapy failure could prolong overall survival (OS) [4-6].

However, after second-line therapy, especially in the third-line setting, clinical information regarding the therapeutic efficacy and safety remains limited. In most of the previously reported studies, a regular number of patients were treated with cytokine therapy [5-10]. However, as the current treatment strategy consists of targeted therapy [11], data from patients without a history of cytokine therapy is warranted. Moreover, the number of studies reporting the reasons for switching to subsequent therapy (e.g., disease progression, not drug intolerability or adverse events [AEs]) is limited. These factors, including a history of prior cytokine therapy or reasons for treatment termination, can influence the analysis of prognostic outcomes related to sequential therapy in mRCC [12,13]. Furthermore, the number of studies evaluating drug tolerability during third-line therapy is limited [10].

Thus, in this study, we investigated the efficacy and tolerability of third-line therapy initiated after disease progression in patients with first-line vascular endothelial growth factor receptor (VEGFR)-tyrosine kinase inhibitor (TKI) and second-line targeted therapy resistant mRCC patients who did not have a prior history of cytokine therapy.

Patients and methods

Study design

The Internal Ethics Review Board of the Tokyo Women's Medical University approved this retrospective study, which was performed in accordance with the principles of the Declaration of Helsinki (ID: 4549).

In our department, 154 patients had received first-line VEGFR-TKI therapy for mRCC without prior cytokine therapy, between January 2007 and June 2017. Detailed clinical data were available for the majority of these patients. Among them, 74 patients had been switched to second-line therapy after disease progression. Finally, 63 patients remained after the exclusion of 11 patients, due to a short second-line therapy duration (n = 5) or lack of detailed data (n = 6). Among them, second-line therapy was terminated in 56 patients. The reasons included disease progression in 52 patients and poor tolerability for AEs in 4 patients. Meanwhile, second-line therapy had been continued in 7 patients at the time of end of follow-up. Since the aim of this study was to evaluate the impact of third-line therapy in sequential targeted therapy, 4 patients receiving immune checkpoint inhibitor agents as third-line therapy were excluded. Among the remaining 48 patients after disease progression following previous therapies, 22 and 26 patients were classified into two groups with and without third-line therapy, respectively. Three patients with a short therapy duration (21, 21, and 12 days) were included in the without third-line therapy group. The other 23 patients did not receive third-line therapy because of a poor general condition mediated by tumor progression (Figure 1).

Patients receiving hemodialysis therapy or kidney transplantation were excluded from the analysis. All clinical and laboratory data were obtained from the electronic database and patient medical records.

Treatment protocol

Our protocol for targeted therapy has been described previously [14,15]. Six therapeutic agents, including 4 VEGFR-TKIs and 2 mammalian target of rapamycin inhibitors (mTORis) were selected based on the insurance coverage guidelines followed in Japan. Based on the current consensus guidelines, the main agent for first-line targeted therapy in our protocol was sunitinib. Axitinib has been included under insurance coverage as second-line or later therapy in Japan. Therefore, we selected axitinib as an agent for second-line therapy. For third-line therapy, we did not have a definitive protocol. TKI and mTORi were preferably chosen as third-line agents after second-line mTORi and TKI failure, respectively. When a durable response was achieved with both first- and second-line TKIs, another TKI could be selected as third-line therapy. Meanwhile, in patients with a history of treatment refractory (i.e., non-efficacy) or intolerability, agents with the same mechanism of action could be avoided.

Post-treatment follow-up scans, using computed tomography or magnetic resonance imaging of the chest, abdomen, and pelvis, were obtained at regular 4 to 12 week intervals depending on the patient's condition.

Drugs were administered until disease progression or intolerable AEs were observed.

Objective response on targeted therapy

Target lesions were selected based on the results of baseline imaging and evaluated according to the standard Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.

Adverse events on targeted therapy

AEs were assessed according to the Common Terminology Criteria for Adverse Events of the National Cancer Institute (CTCAE), version 4.0, and subsequently, dose modifications, including reduction or interruption (i.e., dose-limiting toxicities [DLTs]), were performed as necessary.

Statistical analysis

Continuous variables were analyzed using the Mann-Whitney *U* test, and categorical variables were analyzed using the χ^2 test or Fisher's extract test. Time to progression (TTP) and progression-free survival (PFS) were defined as the time from therapy initiation to the date of progression. OS was defined as the time from therapy initiation to the date of death from any cause. Survival was calculated using the Kaplan-Meier method and compared using the log-rank test. Univariable and multivariable analyses using Cox proportional hazards regression models were used to identify prognosticators for survival. Survival risk was expressed as the hazard ratios (HRs) and 95% confidence intervals (CIs). All statistical analyses were conducted using JMP software (version 11; SAS Institute Inc., Cary, NC, USA), and $p < 0.05$ was considered statistically significant.

Results

Patients' background

Table 1 shows details of the patients' background. The Memorial Sloan Kettering Cancer Center (MSKCC) risk in second- and third-line therapy, was based on Motzer's classification [16]. Patients with third-line therapy had a significantly longer duration of median second-line TTP (7.06 vs. 3.29 months, p = 0.0005), compared to those without third-line therapy. There were no significant differences in other clinicopathological factors, including age, sex, MSKCC risk, pathological type, nephrectomy status, metastatic status, and previous therapy regimens (all, p > 0.05). The median follow-up period was significantly shorter in patients without third-line therapy, compared to those with third-line therapy (13.7 vs. 25.9 months, p = 0.0003).

Therapeutic effect of third-line therapy

During the follow-up period, 39 of 48 patients (81.3%) died of any cause after termination of second-line therapy. Figure 2 shows that patients with third-line therapy had significantly longer median OS after first-line (26.6 [95% CI: 20.3 – 63.1] vs. 14.6 [95% CI: 11.3 – 20.1] months, p = 0.0010) and second-line therapy (18.2 [95% CI: 11.1 – 38.7] vs. 7.4 [95% CI: 4.9 – 9.8] months, p < 0.0001), compared to those without third-line therapy. Table 2 shows the results of univariable and multivariable analyses for OS after second-line therapy. Univariable analysis showed that second-line MSKCC risk (p = 0.0084), number of metastases at second-line therapy initiation (p = 0.0066), and the use of third-line therapy (p = 0.0001) were associated with survival. Multivariable analysis showed that the use of third-line therapy was an independent prognosticator (HR: 0.29, 95% CI: 0.14 – 0.58, p = 0.0005), together with second-line MSKCC risk (HR: 2.76,

95% CI: 1.31 – 5.64, p = 0.0086).

Histological type had a significant influence on treatment strategy and outcome [17,18]. Thus, after the exclusion of 14 patients with a diagnosis of non-clear-cell carcinoma (CCC), we analyzed OS after first- and second-line therapy. Consequently, third-line therapy was performed in 16 of 34 (47.1%) patients with CCC, and the median OS after first- and second-line therapy were significantly longer in patients with third-line therapy, compared to those without third-line therapy (after first-line: 30.6 [95% CI: 19.1 – 81.2] vs. 18.5 [95% CI: 12.8 – 27.0] months, p = 0.0010; after second-line: 21.8 [95% CI: 19.1 – 81.2] vs. 8.34 [95% CI: 12.8 – 27.0] months, p = 0.0013) (Supplementary Figure 1).

Patient prognosis after third-line therapy

During the follow-up period after third-line therapy, 20 of 22 patients (90.9%) experienced disease progression and 16 of 22 patients (72.7%) died from any cause. TKI and mTORi were administered as third-line agents, each, in 11 patients (50.0%). The sequential therapeutic regimens consisted of TKI-TKI-mTORi (n = 11, 50.0%), TKI-mTORI-TKI (n = 6, 27.3%), and TKI-TKI-TKI (n = 5, 22.7%), respectively (Table 1). The objective response rate of the third-line therapy agents was determined for individual patients by a waterfall plot analysis, as shown in Supplementary Figure 2. Figure 3 shows that the median PFS and OS after third-line therapy was 2.76 (95% CI: 1.94 – 7.79) and 8.71 (95% CI: 4.6 – 31.0) months, respectively. Moreover, in the 16 patients with a diagnosis of CCC, the median PFS and OS after third-line therapy was 3.22 (95% CI: 1.94 – 8.28), and 11.0 (95% CI: 4.08 – 31.0) months, respectively.

Objective response rate during sequential therapy

Figure 4 shows the objective response rates during sequential therapy. During first-line therapy, partial response, stable disease, and progressive disease were observed in 6 (27.3%), 12 (54.5%), and 4 (18.2%) patients, respectively. Likewise, during second- and third-line therapy, partial response, stable disease, and progressive disease were observed in 4 (18.2%), 16 (72.7%), and 2 (9.09%), and 4 (18.2%), 7 (31.8%), and 11 (50.0%) patients, respectively. The magnitude of best tumor shrinkage was lower with third-line therapy, compared to that with previous therapies, whereas the proportion of patients who experienced partial response was similar among the sequential therapy regimens.

Dose-limiting toxicity during sequential therapy

As shown in Table 3, 10 of 22 patients (45.5%) experienced DLTs for AEs of grade 2 (n = 9, 40.9%) and ≥ 3 (n = 7, 31.8%) in third-line therapy. Similar frequencies of DLTs were observed between sequential therapy regimens (first-line: 45.5%; second-line: 59.1%). Moreover, the component rates of treatment modifications (i.e., reduction vs. interruption) were similar (reduction: 36.4%, 27.3%, and 22.7% in first-, second-, and third-line therapy).

Discussion

In this study, we demonstrated that third-line targeted therapy after first-line VEGFR-TKI and second-line therapy for mRCC had a beneficial therapeutic effect in patients without previous cytokine therapy and with disease progression after prior therapies. In addition, although patients had a high risk for developing AEs, including DLTs, the frequency was similar among the sequential therapy regimens.

Although the therapeutic effect of sequential therapy has been recognized [4,5], only a limited patient population can switch to the subsequent therapy. It has previously been reported that only a maximum of 13.0% – 21.0% of patients could receive third-line therapy [5,6,19,20]. In this study, 14.3% of patients (n = 22) subsequently underwent third-line therapy. This finding was consistent with those of previous reports. The median OS (from the time of commencing first-line therapy) was shorter than that reported in previous studies; we found that the median OS after first-line therapy was 26.6 months in patients receiving third-line therapy, whereas Ko et al. and Busch et al. have reported a median OS of 39.2 and 35.6 months, respectively [6,10]. In the present study, the median PFS and OS after third-line therapy was 2.76 and 8.71 months, respectively. Wells et al. have reported that the median PFS and OS were 3.9 and 12.4 months [5], respectively, and Busch et al. have reported a median PFS of 3.7 months [10]. Thus, OS, rather than PFS, had a trend towards being shorter in our study. Although it is difficult to explain these differences, two unique features of this study might be considered. First, Escudier et al. have suggested that patients treated with cytokine therapy for a long period of time may have developed an inherently less-aggressive disease or a better general condition, resulting in patient bias [12]. According to Wells et al., the median OS (from the time of cessation of second-line therapy) was 7.6 months in patients without third-line therapy

[5]. Moreover, De Velasco et al. have reported that patients whose reason for therapy withdrawal was intolerability had a superior prognosis after the subsequent therapy, compared to those with disease progression [13]. Thus, it is not surprising that a poorer outcome was observed in the present study as the cohort of this study consisted of patients without a prior history of cytokine therapy and whose reasons for switching to the next therapy was disease progression.

In our analysis, the proportion of patients with a diagnosis of non-CCC was lower in those with third-line therapy, compared to those without third-line therapy. The pathological difference may influence prognosis because the oncological outcome is supposed to differ between CCC and non-CCC populations [18]. Nevertheless, after the exclusion of pathological influence, the therapeutic effect of third-line therapy was confirmed.

In the present study, the objective response rate was also poorer during third-line therapy. Notably, half of the patients had progressive disease as the best response to third-line therapy. Therefore, for such resistance of tumors to targeted therapies, a change in approach might be needed, such as introducing an antibody inhibitor (nivolumab) of the programmed death 1 immune checkpoint protein [3,21]. Meanwhile, there were no differences in partial response rates during sequential therapy. Thus, a proportion of patients achieved a good response, even to third-line therapy. Indeed, these patients had a favorable prognosis after third-line therapy (median third-line PFS: 22.3 months, OS: 31.6 months).

Approximately half of the patients experienced DLTs during third-line therapy (45.5%). Frequencies were similar among the sequential therapies. Busch et al. have reported similar frequencies of AEs between first/second-line and third-line therapy [10].

Furthermore, according to Buchler et al., the incidence of serious toxicities (grades ≥3) was similar between second- and third-line everolimus therapy [8]. Meanwhile, Oudard et al. have indicated that the rate of development of AEs was higher in patients with third-line or later sunitinib rechallenge therapy, compared to those with first-line sunitinib therapy, even though the initial dose was reduced or the treatment schedule was made easier in subsequent therapies [7]. Although in this study, neither the grade nor the types of AEs varied among sequential therapies, hematotoxicity was frequently observed in first-line therapy due to TKI usage.

This study has several limitations. First, this was a retrospective study performed in a single center with a relatively small sample size. Thus, patients with a poor performance status or other patient-related backgrounds could influence the physician's treatment plan. Therefore, unmeasured or immeasurable confounders could have affected our results. Moreover, we could not analyze the superiority among regimens (i.e., TKI-TKI-mTORi vs. TKI-mTORi-TKI) due to the inherent nature of a retrospective observational study. Indeed, as shown in Supplementary Figure 2, mTORi had a lower objective response rate than TKI. Other clinicopathological factors were not associated with objective response rate (data not shown). Moreover, patients with TKI-TKI-mTORi had a shorter third-line PFS and OS, compared to those with other regimens (data not shown). Therefore, these findings should be confirmed in future prospective randomized clinical trials. Second, even though present-day guidelines do not recommend sorafenib as a preferential first-line agent, patients receiving sorafenib as first-line therapy were included in this study, because neither sunitinib nor pazopanib was approved in Japan during the observational period (2007 onwards). Third, due to the heterogeneity of the sequential therapy regimens, we could not calculate the relative dose intensity, an

important factor for evaluating the prognosis and tolerability.

In conclusion, this study showed that third-line targeted therapy had a beneficial therapeutic effect in patients with first-line VEGFR-TKI and second-line resistant mRCC, who do not have a prior history of cytokine therapy. Moreover, similar levels of tolerability were observed in third-line therapy, compared to those in previous therapies. However, there is a need to evaluate, in detail, the high frequency of AEs, including DLTs.

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Compliance with ethical standards

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.

Study design

Patients receiving hemodialysis therapy or kidney transplantation were excluded. None of the patients had undergone prior cytokine therapy. Three patients receiving immune checkpoint inhibitor therapy, programmed cell death 1 (nivolumab), as third-line therapy were excluded, whereas three patients receiving more than four lines of therapy were included in the analysis. Three patients with short therapy durations were categorized into the without third-line therapy group.

VEGFR, vascular endothelial growth factor receptor; TKI, tyrosine kinase inhibitor

Figure 2.

Overall survival after first- and second-line therapy according to the use of third-line therapy

Patients with third-line therapy (n = 22) had a significantly longer overall survival after first- and second-line therapy as compared to those without third-line therapy. (a) Median overall survival after first-line therapy: 26.6 vs. 14.6 months, $p = 0.0010$. (b) Median overall survival after second-line therapy: 18.2 vs. 7.4 months, $p < 0.0001$.

CI, confidence interval

Figure 3.

Progression-free and overall survival after third-line therapy

The Kaplan-Meier survival curve method shows that the median progression-free and overall survival after third-line therapy was 2.76 and 8.71 months, respectively. (a)

progression-free survival. (b) overall survival.

Figure 4.

Objective response rates during sequential therapy

Objective response rates were lower with third-line therapy, compared to that with previous therapies, whereas the proportion of patients who experienced partial response was similar among the sequential therapy regimens.

PR, partial response; SD, stable disease; PD, progression disease

Supplementary materials

Supplementary Figure 1.

Overall survival after first- and second-line therapy according to the use of third-line therapy in 34 patients with a diagnosis of clear-cell carcinoma

Patients with third-line therapy (n = 16) had a significantly longer overall survival after first- and second-line therapy as compared to those without third-line therapy. (a) Median overall survival after first-line therapy: 30.6 vs. 18.5 months, p = 0.0110. (b) Median overall survival after second-line therapy: 21.8 vs. 8.34 months, p = 0.0013.

Supplementary Figure 2.

Waterfall plot analysis

Waterfall plot analysis shows the objective response rate according to the third-line agents used in each patient.

mTORi, mammalian target of rapamycin inhibitor

Table 1. Patients' background

Variable	All (n = 48)	With third-line therapy (n = 22)	Without third-line therapy (n = 26)	p
Age at therapy initiation, years-old*				
First-line	64.5 (56.0 – 73.5)	63.5 (51.5 – 70.3)	67.0 (61.5 – 74.0)	0.203
Second-line	65.5 (57.5 – 73.5)	63.5 (52.8 – 70.5)	68.5 (61.5 – 74.0)	0.165
Third-line	64.5 (54.8 – 72.3)	64.5 (54.8 – 72.3)	NA	NA
Sex				
Male (ref. female)	32 (66.7%)	15 (68.2%)	17 (65.4%)	0.838
First-line MSKCC				
Favorable/intermediate/poor	5 (10.4%)/ 38 (79.2%)/ 5 (10.42%)	1 (4.55%)/ 19 (86.4%)/ 2 (9.09%)	4 (15.4%)/ 19 (73.1%)/ 3 (11.5%)	0.782
Second-line MSKCC**				
Favorable/intermediate/poor	2 (4.17%)/ 31 (64.6%)/ 15 (31.3%)	0/ 17 (77.3%)/ 5 (22.7%)	2 (7.69%)/ 14 (53.9%)/ 10 (38.5%)	0.241
Third-line MSKCC**				
Favorable/intermediate/poor	NA	1 (4.55%)/ 14 (63.6%)/ 7 (31.8%)	NA	NA
Pathology				0.791
Clear-cell carcinoma	34 (70.8%)	16 (72.7%)	18 (69.2%)	
Clear-cell carcinoma with spindle	4 (8.33%)	1 (4.55%)	3 (11.5%)	
Papillary renal cell carcinoma	5 (10.4%)	1 (4.55%)	4 (15.4%)	
Other/unknown	5 (10.4%)	4 (18.2%)	1 (3.85%)	
Prior nephrectomy				
With (ref. without)	44 (91.7%)	20 (90.9%)	24 (92.3%)	0.861

Number of metastatic sites at first-line therapy initiation				
Multiple (ref. single)	26 (54.2%)	10 (45.5%)	16 (61.5%)	0.265
Number of metastatic sites at second-line therapy initiation				
Multiple (single)	34 (70.8%)	13 (59.1%)	21 (80.8%)	0.0997
Number of metastatic sites at third-line therapy initiation				
Multiple (single)	NA	16 (72.7%)	NA	NA
First-line TKI agent				
Sorafenib/sunitinib/pazopanib	14 (29.2%)/ 32 (66.7%)/ 2 (4.17%)	4 (18.2%)/ 17 (77.3%)/ 1 (4.55%)	10 (38.5%)/ 15 (57.7%)/ 1 (3.85%)	0.304
Second-line molecular-targeted agent				
TKI	37 (77.1%)	16 (72.7%)	21 (80.8%)	0.509
Sorafenib/sunitinib/pazopanib/axitinib	2 (4.17%)/10 (20.8%)/ 3 (6.25%)/ 22 (45.8%)	2 (9.09%)/ 3 (13.6%)/ 2 (9.09%)/ 9 (40.9%)	0/ 7 (26.9%)/ 1 (3.85%)/ 13 (50.0%)	
mTORi	11 (22.9%)	6 (27.3%)	5 (19.2%)	
Temsirolimus/everolimus	3 (6.25%)/ 8 (16.7%)	2 (9.09%)/ 4 (18.2%)	1 (3.85%)/ 4 (15.4%)	
Third-line molecular-targeted agent				
TKI	NA	11 (50.0%)	NA	NA
Sorafenib/sunitinib/pazopanib/axitinib		2 (9.09%)/ 2 (9.09%)/ 0/ 7 (31.8%)		
mTORi		11 (50.0%)		
Temsirolimus/everolimus		2 (9.09%)/ 9 (40.9%)		
Regimen of therapy				
TKI-TKI	37 (77.1%)	16 (72.7%)	21 (80.8%)	0.509
TKI-mTORi	11 (22.9%)	6 (27.3%)	5 (19.2%)	NA
TKI-TKI-TKI	NA	5 (22.7%)	NA	
TKI-TKI-mTORi	NA	11 (50.0%)	NA	

TKI-mTORi-TKI	NA	6 (27.3%)	NA	
Time to progression, months*				
First-line	7.91 (5.22 – 11.6)	8.94 (5.18 – 11.5)	6.66 (5.19 – 11.8)	0.555
Second-line	5.50 (3.00 – 8.16)	7.06 (5.24 – 12.4)	3.29 (2.3 – 6.20)	0.0005
Follow-up period, months*	20.2 (12.8 – 34.9)	25.9 (20.0 – 58.2)	13.7 (10.0 – 25.6)	0.0003

*Median (interquartile range)

**Second- and third-line MSKCC risk was defined according to Motzer's risk classification.

ref, reference; MSKCC, Memorial Sloan Kettering Cancer Center; TKI, tyrosine kinase inhibitor; mTORi, mammalian target of rapamycin, NA; not applicable

Table 2. Univariable and multivariable analyses for prognosticators for overall survival after second-line therapy

Variable	Univariable HR (95%CI)	p value	Multivariable HR (95%CI)	p
Age at therapy initiation (continuous variable)				
First-line	0.99 (0.96 – 1.02)	0.373		
Second-line	0.99 (0.96 – 1.01)	0.315		
Sex				
Male (ref. female)	0.79 (0.42 – 1.57)	0.495		
First-line MSKCC				
Poor (ref. favorable and intermediate)	1.55 (0.46 – 3.97)	0.437		
Second-line MSKCC				
Poor (ref. favorable and intermediate)	2.72 (1.31 – 5.45)	0.0084	2.76 (1.31 – 5.64)	0.0086
Pathology				
Clear-cell carcinoma (ref. non-clear-cell carcinoma)	0.63 (0.32 – 1.39)	0.240		
Prior nephrectomy				
With (without)	0.93 (0.28 – 5.74)	0.918		
Number of metastatic sites at first-line initiation				
Multiple (ref. single)	2.24 (1.16 – 4.51)	0.0168		
Number of metastatic sites at second-line initiation				
Multiple (ref. single)	2.80 (1.31 – 6.70)	0.0066	1.67 (0.76 – 4.12)	0.207
Regimen of therapy				
TKI-TKI (ref. TKI-mTORi)	1.66 (0.79 – 3.92)	0.190		

Time to progression (continuous variable)				
First-line	0.97 (0.92 – 1.01)	0.180		
Third-line therapy				
With (ref. without)	0.27 (0.13 – 0.53)	0.0001	0.29 (0.14 – 0.58)	0.0005

HR, hazard ratio; CI, confidence interval

Table 3. Dose-limiting toxicity and adverse events during sequential therapy

	First-line therapy	Second-line therapy	Third-line therapy
Dose-limiting toxicity			
With	10 (45.5%)	13 (59.1%)	10 (45.5%)
Components of modification			
Reduction	8 (36.4%)	6 (27.3%)	5 (22.7%)
Interruption	4 (18.2%)	7 (31.8%)	6 (27.3%)
Reasons for dose-limiting toxicity			
Stomatitis	0	1 (4.55%)	1 (4.55%)
Interstitial lung disease	0	1 (4.55%)	1 (4.55%)
Anemia	0	1 (4.55%)	2 (9.09%)
Diarrhea	0	0	3 (13.6%)
Nausea/ vomiting	0	2 (9.09%)	1 (4.55%)
Hand foot syndrome	3 (13.6%)	1 (4.55%)	1 (4.55%)
Fatigue	2 (9.09%)	2 (9.09%)	1 (4.55%)
Anorexia	0	1 (4.55%)	1 (4.55%)
Pneumonia	0	0	1 (4.55%)
Weight loss	0	1 (4.55%)	1 (4.55%)
Thrombocytopenia	3 (13.6%)	2 (9.09%)	1 (4.55%)
Gastrointestinal bleeding	0	1 (4.55%)	0
Kidney dysfunction	0	2 (9.09%)	0
Liver dysfunction	0	1 (4.55%)	0
Back pain	0	1 (4.55%)	0

Leukocytopenia	3 (13.6%)	0	0
Grades for adverse events inducing dose-limiting toxicity			
Grade 2	7 (31.8%)	6 (27.3%)	9 (40.9%)
Grade ≥ 3	5 (22.7%)	10 (45.5%)	7 (31.8%)

Figure 1

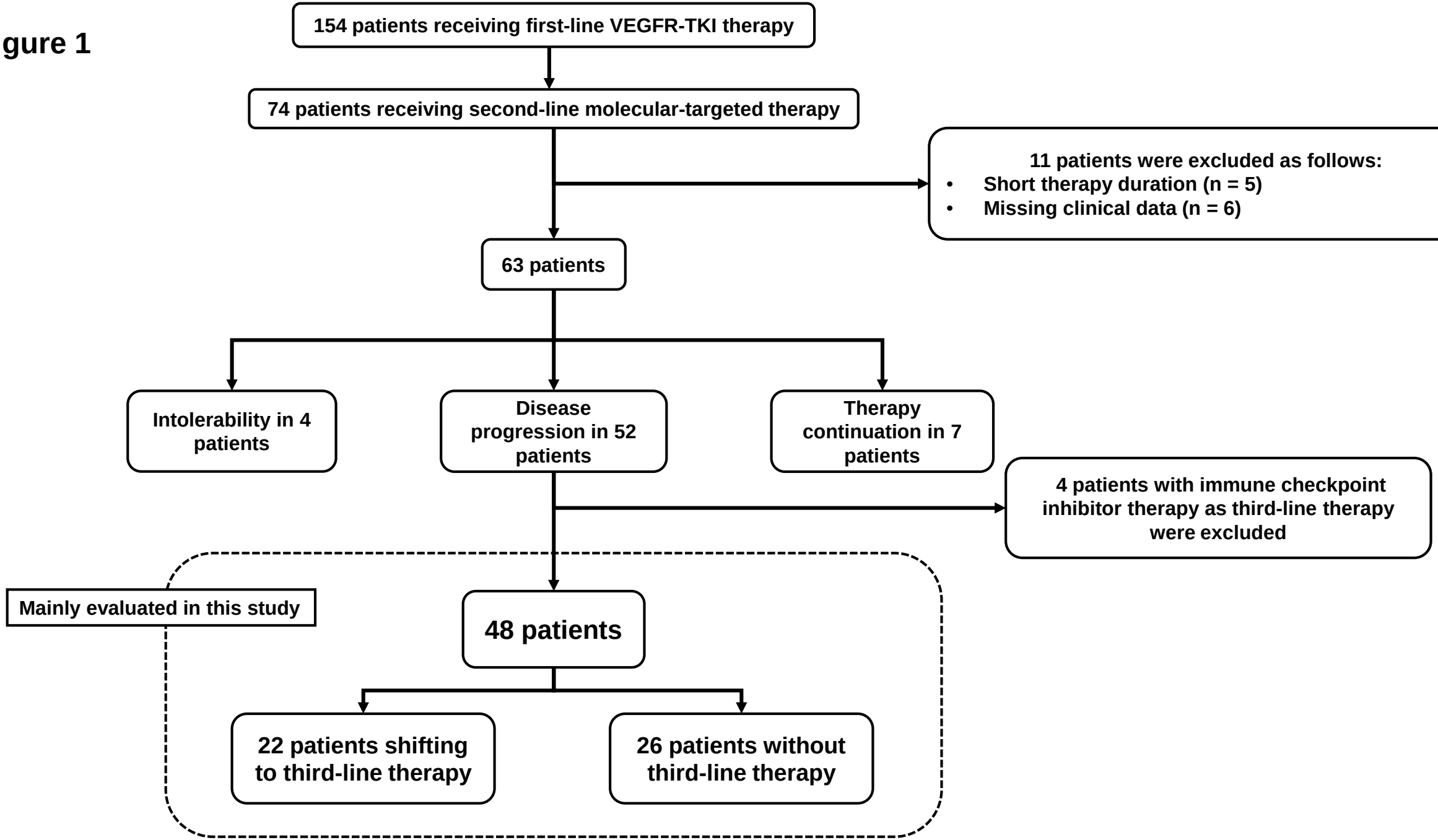
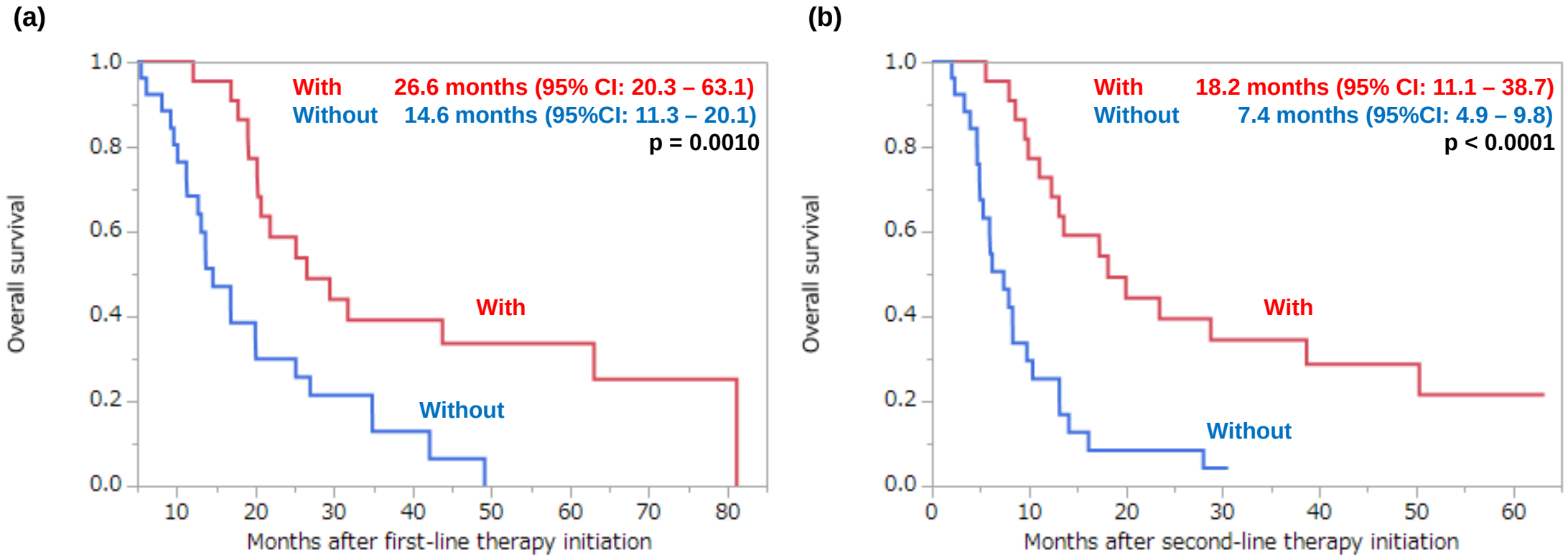
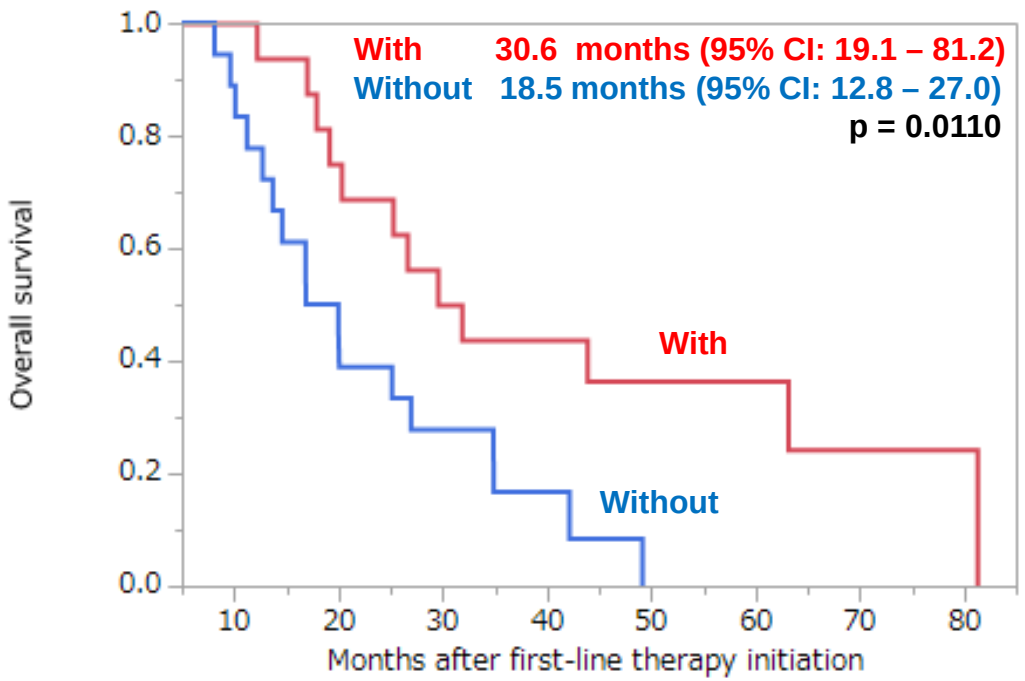

154 patients receiving first-line VEGFR-TKI therapy
74 patients receiving second-line molecular-targeted therapy
11 patients were excluded as follows:
• Short therapy duration (n = 5)
• Missing clinical data (n = 6)
63 patients
Intolerability in 4 patients
Disease progression in 52 patients
Therapy continuation in 7 patients
4 patients with immune checkpoint inhibitor therapy as third-line therapy were excluded
Mainly evaluated in this study
48 patients
22 patients shifting to third-line therapy
26 patients without third-line therapy

Figure 2

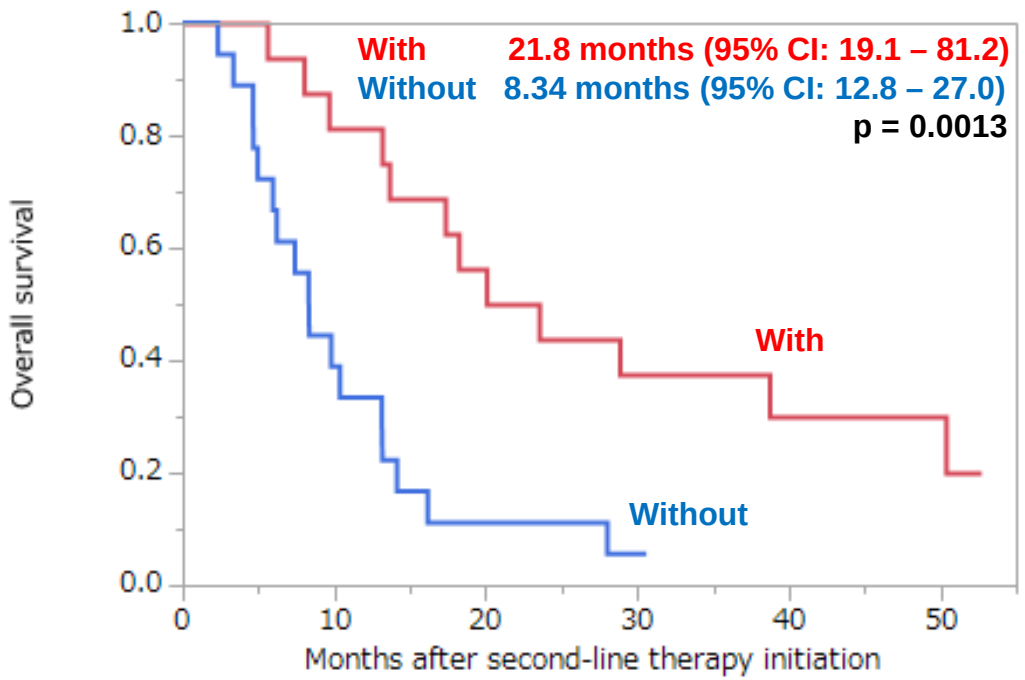

(a)
With 26.6 months (95% CI: 20.3 – 63.1)
Without 14.6 months (95%CI: 11.3 – 20.1)
p = 0.0010
With
Without
Overall survival
1.0
0.8
0.6
0.4
0.2
0.0
10
20
30
40
50
60
70
80
Months after first-line therapy initiation
(b)
With 18.2 months (95% CI: 11.1 – 38.7)
Without 7.4 months (95%CI: 4.9 – 9.8)
p < 0.0001
With
Without
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 initiation

Supplementary Figure 1

(a)



(b)



Supplementary Figure 2

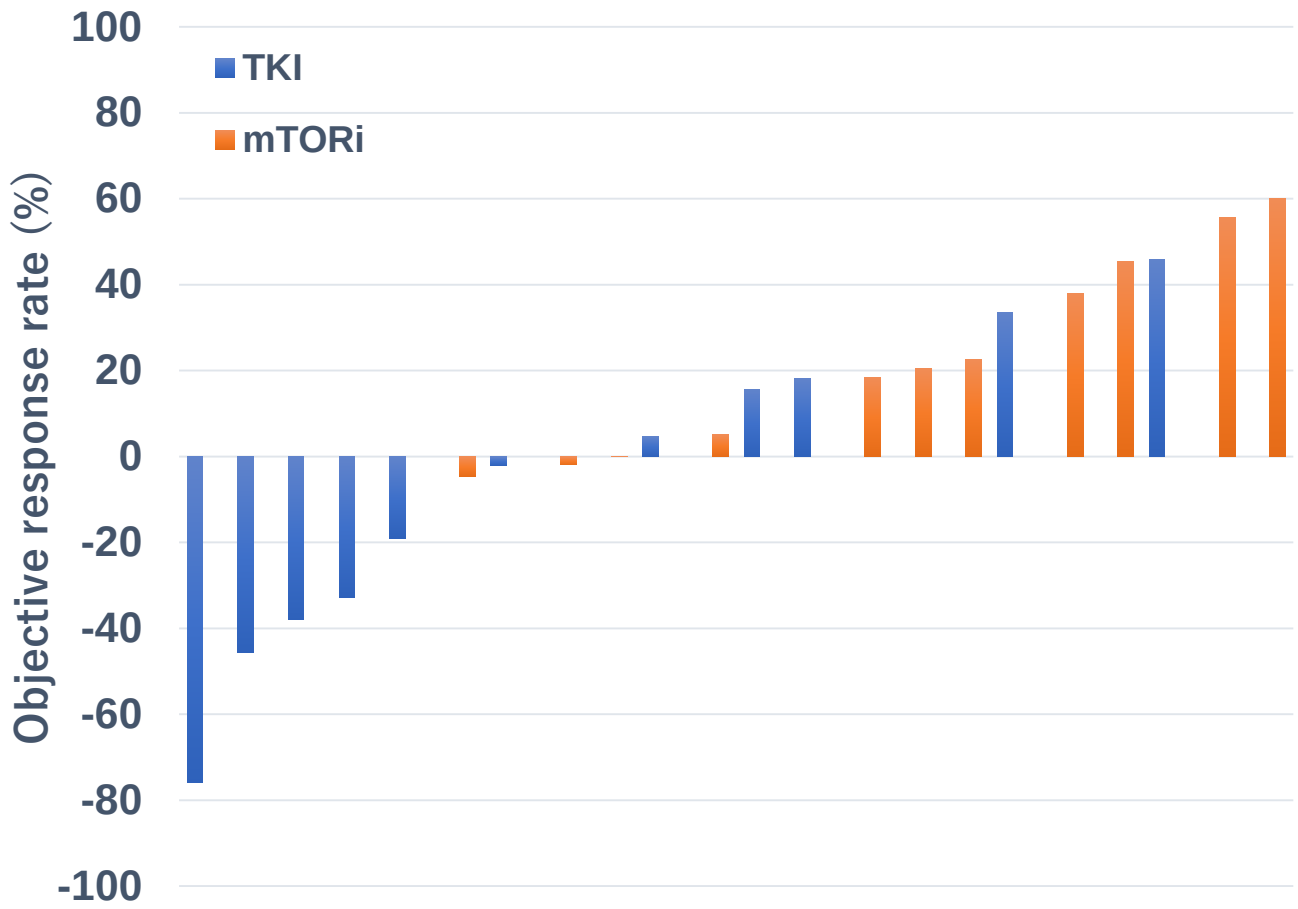


Figure 3

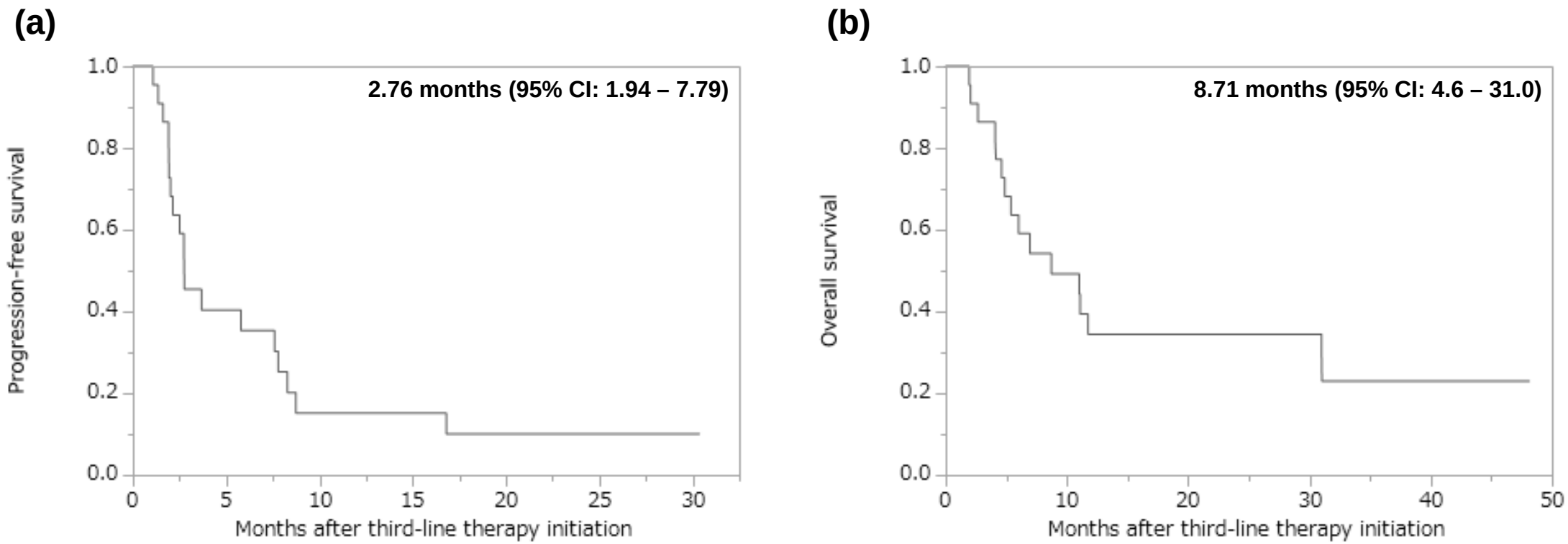
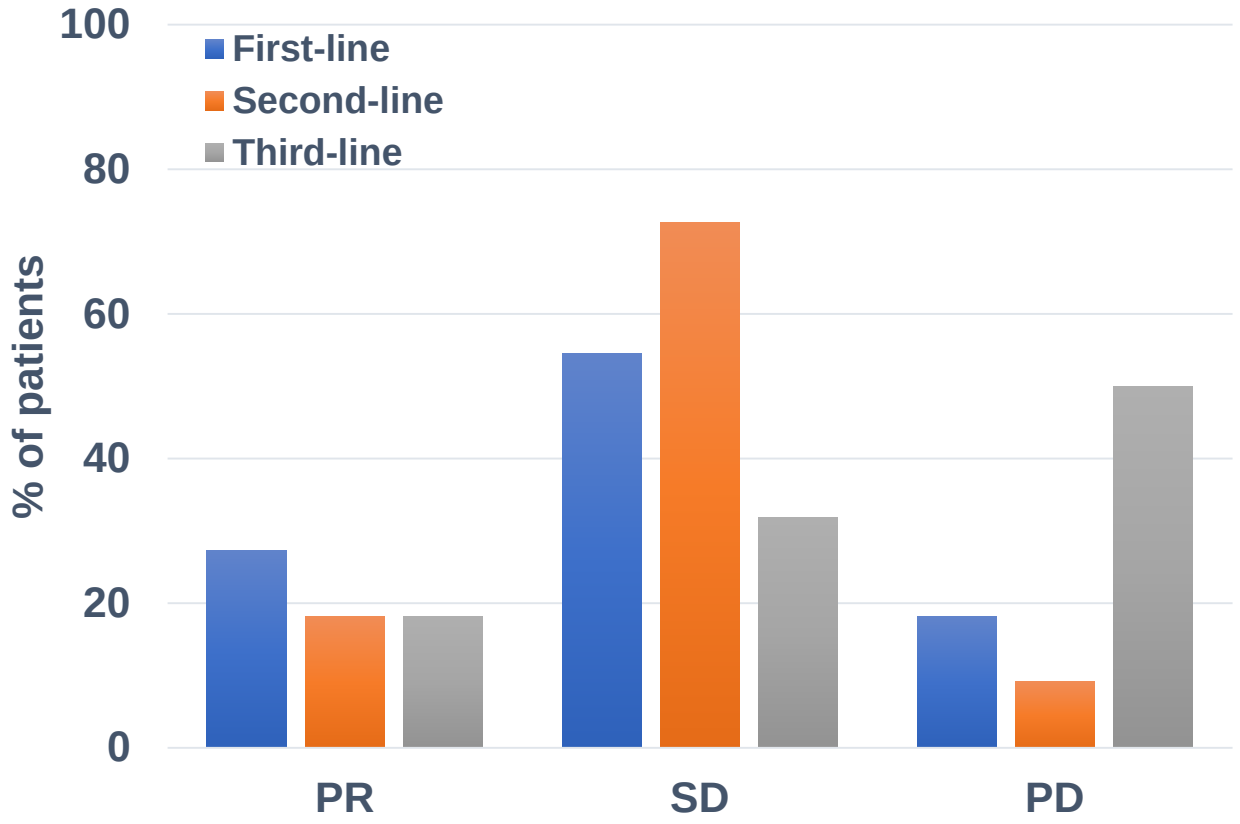

(a)
2.76 months (95% CI: 1.94 – 7.79)
Progression-free survival
1.0
0.8
0.6
0.4
0.2
0.0
0
5
10
15
20
25
30
Months after third-line therapy initiation
(b)
8.71 months (95% CI: 4.6 – 31.0)
Overall survival
1.0
0.8
0.6
0.4
0.2
0.0
0
10
20
30
40
50
Months after third-line therapy initiation

Figure 4


100
80
60
40
20
0
% of patients
First-line
Second-line
Third-line
PR
SD
PD