The magnitude of best tumor shrinkage during second-line targeted therapy affects progression-free survival but not overall survival in patients with metastatic renal cell carcinoma

journal or publication title	Japanese journal of clinical oncology
volume	46
number	6
page range	568-574
year	2016
URL	http://doi.org/10.20780/00031653

doi: 10.1093/jjco/hyw024(http://doi.org/10.1093/jjco/hyw024)

The magnitude of best tumor shrinkage during second-line targeted therapy affects progression-free survival but not overall survival in patients with metastatic renal cell carcinoma

Hiroki Ishihara, Tsunenori Kondo*, Kenji Omae, Toshio Takagi, Jumpei Izuka, Hirohito Kobayashi, Kazunari Tanabe

Department of Urology, Kidney Center, Tokyo Women's Medical University, 8-1 Kawada-cho, Shinjuku-ku, Tokyo, Japan, 162-8666

*Address correspondence to:

Dr. Tsunenori Kondo

Tokyo Women's Medical University

Department of Urology, Kidney Center, Tokyo Women's Medical University

8-1 Kawada-cho, Shinjuku-ku, Tokyo, Japan, 162-8666

Tel: +81-3-3353-8111

FAX: +81-3-3356-0293

E-mail address: tkondo@kc.twmu.ac.jp

Running title: Best TS during second-line TT in mRCC patients

Abstract

Background: The present study aimed to evaluate the influence of the magnitude of best tumor shrinkage (TS) during second-line targeted therapy after first-line tyrosine kinase inhibitor (TKI) failure on metastatic renal cell carcinoma (mRCC) prognosis.

Methods: Fifty-two patients were enrolled. The magnitude of TS was assessed according to the Response Evaluation Criteria in Solid Tumors v. 1.1, and evaluated as a continuous variable and by categorical classification: good responders (≥ -30%), mild responders (-0.1% to -29.9%), poor responders (0% to +19.9%), and non-responders (≥ +20% or new lesions). Overall survival (OS) and progression-free survival (PFS) after second-line therapy initiation were evaluated according to the categorical classification. Factors predicting OS and PFS were also examined.

Results: The mean magnitude of TS was -1.29%, and there were 9, 21, 11, and 11 good responders, mild responders, poor responders, and non-responders, respectively. The OS and PFS significantly improved as the magnitude of TS increased according to the categorical classification (OS: not reached, 27.8, 18.2, and 4.67 months; PFS: 13.4, 8.19, 5.18, and 1.84 months, respectively; $p<0.0001$ for both). For OS, the magnitude of TS was not demonstrated as an independent indicator in the multivariate analysis ($p=0.0872$ for the categorical classification, $p=0.133$ for the continuous variable) whereas for second –line PFS, the magnitude of TS according to both the categorical classification and continuous variable was found to be an independent factor in the multivariate

analysis (p<0.0001 for both).

Conclusions: The magnitude of TS is an independent predictive factor for PFS, and may represent a surrogate marker for OS.

Mini-abstract: We demonstrated that the magnitude of best tumor shrinkage during second-line targeted therapy was an independent predictive factor for progression-free survival, and may represent a surrogate marker for overall survival.

Key words: Molecular targeted therapy, Renal cancer, Prognosis, Response Evaluation Criteria in Solid Tumors

Introduction

Molecular targeted therapy (TT) is a mainstay of treatment of metastatic renal cell carcinoma (mRCC) patients; it has been demonstrated to improve patient survival, including progression-free survival (PFS) and overall survival (OS), compared with cytokine therapy. In mRCC, TT aimed at inhibiting the vascular endothelial growth factor (VEGF) or mammalian target of rapamycin (mTOR) pathways is currently being used. The majority of patients with good or intermediate risk according to the Memorial Sloan-Kettering Cancer Center (MSKCC) criteria are commonly treated with a tyrosine kinase inhibitor (TKI), particularly sunitinib, as first-line therapy, based on the results of previous randomized clinical trials (1, 2). In cases of failure of the first-line therapy, second-line treatment is generally administered. However, it remains controversial whether a TKI-mTOR inhibitor (mTORi) or TKI-TKI combination as sequential treatment provides a better outcome (3, 4).

As the response and survival rates have improved since the introduction of TT, several studies have been performed to indicate the prognostic or predictive indicators for outcome after TT initiation. Especially, the objective response, that is, the tumor shrinkage (TS), according to the standard Response Evaluation Criteria in Solid Tumors (RECIST), has been regarded as a useful marker for outcome (5-8). In most previous studies, the patients were divided into subgroups with several ranges of TS to evaluate the survival (5, 6, 8) . However, it should be noted that those data were obtained from large clinical trials; hence, the enrolled populations might have had tendencies of

being in a better general condition than the mRCC population in the real world. Moreover, some patients had been treated with previous cytokine therapy, and the number of studies on second-line therapy performed in patients who had previously received only TT is limited. In addition, it remains uncertain how the magnitude of TS as a continuous variable affects patient survival.

With this in mind, the aims of the present study were to investigate the correlations between the magnitude of best TS during second-line TT according to the categorical classification and as a continuous variable and to determine patient survival after second-line in patients who failed first-line TKI treatment, without previous cytokine therapy in the real world. Moreover, we compared the magnitude of TS between patients treated with TKIs and mTORis as the second-line agent, and investigated how the magnitude of TS could affect the outcomes in these patients.

Patients and methods

The Internal Ethics Review Board of Tokyo Women's Medical University approved this retrospective study (ID: 3440), which was performed in accordance with the principles outlined in the Declaration of Helsinki.

In our department, between January 2007 and April 2015, overall 77 patients received second-line TT after first-line TKI failure, without previous cytokine therapy. Among these 77 patients, 11 patients who did not receive radical nephrectomy, 7 patients whose reason of shifting to second-line

treatment was adverse events of the first-line agent, 3 patients who received hemodialysis therapy, 1 patient who had undergone prior kidney transplantation, 3 patients who received the second-line TT for less than 4 weeks, and 7 patients who did not have detailed imaging data, were excluded. Finally, the remaining 52 patients were enrolled in the present study.

Clinical and laboratory data were extracted from an electronic database and the patient medical records. The MSKCC risk at second-line TT initiation was identified according to Motzer's risk classification (9).

Imaging methods and imaging evaluation

Baseline imaging examination, 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 4-12 weeks of therapy according to the patients' condition.

The target lesions were selected based on the baseline imaging results, and evaluated according to RECIST v. 1.1 (10). The best TS was defined as the time point with maximum TS (percentage change in the sum diameter of all target lesions). Sclerotic osseous lesions were excluded. The patients were also stratified into 4 subgroups according to our stratification strategy of the magnitude of best TS: good responders (≥ -30%), mild responders (-29.9% to -0.1%), poor responders (0% to

+19.9%), and non-responders (≥ +20% or the occurrence of new lesions). The magnitude of TS (continuous variable) was defined as the change from baseline (in %) in the target lesions only; we ignored the change of the sum diameter of novel lesions in cases of progressive disease (PD) according to RECIST v. 1.1 (10). One investigator (H.I.), who was blinded to all other clinical parameters and the patient outcomes, performed all image analyses.

Statistical analysis

OS and PFS after second-line therapy initiation were calculated using the Kaplan-Meier method, and compared using the log-rank test according to the above-mentioned subgroups and the second-line targeted therapy agents (i.e., TKIs vs. mTORis). The difference in the degree of best TS between TKIs and mTORis was compared using the Mann-Whitney *U* test. We performed univariate and multivariate analyses to identify factors associated with OS and PFS using Cox proportional hazards regression models based on the best TS during second-line treatment according to the above-mentioned subgroup classifications and the continuous variable. A waterfall plot was also created to demonstrate the TS differences between TKIs and mTORis. The second-line OS was defined as the time from second-line therapy initiation to death from any cause. The first- and second-line PFSs were defined as the time from first- and second-line therapy initiation, respectively, to the date of progression or death from any cause, whichever came first. Progression was defined

based on RECIST v. 1.1 (10) as a 20% increase in sum diameter of the target lesion, with at least a 5-mm absolute increase, or as appearance of novel metastatic lesions. That is, in spite of the definition of the magnitude of TS used in this study, all cases with appearance of novel metastatic lesions were diagnosed as PD. Risk was expressed as the hazard ratio (HR) with 95% confidence interval (CI). The level of significance was set at $p < 0.05$. All analyses were performed using the JMP® 11 software package (SAS Institute Inc., Cary, NC, USA).

Results

Patient characteristics

Table 1 shows the patient characteristics. The majority of patients were male (73.1%), and were pathologically diagnosed with clear cell carcinoma (80.8%). The MSKCC risks at second-line therapy initiation were classified as favorable, intermediate, and poor in 11 (21.2%), 28 (53.8%), and 13 (25%) patients, respectively (9). The mean age at second-line initiation was 62.9 years. Previous treatments other than TT were performed in 11(21.2%) patients; these included radiation therapy and metastasectomy in 9 (17.3%) and 4 (7.7%) patients, respectively, with some overlap. As the first-line TKI agent, sunitinib, sorafenib, and pazopanib were used in 27 (51.9%), 24 (46.2%), 1 (1.92%) patients, respectively. As second-line therapy, TKIs were used in 37 (71.2%) patients (sunitinib, 9; sorafenib, 2; pazopanib, 2; axitinib, 24), while mTORis were used in 15 (28.8%) patients

(temsirolimus, 5; evelolimus, 10). The mean first-line PFS was 12.2 months.

Regarding the magnitude of best TS during first-line treatment, a complete response, partial response, stable disease (SD), and PD were found in 2 (3.85%), 12 (23.1%), 34 (65.4%), and 4 (7.7%) patients, respectively. The mean TS (continuous variable) during first-line treatment was -14.1%. The mean follow-up period after second-line therapy initiation was 13.2 months.

Magnitude of best tumor shrinkage during second-line targeted therapy

As seen in Table 2, the mean magnitude of TS (continuous variable) was -1.29% after second-line therapy, and the magnitudes of TS (categorical classification) were as follows: good responders, 9 (17.3%); mild responders, 21 (40.4%); poor responders, 11 (21.2%); and non-responders, 11 (21.2%). TKI and mTORi as second-line agents were administered in 37 (71.2%) and 15 (28.8%) patients, and the mean magnitudes of TS were -0.61% and -2.96% respectively. There was no significant difference in the magnitude of TS between the different second-line agents (p=0.686) (Table 2). The magnitude of TS on target lesions according to the second-line agents is demonstrated by using a waterfall plot for individual patients in Fig. 1.

Associations between the magnitude of best tumor shrinkage and patient survival

Kaplan-Meier curves revealed statistical significant correlations between the magnitude of best TS

and patient survival after second-line therapy initiation (Fig. 2, 3). The OS was significantly higher in patients who showed a higher magnitude of TS (median: not reached, 27.8, 18.2, and 4.67 months in good responders, mild responders, poor responders, non-responders, respectively, $p<0.0001$; Fig. 2). Similarly, the PFS was also significantly higher in patients who showed higher magnitude of TS (median: 13.4, 8.19, 5.18, and 1.84 months, respectively, $p<0.0001$; Fig. 3).

Associations between second-line targeted agents and patient survival

Figure 4 and 5 show Kaplan-Meier curves of the patient survival after second-line therapy initiation according to the use of TKIs or mTORis as the second-line targeted agent. There was no significant association between these agents and OS (median: TKI, 16.2 months vs. mTORi, 25.6 months, $p=0.573$; Fig. 4). Similarly, there was no significant association with PFS (median: 5.69 months vs. 6.68 months, $p=0.858$; Fig. 5).

Prognostic indicators for patient survival

For OS, the magnitude of TS with both the categorical classification ($p<0.0001$) and as a continuous variable (HR, 1.03; 95%CI, 1.02-1.05; $p<0.0001$) was a significant indicator, together with first-line PFS (HR, 0.93; 95%CI, 0.86-0.99; $p=0.0141$) and second-line PFS (HR, 0.71; 95%CI, 0.58-0.83; $p<0.0001$) in the univariate analyses. For PFS, the magnitude of TS with both the

categorical classification (p<0.0001) and as a continuous variable (HR, 1.04; 95%CI, 1.03-1.06; p<0.0001) was a significant indicator, together with the MSKCC risk at second-line treatment (p=0.0093), pathology (clear vs. non-clear cell carcinoma; HR 2.54; 95%CI, 1.16-5.16; p=0.0215), and first-line PFS (HR, 0.94; 95%CI, 0.89-0.98; p=0.0032) in the univariate analyses.

In the multivariate analysis, for OS, the magnitude of TS was not an independent prognostic factor with the categorical classification (p=0.0872) or as a continuous variable (HR, 1.01; 95%CI, 1.00-1.03; p=0.133), whereas second-line PFS was found to be an independent factor (HR, 0.79; 95%CI, 0.65-0.93; p=0.028 for the categorical classification; HR, 0.76; 95%CI, 0.62-0.91; p=0.0012 for the continuous variable). For PFS, the magnitude of TS was an independent prognostic factor according to the magnitude of TS with the categorical classification (p<0.0001) and as a continuous variable (HR, 1.04; 95%CI, 1.02-1.06; p<0.0001) (Tables 3, 4).

Discussion

In the present study, we examined the influence of the best TS during second-line TT on patient survival after first-line TKI failure, without prior cytokine therapy. We demonstrated that the magnitude of best TS was an independent predictive factor for PFS but not OS after second-line therapy initiation according to the categorical classification and as a continuous variable, and that second-line PFS was an independent indicator for OS. Moreover, we demonstrated no significant

difference was observed in either the magnitude of TS or patient survival in patients who received TKIs and those who received mTORis as the second-line agent after first-line TKI failure.

As PFS showed a significant correlation with the magnitude of TS, we should choose an agent associated with a high magnitude of TS for improving PFS. Meanwhile, for OS, we found that PFS, rather than the magnitude of TS, was an independent predictive factor. Hence, as PFS cannot easily be predicted during treatment in clinical practice, we believe that the magnitude of TS may represent a useful surrogate marker for OS after second-line therapy initiation; to some extent, realization of the magnitude of TS could help us to predict OS. Halabi et al. also demonstrated a high dependence between PFS and OS, suggesting that PFS may be used as a surrogate endpoint for OS in patients with mRCC (11).

Several studies have previously been performed to investigate the prognostic factors for mRCC patients after TT introduction. The objective response has been already identified as a useful marker, with the ‘initial’ or ‘best’ TS being a significant indicator for mRCC outcomes during first-line therapy (5-8, 12) . Recently, a large-size retrospective study indicated that the magnitude of best TS during second-line therapy could also be regarded as an effective prognostic factor in addition to that during first-line therapy (8). Grünwald et al. (8) described that patient survival showed a clear and significant proportional relationship to the degree of TS during second-line treatment; the OS and PFS were significantly higher as the magnitude of TS increased in all subgroups. Meanwhile, our

results revealed no significant difference in patient survival between the mild responder and poor responder subgroups (data not shown), which were originally categorized as “SD” according to RECIST (10). This discrepancy may be caused by differences in the cohort sizes or by confounding factors due to differences in the patients’ background between the studies.

Furthermore, the present study also indicated that the magnitude of TS seemed to be lower during second-line than first-line therapy (-1.29% vs. -14.1%, p=0.0861, Mann-Whitney U test). This result was similar to that of an analysis of 103 mRCC patients who received triple-sequence therapies (4); this previous study indicated that the degrees of TS during second- and 3rd-line therapies were lower than those during first-line treatment (4). In other words, the rates of patients with PD and SD were higher than the corresponding rates during first-line therapy. This suggests that the effectiveness of second-line TT may be lower compared with that of first-line treatment. Moreover, other studies have previously demonstrated that resistance to VEGF-inhibitor (VEGFi) during first-line therapy strongly associated with poor clinical outcomes (3, 13, 14). For second-line therapy, a similar tendency was noted in our study; the patients who were refractory to second-line therapy showed a relatively poor survival compared with the other subgroups (Fig. 2, 3).

Powerful evidence for the appropriate strategy of sequential second-line therapy is lacking. Bush et al. (3) suggested that there was no significant difference in the efficacy between TKIs and mTORis as second-line TT following first-line TKI failure. Our results were similar in terms of the efficacy of

TKIs or mTORis as second-line treatments; that is, the second-line agent was not associated with patient survival after second-line therapy initiation. However, it should be noted that these results could be affected by considerable bias; most patients who had a lower degree of TS and poorer outcome received sorafenib as the first-line TKI agent and were sequentially treated with sunitinib as second-line therapy (data not shown). This was because sunitinib had not been approved by the insurance system in Japan at the time of the study. Therefore, we should investigate the differences in magnitude of TS and effectiveness between TKIs, such as axitinib, and mTORis, such as everolimus, after first-line sunitinib failure in the future.

There are several limitations of our study. First, the major limitation is the small number of patients, which makes it difficult to extrapolate the results to the general mRCC patient population. Therefore, our results should be confirmed by a larger and more detailed study. Second, we did not consider the withdrawal period and/ or dose changes of TT caused by the adverse events, and the true duration and/ or density of treatment was hence not assessed. Third, as the timing of imaging evaluation was irregular (every 1 to 3 months), there was an unavoidable time lag in the patients' survival. Meanwhile, we believe that the homogeneous patient backgrounds, with all patients undergoing prior radical nephrectomy and receiving first-line TKI therapy, are some of the main advantages of the present study. Moreover, the strongest point of our study is that we evaluated only patients who had not been treated with prior cytokine therapy. To our knowledge, this is the first study suggesting

the prognostic ability of the magnitude of TS during second-line therapy on patient survival in mRCC patients without prior cytokine treatment.

In conclusion, the present study demonstrated that the magnitude of best TS was an independent predictive factor for PFS, and that it might represent a surrogate marker for OS. Moreover, no significant differences in the effectiveness of TKIs and mTORis as second-line therapy after first-line TKI failure were observed. As there are only a limited number of studies that have demonstrated significant correlations between the magnitude of TS and patient outcome, including PFS and OS, in the real world setting, especially for second-line therapy, the present study may enable more effective prediction of patient outcome by evaluating the magnitude of TS. Meanwhile, further studies are warranted to identify novel prognostic biomarkers and imaging findings, as well as the appropriate regimens of sequential therapies for mRCC in order to improve the clinical outcomes of this malignancy.

Acknowledgment

We would like to thank Editage (www.editage.jp) for English language editing.

References

1. Thompson Coon JS, Liu Z, Hoyle M et al. Sunitinib and bevacizumab for first-line treatment of metastatic renal cell carcinoma: a systematic review and indirect comparison of

clinical effectiveness. Br J Cancer. 2009;101(2):238-43.

2. Mills EJ, Rachlis B, O'Regan C, Thabane L, Perri D. Metastatic renal cell cancer treatments: an indirect comparison meta-analysis. BMC Cancer. 2009;9:34.

3. Busch J, Seidel C, Kempkensteffen C et al. Sequence therapy in patients with metastatic renal cell carcinoma: comparison of common targeted treatment options following failure of receptor tyrosine kinase inhibitors. Eur Urol. 2011;60(6):1163-70.

4. Busch J, Seidel C, Erber B et al. Retrospective comparison of triple-sequence therapies in metastatic renal cell carcinoma. Eur Urol. 2013;64(1):62-70.

5. Seidel C, Busch J, Weikert S, Steffens S, Bokemeyer C, Grunwald V. Tumour shrinkage measured with first treatment evaluation under VEGF-targeted therapy as prognostic marker in metastatic renal cell carcinoma (mRCC). Br J Cancer. 2013;109(12):2998-3004.

6. Busch J, Seidel C, Goranova I et al. Categories of response to first line vascular endothelial growth factor receptor targeted therapy and overall survival in patients with metastatic renal cell carcinoma. Eur J Cancer. 2014;50(3):563-9.

7. Iacovelli R, Lanoy E, Albiges L, Escudier B. Tumour burden is an independent prognostic factor in metastatic renal cell carcinoma. BJU Int. 2012;110(11):1747-53.

8. Grunwald V, McKay RR, Krajewski KM et al. Depth of Remission is a Prognostic Factor for Survival in Patients with Metastatic Renal Cell Carcinoma. Eur Urol. 2015;67(5):952-8.

9. Motzer RJ, Bacik J, Schwartz LH et al. Prognostic factors for survival in previously treated patients with metastatic renal cell carcinoma. J Clin Oncol. 2004;22(3):454-63.

10. Eisenhauer EA, Therasse P, Bogaerts J et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45(2):228-47.

11. Halabi S, Rini B, Escudier B, Stadler WM, Small EJ. Progression-free survival as a surrogate endpoint of overall survival in patients with metastatic renal cell carcinoma. Cancer. 2014;120(1):52-60.

12. Krajewski KM, Guo M, Van den Abbeele AD et al. Comparison of four early posttherapy imaging changes (EPTIC; RECIST 1.0, tumor shrinkage, computed tomography tumor density, Choi criteria) in assessing outcome to vascular endothelial growth factor-targeted therapy in patients with advanced renal cell carcinoma. Eur Urol. 2011;59(5):856-62.

13. Busch J, Seidel C, Weikert S et al. Intrinsic resistance to tyrosine kinase inhibitors is associated with poor clinical outcome in metastatic renal cell carcinoma. BMC Cancer. 2011;11:295.

14. Heng DY, Mackenzie MJ, Vaishampayan UN et al. Primary anti-vascular

endothelial growth factor (VEGF)-refractory metastatic renal cell carcinoma: clinical characteristics, risk factors, and subsequent therapy. Ann Oncol. 2012;23(6):1549-55.

Figure legends

Fig. 1 Waterfall plot showing the magnitude of best tumor shrinkage according to the second-line agent used in each patient, with comparisons of tyrosine kinase inhibitors (TKIs) (n=37) and mammalian target of rapamycin inhibitors (mTORis) (n=15)

Fig. 2 Overall survival after second-line targeted therapy initiation according to the magnitude of best tumor shrinkage (TS) during second-line therapy (categorical classification)

The survival rate was calculated by the Kaplan-Meier method, and statistical significance was compared using the log-rank test (p<0.0001).

Fig. 3 Progression-free survival after second-line targeted therapy initiation according to the magnitude of best tumor shrinkage (TS) during second-line therapy (categorical classification)

The survival rate was calculated by the Kaplan-Meier method, and statistical significance was compared using the log-rank test (p<0.0001).

Fig. 4 Overall survival after second-line targeted therapy initiation according to the second-line agents, with comparisons of tyrosine kinase inhibitors (TKIs) (*n*=37) and mammalian target of rapamycin inhibitors (mTORis) (*n*=15)

The survival rate was calculated by the Kaplan-Meier method, and statistical significance was compared using the log-rank test (p=0.573). (p=0.573).

Fig. 5 Progression-free survival after second-line targeted therapy initiation according to the second-line agents, with comparisons of tyrosine kinase inhibitors (TKIs) and mammalian target of rapamycin inhibitors (mTORis)

The survival rate was calculated by the Kaplan-Meier method, and statistical significance was compared using the log-rank test (p=0.858).

Figure 1: Magnitudes of best tumor shrinkage with TKIs and mTORis as 2nd-line agents

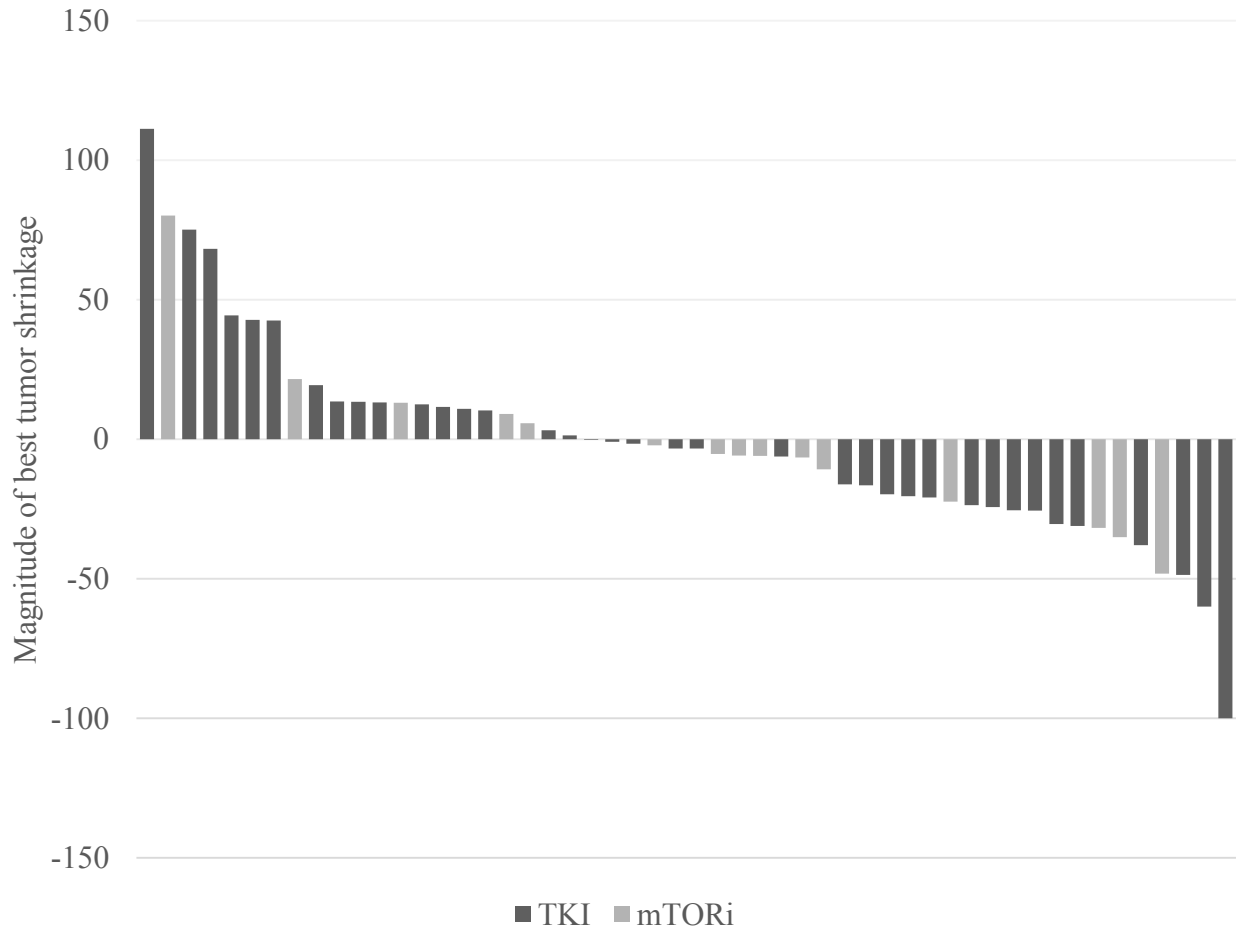
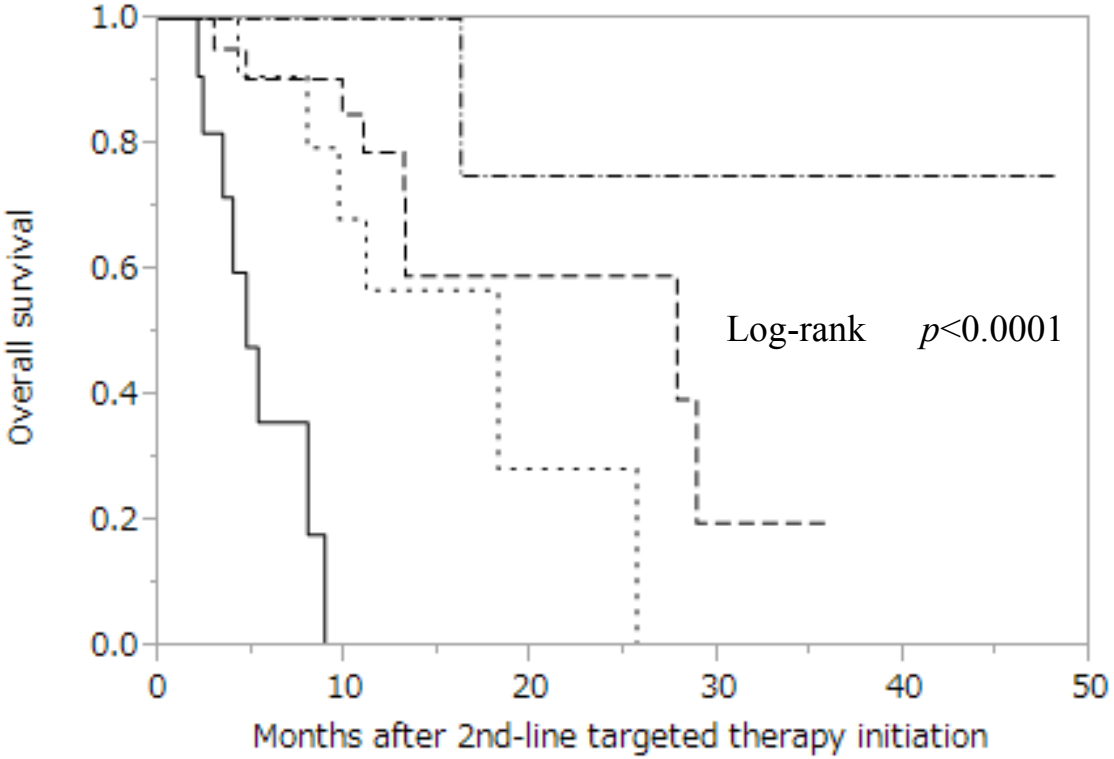
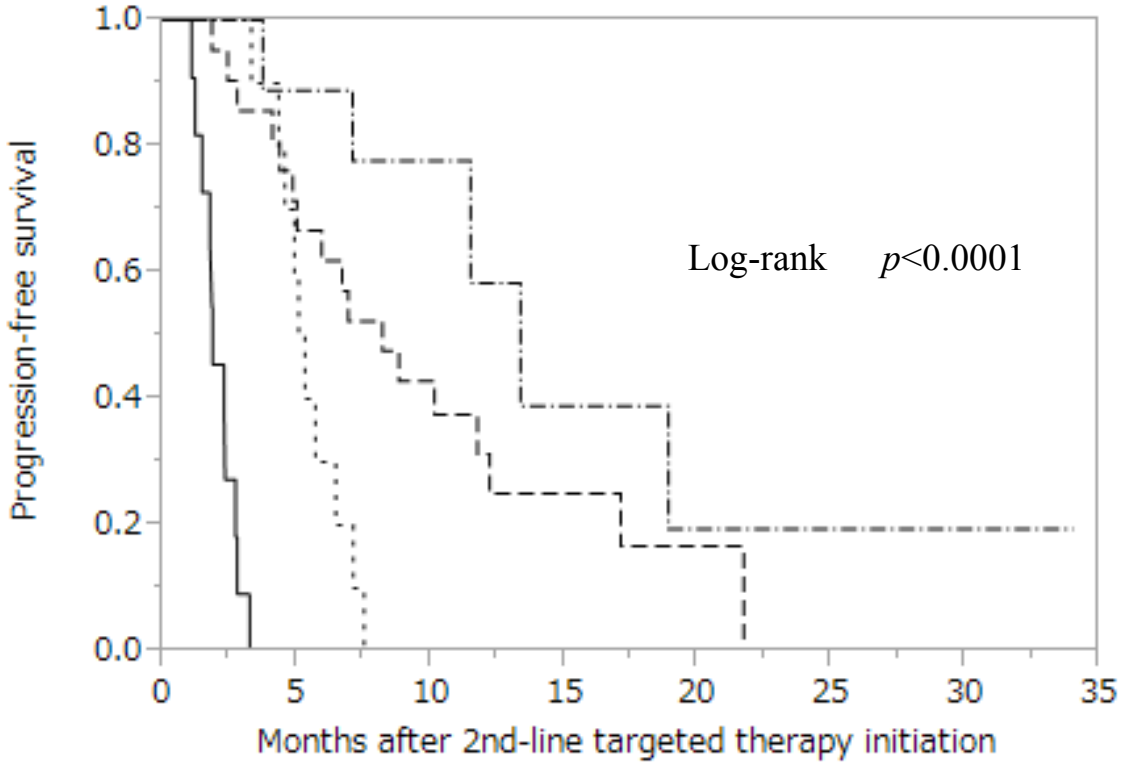


Figure 2: Overall survival after 2nd-line targeted therapy initiation according to the magnitude of best TS during 2nd-line targeted therapy



Magnitude of best TS	Median (months)
Good responder (*n*=9)	Not reached
Mild responder (*n*=21)	27.8
Poor responder (*n*=11)	18.2
Non-responder (*n*=11)	4.67

Figure 3: Progression-free survival after 2nd-line targeted therapy initiation according to the magnitude of best TS during 2nd-line targeted therapy



Magnitude of best TS	Median (months)
Good responder (*n*=9)	13.4
Mild responder (*n*=21)	8.19
Poor responder (*n*=11)	5.18
Non-responder (*n*=11)	1.84

Figure 4: Overall survival after 2nd-line targeted therapy initiation according to the 2nd-line agents

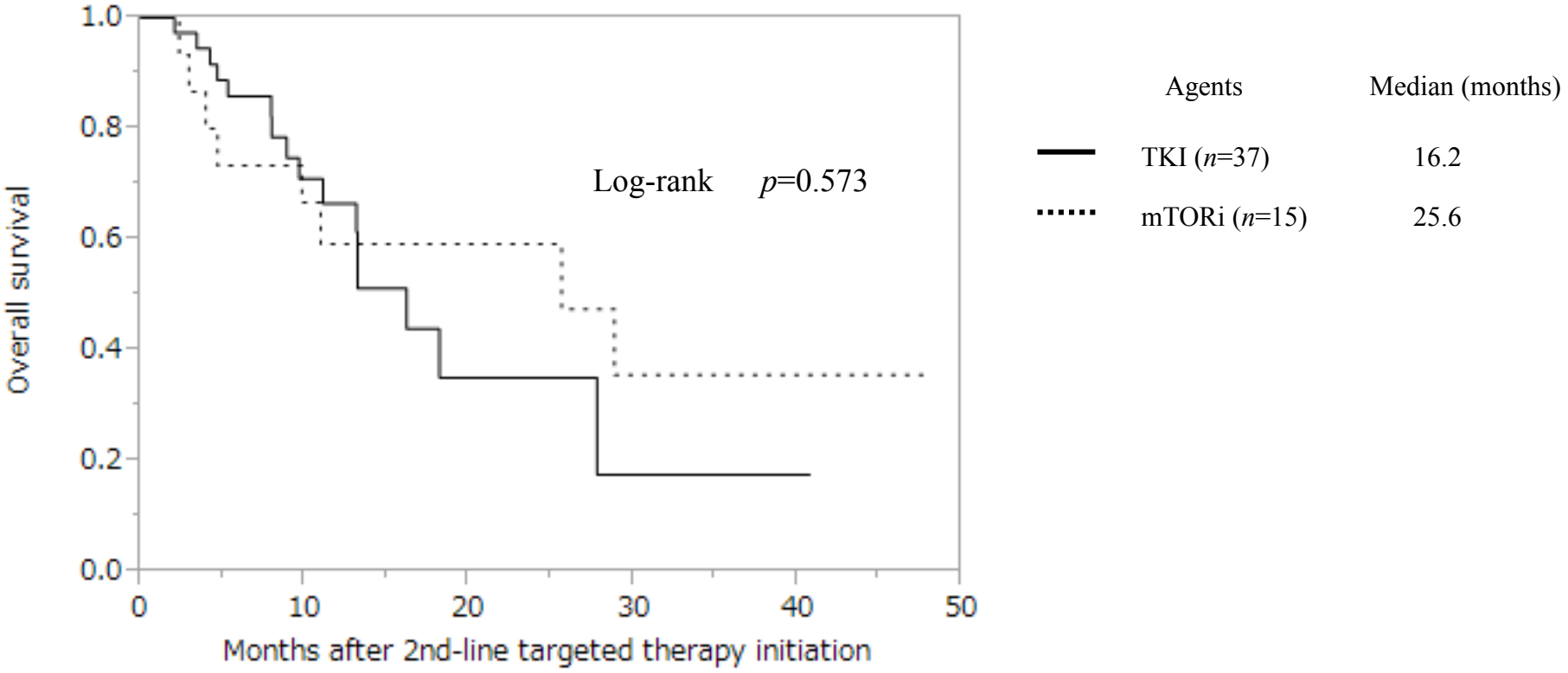


Figure 5: Progression-free survival after 2nd-line targeted therapy initiation according to the 2nd-line agents

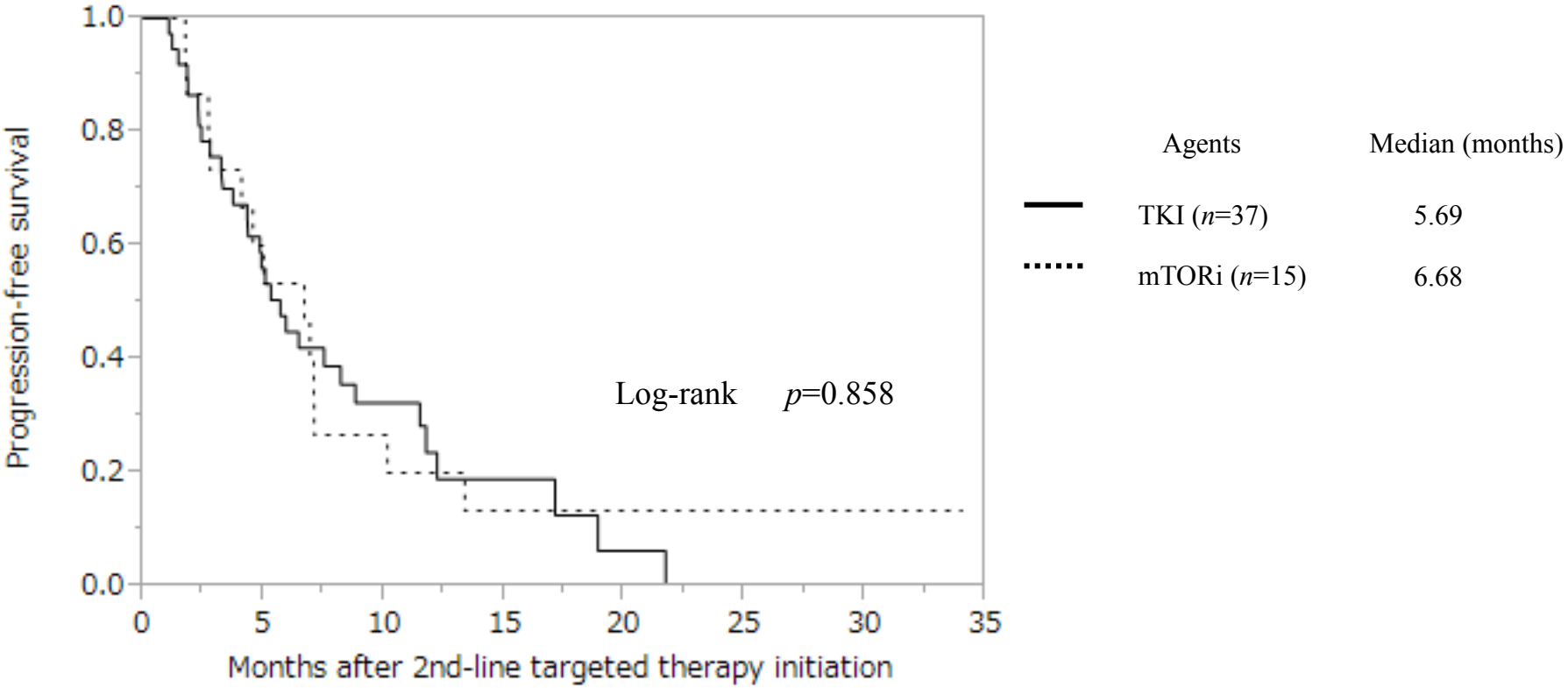


Table 1: Patient characteristics

Characteristics	Total (*n*=52)
Sex	
Male/ female	38 (73.1%)/ 14 (26.9%)
Mean age at 2nd-line therapy initiation , years (median, range)	62.9 (64.0, 29-87)
MSKCC risk at 2nd-line therapy initiation	
Favorable	11 (21.2%)
Intermediate	28 (53.8%)
Poor	13 (25%)
Previous treatments other than targeted therapy for metastatic lesions	
Yes / no	11 (21.2%)/ 41 (78.8%)
Radiation	9 (17.3%)
Metastasectomy	4 (7.7%)
Pathology	
CCC/ non-CCC	42 (80.8%)/ 10 (19.2%)
Best TS during 1st-line therapy according to RECIST	
CR	2 (3.85%)
PR	12 (23.1%)
SD	34 (65.4%)
PD	4 (7.7%)
Mean magnitude of best TS during 1st-line therapy, % (median, range)	-14.1% (-11.7%, -100% to +55.0%)
Mean 1st-line PFS , months (median, range)	12.2 (8.78, 2.01 to 47.8)
TKIs used as 1st-line therapy	
Sunitinib	27 (51.9%)
Sorafenib	24 (46.2%)
Pazopanib	1 (1.92%)
Agents used as 2nd-line therapy	
TKI	37 (71.2%)
Sunitinib	9 (17.3%)
Sorafenib	2 (3.85%)
Pazopanib	2 (3.85%)
Axitinib	24 (46.2%)
mTORi	15 (28.8%)
Temsirolimus	5 (9.62%)
Everolimus	10 (19.2%)
Mean follow-up period after 2nd-line therapy initiation , months (median, range)	13.2 (10.2, 2.04 to 48.1)

MSKCC, Memorial Sloan-Kettering Cancer Center; CCC, clear cell carcinoma; TS, tumor shrinkage; RECIST, Response Evaluation Criteria in Solid Tumors; CR, complete response; PR, partial response; SD, stable disease; PD, progression disease; PFS, progression-free survival; TKI, tyrosine kinase inhibitor; mTORi, mammalian target of rapamycin inhibitor

Table 2: Magnitudes of best TS during 2nd-line targeted therapy

	All (*n*=52)	TKI (*n*=37)	mTORi (*n*=15)	*p*
Categorical classification				
Good responder	9 (17.3%)	6 (16.2%)	3 (20.0%)	
Mild responder	21 (40.4%)	14 (37.8%)	7 (46.7%)	
Poor responder	11 (21.2%)	9 (24.3%)	2 (13.3%)	
Non-responder	11 (21.2%)	8 (21.6%)	3 (20.0%)	
Mean, % (median, range)	-1.29% (-3.30%, -100% to +111.2%)	-0.61% (-1.57%, -100% to +111.2%)	-2.96 % (-5.89%, -48.2 % to +80.1 %)	0.686

TS, tumor shrinkage; TKI, tyrosine kinase inhibitor; mTORi, mammalian target of rapamycin inhibitor

Table 3: Univariate and multivariate analyses of predictors for 2nd-line OS

Variable	Univariate		Multivariate (categorical classifications)		Multivariate (continuous variable)	
	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*P*
MSKCC risk at 2nd-line therapy initiation		0.153				
Favorable	0.65 (0.15-2.04)	0.485				
Intermediate	Reference	-				
Poor	2.09 (0.82-5.04)	0.118				
Previous treatment other than targeted therapies						
Yes	Reference	-				
No	0.95 (0.35-3.32)	0.925				
Pathology						
CCC	Reference	-				
Non-CCC	1.74 (0.77-3.99)	0.179				
Magnitude of best TS during 1st-line therapy according to RECIST		0.658				
CR	4.87 (0-3.42)	0.274				
PR	0.73 (0.24-1.89)	0.532				
SD	Reference	-				
PD	1.11 (0.26-3.36)	0.867				
Magnitude of best TS during 1st-line therapy (continuous variable)	1.01 (0.99-1.03)	0.226				
1st-line PFS	0.93 (0.86-0.99)	0.0141	0.97 (0.88-1.06)	0.557	0.98 (0.91-1.05)	0.581
TKIs used as 1st-line therapy						
Sunitinib	Reference	-				
Sorafenib and pazopanib	1.74 (0.77-3.99)	0.179				
Agents used as 2nd-line therapy						
TKI	Reference	-				
mTORi	0.77 (0.30-1.84)	0.570				
Magnitude of best TS during 2nd-line therapy (categorical classification)		<0.0001		0.0872	-	-
Good responder	0.19 (0.010-1.03)	0.0556	0.63 (0.031-4.30)	0.673		
Mild responder	Reference	-	Reference	-		
Poor responder	2.08 (0.68-6.12)	0.192	0.84 (0.22-3.17)	0.794		
Non-responder	18.6 (5.06-81.6)	<0.0001	4.86 (1.09-25.4)	0.0381		
Magnitude of best TS during 2nd-line therapy (continuous variable)	1.03 (1.02-1.05)	<0.0001	-	-	1.01 (1.00-1.03)	0.133
2nd-line PFS	0.71 (0.58-0.83)	<0.0001	0.79 (0.65-0.93)	0.0028	0.76 (0.62-0.91)	0.0012

OS, overall survival; HR, hazard ratio; CI, confidence interval; MSKCC, Memorial Sloan-Kettering Cancer Center; CCC, clear cell carcinoma; TS, tumor shrinkage; RECIST, Response Evaluation

Criteria in Solid Tumors; CR, complete response; PR, partial response; SD, stable disease; PD, progression disease; PFS, progression-free survival; TKI, tyrosine kinase inhibitor; mTORi, mammalian target of rapamycin inhibitor

Table 4: Univariate and multivariate analyses of predictors for 2nd-line PFS

Variable	Univariate		Multivariate (categorical classifications)		Multivariate (continuous variable)	
	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*
MSKCC risk at 2nd-line therapy initiation		0.0093		0.322		0.374
Favorable	0.47 (0.17-1.09)	0.0790	0.50 (0.17-1.29)	0.155	0.56 (0.20-1.37)	0.214
Intermediate	Reference	-	Reference	-	Reference	-
Poor	2.08 (1.00-4.16)	0.0503	1.02 (0.44-2.27)	0.959	1.13 (0.50-2.44)	0.756
Previous treatment other than targeted therapies						
Yes	Reference	-				
No	0.75 (0.37-1.68)	0.465				
Pathology						
CCC	Reference	-	Reference	-	Reference	-
Non-CCC	2.54 (1.16-5.16)	0.0215	1.22 (0.53-2.65)	0.628	0.99 (0.41-2.23)	0.978
Magnitude of best TS during 1st-line therapy according to RECIST		0.168				
CR	0.44 (0.025-2.10)	0.364				
PR	0.61 (0.28-1.23)	0.172				
SD	Reference	-				
PD	2.28 (0.67-5.98)	0.169				
Magnitude of best TS during 1st-line therapy (continuous variable)	1.01 (1.00-1.03)	0.0593				
1st-line PFS	0.94 (0.89-0.98)	0.0032	1.00 (0.94-1.04)	0.844	0.98 (0.94-1.03)	0.434
TKIs used as 1st-line therapy						
Sunitinib	Reference	-				
Sorafenib and pazopanib	1.04 (0.57-1.88)	0.902				
Agents used as 2nd-line therapy						
TKI	Reference	-				
mTORi	0.94 (0.47-1.78)	0.858				
Magnitude of best TS during 2nd-line therapy (categorical classification)		<0.0001		<0.0001	-	-
Good responder	0.49 (0.16-1.24)	0.136	0.41 (0.13-1.13)	0.0868		
Mild responder	Reference	-	Reference	-		
Poor responder	3.05 (1.23-7.49)	0.0167	2.15 (0.77-6.10)	0.142		
Non-responder	52.4 (13.9-263.9)	<0.0001	38.9 (9.60-210.2)	<0.0001		
Magnitude of best TS during 2nd-line therapy (continuous variable)	1.04 (1.03-1.06)	<0.0001	-	-	1.04 (1.02-1.06)	<0.0001

PFS, progression free survival; HR, hazard ratio; CI, confidence interval; MSKCC, Memorial Sloan-Kettering Cancer Center; CCC, clear cell carcinoma; TS, tumor shrinkage; RECIST, Response Evaluation Criteria in Solid Tumors; CR, complete response; PR, partial response; SD, stable

disease; PD, progression disease; TKI, tyrosine kinase inhibitor; mTORi, mammalian target of rapamycin inhibitor