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Depth of remission is a prognostic factor for survival in patients with metastatic renal cell carcinoma

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Abstract

Background—Response remains an important endpoint in clinical cancer trials. However, the prognostic utility of best tumor response in metastatic renal cell carcinoma (mRCC) remains vague.

Objective—To define the prognostic relevance of the depth of remission in mRCC

Design, setting, and participants—Pooled data of 2,749 patients from phase II and III clinical trials of the Pfizer data-base in mRCC was analyzed. Tumor-shrinkage was categorized by fractions of best percent change in the sum of the largest diameter of target lesions. Outcome was computed by Kaplan-Meier curves and correlation was assessed by Cox regression, including a 6-month landmark.

Intervention—Sunitinib, sorafenib, axitinib, temsirolimus, temsirolimus and/or IFN-α.

Outcome Measurements and Statistical Analysis—Categorized tumor-shrinkage, overall survival (OS), progression free survival (PFS).

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Results and limitations—Major tumor shrinkage of 60% or more occurred in about 10% of patients and was associated with a median overall survival (OS) of 54.5 months. With depth of remission, OS expectations declined steadily (26.4, 16.6, 10.4, and 7.3 months). The association was maintained when stratified by type of therapy, line of therapy, and performance status. The 6-month landmark Cox proportional regression analyses confirmed the prognostic relevance of major tumor shrinkage (HR 0.29; CI 95% 0.22–0.39; p<0.001). The major limitation of our study is the variability of imaging intervals among studies.

Conclusions—This is the first and largest analysis of best tumor response in mRCC. We demonstrate that depth of remission is an independent prognostic factor in mRCC.

Patient summary—It remains unknown whether tumor shrinkage during therapy is needed to achieve clinical activity in mRCC. Our analysis shows that the magnitude of tumor shrinkage correlates with a better survival in patients. This observation may be used as a clinical research tool in future trials.

Trial registration—NCT00054886, NCT00077974, NCT00267748, NCT00338884, NCT00137423, NCT00083889, NCT00065468, NCT00678392

Keywords

Imaging; Prognosis; Renal cell carcinoma; Targeted therapy Tumor response; Tumor shrinkage

Introduction

Treatment of metastatic renal cell carcinoma (mRCC) has undergone a paradigm change in recent years. Targeted agents inhibiting the vascular endothelial growth factor (VEGF) or mammalian target of rapamycin (mTOR) have replaced the former standard of care, which consisted of cytokine treatment. A major criticism of these agents is their inability to induce complete or long-term remissions, a phenomenon which was rendered a cornerstone for treatment outcomes in the cytokine era.

This field remained controversial because retrospective series indicated complete remission (CR) and long-term response were possible in a fraction of patients with mRCC.[1] This data is supported by a recent analysis, which underscored the ineffectiveness of objective response (OR) to predict overall survival (OS) in mRCC treated with targeted agents.[2, 3] More surprisingly, a minority of patients who achieved a CR (2.7%) was able to attain superior OS estimates (63.2 months), indicating that deep responses may benefit clinical outcome.[2]

We hypothesize that deep tumor remission beyond the response evaluation criteria in solid tumors (RECIST)-defined 30% threshold for OR will provide prognostic relevance in mRCC. We therefore utilized a large contemporary clinical trials database of patients with mRCC treated with a broad range of therapies to characterize the significance of depth of remission in these patients.

Methods

Study design

We conducted a pooled analysis from a clinical trials database including patients with mRCC treated on prospective phase II (NCT00054886, NCT00077974, NCT00267748, NCT00338884, NCT00137423) and III (NCT00083889, NCT00065468, NCT00678392) trials sponsored by Pfizer Oncology. We identified 2,749 patients treated for mRCC between January 2003 and November 2011. Baseline demographic, clinical, and laboratory data were collected.

Imaging and imaging assessment

Patients underwent contrast-enhanced or non-contrast enhanced computed tomography (CT) or magnetic resonance imaging (MRI) of the chest, abdomen, and pelvis prior to therapy initiation and continued until disease progression or study withdrawal. Intervals for tumor assessment varied throughout trials. Consecutive scans were performed after 4–8, 9–16, 16–24, 22–36, and 31–48 weeks of therapy, respectively. Further tumor assessment in subsequent cycles was performed at 8–12 weeks intervals. Measurements were performed prospectively by clinical investigators. Target lesions were selected on baseline imaging exams according to RECIST version 1.0.[4] On each baseline and follow-up imaging study, the longest axis of each target lesion was recorded to the nearest millimeter and the sum of the long axis diameter (SLD) of the targets was calculated. Percent change in the tumor burden was assessed at every available study time point. For each patient the time point with the maximum tumor shrinkage was defined as best response by the percent change in the SLD of the target lesions. Novel lesions were not assessed for tumor shrinkage.

Statistical methods

OS and progression-free survival (PFS), both prospectively assessed, were determined by the following tumor response categories: −100% to <−60%, −60% to <−30%, −30% to <0%, 0% to <+20%, ≥+20%, and in the group without post-baseline imaging. Tumor response categories were prospectively defined based on an analysis of 100 mRCC patients.[3] The categories roughly correspond to RECIST response categories, whereby −100% to <−60% and −60% to <−30% categories correspond to CR and partial response (PR), −30% to <0% and 0% to <+20% categories correspond to stable disease (SD), and ≥+20% category represents progressive disease (PD).[4] Furthermore, we tested whether tumor shrinkage cut-off parameters of ≥ −10%, ≥ −20%, and ≥ −30% predict OS and PFS.

OS was defined as the time from start of therapy (phase II studies) or randomization (phase III studies) to death from any cause. PFS was defined as the time from therapy initiation to date of progression or death from any cause, whichever came first. Distributions of OS and PFS were calculated using the Kaplan-Meier method. Median OS and PFS along with 95% confidence intervals (CI) were reported. Associations between OS and PFS were assessed using the Cox proportional regression analysis, adjusted for age, sex, race, and the Memorial Sloan-Kettering Cancer Center (MSKCC) risk factors.[5] To correct for the potential bias of post-baseline factors, such as tumor shrinkage and confounding treatment effects, we also conducted a 6-month landmark analysis. To find out whether subgroup analyses are

justified, we performed an interaction analysis for tumorshrinkage (as a continuous covariate) and therapy type by applying a cox regression model with a 6-month landmark. Subgroup efficacy analyses were performed by: 1) line of therapy, 2) therapy type, and 3) performance status. The temsirolimus group included patients on temsirolimus or the combination of temsirolimus + interferon-alpha (IFN-α).

Results

Patient and disease characteristics

Of the 2,749 patients in the analysis, the majority were less than 65 years of age, male, with good performance status, and clear-cell histology (Table 1). Most patients underwent prior nephrectomy (84%) and 46% received prior therapy. Baseline lung and bone metastases were similar across categories; however liver metastases were more frequent in the ≥+20% group.

Patients received treatment with sunitinib (n=1,059), sorafenib (n=355), axitinib (n=359), temsirolimus (n=208), temsirolimus + IFN-α (n=208), or IFN-α (n=560), of whom 1,759 received first-line therapy. The median baseline total tumor measurement was 103 mm/ patient for the overall cohort. The most frequent category of response was −30% to <0% (42%). 10% of patients had dramatic shrinkage (−100% to <−60%), most of whom (78%) were treated with axitinib, sorafenib, or sunitinib. A minority of patients (6%), 49% of whom received axitinib, sorafenib, or sunitinib, had ≥+20% growth as the best response. 218 patients (8%) had no post-baseline imaging, most commonly due to disease progression (n=77, 35%), adverse events (n=61, 28%), or death (n=43, 20%). When stratified by degree of tumor shrinkage, median baseline tumor load was 70, 95, 114, 132, and 86 mm for the −100% to <−60%, −60% to <−30%, −30% to <0%, 0% to <+20%, and ≥+20% groups, respectively. For patients with no post-baseline imaging, median baseline tumor load was 124.5 mm. The median time on therapy was 5.3 months of the overall cohort and 16.5, 10.1, 5.5, 2.3, and 1.4 months for the −100% to <−60%, −60% to <−30%, −30% to <0%, 0% to <+20%, and ≥+20% groups, respectively.

Impact of tumor response on survival outcomes

Overall, 72% of patients experienced some degree of tumor shrinkage and 30% met the threshold for OR as defined by RECIST. When evaluating the overall cohort, tumor response was found to be an independent prognostic factor for OS and PFS (Table 2). In patients with maximum tumor shrinkage (−100% to <−60%), median OS and PFS were 54.5 and 17.3 months compared to progressively shorter OS and PFS for patients with decreasing degrees of tumor shrinkage.

Six-month landmark analysis

Multivariable analysis with 6-month landmark confirmed that depth of remission was an independent prognostic factor for OS (Table 3). The degree of tumor shrinkage had a differential impact on prognosis among agents. The median time to best response was 2.8 months for the overall cohort. In patients with major tumor shrinkage (−100% to <−60%), there was a significant delay in median time to best response (12.5 months), compared to

patients in the −60% to <−30% (6.4 months) or −30% to <0% groups (2.5 months). A total of 536 deaths (20%) occurred prior to the 6-month landmark, which led to the exclusion of these cases from the landmark analysis.

Tumor shrinkage cut-off parameters and survival

In patients with ≥30% tumor shrinkage, median OS and PFS were 26.6 and 10.7 months compared to 13.7 and 4.5 months for patients with <30% tumor shrinkage (p<0.001, HR 1.50 for OS; p<0.001, HR 1.84 for PFS). This trend was maintained when dichotomizing at 20% (median OS and PFS were 25.5 and 10.2 months for ≥20% tumor shrinkage compared to 12.7 and 3.8 months for <20% tumor shrinkage; p<0.001, HR 1.62 for OS; p<0.001, HR 2.04 for PFS) or 10% tumor shrinkage (median OS and PFS were 22.9 and 8.9 months for ≥10% tumor shrinkage compared to 11.8 and 3.2 months for <10% tumor shrinkage; p<0.001, HR 1.63 for OS; p<0.001, HR 2.32 for PFS).

Stratification by patient and treatment characteristics

To answer the question whether treatment and tumor shrinkage are related, we first tested for interaction for tumor shrinkage and any type of therapy. Both factors interacted significantly (p=0.0093), which justified further subgroup analyses for the agents used.

When stratified by therapy type, OR were higher in patients receiving axitinib, sorafenib, or sunitinib (38%, n=667/1773) compared to temsirolimus (18%, n=74/416). Overall, 79% of patients receiving axitinib, sorafenib, or sunitinib and 66% of patients receiving temsirolimus had some degree of tumor shrinkage, most of which was ≤ 30% for both treatment types.

Tumor response was an independent prognostic factor for OS and PFS when patients were stratified by type of therapy (Table 2). Irrespective of therapy type, patients with a more pronounced tumor response had significantly longer OS and PFS compared to patients with no response or tumor growth. When stratified by first-line and second-line therapy, degree of tumor shrinkage continued to be an independent prognostic factor for OS and PFS (Table 2). Additionally, degree of tumor shrinkage predicted OS and PFS when stratified by performance status (Table 2).

Treatment exposure

In total, 1,070 patients (40%) underwent dose reductions or modifications due to adverse events. When stratified by tumor shrinkage category, 189 (67%), 285 (52%), 421 (37%), 117 (30%), and 26 (17%) patients in the −100% to <−60%, −60% to <−30%, −30% to <0%, 0% to <+20%, and ≥ +20% groups, respectively, underwent dose reductions or modifications, likely reflective of longer duration for therapy.

Discussion

This is the first and largest analysis evaluating the prognostic significance of best tumor response in patients with mRCC treated with a variety of agents in the targeted therapy era. Our analysis was conducted from a clinical trials database, a rich tool for the evaluation of

patient characteristics and outcomes, which includes prospectively collected data. Due to challenges of tumor measurement variability, the use of prospectively acquired measurements is a major strength of our analysis.

This study adds to the growing body of literature that demonstrates that tumor shrinkage is a major outcome of targeted therapies. Historically, VEGF-targeted therapy was reported to achieve higher OR rates (20–30%) compared to mTOR-targeted therapy (≤10%), which is supported by our analysis.[6, 7] More recently, a randomized controlled trial confirmed a superior OR rate for sunitinib (27%) when compared to everolimus (8%).[8] In our analyses, patients with tumor shrinkage were detected in 66% of patients receiving temsirolimus and 79% with axitinib, sorafenib, or sunitinib. Major tumor shrinkage of −100 to <−60% was more frequently found in patients treated with axitinib, sorafenib, or sunitinib (n=221; 12%), compared to temsirolimus (n=19; 5%). Tumor growth during therapy was found in 272 (15%) patients treated with axitinib, sorafenib, or sunitinib, and 83 patients (20%) treated with temsirolimus. However, patient selection factors such as MSKCC risk categories varied between trials and may not allow for definitive conclusions. Of more importance, individual patients may gain benefit from both VEGF and mTOR targeted-therapies given the prolonged survival associated with therapy. A main goal of clinical trials should be the definition of predictive markers, which may secure proper selection of individual treatments.

In this series, we demonstrate that the depth of remission is an independent prognostic factor in mRCC, regardless of the type of treatment. Several prior studies which have evaluated the prognostic significance of “early” or “best” tumor shrinkage on imaging were in patients receiving a specific agent or class of agents.[1–3, 8] In an analysis of 70 mRCC patients receiving first-line VEGF-targeted therapy, Krajewski and colleagues demonstrated that a 10% reduction in tumor diameter at first-follow up CT imaging was an optimal size change threshold to define responders and predict early outcomes.[8] Additionally, Seidel and colleagues confirmed that early tumor shrinkage was prognostic in mRCC.[3] In an analysis of 1,059 mRCC patients treated with sunitinib, there was no difference in OS between early and late responders (≤12 versus >12 weeks), however OS was significantly prolonged in responders (CR/PR) compared to non-responders a (40.1 versus 14.5 months, respectively, $p<0.001$).[1]

Tumor shrinkage has also been explored with mTOR-targeted therapy. Data from a phase III trial of everolimus versus placebo in patients with mRCC showed that early tumor response was a predictive factor of OS.[9] Additionally, they demonstrated that growth of target lesions did not affect OS, except among patients with a >10% increase in tumor diameter. Our observations are consistent with these findings and those demonstrated in other malignancies treated with targeted therapy, including KRAS wild-type metastatic colorectal cancer and advanced non-small cell lung cancer, in which early tumor shrinkage has been shown to be a powerful predictor of outcome.[10, 11] Compared to previously published studies in mRCC, our study has many novel aspects. This is the first and largest comprehensive study demonstrating that the best tumor response on imaging is an independent prognostic factor for survival in mRCC, irrespective of line of treatment or agent applied.

Because response is an event, which is acquired throughout the course of the study it introduces an inherent bias to such analyses, favoring responders.[12, 13] We therefore conducted a landmark analysis to correct for this inherent bias, a technique which has not been employed in several of the prior imaging studies, and verified that tumor shrinkage predicted survival. Despite the inability to distinguish between biology and treatment effect, response remains a desirable outcome because of its prognostic value.

Whether uni-dimensional measurement of tumor response provides sufficient information in the era of targeted agents is a matter of debate. Choi and colleagues were the first to introduce the concept of morphological changes rather than the mere reduction of size in tumor assessment.[14] Today, functional imaging holds promise to assess pharmacodynamic changes during treatment. In RCC, dynamic contrast enhanced ultrasound or MRI were shown to predict PFS and OS.[15, 16]

Our results underscore the prognostic relevance of tumor shrinkage in mRCC. Validation of our data and the definition of an optimal threshold for response could lead to novel endpoints of clinical trials in mRCC. Furthermore, our data can potentially guide urooncologists to counsel patients with mRCC receiving axitinib, sorafenib, sunitinib, temsirolimus, or IFN-α about the relative value of tumor shrinkage using evidence-based data rather than anecdotal experience.

Though our clinical trials database is a powerful tool to assess the impact of tumor response in mRCC, there are several limitations. Overall, this analysis has been performed post-hoc and, hence, will require additional validation studies. A total of 218 patients (8%) had no post-baseline assessments potentially introducing a bias to patient selection. All patients in this database were enrolled on clinical trials, which could lead to bias when applying results to a real-world population. Bevacizumab/IFN-α and everolimus represent additional options in the therapeutic portfolio of mRCC, which are not captured by our analysis.

Additionally, imaging-based limitations include heterogeneity in scan type and frequency and general variability inherent to reimaging. In principle, response is a subjective endpoint in cancer trials and independent central review was thought to compensate for measurement variations. However, central imaging review was shown to introduce informative censoring, and may not solve the problem completely.[17] A recent meta-analysis confirmed that local imaging evaluations provide a reliable estimate on treatment effects.[18] Furthermore, new lesions and progression of non-target lesions has been shown to predict OS in the RECIST 1.1 dataset.[19]

Conclusions

In conclusion, in this analysis, we confirm that depth of remission is an independent prognostic factor for survival in patients with mRCC. These findings have important implications regarding management of treatment expectations and optimizing the care of mRCC patients. Independent studies are needed to better define the optimal threshold of tumor shrinkage and explore its role as putative novel endpoint in clinical trials.

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Table 1

Baseline patient and disease characteristics.

Characteristic *n* (%)	−100% to <− 60% *n*=283 (10%)	−60% to <− 30% *n*=547 (20%)	−30% to <0% *n*=1155 (42%)	0% to <+20% *n*=390 (14%)	≥ +20% *n*=156 (6%)	No Post- Baseline Imaging *n*=218 (8%)	Total Cohort *n*=2749 (100%)
Age at initiation of therapy							
< 65 years	196 (69%)	345 (63%)	762 (66%)	271 (69%)	112 (72%)	142 (65%)	1828 (66%)
≥ 65 years	87 (31%)	202 (37%)	393 (34%)	119 (31%)	44 (28%)	76 (35%)	921 (34%)
Sex							
Male	202 (71%)	389 (71%)	844 (73%)	248 (64%)	110 (71%)	151 (69%)	1944 (71%)
Female	81 (29%)	158 (29%)	311 (27%)	142 (36%)	46 (29%)	67 (31%)	805 (29%)
Race							
White	258 (91%)	436 (80%)	968 (84%)	336 (86%)	135 (87%)	178 (82%)	2311 (84%)
Other	25 (9%)	111 (20%)	187 (16%)	54 (14%)	21 (13%)	40 (18%)	438 (16%)
ECOG Performance Status							
0	169 (60%)	319 (58%)	537 (47%)	153 (39%)	63 (40%)	41 (19%)	1282 (47%)
1	106 (37%)	222 (42%)	594 (51%)	223 (57%)	91 (58%)	151 (69%)	1387 (50%)
2	3 (1%)	4 (1%)	15 (1%)	11 (3%)	0 (0%)	25 (12%)	58 (2%)
Unknown	5 (2%)	2 (<1%)	3 (1%)	3 (1%)	2 (1%)	1 (<1%)	22 (1%)
Pathology							
Clear cell	255 (90%)	493 (90%)	1042 (90%)	344 (88%)	135 (87%)	181 (83%)	2450 (89%)
Non-clear cell	18 (6%)	26 (5%)	51 (4%)	26 (7%)	10 (6%)	9 (4%)	140 (5%)
Unknown	10 (4%)	28 (5%)	62 (5%)	20 (5%)	11 (7%)	28 (13%)	159 (6%)
Baseline metastatic site							
Lung	223 (79%)	421 (77%)	893 (77%)	293 (75%)	122 (78%)	172 (79%)	2124 (77%)
Bone	61 (22%)	129 (24%)	336 (29%)	126 (32%)	48 (31%)	81 (37%)	781 (28%)
Liver	64 (23%)	118 (22%)	314 (27%)	129 (33%)	62 (40%)	79 (36%)	766 (28%)
Other[a]	183 (65%)	423 (77%)	963 (83%)	337 (86%)	126 (81%)	184 (84%)	2216 (81%)
Previous nephrectomy							

Characteristic *n* (%)	−100% to <− 60% *n*=283 (10%)	−60% to <− 30% *n*=547 (20%)	−30% to <0% *n*=1155 (42%)	0% to <+20% *n*=390 (14%)	≥ +20% *n*=156 (6%)	No Post- Baseline Imaging *n*=218 (8%)	Total Cohort *n*=2749 (100%)
Yes	270 (95%)	490 (90%)	938 (81%)	308 (79%)	146 (94%)	145 (64%)	2297 (84%)
No	12 (4%)	26 (5%)	121 (11%)	45 (12%)	3 (2%)	23 (11%)	248 (9%)
Unknown	1 (1%)	28 (5%)	96 (8 %)	37 (9%)	7 (4%)	50 (23%)	204 (7%)
Prior type of therapy							
Any prior therapy	131 (46%)	268 (49%)	546 (47%)	175 (45%)	68 (44%)	81 (37%)	1269 (46%)
Cytokine therapy	62 (22%)	162 (30%)	250 (22%)	55 (14%)	17 (11%)	25 (12%)	571 (21%)
Targeted therapy	15 (5%)	55 (10%)	232 (20%)	100 (26%)	44 (28%)	36 (17%)	482 (18%)
MSKCC risk group							
Favorable	80 (28%)	166 (30%)	250 (22%)	54 (14%)	22 (14%)	13 (6%)	585 (21%)
Intermediate	135 (48%)	226 (41%)	460 (40%)	165 (42%)	61 (39%)	57 (26%)	1104 (40%)
Poor	41 (14%)	91 (17%)	330 (29%)	134 (34%)	61 (39%)	119 (55%)	776 (28%)
Unknown	27 (10%)	64 (12%)	115 (10%)	37 (10%)	12 (8%)	29 (13%)	284 (10%)

[a]Other is defined as any other metastases excluding lung, bone and liver.

ECOG = Eastern Cooperative Oncology Group, MSKCC = Memorial Sloan-Kettering Cancer Center.

Table 2

Cox proportional regression analyses with 6-month landmark stratified by agents. Tumorshrinkage categories are shown for each treatment cohort of patients.

	OS	
	P-Value	**HR (95% CI)**
Overall Cohort		
−100% to <−60%	<0.001	0.29 (0.22–0.39)
−60% to <−30%	0.005	0.77 (0.64–0.93)
−30% to <0%	Reference	Reference
0% to <+20%	0.002	1.39 (1.13–1.71)
≥+20%	0.011	1.52 (1.10–2.09)
No post-baseline imaging	0.5	1.16 (0.73–1.85)
Axitinib, sorafenib, or sunitinib		
−100% to <−60%	<0.001	0.21 (0.15–0.31)
−60% to <−30%	0.009	0.67 (0.53–0.85)
−30% to <0%	Reference	Reference
0% to <+20%	0.002	1.66 (1.20–2.30)
≥+20%	0.2	1.44 (0.81–2.57)
No post-baseline imaging	0.4	0.69 (0.30–1.57)
Temsirolimus		
−100% to <−60%	0.036	0.44 (0.20–0.95)
−60% to <−30%	0.5	0.86 (0.56–1.30)
−30% to <0%	Reference	Reference
0% to <+20%	0.1	1.46 (0.89–2.40)
≥+20%	0.046	2.38 (1.02–5.56)
No post-baseline imaging	0.6	1.42 (0.45–4.47)
IFN-α		
−100% to <−60%	<0.001	0.33 (0.17–0.62)
−60% to <−30%	0.030	0.56 (0.34–0.95)
−30% to <0%	Reference	Reference
0% to <+20%	0.3	1.19 (0.84–1.67)
≥+20%	0.1	1.43 (0,90 -2.28)
No post-baseline imaging	0.4	1.38 (0.69 -2.76)

Table 3

Impact of Tumor Response on OS and PFS. Tumor shrinkage categories are shown for each treatment cohort of patients.

		OS			PFS		
	n	**Median (months)**	**P-Value**	**HR (95% CI)**	**Median (months)**	**P-Value**	**HR (95% CI)**
Overall Cohort							
−100% to <−60%	283	54.5	<0.001	0.27 (0.20–0.35)	17.3	<0.001	0.35 (0.29–0.43)
−60% to <−30%	547	26.4	<0.001	0.70 (0.59–0.83)	10.8	<0.001	0.65 (0.56–0.74)
−30% to <0%	1155	16.6	Reference	Reference	6.5	Reference	Reference
0% to <+20%	390	10.4	<0.001	1.62 (1.38–1.89)	2.5	<0.001	2.65 (2.29–3.07)
≥+20%	156	7.3	<0.001	1.92 (1.54–2.39)	1.4	<0.001	11.78 (9.48–14.63)
No Post-Baseline Imaging	218	2.0	<0.001	4.37 (3.61–5.29)	1.1	<0.001	4.89 (3.99–5.99)
Line of Therapy							
First-Line							
−100% to <−60%	208	NR	<0.001	0.28 (0.20–0.40)	16.7	<0.001	0.38 (0.30–0.47)
−60% to <−30%	336	25.5	<0.001	0.70 (0.58–0.86)	11.1	<0.001	0.62 (0.52–0.74)
−30% to <0%	708	14.9	Reference	Reference	5.5	Reference	Reference
0% to <+20%	247	10.4	<0.001	1.48 (1.22–1.79)	2.3	<0.001	2.55 (2.12–3.07)
≥+20%	101	6.2	<0.001	1.96 (1.52–2.54)	1.4	<0.001	9.39 (7.18–12.19)
No Post-Baseline Imaging	159	1.8	<0.001	4.61 (3.68–5.78)	1.0	<0.001	4.96 (3.94–6.26)
Second-Line							
−100% to <−60%	75	48.1	<0.001	0.21 (0.12–0.36)	19.1	<0.001	0.24 (0.17–0.36)
−60% to <−30%	211	30.1	0.012	0.67 (0.49–0.91)	10.2	<0.001	0.66 (0.53–0.83)
−30% to <0%	447	18.9	Reference	Reference	7.9	Reference	Reference
0% to <+20%	143	10.4	<0.001	1.90 (1.43–2.53)	2.9	<0.001	3.04 (2.38–3.89)
≥+20%	55	9.9	0.008	1.81 (1.17–2.81)	1.4	<0.001	19.00 (13.02–27.71)
No Post-Baseline Imaging	59	3.2	<0.001	3.453 (2.36–5.05)	1.3	<0.001	4.82 (2.97–7.82)
Type of Therapy							
Axitinib, sorafenib, or sunitinib							

		OS			PFS		
	n	Median (months)	P-Value	HR (95% CI)	Median (months)	P-Value	HR (95% CI)
−100% to <−60%	221	54.5	<0.001	0.20 (0.14–0.28)	17.7	<0.001	0.32 (0.26–0.41)
−60% to <−30%	446	26.8	<0.001	0.61 (0.49–0.76)	11.2	<0.001	0.62 (0.52–0.73)
−30% to <0%	737	18.0	Reference	Reference	7.8	Reference	Reference
0% to <+20%	196	10.4	<0.001	1.84 (1.45–2.34)	2.9	<0.001	2.73 (2.20–3.38)
≥+20%	76	9.2	<0.001	1.92 (1.33–2.77)	1.4	<0.001	18.60 (13.42–25.80)
No Post-Baseline Imaging	97	3.2	<0.001	3.09 (2.22–4.28)	1.1	<0.001	4.04 (2.71–6.02)
Temsirolimus[a]							
−100% to <−60%	19	28.4	0.010	0.39 (0.19–0.79)	9.2	0.017	0.51 (0.29–0.89)
−60% to <−30%	55	16.3	0.2	0.79 (0.54–1.15)	7.4	0.1	0.76 (0.55–1.06)
−30% to <0%	202	10.9	Reference	Reference	5.5	Reference	Reference
0% to <+20%	60	6.1	<0.001	1.91 (1.35–2.71)	1.9	<0.001	2.57 (1.80–3.66)
≥+20%	23	5.1	<0.001	2.72 (1.61–4.61)	1.7	<0.001	8.81 (5.08–15.26)
No Post-Baseline Imaging	57	1.6	<0.001	8.21 (5.61–12.01)	1.1	<0.001	7.73 (5.33–11.23)
IFN-α							
−100% to <−60%	43	NR	<0.001	0.27 (0.14–0.50)	18.8	<0.001	0.22 (0.18–0.44)
−60% to <−30%	46	27.4	0.002	0.48 (0.30–0.78)	10.9	0.002	0.54 (0.37–0.80)
−30% to <0%	216	18.0	Reference	Reference	5.3	Reference	Reference
0% to <+20%	134	13.0	0.074	1.29 (0.98–1.71)	2.4	<0.001	2.22 (1.70–2.90)
≥+20%	57	6.6	0.006	1.63 (1.15–2.30)	1.4	<0.001	6.42 (4.42–9.33)
No Post-Baseline Imaging	64	2.1	<0.001	3.62 (2.56–5.12)	0.9	<0.001	3.60 (2.51–5.16)
ECOG Performance Status							
ECOG 0							
−100% to <−60%	169	NR	<0.001	0.21 (0.14–0.34)	19.0	<0.001	0.31 (0.24–0.40)
−60% to <−30%	319	32.2	0.019	0.73 (0.56–0.95)	11.0	<0.001	0.64 (0.53–0.78)
−30% to <0%	537	24.9	Reference	Reference	7.9	Reference	Reference
0% to <+20%	153	19.4	0.008	1.48 (1.11–1.99)	3.7	<0.001	3.14 (2.46–4.01)
≥+20%	63	12.6	0.006	1.74 (1.17–2.59)	1.3	<0.001	30.23 (20.31–45.02)

		OS			PFS		
	n	**Median (months)**	**P-Value**	**HR (95% CI)**	**Median (months)**	**P-Value**	**HR (95% CI)**
No Post-Baseline Imaging	41	32.0	0.028	1.97 (1.17–2.59)	1.9	0.2	1.58 (0.82–3.06)
ECOG 1							
−100% to <−60%	106	41.7	<0.001	0.29 (0.20–0.42)	13.9	<0.001	0.38 (0.29–0.51)
−60% to <−30%	222	20.3	<0.001	0.65 (0.52–0.81)	10.7	<0.001	0.63 (0.52–0.77)
−30% to <0%	594	11.8	Reference	Reference	5.5	Reference	Reference
0% to <+20%	223	7.9	<0.001	1.65 (1.36–2.00)	2.2	<0.001	2.48 (2.05–2.99)
≥+20%	91	5.8	<0.001	2.03 (1.55–2.67)	1.5	<0.001	8.70 (6.62–11.45)
No Post-Baseline Imaging	151	2.0	<0.001	4.51 (3.60–5.64)	1.1	<0.001	4.92 (3.85–6.28)

[a] Includes regimens containing IFN and temsirolimus combination.

CI = confidence interval, ECOG = Eastern Cooperative Oncology Group, HR = hazard ratio, IFN-α = interferon alpha, NR = not reached, OS = overall survival, PFS = progression-free survival.