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Sunitinib Objective Response in Metastatic Renal Cell Carcinoma: Analysis of 1,059 Patients Treated on Clinical Trials

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INTRODUCTION

- Targeted therapies may have both a cytotoxic and a cytostatic effect, complicating assessment of response to treatment. It is unclear to what extent achievement of a tumor objective response (OR) contributes to survival outcomes.
- Sunitinib malate (SUTENT®) is an orally administered multitargeted inhibitor of vascular endothelial growth factor receptors, platelet-derived growth factor receptors, and other receptor tyrosine kinases that has been approved worldwide for the treatment of advanced renal cell carcinoma (RCC).
- The efficacy and safety of sunitinib for first- and second-line (cytokine refractory) treatment of metastatic RCC (mRCC) have been established in six key clinical trials.[1–6]
- In these trials, sunitinib achieved a robust OR rate. Additionally, in the phase III trial of treatment-naïve patients with mRCC, sunitinib significantly improved progression-free survival (PFS) as compared with interferon-alfa.[4]
- We report a retrospective analysis to characterize the OR rate with sunitinib treatment and OR-associated patient features and survival using a pooled database of patients from these six clinical trials.

OBJECTIVES

- To characterize the OR rate with sunitinib treatment in patients with mRCC.
- To investigate patient features and survival outcomes associated with OR to sunitinib in patients with mRCC.

METHODS

Study Designs and Treatment

- This retrospective analysis used pooled data from 1,059 patients with mRCC who received sunitinib in six clinical trials in the first-line (n=783; 74%) and second-line (n=276; 26%) treatment settings.[1–6]
- Sunitinib was administered orally according to one of the following schedules:
  - 50 mg once daily for 4 consecutive weeks followed by 2 weeks off treatment (Schedule 4/2) in repeated 6-week cycles (n=689; 65%)
  - 37.5 mg on a continuous once-daily dosing schedule (n=370; 35%).
- Antitumor efficacy endpoints employed in the six clinical trials included OR rate and PFS, both assessed by investigators using Response Evaluation Criteria for Solid Tumors (RECIST),[7] and overall survival (OS).
  - Tumor response was assessed according to the schedules specified in the protocols of each trial (initially every 4–6 weeks, increasing to every 8–12 weeks after approximately 6 months).
- Adverse events were recorded regularly and graded according to National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0 (version 2.0 in one trial[1]).

Patient Eligibility

- Eligibility criteria common to all patients were:
  - age 18 years or older
  - histologically confirmed mRCC
  - presence of measurable disease
  - no known presence of brain metastases
  - Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1 (or Karnofsky performance status ≥70% in one trial[6])
  - adequate organ function.

Statistical Methods

- Baseline characteristics for responders and non-responders, and early and late responders (first observed response [confirmed at next visit] at ≤12 and >12 weeks, respectively), were compared by Fisher-exact test, *t*-test, or Wilcoxon rank-sum test.
- Median PFS and OS were estimated by the Brookmeyer and Crowley method and compared between responders and non-responders, and early and late responders, by a log-rank test. Hazard ratios for these comparisons were calculated using a Cox proportional-hazards model.
- A Cox proportional regression model was used to analyze the association between PFS and OS and potential prognostic factors by univariate and then multivariate analysis in a step-wise procedure, to identify independent variables significant at P<0.05.
- Covariates analyzed included objective tumor response (yes/no), time on treatment, and baseline pretreatment characteristics comprising prognostic factors reported by the Memorial Sloan-Kettering Cancer Center (MSKCC)[8] and Heng et al.,[9] as well as prior cytokine treatment (yes/no) and presence/absence of lung and bone metastases.

RESULTS

Responders vs. Non-Responders

- In total, 398 patients (38%) had a confirmed OR by RECIST: 12 patients achieved a complete response and the remainder, a partial response.
- Baseline patient characteristics for responders and non-responders are shown in Table 1. Responders had significantly better performance status, more favorable risk factor classification based on published MSKCC criteria, a longer interval since initial diagnosis, higher rates of nephrectomy, and a lower incidence of bone metastases (all P<0.05).
  - The characteristics of responders were generally maintained regardless of treatment setting, although, in the second-line setting, there were no significant differences by response status in time since initial diagnosis or rates of prior nephrectomy.

Table 1. Baseline patient characteristics of sunitinib responders and non-responders.

Characteristic	Responders (n=398)	Non-responders (n=661)	P value
Median (range) age, years	61 (32–87)	60 (24–87)	0.317
Male/female, %	71/29	70/30	0.628
ECOG performance status, n (%)			
0	279 (70)	368 (56)	<0.001
1	114 (29)	276 (42)	
2	5 (1)	17 (3)	
Risk factors based on published MSKCC data, n (%)[a]			
0 (favorable)	216 (54)	200 (30)	<0.001
1–2 (intermediate)	132 (33)	282 (43)	
≥3 (poor)	8 (2)	37 (6)	
Missing	42 (11)	142 (21)	
Mean time (range) since initial diagnosis, years	3.0 (0–25.3)	2.2 (0–28.3)	0.002
Histology, n (%)[b]			
Clear cell	388 (97)	639 (97)	0.515
Non-clear cell	10 (3)	19 (3)	
Prior nephrectomy, n (%)[b]	333 (84)	500 (76)	0.012
Prior cytokine therapy, n (%)[b]	101 (25)	189 (29)	0.256
Sites of metastatic disease, n (%)			
Lung	311 (78)	509 (77)	0.761
Liver	90 (23)	156 (24)	0.764
Bone	95 (24)	216 (33)	0.002

[a]Includes low serum hemoglobin level, elevated corrected serum calcium level, elevated serum lactate dehydrogenase level, poor performance status, and interval of <1 year between diagnosis and sunitinib treatment.[8]
[b]Histology data missing for 3 patients (<1%), nephrectomy status missing for 57 patients (5%), and prior cytokine status missing for 1 patient (<1%).

- PFS and OS were significantly longer in responders vs. non-responders:
  - median PFS: 16.3 vs. 5.3 months, respectively (P<0.001; Figure 1A)
  - median OS: 40.1 vs. 14.5 months, respectively (P<0.001; Figure 1B).
- Survival outcomes were improved in responders compared with non-responders regardless of treatment setting (Table 2).
- Using Cox proportional regression analysis, tumor response was an independent predictor of both PFS and OS (P<0.001), independent of time on treatment, which itself was also predictive of PFS and OS (P<0.001).
- The proportion of patients who discontinued sunitinib treatment because of an adverse event was slightly less in responders compared with non-responders (15% vs. 20%, respectively), a trend that was maintained regardless of treatment setting.

Early vs. Late Responders

- For the 398 patients achieving OR, median time to tumor response was 10.6 weeks (range 2.7–94.4 weeks), which was similar in the first- and second-line treatment settings.
- Among patients with OR, 105 (26%), 243 (61%), 314 (79%), and 342 (86%) responded by 6, 12, 18, and 24 weeks, respectively.

Figure 1. Kaplan–Meier estimates of (A) progression-free survival and (B) overall survival by response status.

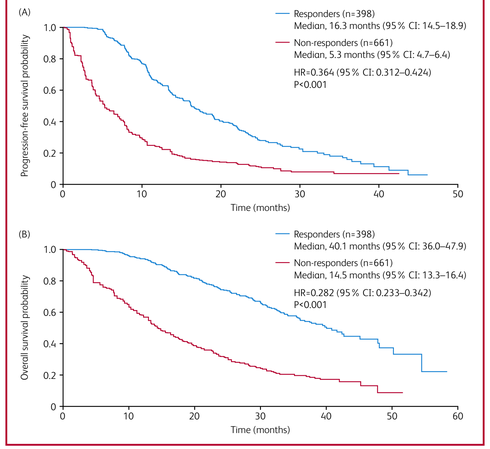


Table 2. Progression-free and overall survival in sunitinib responders and non-responders by treatment setting.

Population	Median time to progression/survival event, months (95% CI)			
	Responders [n]	Non-responders [n]	HR (95% CI)	P value
Progression-free survival				
All patients	16.3 (14.5–18.9) [398]	5.3 (4.7–6.4) [661]	0.364 (0.312–0.424)	<0.001
Treatment-naïve patients	16.3 (15.1–19.1) [301]	5.6 (4.8–6.9) [482]	0.394 (0.331–0.470)	<0.001
Cytokine-refractory patients	16.0 (12.4–19.2) [97]	4.8 (4.2–6.3) [179]	0.197 (0.138–0.282)	<0.001
Overall survival				
All patients	40.1 (36.0–47.9) [398]	14.5 (13.3–16.4) [661]	0.282 (0.233–0.342)	<0.001
Treatment-naïve patients	42.7 (35.5–NR) [301]	15.3 (13.4–17.5) [482]	0.304 (0.243–0.379)	<0.001
Cytokine-refractory patients	39.5 (33.1–47.9) [97]	13.1 (10.6–14.5) [179]	0.224 (0.154–0.328)	<0.001

NR, not reached.

- Overall, 243 of the 398 responders (61%) had a tumor response by ≤12 weeks and were therefore categorized as early responders, compared with 155 responders (39%) who had a response after >12 weeks and were defined as late responders.
  - The proportion of early vs. late responders was similar regardless of treatment setting.
- Baseline patient characteristics for early and late responders are shown in Table 3. Compared with late responders, early responders were younger, had a shorter interval since initial diagnosis, and had more lung metastases (all P<0.05). Tumor burden at baseline was similar in the two groups.
  - These differences in baseline characteristics were broadly similar in each treatment setting, although the interval since initial diagnosis was very similar in early and late responders in the second-line setting.

Table 3. Baseline patient characteristics of early and late responders to sunitinib.

Characteristic	Early responders[a] (n=243)	Late responders[a] (n=155)	P value
Median (range) age, years	59 (35–81)	63 (32–87)	0.006
Male/female, %	73/27	68/32	0.365
ECOG performance status, n (%)			
0	172 (71)	107 (69)	0.712
1	68 (28)	46 (30)	
2	3 (1)	2 (1)	
Risk factors based on published MSKCC data, n (%)[b]			
0 (favorable)	130 (53)	86 (55)	0.732
1–2 (intermediate)	82 (34)	50 (32)	
≥3 (poor)	6 (2)	2 (1)	
Missing	25 (10)	17 (11)	
Mean time (range) since initial diagnosis, years	2.4 (0–20.1)	3.9 (0–25.3)	0.001
Histology, n (%)			
Clear cell	236 (97)	152 (98)	0.747
Non-clear cell	7 (3)	3 (2)	
Prior nephrectomy, n (%)[c]	201 (83)	132 (85)	0.534
Prior cytokine therapy, n (%)	64 (26)	37 (24)	0.637
Sites of metastatic disease, n (%)			
Lung	203 (84)	108 (70)	0.002
Liver	55 (23)	35 (23)	1.0
Bone	66 (27)	29 (19)	0.055
Median (range) tumor burden, mm	83 (10–481)	85 (10–432)	0.803

[a]Early and late responders were defined by tumor response at ≤12 weeks and >12 weeks, respectively.
[b]Includes low serum hemoglobin level, elevated corrected serum calcium level, elevated serum lactate dehydrogenase level, poor performance status, and interval of <1 year between diagnosis and sunitinib treatment.[8]
[c]Nephrectomy status missing for 15 patients (4%).

- Median duration of response was similar in early and late responders in the overall population, as well as in the first-line setting (Table 4). However, in the second-line setting, median duration of response appeared shorter in early compared with late responders (Table 4).
  - The reduction in tumor burden was similar in early and late responders, regardless of treatment setting (Table 4).

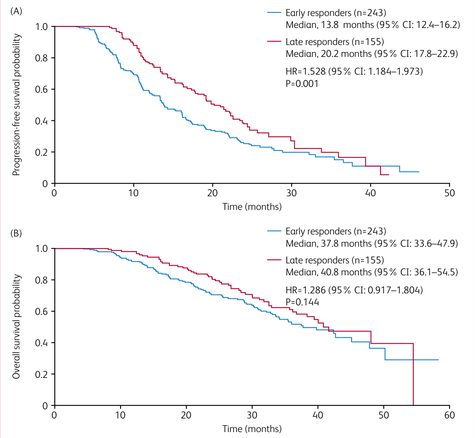
Table 4. Response duration and percent reduction in size of disease in early and late responders by treatment setting.

	All responders		Treatment-naïve responders		Cytokine-refractory responders	
	Early[a] (n=243)	Late[a] (n=155)	Early[a] (n=181)	Late[a] (n=120)	Early[a] (n=62)	Late[a] (n=35)
Median response duration, weeks	52.0	55.0	56.1	55.0	43.0	55.0
Mean (SD) reduction, %	61.85 (20.33)	56.24 (18.56)	62.58 (20.46)	56.32 (18.52)	59.77 (19.94)	55.96 (18.95)
Median (range) reduction, %	58.52 (21.43–100)	52.46 (30.96–100)	59.14 (21.43–100)	53.38 (31.75–100)	55.92 (31.25–100)	51.96 (30.96–98.58)

SD, standard deviation.
[a]Early and late responders were defined by tumor response at ≤12 weeks and >12 weeks, respectively.

- PFS was significantly shorter in early vs. late responders, although OS did not significantly differ between subgroups (results that were similar regardless of treatment setting):
  - median PFS: 13.8 vs. 20.2 months, respectively (P=0.001; Figure 2A)
  - median OS: 37.8 vs. 40.8 months, respectively (P=0.144; Figure 2B).

Figure 2. Kaplan–Meier estimates of (A) progression-free survival and (B) overall survival by time of response.



- The proportion of patients who discontinued sunitinib treatment because of an adverse event was similar in early and late responders in the overall population (13% vs. 17%, respectively) and in the first-line treatment setting (15% vs. 16%); however, in the second-line treatment setting, early responders discontinued less frequently than late responders (8% vs. 20%).

CONCLUSIONS

- OR was achieved in 38% of 1,059 mRCC patients treated with sunitinib and was predicted by favorable pretreatment prognostic factors.
- Responders had significantly longer PFS and OS than non-responders, and tumor response was an independent predictor of survival, independent of time on treatment.
- Median time to tumor response was 10.6 weeks (range 2.7–94.4 weeks), with 39% of patients experiencing a response after 12 weeks of therapy.
- Characteristics and outcomes, including duration of response, were similar in early and late responders, except for a higher frequency of lung metastases among early responders.

REFERENCES

1. Motzer RJ, et al. *J Clin Oncol* 2006;24:16–24.
2. Motzer RJ, et al. *JAMA* 2006;295:2516–2524.
3. Escudier B, et al. *J Clin Oncol* 2009;27:4068–4075.
4. Motzer RJ, et al. *J Clin Oncol* 2009;27:3584–3590.
5. Barrios CH, et al. *Cancer* 2012;118:1252–1259.
6. Motzer RJ, et al. *J Clin Oncol* 2012;30:1371–1377.
7. Therasse P, et al. *J Natl Cancer Inst* 2000;92:205–216.
8. Motzer RJ, et al. *J Clin Oncol* 2002;20:289–296.
9. Heng DYC, et al. *J Clin Oncol* 2009;27:5794–5799.

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