

Sunitinib Therapy for Patients with Metastatic Renal Cell Carcinoma: Updated Results of Two Phase II Trials and Prognostic Factor Analysis for Survival

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Abstract

Background: Two single-arm phase 2 trials reported a 42% objective response rate (ORR) with sunitinib as second-line therapy in mRCC pts.¹ Efficacy results were updated and an analysis of prognostic factors for survival was performed on pooled data.

Methods: Eligibility criteria and treatment plan were nearly identical for both trials. Pts with mRCC who failed 1 prior cytokine-based therapy received sunitinib in repeated 6-week cycles of 50 mg/day orally for 4 weeks, followed by 2 weeks off treatment. Response was assessed by investigators according to RECIST. Pretreatment clinical and biochemical features were examined for prognostic factors by univariate and multivariate analysis (p<0.05 significance level was used in the backward stepwise selection procedure).

Results: Updated efficacy data for 168 evaluable pts showed an ORR of 45% (95% CI: 39%, 54%), median progression-free survival (PFS) of 8.4 months (95% CI: 7.9, 10.7), and median overall survival (OS) of 22.3 months (95% CI: 14.8, 36.0). Twenty pts remain on treatment with sunitinib with the longest pt on the drug for >3.5 years with partial response for >3 years. The median duration of response was 11.6 months (95% CI: 9.9, 15.2), and included 1 pt with a complete response for >2 years. The proportion of pts alive at 2 years is 48%. Final prognostic factors for survival in the multivariate model were ECOG PS 0 vs. ≥1 (p=0.0034); time interval from diagnosis to sunitinib treatment ≥1 yr vs. <1 yr (p=0.0002); hemoglobin ≥13 vs. <13 g/dL for males and ≥11.5 vs. <11.5 g/dL for females (p=0.0002).

Conclusions: Median survival is nearly 2 years, which compares favorably to the historical experience (12.7 months) in second-line therapy with other agents.² The influence of sunitinib therapy on patient survival is being investigated in a randomized phase 3 trial compared to interferon-α in first-line therapy for mRCC. Further study of prognostic factors to sunitinib therapy is warranted in the first-line setting.

Introduction

- Sunitinib malate (SUTENT®) has demonstrated robust clinical activity in two single-arm phase II trials of patients with cytokine-refractory metastatic RCC (mRCC).^{1,3}
- Here, we report updated efficacy results, including overall survival (OS), for the pooled data from the two phase II trials in cytokine-refractory mRCC, as well as identify prognostic factors for survival.

Objectives

- Update the efficacy results for single-agent sunitinib in patients with cytokine-refractory mRCC.
- Identify the prognostic factors for survival.

Methods

Study Population/Design

- Key eligibility criteria were nearly identical for Trial 1³ and Trial 2¹ and included the following:
 - measurable disease with evidence of metastases
 - failure of one cytokine-based therapy due to disease progression or unacceptable toxicity
 - Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1
 - adequate hematologic, hepatic, renal and cardiac function.
- Eligibility differences were as follows:
 - Trial 2 restricted histology to clear-cell RCC (though nearly 90% of patients in Trial 1 also had this cell type)
 - Trial 2 required prior nephrectomy.
- All patients received oral sunitinib at a starting dose of 50 mg/day in repeated 6-week cycles consisting of 4 weeks on treatment followed by 2 weeks off treatment (4/2 schedule).

Study Assessments and Statistical Analysis

- The tumor assessments were determined according to the Response Evaluation Criteria in Solid Tumors (RECIST).
- Time-to-event variables were estimated using the Kaplan-Meier method.
- Efficacy results for the pooled patient population, based on investigator assessment in both trials, are reported.
- The relationship between survival and selected baseline patient characteristics was analyzed using the log-rank test and Cox proportional hazard models in the univariate analysis for categorical variables.
- In the multivariate analysis, a backward stepwise selection process was used with an alpha level of 0.05 to stay in the model to identify the final set of relevant factors.

Results

Patient Disposition and Baseline Characteristics

- All 169 patients included in both trials received at least one dose of sunitinib; however, one patient from Trial 2 was withdrawn after treatment began when a repeat biopsy resulted in a histological diagnosis other than RCC.
 - This patient was included in the pooled safety analysis (N=169) but excluded from the pooled efficacy analyses (N=168).
- The median duration of treatment for the pooled population was 8.6 months (range 0.6–40.8).
- Table 1 summarizes demographics and clinical characteristics for the pooled patient population.

Table 1. Baseline patient demographics and clinical characteristics

	Sunitinib (N=169)
Median age, years (range)	57 (24–87)
Sex, n (%)	
Male	110 (65)
Female	59 (35)
ECOG PS, n (%)	
0	92 (54)
1	77 (46)
Previous cytokine therapy, n (%)	
IFN-α	82 (48)
IL-2	69 (41)
IL-2 + IFN	18 (11)
Disease present at screening, n (%)	
Lung metastases	137 (81)
Lymph nodes	96 (57)
Bone metastases	59 (35)
Liver metastases	39 (23)
Total number of metastatic sites, n (%)	
1	21 (12)
2	54 (32)
≥3	94 (56)
MSKCC risk factors, n (%) [*]	
0 (favorable)	94 (56)
1 (intermediate)	70 (41)
≥2 (poor)	5 (3)

IFN-α = interferon-alpha; IL-2 = interleukin-2

^{*}Risk factors associated with shorter survival according to the Memorial Sloan-Kettering Cancer Center (MSKCC) risk classification for second-line therapy are low serum hemoglobin, elevated corrected serum calcium and poor performance status.

Efficacy

- Investigator-assessed tumor response for the pooled analysis (N=168 evaluable patients) is summarized in Table 2. The objective response rate (ORR) for the pooled analysis was 45% (95% CI: 39–54).
 - The median duration of response for the pooled analysis was 11.9 months (95% CI: 9.9–16.2) and included one patient with a complete response for >2 years.
 - Of 20 patients (12%) who remained on treatment at the time of analysis, one patient had received sunitinib for >3.5 years and had maintained a partial response for >3 years.

Table 2. Investigator-assessed tumor response by RECIST (N=168)

Response, n (%)	Pooled analysis
Overall response	75 (45)
Complete response	1 (<1)
Partial response	74 (44)
Stable disease	53 (32)
Progressive disease	24 (14)
Not evaluable/missing	16 (10)

- For the pooled analysis (N=168), the median progression-free survival (PFS) by investigator assessment was 8.4 months (95% CI: 7.9–10.7) and the median time to tumor progression was 8.7 months (95% CI: 7.9–10.9). The median OS was 19.9 months (95% CI: 14.2–29.6) (Figure 1); 67 patients (40%) were alive at a median follow-up of 30 months and the proportion of patients alive at 2 years is 47%.

Pooled Analyses of Prognostic Factors for Survival

- In the univariate analysis, a longer survival was correlated with the following pretreatment factors: serum hemoglobin ≥ the lower limits of normal, a favorable ECOG PS (= 0) and a time interval from diagnosis to treatment of ≥1 year (all P<0.0001). Table 3 summarizes the results of the univariate analysis.

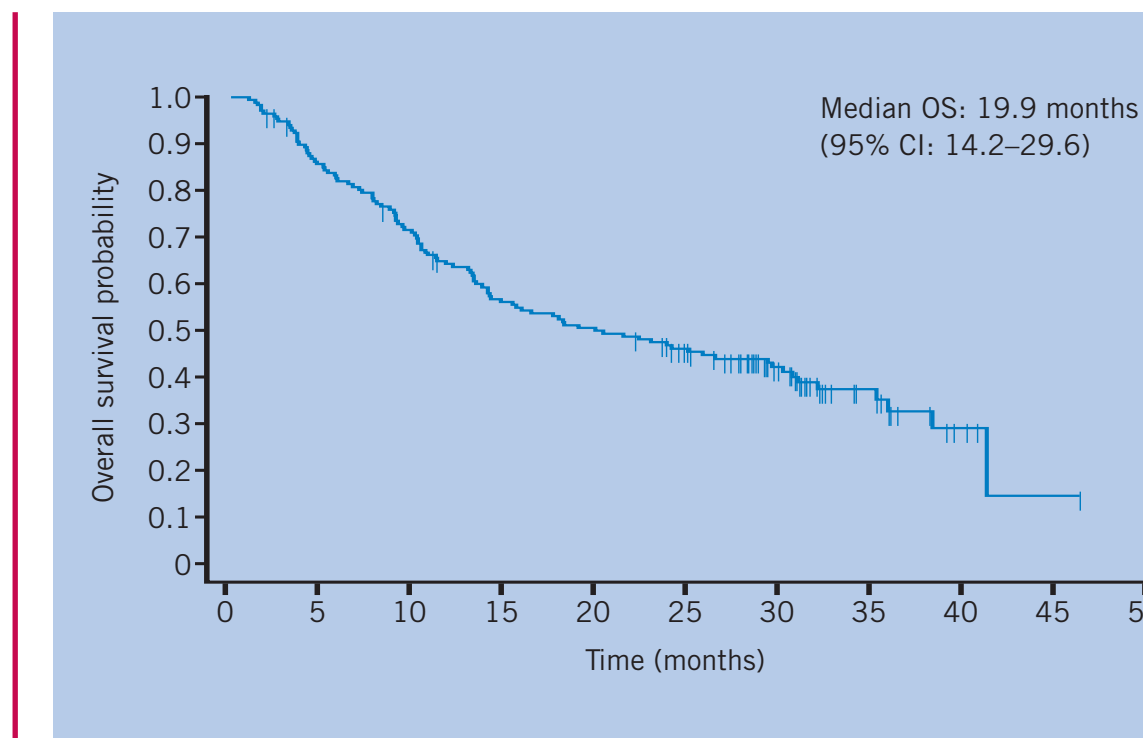


Figure 1. Kaplan-Meier estimate of OS for the pooled analysis

Table 3. Univariate analysis of pretreatment predictors of OS for patients in the pooled analysis

Variable	n	No. alive	Median OS (months)	95% CI	P-value
Hemoglobin*					
≥ 13/11.5 g/dL	92	53	NR	27–NR	<0.0001
< 13/11.5 g/dL	76	14	11	8–14	
Baseline ECOG					
0	91	50	38	24–NR	<0.0001
1 or 2	77	17	10	7–14	
Time interval from diagnosis to treatment					
< 1 year	60	13	10	8–13	<0.0001
≥ 1 year	108	54	31	24–41	
Number of metastatic sites					
0 or 1	28	19	NR	30–NR	0.0026
2 or ≥ 3	140	48	15	13–24	
Liver metastases					
Yes	38	7	13	10–19	0.0070
No	130	60	25	16–38	
Bone metastases					
Yes	59	17	12	9–22	0.0070
No	109	50	26	18–NR	
Alkaline phosphatase					
> 120 U/L	45	12	10	8–19	0.0091
≤ 120 U/L	123	55	25	18–35	
Baseline LDH					
≤ 1.5 x ULN	161	66	22	15–31	0.0114
> 1.5 x ULN	7	1	9	5–14	
Alkaline phosphatase					
> ULN	48	13	13	9–19	0.0195
≤ ULN	120	54	26	18–35	
Prior radiotherapy					
Yes	45	13	14	9–25	0.0253
No	123	54	24	15–41	
Corrected calcium					
≤ 10 mg/dL	162	66	20	14–31	0.0626
> 10 mg/dL	6	1	8	3–29	
Prior nephrectomy					
Yes	163	66	20	14–30	0.3638
No	5	1	10	5–36	
Lung metastases					
Yes	137	56	20	14–31	0.6635
No	31	11	18	13–35	

LDH = lactate dehydrogenase; NR = not reached; ULN = upper limits of normal
^{*}Cut point is 13 g/dL for males and 11.5 g/dL for females.

- Final prognostic factors for survival in the multivariate model were ECOG PS (0 vs. 1 or 2; P=0.0056), time interval from diagnosis to treatment (≥1 year vs. <1 year; P<0.0001), number of metastatic sites (0 or 1 vs. 2 or ≥3; P=0.0257) and serum hemoglobin (≥13 vs. <13 g/dL for males and ≥11.5 vs. <11.5 g/dL for females; P<0.0001). Table 4 summarizes the final results of the multivariate analysis.

Table 4. Final results of a multivariate analysis of pretreatment predictors of OS for patients in the pooled analysis (N=168)

Variable	Hazard ratio	95% CI	P-value
Time interval from diagnosis to treatment			
≥1 year vs. <1 year	0.384	0.255–0.580	<0.0001
Hemoglobin*			
≥13 /11.5 g/dL vs. <13/11.5 g/dL	0.427	0.280–0.651	<0.0001
Baseline ECOG PS			
0 vs. 1 or 2	0.552	0.363–0.840	0.0056
No. of metastatic sites			
0 or 1 vs. 2 or ≥3	0.445	0.218–0.906	0.0257

^{*}Cut point is 13 g/dL for males and 11.5 g/dL for females.

Conclusions

- This updated efficacy result confirms the substantial antitumor activity of sunitinib in patients with cytokine-refractory mRCC.
- Median OS was 19.9 months for the pooled population, which compares favorably with the historical experience with other agents in the second-line setting.²
- Final prognostic factors for survival are similar to previously identified prognostic factors for cytokine therapy.²
- In a recent phase III randomized trial, sunitinib demonstrated statistically significant improvement in PFS and ORR in the first-line mRCC setting compared to interferon-alpha (P<0.001).⁴ Based on these findings, further study of prognostic factors for response to sunitinib therapy is warranted in the first-line setting.

References

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