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ORIGINAL REPORT

Overall Survival and Updated Results for Sunitinib Compared With Interferon Alfa in Patients With Metastatic Renal Cell Carcinoma

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ABSTRACT

Purpose
A randomized, phase III trial demonstrated superiority of sunitinib over interferon alfa (IFN-α) in progression-free survival (primary end point) as first-line treatment for metastatic renal cell carcinoma (RCC). Final survival analyses and updated results are reported.

Patients and Methods
Seven hundred fifty treatment-naïve patients with metastatic clear cell RCC were randomly assigned to sunitinib 50 mg orally once daily on a 4 weeks on, 2 weeks off dosing schedule or to IFN-α 9 MU subcutaneously thrice weekly. Overall survival was compared by two-sided log-rank and Wilcoxon tests. Progression-free survival, response, and safety end points were assessed with updated follow-up.

Results
Median overall survival was greater in the sunitinib group than in the IFN-α group (26.4 *v* 21.8 months, respectively; hazard ratio [HR] = 0.821; 95% CI, 0.673 to 1.001; $P = .051$) per the primary analysis of unstratified log-rank test ($P = .013$ per unstratified Wilcoxon test). By stratified log-rank test, the HR was 0.818 (95% CI, 0.669 to 0.999; $P = .049$). Within the IFN-α group, 33% of patients received sunitinib, and 32% received other vascular endothelial growth factor–signaling inhibitors after discontinuation from the trial. Median progression-free survival was 11 months for sunitinib compared with 5 months for IFN-α ($P < .001$). Objective response rate was 47% for sunitinib compared with 12% for IFN-α ($P < .001$). The most commonly reported sunitinib-related grade 3 adverse events included hypertension (12%), fatigue (11%), diarrhea (9%), and hand-foot syndrome (9%).

Conclusion
Sunitinib demonstrates longer overall survival compared with IFN-α plus improvement in response and progression-free survival in the first-line treatment of patients with metastatic RCC. The overall survival highlights an improved prognosis in patients with RCC in the era of targeted therapy.

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INTRODUCTION

Sunitinib is an orally administered multitargeted tyrosine kinase inhibitor of vascular endothelial and platelet-derived growth factor receptors.[1] A high response rate observed in the second-line treatment setting[2,3] led to the design and conduct of a randomized phase III trial of sunitinib compared with interferon alfa (IFN-α) as first-line treatment of metastatic renal cell carcinoma (RCC).[4] The results of a preplanned interim analysis from the phase III trial were previously reported, which showed superiority of sunitinib over IFN-α in progression-free survival time (11 *v* 5 months, respectively) by independent, third-party radiologic assessment ($P < .001$).[4] At the interim analysis, this primary end point was met, but median overall survival had not been reached in either group. Here, the final overall survival analyses are reported. In addition, updated efficacy and safety results are provided.

PATIENTS AND METHODS

Patients

The study population comprised patients ≥ 18 years of age who had treatment-naïve metastatic RCC

with a clear cell component. Additional eligibility criteria were previously reported.[4] All patients gave written informed consent.

Study Design

This was an international, multicenter, randomized, phase III trial of sunitinib (SUTENT; Pfizer, New York, NY) versus IFN-α as first-line treatment of metastatic RCC. Patients were randomly assigned in a 1:1 ratio to receive sunitinib or IFN-α with random assignment stratified as previously described.[4] The study was approved by the institutional review board or ethics committee at participating centers and conducted in accordance with provisions of the Declaration of Helsinki and Good Clinical Practice guidelines.

Sunitinib was administered orally at 50 mg once daily on a 4 weeks on, 2 weeks off dosing schedule and provided by Pfizer, the trial sponsor. Commercially available IFN-α-2a (Roferon-A; Roche, Nutley, NJ) was used and provided by Pfizer. IFN-α was administered by subcutaneous injection thrice weekly on nonconsecutive days at 3 MU per dose the first week, 6 MU the second week, and 9 MU thereafter. Intrapatient dose reduction or interruption of either drug was allowed for management of adverse events depending on their type and severity, according to the protocol. Treatment in both groups was continued until disease progression, unacceptable adverse events, or consent withdrawal.

Efficacy and Safety Assessments

The primary end point was progression-free survival. Secondary end points included objective response rate, overall survival, patient-reported outcomes, and safety. Tumor response was assessed according to Response Evaluation Criteria in Solid Tumors (RECIST),[5] with the use of imaging studies at scheduled time points by treating physicians and an independent, third-party core imaging laboratory (RadPharm, Princeton, NJ), as previously described.[4] Central review of imaging scans was discontinued in September 2007 because the primary end point had been met at the interim analysis; therefore, only updated investigator-assessed results are reported herein.

Patients were followed off-study every 2 months for survival, and post-study cancer treatment information was collected on case report forms. Safety was assessed by documentation of adverse events, physical examination, and multigated acquisition scanning. Laboratory assessments (hematologic and serum chemistry) were performed throughout the study by a central laboratory. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 3.0), as described previously.[4] Quality-of-life assessment has been reported elsewhere.[6]

Statistical Analysis

The sample size required for the primary end point of progression-free survival also allowed for assessment of differences in overall survival. Per historical data, overall survival of patients treated with IFN-α as first-line therapy had been approximately 13 months.[7] A total of 390 events were required for a two-sided, unstratified log-rank test with an overall two-sided significance level of $P = 0.05$ and 85% power to detect a 35.7% improvement in overall survival. The analysis included all patients randomly assigned to a study treatment group, according to an intent-to-treat basis.

Time-to-event analyses were performed using the Kaplan-Meier method and Cox proportional hazards model with two-sided 95% CIs for the medians and hazard ratios (HRs) for each end point. The statistical methods applied to progression-free survival, objective response rate, and other assessments remain the same as previously reported.[4]

Unstratified and stratified log-rank and Wilcoxon statistics were used to evaluate the robustness of the treatment effect on overall survival. Unstratified log-rank statistics was the primary analysis. The following three prespecified stratification factors were included in the analysis: lactate dehydrogenase more than or $\leq 1.5\times$ the upper limit of normal, Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, and absence or presence of prior nephrectomy.

A Cox proportional hazards model was built to explore potential influences of baseline characteristics, including age, sex, and other known risk factors,[7] on overall survival. Each prognostic factor was preliminarily evaluated by including it and the treatment in the Cox model. For purposes of developing the Cox model, a backward elimination process was applied to all variables, using a 5% level for a given variable to remain in the model, to identify the final set of relevant factors.

Sunitinib was initially approved in January 2006 and is now approved globally for the treatment of advanced RCC. On the basis of this and the fact that this study had met its primary end point of progression-free survival,[4] the study protocol was amended to allow patients in the IFN-α group to cross over to receive sunitinib on documented disease progression, as agreed with the independent data and safety monitoring committee. Additional exploratory analyses were performed to assess the treatment effect of sunitinib compared with IFN-α on overall survival, including censoring of patients at the date that they crossed over to sunitinib.

RESULTS

Patient Characteristics

Between August 2004 and October 2005, 750 patients were randomly assigned (375 patients to each treatment group) at 101 international centers (Fig 1). All 375 patients in the sunitinib group received at least one dose of sunitinib. Fifteen patients (4%) in the IFN-α group withdrew consent before starting treatment; the remaining 360 patients received at least one dose of IFN-α. As previously described,[4] the treatment groups were balanced with respect to baseline characteristics.

Treatment Administration and Safety

Median duration of treatment was 11 months (range, < 1 to 41 months) in the sunitinib group and 4 months (range, < 1 to 40 months) in the IFN-α group. Treatment was ongoing among 52 patients (14%) on the sunitinib arm and among six patients (2%) on the IFN-α arm at the time of this analysis. Reasons for discontinuation were progressive disease (for 60% of patients on sunitinib and 65% on IFN-α), adverse events (19% on sunitinib and 23% on IFN-α), consent withdrawal (6% on sunitinib and 10% on IFN-α), and other reasons (2% on sunitinib and 1% on IFN-α; Fig 1).

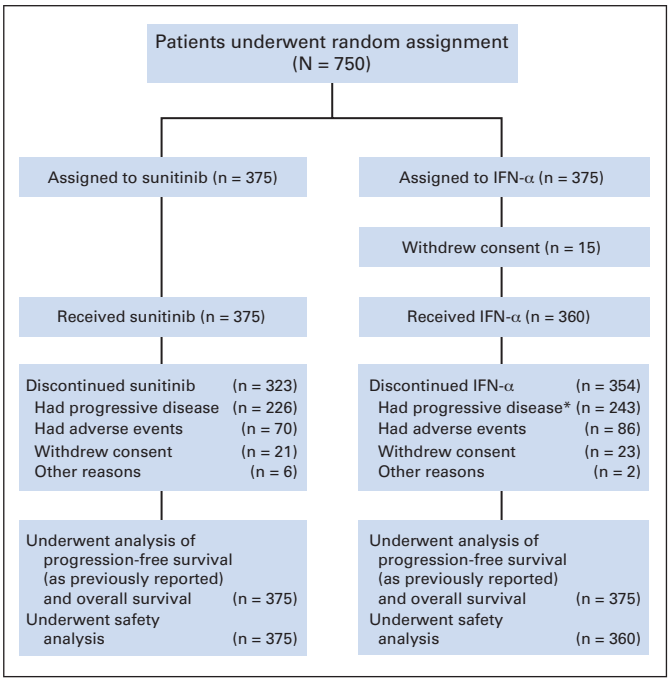

Fig 1. Patient enrollment and outcomes. *Twenty-five patients from the IFN-α group crossed over to receive sunitinib on study. IFN-α, interferon alfa.

Table 1. Treatment-Related Adverse Events and Selected Laboratory Abnormalities

Adverse Events and Laboratory Abnormalities	% of Patients					
	Sunitinib (n = 375)			IFN-α (n = 360)		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
Adverse event						
Diarrhea*	61	9	0	15	1	0
Fatigue	54	11	0	52	13	< 1
Nausea*	52	5	0	35	1	0
Dysgeusia	46	< 1	0	15	0	0
Anorexia	34	2	0	28	2	0
Dyspepsia	31	2	0	5	< 1	0
Vomiting*	31	4	0	12	1	0
Hypertension*	30	12	0	4	1	0
Stomatitis	30	1	0	4	< 1	0
Hand-foot syndrome*	29	9	0	3	1	0
Skin discoloration	27	< 1	0	1	0	0
Mucosal inflammation	26	2	0	3	1	0
Rash	24	1	< 1	8	< 1	0
Dry skin	21	< 1	0	6	0	0
Asthenia*	20	7	< 1	19	4	0
Hair color changes	20	0	0	1	0	0
Epistaxis	18	1	0	2	0	0
Pain in extremity	18	1	0	3	0	0
Headache	14	1	0	16	0	0
Hypothyroidism	14	2	0	2	< 1	0
Decline in ejection fraction	13	3	0	3	1	0
Oral pain	13	1	0	1	0	0
Peripheral edema	13	1	0	1	0	0
Alopecia	12	0	0	9	0	0
Dry mouth	12	0	0	6	< 1	0
Weight decreased	12	< 1	0	14	< 1	0
Constipation	12	< 1	0	4	0	0
Flatulence	11	0	0	2	0	0
Abdominal pain*	11	2	0	3	0	0
Arthralgia	11	< 1	0	14	< 1	0
Dyspnea	10	2	0	8	1	< 1
Erythema	10	1	0	1	0	0
Gastroesophageal reflux disease	10	< 1	0	1	0	0
Decreased appetite	10	< 1	0	11	0	0
Glossodynia	10	0	0	1	0	0
Pyrexia	8	1	0	35	< 1	0
Myalgia	8	< 1	0	17	1	0
Chills	7	1	0	29	0	0
Laboratory abnormality						
Leukopenia*	78	8	0	57	2	0
Neutropenia*	77	16	2	50	8	1
Anemia	79	6	2	70	5	1
Increased creatinine	70	< 1	< 1	51	< 1	0
Thrombocytopenia*	68	8	1	26	1	0
Lymphopenia*	68	16	2	69	24	2
Increased lipase*	56	15	3	46	7	1
Increased AST	56	2	0	38	2	0
Increased ALT	51	2	< 1	40	2	0
Increased creatine kinase	49	2	1	12	1	0
Increased alkaline phosphatase	46	2	0	37	2	0
Increased uric acid*	46	0	14	33	0	8
Hypophosphatemia	31	6	< 1	24	6	0
Increased amylase	35	5	1	32	3	< 1
Increased total bilirubin	20	1	0	2	0	0

NOTE. Listed are all treatment-related adverse events of interest and those occurring in at least 10% of patients in the sunitinib group. All severity was graded according to National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0.

Abbreviation: IFN-α, interferon alfa.

*The comparison between the sunitinib group and the IFN-α group was significant ($P < .05$) with the use of Fisher's exact test applied to the sum of grade 3 and 4 adverse events. (Note: With an overall incidence of < 10%, depression is not shown in the table; however, the sum of grade 3 and 4 adverse events was significantly higher in the IFN-α group [$P = .028$]).

After a protocol amendment (February 2006), 25 patients (7%) on the IFN-α arm crossed over to receive sunitinib on study. Of the 25 patients, 10 remained on sunitinib and 15 had discontinued sunitinib (predominantly as a result of progressive disease [n = 9] and adverse events [n = 3]) at the time of this analysis.

Most treatment-related adverse events occurred more frequently in the sunitinib group than in the IFN-α group (Table 1). In both groups, the proportion of grade 3 or 4 adverse events and laboratory abnormalities remained relatively low and consistent with long-term treatment compared with those reported in the interim analysis.[4]

The treatment-related adverse event of ejection fraction decline was reported in 50 patients (13%) in the sunitinib group compared with 12 patients (3%) in the IFN-α group, including 10 patients (3%) and three patients (1%), respectively, with grade 3 severity. The treatment-related adverse event of hypothyroidism was reported in 51 patients (14%) in the sunitinib group compared with six patients (2%) in the IFN-α group, including six patients (2%) and one patient (< 1%), respectively, with grade 3 severity.

A dose reduction occurred in 50% of patients in the sunitinib group and 27% of patients in the IFN-α group.

There were 23 patients in the sunitinib group (including two patients who had crossed over from IFN-α) and 20 patients in the IFN-α group who died on study (defined as death occurring on treatment up to 28 days after last dose). Causes of death included disease progression (n = 19), acute renal failure (n = 1), gastric hemorrhage (n = 1), respiratory failure (n = 1), and sudden death (n = 1) in the sunitinib group and disease progression (n = 15), cardiac disorder (n = 1), myocardial infarction (n = 1), respiratory failure (n = 1), cerebral hemorrhage (n = 1), and intracranial tumor hemorrhage (n = 1) in the IFN-α group. Three deaths were considered treatment related according to investigator assessment, including one sudden death in the sunitinib group and two deaths in the IFN-α group (one each of cardiac disorder and myocardial infarction).

Objective Response Rate and Progression-Free Survival

Sunitinib treatment was associated with a higher objective response rate than IFN-α (47% in the sunitinib group; 95% CI, 42% to 52%; *v* 12% in the IFN-α group; 95% CI, 9% to 16%; $P < .001$; Table 2). Eleven patients in the sunitinib group and four patients in the IFN-α group achieved a complete response per investigator assessment. Median progression-free survival time was 11 months (95% CI, 11 to 13 months) in the sunitinib group compared with 5 months (95% CI, 4 to 6 months) in the IFN-α group (HR = 0.539; 95% CI, 0.451 to 0.643; $P < .001$; Table 2).

Overall Survival

Median overall survival time was greater in the sunitinib group than in the IFN-α group (26.4 months; 95% CI, 23.0 to 32.9 months; *v* 21.8 months; 95% CI, 17.9 to 26.9 months, respectively; HR = 0.821; 95% CI, 0.673 to 1.001; $P = .051$; Fig 2) based on the primary analysis of the unstratified log-rank test ($P = .013$ using the unstratified Wilcoxon test). By stratified log-rank test, the HR was 0.818 (95% CI, 0.669 to 0.999; $P = .049$).

Table 2. Best Tumor Response and Progression-Free Survival

Response	Sunitinib (n = 375) No. of Patients	Sunitinib (n = 375) %	IFN-α (n = 375) No. of Patients	IFN-α (n = 375) %
Objective response*	176	47	46	12
Complete response	11	3	4	1
Partial response	165	44	42	11
Stable disease	150	40	202	54
Progressive disease	26	7	69	18
Disease could not be evaluated or data missing	23	6	58	15
Progression-free survival†				
Patients in analysis	375		375	
Median, months	11		5	
95% CI, months	11 to 13		4 to 6	

NOTE. Tumor response was assessed by investigators according to the Response Evaluation Criteria in Solid Tumors.
Abbreviation: IFN-α, interferon alfa.
*$P < .001$ for the comparison between the sunitinib group and the IFN-α group.
†Hazard ratio = 0.539; 95% CI, 0.451 to 0.643; $P < .001$.

Overall Survival According to Pretreatment Prognostic Risk Factors

The influence of baseline clinical features and previously identified prognostic risk factors[7] on overall survival was analyzed using a Cox proportional hazards model. The benefit of sunitinib over IFN-α was observed across nearly every subgroup of patients (Fig 3).

In developing the Cox model, the following baseline factors were significant independent predictors for survival: ECOG performance status, serum hemoglobin, time from diagnosis to treatment, corrected calcium, alkaline phosphatase, lactate dehydrogenase, and number of metastatic sites (Table 3). Controlling for these seven prognostic factors, the treatment effect of sunitinib over IFN-α was statistically significant (HR = 0.764; 95% CI, 0.623 to 0.936; $P = .0096$).

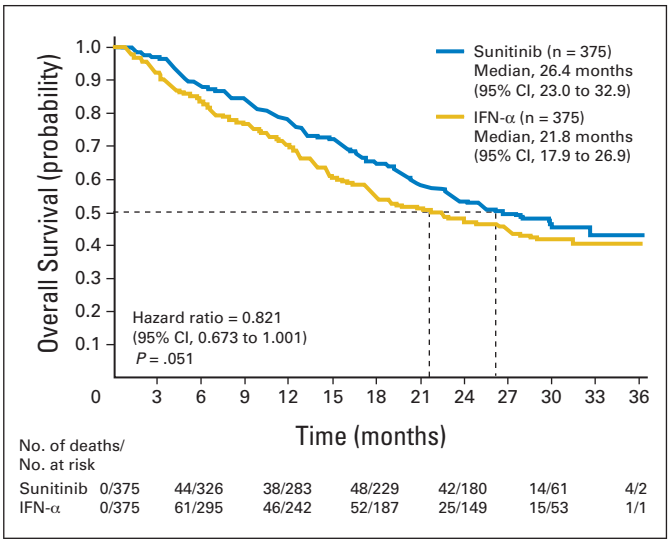

Fig 2. Kaplan-Meier estimates of overall survival. IFN-α, interferon alfa.

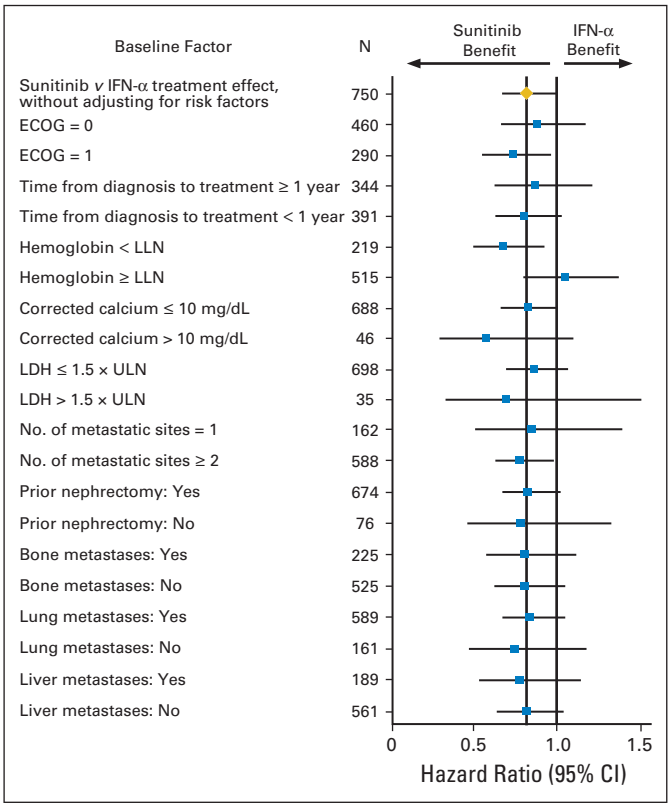

Fig 3. Overall survival subgroup analysis by individual baseline factors. Data are missing for 15 patients for time from diagnosis to treatment, 16 patients for hemoglobin and corrected serum calcium, and 17 patients for lactate dehydrogenase (LDH). IFN-α, interferon alfa; ECOG, Eastern Cooperative Oncology Group; ULN, upper limit of normal; LLN, lower limit of normal.

Patients were grouped on the basis of baseline clinical features using the Memorial Sloan-Kettering Cancer Center (MSKCC) criteria (favorable, intermediate, and poor).[7] (Note that baseline MSKCC data were missing for 17 patients in the IFN-α group.) In the intermediate-risk group (56% of sunitinib group *v* 57% of IFN-α group), median overall survival was 20.7 months (95% CI, 18.2 to 25.6 months) in the sunitinib group compared with 15.4 months (95% CI, 13.6 to 18.2 months) in the IFN-α group (HR = 0.787; 95% CI, 0.617 to 1.004). In the poor-risk group (6% of sunitinib group *v* 7% of IFN-α group), the median overall survival was 5.3 months (95% CI, 4.2 to 10.0 months) for sunitinib compared with 4.0 months (95% CI, 2.7 to 7.2 months) for IFN-α (HR = 0.660; 95% CI, 0.360 to 1.207). Median overall survival had not been reached with either treatment in the favorable-risk group (38% of sunitinib group *v* 32% of IFN-α group); at 12 months, 91% of patients in the sunitinib group were alive compared with 92% of patients in the IFN-α group; and at 2 years, 72% *v* 76%, respectively, were alive.

Exploratory Survival Analyses to Assess Impact of Sunitinib Cross-Over Treatment

An exploratory analysis, which censored 25 patients from the IFN-α group who had crossed over to receive sunitinib on study, resulted in a median overall survival time of 26.4 months (95% CI, 23.0 to 32.9 months) for the sunitinib group compared with 20.0 months (95% CI, 17.8 to 26.9 months) for the IFN-α group (HR = 0.808; 95% CI, 0.661 to 0.987; $P = .036$).

The potential confounding influence of poststudy cancer treatment was reviewed based on the data collected for all patients who discontinued from the trial. Table 4 lists poststudy cancer treatments that patients received after discontinuation. One hundred seventeen (33%) of 359 patients from the IFN-α group received subsequent therapy with sunitinib, and 115 patients (32%) received other vascular endothelial growth factor–signaling inhibitors after discontinuation. The only statistically significant difference in poststudy treatment between the treatment groups was in poststudy sunitinib use ($P < .001$). An exploratory analysis was performed in the subset of patients who did not receive any poststudy cancer treatment (193 patients in the sunitinib group and 162 patients in the IFN-α group). Similar to the overall treatment groups, these subgroups were well balanced with respect to baseline patient characteristics; within the sunitinib and IFN-α subgroups, 37% *v* 28% of patients were classified as favorable risk, 55% *v* 56% were classifiable as intermediate risk, and 8% *v* 7% were classifiable as poor risk, respectively. Within this analysis, median overall survival with sunitinib was twice that of IFN-α (28.1 *v* 14.1 months, respectively; HR = 0.647; 95% CI, 0.483 to 0.870; $P = .003$).

Table 3. Results of an Analysis of OS by Individual Baseline Factors

Factor	OS		
	HR	95% CI	*P*
Treatment (sunitinib *v* IFN-α)	0.764	0.623 to 0.936	.0096
ECOG PS (0 *v* 1)	0.515	0.417 to 0.636	< .0001
Hemoglobin (≥ *v* < LLN)	0.504	0.401 to 0.634	< .0001
Time from diagnosis to treatment (≥ *v* < 1 year)	0.574	0.461 to 0.715	< .0001
Corrected calcium (≤ *v* > 10 mg/dL)	0.466	0.327 to 0.664	< .0001
Alkaline phosphatase (≤ *v* > ULN)	0.676	0.542 to 0.844	.0005
Lactate dehydrogenase (≤ *v* > 1.5× ULN)	0.500	0.337 to 0.742	.0006
No. of metastatic sites (1 *v* ≥ 2)	0.664	0.503 to 0.876	.0037

Abbreviations: OS, overall survival; HR, hazard ratio; IFN-α, interferon alfa; ECOG PS, Eastern Cooperative Oncology Group performance status; LLN, lower limit of normal; ULN, upper limit of normal.

Table 4. Poststudy Cancer Treatment

Treatment	Sunitinib (n = 323)		IFN-α (n = 359)*	
	No. of Patients	%	No. of Patients	%
Any poststudy treatment	182	56	213	59
Sunitinib†	36	11	117	33
Other VEGF inhibitors	106	33	115	32
Cytokines	63	20	47	13
mTOR inhibitors	28	9	16	4
Chemotherapy	21	6	20	6

Abbreviations: IFN-α, interferon alfa; VEGF, vascular endothelial growth factor; mTOR, mammalian target of rapamycin.
*Includes patients who crossed over to sunitinib on study before discontinuation.
†$P < .001$ for the comparison between the sunitinib group and the IFN-α group.

DISCUSSION

This randomized phase III trial compared sunitinib with IFN-α as first-line treatment of patients with metastatic RCC. The primary end point was progression-free survival, which was met at the second interim analysis (November 2005 data cutoff)[4] and remained 11 months for sunitinib compared with 5 months for IFN-α in this updated follow-up.

Sunitinib treatment was associated with longer survival compared with IFN-α (26.4 *v* 21.8 months, respectively). According to a predetermined criterion (unstratified log-rank), the statistical confidence that the improvement is real was marginal ($P = .051$) to the accepted standard. When adjusted according to strata and using the Wilcoxon test, a higher degree of statistical significance in survival was observed (all analyses, $P < .050$).

A stratified analysis typically controls for imbalance in prognostic factors between treatment groups and, therefore, reduces variability. The log-rank test is suitable when the ratio of death rates between two treatment groups is constant over time; the Wilcoxon test is appropriate when the proportional hazards assumption does not hold in such situations where survival data may be confounded by cross over or poststudy treatments.[8]

We propose that availability of new molecularly targeted agents had an impact on survival in both treatment arms. During conduct of this trial, treatment options for patients with metastatic RCC changed dramatically. Phase III trial results and regulatory approval for sunitinib and other molecularly targeted agents resulted in a new treatment paradigm that has improved survival for patients with metastatic RCC.

Therefore, exploratory analyses were performed to study the impact of cross over to sunitinib for patients on the IFN-α arm. These results were consistent with our hypothesis that the survival end point was confounded by cross-over treatment and use of anticancer agents after discontinuation. For example, improvement in median survival was nearly two-fold (28.1 months for sunitinib *v* 14.1 months for IFN-α; $P = .003$) among patients who did not receive any poststudy cancer treatment.

A comparison of survival data from the comparator arm of this trial with historical IFN-α data[7] revealed an improved survival, reflecting improvement in the overall treatment landscape for RCC. For example, within the MSKCC favorable-risk group, 1- and 2-year survival rates for patients randomly assigned to IFN-α treatment in this study were 92% and 76%, respectively, compared with historical rates of 83% and 55%, respectively.[7] The longer survival in patients treated on the sunitinib arm, as well as on the IFN-α arm (with cross over for many patients to sunitinib and molecularly targeted therapy), when compared with historical control with cytokine treatment, reflects an improved prognosis in the era of targeted therapy. Although overall survival remains an appropriate standard end point for establishing clinical benefit, assessment of progression-free survival may be the more relevant end point in assessing treatment effect when the treatment landscape is undergoing substantial change.

Overall survival differed according to MSKCC risk groups (favorable > intermediate > poor risk) for patients treated on each arm of the trial. Also, the influence of baseline clinical features and previously identified prognostic risk factors on overall survival was demonstrated in the Cox proportional hazards model (Table 3). This suggests that underlying tumor biology remains an important factor in determining patient survival, even in the setting of treatment with a highly active agent such as sunitinib.

The overall adverse event profiles for sunitinib and IFN-α are consistent with those reported previously in the interim analysis.[4] As might be expected, patients on sunitinib (for whom median treatment duration had nearly doubled) experienced a comparative increased frequency in overall adverse events. The most commonly reported sunitinib-related grade 3 adverse events included hypertension (12%), fatigue (11%), diarrhea (9%), and hand-foot syndrome (9%). None of these adverse events occurred with grade 4 severity. The predominant grade 3 or 4 laboratory abnormalities were neutropenia, lymphopenia, and increase in lipase (all 18%) for the sunitinib group and lymphopenia (26%) for the IFN-α group.

Hypothyroidism has been associated with sunitinib treatment[9] and was reported by investigators as any grade and grade 3 treatment-related adverse events in 14% and 2% of patients, respectively. Routine monitoring of thyroid function tests was not part of this study. Over the course of its conduct, frequent abnormalities of thyroid function tests associated with sunitinib treatment were reported.[10,11] Routine monitoring of thyroid function is recommended with replacement therapy as appropriate.[9]

Decline in left ventricular ejection fraction is a recognized adverse event associated with sunitinib.[4] In our study, 13% of patients had a sunitinib treatment-related adverse event of ejection fraction decline as reported by investigators, including 3% with grade 3 severity. When compared with its previously reported incidence from the interim analysis (10% all grade; 2% grade 3),[4] these data do not suggest a cumulative effect with long-term sunitinib treatment.

The safety profile of sunitinib has been further established in a trial of more than 4,000 patients with metastatic RCC treated in an expanded-access program.[12] The incidence and type of adverse events were consistent with those reported in this trial, and cumulative serious toxicity was not observed. Overall, the safety profile for sunitinib as an orally administered, chronic outpatient therapy is acceptable, particularly in view of its significant efficacy against metastatic RCC.

The results of health-related quality of life from this trial have been reported elsewhere.[6] Questionnaires included the Functional Assessment of Cancer Therapy–General, the Functional Assessment of Cancer Therapy–Kidney Symptom Index-15 item, and the EuroQOL 5D utility score. By each of these measures, quality of life was significantly more favorable for sunitinib compared with IFN-α.[6]

In summary, sunitinib demonstrates longer overall survival compared with IFN-α plus improvement in response and progression-free survival with an acceptable safety profile in the first-line treatment of patients with metastatic RCC. The overall survival highlights an improved prognosis in patients with RCC in the era of targeted therapy.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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