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Phase I Trial of Sunitinib Malate plus Interferon-α for Patients with Metastatic Renal Cell Carcinoma

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Abstract

Background—Sunitinib malate is an oral, multitargeted tyrosine kinase inhibitor that has demonstrated superior efficacy over interferon (IFN)–α in a phase III trial in first-line, metastatic renal cell carcinoma (RCC). Herein, we report the results of a phase I dose-finding study of sunitinib in combination with IFN-α as first-line treatment in patients with metastatic RCC.

Patients and Methods—Treatment-naive patients with clear-cell metastatic RCC received sunitinib at a starting dose of 50 mg or 37.5 mg orally once daily in 6-week cycles (schedule 4/2) plus IFN-α at a starting dose of 3 MU subcutaneously 3 times a week, with weekly intrapatient dose escalation to a maximum of 9 MU as tolerated. Patients who did not tolerate either drug received lower doses of either or had dose interruptions.

Results—Twenty-five patients were enrolled; their median age was 64 years (range, 45–77 years). All patients experienced grade 3/4 treatment-emergent adverse events; the most common were neutropenia, fatigue, and thrombocytopenia. After a median of 4 cycles (range, 1–9 cycles), 3 patients (12%) had a partial response, and 20 (80%) had stable disease.

Conclusion—Although reduced starting doses were tolerated (37.5 mg for sunitinib and 3 MU for IFN-α), even these lower doses might not be well tolerated for long-term treatment of patients with meta-static RCC. Based on historical data, sunitinib on schedule 4/2 appears to be more effective as single-agent therapy. Further study of sunitinib plus IFN-α on this schedule is not being pursued in RCC.

Keywords

Combination therapy; First-line therapy; Karnofsky performance status; Schedule 4/2; Targeted therapy

Introduction

Renal cell carcinoma (RCC) is the most common cancer of the kidney and was projected to have accounted for > 54,000 new cases of cancer and > 13,000 deaths in the United States in

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2008.[1] Up to 30% of patients present with metastatic disease,[2,3] and approximately 40% of patients who are treated for localized RCC eventually relapse.[2,4] Cytokine therapy with interferon (IFN)–α and/or interleukin (IL)–2 had provided the mainstay of systemic treatment for patients with RCC for many years; however, standard treatment practice has changed over the past few years following an improved understanding of the biology of RCC and successes with targeted agents.[5,6] Such agents are designed to block proliferative, dysregulated tumor pathways and have demonstrated superior antitumor efficacy over cytokines.[5,6]

Sunitinib malate is an oral, multitargeted tyrosine kinase inhibitor of vascular endothelial growth factor (VEGF) receptors and platelet-derived growth factor receptors.[7] Sunitinib has demonstrated robust clinical activity in 2 consecutive single-arm phase II trials of patients with cytokine-refractory metastatic RCC,[8–10] demonstrating an objective response rate (ORR) of 33% (per independent third-party review), a median time to tumor progression (TTP) of 10.7 months, and a median overall survival (OS) of 23.9 months, as recently reported for the second of these trials.[10] In an international, randomized phase III trial of 750 patients with metastatic RCC, sunitinib demonstrated superior first-line efficacy over IFN-α, with significantly greater progression-free survival (PFS) and ORR (11 months vs. 5 months and 31% vs. 6%, respectively; $P < .001$).[11]

Because of, until recently, the widely accepted role of cytokines as first-line therapy for RCC and the antiangiogenic properties of both IFN-α and sunitinib, which might have an additive antitumor effect with a lower risk of developing tumor resistance, there is a rationale for investigating a combination of both agents, as has been recently reported for other targeted agents and IFN-α.[12–14] Interferon-α exerts its antitumor effects via a number of immunotherapeutic mechanisms, but it also has antiangiogenic effects through its inhibition of VEGF[15] and basic fibroblast growth factor.[16] Herein, we report the safety and efficacy results of a phase I dose-finding study of sunitinib in combination with IFN-α as first-line treatment of patients with metastatic RCC.

Patients and Methods

Patients

The study population for this phase I trial consisted of patients aged ≥ 18 years with histologically proven advanced clear-cell RCC and unidimensionally measurable disease. Other inclusion criteria included a Karnofsky performance status (KPS) of ≥ 70%; adequate organ function, defined as absolute neutrophil count = 1,500/μL, platelets ≥ 100,000/μL, hemoglobin ≥ 9 g/dL, serum calcium ≤ 12.0 mg/dL, serum creatinine ≤ 1.5 × the upper limit of normal (ULN), total serum bilirubin ≤ 1.5 × ULN, and serum transaminase levels ≤ 2.5 × ULN (≤ 5 × ULN if hepatic metastases are present); resolution of all acute toxic effects of previous radiation therapy or surgical procedures to grade ≤ 1 severity (National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE]); and signed informed consent. Patient exclusion criteria included previous systemic treatment for advanced RCC; major surgery or radiation therapy within 4 weeks of starting study treatment; NCI CTCAE grade 3 hemorrhage within 4 weeks of starting study treatment; a second malignancy within the previous 5 years; history of or known brain metastases or spinal cord compression; myocardial infarction, severe/unstable angina, coronary/peripheral artery bypass graft, symptomatic congestive heart failure, cerebrovascular accident or transient ischemic attack, or pulmonary embolism in previous 6 months; clinically significant cardiovascular disease, cardiac dysrhythmias, atrial fibrillation, prolongation of the QTc interval, uncontrolled thyroid abnormality, or uncontrolled hypertension; or HIV infection.

Study Design and Treatment

This was a multicenter, single-arm phase I dose-finding study of sunitinib in combination with IFN-α. Sunitinib was provided by Pfizer Inc. and was self-administered at a starting dose of 50 mg or 37.5 mg orally once daily before sleep in repeated 6-week cycles according to a 4/2 schedule (4 weeks on treatment followed by 2 weeks off treatment). Interferon-α2b was provided by Schering-Plough Corporation (Kenilworth, NJ) and was self-administered as a subcutaneous injection 3 times weekly on nonconsecutive days, continuously, starting at 3 MU per dose the first week, with optional intrapatient dose escalation weekly, as tolerated, to a maximum of 9 MU, a schedule previously used in RCC trials.[17] Patients not experiencing a grade ≥ 3 hematologic or nonhematologic treatment-related toxicity after 1 week of treatment at 3 MU had their dose escalated to 6 MU; if no such toxicities occurred after 1 week at 6 MU, patients had their dose further escalated to 9 MU. Patients escalated to 9 MU continued to receive this dose until completion of therapy or development of unacceptable toxicity (ie, grade ≥ 3 hematologic or nonhematologic treatment-related toxicity).

As a result of toxicity observed early in the trial, the protocol was amended after the first 4 patients to reduce the maximum IFN-α dose to 6 MU. Per a final amendment to the protocol, the last 6 enrolled patients received sunitinib 37.5 mg daily and IFN-α 3 MU 3 times weekly in order to assess the tolerability of this combination in patients who were previously untreated.

Patients not tolerating either drug received lower doses of sunitinib (37.5 mg or 25 mg daily) or IFN-α (6 or 3 MU 3 times weekly) or had dose interruptions. Doses of the combination were considered tolerable if at least two thirds of patients who were evaluable for a dose combination completed 2 cycles with < 3 weeks of interruptions per cycle. Sunitinib dosing guidelines for management of toxicity were specified in the protocol, with additional modifications permitted for patient safety at the discretion of the investigator in consultation with the trial sponsor. Patients were evaluable for analysis of the combination if they had received ≥ 2 cycles. Patients continued to receive sunitinib and IFN-α for ≤ 1 year (9 cycles) of treatment or until disease progression, significant toxicity, or withdrawal of consent.

Study Assessments

Baseline evaluations included medical history and physical examination; computed tomography (CT) scan of the chest, abdomen, and pelvis; bone scan; assessment of KPS; complete blood count; biochemical profile (including serum amylase and lipase); 12-lead electrocardiogram; and thyroid function profile.

The primary endpoint of this portion of the study was determination of safe and combinable doses of sunitinib and IFN-α. Safety and tolerability were assessed at regular intervals using NCI CTCAE, version 3.0, by documentation of adverse events, physical examination, hematologic and serum chemistry laboratory measurements, and radiography. As secondary endpoints, the type, incidence, severity, seriousness, and relatedness of adverse events, as well as laboratory abnormalities were examined.

Although not considered formal endpoints, efficacy parameters were also assessed and included ORR, as assessed according to the Response Evaluation Criteria in Solid Tumors,[18] using CT/magnetic resonance imaging scans and bone scans (if bone metastases were present at baseline) after each cycle for the first 4 cycles and every other cycle thereafter until the end of treatment; TTP, defined as the time from treatment assignment to first documentation of objective tumor progression; and OS, defined as the time from treatment assignment to date of death due to any cause.

Statistical Methods

A maximum sample size of 25 patients was judged sufficient to provide data on the safety of sunitinib in combination with IFN-α. A minimum of 6 patients were required to be treated at a predetermined dose level in order for that dose to be considered acceptable for further study. If two thirds of the patients in a given cohort were able to tolerate 2 cycles (12 weeks) of both drugs, then that dose combination would be selected for further study. If fewer than two thirds of the patients were able to tolerate these doses, then a lower dose combination was evaluated. Dose-associated toxicities and overall safety are summarized, but no statistical tests were performed on these data.

Results

Patient Characteristics

Twenty-five patients were enrolled in this study between January 2006 and December 2006. The median age was 64 years, the majority of patients (76%) had a KPS of 90–100, and the median number of disease sites in each patient was 3 (Table 1).

Disposition and Dose Tolerability

Patients had received a median of 4 cycles (range, 1–9 cycles) of sunitinib/IFN-α combination treatment. In total, 18 patients (72%) had discontinued, 9 (36%) because of progressive disease (PD) and 7 (28%) because of adverse events; 1 patient died from a myocardial infarction, but it was not considered related to treatment. Twenty-two patients (88%) experienced dose interruptions: 16 (64%) had interruptions of sunitinib, and 21 (84%) had interruptions of IFN-α.

Twelve patients were treated at a sunitinib starting dose of 50 mg and 13 at a starting dose of 37.5 mg (Table 2). Eighteen patients (72%) experienced dose reductions; 16 (64%) had reductions of sunitinib, and 14 (56%) had reductions of IFN-α. Regardless of the starting dose, most patients during the course of the study were titrated to sunitinib 37.5 mg daily, either alone (n = 2) or in combination with IFN-α 6 MU (n = 5) or 3 MU (n = 10; Table 2).

Tolerability of all possible dose combinations was investigated, the results of which are summarized in Table 3. The 50-mg/9-MU sunitinib/IFN-α combination was not tolerated, and the 9-MU IFN-α dose was subsequently discontinued during cycle 1 of treatment (per an amendment to the study protocol). The 50-mg/6-MU and 37.5-mg/6-MU sunitinib/IFN-α combinations were also not tolerated. The 37.5-mg/3-MU sunitinib/IFN-α combination was reasonably well tolerated, primarily when used as the starting dose combination (all 5 patients who were newly enrolled and evaluable at this dose combination were able to tolerate it). The 25-mg/3-MU sunitinib/IFN-α combination was also well tolerated (4 out of 5 patients).

Eight patients were rolled over into a continuation protocol of single-agent sunitinib, including 5 patients who had discontinued combination therapy, 2 who were still on study and receiving combination therapy at the time of analysis, and 1 patient who had completed the study. A separate 5 patients were switched to single-agent commercial sunitinib.

Safety

All 25 patients experienced grade 3 treatment-emergent adverse events, including 7 patients with serious adverse events (4 who received a starting sunitinib dose of 50 mg and 3 who received a starting dose of 37.5 mg). The most commonly reported grade 3 adverse events were neutropenia (36%), fatigue (28%), and thrombocytopenia (20%; Table 4). Overall, 2 patients developed grade 4 adverse events (hypertension, anemia, hypocalcemia, and

hypokalemia), and 1 patient experienced a grade 5 adverse event (myocardial infarction). Four patients discontinued sunitinib and 7 patients discontinued IFN-α because of adverse events. There were no major differences in the overall incidence of adverse events, or in their severity, in patients who received a sunitinib starting dose of 50 mg compared with a starting dose of 37.5 mg (Table 4).

Of the 6 patients who started enrollment on the 37.5-mg sunitinib/3-MU IFN-α combination, all reported grade 3 treatment-emergent adverse events. One patient reported grade 3 syncope, neutropenia, and dyspnea and grade 4 anemia, hypocalcemia, and hypokalemia. Two patients enrolled on the 37.5-mg sunitinib/3-MU IFN-α combination discontinued the study after 2 cycles because of adverse events, 1 after permanent discontinuation of sunitinib because of grade 3 syncope and 1 after permanent discontinuation of IFN-α because of grade 3 neutropenia.

Efficacy

All patients (N = 25) completed = 1 cycle of treatment and were evaluable for response. At the time of analysis, 3 partial responses were observed, resulting in an ORR of 12% (95% CI, 2.5–31.2; Table 5). Twenty patients (80%) had a best response of stable disease (SD; as confirmed by follow-up tumor assessment after a minimum of 6 weeks). Median TTP was 11.9 months (95% CI, 5.5–12.4 months).

Two patients had died, and 8 had rolled over to single-agent sunitinib in a continuation protocol. Of these 8 patients, 4 patients showed PD, and 4 continued to have SD. Median OS for the entire study cohort had not been reached.

Discussion

In this phase I dose-finding study, we assessed the tolerability of a first-line sunitinib/IFN-α combination in patients with metastatic RCC. When used as single agents, sunitinib is tolerated at 50 mg and IFN-α at 9 MU; however, the requirement for dose reduction in 18 of 25 patients (72%) in this study indicates that these agents, when given at full doses, are not well tolerated in combination. Although reduced starting doses were tolerated (37.5 mg for sunitinib and 3 MU for IFN-α), even these lower doses might not be well tolerated for long-term treatment.

The most common treatment-emergent adverse events in this study were fatigue (100%), diarrhea (76%), and nausea (56%). In comparison, the respective incidences of each adverse event in the phase III trial of sunitinib versus IFN-α (treatment-related assessment) were 51% for both sunitinib and IFN-α, 53% for sunitinib versus 12% for IFN-α, and 44% for sunitinib versus 33% for IFN-α.[11] Similarly, the incidences of the most common grade 3/4 adverse events in this trial, neutropenia (36%) and fatigue (28%), were both greater than for either drug alone in the phase III trial (12% for sunitinib vs. 7% for IFN-α and 7% for sunitinib vs. 12% for IFN-α, respectively).[11] The adverse events reported for combination therapy in this trial reflect an additive effect with the toxicity profile for either drug alone.

As a result of the intolerability of the full effective dose of sunitinib in combination with IFN-α and the subsequent requirement for dose reduction, the tumor response observed with single-agent sunitinib in previous trials was not reproduced here. The ORR for sunitinib plus IFN–α as first-line treatment of patients with metastatic RCC was 12% in this trial compared, for example, with 31% (per independent third-party review) for single-agent sunitinib in the phase III trial.[11] In fact, the response rate achieved in this trial was more consistent with that observed with IFN-α alone as first-line therapy (6%–12%).[3,11,19] The

lower response rate compared with sunitinib alone is consistent with inferior efficacy as a result of inadequate sunitinib dose delivery.

Two recent phase I trials reported on efficacy and toxicity of the multikinase inhibitor sorafenib in combination with IFN-α as first- or second-line therapy in patients with metastatic RCC.[12,13] Response rates varied between the 2 studies. One trial reported a 33% ORR in 40 patients,[12] and the second trial reported a 19% response rate in 62 assessable patients.[13] The prevalence of dose reductions were similar in the first trial, required in 65% of patients, and, again, the toxicity exceeded that of either drug alone[12]; however, unlike the trial reported here, the response rate in the first sorafenib/IFN-α trial (33% per investigator assessment) exceeded the response rate for either drug alone. In addition, the median PFS of 10 months[12] with the combination compared favorably with the PFS for sorafenib alone (5.5 months in cytokine-refractory patients).[20] Likewise, in the second study, 77% of patients experienced grade ≥ 3 adverse events, with 79% of patients having had the IFN dose reduced, and 35% having had the sorafenib dose reduced.[13] Subsequently, the authors from the first study concluded that a strategy that minimizes dose reduction of sorafenib while maintaining tolerability might improve outcomes in this particular combination.[12] The conclusions from the second study were that the toxicity of the combination is dominated by adverse events common to IFN, which limit further development of this regimen.[13] Regardless, demonstration of benefit for the sorafenib/IFN-α combination over sorafenib alone would require data from a randomized phase III trial.

In addition, results of a combination study of the targeted agent temsirolimus, a mammalian target of rapamycin inhibitor, with IFN-α were also recently published.[14] In this phase I/II dose-escalation study of patients with advanced RCC, the investigators found that the recommended dose of intravenous temsirolimus for combination with IFN-α (at 6 MU) was 15 mg, or 40% lower than the recently approved dose of 25 mg. Even so, among the 39 patients treated at this combination dose, dose reduction, dose delays, and withdrawal because of toxicity were required in 51%, 76%, and 21% of patients, respectively. Again, however, the observed median PFS of 9.1 months in this temsirolimus/IFN-α combination study compared favorably with previous single-agent temsirolimus data, leading the authors to conclude that this combination was feasible for further study.[14] Consequently, this combination was investigated in a phase III trial in which patients were randomized to treatment with temsirolimus, IFN-α, or a combination of both.[21] Temsirolimus, as compared with IFN-α, significantly improved OS among patients with metastatic RCC and a poor prognosis; however, the combination of temsirolimus and IFN did not significantly improve survival.

An independently conducted phase III trial showed benefit in ORR and PFS for bevacizumab plus IFN-α compared with IFN-α alone.[22] In general, this regimen was tolerable, with most patients able to tolerate full doses of bevacizumab as chronic therapy. Unlike the combination of IFN-α with sunitinib, sorafenib, or temsirolimus, the combination of IFN-α with bevacizumab appears to be tolerable. This may be due to differences in toxicity profiles for these agents and bevacizumab, specifically the lack of myelosuppression associated with bevacizumab. The most common side effect, fatigue, was likely related to the cytokine. The contribution to efficacy from IFN-α to that of bevacizumab needs to be determined. A randomized trial of bevacizumab plus IFN-α compared with bevacizumab alone would be useful in this regard.

Conclusion

This was an exploratory study to investigate the tolerability of sunitinib plus IFN-α in patients with metastatic RCC. Sunitinib in combination with IFN-α produced greater

toxicity than single-agent sunitinib therapy given at the recommended starting dose. Based on previously reported phase III data, sunitinib on schedule 4/2 is more effective as single-agent therapy than in combination with IFN-α.[8–11] Further study of this combination on this schedule is not being pursued in RCC.

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Table 1

Baseline Patient Characteristics

Characteristic	Sunitinib/IFN-α (N = 25)
Median Age, Years (Range)	64 (45–77)
Male/Female, n	20/5
Previous Therapy for Primary Diagnosis, n (%)	
Surgery	24 (96)
Radiation therapy	3 (12)
Karnofsky Performance Scale, n (%)	
90–100	19 (76)
80–89	6 (24)
MSKCC Risk Factors, * n (%)	
0 (Low)	8 (32)
1 or 2 (Intermediate)	16 (64)
≥ 3 (High)	1 (4)
Median Number of Disease Sites (Range)	3 (1–6)
Common Sites of Metastases, n (%)	
Lung	20 (80)
Lymph nodes	19 (76)
Bone	8 (32)
Liver	6 (24)

* Risk factors include Karnofsky performance scale < 80%, serum lactate dehydrogenase level > 1.5 × the upper limit of normal, serum hemoglobin level < the lower limit of normal, corrected serum calcium level > 10 mg/dL, time since first diagnosis < 1 year.[18]

Abbreviations: IFN = interferon; MSKCC = Memorial Sloan-Kettering Cancer Center

Table 2

Patient Disposition

Starting Combination Dose of Sunitinib, mg/day + IFN-α,* MU 3 Times Weekly (n)	Final† Combination Dose of Sunitinib, mg/day + IFN-α, MU 3 Times Weekly (n)
37.5 + 3 (13)	37.5 + 6 (1) 37.5 + 3 (7) 37.5 + 0 (1) 25 + 3 (3) 25 + 0 (1)
50 + 3 (12)‡	37.5 + 6 (4) 37.5 + 3 (3) 37.5 + 0 (1) 25 + 3 (2) 25 + 0 (2)

*Patients were subject to intrapatient dose escalation of IFN-α weekly, as tolerated, to a maximum dose of 9 MU, which, per a protocol amendment, was discontinued during cycle 1, making 6 MU the highest IFN-α dose thereafter. In addition, 6 patients, per the final protocol amendment, were newly enrolled on sunitinib 37.5 mg plus IFN-α 3 MU and not subject to dose escalation of IFN-α.

†The combination dose received by patients as of the data cutoff.

‡One patient on sunitinib 50 mg/day mistakenly co-administered a starting dose of IFN-α 10 MU, necessitating a dose titration to 3 MU.

Abbreviation: IFN = interferon

Table 3

Dose Tolerability

Sunitinib/IFN-α	Evaluable Patients, n*	Patients Who Tolerated Dose, n (%)†
50 mg/9 MU‡	4	0
50 mg/6 MU	8	1 (12)
50 mg/3 MU	1	0
37.5 mg/6 MU	13	3 (23)
37.5 mg/3 MU (All)	13	7 (54)
37.5 mg/3 MU (previously enrolled)§	8	2 (25)
37.5 mg/3 MU (newly enrolled)//	5	5 (100)
25 mg/6 MU	0	0
25 mg/3 MU	5	4 (80)

*Patients were evaluable for a dose combination if they had received the combination and had not withdrawn for reasons other than toxicity. In addition, a patient could be evaluable for > 1 dose level.

†A dose is tolerable if it is tolerated for 2 consecutive cycles (with interruptions ≤ 3 weeks/cycle).

‡The 9-MU dose of IFN-α was discontinued during cycle 1.

§Patients were on higher doses and had dose reductions before receiving sunitinib 37.5 mg/IFN-α 3 MU.

//Patients were newly enrolled on sunitinib 37.5 mg/IFN-α 3 MU and had not received higher doses of the combination.

Abbreviation: IFN = interferon

Table 4

Treatment-Emergent Grade ≥ 2 Adverse Events Occurring in ≥ 20% of All Patients by Initial Sunitinib Dose

Adverse Event	Maximum CTCAE Grade* by Starting Sunitinib Dose (mg)								
	Grade 2, n (%)			Grade 3, n (%)			Total, n (%)		
	37.5 mg (n = 13)	50 mg (n = 12)	All (N = 25)	37.5 mg (n = 13)	50 mg (n = 12)	All (N = 25)	37.5 mg (n = 13)	50 mg (n = 12)	All (N = 25)
Fatigue	5 (38)	5 (42)	10 (40)	6 (46)	1 (8)	7 (28)	13 (100)	12 (100)	25 (100)
Diarrhea	2 (15)	4 (33)	6 (24)	1 (8)	0	1 (4)	7 (54)	12 (100)	19 (76)
Nausea	3 (23)	2 (17)	5 (20)	0	0	0	7 (54)	7 (58)	14 (56)
Stomatitis	1 (8)	1 (8)	2 (8)	1 (8)	0	1 (4)	5 (38)	8 (67)	13 (52)
Neutropenia	0	3 (25)	3 (12)	4 (31)	5 (42)	9 (36)	4 (31)	8 (67)	12 (48)
Dyspepsia	2 (15)	1 (8)	3 (12)	0	0	0	5 (38)	5 (42)	10 (40)
Dyspnea	0	0	0	1 (8)	1 (8)	2 (8)	4 (31)	5 (42)	9 (36)
Thrombocytopenia	1 (8)	1 (8)	2 (8)	2 (15)	3 (25)	5 (20)	4 (31)	4 (33)	8 (32)
Vomiting	1 (8)	3 (25)	4 (16)	0	0	0	5 (38)	3 (25)	8 (32)
Chills	0	0	0	0	0	0	4 (31)	3 (25)	7 (28)
Dysgeusia	0	0	0	1 (8)	0	1 (4)	2 (15)	5 (42)	7 (28)
Hypertension†	1 (8)	1 (8)	2 (8)	1 (8)	2 (17)	3 (12)	3 (23)	4 (33)	7 (28)
Pyrexia	1 (8)	1 (8)	2 (8)	0	0	0	4 (31)	3 (25)	7 (28)
Decreased Appetite	2 (15)	0	2 (8)	0	0	0	2 (15)	4 (33)	6 (24)
Dry Skin	0	0	0	0	0	0	2 (15)	4 (33)	6 (24)
Influenza-Like Illness	0	0	0	0	0	0	2 (15)	4 (33)	6 (24)
Leukopenia	1 (8)	3 (25)	4 (16)	0	2 (17)	2 (8)	1 (8)	5 (42)	6 (24)
Myalgia	1 (8)	1 (8)	2 (8)	1 (8)	0	1 (4)	5 (38)	1 (8)	6 (24)
Anorexia	1 (8)	0	1 (4)	0	1 (8)	1 (4)	4 (31)	1 (8)	5 (20)
Arthralgia	0	0	0	0	0	0	2 (15)	3 (25)	5 (20)
Constipation	1 (8)	0	1 (4)	0	0	0	2 (15)	3 (25)	5 (20)
Dizziness	0	0	0	1 (8)	0	1 (4)	4 (31)	1 (8)	5 (20)
Epistaxis	0	0	0	0	0	0	2 (15)	3 (25)	5 (20)
Headache	1 (8)	0	1 (4)	0	0	0	4 (31)	1 (8)	5 (20)

Adverse Event	Maximum CTCAE Grade* by Starting Sunitinib Dose (mg)								
	Grade 2, n (%)			Grade 3, n (%)			Total, n (%)		
	37.5 mg (n = 13)	50 mg (n = 12)	All (N = 25)	37.5 mg (n = 13)	50 mg (n = 12)	All (N = 25)	37.5 mg (n = 13)	50 mg (n = 12)	All (N = 25)
Hand-Foot Syndrome	0	0	0	1 (8)	2 (17)	3 (12)	2 (15)	3 (25)	5 (20)
Paresthesia	0	1 (8)	1 (4)	0	0	0	0	5 (42)	5 (20)

*National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0.

†One patient at a starting sunitinib dose of 37.5 mg developed grade 4 hypertension (no other adverse events occurring in ≥ 20% of patients were grade ≥ 4).

Table 5

Best Objective Response to Sunitinib/Interferon-α Combination Therapy

Response	Sunitinib/IFN-α (N = 25)
Patients with Measurable Disease at Baseline, n (%)	25 (100)
Best Objective Response by RECIST, n (%)	
PR	3 (12)
SD	20 (80)
PD	1 (4)
NA	1 (4)
Response Rate (CR + PR), n (%)	3 (12) (95% CI, 2.5–31.2)

Abbreviations: CR = complete response; IFN = interferon; NA = not assessed; PD = progressive disease; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors; SD = stable disease