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PROPRIETARY DRUG NAME®/GENERIC DRUG NAME: Sunitinib® / Sunitinib malate

THERAPEUTIC AREA AND FDA APPROVED INDICATIONS: See USPI.

NATIONAL CLINICAL TRIAL NO.: NCT00083889

PROTOCOL NO.: A6181034

PROTOCOL TITLE: A Phase 3, Randomized Study of SU011248 versus Interferon-α as First-Line Systemic Therapy for Patients with Metastatic Renal Cell Carcinoma

Study Center(s): A total of 101 centers took part in the study, including 39 centers in the United States, 10 centers in Canada, 8 centers in Poland, 8 centers in Russia, 7 centers in Australia, 6 centers in France, 6 centers in Italy, 5 centers in Spain, 5 centers in the United Kingdom, 4 centers in Germany, and 3 centers in Brazil.

Study Initiation and Completion Dates: 10 August 2004 to 19 September 2008

Phase of Development: Phase 3

Study Objective(s): The primary objective was to compare the progression-free survival (PFS) associated with sunitinib versus that associated with interferon-alfa (IFN-α) for the first-line treatment of subjects with metastatic renal cell carcinoma (MRCC).

Secondary objectives were

- to compare the objective response rate (ORR) associated with sunitinib versus that associated with IFN-α for the first-line treatment of MRCC;
- to compare the overall survival (OS) associated with sunitinib versus that associated with IFN-α for the first-line treatment of subjects with MRCC;
- to compare the time to tumor progression (TTP) associated with sunitinib versus that associated with IFN-α for the first-line treatment of subjects with MRCC;
- to compare patient reported outcomes (PROs) between the 2 arms of the study; to evaluate the safety and tolerability of sunitinib;
- to assess the cost effectiveness of sunitinib compared to IFN-α as first-line treatment for MRCC;

- to evaluate SU011248 and SU012662 trough plasma concentrations (C_{trough}) and to correlate these plasma concentrations with efficacy and safety parameters in a subset of subjects; and to assess and explore correlations of potential biomarkers with cancer and treatment-related outcomes in a subset of subjects..

METHODS

Study Design: This study was a randomized, multi-center, international, Phase 3 comparison of sunitinib (Arm A) vs IFN-α (Arm B) as first-line therapy in subjects with MRCC. Subjects received treatment with either sunitinib in repeated 6-week cycles, consisting of 4 weeks of 50 mg daily sunitinib administration followed by 2 weeks off treatment (Schedule 4/2), or IFN-α, administered as a subcutaneous injection on 3 non-consecutive days each week.

Number of Subjects (Planned and Analyzed): Six hundred ninety subjects were planned, and 750 subjects were randomized; 375 subjects (50%) were randomized to sunitinib (Arm A) and 375 (50%) were randomized to IFN-α (Arm B).

Diagnosis and Main Criteria for Inclusion: Subjects with MRCC (with a component of clear cell histology) that had not previously been treated with systemic therapy were eligible to participate in the study if they had unidimensionally measurable disease, were at least 18 years of age, had adequate organ function, and had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.

Study Treatment: Subjects received either sunitinib or IFN-α. Sunitinib was administered as an oral capsule at 50 mg daily for 4 weeks followed by 2 weeks off treatment in repeated 6-week cycles of treatment. IFN-α (Roferon®-A, Roche) was administered as a subcutaneous injection in 6-week cycles on 3 non-consecutive days per week; Subjects received 3 MU per dose during the first week, 6 MU per dose the second week, and 9 MU per dose thereafter. Dose modifications were allowed for toxicity management on both arms. Sunitinib was approved by the US FDA for treatment of patients with advanced RCC in January 2006; following a protocol amendment in February 2006, subjects randomized to the IFN-α arm with documented disease progression were given an option to be treated with sunitinib on study.

Efficacy Evaluations: The primary endpoint was PFS, based on an independent core radiology laboratory assessment, in the intent-to-treat (ITT) population (all subjects who were randomized to treatment); supportive analyses of the primary endpoint were performed in the as-treated population (AT; all subjects with available drug dosing information, with treatment assigned as actual treatment received) and evaluating PFS in the ITT and AT populations based on investigator assessment. The primary endpoint was further analyzed for the effects of baseline and stratification factors.

Secondary endpoints included TTP, ORR, OS, duration of response (DR), safety, and PROs. The PROs were evaluated with the following questionnaires: Functional Assessment of Cancer Therapy (FACT) - General (G), FACT - Advanced Kidney Cancer Symptom Index (FKSI), and the EuroQol EQ-5D Self-Report Questionnaire (EQ-5D). PRO endpoints

include FACT-G Total score and its four subscales (Physical Well Being (PWB), Social/Family Well Being (SWB), Emotional Well Being (EWB) and Functional Well Being (FWB)), FKSI score and its disease related symptoms subscale (FKSI-DRS), EQ-5D's Health State Index (EQ-5D Index) and Visual Analog Scale (EQ-VAS). The FKSI-DRS was pre-specified as the primary PRO endpoint. For all tumor assessments, response and progression were assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST) and evaluated by an independent, third-party core radiology laboratory.

Pharmacokinetic and Pharmacodynamic Evaluations: Blood samples for determination of predose (Day 1) and trough (Day >1) concentrations of sunitinib and its active metabolite, SU012662, were collected at selected sites in subjects receiving sunitinib treatment at Days 1 and 28 of Cycles 1 to 4. Predose and trough concentrations of sunitinib, SU012662, and total drug (sunitinib + SU012662) were summarized by cycle and study day using descriptive statistics.

Additional samples were collected at selected sites for assessment of soluble proteins and RNA expression (Days 1 and 28 of Cycles 1 to 4) and circulating endothelial cell assays (Days 1 and 28 of Cycles 1 and 2 and at end of treatment/withdrawal). Pre-treatment tumor biopsies were collected from a subset of subjects who consented to the procedure.

Safety Evaluations: Safety evaluations included adverse events from the first day of treatment to 28 days after the last dose of study drug; clinical laboratory tests (hematology and serum chemistry) performed throughout the study; multigated acquisition (MUGA) scan to determine left ventricular ejection fraction (LVEF; performed at screening, at Day 28 of Cycles 1 and 3, and at Day 1 of odd-numbered cycles thereafter); electrocardiogram (ECG; performed at screening and at Day 28 of Cycle 1 and as clinically indicated thereafter); and vital signs and ECOG performance status (performed on Days 1 and 28 of Cycles 1 to 4 and Day 1 of each cycle thereafter).

Statistical Methods: Time-to-event endpoints between the 2 treatment arms were compared with a 2-sided unstratified log-rank test at the $\alpha = 0.05$ overall significance level in the intent-to-treat (ITT) population (ie, all subjects randomized to treatment, with treatment assignment according to randomization, regardless of what treatment subjects actually received). A stratified log-rank test and Cox proportional hazards model were used to adjust for the potential influences of baseline and stratification factors on the time-to-event endpoints. The estimated hazard ratio and 2-sided 95% confidence interval (CI) are provided. Additionally for each treatment arm, the median event time and a 2-sided 95% CI are provided for each level of the stratification factors. ORR for the 2 treatment arms were compared unstratified by using the Pearson χ^2 test and compared stratified by the stratification factors by using the Cochran-Mantel-Haenszel (CMH) method. The relative risk ratio was used in the stratified analyses to contrast the treatment effects on ORR. Both a point estimate and a 2-sided 95% CI were calculated using a normal approximation. For binary endpoints, exact 2-sided 95% CIs were calculated using the standard method based on the binomial distribution. Between-treatment differences of the post-baseline measurements of all the PRO endpoints were tested using the repeated measures mixed-effects models adjusting for the time, treatment-by-time interaction and the baseline scores of the same PRO endpoints.

This is the final analysis of the study; there have been 2 prior planned analyses. Interim Analysis 1 was planned to take place when 250 subjects had had the opportunity to receive 3 cycles of treatment; that analysis included 253 subjects and 83 observed PFS events (progressions confirmed by the core imaging laboratory or deaths). In Interim Analysis 2, 250 PFS events had been observed, and the primary objective of the study was met at Interim Analysis 2.

Safety analyses were presented descriptively, comparing sunitinib vs IFN-α in the as-treated (AT) population (ie, all subjects who received treatment, with treatment assignment according to treatment actually received).

RESULTS

Subject Disposition and Demography:

Table S1. Subject Disposition and Subjects Analyzed

Primary Reason for Discontinuation	Sunitinib	IFN-α
Subjects Randomized (ITT Population)	375	375
Subjects Treated (AT Population)	375	360
Primary Reason for Discontinuation		
Adverse Event	76 (20.3)	86 (22.9)
Protocol Violation	2 (0.5)	2 (0.5)
Consent Withdrawn	22 (5.9)	24 (6.4)
Lack of Efficacy	240 (64.0)	219 (58.4)
Decision of Sponsor[a]	32 (8.5)	4 (1.1)
Subject Completed Treatment/Study Per Protocol[a]	3 (0.8)	0 (0.0)
Randomized/Registered but did not take study drug	0 (0.0)	15 (4.0)
Crossover	0 (0.0)	25 (6.7)
Primary Reason for Discontinuation for Crossover Subjects		
Adverse Event		5 (1.3)
Consent Withdrawn		2 (0.5)
Lack of Efficacy		13 (3.5)
Decision of Sponsor[a]		5 (1.3)

Percents are based on the ITT population.

a Since sunitinib was approved in the US in January 2006, 3 subjects chose to discontinue the study and continued treatment with commercially available sunitinib; these subjects are categorized as 'completed treatment/study per protocol'. After the study had met its endpoints, subjects remaining on study treatment were discontinued from the study and were provided with commercially available sunitinib; these subjects are categorized as 'decision of sponsor'.

Table S2. Summary of Demographic and Baseline Characteristics (ITT Population)

Variable	Sunitinib (N=375)	IFN-α (N=375)
Sex [n (%)]		
Male	267 (71.2)	269 (71.7)
Female	108 (28.8)	106 (28.3)
Race [n (%)]		
White	355 (94.7)	341 (90.9)
Black	4 (1.1)	10 (2.7)
Asian	7 (1.9)	12 (3.2)
Not Listed/Not Allowed to Ask	9 (2.4)	12 (3.2)
Age (years)		
Mean (standard deviation)	60.6 (10.1)	60.1 (9.5)
Median (range)	62.0 (27 to 87)	59.0 (34 to 85)
<65	223 (59.5)	252 (67.2)
≥ 65	152 (40.5)	123 (32.8)
Weight (kg)		
Mean (standard deviation)	83.7 (19.1)	83.1 (20.0)
Median (range)	82.0 (44.5 to 181.8)	80.0 (46.0 to 210.5)
ECOG performance status [n (%)]		
0	231 (61.6)	229 (61.1)
1	144 (38.4)	142 (37.9)
2[a]	0 (0.0)	4 (1.1)
LDH [n (%)]		
>1.5 x ULN	15 (4.0)	20 (5.3)
≤1.5 x ULN	360 (96.0)	338 (90.1)
Missing	0 (0.0)	17 (4.5)
Hemoglobin [n (%)]		
<LLN	99 (26.4)	121 (32.3)
≥LLN	276 (73.6)	238 (63.5)
Missing	0 (0.0)	16 (4.3)
Corrected Calcium [n (%)]		
>10 mg/dL	30 (8.0)	17 (4.5)
≤10 mg/dL	345 (92.0)	342 (91.2)
Missing	0 (0.0)	16 (4.3)

a All subjects had ECOG performance status of 0 or 1 at the time eligibility was determined; some subjects' conditions deteriorated such that ECOG performance status was 2 at the last pre-treatment assessment, which is summarized here.

Efficacy Results: The primary endpoint of this study was PFS on sunitinib as compared to that on IFN-α; and secondary efficacy endpoints were TTP, OS, ORR, and DR. The primary objective of the study was met at the second interim analysis; at that time, the median PFS was 47.3 (95% CI: 42.6 to 50.7 weeks) vs 22.0 weeks (95% CI: 16.4 to 24.0 weeks) on sunitinib vs IFN-α, respectively, with a hazard ratio of 0.415 (95% CI: 0.320 to 0.539; p <0.0001). This result exceeded the stopping boundary. Core radiology assessment was discontinued in September 2007 because the primary endpoint had been met.

This final analysis confirms and extends the findings of the interim analysis. The Kaplan-Meier curve of PFS is presented in Figure S1, and PFS, TTP, and OS are summarized in Table S3. In the primary analysis of PFS (core radiology assessment, ITT population), the median PFS on sunitinib was more than double that on IFN-α (48.3 vs 22.1 weeks; hazard ratio of 0.5268, p <0.0001); sunitinib results in a clinically and statistically significant increase in PFS in subjects with MRCC as compared to IFN-α. The results were similar in the supportive analyses using the AT population and in both analysis populations when using the investigators' assessments of PFS, and they were robust when controlling for stratification factors and for other demographic and known risk factors. The Kaplan-Meier curve of PFS based on the investigators' assessments is presented in Figure S2.

The results for TTP were similar to those for PFS (49.1 vs 22.4 weeks). Median OS was 114.6 vs 94.9 weeks on sunitinib vs IFN-α, respectively. Although the difference in OS was not statistically significant (p =0.0510) by the unstratified log-rank test, it was statistically significant by the stratified log-rank test (hazard ratio: 0.8179; 95% CI: 0.6692 to 0.9995; p =0.0490). The statistically significant difference in OS was also demonstrated by the unstratified Wilcoxon tests (p =0.0128). When multiple baseline factors were adjusted in the Cox proportional hazards model, the hazard ratio was 0.762 (95% CI: 0.621 to 0.935; p =0.0090). When censoring subjects who crossed over from IFN-α treatment to sunitinib treatment at the time of crossover, median OS was 114.6 vs 86.7 weeks (unstratified hazard ratio: 0.808; p[log-rank] =0.0361; p[Wilcoxon] =0.0081). When excluding subjects who received post-study anti-cancer therapy to limit the bias introduced by the imbalanced post-study cancer treatments between two arms, median OS was 121.9 vs 61.3 weeks on sunitinib vs IFN-α, respectively (hazard ratio: 0.647; 95% CI: 0.482 to 0.867; p [log-rank]=0.0033).

Other efficacy measures included ORR and DR. The results indicate a statistically significant and robust improvement in ORR with sunitinib. ORR is summarized in Table S4.

Figure S1. Kaplan-Meier Curve of Progression-Free Survival by Treatment (Core Radiology Assessment, ITT Population)

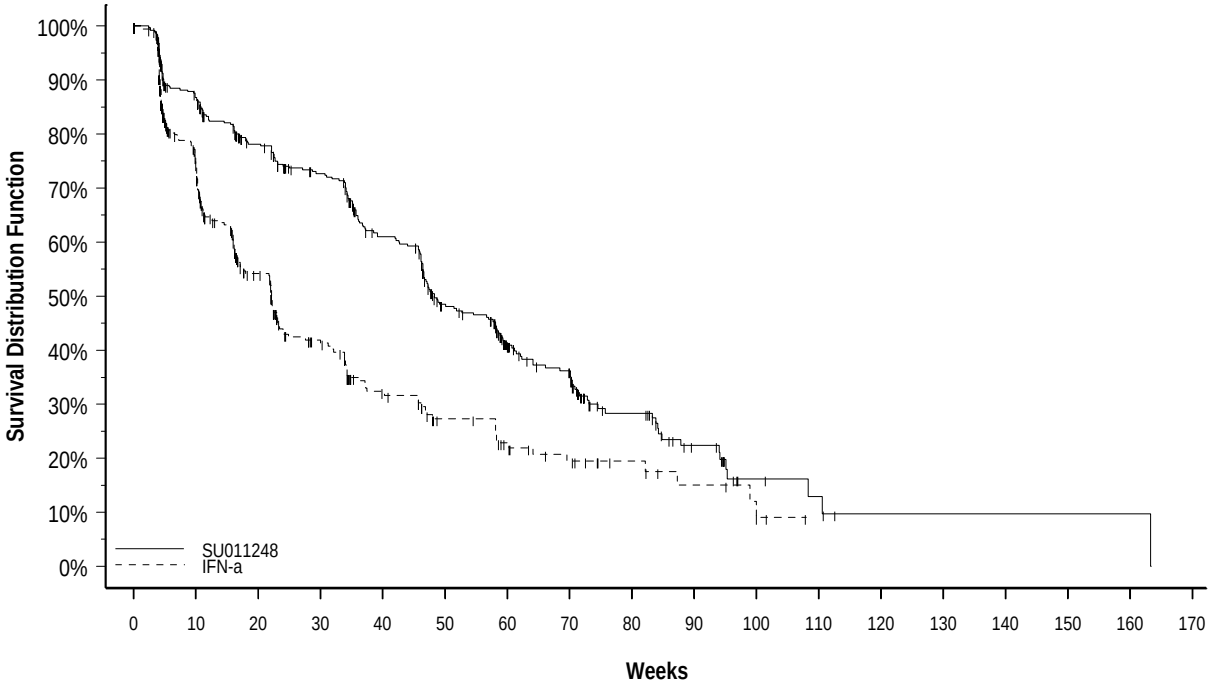

Figure S2. Kaplan-Meier Curve of Progression-Free Survival by Treatment (Investigators' Assessment, ITT Population)

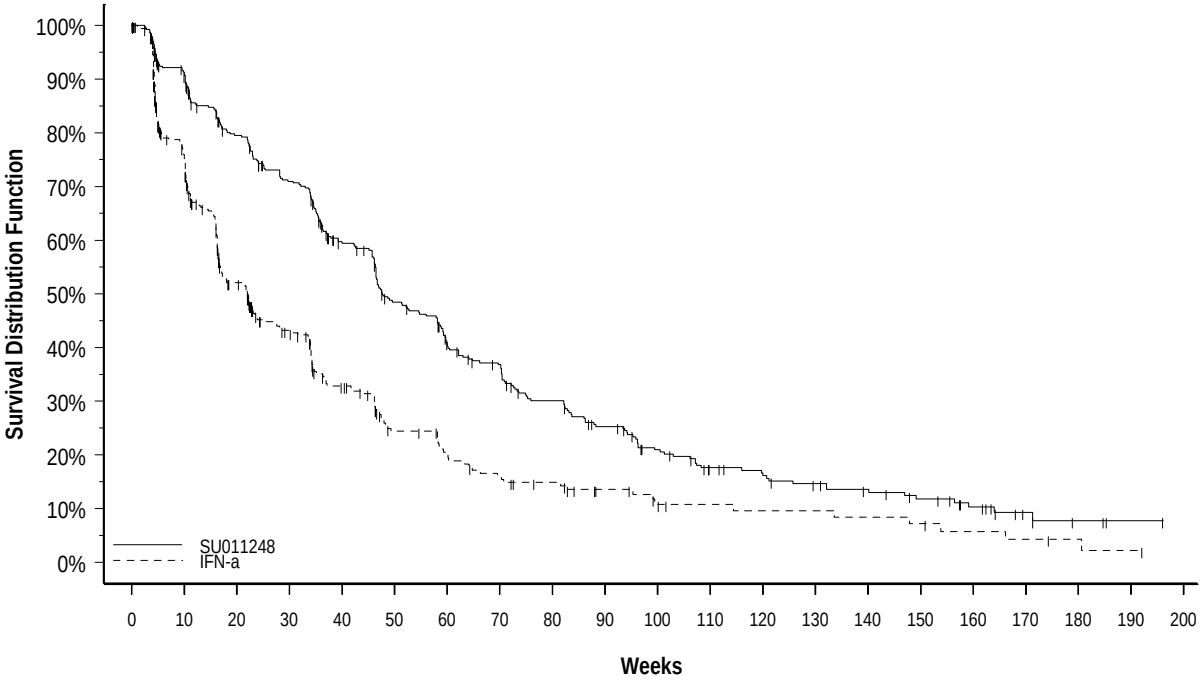

Table S3. Summary of Time-to-Event Endpoints (ITT and AT Populations)

Variable	Number of Events: Sunitinib n (%)	Number of Events: IFN-α n (%)	Hazard Ratio[a]	95% CI of Hazard Ratio	p-value
Progression-Free Survival					
Core Radiology Assessment					
ITT population [N]	375	375			
Events (n [%])	214 (57.1)	199 (53.1)	0.5268	(0.4316 to 0.6430)	<0.0001[a]
Median (weeks)	48.3	22.1			
95% CI	(46.4 to 58.3)	(17.1 to 24.0)			
AT population [N]	375	360			
Events (n [%])	214 (57.1)	199 (55.3)	0.5268	(0.4316 to 0.6430)	<0.0001[a]
Median (weeks)	48.3	22.1			
95% CI	(46.4 to 58.3)	(17.1 to 24.0)			
Investigators' Assessment					
ITT population [N]	375	375			
Events (n [%])	275 (73.3)	247 (65.9)	0.5404	(0.4532 to 0.6444)	<0.0001[a]
Median (weeks)	47.7	22.1			
95% CI	(46.3 to 58.1)	(16.7 to 27.4)			
AT population [N]	375	360			
Events (n [%])	275 (73.3)	247 (68.6)	0.5404	(0.4532 to 0.6444)	<0.0001[a]
Median (weeks)	47.7	22.1			
95% CI	(46.3 to 58.1)	(16.7 to 27.4)			
Time to Tumor Progression					
Core Radiology Assessment					
ITT population [N]	375	375			
Events (n [%])	204 (54.4)	186 (49.6)	0.5332	(0.4345 to 0.6544)	<0.0001
Median (weeks)	49.1	22.4			
95% CI	(46.6 to 59.1)	(21.9 to 31.3)			
AT population [N]	375	360			
Events (n [%])	204 (54.4)	186 (51.7)	0.5332	(0.4345 to 0.6544)	<0.0001
Median (weeks)	49.1	22.4			
95% CI	(46.6 to 59.1)	(21.9 to 31.3)			
Investigators' Assessment					
ITT population [N]	375	375			
Events (n [%])	267 (71.2)	235 (62.7)	0.5454	(0.4558 to 0.6526)	<0.0001
Median (weeks)	49.0	22.3			
95% CI	(46.4 to 59.1)	(17.3 to 31.6)			
AT population [N]	375	360			
Events (n [%])	267 (71.2)	235 (65.3)	0.5454	(0.4558 to 0.6526)	<0.0001
Median (weeks)	49.0	22.3			
95% CI	(46.4 to 59.1)	(17.3 to 31.6)			
Overall Survival					
ITT population [N]	375	375			
Events (n [%])	190 (50.7)	200 (53.3)	0.8209	(0.6730 to 1.0013)	0.0510[a]
Median (weeks)	114.6	94.9			0.0128[b]
95% CI	(100.1 to 142.9)	(77.7 to 117.0)			
AT population [N]	375	360			
Events (n [%])	190 (50.7)	195 (54.2)	0.8324	(0.6816 to 1.0166)	0.0715[a]
Median (weeks)	114.6	95.4			0.0201[b]
95% CI	(100.1 to 142.9)	(77.7 to 117.0)			

a From an unstratified log-rank test.
b From an unstratified Wilcoxon test.

Table S3. Summary of Objective Response Rate (ITT and AT Populations)

Variable	Treatment: Sunitinib n (%)	Treatment: IFN-α n (%)	Treatment Difference (%)	p-value[a]
Core Radiology Assessment				
ITT population [N]	375	375		
ORR	145 (38.7)	29 (7.7)	30.9	<0.001
95% CI[b]	(33.7 to 43.8)	(5.2 to 10.9)	(25.3 to 36.6)	
AT population [N]	375	360		
ORR	145 (38.7)	29 (8.1)	30.6	<0.001
95% CI[b]	(33.7 to 43.8)	(5.5 to 11.4)	(24.9 to 36.3)	
Investigators' Assessment				
ITT population [N]	375	375		
ORR	171 (45.6)	45 (12.0)	33.7	<0.001
95% CI[b]	(40.6 to 50.9)	(8.9 to 15.8)	(27.6 to 39.7)	
AT population [N]	375	360		
ORR	171 (45.6)	45 (12.5)	33.2	<0.001
95% CI[b]	(40.6 to 50.9)	(9.3 to 16.4)	(27.1 to 39.3)	

a From a Pearson χ^2 test.
b Exact method based on binomial distribution for ORR; based on a normal distribution for treatment difference.

The results were consistent when controlling for stratification factors (baseline LDH, ECOG performance status, and prior nephrectomy). The relative risk indicated greater than 5-fold increase in the probability of response with sunitinib as compared to IFN-α based on the core radiology assessment.

On the FACT-G/FKSI questionnaires, completion rates on both arms were >90.0% (based on the number of subjects who completed at least 1 question or for whom a reason for not completion was provided) through Cycle 23, and at least 10 subjects were included on each arm through Cycle 19; compliance was similarly high on the EQ-5D questionnaire. The between-treatment differences in the PRO endpoints over time during the post baseline period with PRO data (from Cycle 1 Day 28 to Cycle 20 Day 28) are summarized in Table S5; the corresponding p values are summarized in Table S6. A score greater than 0 indicated the difference favored sunitinib. The results show that subjects on sunitinib reported statistically significant ($p<0.05$) better outcomes in their kidney disease-related symptoms, FWB, FACT-G, and EQ-VAS than subjects on IFN-α at all assessment time points through Cycle 20. For SWB, PWB, EWB, and weighted health state (as measured by EQ-5D Index), the statistical significance level dropped to below the 0.05 level after Cycle 14, Cycle 13, Cycle 10, and Cycle 8, respectively.

Compared to the pre-established minimum clinically important differences (MIDs) for these endpoints (2 points for FKSI-DRS, 5 points for FACT-G Total, 2 points for PWB, SWB, EWB and FWB, and 3 points for FKSI), the between-treatment differences for kidney cancer related symptoms (FKSI-DRS and FKSI), FACT-G, and FWB were considered clinically meaningful. The EQ-VAS results indicated that sunitinib subjects also had significantly better overall health status.

Table S5. Summary of Between-Treatment Differences (Sunitinib-IFN-α) in the PRO Endpoints Over Time

Assessment Time Point	FKSI-DRS	FACT-G Total	PWB	SWB	EWB	FWB	FKSI	EQ-5D	EQ-VAS
Cycle 1 Day 1	1.913	5.486	1.459	1.214	0.929	1.897	3.165	0.049	4.026
Cycle 1 Day 28	1.935	5.535	1.453	1.216	0.922	1.924	3.205	0.048	4.165
Cycle 2 Day 1	1.948	5.562	1.450	1.217	0.918	1.939	3.228	0.048	4.243
Cycle 2 Day 28	1.970	5.611	1.444	1.220	0.911	1.965	3.268	0.047	4.382
Cycle 3 Day 1	1.983	5.639	1.440	1.221	0.907	1.980	3.291	0.046	4.459
Cycle 3 Day 28	2.005	5.688	1.434	1.224	0.899	2.007	3.331	0.045	4.598
Cycle 4 Day 1	2.018	5.715	1.431	1.225	0.895	2.022	3.354	0.045	4.676
Cycle 4 Day 28	2.040	5.764	1.424	1.228	0.888	2.048	3.395	0.044	4.815
Cycle 5 Day 1	2.053	5.792	1.421	1.229	0.884	2.063	3.417	0.043	4.892
Cycle 5 Day 28	2.075	5.841	1.415	1.232	0.877	2.090	3.458	0.042	5.031
Cycle 6 Day 1	2.088	5.868	1.411	1.233	0.873	2.105	3.480	0.042	5.109
Cycle 6 Day 28	2.110	5.917	1.405	1.236	0.866	2.132	3.521	0.041	5.248
Cycle 7 Day 1	2.123	5.945	1.402	1.237	0.862	2.146	3.543	0.040	5.325
Cycle 7 Day 28	2.146	5.994	1.396	1.240	0.854	2.173	3.584	0.039	5.464
Cycle 8 Day 1	2.158	6.021	1.392	1.241	0.850	2.188	3.606	0.039	5.542
Cycle 8 Day 28	2.181	6.071	1.386	1.244	0.843	2.215	3.647	0.038	5.681
Cycle 9 Day 1	2.193	6.098	1.383	1.245	0.839	2.230	3.669	0.037	5.758
Cycle 9 Day 28	2.216	6.147	1.376	1.248	0.832	2.256	3.710	0.036	5.898
Cycle 10 Day 1	2.228	6.174	1.373	1.249	0.828	2.271	3.733	0.036	5.975
Cycle 10 Day 28	2.251	6.224	1.367	1.251	0.821	2.298	3.773	0.035	6.114
Cycle 11 Day 1	2.263	6.251	1.363	1.253	0.817	2.313	3.796	0.034	6.191
Cycle 11 Day 28	2.286	6.300	1.357	1.255	0.809	2.340	3.836	0.033	6.331
Cycle 12 Day 1	2.298	6.327	1.354	1.257	0.805	2.354	3.859	0.033	6.408
Cycle 12 Day 28	2.321	6.377	1.348	1.259	0.798	2.381	3.899	0.032	6.547
Cycle 13 Day 1	2.333	6.404	1.344	1.261	0.794	2.396	3.922	0.031	6.624
Cycle 13 Day 28	2.356	6.453	1.338	1.263	0.787	2.423	3.962	0.030	6.764
Cycle 14 Day 1	2.369	6.480	1.335	1.265	0.783	2.438	3.985	0.030	6.841
Cycle 14 Day 28	2.391	6.530	1.328	1.267	0.776	2.464	4.026	0.029	6.980
Cycle 15 Day 1	2.404	6.557	1.325	1.269	0.771	2.479	4.048	0.028	7.057
Cycle 15 Day 28	2.426	6.606	1.319	1.271	0.764	2.506	4.089	0.027	7.197
Cycle 16 Day 1	2.439	6.634	1.315	1.273	0.760	2.521	4.111	0.027	7.274
Cycle 16 Day 28	2.461	6.683	1.309	1.275	0.753	2.547	4.152	0.026	7.413
Cycle 17 Day 1	2.474	6.710	1.306	1.276	0.749	2.562	4.174	0.025	7.491
Cycle 17 Day 28	2.496	6.759	1.300	1.279	0.742	2.589	4.215	0.024	7.630
Cycle 18 Day 1	2.509	6.787	1.296	1.280	0.738	2.604	4.237	0.024	7.707
Cycle 18 Day 28	2.531	6.836	1.290	1.283	0.730	2.631	4.278	0.023	7.846
Cycle 19 Day 1	2.544	6.863	1.287	1.284	0.726	2.645	4.300	0.022	7.924
Cycle 19 Day 28	2.566	6.912	1.280	1.287	0.719	2.672	4.341	0.021	8.063
Cycle 20 Day 1	2.579	6.940	1.277	1.288	0.715	2.687	4.364	0.021	8.140
Cycle 20 Day 28	2.602	6.989	1.271	1.291	0.708	2.714	4.404	0.020	8.279

Table S6. Summary of Between-Treatment Differences (p values) in the PRO Endpoints Over Time

Assessment Time Point	FKSI-DRS	FACT-G Total	PWB	SWB	EWB	FWB	FKSI	EQ-5D	EQ-VAS
Cycle 1 Day 1	<.0001	<.0001	<.0001	<.0001	0.0001	<.0001	<.0001	0.0004	<.0001
Cycle 1 Day 28	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	0.0003	<.0001
Cycle 2 Day 1	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	0.0003	<.0001
Cycle 2 Day 28	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	0.0003	<.0001
Cycle 3 Day 1	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	0.0004	<.0001
Cycle 3 Day 28	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	0.0005	<.0001
Cycle 4 Day 1	<.0001	<.0001	<.0001	<.0001	0.0001	<.0001	<.0001	0.0007	<.0001
Cycle 4 Day 28	<.0001	<.0001	<.0001	<.0001	0.0002	<.0001	<.0001	0.0011	<.0001
Cycle 5 Day 1	<.0001	<.0001	<.0001	<.0001	0.0003	<.0001	<.0001	0.0016	<.0001
Cycle 5 Day 28	<.0001	<.0001	<.0001	<.0001	0.0006	<.0001	<.0001	0.0029	<.0001
Cycle 6 Day 1	<.0001	<.0001	<.0001	<.0001	0.0009	<.0001	<.0001	0.0041	<.0001
Cycle 6 Day 28	<.0001	<.0001	<.0001	0.0002	0.0020	<.0001	<.0001	0.0076	<.0001
Cycle 7 Day 1	<.0001	<.0001	0.0001	0.0003	0.0029	<.0001	<.0001	0.0105	<.0001
Cycle 7 Day 28	<.0001	<.0001	0.0003	0.0005	0.0055	<.0001	<.0001	0.0179	<.0001
Cycle 8 Day 1	<.0001	<.0001	0.0005	0.0008	0.0076	<.0001	<.0001	0.0236	0.0001
Cycle 8 Day 28	<.0001	<.0001	0.0012	0.0015	0.0129	<.0001	<.0001	0.0370	0.0002
Cycle 9 Day 1	<.0001	<.0001	0.0018	0.0021	0.0168	<.0001	<.0001	0.0464	0.0003
Cycle 9 Day 28	<.0001	<.0001	0.0035	0.0037	0.0257	<.0001	<.0001	0.0667	0.0004
Cycle 10 Day 1	<.0001	<.0001	0.0049	0.0048	0.0318	<.0001	<.0001	0.0800	0.0006
Cycle 10 Day 28	<.0001	<.0001	0.0084	0.0074	0.0447	<.0001	<.0001	0.1070	0.0009
Cycle 11 Day 1	<.0001	0.0001	0.0110	0.0092	0.0529	0.0001	<.0001	0.1237	0.0011
Cycle 11 Day 28	<.0001	0.0002	0.0168	0.0132	0.0696	0.0003	<.0001	0.1561	0.0015
Cycle 12 Day 1	<.0001	0.0003	0.0208	0.0159	0.0797	0.0004	<.0001	0.1752	0.0018
Cycle 12 Day 28	<.0001	0.0006	0.0293	0.0213	0.0994	0.0007	0.0002	0.2112	0.0025
Cycle 13 Day 1	<.0001	0.0008	0.0348	0.0248	0.1110	0.0009	0.0002	0.2319	0.0029
Cycle 13 Day 28	0.0001	0.0013	0.0459	0.0318	0.1328	0.0014	0.0004	0.2698	0.0037
Cycle 14 Day 1	0.0002	0.0016	0.0528	0.0360	0.1454	0.0017	0.0006	0.2910	0.0042
Cycle 14 Day 28	0.0003	0.0025	0.0663	0.0443	0.1686	0.0025	0.0010	0.3293	0.0053
Cycle 15 Day 1	0.0004	0.0030	0.0744	0.0493	0.1817	0.0030	0.0012	0.3504	0.0059
Cycle 15 Day 28	0.0007	0.0043	0.0898	0.0587	0.2055	0.0042	0.0018	0.3881	0.0072
Cycle 16 Day 1	0.0009	0.0051	0.0988	0.0642	0.2188	0.0049	0.0022	0.4086	0.0079
Cycle 16 Day 28	0.0013	0.0068	0.1156	0.0746	0.2427	0.0064	0.0031	0.4449	0.0093
Cycle 17 Day 1	0.0016	0.0079	0.1252	0.0806	0.2559	0.0073	0.0037	0.4646	0.0101
Cycle 17 Day 28	0.0022	0.0100	0.1429	0.0917	0.2794	0.0091	0.0048	0.4990	0.0117
Cycle 18 Day 1	0.0026	0.0114	0.1529	0.0980	0.2923	0.0103	0.0056	0.5176	0.0126
Cycle 18 Day 28	0.0034	0.0141	0.1711	0.1095	0.3152	0.0125	0.0071	0.5501	0.0144
Cycle 19 Day 1	0.0040	0.0157	0.1813	0.1161	0.3276	0.0138	0.0081	0.5675	0.0153
Cycle 19 Day 28	0.0051	0.0189	0.1998	0.1280	0.3497	0.0164	0.0099	0.5979	0.0172
Cycle 20 Day 1	0.0058	0.0208	0.2100	0.1346	0.3616	0.0179	0.0111	0.6141	0.0182
Cycle 20 Day 28	0.0071	0.0244	0.2283	0.1466	0.3827	0.0208	0.0133	0.6424	0.0201

Pharmacokinetic, Pharmacodynamic, and/or Other Results: Following intermittent dosing of sunitinib on Schedule 4/2, the mean observed C_{trough} (Day 28 of Cycles 1 to 4) for sunitinib, its metabolite, and total drug were within 45.05 to 57.59 ng/mL, 22.11 to 27.35 ng/mL, and 67.15 to 84.94 ng/mL, respectively. Dose-corrected (reference dose: 50 mg) Ctrough values (Day 28 of Cycles 1 to 4) for sunitinib, its metabolite, and total drug were within 54.31 to 64.22 ng/mL, 25.99 to 29.04 ng/mL, and 80.30 to 92.43 ng/mL, respectively. Based on the mean dose-corrected trough values for sunitinib, SU012662, and total drug, steady state was reached within the first cycle and was consistent with the previously

reported pharmacokinetics of sunitinib and SU012662 after dosing on Schedule 4/2 and other schedules in phase 1 and 2 studies of subjects with other solid tumors.

Safety Results: Safety was analyzed in the AT population, which consists of all subjects who received at least 1 dose of study medication with treatment assignments designated according to actual study treatment received. For the 25 subjects who crossed over from IFN-α to treatment with sunitinib, safety data are presented for the pre-crossover period, and adverse events experienced after crossover are summarized separately. On sunitinib, the AT population included all 375 randomized subjects (100.0%), and, on IFN-α, the AT population included 360 of 375 randomized subjects (96.0%), as 15 subjects withdrew consent and discontinued the study before receiving their first dose of study medication. The overall adverse experience is summarized by treatment arm in Table S7.

Table S7. Overall Adverse Event Experience (Number and Percent; AT Population)

Variable	Sunitinib (N=375)	IFN-α (N=360)
Subjects with at least 1 adverse event	372 (99.2)	355 (98.6)
Subjects with at least 1 serious adverse event	170 (45.3)	93 (25.8)
Subjects with at least 1 treatment-related adverse event	358 (95.5)	331 (91.9)
Subjects with at least 1 treatment-related serious adverse event	89 (23.7)	25 (6.9)
Subjects who had adverse event with action taken of drug permanently withdrawn	76 (20.3)	86 (23.9)
Subjects who died on-study	22 (5.9)	20 (5.6)
Treatment-related deaths	1 (0.3)	2 (0.6)

Serious adverse events and treatment-related serious adverse events appeared to be more common on sunitinib. Of note, subjects on sunitinib were on treatment approximately 167% longer on sunitinib vs IFN-α (median duration of treatment was 337 vs 126 days). The most common adverse events (those occurring in ≥10% subjects on either treatment arm) are summarized in Table S8.

Table S8. Summary of the Most Common (≥10% Subjects) Adverse Events by Treatment Arm (AT Population)

	Sunitinib (N = 375)		IFN-α (N = 360)	
Preferred Term	**Number (%) Subjects**	**Number of Events**	**Number (%) Subjects**	**Number of Events**
Any Adverse Events	372 (99.2)	17583	355 (98.6)	5040
Diarrhea	246 (65.6)	1367	76 (21.1)	108
Fatigue	233 (62.1)	1011	202 (56.1)	431
Nausea	216 (57.6)	793	147 (40.8)	226
Dysgeusia	174 (46.4)	460	53 (14.7)	70
Anorexia	154 (41.1)	387	112 (31.1)	151
Vomiting	148 (39.5)	429	62 (17.2)	92
Dyspepsia	128 (34.1)	370	16 (4.4)	19
Hypertension	127 (33.9)	263	13 (3.6)	22
Stomatitis	114 (30.4)	253	12 (3.3)	15
Arthralgia	111 (29.6)	259	69 (19.2)	92
Rash	109 (29.1)	294	39 (10.8)	62
Palmar-plantar erythrodysesthesia syndrome	108 (28.8)	538	3 (0.8)	5
Back pain	105 (28.0)	230	52 (14.4)	78
Pain in extremity	101 (26.9)	308	31 (8.6)	46
Mucosal inflammation	100 (26.7)	275	7 (1.9)	18
Cough	100 (26.7)	157	51 (14.2)	61
Dyspnea	99 (26.4)	168	71 (19.7)	104
Asthenia	96 (25.6)	356	81 (22.5)	172
Skin discoloration	94 (25.1)	211	0 (0.0)	0
Edema peripheral	91 (24.3)	189	17 (4.7)	24
Headache	86 (22.9)	193	69 (19.2)	94
Constipation	85 (22.7)	174	49 (13.6)	59
Dry skin	85 (22.7)	166	26 (7.2)	40
Pyrexia	84 (22.4)	123	134 (37.2)	242
Anemia	81 (21.6)	223	58 (16.1)	112
Epistaxis	80 (21.3)	186	9 (2.5)	10
Hair color changes	75 (20.0)	94	1 (0.3)	1
Thrombocytopenia	72 (19.2)	191	15 (4.2)	28
Neutropenia	70 (18.7)	303	33 (9.2)	77
Abdominal pain	70 (18.7)	115	30 (8.3)	37
Ejection fraction decreased	61 (16.3)	90	19 (5.3)	26
Hypothyroidism	61 (16.3)	75	3 (0.8)	3
Weight decreased	60 (16.0)	147	60 (16.7)	79
Insomnia	57 (15.2)	79	37 (10.3)	48
Oral pain	54 (14.4)	134	2 (0.6)	2
Nasopharyngitis	54 (14.4)	66	8 (2.2)	8
Chills	53 (14.1)	77	111 (30.8)	160
Flatulence	52 (13.9)	106	8 (2.2)	8
Abdominal pain upper	52 (13.9)	97	12 (3.3)	12
Oropharyngeal pain	51 (13.6)	85	9 (2.5)	12
Alopecia	51 (13.6)	54	34 (9.4)	38

continued

Table S8. Summary of the Most Common (≥10% Subjects) Adverse Events by Treatment Arm (AT Population) (continued)

	Sunitinib (N = 375)		IFN-α (N = 360)	
Preferred Term	Number (%) Subjects	Number of Events	Number (%) Subjects	Number of Events
Dry mouth	50 (13.3)	83	27 (7.5)	38
Musculoskeletal pain	50 (13.3)	78	23 (6.4)	28
Chest pain	50 (13.3)	64	24 (6.7)	30
Gastroesophageal reflux disease	47 (12.5)	88	3 (0.8)	3
Myalgia	46 (12.3)	101	68 (18.9)	86
Erythema	46 (12.3)	83	5 (1.4)	6
Decreased appetite	45 (12.0)	83	44 (12.2)	58
Pruritus	44 (11.7)	98	24 (6.7)	45
Dizziness	43 (11.5)	67	50 (13.9)	76
Upper respiratory tract infection	43 (11.5)	58	9 (2.5)	10
Leukopenia	40 (10.7)	136	16 (4.4)	54
Glossodynia	40 (10.7)	80	2 (0.6)	2
Depression	40 (10.7)	55	51 (14.2)	69
Hemorrhoids	38 (10.1)	53	6 (1.7)	6
Influenza like illness	18 (4.8)	19	54 (15.0)	79

The most common treatment-related adverse events are summarized in Table S9. Adverse events leading to treatment discontinuation for >1 subject on either arm are summarized in Table S10.

Twenty-two (5.9%) vs 20 subjects (5.6%) died on treatment or within 28 days of their last dose of study medication. Nineteen deaths (86.4% deaths) vs 18 deaths (90.0% deaths) within 28 days of treatment were due to progressive disease or to events considered to be related to the underlying disease, and 1 death (4.5% deaths) vs 2 deaths (10.0% deaths) were related sunitinib vs IFN-α, respectively. On sunitinib, Subject A6181034-110114-00436, a 69-year-old white male with a 10-year history of MRCC with local recurrence with liver metastases, pleural effusion, and malignant ascites, experienced sudden death of unknown cause on Cycle 1, Day 13, during the sunitinib dosing period. On IFN-α, Subject A6181034-056590-00146, a 79-year-old white male with a 3-month history of MRCC with liver metastases, experienced sudden death due to a suspected cardiac disorder on Cycle 1, Day 10, 3 days after his last treatment with IFN-α. Subject A6181034-068012-00681, a 72-year-old white male with an 8-year history of MRCC with liver, lung, bone, lymph node, and vena caval metastases, experienced a myocardial infarction on Cycle 2, Day 38, 1 day after his last treatment with IFN-α.

Table S9. Summary of the Most Common (≥10% Subjects) Treatment-Related Adverse Events by Treatment Arm (AT Population)

	Sunitinib (N = 375)		IFN-α (N = 360)	
Preferred Term	**Number (%) Subjects**	**Number of Events**	**Number (%) Subjects**	**Number of Events**
Any treatment-related adverse events	358 (95.5)	12891	331 (91.9)	3290
Diarrhea	229 (61.1)	1257	49 (13.6)	66
Fatigue	206 (54.9)	917	186 (51.7)	396
Nausea	195 (52.0)	695	124 (34.4)	194
Dysgeusia	172 (45.9)	451	52 (14.4)	69
Anorexia	129 (34.4)	328	101 (28.1)	136
Dyspepsia	118 (31.5)	333	13 (3.6)	15
Vomiting	117 (31.2)	336	41 (11.4)	59
Hypertension	113 (30.1)	234	6 (1.7)	11
Stomatitis	110 (29.3)	242	10 (2.8)	13
Palmar-plantar erythrodysesthesia syndrome	108 (28.8)	536	2 (0.6)	3
Mucosal inflammation	98 (26.1)	270	6 (1.7)	17
Rash	91 (24.3)	249	25 (6.9)	39
Skin discoloration	89 (23.7)	204	0 (0.0)	0
Dry skin	79 (21.1)	155	19 (5.3)	33
Asthenia	76 (20.3)	301	67 (18.6)	142
Hair color changes	75 (20.0)	93	1 (0.3)	1
Neutropenia	70 (18.7)	301	31 (8.6)	65
Thrombocytopenia	69 (18.4)	181	13 (3.6)	25
Epistaxis	67 (17.9)	153	5 (1.4)	5
Pain in extremity	66 (17.6)	226	11 (3.1)	14
Hypothyroidism	55 (14.7)	68	2 (0.6)	2
Headache	53 (14.1)	110	55 (15.3)	69
Anemia	51 (13.6)	139	31 (8.6)	59
Ejection fraction decreased	51 (13.6)	77	11 (3.1)	16
Oral pain	50 (13.3)	129	1 (0.3)	1
Edema peripheral	48 (12.8)	91	4 (1.1)	9
Weight decreased	46 (12.3)	121	50 (13.9)	65
Alopecia	46 (12.3)	49	31 (8.6)	35
Dry mouth	45 (12.0)	77	24 (6.7)	33
Constipation	44 (11.7)	82	14 (3.9)	17
Flatulence	43 (11.5)	94	6 (1.7)	6
Arthralgia	43 (11.5)	80	49 (13.6)	62
Abdominal pain	42 (11.2)	64	11 (3.1)	13
Leukopenia	40 (10.7)	127	14 (3.9)	49
Gastroesophageal reflux disease	39 (10.4)	78	2 (0.6)	2
Erythema	39 (10.4)	71	3 (0.8)	4
Dyspnea	39 (10.4)	63	30 (8.3)	46
Myalgia	32 (8.5)	65	60 (16.7)	74
Influenza like illness	9 (2.4)	9	54 (15.0)	79
Decreased appetite	37 (9.9)	67	38 (10.6)	52
Pyrexia	31 (8.3)	41	125 (34.7)	220
Chills	28 (7.5)	40	105 (29.2)	148

Table S10. Summary of Adverse Events Leading to Discontinuation for >1 Subject on Either Arm (AT Population)

	Sunitinib (N = 375)		IFN-α (N = 360)	
Preferred Term	**Number (%) Subjects**	**Number of Events**	**Number (%) Subjects**	**Number of Events**
Any adverse event leading to discontinuation	76 (20.3)	120	86 (23.9)	138
Asthenia	10 (2.7)	10	10 (2.8)	10
Disease progression	7 (1.9)	7	7 (1.9)	7
Fatigue	5 (1.3)	5	26 (7.2)	26
Diarrhea	5 (1.3)	5	1 (0.3)	1
Nausea	3 (0.8)	3	4 (1.1)	5
Myocardial infarction	3 (0.8)	3	2 (0.6)	2
Hypothyroidism	3 (0.8)	3	0 (0.0)	0
Hypertension	3 (0.8)	3	0 (0.0)	0
Dyspnea	2 (0.5)	2	6 (1.7)	6
Anemia	2 (0.5)	2	4 (1.1)	4
Vomiting	2 (0.5)	2	2 (0.6)	3
Neutropenia	2 (0.5)	2	1 (0.3)	1
Blood creatinine increased	2 (0.5)	2	1 (0.3)	1
Anorexia	2 (0.5)	2	1 (0.3)	1
Decreased appetite	2 (0.5)	2	1 (0.3)	1
Back pain	2 (0.5)	2	1 (0.3)	1
Platelet count decreased	2 (0.5)	2	0 (0.0)	0
Renal failure acute	2 (0.5)	2	0 (0.0)	0
Pulmonary embolism	2 (0.5)	2	0 (0.0)	0
Deep vein thrombosis	2 (0.5)	2	0 (0.0)	0
Confusional state	1 (0.3)	1	2 (0.6)	2
Ejection fraction decreased	1 (0.3)	1	2 (0.6)	2
General physical health deterioration	1 (0.3)	1	2 (0.6)	2
Pleural effusion	1 (0.3)	1	2 (0.6)	2
Depression	0 (0.0)	0	6 (1.7)	6
Hyperthyroidism	0 (0.0)	0	2 (0.6)	2
Weight decreased	0 (0.0)	0	2 (0.6)	2
Cognitive disorder	0 (0.0)	0	2 (0.6)	2
Pruritus	0 (0.0)	0	2 (0.6)	2

Treatment-related serious adverse events are summarized in Table S12.

Table S11. Summary of Treatment-Related Serious Adverse Events (AT Population)

	Sunitinib (N = 375)		IFN-α (N = 360)	
	Subjects	Events	Subjects	Events
Preferred Term	**n (%)**	**n**	**n (%)**	**n**
Any Treatment—Related Serious Adverse Events	89 (23.7)	192	25 (6.9)	38
Anemia	9 (2.4)	11	5 (1.4)	5
Asthenia	9 (2.4)	11	2 (0.6)	2
Hypothyroidism	8 (2.1)	9	0 (0.0)	0
Vomiting	7 (1.9)	8	1 (0.3)	1
Hypertension	7 (1.9)	7	0 (0.0)	0
Dehydration	6 (1.6)	7	3 (0.8)	4
Nausea	6 (1.6)	9	1 (0.3)	1
Thrombocytopenia	4 (1.1)	4	0 (0.0)	0
Abdominal pain	4 (1.1)	4	0 (0.0)	0
Hyponatremia	4 (1.1)	7	0 (0.0)	0
Febrile neutropenia	3 (0.8)	3	0 (0.0)	0
Diarrhea	3 (0.8)	3	0 (0.0)	0
Anorexia	3 (0.8)	3	0 (0.0)	0
Renal failure acute	3 (0.8)	3	0 (0.0)	0
Pleural effusion	3 (0.8)	3	0 (0.0)	0
Deep vein thrombosis	3 (0.8)	3	0 (0.0)	0
Myocardial infarction	2 (0.5)	2	2 (0.6)	2
Chest pain	2 (0.5)	2	1 (0.3)	1
Pulmonary embolism	2 (0.5)	2	1 (0.3)	1
Atrial fibrillation	2 (0.5)	2	0 (0.0)	0
Dysphagia	2 (0.5)	2	0 (0.0)	0
Gastrointestinal hemorrhage	2 (0.5)	2	0 (0.0)	0
Intestinal perforation	2 (0.5)	2	0 (0.0)	0
Pancreatitis	2 (0.5)	2	0 (0.0)	0
Stomatitis	2 (0.5)	2	0 (0.0)	0
Condition aggravated	2 (0.5)	2	0 (0.0)	0
Pyrexia	2 (0.5)	2	0 (0.0)	0
Ejection fraction decreased	2 (0.5)	2	0 (0.0)	0
Platelet count decreased	2 (0.5)	2	0 (0.0)	0
Hematuria	2 (0.5)	2	0 (0.0)	0
Renal failure	2 (0.5)	2	0 (0.0)	0
Epistaxis	2 (0.5)	2	0 (0.0)	0
Mental status changes	1 (0.3)	2	1 (0.3)	1
Dyspnea	1 (0.3)	1	1 (0.3)	1
Idiopathic thrombocytopenic purpura	1 (0.3)	1	0 (0.0)	0
Leukopenia	1 (0.3)	1	0 (0.0)	0
Neutropenia	1 (0.3)	1	0 (0.0)	0
Thrombotic thrombocytopenic purpura	1 (0.3)	1	0 (0.0)	0
Myocardial ischemia	1 (0.3)	1	0 (0.0)	0
Palpitations	1 (0.3)	1	0 (0.0)	0
Tachycardia	1 (0.3)	1	0 (0.0)	0
Deafness	1 (0.3)	1	0 (0.0)	0
Anal fistula	1 (0.3)	2	0 (0.0)	0

continued

Table S12. Summary of Treatment-Related Serious Adverse Events (AT Population) (continued)

	Sunitinib (N = 375)		IFN-α (N = 360)	
	Subjects	Events	Subjects	Events
Preferred Term	n (%)	n	n (%)	n
Ascites	1 (0.3)	1	0 (0.0)	0
Gastric hemorrhage	1 (0.3)	1	0 (0.0)	0
Gastric ulcer hemorrhage	1 (0.3)	1	0 (0.0)	0
Gastrointestinal obstruction	1 (0.3)	1	0 (0.0)	0
Glossodynia	1 (0.3)	1	0 (0.0)	0
Hematochezia	1 (0.3)	1	0 (0.0)	0
Hemorrhoidal hemorrhage	1 (0.3)	2	0 (0.0)	0
Mouth ulceration	1 (0.3)	1	0 (0.0)	0
Rectal hemorrhage	1 (0.3)	1	0 (0.0)	0
Tongue edema	1 (0.3)	1	0 (0.0)	0
Face edema	1 (0.3)	1	0 (0.0)	0
General physical health deterioration	1 (0.3)	1	0 (0.0)	0
Edema peripheral	1 (0.3)	2	0 (0.0)	0
Sudden death	1 (0.3)	1	0 (0.0)	0
Cholecystitis acute	1 (0.3)	1	0 (0.0)	0
Cholelithiasis	1 (0.3)	1	0 (0.0)	0
Arthritis bacterial	1 (0.3)	1	0 (0.0)	0
Cellulitis	1 (0.3)	1	0 (0.0)	0
Fungal infection	1 (0.3)	1	0 (0.0)	0
Herpes zoster	1 (0.3)	1	0 (0.0)	0
Localized infection	1 (0.3)	1	0 (0.0)	0
Oesophageal candidiasis	1 (0.3)	1	0 (0.0)	0
Blood bilirubin increased	1 (0.3)	1	0 (0.0)	0
Blood creatine phosphokinase increased	1 (0.3)	1	0 (0.0)	0
Electrocardiogram change	1 (0.3)	1	0 (0.0)	0
Hemoglobin decreased	1 (0.3)	1	0 (0.0)	0
Back pain	1 (0.3)	1	0 (0.0)	0
Cerebellar syndrome	1 (0.3)	1	0 (0.0)	0
Cerebral hematoma	1 (0.3)	1	0 (0.0)	0
Convulsion	1 (0.3)	1	0 (0.0)	0
Hemiparesis	1 (0.3)	1	0 (0.0)	0
Incoherent	1 (0.3)	1	0 (0.0)	0
Monoparesis	1 (0.3)	2	0 (0.0)	0
Peripheral sensory neuropathy	1 (0.3)	1	0 (0.0)	0
Reversible posterior leukoencephalopathy syndrome	1 (0.3)	1	0 (0.0)	0
Delirium	1 (0.3)	1	0 (0.0)	0
Nephrotic syndrome	1 (0.3)	1	0 (0.0)	0
Urinary bladder hemorrhage	1 (0.3)	1	0 (0.0)	0
Uterine hemorrhage	1 (0.3)	1	0 (0.0)	0
Vaginal hemorrhage	1 (0.3)	1	0 (0.0)	0
Oropharyngeal pain	1 (0.3)	1	0 (0.0)	0
Dermatitis	1 (0.3)	1	0 (0.0)	0
Diabetic ulcer	1 (0.3)	1	0 (0.0)	0
Palmar—plantar erythrodysesthesia syndrome	1 (0.3)	1	0 (0.0)	0

continued

Table S12. Summary of Treatment-Related Serious Adverse Events (AT Population) (continued)

	Sunitinib (N = 375)		IFN-α (N = 360)	
	Subjects	Events	Subjects	Events
Preferred Term	n (%)	n	n (%)	n
Rash	1 (0.3)	1	0 (0.0)	0
Stevens—Johnson syndrome	1 (0.3)	1	0 (0.0)	0
Malignant hypertension	1 (0.3)	1	0 (0.0)	0
Phlebitis	1 (0.3)	1	0 (0.0)	0
Superior vena caval occlusion	1 (0.3)	1	0 (0.0)	0
Fatigue	0 (0.0)	0	4 (1.1)	4
Performance status decreased	0 (0.0)	0	2 (0.6)	2
Cardiac disorder	0 (0.0)	0	1 (0.3)	1
Pericardial effusion	0 (0.0)	0	1 (0.3)	1
Hyperthyroidism	0 (0.0)	0	1 (0.3)	1
Dry mouth	0 (0.0)	0	1 (0.3)	1
Upper gastrointestinal hemorrhage	0 (0.0)	0	1 (0.3)	2
Pneumonia	0 (0.0)	0	1 (0.3)	1
Diabetes mellitus	0 (0.0)	0	1 (0.3)	1
Hyperkalemia	0 (0.0)	0	1 (0.3)	1
Dizziness	0 (0.0)	0	1 (0.3)	2
Depression	0 (0.0)	0	1 (0.3)	1
Pulmonary edema	0 (0.0)	0	1 (0.3)	1

Hematology variables that appeared to indicate a decline from baseline to the end of Cycle 1 are summarized in Table S13. For all these measures, there did not appear to be a continued mean change during additional cycles beyond Cycle 1. In general, there appeared to be a greater frequency of grade 3/4 abnormalities of thrombocytopenia (35 subjects, 9.6%, vs 2 subjects, 0.6%, on sunitinib vs IFN-α, respectively) and neutropenia (65 subjects, 17.6%, vs 31 subjects (8.6%) on sunitinib.

Table S13. Mean (standard deviation) Change from Baseline to the End of Cycle 1 for Selected Hematology Variables (AT Population)

	Sunitinib (N = 375)		IFN-α (N = 360)	
Variable	Baseline	Cycle 1 Day 28	Baseline	Cycle 1 Day 28
ANC (10^9/L)	5.01 (2.127)	2.41 (1.116)	5.1 (2.057)	3.27 (2.401)
Basophils (10^9/L)	0.03 (0.026)	0.02 (0.018)	0.03 (0.024)	0.02 (0.020)
Eosinophils (10^9/L)	0.20 (0.168)	0.17 (0.148)	0.20 (0.166)	0.07 (0.096)
Lymphocytes (10^9/L)	1.65 (0.668)	1.43 (0.684)	1.65 (0.714)	1.29 (0.641)
Monocytes (10^9/L)	0.51 (0.240)	0.23 (0.129)	0.52 (0.240)	0.47 (0.231)
Neutrophils (bands; 10^9/L)	0.35 (0.279)	0.19 (0.185)	0.28 (0.167)	0.35 (0.341)
Platelets (10^9/L)	304.7 (118.5)	171.9 (84.1)	317.1 (140.9)	254.7 (136.8)
WBC (10^9/L)	7.4 (2.42)	4.3 (1.45)	7.5 (2.32)	5.2 (2.71)

On sunitinib, there was a general increase from baseline to the end of Cycle 1 in liver function tests (AST, ALT, alkaline phosphatase, LDH, indirect bilirubin, and total bilirubin). Mean values for these analytes tended to return to baseline levels during the 2-week off-treatment period at the end of each cycle but to increase again during the treatment period of the subsequent cycle; a similar pattern was observed for creatine kinase, creatinine, and

lipase. For all these analytes, there did not appear to be a cumulative increase across multiple dosing cycles. On IFN-α, there was also an increase from baseline in ALT and AST, but the changes for alkaline phosphatase and LDH were less pronounced on IFN-α than on sunitinib. ALT continued to increase after Cycle 1 on IFN-α, reaching higher levels than sunitinib before reaching a plateau. Of note, 26.4% subjects on sunitinib and 24.0% subjects on IFN-α had liver metastases at baseline. There was little evidence of an increased frequency of shifts from grade 2 or less to grade 3 or greater for any serum chemistry variable during all cycles combined or Cycle 1 only with the exceptions of amylase (21 [5.7%] vs 10 subjects [2.8%] on sunitinib vs IFN-α, respectively), lipase (65 [17.6%] vs 25 subjects [7.1%]), and hyperuricemia (45 [12.1%] vs 19 subjects [5.3%]).

The safety experience during crossover (ie, after switching to treatment with sunitinib for 25 subjects who began treatment with IFN-α) was similar to that on sunitinib during the comparative portion of the study. All crossover subjects experienced adverse events; the most common adverse events were fatigue (13 subjects, 52.0%); hypertension (11 subjects, 44.0%); diarrhea and palmar-plantar erythrodysesthesia syndrome (each 9 subjects, 36.0%); cough and nausea (each 7 subjects, 28.0%); dysgeusia, dyspepsia, mucosal inflammation, rash, and vomiting (each 6 subjects, 24.0%); abdominal pain, anorexia, and dyspnea (each 5 subjects, 20.0%); asthenia, back pain, bone pain, flatulence, hypothyroidism, and insomnia (each 4 subjects, 16.0%); and abdominal pain upper, anemia, arthralgia, constipation, disease progression, ejection fraction decreased, epistaxis, hair color changes, headache, muscle spasms, neutropenia, stomatitis, and weight decreased (each 3 subjects, 12.0%).

Conclusion(s): Sunitinib treatment resulted in a statistically significant, robust, and clinically meaningful improvement in PFS, as compared to IFN-α, in the first-line treatment of subjects with MRCC. The median PFS on sunitinib was more than double that on IFN-α (48.3 weeks vs 22.1 weeks sunitinib vs IFN-α, respectively; hazard ratio: 0.5268, $p < 0.0001$).

Sunitinib resulted in a clinically and statistically significant increase in TTP in subjects with MRCC as compared to IFN-α (49.1 vs 22.4 weeks; hazard ratio: 0.5332, 95% CI: 0.4345 to 0.6544; $p < 0.0001$).

Sunitinib resulted in a clinically and statistically significant increase in ORR in subjects with MRCC as compared to IFN-α. ORR on sunitinib was 38.7%, as compared to 7.7% on IFN-α (treatment difference: 30.9%, 95% CI: 25.3 to 36.6%; $p < 0.001$).

Sunitinib treatment was associated with longer survival compared to IFN-α (114.6 vs 94.9 weeks, respectively; $p = 0.0510$). The difference in the median OS did not reach statistical significance with the unstratified log-rank test; however, when adjusted according to stratification factors, using the Wilcoxon test, fitted with a Cox proportional hazards model and analyzed by other exploratory approaches designed to reduce potential bias introduced by post-study cancer treatment, statistical significance was observed ($p < 0.050$ in all analyses).

Sunitinib resulted in a statistically significant, clinically meaningful, and long lasting improvement in patient reported outcomes as compared to IFN-α and as measured by the validated tools FKSI, FACT-G, and EQ-5D.

The adverse events reported in sunitinib-treated subjects were tolerable and manageable by dosing interruption, dose reduction, and/or standard medical therapy.

Steady state sunitinib and SU012662 levels were reached within the first cycle of dosing on Schedule 4/2 in MRCC subjects without disproportionate accumulation of sunitinib and SU012662 throughout the study.