These results are supplied for informational purposes only.
Prescribing decisions should be made based on the approved package insert.

PROPRIETARY DRUG NAME®/GENERIC DRUG NAME: Torisel® / Temsirolimus

PROTOCOL NO: 3066K1-404 (B1771003)

PROTOCOL TITLE: A Randomized Trial of Temsirolimus Versus Sorafenib as Second-Line Therapy in Patients With Advanced Renal Cell Carcinoma who Have Failed First-Line Sunitinib Therapy

Study Centers: A total of 104 centers took part in the study and randomized subjects; 6 each in Argentina, Italy and Australia, 1 each in Austria, Chile, Denmark, Hungary and Singapore, 10 in Canada, 2 each in Finland, Sweden and Hong Kong, 16 in France, 7 each in Germany and Spain, 4 in the Republic of Korea, 3 each in Netherlands and Switzerland, 5 in the United Kingdom (UK) and 20 in the United States (USA).

Study Initiation Date, Primary Completion Date and Final Completion Date:
Study Initiation Date: 19 September 2007 (First Subject First Visit)
Primary Completion Date: 31 January 2012 (Final data collection date for primary outcome measure) and
Final Completion Date: 04 January 2013 (Last Subject Last Visit)

Phase of Development: Phase 3

Study Objectives:

Primary Objectives:

- To compare the safety and tolerability of temsirolimus and sorafenib when used as single agents in the second-line setting in subjects with advanced renal cell carcinoma (RCC) who have failed prior first-line treatment with sunitinib due to progressive disease (PD).

- To compare the efficacy, as measured by progression free survival (PFS) (determined by centralized independent assessment), of temsirolimus and sorafenib when used as single agents in the second-line setting in subjects with advanced RCC who have failed prior first-line treatment with sunitinib.

Secondary Objectives:

- To examine additional efficacy endpoints including:
    - PFS by investigator assessment.

- Response rate (complete response [CR] and partial response [PR] by Response Evaluation Criteria in Solid Tumors [RECIST] criteria) by independent assessment.
- Overall survival (OS).
- Proportion of subjects with PFS at 12, 24 and 36 weeks by independent assessment.
- Duration of response.

Study Design: This was an international, randomized, open-label, outpatient, multicenter study. Subjects were assigned in a 1:1 ratio to 1 of 2 treatment arms composed of temsirolimus or sorafenib. Subjects were stratified by prior nephrectomy status (yes vs [versus] no), duration of sunitinib therapy (≤180 days vs >180 days), tumor histology (clear cell vs nonclear cell), and Memorial Sloan Kettering Cancer Center (MSKCC) prognostic group (favorable, intermediate, or poor).

Study treatments were administered in 6-week cycles. Temsirolimus (25 mg) was administered by intravenous (IV) infusion once weekly. Sorafenib 400 mg was administered orally twice daily (BID). In the event of toxicity, doses of either study treatment could have been reduced. Subjects continued to receive study treatment until disease progression, unacceptable toxicity, withdrawal of consent, or for a maximum duration of 24 months.

This study was designed to detect a 33% improvement in median PFS with a target enrollment of 480 subjects. Final analysis occurred once 380 PFS events were reported. Efficacy was evaluated in accordance with RECIST criteria through computed tomography scans of the chest, abdomen, and pelvis performed at Screening, Day 1 of Cycle 1, and every 6 weeks on treatment. Safety was monitored throughout the study by an independent data safety monitoring board (DSMB) at regular intervals and DSMB reviewed the final efficacy data.

The schedule of activities is presented in Table 1.

Table 1. Schedule of Activities

Procedure	Screening[a]	One 6–Week Cycle (±2-Day Variance was Allowed With the Exception of Tumor Assessments Which was ± 7 Days)[b]						End of Treatment Visit[c]	Follow-Up Visit[d]	Long-Term Follow-Up[e]
	≤28 Days Before Randomization	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6			
Informed consent[f]	X									
Inclusion and exclusion criteria	X									
Demographic data	X									
Medical and oncology history[g]	X									
Prior and current medications[h]	X	X	X[h]	X	X[h]	X	X[h]	X	X	
Prior and current nonpharmacologic treatments[h]	X	X	X[h]	X	X[h]	X	X[h]	X		
Chest x-ray	X							X		
Tumor site assessments: CT scan (chest, abdomen, pelvis)[i]	X	X[i]						X		
Bone scan[j]	X							X		
CT (or MRI)of the brain[k]	X									
ECG[l]	X	X[l]						X[l]	X[l]	
ECHO or MUGA	X							X		
PFT and O_2 saturation by pulse oximetry[m]	X							X		
Routine urinalysis[n]	X							X		
Serum β-HCG[o]	X									
HbA1c[p]	X	X[p]						X		
CBC with differential[q]	X	X		X		X		X		
Fasting chemistry and electrolytes[r]	X	X[r]		X		X		X[r]	X[r]	
Coagulation[s]	X	X						X		
TSH, uric acid, fasting amylase and lipase[t]	X							X		
Complete physical examination[u]	X	X						X		
Brief physical examination[v]				X		X			X	
AE assessment by qualified healthcare professional[w]	X	X	X[w]	X	X[w]	X	X[w]	X	X[w]	
ECOG performance status[x]	X	X						X		

Table 1. Schedule of Activities

Procedure	Screening[a]	One 6–Week Cycle (±2-Day Variance was Allowed With the Exception of Tumor Assessments Which was ± 7 Days)[b]						End of Treatment Visit[c]	Follow-Up Visit[d]	Long-Term Follow-Up[e]
	≤28 Days Before Randomization	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6			
Vital signs and weight[y]	X	X		X		X		X		
Study treatment administration or dispensing/drug accountability[z]		X	X	X	X	X	X	X		
Post therapy survival status										X

AE = adverse event; AST = aspartate aminotransferase; ALT = alanine aminotransferase; BID = twice daily; BUN = blood urea nitrogen; β-HCG = beta-human chorionic gonadotropin; CNS = central nervous system; CR = complete response; CT = computerized tomography; CBC = complete blood count; DLCO = diffusing capacity of carbon monoxide; ECG = electrocardiogram; ECHO = echocardiogram; ECOG=Eastern Cooperative Oncology Group; FVC = forced vital capacity; FEV1 = forced expiratory volume in 1 second; HEENT = head, ears, eyes, nose, and throat; HbA1C = glycosylated hemoglobin; INR = international normalized ratio; IV = intravenous; LDH = lactate dehydrogenase; MRI = magnetic resonance imaging; MUGA = multiple-gated acquisition; O2 = oxygen; OS = overall survival; PFT = pulmonary function test; PO =by mouth; PR = partial respons; PT = prothrombin time; PTT = partial thromboplastin time; QT = time from electrocardiogram Q wave to the end of the T wave corresponding to electrical systole; QTc = QT corrected for heart rate; RBC = red blood cell; RECIST = response evaluation criteria in solid tumors; SAE = serious adverse event; TSH = thyroid stimulating hormone; TLC = total lung capacity; WBC = white blood cell.

a. Screening evaluations were to be completed within 28 days before randomization, unless otherwise noted. Informed consent could be signed at any time prior to performance of study-specific procedures. AE collection started with signing of the informed consent. Serum pregnancy test was to be performed within 7 days of randomization. Results from CT scans acquired before study participation but within 28 days before randomization could be used as the Screening evaluation as long as digital data or original films were available to be submitted for central independent tumor evaluation, and the subject consented to sharing those results during the consent process.

b. Visit window was relative to first dose of study treatment. If a window/variance was utilized, the subject was to return to their original visit/procedure/dispensing schedule.

c. The end of treatment visit was to occur on the day treatment ended or up to 7 days after the last dose of study treatment. Procedures to be conducted at the end of treatment visit were only required if they were not performed within the previous week. The end of treatment ECG must have been completed on the same day as the fasting chemistry for subjects on the temsirolimus arm. Subjects who already had documented objective disease progression did not need to have scans repeated at the end of treatment visit. Per RECIST to be assigned a status of PR or CR, changes in tumor measurements must have been confirmed by repeat assessments to be performed no less than 4 weeks after the criteria for response were first met.

d. The follow-up visit was to occur 15 to 28 days after the last dose of study treatment. AE information, including SAEs were only to be collected for the first 15 days of the post therapy follow-up period.

e. To assess OS, subject survival status was recorded every 3 months after the follow-up visit until death or notification by the Sponsor that the overall study was complete. The long-term survival status could be documented by telephone interview.

f. Informed consent could be signed at any time before study-specific procedures were conducted.

Table 1. Schedule of Activities

Procedure	Screening[a]	One 6–Week Cycle (±2-Day Variance was Allowed With the Exception of Tumor Assessments Which was ± 7 Days)[b]						End of Treatment Visit[c]	Follow-Up Visit[d]	Long-Term Follow-Up[e]
	≤28 Days Before Randomization	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6			

g. Oncology and medical history were to include detailed assessments of pulmonary and cardiac medical history, and personal and family history of diabetes mellitus.

h. Prior and current medications and current nonpharmacologic treatments were reviewed every week. Subjects on the sorafenib arm had these reviewed at visit Weeks 1, 3, and 5 and via telephone on Weeks 2, 4, and 6 of each cycle (may be done in-person if preferred).

i. The Cycle 1, Week 1, and Day 1 CT scans were not required if the Screening scans were performed within 14 days prior to randomization. CT scan with contrast of chest, abdomen, and pelvis were to be performed within 28 days before randomization and Day 1 of the first week of every cycle as part of routine tumor assessments for efficacy evaluation. Subjects in the temsirolimus arm were to have the evaluation before infusion. To provide time for the completion of tumor evaluations, a variance of ± 7 days was allowed at Day 1 of each cycle. Subjects with a contraindication to IV contrast (i.e, contrast sensitivity or renal insufficiency) may have had an MRI of the abdomen and pelvis instead of a CT. For chest, a noncontrast CT was to be utilized for subjects with contraindication to IV contrast, as this provided the highest sensitivity and specificity for pulmonary lesions and mediastinal disease. Digital scan data, (or original films if digital data could not be submitted), were to be sent for central independent review. Results from CT scans acquired before study participation but within 28 days before randomization could be used as the Screening evaluation as long as digital data or original films were available to be submitted to the central independent tumor evaluation vendor and the subject consented to sharing those results during the consent process.

j. Radionuclide bone scans, and plain films of any bone scan abnormalities were to be performed within 28 days before randomization and at the discretion of the investigator during the treatment period, unless a nontarget bone lesion was identified at Screening. These bone lesions identified at Screening must have been followed according to RECIST. Bone scans were to be performed at the end of treatment visit for all subjects if not performed within 4 weeks before discontinuation of study treatment. Digital scan data and/or original films were to be submitted for central independent review. Results from bone scans and bone plain films acquired before study participation but within 28 days before randomization could be used as the Screening evaluation as long as digital data and/or original films were available to be submitted for central independent tumor evaluation, and the subject consented to sharing those results during the consent process. Bone-only lesions could only be followed as nontarget lesions.

k. CT or MRI of the brain with contrast (to rule out CNS malignancy) must have been performed within 28 days before randomization. Results from CT scans acquired before study participation but within 28 days before randomization could be used as the Screening evaluation as long as digital data or original films were available to be submitted for central independent tumor evaluation, and the subject consented to sharing those results during the consent process. Brain imaging at Screening was not to be submitted for central radiographic review unless subsequent imaging documented the development of new brain metastasis, in which case, both the scan documenting progression and the Screening scan were to be submitted for central radiographic review.

l. All subjects (sorafenib and temsirolimus arms) had an ECG performed at Screening and the end of treatment visits. In addition, subjects randomized to the temsirolimus arm were to have an ECG performed before the first temsirolimus infusion and within 1 hour after the completion of the first temsirolimus infusion. The fasting chemistry, specifically potassium, calcium, and magnesium must have been done on the same day as protocol-required ECGs for the temsirolimus arm on Cycle 1, Day 1, end of treatment, and at the follow-up visit if indicated (if QTc prolongation was evident at the end of treatment a repeat ECG was conducted at the follow-up visit). Fasting chemistry was to be performed prior to temsirolimus administration on Day 1. All ECGs were to be

Table 1. Schedule of Activities

Procedure	Screening[a]	One 6–Week Cycle (±2-Day Variance was Allowed With the Exception of Tumor Assessments Which was ± 7 Days)[b]						End of Treatment Visit[c]	Follow-Up Visit[d]	Long-Term Follow-Up[e]
	≤28 Days Before Randomization	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6			

submitted for central independent review.

m. PFT included: FEV1, FVC, TLC, and DLCO measurements (actual and predicted) within 28 days of randomization.

n. Routine urinalysis consisted of: specific gravity, pH, protein/albumin, glucose/sugar, ketones/acetone, hemoglobin/blood, nitrites, and leukocyte/esterase.

o. For females of childbearing potential, a negative serum ß-HCG test result must have been obtained within 7 days before randomization.

p. HbA1c was to be collected at Screening, Week 1 of every other cycle (Cycle 2, 4, and 6), and at the end of treatment visit.

q. CBC with differential: WBC count with differential, platelet count, RBC count, hemoglobin, and hematocrit. Note: Cycle 1, Week 1, Day 1 laboratory tests did not have to be repeated if Screening laboratory tests were obtained within 3 days before randomization. After Cycle 3, CBC with differential could be assessed every 3 weeks at Weeks 1 and 4 (rather than every other week), if clinically appropriate in the opinion of the investigator.

r. Fasting chemistry and electrolytes included: Sodium, potassium, chloride, BUN or urea, creatinine, glucose, bicarbonate, calcium, phosphorus, total protein, AST, ALT, albumin, total cholesterol, triglycerides, magnesium, LDH, total bilirubin, and alkaline phosphatase (8 hour minimum fasting required). The fasting chemistry, specifically magnesium, potassium, and calcium must have been performed on the same day as the protocol-specified ECGs for the temsirolimus arm on Cycle 1, Day 1, end of treatment, and at the follow-up visit if indicated. If QTc prolongation was evident at the end of treatment, ECG and fasting chemistry were to be repeated at the follow-up visit. Fasting chemistry was to be performed prior to temsirolimus administration on Day 1. After Cycle 3, fasting chemistry and electrolytes could be assessed every 3 weeks at Weeks 1 and 4 (rather than every other week), if clinically appropriate in the opinion of the investigator.

s. Coagulation studies: PT or INR, or prothrombin activity and PTT were to be performed at Screening, the first week of every cycle, and at the end of treatment visit. Subjects taking concomitant coumarin-type anticoagulants were to be monitored regularly for changes in PT, INR or clinical bleeding episodes.

t. Fasting amylase and lipase required a minimum 8-hour fast.

u. Complete physical examinations were to be performed at Screening, on Day 1 of each cycle (before study treatment infusion for subjects assigned to temsirolimus), and at the end of treatment. The complete physical examinations consisted of evaluation of the following body systems: general appearance, skin, HEENT, heart, lungs, breasts, abdomen, external genitalia, extremities, neurological, back/spinal, and lymph nodes. On Day 1 of each cycle the breasts and external genitalia examinations could be done at the investigator's discretion.

v. The brief physical examinations consisted of an evaluation of a limited group of body systems, including: general appearance, skin, HEENT, heart, lungs, and abdomen.

w. AE assessments by qualified health care professionals were to begin when the subject signed the informed consent and continued weekly throughout the study until the follow-up visit. Subjects on the sorafenib arm were to have the assessment performed at visit Weeks 1, 3, and 5 and via telephone at Weeks 2, 4, and 6 (could be done in-person if preferred). AE information was captured for both arms until 15 days after the last dose of the study treatment.

x. ECOG performance status was evaluated at Screening and on Day 1 of each cycle (subjects on the temsirolimus arm were to have the performance status completed prior to dosing of study treatment), and at the end of treatment visit.

y. Vital signs, height, and weight were to be recorded at Screening. Vital signs and weight were to be recorded at Weeks 1, 3, 5 and at the end of treatment visit.

Table 1. Schedule of Activities

Procedure	Screening[a]	One 6–Week Cycle (±2-Day Variance was Allowed With the Exception of Tumor Assessments Which was ± 7 Days)[b]						End of Treatment Visit[c]	Follow-Up Visit[d]	Long-Term Follow-Up[e]
	≤28 Days Before Randomization	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6			

Subjects on the temsirolimus arm were to have these procedures completed prior to study treatment infusion.

z. Temsirolimus was to be administered weekly as a 30- to 60-minute IV infusion. IV diphenhydramine 25 to 50 mg (or an appropriate dose of a comparable IV antihistamine) was to be administered approximately 30 minutes before each temsirolimus infusion. The first dose of temsirolimus must have been administered within 7 days of randomization. Subjects on the sorafenib arm were to be dispensed the study treatment every 4 weeks or as needed. Sorafenib was to be taken PO, BID. Local prescribing information was referred to for instructions on timing the dose administration in relationship to food intake. The first dose of sorafenib must have been taken within 7 days of randomization. Drug accountability was to be performed prior to administration of temsirolimus or dispensing of sorafenib, and at the end of treatment.

Number of Subjects (Planned and Analyzed): Approximately 480 subjects (240 subjects in each treatment arm) were planned to be enrolled in the study. A total of 512 subjects were randomized, of which 259 were assigned to the temsirolimus and 253 were assigned to sorafenib. Ten subjects in the temsirolimus arm and 1 subject in the sorafenib arm were randomized, but not treated.

Diagnosis and Main Criteria for Inclusion: Male and females, aged 18 years and older with a histologically confirmed diagnosis of metastatic renal cell carcinoma (mRCC) with well documented radiological or clinical PD as judged by the investigator while receiving first-line sunitinib therapy. Subjects required at least 1 cycle of sunitinib therapy (minimum of 4 weeks of continuous therapy). At the time of randomization, at least 2 weeks since prior treatment with sunitinib, palliative radiation therapy, and/or surgery, subjects required at least 1 measurable lesion per RECIST criteria. Lesions previously irradiated or embolized could not be selected as target lesions.

Exclusion criteria included: Metastatic central nervous system from RCC. Subjects who discontinued sutent therapy due specifically to intolerance. Prior systemic therapy for mRCC other than sunitinib. Active ketonuria, secondary to poorly controlled diabetes mellitus.

Study Treatment: Study treatments were administered in 6-week cycles. Temsirolimus (25 mg) was administered by IV infusion over a 30-60 minute period once weekly. Subjects were premedicated with 25-50 mg IV diphenhydramine (or a comparable IV antihistamine) approximately 30 minutes before the temsirolimus infusion. Sorafenib-treated subjects received 400 mg orally BID.

Efficacy Endpoints:

Primary Endpoint:

- PFS by independent assessment.

Secondary Endpoints:

- PFS by investigator assessment.
- Response rate (CR and PR) by RECIST criteria by independent assessment.
- OS.
- Proportion of subjects with PFS at 12, 24 and 36 weeks by independent assessment.
- Duration of response.

Safety Evaluations: Safety evaluations included clinical monitoring, physical examinations, vital signs, 12-lead electrocardiograms (ECGs), echocardiograms (ECHOs) or multiple-gated acquisition (MUGA) scans, pulmonary function tests, pulse oximetry, chest X-rays, concomitant medications, adverse events (AEs), safety laboratory tests, and ECOG performance status.

Statistical Methods:

- Intent-to-Treat (ITT) Population: All subjects who were randomized, with treatment assignment according to initial randomization, regardless of whether subjects received any study treatment or received a different treatment from that to which the subjects were randomized. This was the primary population for evaluating all efficacy endpoints as well as subject characteristics.

- Safety Population: All subjects who received at least 1 dose of study treatment with treatment assignments designated according to actual study treatment received. This population was the primary population for evaluating treatment administration / compliance and treatment safety.

The efficacy data was summarized for the ITT population by the randomized treatment. The safety data was summarized for the safety population.

Analysis of Efficacy Parameters:

Primary Endpoint: The primary analysis of PFS was performed in the ITT population based on independent assessments of tumor response. A stratified log-rank test (2-sided) was used to compare PFS time between the 2 treatment arms with nominal significance level of 0.05. The Kaplan-Meier method was used to obtain the estimates of median PFS with corresponding 95% CI. The hazard ratio and its 95% CI was estimated using Cox proportional hazard model.

The potential influences of baseline characteristics such as age, gender, race, MSKCC risk group on the primary endpoints could have been evaluated, if appropriate. In addition, preplanned subgroup analyses were performed on the primary efficacy endpoint for baseline characteristics of age (<65 years old, ≥65 years old), gender (male, female), race (white, nonwhite), MSKCC risk groups (favorable, intermediate, poor), prior nephrectomy status (yes, no), tumor histology (clear cell, nonclear cell), and duration of prior sunitinib treated (≤180 days, >180 days) were also conducted, but no inferential statistics were calculated. Sensitivity analyses were conducted to evaluate the robustness of the result in the primary analysis.

Secondary Endpoints:

- PFS (investigator assessed): data source for progression was based on investigator assessment. Events in this analysis included treatment withdrawal due to symptomatic deterioration as reported on the treatment conclusion form. Otherwise, censoring/event algorithm was the same as the primary analysis.

- OS: OS was assessed by recording the survival status of each subject. Survival was estimated by the time from randomization until the date of death before cutoff date due to any cause. Subjects without death date were censored at the last date known alive.

- RR: Tumor response was categorized as CR, PR, stable disease (SD), progressive disease (PD), indeterminate; or no postbaseline tumor assessment.
  Objective response rate (ORR) was the proportion of the ITT population who achieved tumor response (confirmed CR or PR) assessed by the independent radiologist during the study. The ORR assessed by investigators was also evaluated as a supportive analysis.

- Proportion of Subjects With PFS at 12, 24, and 36 Weeks: Number and percentage of subjects with PFS at specified visit, assessed by investigator and independent assessor, was summarized by treatment group.

- Duration of Response: For subjects with CR or PR duration of response was estimated by the duration from the first date where the response criteria were met to the event date (PD per independent assessment or death) of PFS endpoint. The analysis was restricted to only those subjects with confirmed CR or PR.

RESULTS:

Subject Disposition and Demography: Subject disposition is presented in Table 2. A total of 512 subjects were randomized: 249 subjects in the temsirolimus arm received ≥1 dose (249/259, 96.1%), and 252 subjects in the sorafenib arm received ≥1 dose (252/253, 99.6%).

Table 2. Overall Summary of Subject Disposition at Primary Study Completion

Number of Subjects	TEMSR (N=259)	SORAF (N=253)	Total (N=512)
	n (%)	n (%)	n (%)
Randomized (ITT population)	259 (100)	253 (100)	512 (100)
Treated (safety population)	249 (96.1)	252 (99.6)	501 (97.9)
On treatment	8 (3.1)	6 (2.4)	14 (2.7)
Discontinued treatment[a]	241 (93.1)	246 (97.2)	487 (95.1)
Disease progression[b]	145 (60.2)	169 (68.7)	314 (64.5)
Adverse event[b]	38 (15.8)	29 (11.8)	67 (13.8)
Symptomatic deterioration[b]	14 (5.8)	12 (4.9)	26 (5.3)
Subject request[b]	15 (6.2)	9 (3.7)	24 (4.9)
Death[b]	11 (4.6)	10 (4.1)	21 (4.3)
Other[b]	9 (3.7)	2 (0.8)	11 (2.3)
Phase completed[b]	3 (1.2)	7 (2.8)	10 (2.1)
Investigator request[b]	5 (2.1)	5 (2.0)	10 (2.1)
Protocol violation[b]	1 (0.4)	2 (0.8)	3 (0.6)
Lost to follow-up[b]	0	1 (0.4)	1 (0.2)
In follow-up	38 (14.7)	64 (25.3)	102 (19.9)
Discontinued study[a]	213 (82.2)	183 (72.3)	396 (77.3)
Death	186 (87.3)	162 (88.5)	348 (87.9)
Subject request	15 (7.0)	13 (7.1)	28 (7.1)
Lost to follow-up	4 (1.9)	5 (2.7)	9 (2.3)
Other	4 (1.9)	0	4 (1.0)
Investigator request	2 (0.9)	1 (0.5)	3 (0.8)
Protocol violation	2 (0.9)	0	2 (0.5)
Missing	0	2 (1.1)	2 (0.5)
Total died[c,d]	187 (72.2)	164 (64.8)	351 (68.6)
Total lost to follow-up[d]	4 (1.5)	5 (2.0)	9 (1.8)

ITT = intent-to-treat; N = number of subjects in the group; n = number of subjects for a specific category; SORAF = sorafenib; TEMSR = temsirolimus.

a. Total discontinued was the sum of individual reasons since they were mutually exclusive by subject.
b. Calculated using the n of subjects treated (safety population).
c. Death information was from the Death page on the case report form.
d. Based on the ITT population.

The most common reasons for discontinuation from treatment and discontinuation from the study were similar in both treatment arms (percentages calculated using the safety population).

At primary study completion 14 subjects were still on-treatment (8 subjects in the temsirolimus arm and 6 subjects in the sorafenib arm), of these, 9 discontinued from treatment due to disease progression, 1 subject discontinued from sorafenib treatment due to an AE, 1 subject discontinued from sorafenib treatment due to subject request and 3 subjects discontinued from treatment due to Sponsor's decision.
At primary study completion 102 subjects were being followed up for survival, of these 2 subjects had discontinued the study therefore, in total 100 subjects followed up for survival. Of the 100 subjects, 9 subjects died, 2 subjects were lost to follow-up, 1 subject discontinued from study due to subject request, and the remaining 88 subjects discontinued from the study due to Sponsor's decision.

Overall subject demographics are presented in Table 3. A majority of subjects were white (66.6%), male (75.2%), and <65 years old (67.0%). A total of 133 subjects (26.0%) were 65 to 74 years old (65 [25.1%] temsirolimus arm; 68 [26.9%] sorafenib arm) and 36 subjects (7.0%) were 75 to 82 years old (20 [7.7%] temsirolimus arm; 16 [6.3%] sorafenib arm). The demographic characteristics were well balanced across the treatment groups overall and across the treatment groups within each age group.

Table 3. Subject Demographics (ITT Population)

Characteristic	TEMSR (N=259)	SORAF (N=253)	Total (N=512)
Age (years)			
N	259	253	512
Mean	59.96	59.74	59.85
Standard deviation	10.20	10.33	10.25
Minimum	19.00	21.00	19.00
Maximum	82.00	80.00	82.00
Median	60.00	61.00	60.00
Age group, n (%)			
<65 years	174 (67.2)	169 (66.8)	343 (67.0)
≥65 years	85 (32.8)	84 (33.2)	169 (33.0)
Sex, n (%)			
Male	193 (74.5)	192 (75.9)	385 (75.2)
Female	66 (25.5)	61 (24.1)	127 (24.8)
Race, n (%)			
Asian	38 (14.7)	50 (19.8)	88 (17.2)
Black or African American	2 (0.8)	0	2 (0.4)
Native Hawaiian or Other Pacific Islander	1 (0.4)	0	1 (0.2)
White	178 (68.7)	163 (64.4)	341 (66.6)
Other	40 (15.4)	40 (15.8)	80 (15.6)
Baseline[a] ECOG score			
0	103 (39.8)	113 (44.7)	216 (42.2)
1	150 (57.9)	139 (54.9)	289 (56.4)
2	3 (1.2)	0	3 (0.6)
3	1 (0.4)	0	1 (0.2)
Not reported	2 (0.8)	1 (0.4)	3 (0.6)

ECOG = Eastern Cooperative Oncology Group; ITT = intent-to-treat; N = number of subjects in the group; n = number of subjects for a specific category; SORAF = sorafenib; TEMSR = temsirolimus.
a. Baseline was defined as nonmissing data that were collected on the date closest to but on or prior to the start of study treatment.

Efficacy Results:

Primary Endpoint Results: The results of the primary PFS analysis based on independent assessments are presented in Table 4.

A total of 389 subjects had PFS events (76.0%; defined as the time from randomization to disease progression or death due to any cause). The median PFS for temsirolimus-treated subjects was 4.28 months with a 95% CI of (4.01 months, 5.43 months) compared with 3.91 months with a 95% CI of (2.80 months, 4.21 months) for sorafenib-treated subjects. The observed hazard ratio was 0.87 with a 95% CI of (0.71, 1.07) and a 2-sided

p=0.1933 stratified by prior nephrectomy status, duration of sunitinib therapy, tumor histology, and MSKCC risk group as randomized.

Table 4. Progression-Free Survival by Independent Assessment (ITT Population)

	TEMSR (N=259)	SORAF (N=253)
Median PFS in months (95% CI)	4.28 (4.01, 5.43)	3.91 (2.80, 4.21)
Hazard ratio[a] (95% CI)	0.87 (0.71, 1.07)	
P-value[b]	0.1933	
Subjects with PFS events (n, %)	195 (75.29)	194 (76.68)
Subjects with PD event (n, %)[c]	168 (86.15)	184 (94.85)
Subjects with death event (n, %)[c]	27 (13.85)	10 (5.15)
Subjects censored (n, %)	64 (24.71)	59 (23.32)
No adequate baseline assessment	1 (0.92)	0
No postbaseline tumor assessments	12 (11.01)	12 (13.04)
Received anticancer therapy	3 (2.75)	11 (11.96)
Missing 2 or more consecutive assessments	0	1 (1.09)
On treatment in follow-up for disease progression	3 (2.75)	2 (2.17)
Off treatment	45 (41.28)	33 (35.87)
Phase completed	2	5
Disease progression[d]	16	13
Adverse event	14	9
Symptomatic deterioration	4	0
Subject request	4	4
Investigator request	0	2
Protocol violation	1	0
Other	4	0

Stratification factors from randomization included: nephrectomy status; duration of response to sunitinib therapy (≤180 days vs >180 days); tumor histology (clear cell vs nonclear cell); and MSKCC - Memorial Sloan Kettering Cancer Center (favorable, intermediate, or poor).
CI = confidence interval; ITT = intent-to-treat; N = number of subjects in the group; n = number of subjects for a specific category; PD = progressive disease; PFS = progression-free survival; SORAF = sorafenib; TEMSR = temsirolimus; vs = versus.

a. Compared with sorafenib based on stratified Cox proportional hazard model, where hazard ratio <1 mean temsirolimus was at lower risk.
b. Compared with sorafenib based on stratified log-rank test.
c. Percentages calculated based on number of subjects with PFS events.
d. Determined by investigator assessment, not by independent assessment.

Results for sensitivity analyses were similar to those observed for the primary endpoint; median PFS times were consistently longer in the temsirolimus arm compared with the sorafenib arm, but the differences were not statistically significant.

Secondary Endpoint Results:

- PFS (Investigator Assessment): The results for PFS as assessed by the investigator are presented in Table 5.

Table 5. Progression-Free Survival by Investigator Assessment (ITT Population)

	TEMSR (N=259)	SORAF (N=253)
Median PFS in months (95% CI)	5.43 (4.24, 5.86)	4.14 (3.26, 5.36)
Hazard ratio[a] (95% CI)	0.87 (0.70, 1.07)	
P-value[b]	0.1888	
Subjects with PFS events (n, %)	188 (75.59)	195 (77.08)
Subjects with PD event (n, %)[c]	150 (79.79)	169 (86.67)
Subjects with death event (n, %)[c]	24 (12.77)	15 (7.69)
Events due to symptomatic deterioration (n, %)[c]	14 (7.45)	11 (5.64)
Subjects censored (n, %)	71 (27.41)	58 (22.92)
No postbaseline tumor assessments	11 (9.24)	10 (10.75)
Received anticancer therapy	5 (4.20)	7 (7.53)
On treatment in follow-up for disease progression	7 (5.88)	6 (6.45)
Off treatment	48 (40.34)	35 (37.63)

Stratification factors from randomization included: nephrectomy status; duration of sunitinib therapy (≤180 days vs >180 days); tumor histology (clear cell vs nonclear cell); and MSKCC - Memorial Sloan Kettering Cancer Center (favorable, intermediate, or poor).
CI = confidence interval; ITT = intent-to-treat; N = number of subjects in the group; n = number of subjects for a specific category; PD = progressive disease; PFS = progression-free survival; SORAF = sorafenib; TEMSR = temsirolimus; vs = versus.

a. Compared with sorafenib based on stratified Cox proportional hazard model, where hazard ratio <1 mean temsirolimus was at lower risk.
b. Compared with sorafenib based on stratified log-rank test.
c. Percentages calculated based on number of subjects with PFS events.

- ORR:

The ORR is the proportion of the ITT population who achieved a tumor response (confirmed CR or PR) assessed by an independent imaging service provider. The ORR results by independent assessment are presented in Table 6.

The temsirolimus and sorafenib arms had similar ORRs by independent assessments. The temsirolimus and sorafenib arms had similar proportions of subjects with CR/PRs (7.7% vs 7.9%), SDs (60.6% vs 60.5%), and PDs (22.8% vs 24.1%, respectively). The risk ratio (temsirolimus: sorafenib) was 0.96 (95% CI [0.52, 1.75]) with a 2-sided p=0.5557 (Table 6). A risk ratio >1 indicated a higher likelihood of responding in the temsirolimus arm; a risk <1 indicated a higher likelihood of responding in the sorafenib arm.

Table 6. Best Objective Response Rate by Independent Assessment (ITT Population)

	TEMSR (N=259)	SORAF (N=253)
	n (%)	n (%)
Complete response[a] (n, %)	0	1 (0.4)
Partial response (n, %)	20 (7.7)	19 (7.5)
Stable disease (n, %)	157 (60.6)	153 (60.5)
Progressive disease (n, %)	59 (22.8)	61 (24.1)
Overall confirmed ORR[b] (n, %)	20 (7.7)	20 (7.9)
95% CI[c]	4.8, 11.7	4.9, 11.9
Risk ratio (95% CI)[d]	0.958 (0.524, 1.75)	
P-value[e]	0.5557	

CI = confidence interval; CR = complete response; ITT = intent-to-treat; N = number of subjects in the group; n = number of subjects for a specific category; ORR = overall response rate; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors; SORAF = sorafenib; TEMSR = temsirolimus.

a. For independent assessment: the best overall responses were based on data provided by independent radiologists, per RECIST criteria. For investigator assessment: the best overall responses were derived based on radiographic review by investigators, per RECIST criteria.
b. Complete response + partial response (CR + PR).
c. Using exact method based on binomial distribution.
d. Risk ratio and CI based on the Mantel-Haenszel estimator.
e. P-value is from a stratified 1-sided Cochran-Mantel-Haenszel test of treatment.

- OS:

OS results are presented in Table 7. A total of 351 subjects (68.6%) had died (ie, 187 vs 164 in the temsirolimus and sorafenib arms, respectively) at primary study completion. The observed hazard ratio was 1.31 with a 95% CI of (1.05, 1.63) in favor of the sorafenib arm with a 2-sided p=0.0144, stratified by prior nephrectomy status, duration of sunitinib therapy, tumor histology, and MSKCC risk group. The median OS time was 16.64 months (95% CI: 13.55 months, 18.72 months) in the sorafenib arm, and 12.27 months (95% CI: 10.13 months, 14.80 months) in the temsirolimus arm.

Table 7. Overall Survival (ITT Population)

	TEMSR (N=259)	SORAF (N=253)
Median OS in months (95% CI)	12.27 (10.13, 14.80)	16.64 (13.55, 18.72)
Hazard ratio[a] (95% CI)	1.31 (1.05, 1.63)	
P-value[b]	0.0144	
Deaths (n, %)	187 (72.20)	164 (64.82)
Subjects censored (n, %)	72 (27.80)	89 (35.18)
On treatment	8 (11.11)	6 (6.74)
Alive and in follow-up	37 (51.39)	63 (70.79)
Lost to follow-up	27 (37.50)	20 (22.47)

Stratification factors from randomization included: nephrectomy status; duration of sunitinib therapy (≤180 days vs >180 days); tumor histology (clear cell vs nonclear cell); and MSKCC - Memorial Sloan Kettering Cancer Center (favorable, intermediate, or poor).
CI = confidence interval; ITT = intent-to-treat; N = number of subjects in the group; n = number of subjects for a specific category; OS = overall survival; SORAF = sorafenib; TEMSR = temsirolimus; vs = versus.
a. Compared with sorafenib based on stratified Cox proportional hazard model, where hazard ratio <1 mean temsirolimus was at lower risk.
b. Compared with sorafenib based on stratified log-rank test.

- Proportion of Subjects With PFS by Independent Assessment at 12, 24 and 36 Weeks:

The proportions of subjects with PFS events by independent assessment at 12, 24 and 36 weeks are presented in Table 8. Overall, the highest proportions of subjects with PFS events were observed at Week 12 for each treatment arm regardless of the assessor (independent or investigator). Specifically, at Week 12, the sorafenib arm had a higher proportion of subjects with PFS events than the temsirolimus arm by independent assessments (36.7% vs 31.2%). At Week 24, the treatment arms had similar proportions of subjects with PFS events, irrespective of assessor, which ranged from 20.1% to 21.7%. At Week 36, the treatment arms also had similar proportions of subjects with PFS events, irrespective of assessor, which ranged from 11.2% to 13.1%.

Table 8. Proportion of Subjects With Progression-Free Survival Events by Independent Assessment at 12, 24 and 36 Weeks (ITT Population)

	TEMSR (N=259)	SORAF (N=253)
	n (%)	n (%)
PFS event from randomization to Week 12	79 (31.2)	95 (36.7)
PFS event from Week 13 to Week 24	53 (20.9)	52 (20.1)
PFS event from Week 25 to Week 36	31 (12.3)	29 (11.2)

ITT = intent-to-treat; N = number of subjects in the group; n = number of subjects for a specific category; PFS = progression-free survival; SORAF = sorafenib; TEMSR = temsirolimus.

- Duration of Response:

The durations of response were estimated using Kaplan-Meier method among subjects experienced confirmed PR/CR assessed by independent review. The results are presented in Table 9.

Table 9. Duration of Response (Responding Subjects)

	Independent Assessment	
	TEMSR (N=20)	SORAF (N=20)
Median duration of response in months (95% CI)[a]	8.26 (6.71, 10.36)	6.96 (4.18, 17.50)

CI = confidence interval; CR = complete response; ITT = intent-to-treat; N = number of subjects in the group; n = number of subjects for a specific category; PR = partial response; SORAF = sorafenib; TEMSR = temsirolimus

a. For subjects with an objective response, duration of PR or CR was the time from date of first documentation of PR or CR to date of first documentation of objective progression or death.

No Further efficacy analyses were performed after the primary study completion date.

Safety Results: A total of 501 subjects were included in the safety population, which included 249 subjects in the temsirolimus arm and 252 subjects in the sorafenib arm.

The temsirolimus arm and the sorafenib arm had the same proportion of subjects with any treatment emergent AE (TEAE) (99.6%) and similar proportions of Grade ≥3 TEAEs (70.3% and 69.4%, respectively; Table 10). Similar proportions for each treatment arm were also observed for TEAEs leading to study discontinuation, temporary discontinuations of study treatment, and death, as well as those treatment-related AEs.

Subjects in the temsirolimus arm had a higher incidence of serious adverse events (SAEs) than the sorafenib arm (41.4% vs 34.1%). Conversely, subjects in the sorafenib arm had a notably higher incidence of TEAEs leading to dose reduction than the temsirolimus arm (33.3% vs 15.7%).

Table 10. Summary of Treatment-Emergent Adverse Events at Primary Study Completion (Safety Population)

Event	TEMSR (N=249)	SORAF (N=252)	Total (N=501)
	n (%)	n (%)	n (%)
Any TEAE	248 (99.6)	251 (99.6)	499 (99.6)
Grade ≥3 TEAE	175 (70.3)	175 (69.4)	350 (69.9)
Treatment-emergent SAEs	103 (41.4)	86 (34.1)	189 (37.7)
TEAEs leading to discontinuation	42 (16.9)	34 (13.5)	76 (15.2)
TEAEs leading to dose reduction	39 (15.7)	84 (33.3)	123 (24.6)
TEAEs leading to temporary discontinuation of study treatment	140 (56.2)	136 (54.0)	276 (55.1)
TEAEs leading to death[a]	21 (8.4)	20 (7.9)	41 (8.2)
Treatment-related AEs[b]	231 (92.8)	240 (95.2)	471 (94)

AE/SAE results are not separated out.
AE = adverse event; n = number of subjects for a specific category; N = number of subjects in the group; SAE = serious adverse event; SORAF = sorafenib; TEAE = treatment-emergent adverse event; TEMSR = temsirolimus.

a. Included all TEAEs with toxicity Grade 5.
b. The investigator assessed that there was a reasonable possibility of a causal relationship between the study treatment and the AE.

Non-Serious AEs: All causality non-serious AEs experienced by ≥5% of subjects is presented in Table 11. Overall, similar proportions of commonly occurring TEAEs were reported in each treatment arm, with the following exceptions.

The most commonly occurring TEAEs in the temsirolimus arm that had notably higher proportions compared with the sorafenib arm were cough, anemia, mucosal inflammation dyspnea, peripheral edema, pyrexia, stomatitis, hypertriglyceridemia, hypercholesterolemia, epistaxis, and hyperglycemia.

The most commonly occurring TEAEs in the sorafenib arm that had notably higher proportions compared with the temsirolimus arm were diarrhea, palmar-plantar erythrodysesthesia syndrome, alopecia, hypertension, and dysphonia.

Table 11. Non Serious Treatment Emergent Adverse Events Reported by ≥5% of Subjects (Safety Population)

System Organ Class[a] Preferred Term	Treatment		
	TEMSR N=249	SORAF N=252	Total N=501
Any adverse event[b]	243 (97.6)	249 (98.8)	492 (98.2)
Blood and lymphatic system disorders	102 (41.0)	43 (17.1)	145 (28.9)
Anaemia	83 (33.3)	34 (13.5)	117 (23.4)
Lymphopenia	21 (8.4)	8 (3.2)	29 (5.8)
Thrombocytopenia	23 (9.2)	5 (2.0)	28 (5.6)
Gastrointestinal disorders	180 (72.3)	203 (80.6)	383 (76.4)
Diarrhoea	77 (30.9)	158 (62.7)	235 (46.9)
Nausea	81 (32.5)	71 (28.2)	152 (30.3)
Constipation	57 (22.9)	57 (22.6)	114 (22.8)
Vomiting	54 (21.7)	45 (17.9)	99 (19.8)
Abdominal pain	32 (12.9)	40 (15.9)	72 (14.4)
Stomatitis	54 (21.7)	18 (7.1)	72 (14.4)
Abdominal pain upper	14 (5.6)	25 (9.9)	39 (7.8)
Dyspepsia	15 (6.0)	18 (7.1)	33 (6.6)
Oral pain	13 (5.2)	5 (2.0)	18 (3.6)
General disorders and administration site conditions	202 (81.1)	176 (69.8)	378 (75.4)
Fatigue	100 (40.2)	85 (33.7)	185 (36.9)
Asthenia	64 (25.7)	64 (25.4)	128 (25.5)
Mucosal inflammation	74 (29.7)	35 (13.9)	109 (21.8)
Pyrexia	53 (21.3)	28 (11.1)	81 (16.2)
Oedema peripheral	57 (22.9)	14 (5.6)	71 (14.2)
Chest pain	23 (9.2)	25 (9.9)	48 (9.6)
Pain	20 (8.0)	16 (6.3)	36 (7.2)
Chills	15 (6.0)	6 (2.4)	21 (4.2)
Oedema	16 (6.4)	5 (2.0)	21 (4.2)
Infections and infestations	24 (9.6)	16 (6.3)	40 (8.0)
Nasopharyngitis	24 (9.6)	16 (6.3)	40 (8.0)
Investigations	96 (38.6)	83 (32.9)	179 (35.7)
Weight decreased	35 (14.1)	51 (20.2)	86 (17.2)
Blood alkaline phosphatase increased	26 (10.4)	11 (4.4)	37 (7.4)
Aspartate aminotransferase increased	22 (8.8)	14 (5.6)	36 (7.2)
Blood creatinine increased	30 (12.0)	6 (2.4)	36 (7.2)
Alanine aminotransferase increased	18 (7.2)	16 (6.3)	34 (6.8)
Blood lactate dehydrogenase increased	16 (6.4)	13 (5.2)	29 (5.8)

Table 11. Non Serious Treatment Emergent Adverse Events Reported by ≥5% of Subjects (Safety Population)

System Organ Class[a] Preferred Term	Treatment		
	TEMSR N=249	SORAF N=252	Total N=501
Haemoglobin decreased	19 (7.6)	9 (3.6)	28 (5.6)
Metabolism and nutrition disorders	163 (65.5)	132 (52.4)	295 (58.9)
Decreased appetite	77 (30.9)	93 (36.9)	170 (33.9)
Hypertriglyceridaemia	53 (21.3)	18 (7.1)	71 (14.2)
Hypercholesterolaemia	51 (20.5)	16 (6.3)	67 (13.4)
Hyperglycaemia	45 (18.1)	13 (5.2)	58 (11.6)
Hypophosphataemia	28 (11.2)	30 (11.9)	58 (11.6)
Hyponatraemia	14 (5.6)	14 (5.6)	28 (5.6)
Hypocalcaemia	10 (4.0)	17 (6.7)	27 (5.4)
Hyperkalaemia	11 (4.4)	14 (5.6)	25 (5.0)
Hypokalaemia	14 (5.6)	9 (3.6)	23 (4.6)
Musculoskeletal and connective tissue disorders	114 (45.8)	116 (46.0)	230 (45.9)
Back pain	49 (19.7)	37 (14.7)	86 (17.2)
Arthralgia	46 (18.5)	31 (12.3)	77 (15.4)
Pain in extremity	30 (12.0)	38 (15.1)	68 (13.6)
Musculoskeletal pain	24 (9.6)	20 (7.9)	44 (8.8)
Muscle spasms	18 (7.2)	22 (8.7)	40 (8.0)
Myalgia	20 (8.0)	17 (6.7)	37 (7.4)
Nervous system disorders	76 (30.5)	64 (25.4)	140 (27.9)
Headache	33 (13.3)	44 (17.5)	77 (15.4)
Dizziness	20 (8.0)	20 (7.9)	40 (8.0)
Dysgeusia	22 (8.8)	10 (4.0)	32 (6.4)
Paraesthesia	14 (5.6)	10 (4.0)	24 (4.8)
Psychiatric disorders	32 (12.9)	32 (12.7)	64 (12.8)
Insomnia	15 (6.0)	17 (6.7)	32 (6.4)
Depression	9 (3.6)	13 (5.2)	22 (4.4)
Anxiety	13 (5.2)	7 (2.8)	20 (4.0)
Renal and urinary disorders	25 (10.0)	10 (4.0)	35 (7.0)
Dysuria	13 (5.2)	7 (2.8)	20 (4.0)
Pollakiuria	13 (5.2)	3 (1.2)	16 (3.2)
Respiratory, thoracic and mediastinal disorders	152 (61.0)	108 (42.9)	260 (51.9)
Cough	86 (34.5)	58 (23.0)	144 (28.7)
Dyspnoea	68 (27.3)	39 (15.5)	107 (21.4)
Epistaxis	50 (20.1)	13 (5.2)	63 (12.6)
Dysphonia	5 (2.0)	38 (15.1)	43 (8.6)
Oropharyngeal pain	22 (8.8)	14 (5.6)	36 (7.2)
Rhinorrhoea	15 (6.0)	7 (2.8)	22 (4.4)
Pneumonitis	19 (7.6)	0	19 (3.8)
Productive cough	13 (5.2)	5 (2.0)	18 (3.6)
Skin and subcutaneous tissue disorders	153 (61.4)	205 (81.3)	358 (71.5)
Rash	104 (41.8)	88 (34.9)	192 (38.3)
Palmar-plantar erythrodysaesthesia syndrome	11 (4.4)	131 (52.0)	142 (28.3)
Pruritus	64 (25.7)	65 (25.8)	129 (25.7)
Alopecia	5 (2.0)	78 (31.0)	83 (16.6)
Dry skin	40 (16.1)	37 (14.7)	77 (15.4)
Erythema	15 (6.0)	30 (11.9)	45 (9.0)
Nail disorder	19 (7.6)	0	19 (3.8)
Pain of skin	2 (0.8)	17 (6.7)	19 (3.8)
Vascular disorders	8 (3.2)	38 (15.1)	46 (9.2)

Table 11. Non Serious Treatment Emergent Adverse Events Reported by ≥5% of Subjects (Safety Population)

System Organ Class[a] Preferred Term	Treatment		
	TEMSR N=249	SORAF N=252	Total N=501
Hypertension	8 (3.2)	38 (15.1)	46 (9.2)

Table included events reported for ≥5% of subjects in any treatment group.
MedDRA (v14.1) coding dictionary applied.
Descending order of the incidences was presented at the level of preferred term within each System Organ Class based on the incidences under 'Total' column.
MedDRA = Medical Dictionary For Regulatory Activites; N = number of subjects in the group;
SORAF = sorafenib; TEMSR = temsirolimus; v = version.

a. Totals for the number of subjects at a higher level were not necessarily the sum of those at the lower levels since a subject might report 2 or more different adverse events within the higher level category.
b. Number (%) of subjects who experienced any non-SAEs which was defined as the AEs with ≥5% threshold of incidence.

Treatment-Related AEs:

The investigator assessed TEAEs as treatment-related if there was a reasonable possibility of a causal relationship between the study treatment and the TEAE.

The temsirolimus arm and the sorafenib arm had similar proportion of subjects with at least 1 treatment related AE (92.8% vs 95.2%, respectively; Table 12). Overall, similar proportions of individual events were reported in each treatment arm with the following exceptions.

The most commonly occurring treatment related AEs in the temsirolimus arm that had notably higher proportions compared with the sorafenib arm were mucosal inflammation, anemia, stomatitis, hypercholesterolemia, hypertriglyceridemia, cough, epistaxis, and hyperglycemia.

The most commonly occurring treatment related AEs in the sorafenib arm that had notably higher proportions compared with the temsirolimus arm were diarrhea, palmar-plantar erythrodysesthesia syndrome, alopecia, hypertension, and dysphonia.

Table 12. Treatment-Related Adverse Events in ≥5% of Subjects in Either Treatment Arm (Safety Population)

Event	TEMSR (N=249)	SORAF (N=252)	Total (N=501)
	n (%)	n (%)	n (%)
Any AE	231 (92.8)	240 (95.2)	471 (94.0)
Diarrhoea	56 (22.5)	143 (56.7)	199 (39.7)
Rash	99 (39.8)	85 (33.7)	184 (36.7)
Fatigue	79 (31.7)	70 (27.8)	149 (29.7)
Palmar-plantar erythrodysaesthesia syndrome	10 (4.0)	131 (52.0)	141 (28.1)
Decreased appetite	57 (22.9)	70 (27.8)	127 (25.3)
Nausea	62 (24.9)	51 (20.2)	113 (22.6)
Pruritus	54 (21.7)	59 (23.4)	113 (22.6)
Mucosal inflammation	69 (27.7)	34 (13.5)	103 (20.6)
Asthenia	50 (20.1)	42 (16.7)	92 (18.4)
Alopecia	5 (2.0)	74 (29.4)	79 (15.8)
Dry skin	36 (14.5)	34 (13.5)	70 (14.0)
Anaemia	51 (20.5)	17 (6.7)	68 (13.6)
Stomatitis	51 (20.5)	17 (6.7)	68 (13.6)
Vomiting	30 (12.0)	33 (13.1)	63 (12.6)
Hypercholesterolaemia	47 (18.9)	13 (5.2)	60 (12.0)
Constipation	27 (10.8)	30 (11.9)	57 (11.4)
Hypertriglyceridaemia	43 (17.3)	14 (5.6)	57 (11.4)
Weight decreased	20 (8.0)	34 (13.5)	54 (10.8)
Cough	43 (17.3)	10 (4.0)	53 (10.6)
Epistaxis	35 (14.1)	10 (4.0)	45 (9.0)
Dyspnoea	32 (12.9)	11 (4.4)	43 (8.6)
Headache	14 (5.6)	25 (9.9)	39 (7.8)
Hyperglycaemia	33 (13.3)	5 (2.0)	38 (7.6)
Erythema	9 (3.6)	28 (11.1)	37 (7.4)
Hypophosphataemia	14 (5.6)	23 (9.1)	37 (7.4)
Hypertension	4 (1.6)	31 (12.3)	35 (7.0)
Oedema peripheral	28 (11.2)	6 (2.4)	34 (6.8)
Dysphonia	1 (0.4)	31 (12.3)	32 (6.4)
Arthralgia	17 (6.8)	12 (4.8)	29 (5.8)
Pain in extremity	7 (2.8)	21 (8.3)	28 (5.6)
Pyrexia	19 (7.6)	9 (3.6)	28 (5.6)
Dysgeusia	20 (8.0)	7 (2.8)	27 (5.4)
Muscle spasms	10 (4.0)	17 (6.7)	27 (5.4)
Alanine aminotransferase increased	13 (5.2)	12 (4.8)	25 (5.0)
Lymphopenia	18 (7.2)	7 (2.8)	25 (5.0)
Thrombocytopenia	22 (8.8)	3 (1.2)	25 (5.0)
Myalgia	9 (3.6)	16 (6.3)	25 (5.0)
Aspartate aminotransferase increased	13 (5.2)	10 (4.0)	23 (4.6)
Pneumonitis	23 (9.2)	0	23 (4.6)
Aspartate aminotransferase increased	13 (5.2)	10 (4.0)	23 (4.6)
Pneumonitis	23 (9.2)	0	23 (4.6)
Haemoglobin decreased	17 (6.8)	3 (1.2)	20 (4.0)
Blood creatinine increased	14 (5.6)	4 (1.6)	18 (3.6)
Nail disorder	18 (7.2)	0	18 (3.6)
Pain of skin	1 (0.4)	15 (6.0)	16 (3.2)
Back pain	14 (5.6)	1 (0.4)	15 (3.0)

Table 12. Treatment-Related Adverse Events in ≥5% of Subjects in Either Treatment Arm (Safety Population)

Event	TEMSR (N=249)	SORAF (N=252)	Total (N=501)
	n (%)	n (%)	n (%)

AE/SAE results are not separated out.
MedDRA (v14.1) coding dictionary was applied.
AE = adverse event; MedDRA = Medical Dictionary For Regulatory Activites; N = number of subjects in the group; n = number of subjects for a specific category; SORAF = sorafenib; TEMSR = temsirolimus; v = version.

SAEs: All causality SAEs are presented Table 13. At final study completion a total of 191 (38.1%) subjects reported at least 1 SAE in the study; 104 (41.8%) subjects in the temsirolimus arm and 87 (34.5%) subjects in the sorafenib arm. Between primary study completion to final study completion 7 new SAEs were reported, none of these events were considered related to the study drug and in 4 of the cases, the events resolved completely (2 subjects in the temsirolimus arm [1 SAE of headache and 1 SAE of respiratory distress respectively] and 2 subjects in the sorafenib arm [1 SAE of pneumonia and SAEs of nausea, vomiting and back pain respectively]). The other 3 events were associated with disease progression and ultimately, led to death.

Table 13. Serious Adverse Events by Preferred Term in Descending Order of the Incidences (Safety Population).

Preferred Term	TEMSR (N=249)	SORAF (N=252)	Total (N=501)
	n (%)	n (%)	n (%)
Any Adverse event	104 (41.8)	87 (34.5)	191 (38.1)
General physical health deterioration	8 (3.2)	9 (3.6)	17 (3.4)
Dyspnoea	7 (2.8)	8 (3.2)	15 (3.0)
Pneumonia	7 (2.8)	7 (2.8)	14 (2.8)
Dehydration	7 (2.8)	6 (2.4)	13 (2.6)
Pleural effusion	7 (2.8)	5 (2.0)	12 (2.4)
Pyrexia	7 (2.8)	4 (1.6)	11 (2.2)
Vomiting	6 (2.4)	4 (1.6)	10 (2.0)
Anaemia	5 (2.0)	4 (1.6)	9 (1.8)
Abdominal pain	7 (2.8)	1 (0.4)	8 (1.6)
Pneumonitis	7 (2.8)	0	7 (1.4)
Fatigue	2 (0.8)	4 (1.6)	6 (1.2)
Myocardial infarction	1 (0.4)	4 (1.6)	5 (1.0)
Pain in extremity	2 (0.8)	3 (1.2)	5 (1.0)
Renal failure	4 (1.6)	1 (0.4)	5 (1.0)
Ascites	3 (1.2)	1 (0.4)	4 (0.8)
Asthenia	3 (1.2)	1 (0.4)	4 (0.8)
Chest pain	1 (0.4)	3 (1.2)	4 (0.8)
Diarrhoea	3 (1.2)	1 (0.4)	4 (0.8)
Hypercalcaemia	1 (0.4)	3 (1.2)	4 (0.8)
Respiratory failure	2 (0.8)	2 (0.8)	4 (0.8)
Sepsis	2 (0.8)	2 (0.8)	4 (0.8)
Aspartate aminotransferase increased	0	3 (1.2)	3 (0.6)
Atrial fibrillation	0	3 (1.2)	3 (0.6)
Back pain	0	3 (1.2)	3 (0.6)
Confusional state	0	3 (1.2)	3 (0.6)
Hyperglycaemia	2 (0.8)	1 (0.4)	3 (0.6)
Hyponatraemia	0	3 (1.2)	3 (0.6)
Pain	1 (0.4)	2 (0.8)	3 (0.6)
Pneumothorax	3 (1.2)	0	3 (0.6)
Rash	1 (0.4)	2 (0.8)	3 (0.6)
Spinal cord compression	1 (0.4)	2 (0.8)	3 (0.6)
Abdominal distension	1 (0.4)	1 (0.4)	2 (0.4)
Alanine aminotransferase increased	0	2 (0.8)	2 (0.4)
Arthralgia	2 (0.8)	0	2 (0.4)
Cardio-respiratory arrest	1 (0.4)	1 (0.4)	2 (0.4)
Cardiopulmonary failure	2 (0.8)	0	2 (0.4)
Cerebrovascular accident	2 (0.8)	0	2 (0.4)
Completed suicide	1 (0.4)	1 (0.4)	2 (0.4)
Constipation	1 (0.4)	1 (0.4)	2 (0.4)
Decreased appetite	0	2 (0.8)	2 (0.4)
Device related infection	2 (0.8)	0	2 (0.4)
Gastrointestinal obstruction	2 (0.8)	0	2 (0.4)
Headache	1 (0.4)	1 (0.4)	2 (0.4)
Interstitial lung disease	2 (0.8)	0	2 (0.4)
Lower respiratory tract infection	2 (0.8)	0	2 (0.4)
Lung disorder	2 (0.8)	0	2 (0.4)
Oedema peripheral	2 (0.8)	0	2 (0.4)
Osteolysis	1 (0.4)	1 (0.4)	2 (0.4)

Table 13. Serious Adverse Events by Preferred Term in Descending Order of the Incidences (Safety Population).

Preferred Term	TEMSR (N=249)	SORAF (N=252)	Total (N=501)
	n (%)	n (%)	n (%)
Renal failure acute	1 (0.4)	1 (0.4)	2 (0.4)
Squamous cell carcinoma	0	2 (0.8)	2 (0.4)
Sudden death	1 (0.4)	1 (0.4)	2 (0.4)
Urinary retention	2 (0.8)	0	2 (0.4)
Abdominal infection	1 (0.4)	0	1 (0.2)
Abscess intestinal	0	1 (0.4)	1 (0.2)
Acute myocardial infarction	1 (0.4)	0	1 (0.2)
Anal abscess	0	1 (0.4)	1 (0.2)
Anaphylactic reaction	1 (0.4)	0	1 (0.2)
Asthmatic crisis	0	1 (0.4)	1 (0.2)
Atrial flutter	0	1 (0.4)	1 (0.2)
Bile duct stone	1 (0.4)	0	1 (0.2)
Blood potassium increased	0	1 (0.4)	1 (0.2)
Bone lesion	1 (0.4)	0	1 (0.2)
Bone pain	1 (0.4)	0	1 (0.2)
Bronchitis	1 (0.4)	0	1 (0.2)
Cachexia	1 (0.4)	0	1 (0.2)
Cardiac arrest	1 (0.4)	0	1 (0.2)
Cardiac tamponade	1 (0.4)	0	1 (0.2)
Cerebral infarction	0	1 (0.4)	1 (0.2)
Cerebral ischaemia	0	1 (0.4)	1 (0.2)
Chest wall abscess	0	1 (0.4)	1 (0.2)
Cholangitis suppurative	0	1 (0.4)	1 (0.2)
Cholecystitis	1 (0.4)	0	1 (0.2)
Cholecystitis acute	1 (0.4)	0	1 (0.2)
Cholestasis	1 (0.4)	0	1 (0.2)
Cognitive disorder	0	1 (0.4)	1 (0.2)
Compression fracture	1 (0.4)	0	1 (0.2)
Convulsion	0	1 (0.4)	1 (0.2)
Costochondritis	0	1 (0.4)	1 (0.2)
Diabetes mellitus inadequate control	1 (0.4)	0	1 (0.2)
Drug hypersensitivity	0	1 (0.4)	1 (0.2)
Duodenal perforation	1 (0.4)	0	1 (0.2)
Dysphagia	0	1 (0.4)	1 (0.2)
Enterococcal bacteraemia	0	1 (0.4)	1 (0.2)
Epistaxis	1 (0.4)	0	1 (0.2)
Febrile neutropenia	1 (0.4)	0	1 (0.2)
Flank pain	1 (0.4)	0	1 (0.2)
Gallbladder obstruction	0	1 (0.4)	1 (0.2)
Gastrointestinal haemorrhage	0	1 (0.4)	1 (0.2)
Haematoma	0	1 (0.4)	1 (0.2)
Haematuria	1 (0.4)	0	1 (0.2)
Haemoptysis	0	1 (0.4)	1 (0.2)
Haemorrhage	1 (0.4)	0	1 (0.2)
Hepatitis B	1 (0.4)	0	1 (0.2)
Hepatobiliary disease	0	1 (0.4)	1 (0.2)
Hernial eventration	1 (0.4)	0	1 (0.2)
Herpes zoster	1 (0.4)	0	1 (0.2)
Hiatus hernia	0	1 (0.4)	1 (0.2)

Table 13. Serious Adverse Events by Preferred Term in Descending Order of the Incidences (Safety Population).

Preferred Term	TEMSR (N=249)	SORAF (N=252)	Total (N=501)
	n (%)	n (%)	n (%)
Hip fracture	0	1 (0.4)	1 (0.2)
Humerus fracture	0	1 (0.4)	1 (0.2)
Hypercholesterolaemia	1 (0.4)	0	1 (0.2)
Hyperkalaemia	0	1 (0.4)	1 (0.2)
Hypertension	1 (0.4)	0	1 (0.2)
Hyperthyroidism	0	1 (0.4)	1 (0.2)
Hypertriglyceridaemia	1 (0.4)	0	1 (0.2)
Hypoaesthesia	0	1 (0.4)	1 (0.2)
Hypotension	1 (0.4)	0	1 (0.2)
Infection	0	1 (0.4)	1 (0.2)
Infectious pleural effusion	0	1 (0.4)	1 (0.2)
Infusion related reaction	1 (0.4)	0	1 (0.2)
Intervertebral disc protrusion	0	1 (0.4)	1 (0.2)
Intestinal obstruction	1 (0.4)	0	1 (0.2)
Intestinal ulcer perforation	1 (0.4)	0	1 (0.2)
Large intestine perforation	0	1 (0.4)	1 (0.2)
Ligament sprain	0	1 (0.4)	1 (0.2)
Lobar pneumonia	1 (0.4)	0	1 (0.2)
Lumbar vertebral fracture	1 (0.4)	0	1 (0.2)
Lung infection	1 (0.4)	0	1 (0.2)
Lung operation	1 (0.4)	0	1 (0.2)
Lymphopenia	1 (0.4)	0	1 (0.2)
Malignant pleural effusion	1 (0.4)	0	1 (0.2)
Malnutrition	0	1 (0.4)	1 (0.2)
Medical device implantation	1 (0.4)	0	1 (0.2)
Multi-organ failure	0	1 (0.4)	1 (0.2)
Musculoskeletal chest pain	0	1 (0.4)	1 (0.2)
Musculoskeletal pain	1 (0.4)	0	1 (0.2)
Myocardial ischaemia	0	1 (0.4)	1 (0.2)
Nausea	1 (0.4)	0	1 (0.2)
Neck pain	0	1 (0.4)	1 (0.2)
Nephrotic syndrome	0	1 (0.4)	1 (0.2)
Obstruction gastric	0	1 (0.4)	1 (0.2)
Oesophageal hypomotility	1 (0.4)	0	1 (0.2)
Overdose	0	1 (0.4)	1 (0.2)
Palmar-plantar erythrodysaesthesia syndrome	0	1 (0.4)	1 (0.2)
Palpitations	0	1 (0.4)	1 (0.2)
Paraesthesia	1 (0.4)	0	1 (0.2)
Pathological fracture	1 (0.4)	0	1 (0.2)
Pelvic fracture	1 (0.4)	0	1 (0.2)
Performance status decreased	1 (0.4)	0	1 (0.2)
Pericardial effusion	1 (0.4)	0	1 (0.2)
Peripheral motor neuropathy	0	1 (0.4)	1 (0.2)
Perirectal abscess	1 (0.4)	0	1 (0.2)
Pharyngitis	1 (0.4)	0	1 (0.2)
Pleuritic pain	1 (0.4)	0	1 (0.2)
Pneumocystis jiroveci pneumonia	1 (0.4)	0	1 (0.2)
Pneumonia influenzal	1 (0.4)	0	1 (0.2)
Pneumonia legionella	1 (0.4)	0	1 (0.2)

Table 13. Serious Adverse Events by Preferred Term in Descending Order of the Incidences (Safety Population).

Preferred Term	TEMSR (N=249)	SORAF (N=252)	Total (N=501)
	n (%)	n (%)	n (%)
Prinzmetal angina	1 (0.4)	0	1 (0.2)
Prostatic haemorrhage	0	1 (0.4)	1 (0.2)
Prostatic specific antigen increased	0	1 (0.4)	1 (0.2)
Pulmonary embolism	1 (0.4)	0	1 (0.2)
Pulmonary tuberculosis	0	1 (0.4)	1 (0.2)
Radiation mucositis	0	1 (0.4)	1 (0.2)
Rash popular	0	1 (0.4)	1 (0.2)
Rectal haemorrhage	1 (0.4)	0	1 (0.2)
Renal tubular necrosis	1 (0.4)	0	1 (0.2)
Respiratory arrest	0	1 (0.4)	1 (0.2)
Respiratory distress	1 (0.4)	0	1 (0.2)
Respiratory tract infection	1 (0.4)	0	1 (0.2)
Retinal artery occlusion	0	1 (0.4)	1 (0.2)
Salivary hypersecretion	1 (0.4)	0	1 (0.2)
Septic shock	1 (0.4)	0	1 (0.2)
Spinal disorder	0	1 (0.4)	1 (0.2)
Stomatitis	1 (0.4)	0	1 (0.2)
Subcutaneous abscess	1 (0.4)	0	1 (0.2)
Syncope	0	1 (0.4)	1 (0.2)
Systemic inflammatory response syndrome	0	1 (0.4)	1 (0.2)
Thrombocytopenia	1 (0.4)	0	1 (0.2)
Thrombosis	1 (0.4)	0	1 (0.2)
Tooth abscess	0	1 (0.4)	1 (0.2)
Toxic nodular goitre	0	1 (0.4)	1 (0.2)
Unresponsive to stimuli	0	1 (0.4)	1 (0.2)
Urosepsis	0	1 (0.4)	1 (0.2)
Weight decreased	0	1 (0.4)	1 (0.2)
Wound infection	0	1 (0.4)	1 (0.2)

MedDRA (v15.1) coding dictionary applied.
Descending Order of the Incidences was presented based on the incidences under 'Total' column.
MedDRA = Medical Dictionary For Regulatory Activites; N = number of subjects in the group; n = number of subjects for a specific category; SORAF = sorafenib; TEMSR = temsirolimus; v = version.

Treatment Related SAEs: Subjects in the temsirolimus arm had a higher incidence of treatment-related SAEs than the sorafenib arm (16.1% vs 11.5%; Table 14).

Table 14. Number (%) of Subjects Reporting Treatment-Related Serious Adverse Events

Preferred Term	TEMSR (N=249)	SORAF (N=252)	Total (N=501)
	n (%)	n (%)	n (%)
Any Adverse event	40 (16.1)	29 (11.5)	69 (13.8)
Pneumonitis	7 (2.8)	0	7 (1.4)
Vomiting	3 (1.2)	2 (0.8)	5 (1.0)
Dehydration	2 (0.8)	2 (0.8)	4 (0.8)
Pneumonia	4 (1.6)	0	4 (0.8)
Atrial fibrillation	0	3 (1.2)	3 (0.6)
Diarrhoea	2 (0.8)	1 (0.4)	3 (0.6)
Myocardial infarction	0	3 (1.2)	3 (0.6)
Pyrexia	2 (0.8)	1 (0.4)	3 (0.6)
Anaemia	1 (0.4)	1 (0.4)	2 (0.4)
Dyspnoea	1 (0.4)	1 (0.4)	2 (0.4)
Fatigue	0	2 (0.8)	2 (0.4)
Hyperglycaemia	1 (0.4)	1 (0.4)	2 (0.4)
Hyponatraemia	0	2 (0.8)	2 (0.4)
Interstitial lung disease	2 (0.8)	0	2 (0.4)
Lung disorder	2 (0.8)	0	2 (0.4)
Rash	1 (0.4)	1 (0.4)	2 (0.4)
Abscess intestinal	0	1 (0.4)	1 (0.2)
Alanine aminotransferase increased	0	1 (0.4)	1 (0.2)
Anaphylactic reaction	1 (0.4)	0	1 (0.2)
Ascites	1 (0.4)	0	1 (0.2)
Aspartate aminotransferase increased	0	1 (0.4)	1 (0.2)
Asthenia	1 (0.4)	0	1 (0.2)
Blood potassium increased	0	1 (0.4)	1 (0.2)
Cardio-respiratory arrest	0	1 (0.4)	1 (0.2)
Cerebral infarction	0	1 (0.4)	1 (0.2)
Cholecystitis	1 (0.4)	0	1 (0.2)
Drug hypersensitivity	0	1 (0.4)	1 (0.2)
Febrile neutropenia	1 (0.4)	0	1 (0.2)
Gastrointestinal obstruction	1 (0.4)	0	1 (0.2)
Hypercholesterolaemia	1 (0.4)	0	1 (0.2)
Hypertension	1 (0.4)	0	1 (0.2)
Hypertriglyceridaemia	1 (0.4)	0	1 (0.2)
Infection	0	1 (0.4)	1 (0.2)
Infusion related reaction	1 (0.4)	0	1 (0.2)
Large intestine perforation	0	1 (0.4)	1 (0.2)
Lung infection	1 (0.4)	0	1 (0.2)
Lung operation	1 (0.4)	0	1 (0.2)
Lymphopenia	1 (0.4)	0	1 (0.2)
Myocardial ischaemia	0	1 (0.4)	1 (0.2)
Nephrotic syndrome	0	1 (0.4)	1 (0.2)
Oedema peripheral	1 (0.4)	0	1 (0.2)
Palmar-plantar erythrodysaesthesia syndrome	0	1 (0.4)	1 (0.2)
Pericardial effusion	1 (0.4)	0	1 (0.2)
Perirectal abscess	1 (0.4)	0	1 (0.2)
Pharyngitis	1 (0.4)	0	1 (0.2)
Pleural effusion	0	1 (0.4)	1 (0.2)
Pneumonia legionella	1 (0.4)	0	1 (0.2)
Prinzmetal angina	1 (0.4)	0	1 (0.2)

Table 14. Number (%) of Subjects Reporting Treatment-Related Serious Adverse Events

Preferred Term	TEMSR (N=249)	SORAF (N=252)	Total (N=501)
	n (%)	n (%)	n (%)
Rash papular	0	1 (0.4)	1 (0.2)
Renal failure	0	1 (0.4)	1 (0.2)
Respiratory arrest	0	1 (0.4)	1 (0.2)
Respiratory failure	1 (0.4)	0	1 (0.2)
Respiratory tract infection	1 (0.4)	0	1 (0.2)
Retinal artery occlusion	0	1 (0.4)	1 (0.2)
Salivary hypersecretion	1 (0.4)	0	1 (0.2)
Sepsis	1 (0.4)	0	1 (0.2)
Septic shock	1 (0.4)	0	1 (0.2)
Squamous cell carcinoma	0	1 (0.4)	1 (0.2)
Stomatitis	1 (0.4)	0	1 (0.2)
Systemic inflammatory response syndrome	0	1 (0.4)	1 (0.2)
Unresponsive to stimuli	0	1 (0.4)	1 (0.2)

MedDRA (v14.1) coding dictionary applied.
Descending order of the incidences was presented based on the incidences under 'TOTAL' column.
MedDRA = Medical Dictionary For Regulatory Activites; N = number of subjects in the group; n = number of subjects for a specific category; SORAF = sorafenib; TEMSR = temsirolimus; v = version.

Permanent Discontinuations Due to AEs:

The temsirolimus arm and the sorafenib arm had similar proportions of TEAEs that led to permanent discontinuation of study treatment (16.9% and 13.5%, respectively; Table 15). In the temsirolimus arm, 2 or fewer subjects had any TEAE that led to permanent discontinuation of study treatment.

Table 15. Treatment-Emergent Adverse Events That led to Permanent Discontinuation of Study Treatment in ≥2 Subjects in Either Treatment Arm (Safety Population)

Event	TEMSR (N=249)	SORAF (N=252)	Total (N=501)
	n (%)	n (%)	n (%)
Any TEAE	42 (16.9)	34 (13.5)	76 (15.2)
Pneumonia	2 (0.8)	3 (1.2)	5 (1.0)
Palmar-plantar erythrodysaesthesia syndrome	0	4 (1.6)	4 (0.8)
Fatigue	2 (0.8)	1 (0.4)	3 (0.6)
Pain in extremity	0	3 (1.2)	3 (0.6)
Rash	0	3 (1.2)	3 (0.6)
Asthenia	0	2 (0.8)	2 (0.4)
Atrial fibrillation	0	2 (0.8)	2 (0.4)
Myocardial infarction	0	2 (0.8)	2 (0.4)
Pneumonitis	2 (0.8)	0	2 (0.4)
Pulmonary fibrosis	2 (0.8)	0	2 (0.4)
Respiratory tract infection	2 (0.8)	0	2 (0.4)
Thrombocytopenia	2 (0.8)	0	2 (0.4)

MedDRA (v14.1) coding dictionary was applied.
MedDRA = Medical Dictionary For Regulatory Activites; N = number of subjects in the group; n = number of subjects for a specific category; SORAF = sorafenib; TEMSR = temsirolimus; TEAE = treatment-emergent adverse event; v = version.

Temporary Discontinuation of Study Treatment Due to AEs:

The temsirolimus arm and the sorafenib arm had similar proportions of TEAEs that led to temporary discontinuation of study treatment (56.2% and 54.0%, respectively; Table 16).

Table 16. Treatment-Emergent Adverse Events That led to Temporary Discontinuation of Study Treatment in ≥2% of Subjects in Either Treatment arm (Safety Population)

Event	TEMSR (N=249)	SORAF (N=252)	Total (N=501)
	n (%)	n (%)	n (%)
Any TEAE resulting in temporary discontinuation of study treatment	140 (56.2)	136 (54.0)	276 (55.1)
Palmar-plantar erythrodysaesthesia syndrome	1 (0.4)	47 (18.7)	48 (9.6)
Diarrhoea	3 (1.2)	17 (6.7)	20 (4.0)
Fatigue	12 (4.8)	5 (2.0)	17 (3.4)
Rash	8 (3.2)	9 (3.6)	17 (3.4)
Asthenia	10 (4.0)	5 (2.0)	15 (3.0)
Pyrexia	10 (4.0)	5 (2.0)	15 (3.0)
Anaemia	10 (4.0)	2 (0.8)	12 (2.4)
Pneumonia	9 (3.6)	3 (1.2)	12 (2.4)
Vomiting	1 (0.4)	10 (4.0)	11 (2.2)
Stomatitis	6 (2.4)	3 (1.2)	9 (1.8)
Thrombocytopenia	9 (3.6)	0	9 (1.8)
Dyspnoea	5 (2.0)	3 (1.2)	8 (1.6)
Pruritus	1 (0.4)	7 (2.8)	8 (1.6)
Hypertension	0	7 (2.8)	7 (1.4)
Mucosal inflammation	5 (2.0)	2 (0.8)	7 (1.4)
Alanine aminotransferase increased	1 (0.4)	5 (2.0)	6 (1.2)
Erythema	0	6 (2.4)	6 (1.2)
Hyperglycaemia	6 (2.4)	0	6 (1.2)
Oedema peripheral	6 (2.4)	0	6 (1.2)
Pneumonitis	6 (2.4)	0	6 (1.2)

MedDRA (v14.1) coding dictionary was applied.
MedDRA = Medical Dictionary For Regulatory Activites; N = number of subjects in the group; n = number of subjects for a specific category; SORAF=sorafenib; TEAE=treatment-emergent adverse event; TEMSR = temsirolimus.

Deaths:

A cumulative summary of deaths that occurred in the study is summarized in Table 17. At final study completion a total of 361 (70.5%) deaths were reported during the study; 191 (73.7%) in the temsirolimius arm and 170 (67.2%) in the sorafenib arm. Between primary study completion to final study completion 9 subjects died, of those 9 subjects, 3 subjects were in the temsirolimus arm and 6 subjects were in the sorafenib arm. In addition, 1 subject in the temsirolimus arm died prior to primary study completion, but was censored as 'Lost to follow-up' erroneously. All of these subjects died more than 30 days after the last dose and all of the deaths were due to disease progression; 3 subjects reported the cause of death as serious. None of the deaths were treatment-related. Additionally, since primary study completion, there were 2 updates made to the clinical database for the actual cause of death; (temsirolimus arm) previously reported death due to "acute renal failure" and has since been updated to 'disease progression' and (sorafenib arm), previous cause of death reported as 'not specified' has since been updated to 'disease progression'.

Table 17. Brief Summary of Deaths at Final Study Completion (ITT Population)

Deaths	TEMSR (N=259)	SORAF (N=253)	Total (N=512)
	n (%)	n (%)	n (%)
Overall	191 (73.7)	170 (67.2)	361 (70.5)
In subjects who did not receive study treatment	2 (0.8)	0	2 (0.4)
Within 30 days of last dose	25 (9.7)	23 (9.1)	48 (9.4)
After 30 days from last dose	164 (63.3)	147 (58.1)	311 (60.7)
Within 30 days of randomization	3 (1.2)	3 (1.2)	6 (1.2)
Cause of death (N=361)[a]			
AE	10 (5.2)	9 (5.3)	19 (5.3)
Disease progression	171 (89.5)	158 (92.9)	329 (91.1)
Other[b]	10 (5.2)	3 (1.8)	13 (3.6)

ITT = intent-to-treat; N = number of subjects in the group; n = number of subjects for a specific category; TEMSR = temsirolimus; SORAF = sorafenib.

a. Percentages were based on number of subjects who died in each treatment group.

b. 'Other' included specific reasons as 'unknown' (10 subjects), 'not defined' (1 subject), 'complications arising post nephrectomy' (1 subject), and disease progression (1 subject).

Deaths (grade 5 AEs) occurring within 30 days of last dose are presented in Table 18. Data as at primary study completion.

Table 18. Summary of Deaths Within 30 days of Last Dose at Primary Study Completion

System Organ Class[a] Preferred Term	Treatment		
	TEMSR (N=249)	SORAF (N=252)	Total (N=501)
	n (%)	n (%)	n (%)
Any Adverse Event	21 (8.4)	20 (7.9)	41 (8.2)
Cardiac disorders	5 (2.0)	2 (0.8)	7 (1.4)
Cardio-respiratory arrest	1 (0.4)	1 (0.4)	2 (0.4)
Cardiopulmonary failure	2 (0.8)	0	2 (0.4)
Myocardial infarction	1 (0.4)	1 (0.4)	2 (0.4)
Cardiac arrest	1 (0.4)	0	1 (0.2)
Cardiac tamponade	1 (0.4)	0	1 (0.2)
General disorders and administration site conditions	5 (2.0)	10 (4.0)	15 (3.0)
General physical health deterioration	4 (1.6)	8 (3.2)	12 (2.4)
Sudden death	1 (0.4)	1 (0.4)	2 (0.4)
Multi-organ failure	0	1 (0.4)	1 (0.2)
Infections and infestations	2 (0.8)	3 (1.2)	5 (1.0)
Pneumonia	0	3 (1.2)	3 (0.6)
Pneumocystis jiroveci pneumonia	1 (0.4)	0	1 (0.2)
Pneumonia legionella	1 (0.4)	0	1 (0.2)
Injury, poisoning and procedural complications	1 (0.4)	1 (0.4)	2 (0.4)
Hip fracture	0	1 (0.4)	1 (0.2)
Infusion related reaction	1 (0.4)	0	1 (0.2)
Metabolism and nutrition disorders	1 (0.4)	0	1 (0.2)
Cachexia	1 (0.4)	0	1 (0.2)
Musculoskeletal and connective tissue disorders	0	1 (0.4)	1 (0.2)
Osteolysis	0	1 (0.4)	1 (0.2)
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	1 (0.4)	0	1 (0.2)
Malignant pleural effusion	1 (0.4)	0	1 (0.2)
Psychiatric disorders	1 (0.4)	1 (0.4)	2 (0.4)
Completed suicide	1 (0.4)	1 (0.4)	2 (0.4)
Renal and urinary disorders	2 (0.8)	0	2 (0.4)
Renal failure	2 (0.8)	0	2 (0.4)
Respiratory, thoracic and mediastinal disorders	2 (0.8)	2 (0.8)	4 (0.8)
Respiratory failure	2 (0.8)	1 (0.4)	3 (0.6)
Respiratory arrest	0	1 (0.4)	1 (0.2)
Vascular disorders	1 (0.4)	0	1 (0.2)
Haemorrhage	1 (0.4)	0	1 (0.2)

MedDRA (v14.1) coding dictionary applied.
Descending order of the incidences was presented at the level of preferred term within each System Organ Class based on the incidences under 'Total' column.
MedDRA = Medical Dictionary For Regulatory Activites; N = number of subjects in the group; n = number of subjects for a specific category; SORAF = sorafenib; TEMSR = temsirolimus; v = version.
a. Totals for the no. of subjects at a higher level were not necessarily the sum of those at the lower levels since a subject might report 2 or more different adverse events within the higher level category.

ECG abnormalities reported as TEAEs in both arms were reviewed and no abnormal QT interval, torsade de pointes, ventricular tachycardia, long QT syndrome, or long QT syndrome congenital AEs were reported.

CONCLUSIONS:

- Temsirolimus 25 mg administered by IV infusion once weekly showed no statistically significant differences in the efficacy assessments compared with sorafenib 400 mg orally BID. However, OS analysis suggests subjects in sorafenib arm had a longer median OS time compared with those in temsirolimus arm.

- Temsirolimus 25 mg had a manageable and acceptable safety profile in this subject population.

- This study was discontinued because the study failed to meet its primary endpoint to demonstrate that temsirolimus was superior to sorafenib in PFS for subjects with advanced RCC who failed prior sunitinib.