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PROPRIETARY DRUG NAME® / GENERIC NAME: Sutent® / Sunitinib Malate

PROTOCOL NO.: A6181120

PROTOCOL TITLE: A Multicenter, Randomized, Double-Blind, Phase 3 Study of Sunitinib Plus Prednisone Versus Prednisone in Patients With Progressive Metastatic Castration-Resistant Prostate Cancer After Failure of a Docetaxel-Based Chemotherapy Regimen

Study Centers: A total of 169 centers took part in the study and enrolled subjects; 43 centers in the United States (US), 13 in Spain, 11 in France, 10 each in Germany and the United Kingdom (UK), 9 in Italy, 7 each in Belgium and Canada, 6 in Brazil, 5 each in China, Portugal, the Republic of Korea, and Slovakia, 4 each in Australia, the Czech Republic, Denmark, Israel, Poland, Sweden, and Taiwan, 3 in Peru, and 2 in Finland.

Study Initiation Date and Final Completion Date: 09 July 2008 to 21 December 2011. The study was terminated on 27 September 2010.

Phase of Development: Phase 3

Study Objectives:

Primary Objective: To demonstrate superiority in the overall survival (OS) of subjects with progressive metastatic castration-resistant prostate cancer (mCRPC) treated with sunitinib plus prednisone (SP) versus placebo plus prednisone (PP) after failure of a docetaxel-based chemotherapy regimen.

Secondary Objectives:

- To demonstrate superiority in the progression-free survival (PFS) of subjects with progressive mCRPC treated with SP versus PP after failure of a docetaxel-based chemotherapy regimen

- To compare the objective response rate (ORR) and duration of response (DR) in subjects with progressive mCRPC treated with SP versus PP after failure of a docetaxel-based chemotherapy regimen

- To compare patientreported outcomes (PROs) of pain severity, health-related quality of life, prostate cancer-specific symptoms, and general health status in subjects with progressive CRPC treated with SP versus PP after failure of a docetaxel-based chemotherapy regimen

- To evaluate the safety and tolerability of sunitinib in combination with prednisone

METHODS:

Study Design: This was a randomized (2:1), multicenter, double-blind, placebo-controlled, Phase 3 clinical trial evaluating the efficacy and safety of SP versus PP in subjects with CRPC whose disease failed treatment with a docetaxel-based chemotherapy regimen.

Subjects remained on study as long as they continued to derive clinical benefit and were followed for safety and efficacy as per the schedule of assessments until death. Subjects discontinuing all treatment prior to disease progression continued to have scheduled disease assessments until progression, until the initiation of a subsequent anticancer therapy in the absence of documented disease progression, or until death, whichever came first.

A total of 873 subjects were enrolled in the study. An interim analysis for safety and futility was performed when approximately 400 subjects were enrolled (120 PFS events expected). A second interim analysis of safety was performed, together with an interim analysis of efficacy and futility based on OS, after 819 subjects were enrolled. At that time, an estimated 225 OS events had occurred.

The schedule of activities during the study is provided in Table 1.

Table 1. Schedule of Activities

Protocol Activities	Screening	One Cycle = 4 Weeks (28 Days)			Posttreatment		
		Cycle 1		Cycles 2+			
	≤21 Days Prior to Dosing	Day 1 (-3)[a]	Day 15 (±3)	Day 1 (-3)	End of Treatment/ Withdrawal[b]	Post Tx[c]	Survival Follow-up
Baseline documentation							
Informed consent(s)[d]	X						
Medical/oncological history[e]	X						
Physical examination[f]	X	(X)		X	X		
Baseline signs/symptoms		X					
Laboratory studies							
Hematology[g]	X	(X)	X	X	X		
Blood chemistry[g]	X	(X)	X	X	X		
Urinalysis (protein)[g]	X			Cycle 3 Day 1 only	X		
Thyroid-stimulating hormone[g]	X			Cycle 3 Day 1 only			
BSAP and serum NTX[h]	X			Every 8 weeks	X		
Urine NTX[h]	X			Every 8 weeks	X		
PSA	X	(X)		X	X		
Testosterone	X	(X)					
12-lead ECG[i]	X			Cycle 2 Day 1 only			
MUGA scan or ECHO[j]	X						
Study randomization[k]	X						
Study treatment – sunitinib[l]		X→	→	→			
Study treatment – placebo[m]		X→	→	→			
Study treatment – prednisone[n]		X→	→	→			
Efficacy assessments							
Tumor imaging[o]	X			Every 8 weeks	X	(X)	
Bone scan[p]	X			Every 8 weeks	X	(X)	
Other clinical assessments							
ECOG, body weight, and vital signs	X	X		X	X		
Adverse events[q]	X	X	X	X	X	X	
Concomitant medications/treatments[r]	X	X	X	X	X	X	
Study drug compliance[s]				X	X		
Post-study survival status[t]							X

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		Cycle 1		Cycles 2+			
	≤21 Days Prior to Dosing	Day 1 (-3)[a]	Day 15 (±3)	Day 1 (-3)	End of Treatment/ Withdrawal[b]	Post Tx[c]	Survival Follow-up
Sample banking for exploratory research[u]	(X)	(X)					
Patientreported outcomes							
mBPI-sf and analgesic use diary[v]	X	X		X	X		
SSQ[v]		X		X	X		
FACT-P and EQ-5D[w]		X		X	X		
Subject's best guess[w]		X		X	X		

AE = adverse event; BID = twice daily; BSAP = bone-specific alkaline phosphatase; CT = computed tomography; ECG = electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; EQ-5D = EuroQol quality of life questionnaire; FACT-P = functional assessment of cancer therapy-prostate; mBPI-sf = modified Brief Pain Inventory-short form; MRI = magnetic resonance imaging; MUGA = multiple gated acquisition scan; NTX = N-telopeptide; PRO = patient-reported outcome; PSA = prostate-specific antigen; SSQ = subjective significance question; Tx = treatment.

a. Day 1 Cycle 1 assessments: physical examination, hematology, blood chemistry, PSA, and testosterone did not have to be obtained on Day 1 if screening samples had been performed within 7 days.
b. End of treatment/ withdrawal: these assessments did not need to be completed if they had been performed within 2 weeks of study withdrawal (within the last 8 weeks for tumor assessments, and within the last 4 weeks for PROs). Subjects discontinuing all treatment prior to disease progression were asked to return to the clinic at 8-week intervals for disease assessments.
c. Posttreatment follow-up: subjects discontinuing all treatment prior to disease progression were followed for tumor assessments until progression, until initiation of a subsequent anticancer therapy in the absence of documented progression, or until death, whichever occurred first. Subjects were evaluated for safety up to 28 days after the last dose of study treatment. AEs were followed until all serious or study drug-related toxicities had resolved or were determined to be "chronic" or "stable," whichever was later.
d. Informed consent: must have been obtained prior to undergoing any study specific procedure and might have occurred prior to the 21-day screening period.
e. Medical/oncological history: included oncologic history, demographics, history of other disease processes (active or resolved) and concomitant illnesses.
f. Physical examination: examination of major body systems.
g. Samples for hematology, blood chemistry, and urinalysis (protein): all laboratory assessments were performed by a central laboratory. Sites could perform additional local assays for the purposes of planning treatment administration, dose modification, or monitoring AEs. A dipstick protein urinalysis was performed at Screening, Cycle 3 Day 1 (as clinically indicated), and at the end of treatment/withdrawal visit. If the results of the dipstick test indicated a ≥2+ proteinuria, follow-up was to be performed with a quantitative urine protein analysis according to local standard practices. Thyroid-stimulating hormone was only performed at screening, Cycle 3 Day 1, and as clinically indicated thereafter.
h. BSAP and NTX: assessment of BSAP and serum and urine Type I collagen cross-linked NTX concentrations occurred at Screening, every 8 weeks from the start of study drug administration, and at the end of treatment/withdrawal visit, coinciding with tumor assessments.
i. ECG: 3 consecutive 12-lead ECGs approximately 2 minutes apart were obtained at Screening and on Cycle 2 Day 1 to determine the mean corrected QT (QTc) interval. During the study, if the mean QTc interval was prolonged (Grade >1), the ECGs were to be over read by a cardiologist at the site for confirmation. Additional ECGs could be performed as clinically indicated and following intrasubject sunitinib dose adjustments.
j. MUGA scan or echocardiogram (ECHO): performed at Screening visit and as clinically indicated thereafter.

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		Cycle 1		Cycles 2+			
	≤21 Days Prior to Dosing	Day 1 (-3)[a]	Day 15 (±3)	Day 1 (-3)	End of Treatment/ Withdrawal[b]	Post Tx[c]	Survival Follow-up

k. Study registration: subject number and treatment assignment were obtained via centralized randomization.
l. Study treatment (sunitinib): subjects received oral daily sunitinib continuously, starting on Cycle 1 Day 1. One cycle consisted of 28 days.
m. Study treatment (placebo): subjects received oral daily placebo continuously, starting on Cycle 1 Day 1. One cycle consisted of 28 days.
n. Study treatment (prednisone): subjects received prednisone (or prednisolone) orally 5 mg BID continuously, starting on Cycle 1 Day 1.
o. Tumor imaging: CT or MRI scans of chest, abdomen, and pelvis were performed to assess disease status at Screening, every 8 weeks from the start of study drug independent of cycle length, whenever disease progression was suspected, to confirm a partial or complete response (at least 4 weeks after initial documentation of response), and at the end of treatment/withdrawal visit. Tumor imaging was to continue on this calendar schedule regardless of any delays in dosing.
p. Bone scan: bone scan was performed at the same time points as the CT or MRI scans of the chest, abdomen, and pelvis.
q. Adverse events: subjects were followed for AEs from the first day of study treatment until at least 28 days after the last dose of study treatment, or until all serious or study drug-related toxicities were resolved or were determined to be "chronic" or "stable," whichever was later. Serious adverse events were to be monitored and reported from the time the subject provided informed consent as described in the protocol.
r. Concomitant medications/treatments: concomitant medications and treatments were recorded from 30 days prior to the start of study treatment, during the study, and up to 28 days after the last dose of study treatment.
s. Study drug compliance: sunitinib and placebo bottle(s) including any unused capsules were returned at the beginning of every cycle starting at Cycle 2 Day 1 and at the end of treatment/withdrawal visit for drug accountability.
t. Post-study survival status: follow-up survival information was collected by the site via clinic visit or telephone contact every 2 months until death.
u. Sample banking for exploratory research (optional), This research component was entirely optional for the subject and required a separate consent prior to the collection of a blood sample for pharmacogenomics and/or an archival tumor sample.
v. mBPI-sf, analgesic use diary, and SSQ: the mBPI-sf questionnaire and analgesic use diary were completed for the 7 consecutive days prior to the start of each new cycle, starting during the screening period (7 days prior to Cycle 1), at each subsequent cycle, and at the end of treatment/withdrawal visit. The SSQ was administered in conjunction with the diary on the first day of each 7-day period of recording, starting with Cycle 1 Day 22 (7 days prior to Cycle 2 Day 1).
w. FACT-P, EQ-5D, and subject's best guess questionnaires: subjects completed the FACT-P and EQ-5D at the clinic prior to dosing or other clinical activities on every Day 1 of each cycle, starting with Cycle 1, and at the end of treatment/withdrawal visit. At the end of the treatment/withdrawal visit, the subject's best guess questionnaire was completed.

Number of Subjects (Planned and Analyzed): A total of 819 subjects were planned for enrollment to observe the necessary number of events. A total of 873 subjects were assigned to study treatment and 866 subjects (99.2%) were treated of which 581 subjects were in the sunitinib arm and 285 in the placebo arm.

Of 873 subjects, 142 subjects were randomized in the US, 122 in France, 83 in the UK, 60 in Germany, 52 in Canada, 49 each in Denmark and Spain, 42 in Italy, 32 in Taiwan, 31 subjects in China, 28 each in Brazil and Sweden, 23 in Israel, 20 in Slovakia, 18 in Republic of Korea, 16 in Poland, 15 each in Belgium and Portugal, 14 each in Australia and Czech Republic, 11 in Peru and 9 in Finland.

Diagnosis and Main Criteria for Inclusion: Male subjects aged 18 years or older diagnosed with histologically or cytologically confirmed adenocarcinoma of the prostate with performance status 0 or 1, measured using the Eastern Cooperative Oncology Group (ECOG) performance scale were enrolled in this study. Subjects had progressive mCRPC after failure of docetaxel chemotherapy (resistant or intolerant), and had progressive disease that was based on prostate-specific antigen (PSA) progression, assessment using Response Evaluation Criteria in Solid Tumors (RECIST), or a positive bone scan. Subjects who were previously treated with sunitinib, or who had received more than 1 prior chemotherapy regimen for metastatic disease, chemotherapy within 3 weeks, subjects with impending complications from bone metastases, ongoing urinary obstruction, cardiac dysfunction (a value of corrected-QT interval >470 msec), or CNS involvement were excluded.

Study Treatment: Sunitinib (starting dose of 37.5 mg/day)/placebo was given on a continuous daily dosing (CDD) regimen for a total of 28 doses per cycle (a treatment cycle consisted of 4 weeks). Oral self-administration of sunitinib/placebo took place on an outpatient basis, once daily in the morning without regard to meals, except on the clinic visit days (eg, start of a new cycle). Sunitinib could be escalated to 50 mg at Cycle 3, provided there were no Grade >1 nonhematologic or Grade >2 hematologic toxicities.

Prednisone was administered in both treatment arms as background therapy. Prednisone was given on a CDD regimen of 5 mg twice daily (BID). Oral self-administration of prednisone took place on an outpatient basis, outpatient basis BID with food. Intrasubject dose interruptions and/or reductions were permitted in case a subject had experienced unacceptable toxicity provided that study discontinuation criteria were not met.

Sunitinib was supplied as capsule and prednisone was supplied as a tablet or as a liquid or concentrated solution.

Efficacy and Safety Endpoints:

The study was terminated for futility; therefore, all study efficacy findings were reported in an abbreviated report format. Efficacy analyses were performed only for OS, PFS, and ORR.

Primary Efficacy Endpoint: The primary efficacy endpoint was OS, defined as the time from randomization to date of death due to any cause.

Secondary Efficacy Endpoints: Secondary efficacy endpoints focused on PFS and ORR. PFS was the time from randomization to first documentation of objective progressive disease (PD) or to death on-study due to any cause, whichever occurred first. ORR was the percent of subjects with confirmed complete response (CR) or partial response (PR) according to RECIST, relative to the full analysis population. Confirmed responses were those that persisted on repeat imaging study ≥4 weeks after initial documentation of response. Designation of best response of stable disease (SD) required criteria to be satisfied at least 7 weeks after randomization.

The secondary endpoints of pain severity, health-related quality of life and prostate cancer-specific symptoms, and general health status were not analyzed due to early termination of the study.

Safety Endpoints: Type, incidence, severity (graded by the National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE Version 3.0]), timing, seriousness, and relatedness of adverse events (AEs) and laboratory abnormalities.

Safety Evaluations:

AEs: Assessment of AEs (including adverse drug reactions, worsening of baseline tumor-related signs and symptoms, illnesses with onset during the study, exacerbation of previous illnesses, any clinically significant changes in physical examination findings, and abnormal objective test findings).

Laboratory Evaluations: Laboratory evaluations included hematology, blood chemistry, and urinalysis. Bone-specific alkaline phosphatase, PSA, and serum and urine Type I collagen cross-linked N-telopeptide concentrations were be assessed as markers of tumor activity.

Other Safety Measures: Other safety measures included physical examination, vital signs (temperature, blood pressure, heart rate, and respiratory rate after 5 minutes of rest), ECOG performance status, 12-lead electrocardiograms (ECGs), and multiple gated acquisition scan or echocardiogram for left ventricular ejection fraction.

Statistical Methods:

Full Analysis Set (FAS): The FAS included all subjects who were randomized, with study drug assignment designated according to initial randomization, regardless of whether subjects received study drug according to the randomization schedule, or received a different drug from that to which they were randomized. The FAS was the primary population for evaluating all efficacy endpoints.

Safety Analysis Set: The safety population consisted of all subjects who had taken at least 1 dose of study medication.

OS and PFS were summarized using Kaplan-Meier methods and displayed graphically where appropriate. The median event time and corresponding 2-sided 95% confidence interval (CI) for the median were provided for OS and PFS. The hazard ratio and its 95% CIs were estimated. A stratified log-rank test (1-sided, ≤0.025) was used to compare OS and PFS

between the 2 treatment arms stratifying for ECOG status (0 versus 1) and type of disease progression (based on PSA progression only versus radiographic progression). The Cox regression model was used to explore the potential influences of the stratification factors on the primary OS endpoint and PFS. The ORR was summarized for each treatment arm along with the corresponding exact 2-sided 95% CI using a method based on the F distribution odds ratio estimator and used to contrast the treatment effects on response rates. A point estimate and a 2-sided 95% CI were calculated using the normal approximation. The best response (CR, PR, SD, or PD) for each subject was summarized by treatment arm. SD was also summarized by <3 months versus ≥3 months.

RESULTS:

Subject Disposition and Demography: Table 2 presents summary of subject disposition and subjects analyzed. A total of 873 subjects were assigned to study treatment, and 866 subjects (99.2%) were treated with study medication. Of these, 581 received sunitinib and 285 received placebo. Overall, the proportion of subjects in each arm was similar with respect to subject disposition.

Table 2. Summary of Subject Disposition and Subjects Analyzed

	Sunitinib + Prednisone	Placebo + Prednisone	Total
Number (%) of Subjects			
Assigned to study treatment[a]	584	289	873
Treated	581 (99.5)	285 (98.6)	866 (99.2)
Discontinued	581 (99.5)	285 (98.6)	866 (99.2)
Primary reason for withdrawal from study[b,c]			
Subject died	45 (7.7)	14 (4.9)	59 (6.8)
Adverse event	159 (27.4)	21 (7.4)	180 (20.8)
Global deterioration of health status	66 (11.4)	31 (10.9)	97 (11.2)
Lost to follow up	0	1 (0.4)	1 (0.1)
Objective progression or relapse	189 (32.5)	140 (49.1)	329 (38.0)
Other	14 (2.4)	10 (3.5)	24 (2.8)
Protocol violation	3 (0.5)	1 (0.4)	4 (0.5)
Study terminated by sponsor	57 (9.8)	43 (15.1)	100 (11.5)
Subject refused continued treatment for reason other than adverse event	48 (8.3)	24 (8.4)	72 (8.3)
Analyzed for efficacy[a]			
Full analysis set	584 (100)	289 (100)	873 (100)
Analyzed for safety[d]			
Adverse events	581 (100)	285 (100)	866 (100)
Laboratory data	575 (99.0)	279 (97.9)	854 (98.6)
Total months on study[e]	2899	1300	4199

Both discontinuations from treatment and study are included in table.
Both TEAEs and non-TEAEs are counted in "analyzed for adverse events" row.
Three subjects in sunitinib + prednisolone group and 4 subjects in placebo group were randomized but not treated.
Only deaths on study (ie, occurred within 28 days after the last dose of study medication) are included. Therefore, 2 subjects in sunitinib arm, and 3 subjects in placebo arm are not displayed.
TEAE = treatment-emergent adverse event.
a. Percentages based on the number of subjects assigned to study treatment within each treatment arm.
b. Discontinuations from treatment are not counted in table; only discontinuations from study.
c. Percentages based on the number of subjects in the safety population within each row.
d. Percentages based on the number of treated subjects within each treatment arm.
e. Months on study defined as (last dose date - first dose date +1)/30.44.

A summary of demographic characteristics is provided in Table 3.

Table 3. Demographic Characteristics (Full Analysis Population)

	Sunitinib + Prednisone N=584	Placebo + Prednisone N=289	Total N=873
Age, years			
18-44	3 (0.5)	0	3 (0.3)
45-64	177 (30.3)	97 (33.6)	274 (31.4)
≥65	404 (69.2)	192 (66.4)	596 (68.3)
Mean	68.1	67.8	68.0
SD	7.8	7.6	7.7
Range	39.0-90.0	47.0-86.0	39.0-90.0
Race, n (%)			
White	448 (76.7)	218 (75.4)	666 (76.3)
Black	24 (4.1)	12 (4.2)	36 (4.1)
Asian	56 (9.6)	28 (9.7)	84 (9.6)
Other	56 (9.6)	31 (10.7)	87 (10.0)

N = number of subjects in each treatment group; n (%) = number (percent) of subjects in specified category; SD = standard deviation.

Efficacy Results:

Table 4 summarizes OS by treatment. The median survival time was longer in the sunitinib arm (13.1 months: 95% CI; 12.0, 14.1) than in the placebo arm (11.8 months: 95% CI; 10.8, 14.2) but not statistically significant. When the survival data were adjusted for stratification factors (ie, ECOG 0 versus 1, and disease progression based on PSA only versus radiographic progression), the hazard ratio was 0.914 (sunitinib versus placebo) with a 95% CI of 0.762, 1.097 and a p-value of 0.1678. Approximately 40% of the subjects in each treatment arm were censored. The most frequent reason for censoring was that the subject was still alive at the time he or she completed the study. The study failed to meet its primary endpoint of improvement in OS based on this outcome.

Table 4. Summary of Overall Survival by Treatment (Full Analysis Population)

	Sunitinib + Prednisone N=584	Placebo + Prednisone N=289
Number of deaths, n (%)	338 (57.9)	178 (61.6)
Cause of death		
Disease under study	281 (48.1)	151 (52.2)
Study treatment toxicity	1 (<1.0)	1 (<1.0)
Unknown	33 (5.7)	12 (4.2)
Other	28 (4.8)	15 (5.2)
Number censored, n (%)	246 (42.1)	111 (38.4)
Reason for censorship, n (%)		
Alive	217 (37.2)	95 (32.9)
Subject no longer willing to participate	15 (2.6)	10 (3.5)
Lost to follow-up	14 (2.4)	6 (2.1)
Kaplan-Meier estimates of time to event (month)		
Quartiles (95% CI)[a]		
25%	6.9 [5.8, 7.9]	6.5 [5.1, 7.8]
50%	13.1 [12.0, 14.1]	11.8 [10.8, 14.2]
75%	23.7 [22.7, --]	19.9 [18.5, --]
Versus placebo + prednisone		
Hazard ratio[b]	0.914	--
95% CI of hazard ratio	0.762-1.097	--
p-value[c]	0.1678	--

Percentages are based on the number of subjects in the full analysis population within each treatment arm.
CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; N = number of subjects in each treatment group; n (%) = number (percent) of subjects in specified category; PSA = prostate-specific antigen.

a. Based on the Brookmeyer and Crowley Method.
b. Based on the Cox proportional hazards model stratified by ECOG 0 versus 1 and disease progression based on PSA only versus radiographic progression.
c. One-sided p-value from the log-rank test stratified by ECOG 0 versus 1, and disease progression based on PSA only versus radiographic progression.

Table 5 presents the results of the Cox proportional hazards analysis of OS treatment comparison controlling for selected baseline or stratification factors.

Table 5. Results of Cox Proportional Hazards Analysis of Overall Survival Treatment Comparison Controlling for Selected Baseline or Stratification Factors Simultaneously-Derived Investigator's Assessment (Full Analysis Population)

Variables Included in the Model[a]	Sunitinib (N=584)	Placebo (N=289)	Hazard Ratio	95 % CI for HR	p-Value[b]
Number of subjects with an event (%)	338 (57.9)	178 (61.6)			
Treatment (sunitinib vs. placebo)			0.918	(0.765, 1.103)	0.3608
ECOG(1 vs. 0)			1.85	(1.550, 2.208)	<0.0001
Disease progression (PSA vs. radiographic)			0.767	(0.644, 0.913)	0.0029
Ethnicity (White vs. Non-White)			1.309	(1.054, 1.625)	0.0147
Time since primary diagnosis (>1 year vs. ≤1 year)			0.811	(0.654, 1.006)	0.0566

CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; HR = hazard ratio; N = number of subjects in each treatment group; PSA = prostate-specific antigen; vs = versus.

a. Except treatment factor all covariates used backward selection process. Only variables significant at 10% level were included in the final model. Covariates included ECOG (0 vs. 1), disease progression base (PSA only vs. Radiographic), age (≥65 vs. < 65), Ethnicity (white vs. non-white), time from initial diagnosis, and number of prior regimens.

b. P-value was from the Cox proportional hazard model for treatment comparison controlling for individual covariates.

PFS: Table 6 summarizes PFS (derived Investigator's assessment) by treatment. The median PFS was longer in the sunitinib arm (24.1 weeks: 95% CI; 23.4, 28.1) than in the placebo arm (17.9 weeks: 95% CI; 15.8, 24.1). When PFS was adjusted for stratification factors (ie, ECOG 0 versus 1, and disease progression based on PSA only versus radiographic progression, the hazard ratio was 0.725 (sunitinib versus placebo), with a 95% CI of 0.591, 0.890 and a p-value of <0.001. Although there was a high censoring rate for PFS (56% and 48% in the sunitinib and placebo arms, respectively) these data support longer PFS with sunitinib. The most frequent reason for censoring was being off treatment prior to progression and not followed by further disease assessments.

Table 6. Summary of Progression-Free Survival, Derived Investigator's Assessment (Full Analysis Population)

	Sunitinib + Prednisone N=584	Placebo + Prednisone N=289
Number with event, n (%)	255 (43.7)	149 (51.6)
Type of event		
Objective progression	210 (36.0)	135 (46.7)
Death without objective progression	45 (7.7)	14 (4.8)
Number censored, n (%)	329 (56.3)	140 (48.4)
Reason for censorship, n (%)		
No adequate Baseline assessments	8 (1.4)	3 (1.0)
No on-study disease assessments	69 (11.8)	33 (11.4)
Given new anti-cancer treatment prior to tumor progression	29 (5.0)	25 (8.7)
Off treatment prior to progression	223 (38.2)	78 (27.0)
Withdrew consent for follow-up	0	0
Lost to follow-up	0	0
Unacceptable gap (>20 weeks) between PD or death to the most recent prior adequate assessment	0	1 (<1.0)
In follow-up for progression	0	0
Kaplan-Meier estimates of time to event (week)		
Quartiles (95% CI)[a]		
25%	13.7 (9.4, 15.7)	8.1 (8.0, 8.3)
50%	24.1 (23.4, 28.1)	17.9 (15.8, 24,1)
75%	48.7 (47.4, 74.4)	39.0 (32.1, 49.6)
Versus placebo + prednisone		
Hazard ratio[b]	0.725	--
95% CI of hazard ratio	0.591-0.890	--
p-value[c]	<0.001	--

Percentages are based on the number of subjects in the full analysis population within each treatment arm.
CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; N = number of subjects in each treatment group; n (%) = number (percent) of subjects in specified category; PD = progressive disease; PSA = prostate-specific antigen.

a. Based on the Brookmeyer and Crowley Method.
b. Based on the Cox Proportional hazards model stratified by ECOG 0 versus 1, and disease progression based on PSA only versus radiographic progression.
c. One-sided p-value from the unstratified log-rank test stratified by ECOG 0 versus 1, and disease progression based on PSA only versus radiographic progression.

Table 7 presents the results of the Cox proportional hazards analysis of PFS treatment comparison controlling for selected Baseline or stratification factors.

Table 7. Results of Cox Proportional Hazards Analysis of Progression-Free Survival Treatment Comparison Controlling for Selected Baseline or Stratification Factors Simultaneously-Derived Investigator's Assessment (Full Analysis Population)

Variables Included in the Model[a]	Sunitinib (N=584)	Placebo (N=289)	Hazard Ratio	95 % CI for HR	p-Value[b]
Number of subjects with an event	255 (43.7)	149 (51.6)			
Treatment (sunitinib vs. placebo)			0.721	(0.588, 0.885)	0.0018
ECOG (1 vs. 0)			1.586	(1.302, 1.933)	<0.0001
Disease progression (PSA vs. radiographic)			0.722	(0.593, 0.880)	0.0012
Age (≥65 vs. < 65)			0.796	(0.649, 0.978)	0.0295
Ethnicity (White vs. Non-White)			1.302	(1.027, 1.649)	0.0289
Time since primary diagnosis (>1 year vs. ≤1 year)			0.686	(0.545, 0.864)	0.0014

CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; HR = hazard ratio; N = number of subjects in each treatment group; PSA = prostate-specific antigen; vs = versus.

a. Except treatment factor all covariates used backward selection process. Only variables significant at 10% level were included in the final model. Covariates included ECOG (0 vs. 1), disease progression base (PSA only vs. Radiographic), age (≥65 vs. < 65), Ethnicity (White vs. Non-White), time since primary diagnosis, and number of prior regimens.

b. p-value was from the Cox proportional hazard model for treatment comparison controlling for individual covariates.

Best Overall Response: The ORR was 6.1% (95% CI; 3.8, 9.3) in the sunitinib arm and 1.8% (95% CI; 0.4, 5.2) in the placebo arm. The odds ratio was 3.561 (sunitinib versus placebo), with a 95% CI of 1.0, 19.0, and a p-value of 0.040. None of the subjects had aCR. Table 8 presents a summary of best overall response in full analysis population.

Table 8. Summary of Best Overall Response, Derived Investigator's Assessment (Full Analysis Population)

	Sunitinib + Prednisone N=584	Placebo + Prednisone N=289
Number of subjects with Baseline target assessments, n (%)	327 (56.0)	167 (57.8)
Best overall response, n (%)		
Complete response (CR)	0	0
Partial response (PR)	20 (6.1)	3 (1.8)
Stable/No response (SD)	197 (60.2)	83 (49.7)
Objective progression (PD)	60 (18.3)	57 (34.1)
Indeterminate (IND)	50 (15.3)	24 (14.4)
Stable disease (SD)		
Duration <3 months	145 (73.6)	58 (69.9)
Duration ≥3 months	52 (26.4)	25 (30.1)
Objective response rate (CR + PR)	20 (6.1)	3 (1.8)
95% exact CI[a]	[3.8, 9.3]	[0.4, 5.2]
Versus placebo + prednisone		
Odds ratio (sunitinib vs placebo)[b]	3.561	--
95% CI of odds ratio[c]	[1.0, 19.0]	--
p-value[c]	0.040	--

All PD events occurring after randomization date were assessed as 'Progressive Disease' for best overall response if other criteria were not applicable.
The minimum days after start date for assessing the best overall response of SD was 42 days (6 weeks).
Subjects with best overall response of 'Indeterminate' were defined as subjects for which no other response category applied.
CI = confidence interval; N = number of subjects in each treatment group; n (%) = number (percent) of subjects in specified category; PD = progressive disease; SD = stable disease; vs = versus.
a. Using exact method based on a binomial distribution.
b. Calculated based on a normal distribution.
c. p-value from a 2-sided Fisher's Exact test.

Safety Results: A summary of treatment-emergent adverse events (TEAEs, [all causality and treatment related]) is provided in Table 9.

Table 9. Summary of All-Causality and Treatment-Related Treatment-Emergent Adverse Events (Safety Population)

Number (%) of Subjects	Sunitinib + Prednisone N=581	Placebo + Prednisone N=285	Total N=866
All Causality			
Evaluable for AEs	581	285	866
Number of AEs	7154	1915	9069
Subjects with AEs	576 (99.1)	260 (91.2)	836 (96.5)
Subjects with SAEs	275 (47.3)	86 (30.2)	361 (41.7)
Subjects with Grade 3 or 4 AEs	432 (74.4)	118 (41.4)	550 (63.5)
Subjects with Grade 5 AEs	66 (11.4)	32 (11.2)	98 (11.3)
Subjects discontinued due to AEs[a]	197 (33.9)	32 (11.2)	229 (26.4)
Subjects with dose reduced due to AE[a]	131 (22.5)	11 (3.9)	142 (16.4)
Subjects with temporary discontinuation due to AE[a]	367 (63.2)	78 (27.4)	445 (51.4)
Treatment-Related			
Evaluable for AEs	581	285	866
Number of AEs	4342	652	4994
Subjects with AEs	547 (94.1)	176 (61.8)	723 (83.5)
Subjects with SAEs	149 (25.6)	19 (6.7)	168 (19.4)
Subjects with Grade 3 or 4 AEs	339 (58.3)	45 (15.8)	384 (44.3)
Subjects with Grade 5 AEs	12 (2.1)	1 (0.4)	13 (1.5)
Subjects discontinued due to AEs[a]	124 (21.3)	5 (1.8)	129 (14.9)
Subjects with dose reduced due to AEs[a]	127 (21.9)	9 (3.2)	136 (15.7)
Subjects with temporary discontinuation due to AE[a]	311 (53.5)	40 (14.0)	351 (40.5)

AEs and SAEs are not separated out.
Except for the number of AEs, subjects are counted only once per treatment in each row.
SAEs based on Investigator's assessment.
Percentages based on the number of subjects in the safety population within each treatment arm.
MedDRA (version 14.1) coding dictionary applied.
All causality: One subject (sunitinib) died on study but did not have a Grade 5 event designated on the AE page. Some subjects died beyond 28 days after the last dose of study medication but had Grade 5 entered in the database: sunitinib: 10, placebo: 2.
Treatment related: One subject (placebo) died after 28 days of the last dose of study medication but had Grade 5 entered in the database.
AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects in the study population; SAE = serious adverse event.
a. Sunitinib/placebo only.

TEAEs: Table 10 presents the TEAEs (all causality) experienced in ≥5% of safety population. Among the most common TEAEs in the sunitinib arm (all grades and all causalities) were diarrhea, nausea, decreased appetite, fatigue, and vomiting. TEAEs that were reported at a frequency of 10% or higher in the sunitinib arm included: diarrhea, nausea, decreased appetite, fatigue, vomiting, palmar-plantar erythrodysesthesia (PPE) syndrome, dysgeusia, asthenia, hypertension, mucosal inflammation, weight decreased, dyspepsia, neutropenia, stomatitis, yellow skin, and thrombocytopenia. None of the TEAEs in the placebo arm were reported at a frequency of 10% or higher than in the sunitinib arm. Back pain and bone pain were reported more frequently in the placebo arm.

Table 10. Treatment-Emergent Adverse Events (All Causality) Reported in ≥5% of Safety Population

System Organ Class MedDRA (v14.1) Preferred Term[a]	Sunitinib + Prednisone (N=581)	Placebo + Prednisone (N=285)	Total (N=866)
Blood and lymphatic system disorders	216 (37.2)	57 (20.0)	273 (31.5)
Anaemia	140 (24.1)	53 (18.6)	193 (22.3)
Leukopenia	60 (10.3)	2 (0.7)	62 (7.2)
Neutropenia	84 (14.5)	1 (0.4)	85 (9.8)
Thrombocytopenia	72 (12.4)	8 (2.8)	80 (9.2)
Gastrointestinal disorders	451 (77.6)	145 (50.9)	596 (68.8)
Abdominal pain	41 (7.1)	13 (4.6)	54 (6.2)
Abdominal pain upper	39 (6.7)	10 (3.5)	49 (5.7)
Constipation	112 (19.3)	56 (19.6)	168 (19.4)
Diarrhoea	267 (46.0)	43 (15.1)	310 (35.8)
Dry mouth	41 (7.1)	13 (4.6)	54 (6.2)
Dyspepsia	99 (17.0)	11 (3.9)	110 (12.7)
Nausea	240 (41.3)	68 (23.9)	308 (35.6)
Stomatitis	81 (13.9)	11 (3.9)	92 (10.6)
Vomiting	189 (32.5)	39 (13.7)	228 (26.3)
General disorders and administration site conditions	393 (67.6)	137 (48.1)	530 (61.2)
Asthenia	153 (26.3)	41 (14.4)	194 (22.4)
Fatigue	202 (34.8)	69 (24.2)	271 (31.3)
Mucosal inflammation	118 (20.3)	14 (4.9)	132 (15.2)
Oedema peripheral	63 (10.8)	23 (8.1)	86 (9.9)
Pain	49 (8.4)	24 (8.4)	73 (8.4)
Pyrexia	57 (9.8)	12 (4.2)	69 (8.0)
Infections and infestations	51 (8.8)	12 (4.2)	63 (7.3)
Urinary tract infection	51 (8.8)	12 (4.2)	63 (7.3)
Investigations	180 (31.0)	44 (15.4)	224 (25.9)
Aspartate aminotransferase increased	29 (5.0)	6 (2.1)	35 (4.0)
Blood alkaline phosphatase increased	37 (6.4)	17 (6.0)	54 (6.2)
Haemoglobin decreased	36 (6.2)	6 (2.1)	42 (4.8)
Weight decreased	115 (19.8)	25 (8.8)	140 (16.2)
Metabolism and nutrition disorders	259 (44.6)	56 (19.6)	315 (36.4)
Decreased appetite	237 (40.8)	52 (18.2)	289 (33.4)
Dehydration	32 (5.5)	5 (1.8)	37 (4.3)
Hypokalaemia	35 (6.0)	8 (2.8)	43 (5.0)
Musculoskeletal and connective tissue disorders	246 (42.3)	142 (49.8)	388 (44.8)
Arthralgia	56 (9.6)	26 (9.1)	82 (9.5)
Back pain	87 (15.0)	58 (20.4)	145 (16.7)
Bone pain	62 (10.7)	45 (15.8)	107 (12.4)
Muscle spasms	21 (3.6)	16 (5.6)	37 (4.3)
Muscular weakness	32 (5.5)	13 (4.6)	45 (5.2)
Musculoskeletal pain	37 (6.4)	14 (4.9)	51 (5.9)
Pain in extremity	75 (12.9)	38 (13.3)	113 (13.0)
Nervous system disorders	222 (38.2)	55 (19.3)	277 (32.0)
Dizziness	49 (8.4)	16 (5.6)	65 (7.5)
Dysgeusia	170 (29.3)	27 (9.5)	197 (22.7)
Headache	50 (8.6)	17 (6.0)	67 (7.7)
Psychiatric disorders	40 (6.9)	19 (6.7)	59 (6.8)
Insomnia	40 (6.9)	19 (6.7)	59 (6.8)
Renal and urinary disorders	46 (7.9)	15 (5.3)	61 (7.0)
Haematuria	46 (7.9)	15 (5.3)	61 (7.0)
Respiratory, thoracic and mediastinal disorders	146 (25.1)	31 (10.9)	177 (20.4)
Cough	46 (7.9)	12 (4.2)	58 (6.7)
Dyspnoea	71 (12.2)	18 (6.3)	89 (10.3)
Epistaxis	57 (9.8)	3 (1.1)	60 (6.9)
Skin and subcutaneous tissue disorders	277 (47.7)	46 (16.1)	323 (37.3)

Table 10. Treatment-Emergent Adverse Events (All Causality) Reported in ≥5% of Safety Population

System Organ Class MedDRA (v14.1) Preferred Term[a]	Sunitinib + Prednisone (N=581)	Placebo + Prednisone (N=285)	Total (N=866)
Dry skin	60 (10.3)	18 (6.3)	78 (9.0)
Palmar-plantar erythrodysaesthesia syndrome	172 (29.6)	8 (2.8)	180 (20.8)
Petechiae	41 (7.1)	4 (1.4)	45 (5.2)
Rash	51 (8.8)	17 (6.0)	68 (7.9)
Skin discolouration	33 (5.7)	4 (1.4)	37 (4.3)
Yellow skin	78 (13.4)	6 (2.1)	84 (9.7)
Vascular disorders	150 (25.8)	17 (6.0)	167 (19.3)
Hypertension	150 (25.8)	17 (6.0)	167 (19.3)

Subjects were only counted once per treatment for each row.
MedDRA (v14.1) = Medical Dictionary for Regulatory Activities (version 14.1); N = number of subjects in each treatment group; n = number of subjects with reported adverse event.
a. MedDRA (version 14.1) dictionary was applied.

Treatment-Related TEAEs: Table 11 presents treatment-related TEAEs experienced in ≥5% of safety population. The percentages of TEAEs considered related to the study treatment were higher in the sunitinib arm than in the placebo arm, except for the event of constipation. Treatment-related TEAEs that were reported with a frequency of 20% or higher in the sunitinib arm included diarrhea, nausea, decreased appetite, and PPE syndrome.

Table 11. Treatment-Emergent Treatment-Related (Sunitinib/Placebo) Adverse Events Reported in ≥5% of Safety Population

System Organ Class MedDRA (v14.1) Preferred Term[a]	Sunitinib + Prednisone (N=581)	Placebo + Prednisone (N=285)	Total (N=866)
Blood and lymphatic system disorders	199 (34.3)	26 (9.1)	225 (26.0)
Anaemia	111 (19.1)	20 (7.0)	131 (15.1)
Leukopenia	60 (10.3)	1 (0.4)	61 (7.0)
Neutropenia	81 (13.9)	0	81 (9.4)
Thrombocytopenia	69 (11.9)	5 (1.8)	74 (8.5)
Gastrointestinal disorders	438 (75.4)	97 (34.0)	535 (61.8)
Constipation	39 (6.7)	21 (7.4)	60 (6.9)
Diarrhoea	239 (41.1)	27 (9.5)	266 (30.7)
Dry mouth	36 (6.2)	11 (3.9)	47 (5.4)
Dyspepsia	71 (12.2)	5 (1.8)	76 (8.8)
Nausea	201 (34.6)	35 (12.3)	236 (27.3)
Stomatitis	77 (13.3)	11 (3.9)	88 (10.2)
Vomiting	143 (24.6)	19 (6.7)	162 (18.7)
General disorders and administration site conditions	338 (58.2)	84 (29.5)	422 (48.7)
Asthenia	128 (22.0)	29 (10.2)	157 (18.1)
Fatigue	175 (30.1)	42 (14.7)	217 (25.1)
Mucosal inflammation	116 (20.0)	13 (4.6)	129 (14.9)
Investigations	173 (29.8)	28 (9.8)	201 (23.2)
Weight decreased	84 (14.5)	10 (3.5)	94 (10.9)
Metabolism and nutrition disorders	228 (39.2)	43 (15.1)	271 (31.3)
Decreased appetite	201 (34.6)	33 (11.6)	234 (27.0)
Musculoskeletal and connective tissue disorders	91 (15.7)	23 (8.1)	114 (13.2)
Pain in extremity	30 (5.2)	6 (2.1)	36 (4.2)
Nervous system disorders	239 (41.1)	49 (17.2)	288 (33.3)
Dysgeusia	164 (28.2)	24 (8.4)	188 (21.7)
Respiratory, thoracic and mediastinal disorders	133 (22.9)	17 (6.0)	150 (17.3)
Dyspnoea	40 (6.9)	4 (1.4)	44 (5.1)
Epistaxis	48 (8.3)	1 (0.4)	49 (5.7)
Skin and subcutaneous tissue disorders	314 (54.0)	54 (18.9)	368 (42.5)
Dry skin	55 (9.5)	16 (5.6)	71 (8.2)
Palmar-plantar erythrodysaesthesia syndrome	169 (29.1)	8 (2.8)	177 (20.4)
Rash	38 (6.5)	10 (3.5)	48 (5.5)
Skin discolouration	33 (5.7)	4 (1.4)	37 (4.3)
Yellow skin	77 (13.3)	6 (2.1)	83 (9.6)
Vascular disorders	152 (26.2)	27 (9.5)	179 (20.7)
Hypertension	126 (21.7)	14 (4.9)	140 (16.2)

AEs and SAEs are not separated out.
AEs = adverse events; MedDRA (v14.1) = Medical Dictionary for Regulatory Activities (version 14.1); N = number of subjects in each treatment group; n = number of subjects with reported adverse event; SAEs = serious adverse events.
a. MedDRA (v14.1) dictionary is applied.

Severity of AEs as per CTCAE Criteria: Of the 581 subjects in the sunitinib arm, 432 (74.4%) and 339 (58.3%) subjects reported treatment-emergent and treatment-related Grade 3 or 4 AEs, respectively. In the placebo arm out of 285 subjects, 118 (41.4%) and 45 (15.8%) subjects reported treatment-emergent and treatment-related Grade 3 or 4 AEs, respectively. Grade 5 TEAEs were reported by 66 (11.4%) subjects in the sunitinib arm and 32 (11.2%) subjects in the placebo arm, while 12 (2.1%) subjects in the sunitinib arm and 1 (0.4) subject in the placebo arm reported Grade 5 treatment-related AEs.

Grade 3 or 4 TEAEs (fatigue and asthenia) were reported at a frequency of 10% or higher in only the sunitinib arm. Grade 3 or 4 TEAEs that were reported at a frequency of 5% or

higher in the sunitinib versus placebo arms included asthenia (10.8% versus 4.6%), fatigue (10.8% versus 3.5%), PPE syndrome (6.5% versus 0%). The majority of the Grade 3 or 4 TEAEs were treatment-related.

Treatment-Emergent SAEs (All Causality): Table 12 presents treatment-emergent serious AEs (SAEs, [all causality]) reported during the study in the safety population. The majority of SAEs was due to disease progression (5.5% and 6.7% in the sunitinib and placebo arms, respectively).

Table 12. Treatment-Emergent Serious Adverse Events (All Causality) Reported in Safety Population)

System Organ Class MedDRA (v14.1) Preferred Term	Sunitinib + Prednisone (N=581)	Placebo + Prednisone (N=285)	Total (N=866)
Number of subjects with at least one serious adverse event n (%)	275 (47.3)	86 (30.2)	361 (41.7)
Blood and lymphatic system disorders	33 (5.7)	5 (1.8)	38 (4.4)
Anaemia	21 (3.6)	3 (1.1)	24 (2.8)
Disseminated intravascular coagulation	1 (0.2)	1 (0.4)	2 (0.2)
Febrile bone marrow aplasia	1 (0.2)	0	1 (0.1)
Febrile neutropenia	2 (0.3)	0	2 (0.2)
Leukopenia	3 (0.5)	0	3 (0.3)
Neutropenia	1 (0.2)	0	1 (0.1)
Pancytopenia	3 (0.5)	0	3 (0.3)
Thrombocytopenia	8 (1.4)	1 (0.4)	9 (1.0)
Thrombotic thrombocytopenic purpura	1 (0.2)	0	1 (0.1)
Cardiac disorders	11 (1.9)	3 (1.1)	14 (1.6)
Acute coronary syndrome	1 (0.2)	0	1 (0.1)
Acute myocardial infarction	3 (0.5)	0	3 (0.3)
Atrial flutter	1 (0.2)	0	1 (0.1)
Atrioventricular block second degree	1 (0.2)	0	1 (0.1)
Cardiac failure	2 (0.3)	0	2 (0.2)
Cardiac failure congestive	1 (0.2)	0	1 (0.1)
Cardio-respiratory arrest	2 (0.3)	1 (0.4)	3 (0.3)
Cardiogenic shock	1 (0.2)	0	1 (0.1)
Left ventricular dysfunction	1 (0.2)	0	1 (0.1)
Myocardial infarction	1 (0.2)	1 (0.4)	2 (0.2)
Myocardial ischaemia	0	1 (0.4)	1 (0.1)
Congenital, familial and genetic disorders	1 (0.2)	0	1 (0.1)
Cerebral arteriovenous malformation haemorrhagic	1 (0.2)	0	1 (0.1)
Ear and labyrinth disorders	2 (0.3)	0	2 (0.2)
Vertigo	1 (0.2)	0	1 (0.1)
Vestibular disorder	1 (0.2)	0	1 (0.1)
Endocrine disorders	0	2 (0.7)	2 (0.2)
Adrenal insufficiency	0	1 (0.4)	1 (0.1)
Inappropriate antidiuretic hormone secretion	0	1 (0.4)	1 (0.1)
Eye disorders	3 (0.5)	0	3 (0.3)
Conjunctival oedema	1 (0.2)	0	1 (0.1)
Diplopia	1 (0.2)	0	1 (0.1)
Optic ischaemic neuropathy	1 (0.2)	0	1 (0.1)
Gastrointestinal disorders	73 (12.6)	13 (4.6)	86 (9.9)
Abdominal pain	3 (0.5)	1 (0.4)	4 (0.5)
Abdominal pain upper	2 (0.3)	0	2 (0.2)
Anal fistula	2 (0.3)	0	2 (0.2)
Anal haemorrhage	1 (0.2)	0	1 (0.1)
Anal ulcer	1 (0.2)	0	1 (0.1)
Colitis	1 (0.2)	0	1 (0.1)
Constipation	3 (0.5)	3 (1.1)	6 (0.7)
Diarrhoea	7 (1.2)	1 (0.4)	8 (0.9)
Diverticular perforation	1 (0.2)	0	1 (0.1)
Duodenitis	1 (0.2)	0	1 (0.1)
Gastric ulcer	4 (0.7)	0	4 (0.5)
Gastrointestinal haemorrhage	7 (1.2)	1 (0.4)	8 (0.9)
Gingival bleeding	2 (0.3)	0	2 (0.2)
Haematemesis	1 (0.2)	0	1 (0.1)
Haematochezia	1 (0.2)	0	1 (0.1)
Haemorrhoidal haemorrhage	1 (0.2)	0	1 (0.1)
Intestinal haemorrhage	1 (0.2)	0	1 (0.1)
Intestinal ischaemia	1 (0.2)	0	1 (0.1)

Table 12. Treatment-Emergent Serious Adverse Events (All Causality) Reported in Safety Population)

System Organ Class MedDRA (v14.1) Preferred Term	Sunitinib + Prednisone (N=581)	Placebo + Prednisone (N=285)	Total (N=866)
Intestinal obstruction	2 (0.3)	0	2 (0.2)
Large intestine perforation	2 (0.3)	0	2 (0.2)
Lower gastrointestinal haemorrhage	1 (0.2)	0	1 (0.1)
Melaena	3 (0.5)	0	3 (0.3)
Mouth haemorrhage	1 (0.2)	0	1 (0.1)
Nausea	13 (2.2)	4 (1.4)	17 (2.0)
Oesophagitis	3 (0.5)	0	3 (0.3)
Pancreatitis acute	1 (0.2)	0	1 (0.1)
Peptic ulcer	1 (0.2)	0	1 (0.1)
Proctitis	1 (0.2)	0	1 (0.1)
Rectal haemorrhage	2 (0.3)	1 (0.4)	3 (0.3)
Rectal ulcer	2 (0.3)	0	2 (0.2)
Rectal ulcer haemorrhage	1 (0.2)	0	1 (0.1)
Rectourethral fistula	1 (0.2)	0	1 (0.1)
Small intestinal obstruction	1 (0.2)	0	1 (0.1)
Stomatitis	1 (0.2)	0	1 (0.1)
Vomiting	16 (2.8)	5 (1.8)	21 (2.4)
General disorders and administration site conditions	85 (14.6)	34 (11.9)	119 (13.7)
Asthenia	14 (2.4)	1 (0.4)	15 (1.7)
Chest pain	3 (0.5)	2 (0.7)	5 (0.6)
Death	5 (0.9)	1 (0.4)	6 (0.7)
Device occlusion	2 (0.3)	1 (0.4)	3 (0.3)
Disease progression	32 (5.5)	19 (6.7)	51 (5.9)
Fatigue	2 (0.3)	1 (0.4)	3 (0.3)
General physical health deterioration	10 (1.7)	2 (0.7)	12 (1.4)
Ill-defined disorder	2 (0.3)	0	2 (0.2)
Impaired healing	1 (0.2)	0	1 (0.1)
Influenza like illness	1 (0.2)	0	1 (0.1)
Malaise	2 (0.3)	0	2 (0.2)
Medical device complication	1 (0.2)	0	1 (0.1)
Mucosal inflammation	1 (0.2)	0	1 (0.1)
Multi-organ failure	1 (0.2)	0	1 (0.1)
Oedema peripheral	2 (0.3)	0	2 (0.2)
Pain	2 (0.3)	4 (1.4)	6 (0.7)
Performance status decreased	2 (0.3)	0	2 (0.2)
Pyrexia	11 (1.9)	3 (1.1)	14 (1.6)
Sudden cardiac death	1 (0.2)	0	1 (0.1)
Sudden death	0	1 (0.4)	1 (0.1)
Hepatobiliary disorders	8 (1.4)	3 (1.1)	11 (1.3)
Cholecystitis acute	4 (0.7)	0	4 (0.5)
Cholelithiasis	0	1 (0.4)	1 (0.1)
Gallbladder disorder	1 (0.2)	0	1 (0.1)
Hepatic failure	1 (0.2)	1 (0.4)	2 (0.2)
Hepatitis cholestatic	1 (0.2)	0	1 (0.1)
Hepatorenal failure	0	1 (0.4)	1 (0.1)
Hepatotoxicity	1 (0.2)	0	1 (0.1)
Infections and infestations	47 (8.1)	16 (5.6)	63 (7.3)
Anal abscess	6 (1.0)	0	6 (0.7)
Appendicitis	1 (0.2)	0	1 (0.1)
Bronchitis	1 (0.2)	0	1 (0.1)
Cellulitis	1 (0.2)	0	1 (0.1)
Cholecystitis infective	1 (0.2)	0	1 (0.1)
Clostridial infection	1 (0.2)	0	1 (0.1)
Device related infection	1 (0.2)	0	1 (0.1)
Diverticulitis	4 (0.7)	0	4 (0.5)

Table 12. Treatment-Emergent Serious Adverse Events (All Causality) Reported in Safety Population)

System Organ Class MedDRA (v14.1) Preferred Term	Sunitinib + Prednisone (N=581)	Placebo + Prednisone (N=285)	Total (N=866)
Febrile infection	0	1 (0.4)	1 (0.1)
Gastroenteritis	2 (0.3)	0	2 (0.2)
Herpes zoster	1 (0.2)	1 (0.4)	2 (0.2)
Infection	4 (0.7)	0	4 (0.5)
Infectious peritonitis	1 (0.2)	0	1 (0.1)
Lower respiratory tract infection	1 (0.2)	0	1 (0.1)
Meningitis bacterial	0	1 (0.4)	1 (0.1)
Oral fungal infection	1 (0.2)	0	1 (0.1)
Otitis media chronic	1 (0.2)	0	1 (0.1)
Paronychia	0	1 (0.4)	1 (0.1)
Perirectal abscess	1 (0.2)	0	1 (0.1)
Pneumonia	4 (0.7)	4 (1.4)	8 (0.9)
Pseudomonas infection	1 (0.2)	0	1 (0.1)
Pyelonephritis	1 (0.2)	0	1 (0.1)
Rectal abscess	1 (0.2)	0	1 (0.1)
Sepsis	3 (0.5)	0	3 (0.3)
Septic shock	2 (0.3)	0	2 (0.2)
Staphylococcal bacteraemia	0	1 (0.4)	1 (0.1)
Subcutaneous abscess	1 (0.2)	0	1 (0.1)
Tooth infection	1 (0.2)	0	1 (0.1)
Upper respiratory tract infection	1 (0.2)	0	1 (0.1)
Urinary tract infection	10 (1.7)	7 (2.5)	17 (2.0)
Urinary tract infection bacterial	0	1 (0.4)	1 (0.1)
Urosepsis	1 (0.2)	1 (0.4)	2 (0.2)
Injury, poisoning and procedural complications	15 (2.6)	3 (1.1)	18 (2.1)
Compression fracture	0	1 (0.4)	1 (0.1)
Cystitis radiation	2 (0.3)	0	2 (0.2)
Fall	5 (0.9)	1 (0.4)	6 (0.7)
Fracture	1 (0.2)	0	1 (0.1)
Hand fracture	0	1 (0.4)	1 (0.1)
Head injury	2 (0.3)	0	2 (0.2)
Hip fracture	1 (0.2)	0	1 (0.1)
Humerus fracture	1 (0.2)	0	1 (0.1)
Jaw fracture	1 (0.2)	0	1 (0.1)
Laceration	0	1 (0.4)	1 (0.1)
Procedural complication	1 (0.2)	0	1 (0.1)
Subdural haemorrhage	0	1 (0.4)	1 (0.1)
Toxicity to various agents	2 (0.3)	0	2 (0.2)
Investigations	10 (1.7)	1 (0.4)	11 (1.3)
Aspartate aminotransferase increased	1 (0.2)	0	1 (0.1)
Blood alkaline phosphatase increased	1 (0.2)	0	1 (0.1)
Blood creatine phosphokinase increased	1 (0.2)	0	1 (0.1)
Blood creatinine increased	2 (0.3)	0	2 (0.2)
Blood urea increased	2 (0.3)	0	2 (0.2)
C-reactive protein increased	0	1 (0.4)	1 (0.1)
Eastern Cooperative Oncology Group performance status worsened	1 (0.2)	0	1 (0.1)
Haemoglobin decreased	2 (0.3)	0	2 (0.2)
Prothrombin time prolonged	1 (0.2)	0	1 (0.1)
Urine output decreased	1 (0.2)	0	1 (0.1)
Metabolism and nutrition disorders	35 (6.0)	7 (2.5)	42 (4.8)
Decreased appetite	6 (1.0)	2 (0.7)	8 (0.9)
Dehydration	17 (2.9)	2 (0.7)	19 (2.2)
Diabetes mellitus	1 (0.2)	0	1 (0.1)
Diabetic ketoacidosis	0	1 (0.4)	1 (0.1)

Table 12. Treatment-Emergent Serious Adverse Events (All Causality) Reported in Safety Population)

System Organ Class MedDRA (v14.1) Preferred Term	Sunitinib + Prednisone (N=581)	Placebo + Prednisone (N=285)	Total (N=866)
Failure to thrive	2 (0.3)	0	2 (0.2)
Hyperkalaemia	1 (0.2)	0	1 (0.1)
Hypocalcaemia	1 (0.2)	0	1 (0.1)
Hypoglycaemia	4 (0.7)	0	4 (0.5)
Hypokalaemia	2 (0.3)	0	2 (0.2)
Hypomagnesaemia	1 (0.2)	0	1 (0.1)
Hyponatraemia	2 (0.3)	2 (0.7)	4 (0.5)
Hypophosphataemia	1 (0.2)	0	1 (0.1)
Hypovolaemia	1 (0.2)	0	1 (0.1)
Malnutrition	1 (0.2)	0	1 (0.1)
Musculoskeletal and connective tissue disorders	25 (4.3)	13 (4.6)	38 (4.4)
Arthralgia	2 (0.3)	1 (0.4)	3 (0.3)
Back pain	2 (0.3)	3 (1.1)	5 (0.6)
Bone pain	10 (1.7)	5 (1.8)	15 (1.7)
Bursitis	1 (0.2)	0	1 (0.1)
Muscle haemorrhage	1 (0.2)	0	1 (0.1)
Muscular weakness	1 (0.2)	1 (0.4)	2 (0.2)
Musculoskeletal pain	2 (0.3)	0	2 (0.2)
Osteitis	1 (0.2)	1 (0.4)	2 (0.2)
Osteonecrosis	2 (0.3)	0	2 (0.2)
Osteonecrosis of jaw	2 (0.3)	0	2 (0.2)
Pain in extremity	2 (0.3)	0	2 (0.2)
Polymyalgia rheumatica	0	1 (0.4)	1 (0.1)
Spinal column stenosis	0	1 (0.4)	1 (0.1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	8 (1.4)	3 (1.1)	11 (1.3)
Bladder cancer	0	1 (0.4)	1 (0.1)
Cancer pain	1 (0.2)	0	1 (0.1)
Malignant pleural effusion	0	1 (0.4)	1 (0.1)
Pancreatic carcinoma	1 (0.2)	0	1 (0.1)
Prostate cancer	2 (0.3)	0	2 (0.2)
Prostate cancer metastatic	1 (0.2)	1 (0.4)	2 (0.2)
Rectal cancer	1 (0.2)	0	1 (0.1)
Transitional cell carcinoma	1 (0.2)	0	1 (0.1)
Tumour pain	1 (0.2)	0	1 (0.1)
Nervous system disorders	27 (4.6)	8 (2.8)	35 (4.0)
Aphasia	0	1 (0.4)	1 (0.1)
Cerebral ischaemia	1 (0.2)	0	1 (0.1)
Cerebrovascular accident	3 (0.5)	0	3 (0.3)
Convulsion	2 (0.3)	0	2 (0.2)
Depressed level of consciousness	1 (0.2)	0	1 (0.1)
Dizziness	3 (0.5)	0	3 (0.3)
Facial paresis	0	1 (0.4)	1 (0.1)
Haemorrhage intracranial	2 (0.3)	0	2 (0.2)
Headache	1 (0.2)	0	1 (0.1)
Hydrocephalus	0	1 (0.4)	1 (0.1)
Ischaemic stroke	2 (0.3)	0	2 (0.2)
Nervous system disorder	1 (0.2)	0	1 (0.1)
Paraesthesia	2 (0.3)	0	2 (0.2)
Partial seizures	0	1 (0.4)	1 (0.1)
Peripheral motor neuropathy	1 (0.2)	0	1 (0.1)
Peripheral sensory neuropathy	0	1 (0.4)	1 (0.1)
Polyneuropathy in malignant disease	0	1 (0.4)	1 (0.1)
Post herpetic neuralgia	0	1 (0.4)	1 (0.1)
Spinal cord compression	3 (0.5)	3 (1.1)	6 (0.7)

Table 12. Treatment-Emergent Serious Adverse Events (All Causality) Reported in Safety Population)

System Organ Class MedDRA (v14.1) Preferred Term	Sunitinib + Prednisone (N=581)	Placebo + Prednisone (N=285)	Total (N=866)
Subarachnoid haemorrhage	1 (0.2)	0	1 (0.1)
Syncope	3 (0.5)	0	3 (0.3)
Transient ischaemic attack	2 (0.3)	0	2 (0.2)
VIIth nerve paralysis	1 (0.2)	0	1 (0.1)
Psychiatric disorders	6 (1.0)	3 (1.1)	9 (1.0)
Confusional state	3 (0.5)	3 (1.1)	6 (0.7)
Hallucination	1 (0.2)	0	1 (0.1)
Mental disorder due to a general medical condition	2 (0.3)	0	2 (0.2)
Renal and urinary disorders	31 (5.3)	12 (4.2)	43 (5.0)
Azotaemia	1 (0.2)	0	1 (0.1)
Bladder obstruction	1 (0.2)	0	1 (0.1)
Bladder tamponade	1 (0.2)	0	1 (0.1)
Dysuria	1 (0.2)	1 (0.4)	2 (0.2)
Haematuria	13 (2.2)	3 (1.1)	16 (1.8)
Hydronephrosis	1 (0.2)	2 (0.7)	3 (0.3)
Nephrolithiasis	1 (0.2)	0	1 (0.1)
Nephrotic syndrome	1 (0.2)	0	1 (0.1)
Obstructive uropathy	1 (0.2)	1 (0.4)	2 (0.2)
Renal failure	1 (0.2)	1 (0.4)	2 (0.2)
Renal failure acute	8 (1.4)	2 (0.7)	10 (1.2)
Renal impairment	1 (0.2)	0	1 (0.1)
Ureteric obstruction	2 (0.3)	0	2 (0.2)
Urethral haemorrhage	1 (0.2)	0	1 (0.1)
Urinary bladder haemorrhage	3 (0.5)	0	3 (0.3)
Urinary retention	3 (0.5)	3 (1.1)	6 (0.7)
Urinary tract obstruction	1 (0.2)	1 (0.4)	2 (0.2)
Reproductive system and breast disorders	1 (0.2)	0	1 (0.1)
Pelvic pain	1 (0.2)	0	1 (0.1)
Respiratory, thoracic and mediastinal disorders	37 (6.4)	5 (1.8)	42 (4.8)
Chronic obstructive pulmonary disease	0	1 (0.4)	1 (0.1)
Dyspnoea	8 (1.4)	0	8 (0.9)
Epistaxis	4 (0.7)	0	4 (0.5)
Haemoptysis	1 (0.2)	0	1 (0.1)
Hydropneumothorax	1 (0.2)	0	1 (0.1)
Hypoxia	1 (0.2)	0	1 (0.1)
Lung infiltration	1 (0.2)	0	1 (0.1)
Pleural effusion	2 (0.3)	1 (0.4)	3 (0.3)
Pneumonia aspiration	1 (0.2)	0	1 (0.1)
Pneumonitis	1 (0.2)	0	1 (0.1)
Pulmonary embolism	19 (3.3)	3 (1.1)	22 (2.5)
Respiratory arrest	1 (0.2)	0	1 (0.1)
Skin and subcutaneous tissue disorders	1 (0.2)	0	1 (0.1)
Skin hyperpigmentation	1 (0.2)	0	1 (0.1)
Surgical and medical procedures	1 (0.2)	0	1 (0.1)
Pain management	1 (0.2)	0	1 (0.1)
Vascular disorders	13 (2.2)	3 (1.1)	16 (1.8)
Circulatory collapse	1 (0.2)	0	1 (0.1)
Deep vein thrombosis	4 (0.7)	1 (0.4)	5 (0.6)
Haematoma	1 (0.2)	0	1 (0.1)
Haemorrhage	1 (0.2)	0	1 (0.1)
Hypertension	4 (0.7)	0	4 (0.5)
Hypotension	0	1 (0.4)	1 (0.1)
Peripheral vascular disorder	1 (0.2)	0	1 (0.1)
Phlebitis	0	1 (0.4)	1 (0.1)
Venous thrombosis limb	1 (0.2)	0	1 (0.1)

Table 12. Treatment-Emergent Serious Adverse Events (All Causality) Reported in Safety Population)

System Organ Class MedDRA (v14.1) Preferred Term	Sunitinib + Prednisone (N=581)	Placebo + Prednisone (N=285)	Total (N=866)

MedDRA (v14.1) = Medical Dictionary for Regulatory Activities (version 14.1); N = number of subjects in each treatment group; n = number of subjects with reported adverse event.

Treatment-Emergent Treatment-Related SAEs: A total of 149 (25.6%) subjects out of 581 in the sunitinib arm and a total of 19 subjects (6.7%) out of 285 in the placebo arm reported a treatment-emergent treatment-related SAE during the study.

Discontinuations Due to AEs: A total of 201 subjects (34.6%) in the sunitinib arm and 35 subjects (12.3%) in the placebo arm discontinued from sunitinib/placebo and prednisone treatments due to 1 or more TEAEs. A summary of the TEAEs resulting in permanent discontinuations is provided in Table 13.

Table 13. Summary of Treatment-Emergent Adverse Events Resulting in Permanent Discontinuation, Occurring in ≥2 Subjects (Safety Population)

MedDRA Preferred Term	Sunitinib + Prednisone N=581	Placebo + Prednisone N=285	Total N=866
Any AEs	201 (34.6)	35 (12.3)	236 (27.3)
Disease progression	17 (2.9)	7 (2.5)	24 (2.8)
Fatigue	14 (2.4)	0	14 (1.6)
Asthenia	14 (2.4)	0	14 (1.6)
General physical health deterioration	11 (1.9)	1 (0.4)	12 (1.4)
Nausea	8 (1.4)	1 (0.4)	9 (1.0)
Diarrhea	6 (1.0)	0	6 (0.7)
Palmar-plantar erythrodysesthesia syndrome	6 (1.0)	0	6 (0.7)
Vomiting	5 (0.9)	1 (0.4)	6 (0.7)
Gastrointestinal hemorrhage	4 (0.7)	0	4 (0.5)
Pulmonary embolism	4 (0.7)	0	4 (0.5)
Decreased appetite	4 (0.7)	0	4 (0.5)
Dehydration	4 (0.7)	0	4 (0.5)
Spinal cord compression	3 (0.5)	2 (0.7)	5 (0.6)
Thrombocytopenia	3 (0.5)	0	3 (0.3)
Melena	3 (0.5)	0	3 (0.3)
Mucosal inflammation	3 (0.5)	0	3 (0.3)
Pneumonia	2 (0.3)	1 (0.4)	3 (0.3)
Dizziness	2 (0.3)	1 (0.4)	3 (0.3)
Death	2 (0.3)	0	2 (0.2)
Neutropenia	2 (0.3)	0	2 (0.2)
Gastric ulcer	2 (0.3)	0	2 (0.2)
Gastroesophageal reflux disease	2 (0.3)	0	2 (0.2)
Large intestine perforation	2 (0.3)	0	2 (0.2)
Rectal hemorrhage	2 (0.3)	0	2 (0.2)
Stomatitis	2 (0.3)	0	2 (0.2)
Pain	2 (0.3)	0	2 (0.2)
Cholecystitis acute	2 (0.3)	0	2 (0.2)
Diverticulitis	2 (0.3)	0	2 (0.2)
Infection	2 (0.3)	0	2 (0.2)
Sepsis	2 (0.3)	0	2 (0.2)
Osteonecrosis	2 (0.3)	0	2 (0.2)
Ischemic stroke	2 (0.3)	0	2 (0.2)
Confusional state	2 (0.3)	0	2 (0.2)
Hematuria	2 (0.3)	0	2 (0.2)
Deep vein thrombosis	2 (0.3)	0	2 (0.2)
Hypertension	2 (0.3)	0	2 (0.2)
Anemia	1 (0.2)	1 (0.4)	2 (0.2)
Bone pain	0	2 (0.7)	2 (0.2)

Subjects counted only once per treatment for each row.
Both TEAEs leading to discontinuation from sunitinib/placebo and prednisone presented in table.
Percentages based on the number of subjects in the safety population within each treatment arm.
Discontinuations presented in decreasing order for sunitinib + prednisone.
MedDRA (v14.1) coding dictionary applied.
AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities (version 14.1); N = number of subjects in the safety population; TEAE = treatment-emergent adverse event.

Table 14 presents a summary of the all-causality TEAEs leading to a temporary discontinuation or dose reduction in 5 or more total subjects in the safety population. The most common TEAEs that caused a dose reduction or temporary discontinuation in the sunitinib arm included: PPE syndrome, diarrhea, fatigue, and asthenia. None of the dose reductions or temporary discontinuations were greater than 5% in the placebo arm.

Table 14. Summary of Treatment-Emergent Adverse Events Resulting in Dose Reduction or Temporary Discontinuation Occurring in ≥5 Subjects (Safety Population)

MedDRA Preferred Term	Sunitinib + Prednisone N=581 n (%)	Placebo + Prednisone N=285 n (%)	Total N=866 n (%)
Subjects with at least 1 treatment-emergent AE[a]	403 (69.4)	82 (28.8)	485 (56.0)
Palmar-plantar erythrodysesthesia syndrome	62 (10.7)	0	62 (7.2)
Diarrhea	55 (9.5)	3 (1.1)	58 (6.7)
Fatigue	50 (8.6)	8 (2.8)	58 (6.7)
Asthenia	50 (8.6)	3 (1.1)	53 (6.1)
Nausea	39 (6.7)	7 (2.5)	46 (5.3)
Vomiting	38 (6.5)	7 (2.5)	45 (5.2)
Decreased appetite	36 (6.2)	3 (1.1)	39 (4.5)
Mucosal inflammation	33 (5.7)	0	33 (3.8)
Neutropenia	24 (4.1)	0	24 (2.8)
Anemia	21 (3.6)	7 (2.5)	28 (3.2)
Hypertension	21 (3.6)	0	21 (2.4)
Thrombocytopenia	19 (3.3)	6 (2.1)	25 (2.9)
Stomatitis	15 (2.6)	0	15 (1.7)
Neutrophil count decreased	13 (2.2)	1 (0.4)	14 (1.6)
Pyrexia	11 (1.9)	2 (0.7)	13 (1.5)
Leukopenia	11 (1.9)	0	11 (1.3)
Pulmonary embolism	10 (1.7)	3 (1.1)	13 (1.5)
Weight decreased	10 (1.7)	0	10 (1.2)
Hematuria	8 (1.4)	3 (1.1)	11 (1.3)
Abdominal pain upper	7 (1.2)	0	7 (0.8)
Platelet count decreased	7 (1.2)	0	7 (0.8)
White blood cell count decreased	7 (1.2)	0	7 (0.8)
Dysgeusia	7 (1.2)	0	7 (0.8)
Epistaxis	7 (1.2)	0	7 (0.8)
Dehydration	6 (1.0)	2 (0.7)	8 (0.9)
Dyspnea	6 (1.0)	1 (0.4)	7 (0.8)
Abdominal pain	6 (1.0)	1 (0.4)	7 (0.8)
Esophagitis	6 (1.0)	0	6 (0.7)
Renal failure acute	6 (1.0)	0	6 (0.7)
Bone pain	5 (0.9)	2 (0.7)	7 (0.8)
Blood creatinine increased	5 (0.9)	1 (0.4)	6 (0.7)
Anal abscess	5 (0.9)	0	5 (0.6)
Blister	5 (0.9)	0	5 (0.6)
Rash	5 (0.9)	0	5 (0.6)
Urinary tract infection	4 (0.7)	3 (1.1)	7 (0.8)
Rectal hemorrhage	4 (0.7)	2 (0.7)	6 (0.7)
Dyspepsia	4 (0.7)	1 (0.4)	5 (0.6)
Arthralgia	4 (0.7)	1 (0.4)	5 (0.6)
Hydronephrosis	4 (0.7)	1 (0.4)	5 (0.6)
Pain	3 (0.5)	4 (1.4)	7 (0.8)
Constipation	3 (0.5)	2 (0.7)	5 (0.6)
Pain in extremity	3 (0.5)	2 (0.7)	5 (0.6)
Confusional state	3 (0.5)	2 (0.7)	5 (0.6)

Subjects counted only once per treatment for each row.
Presented in decreasing order for sunitinib + prednisone.
Dose reduction and temporary discontinuation for both sunitinib/placebo and prednisone.
Percentages based on the number of subjects in the safety population within each treatment arm.
Dose reductions and temporary discontinuations presented in decreasing order for sunitinib + prednisone.
AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities (Version 14.1); N = number of subjects in the study population; n = number of subjects with adverse events.
a. Resulting in dose reduction or temporary discontinuation.

Deaths: A summary of deaths that were reported on study (ie, within 28 days of the last dose of study medication) and during follow up (ie, after 28 days of the last dose of study medication) is presented in Table 15. A total of 57 subjects (9.8%) in the sunitinib arm and 30 subjects (10.5%) in the placebo arm died during the study. A total of 279 subjects (48.0%) in the sunitinib arm and 147 subjects (51.6%) in the placebo arm died during follow up. The majority of deaths was due to disease under study.

Table 15. Summary of Deaths - Safety Population

Number (%) of Subjects	Sunitinib + Prednisone N=581	Placebo + Prednisone N=285	Total N=866
On Study			
Death from all causes	57 (9.8)	30 (10.5)	87 (10.0)
Cause of death			
Disease under study	41 (71.9)	24 (80.0)	65 (74.7)
Other[a]	10 (17.5)	5 (16.7)	15 (17.2)
Unknown	6 (10.5)	0	6 (6.9)
Study treatment toxicity	1 (1.8)	1 (3.3)	2 (2.3)
During Follow-up Period			
Death from all causes	279 (48.0)	147 (51.6)	426 (49.2)
Cause of death			
Disease under study	238 (85.3)	127 (86.4)	365 (85.7)
Unknown	27 (9.7)	11 (7.5)	38 (8.9)
Other	18 (6.5)	10 (6.8)	28 (6.6)
Lost to follow-up	5 (<1.0)	2 (<1.0)	7 (<1.0)

Deaths on study are deaths that occurred within 28 days of the last dose of study medication.
Deaths during follow up defined as any death occurring after 28 days of the last dose of study medication.
Subjects who died may have more than 1 reason for cause of death.
Percentages based on the total number of subjects in the safety population within each treatment arm except for 'Cause of Death' where it's on the number of deaths.
One subject (sunitinib) died on study but did not have a Grade 5 event in the database.
Some subjects died beyond 28 days after the last dose but had Grade 5 events entered in the database (sunitinib: 10, placebo: 2).
Two randomized subjects in sunitinib arm and 1 in placebo arm died on study but were never treated. Therefore these subjects were not part of the safety population.
N = number of subjects in the safety population

a. Other causes of death were listed as pneumonia (2), sepsis (2), cardiopulmonary arrest (2), septic shock, cardiac-respiratory arrest, suspicion of cardiac infarction, urosepsis, tarry stool, acute myocardial infarction, suspected pulmonary embolism, subdural hemorrhage, and meningitis.

Laboratory Results, Vital Signs, and ECG Findings: There were no new or unexpected findings in the clinical laboratory data, vital signs, or ECG findings.

CONCLUSIONS:

- Median OS was 13.1 and 11.8 months in the sunitinib and placebo arms, respectively ($p>0.05$). The study failed to meet its primary efficacy endpoint (improvement in OS).

- Median PFS was 24.1 and 17.9 weeks in the sunitinib and placebo arms, respectively ($p<0.001$). There was a high censoring rate for PFS (56% in the sunitinib arm and 48% in the placebo arm).

- ORR was significantly higher in the sunitinib arm (6% versus 2%, P=0.04). None of the subjects had a CR.

- Less back pain and bone pain were reported in the sunitinib arm versus placebo arm: back pain (15.3% versus 21.4%), and bone pain (12.0% versus 16.5%).

- The safety profile of sunitinib in this study was consistent with that reported in the labeling for sunitinib malate (Sutent). No new or unexpected AEs were observed in this study.