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

PROTOCOL NO: A6181058

PROTOCOL TITLE: Randomized, Double-Blind, Phase 2 Study of Erlotinib With or Without SU011248 in the Treatment of Metastatic Non-Small Cell Lung Cancer (NSCLC)

Study Centers: A total of 24 centers took part in the study and enrolled subjects; 2 in Canada, 2 in Hungary, 2 in Italy, 2 in the Netherlands, 2 in Poland, 3 in Romania, 1 in Spain, and 10 in the United States (US).

Study Initiation Date, Primary Completion Date and Final Completion Date:
Study Initiation Date: 01 June 2006 (First Subject First Visit)
Primary Completion Date: 21 January 2010 (Final data collection date for primary outcome measure) and
Final Completion Date: 31 January 2012 (Last Subject Last Visit)
The study was terminated after the final analyses of the primary and secondary efficacy endpoints were fully conducted and results were reported.

Phase of Development: Phase 2

Study Objectives:

Primary Objective:

- To compare the progression-free survival (PFS) for sunitinib plus erlotinib versus (vs) placebo plus erlotinib in subjects with platinum-refractory NSCLC

Secondary Objectives:

- To compare the objective response rate (ORR) for sunitinib plus erlotinib vs placebo plus erlotinib as treatment for platinum-refractory NSCLC.
- To estimate measures of duration of tumor control and compare survival.
- To compare the safety and tolerability of sunitinib plus erlotinib vs placebo plus erlotinib
- To evaluate the plasma pharmacokinetics (PK) of erlotinib and, and sunitinib and its active metabolite SU-012662 when these drugs are co-administered

- To explore the relationships of cancer biomarkers with cancer- and treatment-related outcomes

- To compare patient-reported outcomes (PRO) including health-related quality of life (HRQOL) and lung cancer-related symptoms in subjects treated with sunitinib plus erlotinib vs placebo plus erlotinib

METHODS

Study Design: This study was a randomized, double-blind, multi-center, Phase 2 clinical study evaluating the antitumor efficacy and safety of sunitinib in combination with erlotinib compared with erlotinib alone (administered as erlotinib plus placebo) in subjects with NSCLC who had received previous treatment with a platinum-based regimen in the locally advanced (Stage IIIB) or metastatic setting. Subjects who previously received treatment with antiangiogenesis agents including thalidomide or inhibitors of vascular endothelial growth factor (VEGF) (with the exception of bevacizumab), vascular endothelial growth factor receptor (VEGFR), platelet-derived growth factor receptor (PDGFR), or epidermal growth factor receptor (EGFR) were ineligible for study entry. Subjects who were previously treated with an insulin-like growth factor receptor (IGFR) inhibitor were considered eligible for study entry.

The study consisted of 3 portions: the original lead-in cohort, the amended lead-in cohort and the randomized cohort. Throughout this report the combination of erlotinib plus placebo will generally be referred to as 'erlotinib'.

- Lead-In Cohort (Original): The study began with a lead-in cohort: 10 subjects were to be treated with sunitinib at 37.5 mg once-daily (QD) and erlotinib 150 mg QD. These subjects were assessed for safety and underwent blood sampling for full PK profiles. If fewer than 6 subjects completed full PK profiles then subsequent subjects in the cohort were to be enrolled concurrently with the randomized cohort, once 10 subjects completed the 28-day observation period. If there were no more than 3 dose-limiting toxicities (DLTs), excluding dyspnea, and no more than 4 DLTs due to dyspnea during a 28-day period of treatment with sunitinib in combination with erlotinib, then the randomized phase proceeded. If >3 DLTs excluding dyspnea (or >4 DLTs related to dyspnea) were observed in the initial cohort, then the dose and/or schedule of either or both medications could have been modified for the randomized cohort.

- Lead-In Cohort (Amended): The protocol was amended to include another lead-in cohort (amended lead-in cohort) to further investigate the potential for a drug-drug interaction between sunitinib and erlotinib, the effect of sunitinib on erlotinib (Arm A), and the effect of erlotinib on sunitinib (Arm B). The amended cohort was to consist of 12 subjects; 6 subjects per arm, and could have been expanded if fewer than 12 evaluable subjects completed full PK sampling (6 on each arm). These subjects were to have been <70 years of age and nonsmokers or ex-smokers for ≥6 months (as smokers are known to have lower erlotinib levels).

- Randomized Cohort: A total of 126 subjects were planned to be randomized to treatment with either sunitinib in combination with erlotinib or erlotinib alone. Randomization was stratified by smoking history (current smokers vs never smokers vs previous smokers who quit ≥1 year) and EGFR status (positive vs negative vs unmeasured), as defined by any test conducted by the site, eg, immunohistochemistry (IHC), copy number etc.

Subjects continued to receive treatment as assigned at randomization until Response Evaluation Criteria in Solid Tumors Version 1.0 (RECIST) defined disease progression or for up to 18 cycles (Note: 1 cycle = 4 weeks). At the time of progression or after 18 cycles on study, subjects were unblinded to treatment assignment and all subjects were offered continued access to sunitinib through participation on a separate protocol at the discretion of the Investigator.

A schedule of study events for the lead-in (original), lead-in (amended), and randomized cohorts of the study are presented in Table 1, Table 2 and Table 3 respectively.

Table 1. Schedule of Events for Subjects in the Lead-In Cohort (Original)

Protocol Activity	Screening ≤21 Days	Cycle 1			Cycle 2-4		Cycle 5+	Post-Treatment		
		D1[a]	D15±3	D28±3	D1±3	D15±3	Day 1±3	End of Treatment[b]	28 Days Post-Treatment	Survival Follow-Up
Baseline documentation										
Informed consent	X									
Medical/oncological history[c]	X									
Physical examination, ECOG PS, body weight and vital signs[d]	X	(X)	X (BP only)	X	X		X	X	(X)	
Baseline signs/symptoms		X								
Laboratory studies										
Hematology and chemistry[e]	X	(X)	X	X	X	X	X	X	(X)	
Protime (PT)[f]	X									
Urinalysis[g]		X			X		(X)			
Pregnancy test[h]	X									
12-lead ECG[i]	X				X {C2}			X		
Study registration[j]	X									
Drug dosing										
Sunitinib dosing[k]		X→	→	→X	X→ {Day 2 C2}	→	→			
Erlotinib dosing[l]		X→	→	→	→	→	→			
Assessments										
CT or MRI scans[m]	X				X		(X) {even cycles}	X		
Brain CT scan[n]	X				(X)		(X)	(X)		
Bone scan[o]	X				(X)		(X) {even cycles}	(X)		
Adverse events[p]	X	X	X	X	X	X	X	X	X	
Sunitinib compliance[q]					X		X	X		
Concomitant treatments[r]	X	X	X	X	X	X	X	X	X	
Survival follow-up[s]										X
Special laboratory studies										
Sunitinib PK profile[t]			X							

Table 1. Schedule of Events for Subjects in the Lead-In Cohort (Original)

Protocol Activity	Screening ≤21 Days	Cycle 1			Cycle 2-4		Cycle 5+	Post-Treatment		
		D1[a]	D15±3	D28±3	D1±3	D15±3	Day 1±3	End of Treatment[b]	28 Days Post-Treatment	Survival Follow-Up
Erlotinib PK profile[u]			X		X {C2 only}					
Sunitinib and erlotinib troughs[v]		X			X		X			
Tumor biopsy/ slides[w]		X			(X)		(X)			
Blood for pharmacogenomics[x]		X								

() = if applicable; {} = specifies applicable cycles; X→ = start dosing; → = dosing continuation; →X = end dosing; BP = blood pressure; CT = computerized tomography; D = day; ECG = electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group Performance Status; MRI = magnetic resonance imaging; PK = pharmacokinetic; QTc = QT interval corrected.

a. Physical examination, hematology and blood chemistry not required if obtained within 7 days of Screening.
b. Assessments not required if performed within 1 week of study withdrawal (within the last 8 weeks for tumor assessments).
c. Included oncology history, demographics, history of other diseases (active or resolved), concomitant illnesses, and response during prior cancer treatments. Changes in BP medications (new prescriptions, discontinuations, or changes in dose) were also to be recorded.
d. Examination of major body systems, height at Screening only vital signs included temperature, BP, heart rate, and respiratory rate. BP was to be taken in triplicate. Only triplicate BP was to be recorded on Cycle 1 Day 15±3.
e. Required tests were listed in the protocol.
f. Protime was to be performed at Screening.
g. Performed at a local laboratory during Cycles 1-4 and repeated in subsequent cycles if most recent sample showed ≥1+ proteinuria. Subjects were to undergo a 24-hour urine collection for local laboratory testing for total protein if urinalysis showed ≥3+ proteinuria.
h. Serum or urine test must have been performed for all women of childbearing potential
i. Three consecutive 12-lead ECGs approximately 2 minutes apart were to be performed at Screening and on Cycle 2, Day 1 to determine the mean QTc interval. Attempts were made for the ECGs to be performed in the morning and time-matched (± 1 hour). ECGs were to be done before blood was drawn or 30 minutes afterwards. If the mean QTc interval was prolonged (>500 msec), the ECGs were to be read by a cardiologist at the site for confirmation. Additional ECGs were to be performed as clinically indicated.
j. Subject numbers were obtained from the study team.
k. Subjects self-administered sunitinib orally (PO) once daily (QD) at 37.5 mg/day in 4 week cycles. Dosing was to be observed in the clinic on the day of full PK profiling. In Cycle 1 sunitinib dosing started on Day 1, the same day of erlotinib dosing. The cycle length for the 1st cycle was 35 days; during this cycle, sunitinib treatment was to be completed on Day 28 and resumed on Day 2 of Cycle 2. Subjects continued with therapy until disease progression, unacceptable toxicity, or withdrawal of subject consent.
l. Subjects self-administered erlotinib PO QD at 150 mg/day. Dosing was to be observed in the clinic on the days of full PK profiling. The 1st cycle was 35 days, and erlotinib was dosed alone on Days 29 to 35 of Cycle 1.
m. Scans of the chest and abdomen and any other sites of disease at Screening, Day 1±3 of Cycles 2 to 4 and every even-numbered cycle thereafter, whenever disease progression was suspected, to confirm a partial or complete response ≥ 4 weeks after initial documentation of response, and at the End of Treatment/Withdrawal.
n. At Screening and whenever brain metastases were suspected.
o. At Screening and on Day 1±3 of Cycles where tumor imaging was performed if bone metastases were present or suspected.
p. Subjects were to be followed for adverse events (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 (SAEs) were to be monitored and reported from the time that the subject provided informed consent.
q. Sunitinib compliance: Sunitinib including unused drug were to be returned to the clinic for drug compliance at the beginning of each cycle except for Cycle 1, where unused

Table 1. Schedule of Events for Subjects in the Lead-In Cohort (Original)

Protocol Activity	Screening ≤21 Days	Cycle 1			Cycle 2-4		Cycle 5+	Post-Treatment		
		D1[a]	D15±3	D28±3	D1±3	D15±3	Day 1±3	End of Treatment[b]	28 Days Post-Treatment	Survival Follow-Up

drug was returned on Day 28.

r. Concomitant medications and treatments were to be recorded from 28 days prior to the start of study treatment, during the study, and up to 28 days post the last dose of study treatment.

s. Follow-up survival information was to be collected by clinic visit or telephone contact every 2 months until death or up to 2 years from last dose.

t. Blood samples for PK profiling of sunitinib and SU-012662 were obtained on Cycle 1 Day 15 at the following time points: pre-dose, 1, 2, 4, 6, 8, 10, and 24 hours postdose.

u. Subjects in the original lead-in portion of the study provided blood samples for PK profiling of erlotinib on Cycle 1 Day 15 and Cycle 2 Day 1 at the following time points: pre-dose, 1, 2, 4, 6, 8, 10, and 24 hours postdose.

v. Subjects were to undergo trough blood level testing for both drugs on Day 1 of each cycle (including Cycle 1 before any study drug dosing).

w. Collection of tumor tissue for original lead-in subjects was optional. Tumor blocks or slides cut from paraffin blocks were to be collected for correlative laboratory analysis.

x. Blood for pharmacogenomics was to be collected prior to on-study treatment.

Table 2. Schedule of Events for Subjects in the Lead-in Cohort (Amended)

Protocol Activity	Screening ≤28 Days	Cycle 1			Cycle 2-4		Cycle 5+	Post-Treatment		
		D1[a]	D15±3	Various	D1±3	D15±3	Day 1±3	End of Treatment[b]	28 Days Post-Treatment	Survival Follow-Up
Baseline documentation										
Informed consent	X									
Medical/oncological history[c]	X									
PE, ECOG PS, Wt and vital signs[d]	X	(X)	X (BP only)		X		X	X	(X)	
Baseline signs/symptoms		X								
Laboratory studies										
Hematology and Chemistry[e]	X	(X)	X		X	X	X	X	(X)	
TSH, protime (PT or INR)[f]	X									
Urinalysis[g]	X	(X)			X		(X)	X		
Pregnancy test[h]	X									
12-lead ECG[i]	X				X {C2}			X		
MUGA scan or ECHO[j]	X									
Study registration[k]	X									
Drug dosing										
Sunitinib dosing[l] Arm A ARM B		D2→ D1	→ D15	→X D18→	X→ X→	→ →	X→ X→			
Erlotinib dosing[m] Arm A ARM B		D1 -	- D3→	D22,24→X →X	X→ X→	→ →	X→ X→			
Assessments										
CT or MRI scans[n]	X				(X)	X				
Brain CT scan[o]	X				Only if clinically indicated	(X)				
Bone scan[p]	X				(X)	(X)				
Adverse events[q]	X	X	X	X	X	X	X	X	X	
Sunitinib compliance[r]					X		X	X		
Concomitant treatments[s]	X	X	X	X	X	X	X	X	X	
Survival follow-up[t]										X
Special laboratory studies										

Table 2. Schedule of Events for Subjects in the Lead-in Cohort (Amended)

Protocol Activity	Screening ≤28 Days	Cycle 1			Cycle 2-4		Cycle 5+	Post-Treatment		
		D1[a]	D15±3	Various	D1±3	D15±3	Day 1±3	End of Treatment[b]	28 Days Post-Treatment	Survival Follow-Up
Sunitinib PK profile[u] Arm B		X	D15							
Erlotinib PK profile[v] Arm A		X		D22						
Sunitinib trough samples[w] Arm A			-	D22, 23	X		X			
Erlotinib trough samples[w] Arm B			D15, 16, 17	-	X		X			
Tumor biopsy/ slides[x]		(X)			(X)		(X)			
Blood for pharmacogenomics[y]		X								

() = if applicable; {} = specifies applicable cycles; X→ = start dosing; → = dosing continuation; →X = end dosing
BP = blood pressure; CT = computerized tomography; D = day; ECG = electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group Performance Status; ECHO = echocardiogram; INR = international normalized ratio; MUGA = multigated acquisition scan; MRI = magnetic resonance imaging; PE = physical examination; PK = pharmacokinetic; PT = prothrombin time; QTc = QT interval corrected; Wt = weight.

a. Physical examination, hematology, blood chemistry and urinalysis were not required if an acceptable Screening assessment was obtained within 7 days prior to the start of study medication without suggestion of clinical deterioration.
b. Assessments were not required if performed within 1 week of study withdrawal (within the last 8 weeks for radiological tumor assessments).
c. Included oncologic history, demographics, history of other diseases (active or resolved), concomitant illnesses, and information on prior cancer treatments that included best response observed, smoking history, and epidermal growth factor receptor (EGFR) status. Changes in blood pressure (BP) medications (new prescriptions, discontinuations, or dose changes) were also to be recorded.
d. The examination of major body systems, height (Screening only), vital signs such as temperature, BP, heart rate, and respiratory rate. BP was to be taken in triplicate. Only triplicate BP was recorded on Cycle 1 Day 15±3.
e. Electrolyte levels, particularly potassium and magnesium, were to be monitored throughout the study (from Amendment 3 onwards), correcting abnormalities that were observed.
f. Performed at Screening, then as clinically indicated thereafter.
g. Performed at a local laboratory during Screening, at Cycles 2 to 4, and repeated in subsequent cycles if the most recent sample showed a ≥1+ proteinuria. A urinalysis was also to be performed at end of treatment. If the urinalysis showed a ≥2+ proteinuria, a 24-hour urine collection for total protein was to be performed.
h. A serum or urine pregnancy test was to be performed for all women of childbearing potential.
i. Three consecutive 12-lead electrocardiograms (ECGs) approximately 2 minutes apart were to be performed at screening, Cycle 2, Day 1 and at the end of study to determine the mean QTc. If the mean QTc interval was prolonged (>500 msec), the ECGs were to be read by a cardiologist at the center for confirmation. Additional ECGs were to be performed as clinically indicated to include approximately 2 weeks following intrasubject sunitinib dose adjustments).
j. Performed at Screening, and clinically indicated thereafter.
k. Subject number was obtained from the study team.
l. Subjects self-administered sunitinib orally (PO) once daily (QD) at 37.5 mg/day (starting dose) in 4 week cycles. Dosing was to be observed in the clinic on the day of full

Table 2. Schedule of Events for Subjects in the Lead-in Cohort (Amended)

Protocol Activity	Screening ≤28 Days	Cycle 1			Cycle 2-4		Cycle 5+	Post-Treatment		
		D1[a]	D15±3	Various	D1±3	D15±3	Day 1±3	End of Treatment[b]	28 Days Post-Treatment	Survival Follow-Up

pharmacokinetic (PK) profiling. In Cycle 1 Arm A: Sunitinib dosing started on Day 2. Arm B: A single dose of sunitinib was to be administered on Days 1 and 15 and daily dosing resumed on Day 18. Subjects continued with therapy until disease progression, unacceptable toxicity, or withdrawal of subject consent.

m. Subjects self-administered erlotinib PO QD at 150 mg/day (starting dose) in 4 week cycles. Dosing was to be observed in the clinic on the days of full PK profiling. In Cycle 1 Arm A: A single dose of erlotinib was to be administered on Days 1 and 22 and daily dosing resumed on Day 24. Arm B: erlotinib dosing started on Day 3.

n. CT or MRI scans of the chest and abdomen and any other sites of disease at Screening, 8, and 12 weeks ±3 days, and every 8 weeks thereafter ±7 days from the start of treatment whenever disease progression was suspected to confirm a PR or CR ≥4 weeks after initial documentation of response, and at the end of treatment/withdrawal.

o. Required at Screening to confirm eligibility. A repeat brain scan was required on study if new brain metastases were suspected.

p. Repeat bone scans were required at 8, and 12 weeks ±3 days, and every 8 weeks thereafter ±7 days from the start of treatment only if bone metastases were present at Screening or if new bone metastases were suspected. If uptake was seen on bone scan, but this finding was considered nonmalignant, the bone scan was to be repeated at confirmation of response.

q. Subjects were to be followed for adverse events (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 medication-related toxicities resolved or were determined to be chronic or stable, whichever was later. Serious adverse events (SAEs) were to be monitored and reported from the time that the subject provided informed consent.

r. Sunitinib, including unused medications, were to be returned to the clinic for drug compliance at the beginning of each cycle starting from Cycle 2.

s. Concomitant medications and treatments were to be recorded from 28 days prior to the start of study treatment, during the study, and up to 28 days post the last dose of study treatment.

t. Follow-up survival information, including post-study anticancer treatment, was to be collected by clinic visit or telephone contact every 2 months until death or 18 months from last subject's first dose of study treatment.

u. Subjects in the lead-in phase of the study provided blood samples for full PK profiling of sunitinib and SU-012662 on Arm B (Cycle 1, Days 1 and 15) at the following time points: pre-dose, 1, 2, 4, 6, 8, 24, and 48 hours postdose.

v. Subjects in the lead-in phase of the study provided blood samples for full PK profiling of erlotinib on Arm A (Cycle 1, Days 1 and 22) at the following time points: pre dose, 1, 2, 4, 6, 8, and 24 and hours postdose.

w. In Cycle 1, subjects in Arm A provided blood samples for sunitinib C_{trough} at Days 22 and 23, while subjects in the Arm B provided blood samples for erlotinib C_{trough} on Days 15, 16, and 17. All subjects were to undergo trough level testing for both drugs on Day 1 of Cycles 2 to 13 inclusive.

x. Collection of tumor tissue was optional. Tumor blocks or slides cut from paraffin blocks were to be collected for correlative laboratory analysis.

y. Blood for genotyping was to be collected prior to on study treatment.

Table 3. Schedule of Events for Subjects in the Randomized Cohort

Protocol Activity	Screening ≤28 Days	Cycle 1		Cycle 2-4		Cycle 5+	Post-Treatment		
		D1[a]	D15±3	D1±3	D15±3	Day 1±3	End of Treatment[b]	28 Days Post-Treatment	Survival Follow-Up
Baseline documentation									
Informed consent	X								
Medical/oncological history[c]	X								
Physical examination, ECOG PS, weight, vital signs[d]	X	X	X (BP)	X		X	X	(X)	
Baseline signs/symptoms		X							
Laboratory studies									
Hematology and chemistry[e]	X	(X)	X	X	X	X	X	(X)	
TSH , Protime (PT or INR)[f]	X								
Urinalysis[g]	X	(X)		X		(X)	X		
Pregnancy test[h]	X								
12-lead ECG[i]	X			X {Cycle 2}			X		
MUGA scan or ECHO[j]	X								
Study randomization[k]	X								
Drug dosing									
Dosing of blinded study drug[l]		X→	→	→	→	→	→X		
Erlotinib dosing[m]		X→	→	→	→	→	→X		
Assessments									
CT or MRI scans[n]	X			(X)	X				
Brain CT scan[o]	X			Only if clinically indicated	(X)				
Bone scan[p]	X			(X)	(X)				
EORTC QLQ-C30 and LC13[q]		X		X		X	X		
Adverse events[r]	X	X	X	X	X	X	X	X	
Study drug compliance[s]				X		X	X		
Concomitant treatments[t]	X	X	X	X	X	X	X	X	
Survival follow-up[u]									X
Special laboratory studies									

Table 3. Schedule of Events for Subjects in the Randomized Cohort

Protocol Activity	Screening ≤28 Days	Cycle 1		Cycle 2-4		Cycle 5+	Post-Treatment		
		D1[a]	D15±3	D1±3	D15±3	Day 1±3	End of Treatment[b]	28 Days Post-Treatment	Survival Follow-Up
SU-011248 and erlotinib troughs[v]		X		X		X			
Tumor biopsy / slides[w]		X		(X)		(X)			
Blood for pharmacogenomics[x]		X							
Soluble proteins[y]		X		X {C2-3}					

() = if applicable; {} = specifies applicable cycles; X→ = start dosing; → = dosing continuation; →X = end dosing.
BP = blood pressure; CT = computerized tomography; D = day; ECG = electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group Performance Status; EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer- Quality of Life Questionnaire; ECHO = echocardiogram; INR = international normalized ratio; MUGA = multigated acquisition scan; MRI = magnetic resonance imaging; PE = physical examination; PK = pharmacokinetic; PT = prothrombin time.

a. Physical examination, hematology, blood chemistry and urinalysis were not required if acceptable Screening assessments were obtained within 7 days prior to the start of study treatment without suggestion of clinical deterioration.
b. Assessments were not required if performed within 1 week of study withdrawal (within the last 8 weeks for radiological tumor assessments).
c. Included oncologic history, demographics, history of other diseases (active or resolved), concomitant illnesses, and information on prior cancer treatments including best response observed, smoking history and epidermal growth factor receptor (EGFR) status. Changes in blood pressure (BP) medications (new prescriptions, discontinuations, or changes in dose) were also to be recorded.
d. The examination of major body systems, height (Screening only), Eastern Cooperative Oncology Group (ECOG) performance status, vital signs such as temperature, BP, heart rate, and respiratory rate. BP was to be taken in triplicate. On Cycle 1 Day 15, only triplicate BP was to be recorded.
e. Electrolyte levels, particularly potassium and magnesium, were to be monitored throughout the study, correcting abnormalities that were observed.
f. Thyroid-stimulating hormone (TSH) was to be performed at screening, then as clinically indicated thereafter. Prothrombin time (PT) or international normalized ratio (INR) were to be taken at screening, then as clinically indicated thereafter.
g. Performed at a local laboratory during Screening, at Cycles 2 to 4, and repeated in subsequent cycles if most recent sample showed a ≥1+ proteinuria. A urinalysis was also performed at end of treatment. If urinalysis showed a ≥2+ proteinuria, a 24-hour urine collection for total protein was to be performed.
h. A serum or urine pregnancy test was to be performed for all women of childbearing potential.
i. Three consecutive 12-lead electrocardiograms (ECGs) approximately 2 minutes apart were to be performed at Screening, on Cycle 2, Day 1 and at the end of study to determine the mean QTc. If mean QTc interval was prolonged (>500 msec), the ECGs were to be read by a cardiologist at the center for confirmation. Additional ECGs were to be performed as clinically indicated to include approximately 2 weeks following intrasubject sunitinib dose adjustments.
j. Performed at Screening and clinically indicated thereafter.
k. Subject number and randomization assignment were obtained from a centralized source (Interactive Voice Response System [IVRS]). Every effort was made to start study medication within 2 days after randomization.
l. Subjects self-administered sunitinib (or matching placebo) per oral (PO) once daily (QD) at 37.5 mg/day (starting dose) in 4 week cycles. Subjects were able to continue with therapy until disease progression, unacceptable toxicity, or withdrawal of informed consent.
m. Subjects self-administered erlotinib PO QD at 150 mg/day (starting dose).
n. Computerized tomography (CT) or magnetic resonance imaging (MRI) scans of the chest and abdomen and any other applicable sites of disease were to be performed at Screening, 8, 12 weeks ±3, and every 8 weeks ±7 days thereafter from the start of treatment when disease progression was suspected, to confirm a partial response (PR) or complete response (CR) (at least 4 weeks after initial documentation of response), and at the End of Treatment/Withdrawal. For subjects who discontinued the study due to toxicity (or other reasons) prior to disease progression, every effort was made to continue to collect tumor assessment data according to the protocol schedule until disease

Table 3. Schedule of Events for Subjects in the Randomized Cohort

Protocol Activity	Screening ≤28 Days	Cycle 1		Cycle 2-4		Cycle 5+	Post-Treatment		
		D1[a]	D15±3	D1±3	D15±3	Day 1±3	End of Treatment[b]	28 Days Post-Treatment	Survival Follow-Up

progression or start of new anticancer therapy.

o. Required at Screening to confirm eligibility. A repeat brain scan was required on study if new brain metastases were suspected.

p. Required at Screening. Repeat bone scans were required 8, 12 weeks ±3 days, and every 8 weeks ±7 days thereafter only if bone metastases were present at Screening or if new bone metastases were suspected. If uptake was seen on bone scan, but this finding was considered nonmalignant, the bone scan was to be repeated at confirmation of response. Documentation of Progression for Eligibility: The center was responsible for sending Central Imaging Vendor those images (or reports, as applicable) that were deemed by the investigator to document progression, as well as a prior exam that was thought to represent the nadir of the tumor burden.

q. Completed on Day 1 of each cycle and at the end of treatment/withdrawal. The questionnaires were to be completed prior to other clinical assessments.

r. Subjects were to be followed for adverse events 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 medication-related toxicities resolved or were determined as chronic or stable, whichever was later. Serious adverse events (SAE) were to be monitored and reported from the time that the subject provided informed consent as described in the protocol.

s. Blinded study medication (sunitinib or placebo) was to be returned to the clinic for drug accountability at the beginning of each subsequent cycle starting from Cycle 2.

t. Concomitant medications and treatments were to be recorded from 28 days prior to the start of study treatment during the study and up to 28 days post the last dose of study treatment.

u. Follow-up survival information, including post-study anticancer treatment, was to be collected during the clinic visit or telephone contact every 2 months until death or 18 months from the last subject's first dose of study treatment

v. Subjects underwent trough blood level testing for both medications on Day 1 of Cycles 1 to 13, inclusive (including Cycle 1 before any study medication dosing).

w. Tumor blocks or slides cut from paraffin blocks were to be collected for correlative laboratory analysis. The most recent tumor tissue collected prior to enrollment into this study and tissue collected at the time of progression was preferred.

x. Blood for genotyping was to be collected prior to on-study treatment.

y. Blood sample was to be collected pre-dose on Day 1 of Cycles 1 to 3.

Number of Subjects (Planned and Analyzed): It was planned to recruit 10 subjects into the lead-in cohort (original), 12 subjects into the lead-in cohort (amended) and 126 subjects into the randomized cohort. A total of 162 subjects were actually enrolled out of which 30 subjects participated in the lead-in cohort (13 subjects in the original cohort and 17 subjects in the amended cohort) and 132 subjects were randomized in the randomized cohort, with 65 subjects assigned to sunitinib + erlotinib and 67 subjects assigned to erlotinib.

Diagnosis and Main Criteria for Inclusion: Male or female subjects ≥18 years old (subjects enrolled in the amended lead-in cohort must have been <70 years of age) with NSCLC who had received previous treatment with no >2 chemotherapy regimens including a platinum-based regimen in the locally advanced (Stage IIIB) or metastatic setting. Subjects who previously received treatment with antiangiogenesis agents including thalidomide or inhibitors of VEGF (with the exception of bevacizumab), VEGFR, PDGFR, or EGFR were ineligible for study entry. All subjects had to have Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, measurable disease per RECIST, evidence of disease progression prior to study enrollment and available archival tumor tissue (randomized cohort only). Subjects with history of or known brain metastases, hypertension that could not be controlled by medications, or evidence of hemoptysis <4 weeks of starting study treatment were ineligible for study entry.

Study Treatment: Erlotinib (Tarceva) was supplied from commercial sources as 25, 100, and 150 mg tablets. For the original lead-in cohort, during Cycle 1, erlotinib was dosed for 35 days and additional tablets were dispensed in this cycle only. For the amended lead-in cohort, during Cycle 1, erlotinib was dosed as follows: Arm A: 7 days in total (Days 1, 22, and 24 to 28 inclusive) or Arm B 26 days in total (Days 3 to 28 inclusive). For the randomized cohort, subjects received study treatment at 150 mg of erlotinib taken QD with blinded study medication in a continuous regimen expressed in 4 week cycles. Erlotinib was to be administered at least 1 hour before or 2 hours after food ingestion.

Blinded study medication consisting of sunitinib (12.5 mg, 25 mg and 50 mg capsules) or matching placebo was supplied by the sponsor. Subjects began study treatment with sunitinib 37.5 mg or matching placebo QD in a continuous regimen expressed in 4 week cycles. For the original lead-in cohort, Cycle 1 was extended to 35 days and sunitinib dosing was stopped on Day 28, and resumed on Day 2 of Cycle 2. For the amended lead-in cohort, during Cycle 1, sunitinib was dosed as follows: Arm A: 27 days in total (Days 2 to 28 inclusive) or Arm B 13 days in total (Days 1, 15, and 18 to 28 inclusive). For the randomized cohort, subjects received blinded study medication continuously in 4-week cycles. Self-administration of sunitinib or matching placebo capsules took place on an outpatient basis (except in the lead-in phase on days when PK testing was conducted). Capsules were to be taken QD in the morning and could be taken concurrently with erlotinib.

Efficacy, Pharmacokinetic and Outcomes Research Endpoints:

Primary Endpoint:

- Progression-Free Survival (PFS)

Secondary Endpoints:

- Objective Response
- Time to Progression (TTP)
- Duration of Response (DR)
- Overall Survival (OS)
- Probability of survival at 1 year
- Type, incidence, severity (graded by the National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE], Version 3.0), timing, seriousness, and relatedness of adverse events (AEs) and laboratory abnormalities. Incidence of blood pressure (BP) >150/100 mmHg and BP >200/110 mmHg during combination treatment and the proportion controlled with anti-hypertensive medications
- PK parameters of erlotinib, sunitinib and SU-012662. AUC_{0-24}, AUC_{0-inf}, maximum plasma concentration (C_{max}), time for C_{max} (T_{max}), C_{trough}, Clearance and t½, as appropriate
- C_{trough} values of erlotinib, , sunitinib and SU-012662
- Proportion of subjects with EGFR mutations, increased EGFR copy number, EGFR expression, and activating Kirsten rat sarcoma viral oncogene homolog (KRAS) mutations in tumors, germline VEGFR and PDGFR polymorphisms, tumor VEGFR mutations, and correlations with outcome
- Correlations of polymorphisms in c-KIT, FLT3 and c-FMS with blood counts during treatment with sunitinib
- Ribonucleic acid (RNA) expression profiles of tumors and correlation with outcome
- Levels of plasma proteins (eg., soluble VEGFR2, VEGF, soluble KIT) that may be associated with angiogenesis or tumor cell proliferation
- PROs including HRQOL and lung cancer related symptoms, as assessed using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ-C30) and its lung cancer module (LC13).

Safety Evaluations: Safety evaluations included AEs, clinical laboratory evaluations, vital signs, physical examinations, performance status (ECOG), electrocardiograms (ECGs), and assessment of left ventricular ejection fraction (LVEF).

Statistical Methods:

Population Sets:

Full Analysis Set (FAS): All subjects in the randomized phase who were randomized with study medication assignment designated according to initial randomization, regardless of whether subjects actually received study medication or received a different medication from

that to which they were randomized. The FAS was the primary set for evaluating all efficacy endpoints and subject characteristics for data collected in the randomized phase.

Per Protocol (PP) Set: All subjects who received at least 1 dose of study medication (either erlotinib or blinded medication) with treatment assignments designated according to actual study medication received.

The following subsets were defined for the PP set:

- Data from subjects in the randomized phase, up to the time of unblinding. This set was the primary set for safety and treatment evaluations for data collected in the randomized phase
- Data from subjects in the randomized phase, starting from the time of unblinding. This group included all subjects treated with sunitinib
- Data from subjects in the lead-in phase. This subset was the primary set for evaluating all safety, efficacy, and treatment evaluations for data collected in the lead-in phase. Data from the original lead-in cohort were summarized separately from data in the amended lead-in cohort

The safety analysis set was the same as the PP set.

PRO Analysis Set: Subjects who received at least 1 dose of study drug and had a baseline PRO assessment and at least 1 post-treatment PRO assessment.

Statistical Analyses:

The primary endpoint, PFS, using results of the central review of disease assessment, was assessed using Kaplan-Meier methods on the Full Analysis (FA) set, ie, all randomized subjects. Time-to-event endpoints such as PFS were compared between the 2 treatment groups using a 1-sided, unstratified log-rank test. Hazard ratio and its 80% and 95% confidence intervals (CIs) were estimated. For PFS, a stratified log-rank test was used to explore the potential influences of the baseline stratification factors.

Secondary efficacy analyses included analysis of PFS based on central review disease assessment in subgroups defined by baseline subject characteristics and other subgroups. The unstratified log-rank test was also used to evaluate PFS based on central review disease assessment in the PP set, ie, all subjects who received at least 1 dose of study medication. Supportive analyses were performed for PFS based on the Investigator's assessment of tumor data on FA population. PFS based on Investigator's assessment was also summarized for subjects in the lead-in cohorts.

Of the other efficacy endpoints, TTP, DR and OS were analyzed in a similar manner to PFS; ORR was evaluated by the number and percentage of subjects that achieved an objective response (complete [CR] or partial [PR] response) and summarized along with the corresponding exact 2-sided 95% CIs, with a χ^2 test used to compare ORR between the

2 treatment groups; and 1-year survival probability was estimated using the Kaplan-Meier method and a 2-sided 95% CI for the log was calculated using a normal approximation and then transformed back to give a CI for the 1-year survival probability itself.

All tumor biomarker variables were treated as categorical variables. PFS was compared between the 2 treatment groups and summarized on each subgroup defined by the tumor biomarker variable using the Kaplan-Meier method and displayed graphically, when appropriate. The p-value from unstratified log-rank test comparing the 2 treatment groups on each subgroup defined by the tumor biomarker variable was reported. The estimated hazard ratio and 95% CI were reported. Median event times and 95% CI for each median were provided.

The significance of changes in soluble protein levels from baseline (expressed as ratios to baseline) was determined using the Wilcoxon signed rank test using a hypothetical median value of 1.0. Soluble protein concentrations at baseline, and ratios to baseline at each time point, were compared after stratification by response using the Wilcoxon rank sum test. Time-to-event data (TTP, PFS and OS) were analyzed by comparison within each treatment arm of Kaplan-Meier curves using the Log-rank (Mantel-Cox) test and the Cox proportional hazard model.

The magnitude of change in PRO scores considered to be clinically meaningful was at least 10 points for each EORTC QLQ-C30 and LC13 scale. Changes less than 10 points were not considered to be clinically meaningful. Mean change from baseline scores and 95% CIs were used to estimate the effect of treatment on outcomes.

Summary descriptive statistics for plasma concentrations by nominal time and PK parameters are presented only for paired observations with respect to each parameter for each analyte. In the case where the dose for one of the paired observations was different than the other observation, dose correction to the intended dose was performed (correction factor: intended dose/actual dose).

The effect of erlotinib co-administration on the PK of SU-011248 was explored by presenting the 90% CIs around the differences in log transformed parameters (C_{max}, AUC_{24}) or the ratio of geometrics means between collection days. The effect of SU-011248's co-administration on the PK of erlotinib was explored in a similar fashion (C_{max}, AUC_{24} and AUC_{48}).

The number and percentage of subjects who experienced an AE, a serious adverse event (SAE), a treatment-related AE, a treatment-related SAE, and discontinuation due to an AE are presented. Summaries of AEs by preferred term and maximum Common Terminology Criteria for Adverse Events (CTCAE) grade were presented.

Descriptive statistics for hematology and serum chemistry are provided for each test result, and for change from baseline visit. Hematology and blood chemistry results were graded according to the CTCAE. Shift tables by CTCAE grade are presented. Subjects who developed a Grade ≥3 toxicity were also listed. Urinalysis results were listed and also summarized by time point. Shift tables of urine protein were presented.

Data for each vital sign were summarized and subjects with changes in vital signs that met defined categorical criteria were listed. All summary statistics and data presentations used averaged data (from triplicate measurements) for vital sign results.

Changes from baseline (defined as the screening value closest to but prior to first dose) for the ECG QTc interval were calculated to describe and display the frequency of subjects who experienced QTc interval prolongation. Post-baseline QTc values are displayed by category according to CTCAE grade and a shift summary table presented.

RESULTS

The results presented here are the final analyses of primary and secondary endpoints based on data with a 21 January 2010 cutoff date. Five subjects continued to receive sunitinib after the data cutoff date (2 subjects in the amended lead-in cohort and 3 subjects in the randomized cohort). The additional data collected for these subjects after the cutoff date did not change any of the conclusions regarding the PFS, OS, ORR, DR and PRO endpoints, and with the additional drug exposure to these 5 subjects, the safety profile remained similar.

Subject Disposition and Demography: At the time of data cutoff, 2 subjects were ongoing, both in the amended cohort, and the other 28 subjects discontinued from the study. Duration of follow-up for the lead-in subjects ranged from 1.7-40.6 months. Subject disposition is presented for the lead-in set in Table 4. The 2 subjects who were ongoing later discontinued due to objective progression or relapse.

Table 4. Summary of Subject Disposition-Lead-In Set

Number (%) of Subjects	Original	Amended	Total
Lead-in set[a]	13	17	30
Number (%) of subjects			
Ongoing	0	2 (11.8)	2 (6.7)
Discontinued from study	13 (100.0)	15 (88.2)	28 (93.3)
Completed	1 (7.7)	0	1 (3.3)
Other	12 (92.3)	15 (88.2)	27 (90.0)
Objective progression or relapse	6 (46.2)	9 (52.9)	15 (50.0)
Adverse event	2 (15.4)	1 (5.9)	3 (10.0)
Subject died	3 (23.1)	5 (29.4)	8 (26.7)
Subject refused continued treatment for reason other than adverse events.	1 (7.7)	0	1 (3.3)

a. Included all subjects who received at least 1 dose of study treatment in the lead-in safety portion.

Randomized Cohort: At the time of data cutoff, 3 subjects were ongoing (1 and 2 subjects in the sunitinib + erlotinib and erlotinib groups, respectively) and 129 subjects discontinued from the study (64 and 65 subjects, respectively). Of the 65 subjects assigned to sunitinib + erlotinib, 1 subject (1.5%) completed the study. Of the 129 discontinuations, 3 subjects completed 18 cycles and hence were classified as having completed the study (1 and 2 subjects in the sunitinib + erlotinib and erlotinib groups, respectively), with the remaining subjects discontinuing for other reasons, mainly objective progression or relapse (74 subjects, 56.1%; 37 subjects in each group). Of the 132 subjects who were randomized, 4 subjects were withdrawn during pre-treatment and were not included in the PP set. Subject disposition is presented for the randomized cohort in Table 5.

Of the 3 subjects in the randomized cohort who were still on study at the time of data cutoff, 1 subject (sunitinib + erlotinib group) discontinued due to study termination; 1 subject (erlotinib group) discontinued due to objective progression or relapse; 1 subject (erlotinib group) discontinued due to "other" reasons (by the Investigator due to noncompliance).

Table 5. Summary of Subject Disposition (Randomized Cohort)

Number (%) of Subjects	Sunitinib + Erlotinib	Erlotinib	Total
Subjects randomized	65	67	132
Full analysis set[a]	65	67	132
Per-protocol/safety set[b]	64	64	128
Patient reported outcomes analysis set[c]	49	54	103
Evaluable for pharmacokinetics (trough levels)	60	60	120
Number (%) of subjects			
Ongoing	1 (1.5)	2 (3.0)	3 (2.3)
Discontinued from study	64 (98.5)	65 (97.0)	129 (97.7)
Completed	1 (1.5)	2 (3.0)	3 (2.3)
Other	63 (96.9)	63 (94.0)	126 (95.5)
Objective progression or relapse	37 (56.9)	37 (55.2)	74 (56.1)
Global deterioration of health status	3 (4.6)	0	3 (2.3)
Adverse event	7 (10.8)	5 (7.5)	12 (9.1)
Subject died	12 (18.5)	15 (22.4)	27 (20.5)
Protocol violation	1 (1.5)	4 (6.0)	5 (3.8)
Lost to follow-up	0	1 (1.5)	1 (0.8)
Subject refused continued treatment for reason other than adverse event	2 (3.1)	1 (1.5)	3 (2.3)
Other[d]	1 (1.5)	0	1 (0.8)
Duration of follow-up, months[e]			
Median	15.7	19.6	17.7
95% Confidence interval	(11.1, 21.9)	(13.3, 21.5)	(13.3, 21.0)

a. Included all subjects who were randomized, with study drug assignment according to initial randomization, regardless of whether subjects received study drug according to randomization schedule or received a different drug than they were randomized.
b. Included all subjects who received at least 1 dose of study medication (erlotinib or blinded study medication), with treatment assignments designated according to actual study treatment received.
c. Subjects from the Full Analysis Set that had at least 1 questionnaire assessment while on treatment.
d. Subject's decision to withdraw from treatment due to toxicities.
e. Calculated based on the Kaplan-Meier potential follow-up method (reversed Kaplan-Meier estimate) of overall survival time, where death was censored and alive was an event.

Demographic characteristics for the original and amended lead-in cohorts, and randomized cohort are presented in Table 6.

Table 6. Summary of Demographic and Baseline Characteristics

Lead-In Set			
	Original (N=13)	**Amended (N=17)**	**Total (N=30)**
Sex, number (%) of subjects			
Male	7 (53.8)	11 (64.7)	18 (60.0)
Female	6 (46.2)	6 (35.3)	12 (40.0)
Age (years)			
<65, number (%) of subjects	7 (53.8)	10 (58.8)	17 (56.7)
≥65, number (%) of subjects	6 (46.2)	7 (41.2)	13 (43.3)
Mean (standard deviation), years	63.5 (9.67)	60.3 (7.78)	61.7 (8.64)
Median (minimum, maximum), years	64 (47, 75)	64 (43, 69)	64 (43, 75)
ECOG performance status, number (%) of subjects			
0	2 (15.4)	8 (47.1)	10 (33.3)
1	11 (84.6)	9 (52.9)	20 (66.7)
Smoking status, number (%) of subjects			
Never smoked	4 (30.8)	4 (23.5)	8 (26.7)
Ex-smoker	7 (53.8)	11 (64.7)	18 (60.0)
Current smoker	2 (15.4)	2 (11.8)	4 (13.3)
Randomized Cohort			
	Sunitibib + Erlotinib (N=65)	**Erlotibib (N=67)**	**Total (N=132)**
Sex, number (%) of subjects			
n	64[a]	67	131[a]
Male	39 (60.0)	45 (67.2)	84 (63.6)
Female	25 (38.5)	22 (32.8)	47 (35.6)
Age			
n	64[a]	67	131[a]
<65, number (%) of subjects	47 (72.3)	43 (64.2)	90 (68.2)
≥65, number (%) of subjects	17 (26.2)	24 (35.8)	41 (31.1)
Mean (standard deviation), years	58.2 (9.90)	60.7 (8.71)	59.5 (9.36)
Median (minimum, maximum), years	58.5 (37, 79)	61.0 (39, 81)	60.0 (37, 81)
ECOG performance status, number (%) of subjects			
0	21 (32.3)	21 (31.3)	42 (31.8)
1	43 (66.2)	45 (67.2)	88 (66.7)
2	0	1 (1.5)	1 (0.8)
Not done	1 (1.5)	0	1 (0.8)
Smoking history (stratification factor), number (%) of subjects			
Current (<1 year)	26 (40.0)	24 (35.8)	50 (37.9)
Never	7 (10.8)	9 (13.4)	16 (12.1)
Prior (≥1 year)	31 (47.7)	33 (49.3)	64 (48.5)
Missing	1 (1.5)	1 (1.5)	2 (1.5)
EGFR status at study entry, number (%) of subjects			
Negative	1 (1.5)	3 (4.5)	4 (3.0)
Unmeasured (includes unknown or not done)	63 (96.9)	64 (95.5)	127 (96.2)
Missing	1 (1.5)	0	1 (0.8)

ECOG = Eastern Cooperative Oncology Group; EGFR = epidermal growth factor receptor; N = number of subjects; n = number of subjects with data.

a. Data not collected for 1 subject who was randomized in error with no informed consent.

Efficacy, Pharmacokinetic and Outcomes Research Results:

Primary Endpoint:

Progression-Free Survival (Randomized Cohort): Based on third party review, the proportion of subjects with a PFS event was similar for the 2 groups: 55.4% and 62.7% of subjects in the sunitinib + erlotinib and erlotinib groups, respectively. In most cases (>85% of PFS events in each group) the event was objective progression, rather than death without objective progression. PFS data were censored for 44.6% and 37.3% of subjects in the sunitinib + erlotinib and erlotinib groups, respectively, primarily due to subjects starting new treatments without progression (27.6% and 40.0% of subjects with censored data in the sunitinib + erlotinib and erlotinib groups, respectively) or subjects discontinuing without progression (62.1% and 44.0%, respectively).

Only 78 of 115 expected events were observed (due to a greater than expected dropout rate and the tendency for subjects to be withdrawn when identified as experiencing progression by the investigator with progression not subsequently confirmed by central third-party review), and although the hazard ratio was <1 (0.898; 80% CI: 0.671, 1.203), favoring the sunitinib + erlotinib group, the log rank test was not statistically significant (p=0.3206). Median time to progression or death was longer for the sunitinib + erlotinib group (12.3 weeks; 95% CI: 8.1, 19.5 weeks) compared to the erlotinib group (8.5 weeks; 95% CI: 8.0, 12.3 weeks).

Secondary Efficacy Endpoints (Randomized Cohort):

No subjects had CR. The OR was similar for the 2 groups: 5 subjects had PR: 3/65 subjects (4.6%) in the sunitinib + erlotinib group and 2/67 subjects (3.0%) in the erlotinib group. Duration of response was not analyzed due to the low number of subjects with an OR, however DR ranged from 31 to 430 days in the sunitinib + erlotibib group and 113 to 333 days in the erlotinib group.

For TTP, the hazard ratio of 0.921 (95% CI: 0.572, 1.485) slightly favored the sunitinib + erlotinib group and the difference between treatments was not significant (p=0.3732). Median TTP was longer for the sunitinib + erlotinib group (12.3 weeks) compared to the erlotinib group (10.1 weeks).

There was no significant treatment difference between the groups in terms of OS (hazard ratio = 1.066, 95% CI: 0.705, 1.612, p=0.6171), although this may have been confounded by crossover and by an imbalance in post-study treatments. Approximately 70% of study subjects died, and 30% of subjects were censored.

An overview of efficacy endpoints for the randomized cohort is presented in Table 7.

Table 7. Overview of Efficacy Endpoints – Full Analysis Set (Randomized Cohort)

Endpoint	Sunitinib + Erlotinib (N=65)	Erlotinib (N=67)	Hazard or Risk Ratio (CI)	p-Value
Progression Free Survival (PFS)				
Events, number (%) of subjects	36 (55.4)	42 (62.7)		
Median (weeks)	12.3	8.5	0.898	0.3206
95% CI	(8.1, 19.5)	(8.0, 12.3)		
80% CI			(0.671, 1.203)	
Objective Response Rate (ORR)				
Objective response, number (%) of subjects	3 (4.62)	2 (2.99)	1.546[a]	0.6251
95% Exact CI	(0.96, 12.90)	(0.36, 10.37)	(0.267, 8.954)	
Time to Tumor Progression (TTP)				
Number (%) progressed	32 (49.2)	36 (53.7)		
Median, weeks	12.3	10.1	0.921	0.3732
95% CI	(8.8, 20.1)	(8.1, 13.0)	(0.572, 1.485)	
Overall Survival (OS)				
Number (%) of deaths	44 (67.7)	48 (71.6)		
Median, months	8.2	7.6	1.066	0.6171
95% CI	(5.7, 11.3)	(5.3, 13.4)	0.705, 1.612	
1-Year Survival Probability	0.32	0.42		
95% CI	(0.197, 0.443)	(0.301, 0.542)		

One-sided p-value was based on unstratified log-rank test for PFS, TTP and OS.
PFS, TTP, and ORR were based on the third party independent imaging review laboratory data.
CI = confidence interval; N = number of randomized subjects; ORR = objective response rate; OS = overall survival; PFS = progression free survival; TTP = time to tumor progression.
a. Risk ratio.

Patient Reported Outcomes (Randomized Cohort): Subjects in the 2 treatment groups were numerically similar in most functioning scales and subjects' global QoL did not change significantly in both treatment groups overall compared to baseline, nor did the functioning domains. Many symptoms also remained relatively stable without clinically and statistically significant change. However, subjects did report worsening in certain symptoms including diarrhea, sore mouth, and appetite loss, which are commensurate with known toxicities of the treatments.

Tumor Biopsy:

Tumor biopsy data (EGFR protein expression by IHC, EGFR DNA copy number variation, and EGFR and KRAS DNA mutation) are summarized in Table 8 for the lead-in cohort and Table 9 for the randomized cohort.

Table 8. Summary of Tumor Biopsy Data – Lead-In Cohort

	Number (%) of Samples			
	Positive	**Negative**	**Unmeasured**	**N**
EGFR expression based on DAKO kit (positive >0%)	2 (29)	5 (71)	0	7
EGFR expression based on BR21 trial (positive >10%)	2 (29)	5 (71)	0	7
	Yes	**No**	**Unmeasured**	**N**
EGFR copy number increase (>4)	0	3 (43)	4 (57)	7
EGFR gene amplification (>15)	0	3 (43)	4 (57)	7
	Mutated	**Wild Type**	**Indeterminate**	**N**
EGFR mutation	0	2 (29)	5 (71)	7
KRAS mutation	1 (14)	1 (14)	5 (71)	7

All subjects were in the original lead-in cohort. Tumor tissue collection was optional for lead-in cohorts.
EGFR = epidermal growth factor receptor; KRAS = Kirsten rat sarcoma viral oncogene homolog; N = total number of samples.

Table 9. Summary of Tumor Biopsy Data – Randomized Cohort

	Number (%) of Samples			
	Positive	**Negative**	**Unmeasured**	**N**
Sunitinib + Erlotinib				
EGFR expression based on DAKO kit (positive >0%)	29 (57)	19 (37)	3 (6)	51
EGFR expression based on BR21 trial (positive >10%)	23 (45)	25 (49)	3 (6)	51
Erlotinib				
EGFR expression based on DAKO kit (positive >0%)	36 (68)	12 (23)	5 (9)	53
EGFR expression based on BR21 trial (positive >10%)	24 (45)	24 (45)	5 (9)	53
	Yes	**No**	**Unmeasured**	**N**
Sunitinib + Erlotinib				
EGFR copy number increase (>4)	0	31 (61)	20 (39)	51
EGFR gene amplification (>15)	0	31 (61)	20 (39)	51
Erlotinib				
EGFR copy number increase (>4)	1 (2)	28 (53)	24 (45)	53
EGFR gene amplification (>15)	0	29 (55)	24 (45)	53
	Mutated	**Wild Type**	**Indeterminate**	**N**
Sunitinib + Erlotinib				
EGFR mutation	4 (8)	21 (41)	26 (51)	51
KRAS mutation	6 (12)	22 (43)	23 (45)	51
Erlotinib				
EGFR mutation	1 (2)	19 (36)	33 (62)	53
KRAS mutation	4 (8)	19 (36)	30 (57)	53

EGFR = epidermal growth factor receptor; KRAS = Kirsten rat sarcoma viral oncogene homolog; N = total number of subjects who submitted samples.

Sunitinib, SU-012662, and Total Drug PK:

Plasma PK parameter values and geometric mean ratios for subjects with paired observations for sunitinib, SU-011262 and total drug following a dose of either sunitinib alone or co-administered with erlotinib are summarized in Table 10 for the original and amended lead-in cohorts.

Table 10. Sunitinib, SU-012662 and Total Drug Pharmacokinetic Parameters in Lead-In Cohort

Dose (Sunitinib / Erlotinib) Analyte Parameter	Mean (%CV) [Median] (Sunitinib Alone)[a]	Mean (%CV) [Median] (Erlotinib+Sunitinib)	Geometric Mean Ratio (Combination/Sunitinib Alone)
Lead-in Cohort - 37.5 mg/150 mg, n=8			
Sunitinib			
T_{max} (hr)[b]	6.0 (1.0-10.0)	7.0 (4.0-10.0)	NA
C_{max} (ng/mL)	51.1 (39) [44.3]	38.4 (29) [39.3]	0.77
AUC_{24} (ng•hr/mL)	1056 (41) [970]	619 (23) [628]	0.62
CL/F (L/hr)	40.8 (37) [38.8]	63.3 (21) [59.8]	1.62
SU-012662			
T_{max} (hr)[b]	6.0 (2.0-24.0)	7.0 (4.0-24.0)	NA
C_{max} (ng/mL)	18.8 (41) [17.3]	31.2 (35) [32.7]	1.67
AUC_{24} (ng•hr/mL)	403 (39) [375]	575 (30) [593]	1.46
Total Drug[c]			
T_{max} (hr)[b]	6.0 (1.0-10.0)	7.0 (4.0-10.0)	NA
C_{max} (ng/mL)	69.0 (37) [59.3]	69.5 (26) [62.8]	1.03
AUC_{24} (ng•hr/mL)	1460 (36) [1341]	1194 (16) [1254]	0.86
Amended Lead-in Cohort, Arm B (Subjects with Paired Observations Only) - 37.5 mg /150 mg, n=8			
Sunitinib			
T_{max} (hr)[b]	6.0 (4.0-8.0)	6.0 (4.0-24.0)	NA
C_{max} (ng/mL)	21.6 (31) [23]	13.6 (43) [12.1]	0.62
AUC_{24} (ng·hr/mL)	373 (28) [397]	232 (30) [222]	0.62
AUC_{48} (ng·hr/mL)	653 (25) [696]	370 (23) [378]	0.57
SU-012662			
T_{max} (hr)[b]	4.0 (2.0-48.0)	4.0 (4.0-8.0)	NA
C_{max} (ng/mL)	3.09 (43) [3.28]	6.83 (62) [5.29]	2.13
AUC_{24} (ng•hr/mL)	50.1 (45) [47.1]	99.6 (40) [84.6]	2.07
AUC_{48} (ng•hr/mL)	96.9 (45) [81.4]	170 (31) [149]	1.84
Total Drug[c]			
T_{max} (hr)[b]	6.0 (4.0-8.0)	5.0 (4.0-24.0)	NA
C_{max} (ng/mL)	24.5 (31) [25.3]	20.1 (39) [18.6]	0.81
AUC_{24} (ng•hr/mL)	423 (29) [445]	331 (27) [327]	0.79
AUC_{48} (ng•hr/mL)	750 (26) [778]	541 (20) [557]	0.73

AUC_{24} = area under plasma concentration-time profile from time 0 to 24 hours; AUC_{48} = area under plasma concentration-time profile from time zero to 48 hours; CL/F = clearance at steady state after oral administration; C_{max} = maximum plasma concentration; CV = coefficient of variation; n = number of subjects with observations; NA = not applicable; T_{max} = time for C_{max}.

a. Historical controls from study (Phase I Study of SU011248 in Combination With Pemetrexed, Pemetrexed / Cisplatin and Pemetrexed / Carboplatin in Patients With Advanced Solid Malignancies [NCT00528619]), sunitinib was dosed at 37.5 mg alone on Day 15 of Cycle 1 on a continuous daily dosing schedule in subjects with advanced solid malignances, n=12.
b. T_{max}: median (min, max).
c. Total Drug = sunitinib + SU-012662.

Dose-corrected (reference dose: 37.5 mg) mean C_{trough} values for sunitinib, its metabolite, and total drug at steady state ranged from 11.7 to 24.9 ng/mL, 11.6 to 21.0 ng/mL, and 23.3 to 44.0 ng/mL, respectively (combined data from original, amended, and randomized cohorts).

Erlotinib PK:

Plasma PK parameter values and geometric mean ratios for subjects with paired observations for erlotinib following a dose of either erlotinib alone or co-administered with erlotinib are summarized in Table 11 for the original and amended lead-in cohorts.

Table 11. Erlotinib Pharmacokinetic Parameters Lead-In Cohort

Dose (Sunitinib/Erlotinib) Analyte Parameter	Mean (%CV) [Median] (Erlotinib Alone)[a]	Mean (%CV) [Median] (Erlotinib+Sunitinib)	Geometric Mean Ratio (Combination/ Erlotinib Alone)
Original Lead-in Cohort - 150 mg/37.5 mg, n=8			
Erlotinib			
T_{max} (hr)[b]		3.0 (1.0-8.0)	NA
C_{max} (ng/mL)	2.0 ± 0.91[a]	2.40 (51) [2.35]	-
AUC_{24} (ng•hr/mL)	41.3 ± 22[a]	37.7 (58) [30.5]	-
CL/F (L/hr)	3.95[a]	5.52 (66) [4.92]	-
Original Lead-in Cohort (Subjects With Paired Observations Only) - 150 mg / 37.5 mg, n=2			
Erlotinib			
T_{max} (hr))[b]	4.0 (2.0-6.0)	2.0 (2.0-2.0)	NA
C_{max} (ng/mL)	1.81 (60) [1.81]	2.11 (66) [2.11]	1.14
AUC_{24} (ng•hr/mL)	24.4 (24) [24.4]	34.7 (59) [34.7]	1.31
CL/F (L/hr)	6.33 (24) [6.33]	5.23 (59) [5.23]	0.76
Amended Lead-in Cohort, Arm A (Subjects With Paired Observations Only) - 150 mg / 37.5 mg, n=7			
Erlotinib			
T_{max} (hr))[b]	2.0 (1.0-6.0)	2.0 (1.0-24.0)	NA
C_{max} (ng/mL)	0.99 (49) [0.70]	0.85 (43) [0.92]	0.81
AUC_{24} (ng•hr/mL)	13.0 (31) [11.3]	11.9 (37) [12.5]	0.87
Amended Lead-in Cohort, Arm A (Subjects With Paired Observations Only)[c] - 150 mg / 37.5 mg, n=6			
Erlotinib			
T_{max} (hr))[b]	3.0 (1.0-6.0)	2.0 (1.0-6.0)	NA
C_{max} (ng/mL)	0.99 (53) [0.70]	0.97 (24) [0.94]	1.05
AUC_{24} (ng•hr/mL)	13.2 (33) [12.4]	13.3 (19) [13.4]	1.03s

AUC_{24} = area under plasma concentration-time profile from time 0 to 24 hours; CL/F = clearance at steady state after oral administration; C_{max} = maximum plasma concentration; CV = coefficient of variation; n = number of subjects with observations; NA = not applicable; T_{max} = time for C_{max}.

a. Typical pharmacokinetic values for a randomized, double blind, placebo controlled study, BR.21, which took subjects with non-small cell lung cancer and randomized to erlotinib 150 mg or placebo (n=731; 591 in the erlotinib arm).
b. T_{max}: median (min, max).
c. One subject excluded.

Dose-corrected (reference dose: 150 mg) mean C_{trough} values for erlotinib at steady state ranged from 0.57 to 1.94 µg/mL.

Tumor Biomarker Results:

Baseline concentrations of VEGF-C, sVEGFR-2, sVEGFR-3 and sKIT, and ratios to baseline at Cycle 2 Day 1 and Cycle 3 Day 1, were compared. No significant differences were seen between treatment arms for baseline levels of any of the soluble proteins analyzed. In contrast, ratios to baseline for sVEGFR-2, sVEGFR-3 and sKIT were significantly lower in the sunitinib + erlotinib arm than in the erlotinib arm at Cycle 2 Day 1 ($p < 0.0001$ in all cases) and Cycle 3 Day 1 ($p < 0.0001$ in all cases), while VEGF-C ratios to baseline did not differ at either time point.

Exploratory biomarker analyses showed that, for subjects with low (less than median) tumor PDGFRα RNA levels, the comparison of PFS between the 2 arms favored the sunitinib + erlotinib arm (hazard ratio = 0.386, log-rank one-sided p-value = 0.0401). For subjects with high (greater than median) tumor PDGFRα RNA levels, no arm was favored in comparison of PFS.

Safety Results:

Overall Summary of AEs:

Lead-in Cohorts: An overall summary of AEs for the lead-in cohort is presented in Table 12. The number of AEs reported was greater for the original cohort (302 AEs) compared to the amended cohort (91 AEs), with 100% of subjects in the original cohort experiencing AEs compared to 88% of subjects in the amended cohort.

After the data cut-off date (21 January 2010) for the 2 subjects in the amended lead-in cohort who were still ongoing, no deaths were reported, no subjects experienced SAEs and no subjects permanently discontinued, temporarily discontinued, or had dose reductions due to AEs. However, death was reported for 1 subject in the amended lead-in cohort after the required reporting period.

Table 12. Overall Summary of Adverse Events- (Lead-In Set)

Number (%) of Subjects	Original Cohort (N=13)	Amended Cohort (N=17)
Evaluable for AEs	13 (100.0)	17 (100.0)
Number of AEs	302	91
With AEs	13 (100.0)	15 (88.2)
With erlotinib or sunitinib related AEs	13 (100.0)	13 (76.5)
With erlotinib related AEs	12 (92.3)	13 (76.5)
With sunitinib related AEs	12 (92.3)	9 (52.9)
With erlotinib and sunitinib related AEs	11 (84.6)	7 (41.2)
With SAEs	5 (38.5)	7 (41.2)
With erlotinib or sunitinib related SAEs	3 (23.1)	4 (23.5)
With erlotinib related SAEs	2 (15.4)	3 (17.6)
With sunitinib related SAEs	3 (23.1)	3 (17.6)
With erlotinib and sunitinib related SAEs	2 (15.4)	2 (11.8)
With grade 3/4 AEs	10 (76.9)	7 (41.2)
With erlotinib or sunitinib related AEs	10 (76.9)	6 (35.3)
With erlotinib related AEs	9 (69.2)	6 (35.3)
With sunitinib related AEs	8 (61.5)	4 (23.5)
With erlotinib and sunitinib related AEs	7 (53.8)	4 (23.5)
With grade 5 AEs	2 (15.4)	4 (23.5)
With erlotinib or sunitinib related AEs	0	0
With erlotinib related AEs	0	0
With sunitinib related AEs	0	0
With erlotinib and sunitinib related AEs	0	0
Discontinued erlotinib due to AEs	4 (30.8)	4 (23.5)
Discontinued sunitinib due to AEs	4 (30.8)	4 (23.5)
Dose reduced erlotinib due to AEs	4 (30.8)	3 (17.6)
Dose reduced sunitinib due to AEs	3 (23.1)	2 (11.8)
Temporary stopped erlotinib due to AEs	9 (69.2)	7 (41.2)
Temporary stopped sunitinib due to AEs	9 (69.2)	7 (41.2)

Except for number of AEs, subjects were counted once per treatment in each row.
Serious adverse events-per Investigator's assessment.
AEs and SAEs are not separated out.
AE = adverse event; N = number of subjects; SAE = serious adverse event.

Randomized Cohort: An overall summary of AEs for the randomized cohort is presented in Table 13 . Three subjects enrolled in the randomized cohort continued on-study; AE data for these subjects was collected until withdrawal from study. The number of AEs was greater for the sunitinib + erlotinib treatment group (847 AEs) compared to the erlotinib treatment group (729 AEs); approximately 95% of subjects in each treatment group experienced AEs.

After the data cut-off date (21 January 2010) for the 3 ongoing subjects in the randomized cohort, no deaths were reported. However, death was reported for 1 subject in the erlotinib treatment group after the required reporting period.

Table 13. Overall Summary of Adverse Events – Per-Protocol Set (Randomized Cohort)

Number (%) of Subjects	Sunitinib + Erlotinib (N=64) n (%)	Erlotinib (N=64) n (%)
Subjects with reported AE data	64 (100.0)	64 (100.0)
Number of AEs	847	729
Subjects with ≥1 AE	61 (95.3)	61 (95.3)
With ≥1 erlotinib or sunitinib/placebo-related AE	55 (85.9)	55 (85.9)
With ≥1 erlotinib-related AE	52 (81.3)	55 (85.9)
With ≥1 sunitinib/placebo-related AE	45 (70.3)	36 (56.3)
With ≥1 erlotinib and sunitinib/placebo-related AE	37 (57.8)	30 (46.9)
Subjects with ≥1 SAE	29 (45.3)	28 (43.8)
With ≥1 erlotinib or sunitinib/placebo-related SAE	12 (18.8)	6 (9.4)
With ≥1 erlotinib-related SAE	9 (14.1)	4 (6.3)
With ≥1 sunitinib/placebo-related SAE	8 (12.5)	4 (6.3)
With ≥1 erlotinib and sunitinib/placebo-related SAE	5 (7.8)	2 (3.1)
Subjects with Grade 3/4 AEs	42 (65.6)	31 (48.4)
With ≥1 erlotinib or sunitinib/placebo-related Grade 3/4 AE	29 (45.3)	9 (14.1)
With ≥1 erlotinib-related Grade 3/4 AE	25 (39.1)	7 (10.9)
With ≥1 sunitinib/placebo-related Grade 3/4 AE	22 (34.4)	6 (9.4)
With ≥1 erlotinib and sunitinib/placebo-related Grade 3/4 AE	18 (28.1)	4 (6.3)
Subjects with Grade 5 AEs	10 (15.6)	11 (17.2)
With ≥1 erlotinib or sunitinib/placebo-related Grade 5 AE	1 (1.6)	0
With ≥1 erlotinib-related Grade 5 AE	1 (1.6)	0
With ≥1 sunitinib/placebo-related Grade 5 AE	1 (1.6)	0
With ≥1 erlotinib and sunitinib/placebo-related Grade 5 AE	1 (1.6)	0
Subjects who discontinued erlotinib due to AEs	18 (28.1)	17 (26.6)
Subjects who discontinued sunitinib/placebo due to AEs	18 (28.1)	16 (25.0)
Subjects who stopped erlotinib temporarily due to AEs	30 (46.9)	20 (31.3)
Subjects who stopped sunitinib/placebo temporarily due to AEs	31 (48.4)	16 (25.0)
Subjects with erlotinib dose-reduced due to AEs	10 (15.6)	5 (7.8)
Subjects with sunitinib/placebo dose-reduced due to AEs	9 (14.1)	4 (6.3)

% = (n/N) × 100.
All AEs that occurred on or after the first dose of the study treatment were included in this table. Except for number of AEs, subjects were counted only once per treatment in each row.
SAEs were according to the Investigator's assessment.
AEs and SAEs are not separated out.
Treatment-related AEs had causality on AE CRF pages checked as "Yes" or "Unknown."
AE = adverse event; CRF = case report form; N = number of subjects who received at least 1 dose of study treatment; n = number of subjects who had data for summary; SAE = serious adverse event.

All Causality AEs:

Lead-In Cohort: Treatment-emergent AEs (all causalities) reported by ≥5% of subjects in the original or amended lead-in cohorts are presented in Table 14.

Table 14. Treatment-Emergent All Causality Other (Not Including Serious) Adverse Events Reported in ≥5% Subjects (Lead-In Set)

System Organ Class Preferred Term	Original Lead-In (N=13)	Amended Lead-In (N=17)	Total Lead-In (N=30)
	n (%)	n (%)	n (%)
Any AE	13 (100.0)	15 (88.2)	28 (93.3)
Blood and lymphatic system disorders	5 (38.5)	1 (5.9)	6 (20.0)
Anaemia	3 (23.1)	1 (5.9)	4 (13.3)
Leukopenia	1 (7.7)	0	1 (3.3)
Neutropenia	3 (23.1)	0	3 (10.0)
Thrombocytopenia	1 (7.7)	0	1 (3.3)
Cardiac disorders	1 (7.7)	3 (17.6)	4 (13.3)
Atrial fibrillation	0	1 (5.9)	1 (3.3)
Cyanosis	0	1 (5.9)	1 (3.3)
Sinus bradycardia	1 (7.7)	0	1 (3.3)
Tachycardia	0	1 (5.9)	1 (3.3)
Eye disorders	1 (7.7)	0	1 (3.3)
Vision blurred	1 (7.7)	0	1 (3.3)
Gastrointestinal disorders	12 (92.3)	10 (58.8)	22 (73.3)
Abdominal pain	2 (15.4)	1 (5.9)	3 (10.0)
Abdominal pain upper	1 (7.7)	3 (17.6)	4 (13.3)
Constipation	1 (7.7)	0	1 (3.3)
Diarrhoea	10 (76.9)	9 (52.9)	19 (63.3)
Duodenogastric reflux	1 (7.7)	0	1 (3.3)
Dyspepsia	1 (7.7)	1 (5.9)	2 (6.7)
Flatulence	1 (7.7)	0	1 (3.3)
Gastrooesophageal reflux disease	1 (7.7)	0	1 (3.3)
Haemorrhoids	2 (15.4)	0	2 (6.7)
Nausea	5 (38.5)	1 (5.9)	6 (20.0)
Oral pain	2 (15.4)	0	2 (6.7)
Stomatitis	2 (15.4)	0	2 (6.7)
Vomiting	3 (23.1)	2 (11.8)	5 (16.7)
General disorders and administration site conditions	12 (92.3)	3 (17.6)	15 (50.0)
Asthenia	3 (23.1)	0	3 (10.0)
Chest discomfort	2 (15.4)	0	2 (6.7)
Chest pain	1 (7.7)	0	1 (3.3)
Chills	1 (7.7)	0	1 (3.3)
Fatigue	8 (61.5)	2 (11.8)	10 (33.3)
Mucosal inflammation	1 (7.7)	0	1 (3.3)
Oedema peripheral	2 (15.4)	1 (5.9)	3 (10.0)
Pain	1 (7.7)	0	1 (3.3)
Pyrexia	4 (30.8)	1 (5.9)	5 (16.7)
Suprapubic pain	1 (7.7)	0	1 (3.3)
Hepatobiliary disorders	1 (7.7)	0	1 (3.3)
Hyperbilirubinaemia	1 (7.7)	0	1 (3.3)
Infections and infestations	6 (46.2)	2 (11.8)	8 (26.7)
Infection	2 (15.4)	0	2 (6.7)
Nasopharyngitis	0	1 (5.9)	1 (3.3)
Oral candidiasis	0	1 (5.9)	1 (3.3)
Paronychia	2 (15.4)	0	2 (6.7)
Pneumonia	1 (7.7)	0	1 (3.3)
Respiratory tract infection	0	1 (5.9)	1 (3.3)
Sinusitis	1 (7.7)	0	1 (3.3)
Urinary tract infection	2 (15.4)	1 (5.9)	3 (10.0)
Investigations	5 (38.5)	0	5 (16.7)
Alanine aminotransferase increased	1 (7.7)	0	1 (3.3)
Aspartate aminotransferase increased	1 (7.7)	0	1 (3.3)
Blood alkaline phosphatase increased	1 (7.7)	0	1 (3.3)
Blood creatinine increased	2 (15.4)	0	2 (6.7)

Table 14. Treatment-Emergent All Causality Other (Not Including Serious) Adverse Events Reported in ≥5% Subjects (Lead-In Set)

System Organ Class Preferred Term	Original Lead-In (N=13)	Amended Lead-In (N=17)	Total Lead-In (N=30)
	n (%)	n (%)	n (%)
Haemoglobin decreased	1 (7.7)	0	1 (3.3)
Platelet count decreased	1 (7.7)	0	1 (3.3)
Vitamin B12 decreased	1 (7.7)	0	1 (3.3)
Weight decreased	1 (7.7)	0	1 (3.3)
White blood cell count decreased	2 (15.4)	0	2 (6.7)
Metabolism and nutrition disorders	11 (84.6)	4 (23.5)	15 (50.0)
Decreased appetite	7 (53.8)	1 (5.9)	8 (26.7)
Dehydration	5 (38.5)	2 (11.8)	7 (23.3)
Hyperglycaemia	1 (7.7)	0	1 (3.3)
Hypoglycaemia	1 (7.7)	0	1 (3.3)
Hypokalaemia	2 (15.4)	1 (5.9)	3 (10.0)
Hypomagnesaemia	3 (23.1)	0	3 (10.0)
Hypophosphataemia	1 (7.7)	0	1 (3.3)
Musculoskeletal and connective tissue disorders	6 (46.2)	0	6 (20.0)
Arthralgia	3 (23.1)	0	3 (10.0)
Arthritis	1 (7.7)	0	1 (3.3)
Back pain	1 (7.7)	0	1 (3.3)
Bone pain	1 (7.7)	0	1 (3.3)
Groin pain	1 (7.7)	0	1 (3.3)
Muscle atrophy	1 (7.7)	0	1 (3.3)
Musculoskeletal chest pain	2 (15.4)	0	2 (6.7)
Myalgia	1 (7.7)	0	1 (3.3)
Pain in extremity	1 (7.7)	0	1 (3.3)
Nervous system disorders	6 (46.2)	1 (5.9)	7 (23.3)
Ageusia	1 (7.7)	0	1 (3.3)
Dizziness	2 (15.4)	0	2 (6.7)
Dysgeusia	4 (30.8)	1 (5.9)	5 (16.7)
Headace	1 (7.7)	0	1 (3.3)
Paraesthesia	1 (7.7)	0	1 (3.3)
Peripheral sensory neuropathy	0	1 (5.9)	1 (3.3)
Somnolence	1 (7.7)	0	1 (3.3)
Psychiatric disorders	3 (23.1)	1 (5.9)	4 (13.3)
Anxiety	1 (7.7)	1 (5.9)	2 (6.7)
Depression	1 (7.7)	0	1 (3.3)
Hallucination	1 (7.7)	0	1 (3.3)
Renal and urinary disorders	1 (7.7)	1 (5.9)	2 (6.7)
Dysuria	1 (7.7)	1 (5.9)	2 (6.7)
Respiratory, thoracic and mediastinal disorders	10 (76.9)	7 (41.2)	17 (56.7)
Cough	6 (46.2)	2 (11.8)	8 (26.7)
Dysphonia	1 (7.7)	0	1 (3.3)
Dyspnoea	4 (30.8)	3 (17.6)	7 (23.3)
Dyspnoea exertional	2 (15.4)	1 (5.9)	3 (10.0)
Epistaxis	1 (7.7)	1 (5.9)	2 (6.7)
Haemoptysis	0	2 (11.8)	2 (6.7)
Hypoxia	0	1 (5.9)	1 (3.3)
Oropharyngeal pain	2 (15.4)	0	2 (6.7)
Pleural effusion	1 (7.7)	0	1 (3.3)
Productive cough	1 (7.7)	0	1 (3.3)
Pulmonary haemorrhage	0	1 (5.9)	1 (3.3)
Sinus disorder	1 (7.7)	0	1 (3.3)
Skin and subcutaneous tissue disorders	11 (84.6)	11 (64.7)	22 (73.3)
Acne	6 (46.2)	0	6 (20.0)
Dermatitis acneiform	1 (7.7)	3 (17.6)	4 (13.3)

Table 14. Treatment-Emergent All Causality Other (Not Including Serious) Adverse Events Reported in ≥5% Subjects (Lead-In Set)

System Organ Class Preferred Term	Original Lead-In (N=13)	Amended Lead-In (N=17)	Total Lead-In (N=30)
	n (%)	n (%)	n (%)
Dry skin	1 (7.7)	1 (5.9)	2 (6.7)
Palmar erythema	1 (7.7)	0	1 (3.3)
Palmar-plantar erythrodysaesthesia syndrome	0	1 (5.9)	1 (3.3)
Plantar erythema	1 (7.7)	0	1 (3.3)
Pruritus	1 (7.7)	0	1 (3.3)
Rash	6 (46.2)	7 (41.2)	13 (43.3)
Rash generalised	1 (7.7)	0	1 (3.3)
Skin disorder	1 (7.7)	0	1 (3.3)
Skin exfoliation	1 (7.7)	0	1 (3.3)
Skin toxicity	0	3 (17.6)	3 (10.0)
Vascular disorders	2 (15.4)	4 (23.5)	6 (20.0)
Hypertension	1 (7.7)	4 (23.5)	5 (16.7)
Hypotension	1 (7.7)	0	1 (3.3)
Vena cava thrombosis	1 (7.7)	0	1 (3.3)

All AEs (not including SAEs) that occurred on or after the first dose of the study treatment were included in the table.
Except for the number of adverse events, subjects were counted only once per treatment in each row.
Included data as reported in the database on 27 February 2012.
% = (n/N)*100; AE = adverse event; N = number of subjects who received at least 1 dose of study treatment; n = number of subjects who had data for summary; SAE = serious adverse event.

Randomized Cohort: Treatment-emergent AEs (all causalities) reported by ≥5% of subjects in either treatment group in the randomized cohort are presented in Table 15.

Table 15. Treatment-Emergent All Causality Other (Not Including Serious) Adverse Events Reported in ≥5% Subjects in Either Treatment Group (Randomized Cohort)

System Organ Class Preferred Term	Sunitinib + Erlotinib N=64 n (%)	Erlotinib N=64 n (%)	Total N=128 n (%)
Any AE	60 (93.8)	61 (95.3)	121 (94.5)
Blood and lymphatic system disorders	15 (23.4)	5 (7.8)	20 (15.6)
Anaemia	7 (10.9)	4 (6.3)	11 (8.6)
Neutropenia	6 (9.4)	0	6 (4.7)
Thrombocytopenia	8 (12.5)	0	8 (6.3)
Eye disorders	9 (14.1)	11 (17.2)	20 (15.6)
Dry eye	4 (6.3)	3 (4.7)	7 (5.5)
Gastrointestinal disorders	46 (71.9)	38 (59.4)	84 (65.6)
Abdominal pain	7 (10.9)	4 (6.3)	11 (8.6)
Constipation	9 (14.1)	9 (14.1)	18 (14.1)
Diarrhoea	37 (57.8)	22 (34.4)	59 (46.1)
Dyspepsia	4 (6.3)	6 (9.4)	10 (7.8)
Nausea	22 (34.4)	15 (23.4)	37 (28.9)
Oral pain	6 (9.4)	0	6 (4.7)
Stomatitis	5 (7.8)	4 (6.3)	9 (7.0)
Vomiting	13 (20.3)	14 (21.9)	27 (21.1)
General disorders and administration site conditions	40 (62.5)	39 (60.9)	79 (61.7)
Chest pain	2 (3.1)	7 (10.9)	9 (7.0)
Fatigue	29 (45.3)	33 (51.6)	62 (48.4)
Mucosal inflammation	12 (18.8)	7 (10.9)	19 (14.8)
Oedema peripheral	3 (4.7)	4 (6.3)	7 (5.5)
Pyrexia	3 (4.7)	6 (9.4)	9 (7.0)
Infections and infestations	23 (35.9)	16 (25.0)	39 (30.5)
Nasopharyngitis	1 (1.6)	4 (6.3)	5 (3.9)
Urinary tract infection	6 (9.4)	0	6 (4.7)
Investigations	17 (26.6)	13 (20.3)	30 (23.4)
Weight decreased	10 (15.6)	6 (9.4)	16 (12.5)
Metabolism and nutrition disorders	29 (45.3)	27 (42.2)	56 (43.8)
Decreased appetite	24 (37.5)	20 (31.3)	44 (34.4)
Dehydration	4 (6.3)	0	4 (3.1)
Hypokalaemia	6 (9.4)	4 (6.3)	10 (7.8)
Musculoskeletal and connective tissue disorders	23 (35.9)	21 (32.8)	44 (34.4)
Back pain	5 (7.8)	9 (14.1)	14 (10.9)
Musculoskeletal chest pain	5 (7.8)	3 (4.7)	8 (6.3)
Pain in extremity	7 (10.9)	2 (3.1)	9 (7.0)
Nervous system disorders	22 (34.4)	21 (32.8)	43 (33.6)
Dysgeusia	12 (18.8)	6 (9.4)	18 (14.1)
Paraesthesia	3 (4.7)	4 (6.3)	7 (5.5)
Psychiatric disorders	6 (9.4)	12 (18.8)	18 (14.1)
Insomnia	0	5 (7.8)	5 (3.9)
Respiratory, thoracic and mediastinal disorders	28 (43.8)	28 (43.8)	56 (43.8)
Cough	13 (20.3)	9 (14.1)	22 (17.2)
Dyspnoea	9 (14.1)	17 (26.6)	26 (20.3)
Epistaxis	3 (4.7)	4 (6.3)	7 (5.5)
Haemoptysis	4 (6.3)	3 (4.7)	7 (5.5)
Lung infiltration	0	1 (1.6)	1 (0.8)
Pulmonary haemorrhage	5 (7.8)	4 (6.3)	9 (7.0)
Skin and subcutaneous tissue disorders	47 (73.4)	46 (71.9)	93 (72.7)
Acne	7 (10.9)	8 (12.5)	15 (11.7)
Alopecia	1 (1.6)	6 (9.4)	7 (5.5)
Dermatitis acneiform	6 (9.4)	12 (18.8)	18 (14.1)

Table 15. Treatment-Emergent All Causality Other (Not Including Serious) Adverse Events Reported in ≥5% Subjects in Either Treatment Group (Randomized Cohort)

System Organ Class Preferred Term	Sunitinib + Erlotinib N=64 n (%)	Erlotinib N=64 n (%)	Total N=128 n (%)
Dry skin	20 (31.3)	17 (26.6)	37 (28.9)
Exfoliative rash	3 (4.7)	7 (10.9)	10 (7.8)
Palmar-plantar erythrodysaesthesia syndrome	5 (7.8)	2 (3.1)	7 (5.5)
Pruritus	9 (14.1)	15 (23.4)	24 (18.8)
Rash	27 (42.2)	19 (29.7)	46 (35.9)
Skin exfoliation	7 (10.9)	4 (6.3)	11 (8.6)
Vascular disorders	10 (15.6)	6 (9.4)	16 (12.5)
Hypertension	5 (7.8)	1 (1.6)	6 (4.7)

All AEs (not including SAEs) that occurred on or after the first dose of the study treatment were included in the table.
Except for the number of adverse events, subjects werre counted only once per treatment in each row.
Included data as reported in the database on 27 February 2012.
% = (n/N)*100; AE = adverse event; N = number of subjects who received at least 1 dose of study treatment; n = number of subjects who had data for summary; SAE = serious adverse event.

Treatment-Related AEs:

Lead-In Cohort: Treatment-emergent treatment-related AEs reported by ≥5% of subjects in the original or amended lead-in cohorts are presented in Table 16.

Table 16. Summary of Erlotinib or Sunitinib Related Treatment-Emergent Adverse Events in ≥5% of Subjects (Lead-In Set)

System Organ Class Preferred Term	Original Lead-in (N=13) n (%)	Amended Lead-in (N=17) n (%)
Any AE	13 (100)	13 (76.5)
Blood and lymphatic system disorders	4 (30.8)	1 (5.9)
Anaemia	2 (15.4)	1 (5.9)
Leukopenia	1 (7.7)	0
Neutropenia	3 (23.1)	0
Thrombocytopenia	1 (7.7)	0
Eye disorders	1 (7.7)	0
Vision blurred	1 (7.7)	0
Gastrointestinal disorders	12 (92.3)	9 (52.9)
Abdominal pain	2 (15.4)	2 (11.8)
Abdominal pain upper	0	1 (5.9)
Diarrhoea	10 (76.9)	9 (52.9)
Duodenogastric reflux	1 (7.7)	0
Dyspepsia	1 (7.7)	0
Flatulence	1 (7.7)	0
Gastrooesophageal reflux disease	1 (7.7)	0
Nausea	5 (38.5)	1 (5.9)
Oral pain	2 (15.4)	0
Stomatitis	2 (15.4)	0
Vomiting	3 (23.1)	2 (11.8)
General disorders and administration site conditions	8 (61.5)	2 (11.8)
Asthenia	0	1 (5.9)
Fatigue	8 (61.5)	1 (5.9)
Mucosal inflammation	1 (7.7)	0
Oedema peripheral	2 (15.4)	0
Pyrexia	1 (7.7)	0
Hepatobiliary disorders	1 (7.7)	0
Hyperbilirubinaemia	1 (7.7)	0
Infections and infestations	3 (23.1)	0
Gastroenteritis	1 (7.7)	0
Infection	1 (7.7)	0
Paronychia	1 (7.7)	0
Urinary tract infection	2 (15.4)	0
Investigations	3 (23.1)	0
Alanine aminotransferase increased	1 (7.7)	0
Aspartate aminotransferase increased	1 (7.7)	0
Blood alkaline phosphatase increased	1 (7.7)	0
Haemoglobin decreased	1 (7.7)	0
Platelet count decreased	1 (7.7)	0
White blood cell count decreased	2 (15.4)	0
Metabolism and nutrition disorders	8 (61.5)	3 (17.6)
Decreased appetite	5 (38.5)	1 (5.9)
Dehydration	1 (7.7)	2 (11.8)
Hypokalaemia	2 (15.4)	0
Hypomagnesaemia	2 (15.4)	0
Hypophosphataemia	1 (7.7)	0
Musculoskeletal and connective tissue disorders	1 (7.7)	0
Muscle atrophy	1 (7.7)	0
Nervous system disorders	6 (46.2)	1 (5.9)
Ageusia	1 (7.7)	0
Dizziness	1 (7.7)	0
Dysgeusia	4 (30.8)	1 (5.9)
Psychiatric disorders	1 (7.7)	0
Hallucination	1 (7.7)	0
Respiratory, thoracic and mediastinal disorders	5 (38.5)	3 (17.6)

Table 16. Summary of Erlotinib or Sunitinib Related Treatment-Emergent Adverse Events in ≥5% of Subjects (Lead-In Set)

System Organ Class Preferred Term	Original Lead-in (N=13) n (%)	Amended Lead-in (N=17) n (%)
Cough	1 (7.7)	0
Dyspnoea	2 (15.4)	0
Dyspnoea exertional	1 (7.7)	0
Epistaxis	0	2 (11.8)
Haemoptysis	0	1 (5.9)
Oropharyngeal pain	1 (7.7)	0
Productive cough	1 (7.7)	0
Pulmonary embolism	1 (7.7)	0
Skin and subcutaneous tissue disorders	11 (84.6)	10 (58.8)
Acne	6 (46.2)	0
Dermatitis acneiform	1 (7.7)	3 (17.6)
Dry skin	1 (7.7)	1 (5.9)
Palmar erythema	1 (7.7)	0
Palmar-plantar erythrodysaesthesia syndrome	0	1 (5.9)
Plantar erythema	1 (7.7)	0
Pruritus	1 (7.7)	0
Rash	6 (46.2)	6 (35.3)
Rash generalized	1 (7.7)	0
Skin disorder	1 (7.7)	0
Skin exfoliation	1 (7.7)	0
Skin toxicity	0	3 (17.6)
Vascular disorders	1 (7.7)	2 (11.8)
Hypertension	1 (7.7)	2 (11.8)

Included data through visits occurring by 21 January 2010.
All AEs that occurred on or after the first dose of the study treatment were included in the table.
% = (n/N)*100; AE = adverse event; N = number of subjects who received at least one dose of study treatment; n = number of subjects who had data for summary.

Randomized Cohort: Treatment-emergent treatment-related AEs reported by ≥5% of subjects in either treatment group in the randomized cohort are presented in Table 17.

Table 17. Summary of Erlotinib or Sunitinib Related Treatment-Emergent Adverse Events in ≥5% of Subjects in Either Treatment Group (Randomized Cohort)

System Organ Class Preferred Term	Sunitinib + Erlotinib N=64 n (%)	Erlotinib N=64 n (%)
Any AE	55 (85.9)	54 (84.4)
Blood and lymphatic system disorders	12 (18.8)	1 (1.6)
Anaemia	5 (7.8)	1 (1.6)
Neutropenia	4 (6.3)	0
Thrombocytopenia	8 (12.5)	0
Eye disorders	7 (10.9)	7 (10.9)
Dry eye	4 (6.3)	1 (1.6)
Gastrointestinal disorders	43 (67.2)	31 (48.4)
Abdominal pain	4 (6.3)	2 (3.1)
Diarrhoea	35 (54.7)	21 (32.8)
Dyspepsia	3 (4.7)	5 (7.8)
Nausea	18 (28.1)	9 (14.1)
Oral pain	6 (9.4)	0
Stomatitis	5 (7.8)	3 (4.7)
Vomiting	10 (15.6)	7 (10.9)
General disorders and administration site conditions	28 (43.8)	22 (34.4)
Fatigue	20 (31.3)	16 (25.0)
Mucosal inflammation	11 (17.2)	6 (9.4)
Investigations	9 (14.1)	7 (10.9)
Weight decreased	4 (6.3)	4 (6.3)
Metabolism and nutrition disorders	22 (34.4)	10 (15.6)
Decreased appetite	19 (29.7)	8 (12.5)
Dehydration	4 (6.3)	2 (3.1)
Nervous system disorders	18 (28.1)	11 (17.2)
Dysgeusia	12 (18.8)	6 (9.4)
Skin and subcutaneous tissue disorders	46 (71.9)	44 (68.8)
Acne	7 (10.9)	8 (12.5)
Alopecia	0	6 (9.4)
Dermatitis acneiform	6 (9.4)	11 (17.2)
Dry skin	18 (28.1)	15 (23.4)
Exfoliative rash	3 (4.7)	7 (10.9)
Palmar-plantar erythrodysaesthesia syndrome	5 (7.8)	2 (3.1)
Pruritus	7 (10.9)	14 (21.9)
Rash	26 (40.6)	19 (29.7)
Skin exfoliation	6 (9.4)	4 (6.3)

Included data through visits occurring by 21 January 2010.
All AEs that occurred on or after the first dose of the study treatment were included in the table.
% = (n/N)*100, AE = adverse event; N = number of subjects who received at least 1 dose of study treatment, n = number of subjects who had data for summary.

Serious Adverse Events (SAEs):

Lead-In Cohort: SAEs for the lead-in cohort are summarized in Table 18. The only SAEs reported for more than 1 subject were disease progression (1 and 2 subjects in the original and amended cohorts, respectively), dyspnea (2 subjects in the original cohort), and respiratory failure (1 subject in each cohort).

Table 18. Summary of Serious Treatment-Emergent Adverse Events by MedDRA System Organ Class, Preferred Term (Lead-In Set)

System Organ Class Preferred Term	Original Lead-In Cohort (N=13) n (%)	Amended Lead-In Cohort (N=17) n (%)
Any SAE	5(38.5)	7 (41.2)
Blood and lymphatic system disorders	1 (7.7)	0
Anaemia	1 (7.7)	0
Thrombocytopenia	1 (7.7)	0
Cardiac disorders	1 (7.7)	1 (5.9)
Congestive cardiomyopathy	0	1 (5.9)
Tachycardia	1 (7.7)	0
Gastrointestinal disorders	1 (7.7)	2 (11.8)
Abdominal pain	0	1 (5.9)
Anal fistula	1 (7.7)	0
Diarrhoea	0	1 (5.9)
Oesophageal stenosis	0	1 (5.9)
General disorders and administration site conditions	1 (7.7)	2 (11.8)
Asthenia	0	1 (5.9)
Disease progression	1 (7.7)	2 (11.8)
Hepatobiliary disorders	0	1 (5.9)
Jaundice	0	1 (5.9)
Infections and infestations	2 (15.4)	1 (5.9)
Gastroenteritis	1 (7.7)	0
Pneumonia fungal	1 (7.7)	0
Pneumonia staphylococcal	0	1 (5.9)
Sepsis	1 (7.7)	0
Metabolism and nutrition disorders	0	1 (5.9)
Dehydration	0	1 (5.9)
Respiratory, thoracic and mediastinal disorders	4 (30.8)	2 (11.8)
Dyspnoea	2 (15.4)	0
Epistaxis	0	1 (5.9)
Pulmonary embolism	1 (7.7)	0
Respiratory failure	1 (7.7)	1 (5.9)

Included data through visits occurring by 21 January 2010.
All AEs that occurred on or after the first dose of the study treatment were included in the table.
% = (n/N)*100; AEs = adverse events; MedDRA = Medical Dictionary of Regulatory Activities; N = number of subjects who received at least 1 dose of study treatment; n = number of subjects who had data for summary; SAE = serious adverse event.

Treatment-related SAEs in the lead-in cohort are presented in Table 19.

Table 19. Summary of Erlotinib or Sunitinib Related Serious Treatment-Emergent Adverse Events by MedDRA System Organ Class, Preferred Term (Lead-In Set)

System Organ Class Preferred Term	Original Lead-In Cohort (N=13) n (%)	Amended Lead-In Cohort (N=17) n (%)
Any AE	3 (23.1)	4 (23.5)
Gastrointestinal disorders	0	2 (11.8)
Abdominal pain	0	1 (5.9)
Diarrhoea	0	1 (5.9)
General disorders and administration site conditions	0	1 (5.9)
Asthenia	0	1 (5.9)
Infections and infestations	1 (7.7)	0
Gastroenteritis	1 (7.7)	0
Metabolism and nutrition disorders	0	1 (5.9)
Dehydration	0	1 (5.9)
Respiratory, thoracic and mediastinal disorders	2 (15.4)	1 (5.9)
Dyspnoea	1 (7.7)	0
Epistaxis	0	1 (5.9)
Pulmonary embolism	1 (7.7)	0

Included data through visits occurring by 21 January 2010.
All AEs that occurred on or after the first dose of the study treatment were included in the table.
% = (n/N)*100; AEs = adverse events; N = number of subjects who received at least 1 dose of study treatment; n = number of subjects who had data for summary.

Randomized Cohort:

SAEs (all causalities) for the randomized cohort are summarized in Table 20. The most common SAE was disease progression which was reported for 8 subjects (12.5%) in each group. Diarrhea was a more common SAE for the sunitinib + erlotinib group (5/64 subjects, 7.8%) than for the erlotinib group (1/64 subjects, 1.6%).

Table 20. Summary of Serious Treatment-Emergent Adverse Events by MedDRA System Organ Class, Preferred Term (Randomized Cohort)

System Organ Class Preferred Term	Sunitinib + Erlotinib (N=64) n (%)	Erlotinib (N=64) n (%)
Any SAE	29 (45.3)	27 (42.2)
Blood and lymphatic system disorders	1 (1.6)	0
Thrombocytopenia	1 (1.6)	0
Cardiac disorders	0	2 (3.1)
Cardiopulmonary failure	0	2 (3.1)
Gastrointestinal disorders	10 (15.6)	7 (10.9)
Abdominal distension	0	1 (1.6)
Abdominal pain	1 (1.6)	1 (1.6)
Ascites	1 (1.6)	0
Constipation	0	2 (3.1)
Diarrhoea	5 (7.8)	1 (1.6)
Dysphagia	0	1 (1.6)
Femoral hernia, obstructive	0	1 (1.6)
Gastrointestinal haemorrhage	2 (3.1)	0
Ileus	1 (1.6)	0
Intestinal obstruction	1 (1.6)	0
Nausea	1 (1.6)	2 (3.1)
Oesophagitis	1 (1.6)	0
Pancreatitis acute	1 (1.6)	0
Vomiting	2 (3.1)	4 (6.3)
General disorders and administration site conditions	11 (17.2)	11 (17.2)
Asthenia	0	1 (1.6)
Disease progression	8 (12.5)	8 (12.5)
Fatigue	1 (1.6)	0
Mucosal inflammation	1 (1.6)	1 (1.6)
Non-cardiac chest pain	1 (1.6)	0
Pyrexia	1 (1.6)	0
Thrombosis in device	0	1 (1.6)
Ulcer haemorrhage	0	1 (1.6)
Hepatobiliary disorders	1 (1.6)	0
Cholecystitis	1 (1.6)	0
Infections and infestations	6 (9.4)	2 (3.1)
Bronchitis	1 (1.6)	0
Bronchitis bacterial	0	1 (1.6)
Bronchopneumonia	0	1 (1.6)
Gastroenteritis	1 (1.6)	0
Infection	1 (1.6)	0
Pneumonia	1 (1.6)	0
Urinary tract infection	2 (3.1)	0
Injury, poisoning and procedural complications	1 (1.6)	0
Ankle fracture	1 (1.6)	0
Metabolism and nutrition disorders	6 (9.4)	3 (4.7)
Decreased appetite	2 (3.1)	0
Dehydration	1 (1.6)	3 (4.7)
Failure to thrive	1 (1.6)	0
Hypercalcaemia	0	1 (1.6)
Hyponatraemia	2 (3.1)	0
Musculoskeletal and connective tissue disorders	1 (1.6)	4 (6.3)
Arthralgia	1 (1.6)	0
Back pain	0	2 (3.1)
Bone pain	0	1 (1.6)
Musculoskeletal pain	0	1 (1.6)
Nervous system disorders	2 (3.1)	1 (1.6)
Depressed level of consciousness	1 (1.6)	0
Diabetic hyperosmolar coma	0	1 (1.6)

Table 20. Summary of Serious Treatment-Emergent Adverse Events by MedDRA System Organ Class, Preferred Term (Randomized Cohort)

System Organ Class Preferred Term	Sunitinib + Erlotinib (N=64) n (%)	Erlotinib (N=64) n (%)
Haemorrhage intracranial	1 (1.6)	0
Hypoglycaemic coma	0	1 (1.6)
Nervous system disorder	1 (1.6)	0
Psychiatric disorders	1 (1.6)	1 (1.6)
Completed suicide	1 (1.6)	0
Mental status changes	0	1 (1.6)
Renal and urinary disorders	1 (1.6)	1 (1.6)
Haematuria	0	1 (1.6)
Renal failure	1 (1.6)	0
Respiratory, thoracic and mediastinal disorders	5 (7.8)	5 (7.8)
Chronic obstructive pulmonary disease	0	1 (1.6)
Dyspnoea	2 (3.1)	1 (1.6)
Haemoptysis	2 (3.1)	0
Pleural effusion	1 (1.6)	0
Pulmonary embolism	0	2 (3.1)
Pulmonary oedema	0	1 (1.6)
Vascular disorders	1 (1.6)	1 (1.6)
Ischaemia	1 (1.6)	0
Thrombophlebitis	0	1 (1.6)

Included data through visits occurring by 21 January 2010.
All AEs that occurred on or after the first dose of the study treatment were included in the table.
% = (n/N)*100; AEs = adverse events; N = number of subjects who received at least 1 dose of study treatment; n = number of subjects who had data for summary; SAE = serious adverse event.

Treatment-related SAEs are summarized in Table 21.

Table 21. Summary of Erlotinib or Sunitinib Related Serious Treatment-Emergent Adverse Events by MedDRA System Organ Class, Preferred Term (Randomized Cohort)

System Organ Class Preferred Term	Sunitinib + Erlotinib (N=64) n (%)	Erlotinib (N=64) n (%)
Any AE	12 (18.8)	6 (9.4)
Blood and lymphatic system disorders	1 (1.6)	0
Thrombocytopenia	1 (1.6)	0
Gastrointestinal disorders	9 (14.1)	2 (3.1)
Abdominal pain	1 (1.6)	0
Diarrhoea	5 (7.8)	1 (1.6)
Gastrointestinal haemorrhage	2 (3.1)	0
Oesophagitis	1 (1.6)	0
Pancreatitis acute	1 (1.6)	0
Vomiting	1 (1.6)	1 (1.6)
General disorders and administration site conditions	1 (1.6)	1 (1.6)
Mucosal inflammation	1 (1.6)	0
Ulcer haemorrhage	0	1 (1.6)
Metabolism and nutrition disorders	1 (1.6)	2 (3.1)
Decreased appetite	1 (1.6)	0
Dehydration	0	2 (3.1)
Nervous system disorders	1 (1.6)	0
Haemorrhage intracranial	1 (1.6)	0
Respiratory, thoracic and mediastinal disorders	0	1 (1.6)
Pulmonary embolism	0	1 (1.6)
Vascular disorders	1 (1.6)	0
Ischaemia	1 (1.6)	0

Included data through visits occurring by 21 January 2010.
All AEs that occurred on or after the first dose of the study treatment were included in the table.
% = (n/N)*100; AEs = adverse events; N = number of subjects who received at least 1 dose of study treatment; n = number of subjects who had data for summary.

Permanent Discontinuations due to AEs: AEs leading to discontinuation from study drug for lead-in cohort and randomized cohort are summarized in Table 22.

Table 22. Discontinuations due to Adverse Events

Serial Number	Preferred Term	Day	Grade	Serious Adverse Event	Causality
Lead-In-Cohort					
Original (N=13)					
1	Pulmonary embolism	142	4	Yes	Sunitinib
2	Fatigue	15	3	No	Sunitinib
3	Respiratory failure	54	5[a]	Yes	Other illness
4	Dyspnea	22	3	Yes	Sunitinib/erlotinib
Amended (N=17)					
5	Dehydration	4	2	No	Sunitinib/erlotinib
	Pneumonia staphylococcal	15	4	Yes	Other illness
	Abdominal pain	36	4	Yes	Sunitinib/erlotinib
6	Fatigue	281	2	No	Other illness
	Edema peripheral	281	2	No	Other illness
	Dyspnea	281	2	No	Other illness
	Congestive cardiomyopathy	284	5[a]	Yes	Other illness
7	Fatigue	55	2	No	Sunitinib/erlotinib
8	Diarrhea	98	3	Yes	Sunitinib/erlotinib
Randomized Cohort					
Sunitinib + Erlotinib (N=64)					
9	Nervous system disorder	24	4	Yes	Other
10	Bronchitis	286	3	Yes	Disease under study
11	Disease progression	25	5[a]	Yes	Disease under study
12	Non-cardiac chest pain	40	3	Yes	Disease under study
13	Fatigue	21	3	No	Sunitinib/placebo and erlotinib
14	Failure to thrive	14	3	Yes	Disease under study
15	Nausea	28	2	No	Sunitinib/placebo and erlotinib
	Weight decreased	28	1	No	Other illness
16	Intestinal obstruction	4	2	Yes	Disease under study
17	Fatigue	30	3	Yes	Disease under study
18	Pancreatitis acute	65	3	Yes	Sunitinib/placebo and erlotinib
19	Disease progression	196	5[a]	Yes	Disease under study
20	Thrombocytopenia	38	3	Yes	Sunitinib/placebo
21	Ischemia	226	4	Yes	Sunitinib/placebo
22	Diarrhea	44	2	No	Sunitinib/placebo and erlotinib
23	Esophagitis	89	3	Yes	Sunitinib/placebo and erlotinib
24	Pulmonary hemorrhage	9	2	No	Sunitinib/placebo
25	Disease progression	55	5[a]	Yes	Disease under study
26	Dyspnea	2	3	No	Disease under study
	Hypertension	2	3	No	Other
Erlotinib (N =64)					
27	Alveolar proteinosis	118	1	No	Sunitinib/placebo and erlotinib
28	Vomiting[b]	41	1	No	Erlotinib
29	Disease progression	15	5[a]	Yes	Disease under study
30	Bronchopneumonia	110	3	Yes	Disease under study
31	Disease progression	78	5[a]	Yes	Disease under study
32	Pulmonary edema	3	5[a]	Yes	Disease under study
33	Disease progression	30	5[a]	Yes	Disease under study
34	Disease progression	84	5[a]	Yes	Disease under study
35	Spinal cord edema	53	3	No	Disease under study
36	Back pain	52	4	Yes	Disease under study

Table 22. Discontinuations due to Adverse Events

Serial Number	Preferred Term	Day	Grade	Serious Adverse Event	Causality
37	Disease progression	31	5[a]	Yes	Disease under study
38	Asthenia	174	3	No	Other
39	Pulmonary embolism	11	4	Yes	Disease under study
40	Bone pain	36	3	Yes	Disease under study
41	Deep vein thrombosis	25	3	No	Sunitinib/placebo
42	Disease progression	8	5[a]	Yes	Disease under study
43	Cardiopulmonary failure	126	5[a]	Yes	Disease under study

N = number of subjects.
a. Fatal.
b. Adverse event did not lead to discontinuation of placebo.

Deaths: Most subjects in the original lead-in cohort died (12/13 subjects, 92.3%), mainly due to the disease under study during follow-up (8/13 subjects, 61.5%) (Table 23). Approximately half of the subjects in the amended lead-in cohort died (9/17 subjects, 52.9%), also most commonly due to the disease under study during follow-up (4/17 subjects, 23.5%). Approximately 70% of subjects in the randomized cohort died (44/64 subjects [68.8%] and 46/64 subjects [71.9%] in the sunitinib + erlotinib and erlotinib groups, respectively), mainly due to the disease under study during the follow-up (32/64 subjects [50.0%] and 33/64 subjects [51.6%], respectively). No subjects died due to a study treatment toxicity (Table 24 and Table 25).

Table 23. Summary of Deaths-Per-Protocol Set

Number (%) of Subjects	Lead-In Cohort		Randomized Cohort	
	Original Cohort (N=13)	Amended Cohort (N=17)	Sunitinib + Erlotinib (N=64)	Erlotinib (N=64)
Deaths	12 (92.3)	9 (52.9)	44 (68.8)	46 (71.9)
Subjects who died while on study[a]	2 (15.4)	4 (23.5)	9 (14.1)	11 (17.2)
Disease under study	2 (15.4)	2 (11.8)	8 (12.5)	8 (12.5)
Study treatment toxicity	0	0	0	0
Other	1 (7.7)[b]	2 (11.8)	1 (1.6)[c]	3 (4.7)[d]
Subjects who died during follow-up[e]	10 (76.9)	5 (29.4)	35 (54.7)	35 (54.7)
Disease under study	8 (61.5)	4 (23.5)	32 (50.0)	33 (51.6)
Study treatment toxicity	0	0	0	0
Unknown	2 (15.4)	1 (5.9)	2 (3.1)	1 (1.6)
Other	0	0	1 (1.6)[f]	1 (1.6)[g]

N = number of subjects.
a. On-study deaths were those that occurred after the first dose of study medication and within 28 days of the last dose of study medication.
b. One subject had reason of death given as disease under study in the death page of the case report form and as respiratory failure in the adverse event page of the case report form.
c. Suicide
d. Pulmonary edema, cardiopulmonary failure (2 subjects).
e. Follow-up deaths were those that occurred more than 28 days after the last dose of study drug.
f. Intracranial hemorrhage
g. Cardiorespiratory failure

Table 24. Summary of Deaths - Subjects With On-Study Grade 5 Adverse Events (Lead-In Cohort)

Serial Number	Cause of Death	Day	Causality
Original (N=13)			
1	Disease progression	159	Disease under study
2	Respiratory failure	54	Unrelated
Amended (N=17)			
3	Fatal disease progression	202	Disease under study
4	Respiratory insufficiency	55	Unrelated
5	Dilatative cardiomyopathy	284	Unrelated
6	Fatal disease progression	72	Disease under study

Included data through visits occurring by 21 January 2010.
N = number of subjects.

Table 25. Summary of Deaths - Subjects With On-Study Grade 5 Adverse Events (Randomized Cohort)

Serial Number	Cause of Death	Days Since First Dose of Study Drug	Causality
Sunitinib + Erlotinib (N=64)			
1	Disease under study	25	Disease under study
2	Suicide	18	Unrelated
3	Disease progression	40	Disease under study
4	Disease progression	65	Disease under study
5	Disease progression	196	Disease under study
6	Disease progression	42	Disease under study
7	Disease progression	55	Disease under study
8	Disease progression	14	Disease under study
9	Disease progression	64	Disease under study
Erlotinib (N=64)			
10	Disease progression	33	Disease under study
11	Disease progression	52	Disease under study
12	Disease progression	116	Disease under study
13	Pulmonary edema	3	Disease under study
14	Disease progression	73	Disease under study
15	Disease progression	98	Disease under study
16	Disease progression	67	Disease under study
17	Disease progression	33	Disease under study
18	Disease progression	38	Disease under study
19	Cardiopulmonary failure	35	Disease under study
20	Cardiopulmonary failure	144	Disease under study

Included data through visits occurring by 21 January 2010.
N = number of subjects.

Overall, there were no clinically important trends in the vital signs and ECG data. One subject in the erlotinib group was reported as having a clinically significant LVEF finding: on Day 7; LVEF was 40%, equivalent to the lower limit of the normal range.

Grade 3 hematology abnormalities were most commonly reported with lymphocytes, in 9/55 subjects (16.4%) and 11/54 subjects (20.4%) in the sunitinib + erlotinib and erlotinib groups, respectively. The only other Grade 3 abnormality reported by >5% of subjects in either group was for platelets, reported for 4/64 subjects (6.3%) and 1/63 subjects (1.6%) in the sunitinib + erlotinib and erlotinib groups, respectively. Two subjects in the erlotinib

group had Grade 4 hematology abnormalities (low lymphocytes and hemoglobin). The most common Grade 3 biochemistry abnormalities were hyponatremia, reported for 7/64 subjects (10.9%) and 3/63 subjects (4.8%) in the sunitinib + erlotinib and erlotinib groups, respectively, and hypophosphatemia, reported for 6/59 subjects (10.2%) and 1/61 subjects (1.6%), respectively. No other biochemistry abnormalities were reported for >10% of subjects in either group. Four subjects in the erlotinib group had a Grade 4 biochemistry abnormality (hypercalcemia [2 subjects], elevated liver function enzymes, and hypokalemia).

Overall, there were no clinically important trends in the vital signs and ECG data.
One subject in the erlotinib group was reported as having a clinically significant LVEF finding: on Day -7; LVEF (measured by echocardiogram) was 40%, equivalent to the lower limit of the normal range.

CONCLUSIONS:

In the lead-in cohorts:

- The safety of dosing sunitinib at 37.5 mg per day concurrently with erlotinib at 150 mg per day was confirmed in subjects with NSCLC after failure of platinum-based chemotherapy

- DLTs were assessed in 11 evaluable subjects in the original lead-in cohort; 3 subjects developed DLTs, most commonly fatigue (2 subjects)

- Sunitinib had no effect on the PK of erlotinib

- Erlotinib appeared to cause induction of cytochrome P450 3A4 which led to a decrease in the plasma exposure to sunitinib and an increase in plasma exposure to the active metabolite SU-012662. The overall effect of erlotinib on the plasma exposure to total drug (sunitinib + SU-012662) was not considered to be clinically relevant

In the randomized cohort:

- There was no statistically significant improvement in PFS with the addition of sunitinib to erlotinib therapy, although the hazard ratio favored the sunitinib + erlotinib group

- The sample size for the study was calculated to require 115 events of death or objective progression; however, only 78 such events occurred. Consequently, interpretation of the primary endpoint is difficult, and the results should be treated with caution

- There was no significant treatment difference between the groups in terms of OS, although this may have been confounded by crossover and by an imbalance in post-study anticancer treatments

- The combination of sunitinib and erlotinib was well tolerated. No subjects died due to an on-study treatment toxicity (ie, within 28 days of the final dose), although 1 subject in the sunitinib + erlotinib group died due to treatment-related intracranial hemorrhage during

the follow-up period. Treatment-related SAEs were reported for <25% of subjects, most commonly diarrhea. The most common AEs were diarrhea and rash

- Global health status/ quality of life (QoL) and functioning scales did not have statistically significant and clinically meaningful changes in the sunitinib + erlotinib group, indicating that subject QoL was maintained during the combination therapy. Similar results were found for subjects treated with erlotinib therapy only

- In the sunitinib + erlotinib group, plasma levels of sVEGFR-2, sVEGFR-3 and sKIT decreased significantly from baseline at the end of Cycles 2 and 3, whereas plasma levels of these soluble receptor fragments did not change during treatment with erlotinib. Plasma levels of VEGF-C did not change significantly in either treatment arm

- There was no evidence that EGFR status had an influence on efficacy of sunitinib

- Comparisons of PFS between the 2 treatment arms in subgroups defined by *EGFR* and *KRAS* mutation status did not result in any statistically significant differences, although the sample size was small

- A statistically significant difference was observed between the 2 treatment arms in PFS, favoring the sunitinib + erlotinib arm, for subjects with low tumor PDGFRα RNA levels. However, it is not clear how changes in these RNA levels might be associated with changes in the activity of this receptor