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

PROTOCOL NO.: A6181087

PROTOCOL TITLE: A Multicenter, Randomized, Double-Blind, Controlled Phase 3, Efficacy and Safety Study of Sunitinib (SU011248) in Patients With Advanced/Metastatic Non-Small Cell Lung Cancer Treated With Erlotinib

Study Centers: A total of 203 centers took part in the study of which 164 centers randomized subjects; 28 in the United States (US), 13 in Germany, 11 each in Italy and the United Kingdom (UK), 10 in Spain, 9 in Czech Republic, 8 each in Canada and the Netherlands, 7 in Hungary, 6 in Poland, 5 in Norway, 4 each in Argentina, Greece, Belgium, Brazil, Denmark, Russian Federation, and Slovakia, 3 each in Austria, Chile, Hong Kong, Republic of Korea, Taiwan, and Thailand, and 1each in Colombia and Switzerland.

Study Initiation, Primary Completion, and Final Completion Dates:

Study Initiation Date: 31 July 2007

Primary Completion Date: 21 May 2010

Final Completion Dates: 20 December 2012

Phase of Development: Phase 3

Study Objectives:

Primary Objective: To demonstrate that the combination of sunitinib plus erlotinib is superior to erlotinib plus placebo in prolonging the overall survival (OS) for advanced/metastatic non-small cell lung cancer (NSCLC) subjects who had received 1 to 2 prior chemotherapy regimens.

Secondary Objectives:

- To compare measures of antitumor response (progression free survival [PFS], objective response rate [ORR]) between both treatment arms and estimate duration of tumor control (duration of response [DR]);

- To compare the safety and tolerability of erlotinib plus sunitinib versus erlotinib plus placebo in this subject population;

- To assess patient-reported outcomes (PRO).

METHODS:

Study Design: This study was a multinational, multicenter, randomized, double-blind, controlled, Phase 3 efficacy and safety study of sunitinib in subjects with advanced/metastatic NSCLC.

Subjects were randomized 1:1 in a double-blind fashion to treatment with erlotinib plus sunitinib or erlotinib plus placebo. Randomization was stratified by smoking history (ever versus never smoked), prior treatment with bevacizumab (yes versus no) and epidermal growth factor receptor (EGFR) status (positive versus negative versus unknown). The EGFR status for subjects classified as "unknown" at randomization could later have been determined to be "positive" or "negative" if subsequent testing was performed.

Treatment on-study was administered in 4-week cycles. In both treatment arms, erlotinib was administered orally (PO) at a dose of 150 mg once daily (QD) and was dose reduced (to 100 or 50 mg) based on tolerability. Blinded study medication (sunitinib or placebo) was administered PO in a continuous daily dosing (CDD) regimen with a starting dose of 37.5 mg QD. Subjects were monitored for toxicity, and the erlotinib and blinded study medication doses could be adjusted according to individual subject tolerance.

Subjects were to receive treatment as assigned at randomization until Response Evaluation Criteria in Solid Tumors (RECIST, Version 1.0, 2000)-defined disease progression (as determined by the Investigator; no central radiologic imaging review was performed for this study) or withdrawal from the study for another reason. Disease progression and OS were to be assessed in all subjects who were to be followed until death (or until 28 days after the last dose of study medication for the last subject on study). There was no crossover between the 2 treatment groups on this study.

This study was designed to have 2 interim analyses and the final analysis. An independent Data Monitoring Committee (DMC) was used to monitor the safety of the subjects and to evaluate efficacy data at the time of pre-specified interim analyses. Following the meeting for the second interim analysis, the DMC recommended that a third interim analysis of efficacy be conducted after 500 OS events were recorded. The Sponsor accepted this recommendation.

The results from the final analysis demonstrated a statistically significant improvement in the secondary endpoint of PFS. Based on these study results, it was considered important to permit subjects to continue on the study if in the Investigator's opinion the subject was deriving clinical benefit, and to continue the collection of survival follow-up data. A protocol amendment was issued based on the results of the final analysis to continue the collection of survival and post treatment follow-up data in addition to reducing the scope of data collected.

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

Table 1. Schedule of Activities

Protocol Activities		Study Treatment[a]			Post Treatment	
	Screening	Cycles 1-3		Cycle 4+	End of Treatment/ Withdrawal[b]	Post Treatment/ Follow-up[c]
	≤28 Days Prior to Dosing	Day 1[d] ±3 (C2 & 3 only)	Day 15±2	Day 1[e] ±3		
Informed consent[f]	X					
Medical/oncologic history[g]	X					
Physical examination[h]	X	X		X	X	
Baseline signs & symptoms		X				
Hematology	X	X	X	X	X	
Blood chemistry	X	X		X	X	
TSH[i]	X	(X)	(X)	(X)	(X)	
Coagulation[j]	X	(X)	(X)	(X)	(X)	
Urinalysis (dipstick – protein only)[k]	X	X C2 (X) C1D1 & C3D1	(X)	(X)	X	
Pregnancy test (as appropriate)[l]	X	(X)	(X)	(X)	(X)	
12-lead ECG[m]	X	X C2 (X) C1D1 & C3D1	(X)	(X)	X	
MUGA scan or echocardiogram[n]	X	(X)	(X)	(X)	(X)	
Study randomization[o]	X					
Erlotinib (background medication)[p]		X→	→	→		
Blinded study medication[q]		X→	→	→		
CT or MRI scans of chest and abdomen and other applicable sites of disease[r]	X	X – At Week 8 and every 8 weeks thereafter ±7 days from the start of treatment			(X)	
Brain CT or MRI scan[s]	X	(X) - Repeated only if clinically indicated			(X)	
Bone scan[t]	X	(X) - Every 8 weeks ±7 days from the start of treatment			(X)	
EQ-5D[u]		X		X	X	
Adverse events[v]	X	X	X	X	X	X
Blinded study medication compliance[w]		X		X	X	
Concomitant medications/treatments[x]	X	X	X	X	X	X
Post erlotinib/blinded study medication anticancer therapy[y]					(X)	X
Survival follow-up[y]						X

(X) indicates if applicable.

AE = adverse event; C = cycle; CDD = continuous daily dosing; CT = computed tomography; D = day; ECG = electrocardiogram; EQ-5D = EuroQOL 5-Dimension questionnaire; MRI = magnetic resonance imaging; MUGA = multiple-gated acquisition scan; QD = once daily; TSH = thyroid stimulating hormone.

a. All assessments were performed prior to dosing with erlotinib or blinded study medication unless otherwise indicated. Acceptable time windows for performing each assessment are indicated in the column headings. Each treatment cycle was 28 days (4 weeks) in duration. A maximum of a 4-week delay was allowed for erlotinib

Table 1. Schedule of Activities

and blinded study medication due to persistent toxicity. Longer delays prompted discussion with the Sponsor. Subjects who dose escalated blinded study medication to 50 mg daily (QD) underwent hematology and adverse event (AE) assessments at Day 15 for the first cycle to establish toleration of the higher blinded study medication dose level.

b. These assessments were obtained if not completed during the last week on-study with the following exception: during the last 8 weeks on study for radiological tumor assessments.

c. Subjects were evaluated for AEs and concomitant medications up to 28 days after last dose of study treatment and were followed for subsequent cancer treatment(s) and survival until death.

d. Day 1, Cycle 1: hematology, blood chemistry, and physical examination were not required if acceptable screening assessment was performed within 7 days prior to the start of study treatment without suggestion of clinical deterioration.

e. Day 1, Cycles 2+: visit window was ±3 days.

f. Informed consent was to be obtained prior to undergoing any study specific procedure and could have occurred prior to the 28-day screening period.

g. Included information on prior anticancer regimens including best response observed. Disease progression on previous systemic anticancer treatment was documented. Smoking history and epidermal growth factor receptor (EGFR) status was also documented.

h. Examination of major body systems, Eastern Cooperative Oncology Group (ECOG) performance status, body weight, height (at screening visit only), and vital signs (temperature, blood pressure [BP], heart rate [HR], respiratory rate [RR]).

i. Performed at Screening and then as clinically indicated thereafter.

j. Performed at Screening and then as clinically indicated thereafter.

k. Dipstick protein performed at Screening, Cycle 2 Day 1, end of treatment, and as clinically indicated. If the results of the dipstick test indicated a ≥2+ proteinuria, follow-up was performed with a quantitative urine protein analysis according to local standard practices with data captured on the AE electronic Case Report Form (eCRF) if AE criteria were met.

l. Additional testing could be repeated as appropriate, as per the request from Institutional Review Boards (IRBs)/Independent Ethics Committee (IECs), or if required by local regulations.

m. Three consecutive 12-lead ECGs were performed approximately 2 minutes apart to determine the mean corrected QT interval (QTc). The ECGs were to be performed in the morning (preferred) and time matched (±1 hour). If the mean QTc interval was prolonged (>500 msec), then the ECGs were to be re-read by a cardiologist at the site for confirmation. Additional ECGs were performed as clinically indicated to include approximately 2 weeks following intrasubject blinded study medication dose adjustments.

n. MUGA scan or echocardiogram was performed at Screening and as clinically indicated thereafter.

o. 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.

p. Erlotinib was administered orally once daily (QD) at least 1 hour before or 2 hours after food in a continuous daily dosing (CDD) regimen expressed in 4-week cycles. The starting dose was 150 mg QD.

q. Blinded study medication was administered orally from Day 1 in a CDD regimen. The starting dose for blinded study medication was 37.5 mg QD.

r. Computerized tomography (CT) or magnetic resonance imaging (MRI) scans of the chest and abdomen, and other applicable sites of disease were performed at Screening and at fixed 8-week intervals during the study. Disease assessment was performed at 8 weeks and every 8 weeks thereafter after the start of treatment, whenever disease progression was suspected and to confirm a partial response (PR) or complete response (CR) (at least 4 weeks after initial documentation of response; these confirmatory scans did not alter the fixed, 8 week timing). The schedule of assessments was fixed according to the calendar, regardless of treatment delays. Allowable window for disease assessments was ±7 days.

s. Brain scans were required at Screening to confirm eligibility. A repeat brain scan was required on-study if new brain metastases were suspected.

t. Bone scan was required at Screening. Repeat bone scans were required only if bone metastases were present at Baseline and if new bone metastases were suspected. A bone scan was required at the time of confirmation of response for subjects who had bone metastases.

Table 1. Schedule of Activities

u. Subjects completed the EQ-5D at the clinic prior to being informed about disease status and prior to dosing with any study medications and the conduct of other clinical activities.

v. Subjects were followed for AEs from the first day of study treatment until at least 28 days after the last dose of study treatment, or until all serious or study medication-related toxicities resolved or were determined to be "chronic" or "stable", whichever was later. Serious AEs (SAEs) were monitored and reported from the time that the subject provided informed consent.

w. Blinded study medication bottle(s) including any unused capsules were returned to the clinic for drug accountability at clinic visits starting with Cycle 2. Erlotinib drug accountability was performed as per local institution rules.

x. Concomitant medications and treatments were recorded from 28 days prior to the start of study treatment and at least 28 days following the last dose of study treatment to coincide with the safety evaluation period.

y. After discontinuation of study treatment, post-study anticancer treatment was to be recorded until death, and survival status was to be determined by telephone contact every 2 months until death.

Number of Subjects (Planned and Analyzed): A total sample size of 956 subjects (478 subjects in each treatment arm) was planned; 960 subjects were randomized and analyzed, with 480 subjects assigned to each group.

Of these 960 subjects; 113 subjects were randomized in Poland, 103 in Germany, 94 in Hungary, 59 in the Russian Federation, 57 in the UK, 54 in the US, 52 in Spain, 50 in Italy, 47 in Canada, 43 in Brazil, 42 in Czech Republic, 39 in the Netherlands, 25 in Republic of Korea, 24 in Thailand, 23 in Hong Kong, 22 in Slovakia, 21 in Denmark, 20 in Taiwan, 18 in Belgium, 13 in Argentina, 12 in Norway, 11 in Chile, 9 in Greece, 7 in Austria, and 1 each in Colombia and Switzerland.

Diagnosis and Main Criteria for Inclusion: Both male and female subjects aged 18 years and older, who were diagnosed with locally advanced/metastatic NSCLC and received prior treatment with no more than 2 chemotherapy regimens including a platinum-based regimen, were included in the study. Subjects with history of or known brain metastases and subjects who received prior treatment with any receptor tyrosine kinase inhibitors, vascular endothelial growth factor inhibitor (with the exception of bevacizumab) or other angiogenesis inhibitors were excluded from the study.

Study Treatment: Commercially available erlotinib (Tarceva) was used. Blinded study medication consisting of sunitinib or matching placebo was supplied by the Sponsor.

Erlotinib QD was to be taken orally concurrently with blinded study medication (sunitinib or placebo) QD in a CDD regimen expressed in 4-week cycles. Erlotinib was to be administered at least 1 hour before or 2 hours after food. Blinded study medication was to be taken orally in the morning without regard to food. Erlotinib treatment started at 150 mg and blinded study medication at 37.5 mg. Subjects experiencing treatment-related toxicity were permitted dose interruptions (eg, insertion of off-treatment periods as needed) and/or dose reductions. Blinded study medication dose could be reduced to 25 mg depending on individual tolerability. Based on tolerability, dose escalation to 50 mg blinded study medication was also permitted.

Efficacy, Safety, and PRO Endpoints:

Primary Endpoint: The primary efficacy endpoint of the study was OS.

Secondary Endpoint:

- PFS;
- ORR;
- 1-year survival probability;
- DR;
- PRO as measured by the EuroQol 5-Dimension (EQ-5D) questionnaire;

- Type, incidence, severity, timing, seriousness, and relationship to study therapy of adverse events (AEs); laboratory abnormalities.

OS was defined as the time from the date of randomization to the date of death due to any cause. For subjects still alive at the time of the analysis, the OS time was censored on the last date that subjects were known to be alive. Every effort was made to follow each subject until death. However, for subjects that were lost to follow-up, the OS was censored on the last date that subjects were known to be alive (including details obtained by sites from public records for these subjects, if allowed by local regulations). Subjects lacking data beyond randomization had their OS censored at the date of randomization.

PFS was defined as the time from the date of randomization to the date of the first documentation of objective tumor progression, or to death on-study (where "on-study" included the period from randomization until 28 days after the last dose of study medication) due to any cause, whichever occurred first.

ORR was defined as the percent of subjects with confirmed CR or confirmed PR according to RECIST 1.0, according to Investigator's assessment, relative to all randomized subjects. Confirmed responses were those that persisted on repeat imaging study ≥4 weeks (28 days) after initial documentation of response.

DR was defined as the time from the first documentation of objective tumor response (CR or PR) that was subsequently confirmed to the first documentation of objective tumor progression or death on-study due to any cause, whichever occurred first. DR was only calculated for the subgroup of subjects with confirmed objective tumor response.

The 1-year survival probability was defined as the probability of survival at 1 year after the date of randomization based on the Kaplan-Meier estimate.

The EQ-5D is a self-administered, international, standardized, generic questionnaire that describes health status in 5 dimensions. It generates 2 types of data for each subject: a profile indicating the extent of problems across the 5 dimensions (the EQ-5D descriptive system) and a weighted health state index by applying scores from a standard set of preference weights derived from general population samples (the EQ-5D Index). The EQ-5D descriptive system is made up of 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The EQ-5D was scored according to the EQ-5D User Guide.

PRO assessments were to be performed on Day 1 of each treatment cycle (prior to any clinical assessments) and at end of treatment/withdrawal. Every effort was to be made to have the subject complete the self-assessment questionnaires in the clinic while awaiting Investigator follow-up and before any clinical assessments. The questionnaire was anticipated to take about 5 to 10 minutes to complete.

Analyses of endpoints dependent on disease assessments (PFS, ORR, and DR), were based on the application of RECIST 1.0 to tumor lesion data reported by the Investigator.

Safety Evaluations:

Nonserious AEs were to be recorded on the electronic case report form (eCRF) from the time the subject had taken at least 1 dose of study medication through last subject visit.

The Investigator obtained and recorded on the eCRF all observed or volunteered AEs, the severity Common Terminology Criteria for Adverse Events (CTCAE) of the events, and the Investigator's opinion of the relationship to the study treatment. AEs included adverse drug reactions, illnesses with onset during the study, and exacerbation of previous illnesses. Additionally, the Investigator recorded as AEs any clinically significant changes in physical examination findings and abnormal objective test findings (eg, electrocardiogram [ECG], X-ray, laboratory tests).

For all AEs, the Investigator pursued and obtained information adequate to determine both the outcome of the AE and whether it met the criteria for classification as a serious AE (SAE). If the AE or its sequelae persisted, follow-up was required until resolution or stabilization occurred at a level acceptable to the Investigator and Sponsor. For AEs with a causal relationship to the study medication, follow-up by the Investigator was required until the event or its sequelae resolved or stabilized at a level acceptable to the Investigator, and the Sponsor concurred with that assessment.

Statistical Methods: The statistical analyses sets and methods used for this study are as follows:

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

Per Protocol (PP) Set/Safety Analysis Set: The PP set included all randomized 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 PP set was the primary set for safety and treatment evaluations.

PRO Analysis Set: Subjects from the FAS population who had at least 1 EQ-5D Questionnaire assessment while on treatment formed the PRO analysis set.

Statistical Methods: Estimates of the OS curves were obtained from the Kaplan-Meier method. The median (and other quartiles) event time and corresponding two-sided 95% confidence interval (CI) for the median were provided for each treatment arm. Differences in OS between treatment arms were analyzed by the log-rank test stratified for smoking status, prior bevacizumab therapy, and EGFR status. PFS was analyzed in a similar fashion. The Cox regression model, stratified for Baseline stratification factors, was fitted. The estimated hazard ratio and 2-sided 95% CI were provided. An unstratified log-rank test (1-sided, α=0.025) and Cox regression model was used for secondary analyses of OS and PFS. The potential influences of the stratification factors and other Baseline subject characteristics were evaluated.

ORR was summarized for each treatment arm along with the corresponding exact 2-sided 95% CI using a method based on the F distribution. The Cochran-Mantel-Haenszel test stratified by Baseline stratification factors was used to compare ORR between the 2 treatment arms. The relative risk ratio estimator was used to contrast the treatment effects on response rates. A point estimate and a 2-sided 95% CI were calculated using the normal approximation. Additionally, the Pearson χ^2 test was used to compare ORR between the treatment arms.

DR was summarized for the subgroup of subjects with objective disease response using the Kaplan-Meier method. The median event time (if appropriate) and 2-sided 95% CI for the median for each treatment arm were provided.

The 1-year survival probability was estimated using the Kaplan-Meier method and a two-sided 95% CI for the log (-log [1-year survival probability]) was calculated using a normal approximation and then back transformed to give a CI for the 1-year survival probability itself.

PROs were evaluated in subjects from the FAS population who had at least 1 EQ-5D assessment while on treatment. For each treatment arm and at each time point, the number and percentage of subjects who completed the EQ-5D were summarized. Additionally, the number and percentage of subjects in each arm who completed each individual question of the EQ-5D at each time point were tabulated. For each treatment arm, the mean (standard error [SE]), median (range) of the absolute index score of the EQ-5D and the number of available subjects at each time point was estimated.

The number and percentage of subjects who experienced any AE, who experienced any SAE, who experienced any treatment-related AE, or who experienced any treatment-related SAE, were presented. Subjects who discontinued because of an AE were presented. All AEs (including treatment-related AEs) were summarized by Medical Dictionary for Regulatory Activities (MedDRA, version 13) system organ class (SOC) and preferred term. Treatment-related AEs for each treatment arm were summarized by relatedness to blinded study medication or erlotinib. The most commonly reported AEs (10% or more of subjects) were summarized by SOC, preferred term, and maximum CTCAE (version 3.0) grade. Treatment-emergent SAEs and treatment-related SAEs were summarized by MedDRA SOC and preferred term. Deaths were summarized by time period (on-treatment versus during follow-up) and cause of death.

Clinical laboratory test results were presented descriptively. Vital signs and ECG data were summarized. Left ventricular ejection fraction (LVEF) data were listed.

RESULTS:

Subject Disposition and Demography: A summary of subject disposition is presented in Table 2. A total of 960 subjects were randomized, with 480 subjects assigned to each group. A total of 32 subjects were ongoing at the time of the final analysis (15 and 17 subjects in the sunitinib + erlotinib and erlotinib groups, respectively). Additional data was collected on

those subjects who continued to receive treatment after the cutoff date for the full CSR. All subjects subsequently discontinued from the study.

Overall, median duration of follow-up was 46.2 months (95% CI: 43.3, 47.2 months); 45.6 months (95% CI: 41.7, 48.5 months) for the sunitinib + erlotinib group and 46.2 months (95% CI: 41.9, 47.2 months) for the erlotinib group.

Table 2. Subject Disposition

	Sunitinib + Erlotinib N=480 n (%)	Erlotinib N=480 n (%)	Total N=960 n (%)
Subjects randomized	480	480	960
Full analysis set[a]	480	480	960
Per-protocol set[b]	473[c]	477[d]	950[c,d]
Subject status, number (%) of subjects[e]			
Subjects who discontinued from study	480 (100)	480 (100)	960 (100)
Number (%) of subjects withdrawn from sunitinib/placebo	479 (99.8)[f]	480 (100.0)	959 (99.9)
Number (%) of subjects withdrawn from erlotinib	479 (99.8)[f]	480 (100.0)	959 (99.9)
Primary reason for withdrawal from study			
Objective progression or relapse	229 (47.7)	296 (61.7)	525 (54.7)
Subject died	106 (22.1)	106 (22.1)	212 (22.1)
Adverse event	84 (17.5)	41 (8.5)	125 (13.0)
Global deterioration of health status	22 (4.6)	8 (1.7)	30 (3.1)
Subject refused continued treatment for reason other than adverse event	14 (2.9)	8 (1.7)	22 (2.3)
Lost to follow-up	6 (1.3)	7 (1.5)	13 (1.4)
Protocol violation	4 (0.8)	3 (0.6)	7 (0.7)
Study terminated by Sponsor	1 (0.2)	4 (0.8)	5 (0.5)
Other	14 (2.9)	7 (1.5)	21 (2.2)
Duration of follow-up, months[g]			
Median	45.6	46.2	46.2
95% confidence interval	(41.7, 48.5)	(41.9, 47.2)	(43.3, 47.2)

Includes data through last subject last visit.
A cycle had 4 weeks. Cycle 0 included randomized subjects without dose.
N = number of randomized subjects; n = number of subjects with data.

a. Full analysis set 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 from that to which they were randomized.
b. Per-protocol set included all subjects who received at least 1 dose of study medication (erlotinib or sunitinib/placebo), with treatment assignments designated according to actual study treatment received.
c. Exclusion from per-protocol set: 7 subjects; these subjects were withdrawn during pre-treatment and not dosed.
d. Exclusion from per-protocol set: 3 subjects; these subjects were withdrawn during pre-treatment and not dosed
e. Denominator for percentages was the full analysis set.
f. One subject was randomized but never dosed and withdrew from study due to protocol violation. The End of Treatment information was not completed for this subject.
g. Duration of follow-up was calculated on full analysis set based on the Kaplan-Meier (KM) potential follow-up method (reversed KM estimate) of overall survival time, where death was censored and alive was an event.

Table 3 presents demographic and Baseline characteristics. Overall, 581 subjects (60.5%) were male and 379 subjects (39.5%) were female. Median age was approximately 61 years, with age for individual subjects ranging from 30 to 85 years; 36.9% of subjects were aged ≥65 years. The majority of subjects (825 subjects, 85.9%) were white. Demographic and Baseline characteristics were well balanced between the 2 treatment groups. One subject (0.2%) in the sunitinib + erlotinib group had an ECOG performance status >1: this was a

protocol deviation; all other subjects had status of 0 or 1. There were 186 subjects (19.4%) who had never smoked; the majority of subjects were ex-smokers (558 subjects, 58.1%), with 216 subjects (22.5%) being current smokers.

Table 3. Demographic and Baseline Characteristics

	Sunitinib + Erlotinib (N=480)	Erlotinib (N=480)	Total (N=960)
Sex, number (%) of subjects			
Male	297 (61.9)	284 (59.2)	581 (60.5)
Female	183 (38.1)	196 (40.8)	379 (39.5)
Age, years			
Median (minimum-maximum)	61 (31-85)	61 (30-82)	61 (30-85)
Race, number (%) of subjects			
White	412 (85.8)	413 (86.0)	825 (85.9)
Asian	52 (10.8)	51 (10.6)	103 (10.7)
Black	6 (1.3)	6 (1.3)	12 (1.3)
Other	10 (2.1)	10 (2.1)	20 (2.1)
Weight, kg			
Mean (standard deviation)	72.5 (15.20)	72.6 (16.51)	72.6 (15.86)
Median (minimum-maximum)	72 (40-126)	70 (35-130)	71 (35-130)
n	478	479	957
Height, cm			
Mean (standard deviation)	168.1 (9.52)	167.5 (9.51)	167.8 (9.52)
Minimum-maximum	144-194	142-194	142-194
n	479	479	958
Smoking classification, number (%) of subjects			
Ex-smoker	282 (58.8)	276 (57.5)	558 (58.1)
Current smoker	102 (21.3)	114 (23.8)	216 (22.5)
Never smoked	96 (20.0)	90 (18.8)	186 (19.4)
ECOG performance status, number (%) of subjects			
0	184 (38.3)	175 (36.5)	359 (37.4)
1	294 (61.3)	304 (63.3)	598 (62.3)
>1	1 (0.2)[a]	0	1 (0.1)[a]
Not done	1 (0.2)[b]	1 (0.2)[c]	2 (0.2)[b,c]

ECOG = Eastern Cooperative Oncology Group; N = number of subjects in each group; n = number of subjects with an observation.

a. Subject had ECOG performance status of 1 at Screening and 2 at Cycle 1 Day 1.
b. Subject was not dosed due protocol deviation.
c. Subject was randomized in error, duplicate of another subject.

Efficacy Results:

Primary Endpoint (OS) and Seondary Endpoint (1-Year Survival Probability) Results: OS data are summarized in Table 4. Approximately 89% of subjects died and 11% of subjects were censored for each group, primarily due to subjects still in follow-up as of the study closure date. The analyses of OS were conducted on 858 OS events. The study did not demonstrate a statistically significant improvement in OS, with hazard ratio for the comparison of sunitinib + erlotinib versus erlotinib being 0.942 (95% CI: 0.822, 1.079), 1-sided p-value=0.1933. Median OS was 9.0 months (95% CI: 8.4, 10.2 months) for the sunitinib + erlotinib group and 8.5 months (95% CI: 7.4, 9.8 months) for the erlotinib group. Survival probability at 1 year was approximately 0.4 for both groups.

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

	Sunitinib + Erlotinib (N=480)	Erlotinib (N=480)
Number (%) of deaths	428 (89.2)	430 (89.6)
Number (%) alive/censored[a]	52 (10.8)	50 (10.4)
In follow-up as of study closure date[b]	28 (5.8)	25 (5.2)
Subject withdrew consent for additional follow-up	8 (1.7)	5 (1.0)
Lost to follow-up	16 (3.3)	20 (4.2)
Survival time (months)		
Quartiles (95% CI)		
25%	3.9 (3.3, 4.7)	3.5 (3.1, 4.1)
50%	9.0 (8.4, 10.2)	8.5 (7.4, 9.8)
75%	18.6 (16.7, 22.3)	17.9 (15.4, 20.4)
Range (minimum, maximum)	(0.0, 43.0)	(0.3, 49.9)
Hazard ratio (sunitinib + erlotinib versus erlotinib)[c]	0.942	
95% CI for hazard ratio	0.822, 1.079	
Log-rank test statistic[d]	-0.8656	
p-value[d]	0.1933	
Survival probability at 1 year (95% CI)[e]	0.40 (0.354, 0.442)	0.37 (0.328, 0.416)

CI = confidence interval; N = number of subjects.

a. Subjects not known to be dead at the time the database was closed for analysis were censored on the date they were last known to be alive.

b. Included subjects on treatment and on long-term follow-up.

c. Assuming proportional hazards, a hazard ratio less than 1 indicated a reduction in hazard rate in favor of sunitinib + erlotinib.

d. Log-rank test (standardized) stratified for smoking status (ever, never), prior bevacizumab therapy (yes, no) and epidermal growth factor receptor status (positive, negative, unknown) and 1-sided p-value from the stratified log-rank test.

e. Estimated using the Kaplan-Meier method.

Subgroup analyses for OS was performed for the data collected until the data cutoff date for primary outcome measure. As with the overall population, there was generally no treatment differences in OS for the subgroups; exceptions (where exploratory p-value was ≤0.025 without multiple comparison adjustment) included male subjects (p-value=0.0139), Asian subjects (p-value=0.0042), and subjects enrolled in geographic regions of Asia (p-value=0.0172) or North America (p-value=0.0074).

Univariate and multivariate Cox proportional hazard models (with treatment in the models) were implemented on the data sets collected until the data cutoff date to assess the potential influences of Baseline stratification factors and other pre-specified Baseline characteristics on OS. The hazard ratio and the 2-sided CI for treatment were also calculated to assess the treatment effect when the outcomes of the stratification factors or other Baseline characteristics were adjusted in the models. In univariate analysis, the following variables were identified as the important favorable prognostic factors (p-value <0.1) in OS: never-smoking status, female, Asian, ECOG performance status of 0, ≤2 disease sites, and histologic subtype of non-squamous. In multivariate analysis, a backward selection (with 2-sided alpha level of 0.1) was used to select the important prognostic factors for the final multivariate Cox proportional hazard model. All prognostic factors that were identified in the univariate analysis were selected in the multivariate analysis with the exception of histology. In addition, disease stage of IIIB was identified as a favorable prognostic factor in OS. In both univariate and multivariate analyses, the adjusted treatment effect was similar to the primary analysis result with hazard ratio ranging from 0.908 to 0.944.

Seconadry Endpoints Results: Secondary endpoints were assessed for the data collected until the implementation of Protocol Amendments.

PFS: The summary of results of PFS assessments performed is presented in Table 5. The results demonstrated a statistically significant improvement in PFS.

At the time of PFS analysis, it was found that the proportion of subjects with a PFS event was greater for the erlotinib group (395/480 subjects, 82.3%) compared to the sunitinib + erlotinib group (338/480 events, 70.4%). In both groups, for approximately 50% of subjects who had an event, the event was a new lesion. PFS data were censored for 29.6% and 17.7% of subjects in the sunitinib + erlotinib and erlotinib groups, respectively, primarily due to subjects discontinuing without progression (69.0% and 56.5% of subjects with censored data in the sunitinib + erlotinib and erlotinib groups, respectively). Median PFS was longer for the sunitinib + erlotinib group (15.5 weeks [approximately 3.5 months]) compared to the erlotinib group (8.7 weeks [approximately 2 months]). The hazard ratio was 0.807 (95% CI: 0.695, 0.937), favoring the sunitinib + erlotinib group, and the 1-sided stratified log-rank test was statistically significant (p-value=0.0023).

Table 5. Summary of Progression-Free Survival by Treatment and EGFR Status (Full Analysis Set)

	Sunitinib + Erlotinib (N=480)	Erlotinib (N=480)
Subjects (%) who had disease progression or death due to any cause on study[a]	338 (70.4)	395 (82.3)
Type of event[b]		
New lesion	171 (50.6)	192 (48.6)
≥20% increased in target lesions	87 (25.7)	115 (29.1)
Progression of non-target lesion	23 (6.8)	33 (8.4)
Death without objective progression	57 (16.9)	55 (13.9)
Subjects (%) without progression or death due to any cause on study[a]	142 (29.6)	85 (17.7)
In follow-up for progression	11 (7.7)	9 (10.6)
Withdrew consent for additional follow-up	7 (4.9)	2 (2.4)
Lost to follow-up	5 (3.5)	4 (4.7)
Started new treatment without progression	17 (12.0)	19 (22.4)
Discontinued without progression	98 (69.0)	48 (56.5)
PD/death after 16 weeks post last on-study assessment	4 (2.8)	3 (3.5)
Kaplan-Meier estimates of time to event (week)		
Quartiles (95% CI)		
25%	7.8 (7.4, 8.0)	7.4 (7.1, 7.7)
50%	15.5 (13.1, 16.1)	8.7 (8.3, 12.8)
75%	31.2 (24.4, 39.2)	24.1 (20.7, 26.5)
Range (minimum, maximum)	(1.1, 95.2)	(1.1, 106.6)
Hazard ratio (sunitinib + erlotinib versus erlotinib)[c]	0.807	
95% CI for hazard ratio	0.695, 0.937	
Log-rank test statistic[d]	-2.8272	
p-value[d]	0.0023	

CI = confidence interval; EGFR = epidermal growth factor receptor; N = number of subjects; PD = progressive disease.

a. Subjects considered on study within 28 days after last dose of study treatment.

b. Type of event determined by first evaluating new lesions, then increase in target lesions, then non-target lesions and then death status.

c. Assuming proportional hazards, a hazard ratio <1 indicates a reduction in hazard rate in favor of sunitinib + erlotinib.

d. Log-rank test (standardized) stratified for smoking status (ever, never), prior bevacizumab therapy (yes, no) and EGFR status (positive, negative, unknown) and 1-sided p-value from the stratified log-rank test.

ORR: The summary of results of ORR assessments performed is presented in Table 6.

At the time of analysis, an OR (CR or PR) was observed for 51/480 subjects (10.6%) in the sunitinib + erlotinib group and 33/480 subjects (6.9%) in the erlotinib group. With the exception of 5 subjects in the sunitinib + erlotinib group who had a CR, these were PRs. The risk ratio was 1.514 (95% CI: 1.002, 2.289), p-value=0.0471.

Table 6. Summary of Best Overall Response by Treatment, Based on Derived Investigator's Assessment of Tumor Data (Full Analysis Set)

Number (%) of Subjects	Sunitinib + Erlotinib (N=480)	Erlotinib (N=480)
Subjects with baseline assessment	472 (98.3)	476 (99.2)
Subjects with measurable disease at baseline	453 (94.4)	454 (94.6)
Best overall response		
Complete response (CR)	5 (1.0)	0
Partial response (PR)	46 (9.6)	33 (6.9)
Stable disease (SD)	155 (32.3)	135 (28.1)
SD (8-16 weeks)	143 (29.8)	126 (26.3)
SD >16 weeks	12 (2.5)	9 (1.9)
Progressive disease (PD)	156 (32.5)	230 (47.9)
Early death[a]	17 (3.5)	18 (3.8)
Indeterminate[b]	36 (7.5)	20 (4.2)
Missing	65 (13.5)	44 (9.2)
Objective response (% CR + PR)	51 (10.6)	33 (6.9)
95% exact CI[c]	8.01, 13.73	4.78, 9.52
Risk ratio (95% CI)[d]	1.514 (1.002, 2.289)	
p-value[e]	0.0471	

CI = confidence interval; N = number of subjects; vs = versus.

a. Subject died within 30 days of randomization and prior to having sufficient evaluations for overall response.
b. Included not evaluable, not assessed, and indeterminate.
c. Calculated based on the F-distribution.
d. A risk ratio >1 favors sunitinib + erlotinib.
e. From a Cochran-Mantel-Haenszel test stratified by smoking status (ever vs. never) and prior bevacizumab therapy (yes vs. no).

DR: A summary of results of DR analyzed for the data collected until the data cutoff date is presented in Table 7. Of the subjects with a confirmed OR, the proportion of subjects without progression or death while on study was higher for the sunitinib + erlotinib group (20/51 subjects, 39.2%) than for the erlotinib group (8/33 subjects, 24.2%). Median DR was 39.6 weeks for the sunitinib + erlotinib group and 32.3 weeks for the erlotinib group. The 75th percentile for DR was similar for both groups (55.8 weeks).

Table 7. Summary of Duration of Response (DR) by Treatment (Subjects With Objective Disease Response)

Number (%) of Subjects	Sunitinib + Erlotinib (N=480)	Erlotinib (N=480)
Subjects with a confirmed objective tumor response	51	33
Subjects who had disease progression or death due to any cause on study[a]	31 (60.8)	25 (75.8)
Subjects without progression or death due to any cause on study[a]	20 (39.2)	8 (24.2)
Duration of response in weeks		
Quartile (95% CI)		
25%	27.1 (18.1, 32.3)	23.4 (16.2, 24.2)
50% (median)	39.6 (31.3, 48.9)	32.3 (24.2, 48.0)
75%	55.8 (41.6, NR)	55.8 (39.9, 92.0)
Range (minimum, maximum)	(8.1, 56.0)	(12.1, 92.0)

CI = confidence interval; N = number of subjects; NR = not reached.

a. On study includes treatment plus 28-day follow-up period.

PRO: Among subjects who were available for PRO assessment, the completion rate was generally high throughout the study in both treatment groups, with ≥90% of the questionnaires completed at most treatment cycles (23/30 cycles sunitinib + erlotinib;

28/30 cycles placebo + erlotinib). The completion rate at study withdrawal/end of treatment was at 62.9% and 65.5% on the sunitinib + erlotinib and erlotinib groups, respectively.

At Baseline, a majority of subjects reported having "some or an extreme problem" with pain/discomfort (56.9% and 63.0% in the sunitinib + erlotinib and erlotinib groups, respectively). Furthermore, among the remaining treatment cycles only 33.3% (10/30 cycles) and 38.7% (12/31 cycles) of cycles in the sunitinib + erlotinib and erlotinib groups respectively, observed majorities of subjects reporting some or extreme problems with pain/discomfort. A smaller portion (maximum 21.4% at Cycle 17 in sunitinib + erlotinib) of subjects reported having "some or extreme problems" with self care at Baseline or during the study in both treatment groups. The proportion of subjects who reported having some or extreme problems in mobility (maximum 32.4% at Cycle 16 in sunitinib + erlotinib; maximum 36.4% at Cycle 24 in erlotinib) and usual activities (maximum 46.2% at Cycle 2 in sunitinib + erlotinib; maximum 44.2% at Cycle 2 in erlotinib) varied. Four cycles out of 31 (12.9%; Cycles 27-30) showed over half of subjects with some or extreme problems with anxiety/depression in the erlotinib group. Overall, only a very small percentage of subjects (≤10%) reported having an extreme problem with any of the dimensions of the EQ-5D at Baseline and during subsequent treatment cycles.

The mean health index score at Baseline in both treatment groups were similar to that of the subjects with advanced lung cancer observed in another study. During treatment, mean health index scores in both treatment groups remained stable compared to Baseline. The mean health index score at withdrawal/end of treatment was substantially lower than that at Baseline or other treatment cycles, which is in accordance with the fact that the majority of subjects withdrew from the study due to disease progression and AEs.

Safety Results: Table 8 presents an overall summary of AEs by treatment. The number of AEs reported was greater for the sunitinib + erlotinib group (5829 AEs) compared to the erlotinib group (4328 AEs), with all but 8 subjects with reported AE data (3 subjects in the sunitinib + erlotinib group and 5 subjects in the erlotinib group) experiencing at least 1 AE. AEs related to erlotinib or sunitinib/placebo were reported for 91.5% and 86.8% of subjects in the sunitinib + erlotinib and erlotinib groups, respectively. SAEs were experienced by approximately 41% of subjects. A total of 98 subjects (20.7%) in the sunitinib + erlotinib group and 104 subjects (21.8%) in the erlotinib group had a Grade 5 (fatal) AE. Erlotinib treatment was permanently discontinued due to AEs for 34.9% and 22.0% of subjects in the sunitinib + erlotinib and erlotinib groups, respectively, with similar percentage of subjects discontinuing from sunitinib/placebo due to AEs.

Table 8. Overall Summary of Adverse Events by Treatment (Per Protocol Set)

Number (%) of Subjects	Sunitinib + Erlotinib (N=473)	Erlotinib (N=477)	Total (N=950)
Subjects with reported AE data[a]	472 (99.8)	477 (100.0)	949 (99.9)
Number of AEs	5829	4328	10157
Subjects with ≥1 AEs	469 (99.2)	472 (99.0)	941 (99.1)
Subjects with ≥1 erlotinib and/or sunitinib/placebo related AEs	433 (91.5)	414 (86.8)	847 (89.2)
Subjects with ≥1 erlotinib related AEs	427 (90.3)	406 (85.1)	833 (87.7)
Subjects with ≥1 sunitinib/placebo related AEs	407 (86.0)	349 (73.2)	756 (79.6)
Subjects with ≥1 erlotinib and sunitinib/placebo related AEs	376 (79.5)	318 (66.7)	694 (73.1)
Subjects with ≥1 SAEs	207 (43.8)	181 (37.9)	388 (40.8)
Subjects with ≥1 erlotinib and/or sunitinib/placebo related SAEs	78 (16.5)	30 (6.3)	108 (11.4)
Subjects with ≥1 erlotinib related SAEs	61 (12.9)	26 (5.5)	87 (9.2)
Subjects with ≥1 sunitinib/placebo related SAEs	74 (15.6)	27 (5.7)	101 (10.6)
Subjects with ≥1 Erlotinib and sunitinib/placebo related SAEs	57 (12.1)	23 (4.8)	80 (8.4)
With Grade 3 or 4 AEs	328 (69.3)	239 (50.1)	567 (59.7)
Subjects with ≥1 erlotinib and/or sunitinib/placebo related Grade 3 or 4 AE	230 (48.6)	123 (25.8)	353 (37.2)
Subjects with ≥1 erlotinib related Grade 3 or 4 AE	199 (42.1)	111 (23.3)	310 (32.6)
Subjects with ≥1 sunitinib/placebo related Grade 3 or 4 AE	207 (43.8)	89 (18.7)	296 (31.2)
Subjects with ≥1 erlotinib and sunitinib/placebo related Grade 3 or 4 AE	168 (35.5)	76 (15.9)	244 (25.7)
With Grade 5 AEs	98 (20.7)	104 (21.8)	202 (21.3)
Subjects with ≥1 erlotinib and/or sunitinib/placebo related Grade 5 AE	4 (0.8)	4 (0.8)	8 (0.8)
Subjects with ≥1 erlotinib related Grade 5 AE	2 (0.4)	4 (0.8)	6 (0.6)
Subjects with ≥1 sunitinib/placebo related Grade 5 AE	4 (0.8)	3 (0.6)	7 (0.7)
Subjects with ≥1 erlotinib and sunitinib/placebo related Grade 5 AE	2 (0.4)	3 (0.6)	5 (0.5)
Discontinued erlotinib due to AEs	165 (34.9)	105 (22.0)	270 (28.4)
Discontinued sunitinib/placebo due to AEs	169 (35.7)	106 (22.2)	275 (28.9)
Temporary erlotinib discontinuation due to AEs	216 (45.7)	128 (26.8)	344 (36.2)
Temporary sunitinib/placebo discontinuation due to AEs	222 (46.9)	119 (24.9)	341 (35.9)
Erlotinib dose reduced due to AE	107 (22.6)	55 (11.5)	162 (17.1)
Sunitinib/placebo dose reduced due to AE	56 (11.8)	24 (5.0)	80 (8.4)

AEs and SAEs are not separated out.
All AEs that occurred on or after the first dose of the study treatment were included in the table.
Treatment-related AEs had causality on AE case report form pages checked as yes or unknown.
Except for number of AEs, subjects were counted once per treatment in each row.
SAEs – According to the Investigator's assessment
AE = adverse event; N = number of subjects; SAE = serious adverse event.
a. Included subjects checked "No Adverse Event" and subjects who reported any AE.

All-Causality Treatment-Emergent Adverse Events (TEAEs): Table 9 presents the TEAEs, (all-causality) experienced in ≥5% of subjects in any treatment group. Majority of the AEs reported were skin and subcutaneous tissue disorders, gastrointestinal disorders, general disorders and administration site conditions, and respiratory, thoracic and mediastinal disorders. The most common AEs, reported were diarrhea, rash, and decreased appetite.

Table 9. Treatment-Emergent, All-Causality Adverse Events Reported in ≥5% of Subjects in any Treatment Group (Per Protocol Set) by System Organ Class and Preferred Term

MedDRA System Organ Class / Preferred Term	Sunitinib + Erlotinib (N=473)		Erlotinib (N=477)		Total (N=950)	
	Number (%) of Subjects	Number of Events	Number (%) of Subjects	Number of Events	Number (%) of Subjects	Number of Events
Any adverse event	463 (97.9)	5424	461 (96.6)	4008	924 (97.3)	9432
Blood and lymphatic system disorders	99 (20.9)	265	37 (7.8)	59	136 (14.3)	324
Anaemia	51 (10.8)	82	23 (4.8)	40	74 (7.8)	122
Neutropenia	34 (7.2)	60	4 (0.8)	7	38 (4.0)	67
Thrombocytopenia	32 (6.8)	69	2 (0.4)	3	34 (3.6)	72
Gastrointestinal disorders	390 (82.5)	1326	288 (60.4)	762	678 (71.4)	2088
Abdominal pain	30 (6.3)	33	24 (5.0)	28	54 (5.7)	61
Constipation	29 (6.1)	34	42 (8.8)	48	71 (7.5)	82
Diarrhoea	335 (70.8)	690	188 (39.4)	266	523 (55.1)	956
Dyspepsia	41 (8.7)	48	34 (7.1)	41	75 (7.9)	89
Nausea	114 (24.1)	169	90 (18.9)	121	204 (21.5)	290
Stomatitis	28 (5.9)	34	21 (4.4)	27	49 (5.2)	61
Vomiting	86 (18.2)	137	66 (13.8)	89	152 (16.0)	226
General disorders and administration site conditions	261 (55.2)	529	233 (48.8)	429	494 (52.0)	958
Asthenia	49 (10.4)	80	50 (10.5)	69	99 (10.4)	149
Chest pain	44 (9.3)	55	47 (9.9)	54	91 (9.6)	109
Fatigue	128 (27.1)	197	100 (21.0)	135	228 (24.0)	332
Mucosal inflammation	40 (8.5)	56	27 (5.7)	39	67 (7.1)	95
Oedema peripheral	27 (5.7)	31	26 (5.5)	32	53 (5.6)	63
Pyrexia	43 (9.1)	51	37 (7.8)	45	80 (8.4)	96
Infections and infestations	150 (31.7)	256	145 (30.4)	278	295 (31.1)	534
Paronychia	25 (5.3)	37	19 (4.0)	31	44 (4.6)	68
Investigations	133 (28.1)	292	114 (23.9)	192	247 (26.0)	484
Weight decreased	79 (16.7)	137	64 (13.4)	80	143 (15.1)	217
Metabolism and nutrition disorders	233 (49.3)	424	164 (34.4)	252	397 (41.8)	676
Decreased appetite	190 (40.2)	256	133 (27.9)	158	323 (34.0)	414
Hypokalaemia	33 (7.0)	54	13 (2.7)	14	46 (4.8)	68
Musculoskeletal and connective tissue disorders	110 (23.3)	182	122 (25.6)	223	232 (24.4)	405
Back pain	29 (6.1)	40	32 (6.7)	41	61 (6.4)	81
Pain in extremity	23 (4.9)	26	26 (5.5)	32	49 (5.2)	58
Nervous system disorders	152 (32.1)	213	104 (21.8)	179	256 (26.9)	392
Dizziness	21 (4.4)	22	27 (5.7)	27	48 (5.1)	49
Dysgeusia	64 (13.5)	73	27 (5.7)	30	91 (9.6)	103
Headache	25 (5.3)	25	23 (4.8)	34	48 (5.1)	59
Psychiatric disorders	58 (12.3)	72	65 (13.6)	78	123 (12.9)	150
Insomnia	21 (4.4)	23	28 (5.9)	28	49 (5.2)	51
Respiratory, thoracic and mediastinal disorders	216 (45.7)	454	222 (46.5)	398	438 (46.1)	852
Cough	81 (17.1)	109	96 (20.1)	111	177 (18.6)	220
Dyspnoea	95 (20.1)	125	103 (21.6)	127	198 (20.8)	252
Epistaxis	43 (9.1)	49	21 (4.4)	27	64 (6.7)	76
Haemoptysis	34 (7.2)	45	29 (6.1)	30	63 (6.6)	75
Skin and subcutaneous tissue disorders	385 (81.4)	1046	360 (75.5)	887	745 (78.4)	1933
Alopecia	28 (5.9)	32	18 (3.8)	19	46 (4.8)	51
Dermatitis acneiform	65 (13.7)	115	64 (13.4)	96	129 (13.6)	211
Dry skin	52 (11.0)	55	58 (12.2)	64	110 (11.6)	119

Table 9. Treatment-Emergent, All-Causality Adverse Events Reported in ≥5% of Subjects in any Treatment Group (Per Protocol Set) by System Organ Class and Preferred Term

MedDRA System Organ Class Preferred Term	Sunitinib + Erlotinib (N=473)		Erlotinib (N=477)		Total (N=950)	
	Number (%) of Subjects	Number of Events	Number (%) of Subjects	Number of Events	Number (%) of Subjects	Number of Events
Palmar-plantar erythrodysaesthesia syndrome	42 (8.9)	54	20 (4.2)	25	62 (6.5)	79
Pruritus	33 (7.0)	40	53 (11.1)	66	86 (9.1)	106
Rash	277 (58.6)	575	255 (53.5)	437	532 (56.0)	1012
Vascular disorders	58 (12.3)	72	32 (6.7)	37	90 (9.5)	109
Hypertension	37 (7.8)	44	11 (2.3)	12	48 (5.1)	56

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 AEs, subjects were counted only once per treatment in each row.
% = (n/N) × 100.
AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects who received at least one dose of study treatment; n = number of subjects who had data for summary; SAE = serious adverse event.

Treatment-Related TEAEs: Table 10 presents treatment-related TEAEs by experienced in ≥5% of subjects in any treatment group. For the sunitinib + erlotinib group, the most common treatment-related (sunitinib/placebo or erlotinib related) AEs, each reported for >25% of subjects, were diarrhea (334/473 subjects, 70.6%), rash (273/473 subjects, 57.7%), and decreased appetite (137/473 subjects, 29.0%). For the erlotinib group, incidence of diarrhea was approximately 35% lower (168/477 subjects, 35.2%), and the incidence of decreased appetite was approximately 12% lower (78/477 subjects, 16.4%).

Table 10. Treatment-Emergent Treatment-Related (Erlotinib or Sunitinib/Placebo) Adverse Events Reported in ≥5% of Subjects in any Treatment Group (Per Protocol Set)

Number (%) of Subjects With Preferred Term Adverse Event	Sunitinib + Erlotinib (N=473)	Erlotinib (N=477)
Diarrhoea	334 (70.6)	168 (35.2)
Rash	273 (57.7)	249 (52.2)
Decreased appetite	137 (29.0)	78 (16.4)
Nausea	96 (20.3)	65 (13.6)
Fatigue	89 (18.8)	61 (12.8)
Vomiting	69 (14.6)	39 (8.2)
Dermatitis acneiform	66 (14.0)	64 (13.4)
Dysgeusia	62 (13.1)	24 (5.0)
Dry skin	51 (10.8)	54(11.3)
Palmar-plantar erythrodysaesthesia syndrome	43 (9.1)	18 (3.8)
Mucosal inflammation	40 (8.5)	26 (5.5)
Weight decreased	39 (8.2)	22 (4.6)
Asthenia	34 (7.2)	28 (5.9)
Epistaxis	33 (7.0)	16 (3.4)
Thrombocytopenia	32 (6.8)	2 (0.4)
Neutropenia	31 (6.6)	4 (0.8)
Pruritis	31 (6.6)	48 (10.1)
Dyspepsia	29 (6.1)	22 (4.6)
Anemia	28 (5.9)	13 (2.7)
Stomatitis	26 (5.5)	20 (4.2)
Alopecia	24 (5.1)	14 (2.9)

AEs and SAEs are not separated out.
All AEs that occurred on or after the first dose of the study treatment were included in the table.
Adverse events reported for ≥5% of subjects in either group are presented, ranked in order of decreasing frequency in the sunitinib + erlotinib group.
AE = adverse event; N = number of subjects; SAE = serious adverse event.

Severity of AEs as per CTCAE Criteria: A total of 98 subjects (20.7%) in the sunitinib + erlotinib group and 104 subjects (21.8%) in the erlotinib group had a Grade 5 (fatal) AE. The most common Grade 3 AEs for the sunitinib + erlotinib group, each reported for >10% of subjects, were diarrhea (76/473 subjects, 16.1%) and rash (61/473 subjects, 12.9%). The incidence of each of these Grade 3 AEs was lower for the erlotinib group; for diarrhea the incidence was approximately 12% lower (3.6%) compared to the sunitinib + erlotinib group. Grade 4 rash was reported for 5 subjects (1.1%) in the sunitinib + erlotinib group and 2 subjects (0.4%) in the erlotinib group.

Treatment-Emergent SAEs (All-Causality): Table 11 presents treatment-emergent SAEs (all-causality) reported during the study. For both groups, the most common SAE was disease progression, reported for 70/473 (14.8%) and 61/477 subjects (12.8%) in the sunitinib + erlotinib and erlotinib groups, respectively. All other SAEs were reported for <5% of subjects in each group. Incidence of diarrhea as an SAE was approximately 4% higher for the sunitinib + erlotinib group (4.7%) compared to the erlotinib group (1.0%).

Table 11. Summary of Treatment-Emergent, All-Causality, Serious Adverse Events by Treatment, MedDRA System Organ Class and Preferred Term (Per-Protocol Set)

System Organ Class Preferred Term	Sunitinib + Erlotinib		Erlotinib		Total	
	Number (%) of Subjects	Number of Events	Number (%) of Subjects	Number of Events	Number (%) of Subjects	Number of Events
Any SAE	207 (43.8)	405	181 (37.9)	320	388 (40.8)	725
Blood and lymphatic system disorders	6 (1.3)	8	6 (1.3)	6	12 (1.3)	14
Anaemia	3 (0.6)	3	5 (1.0)	5	8 (0.8)	8
Anaemia of malignant disease	1 (0.2)	2	0	0	1 (0.1)	2
Febrile neutropenia	1 (0.2)	1	0	0	1 (0.1)	1
Neutropenia	0	0	1 (0.2)	1	1 (0.1)	1
Thrombocytopenia	2 (0.4)	2	0	0	2 (0.2)	2
Cardiac disorders	15 (3.2)	16	8 (1.7)	11	23 (2.4)	27
Acute myocardial infarction	0	0	1 (0.2)	1	1 (0.1)	1
Atrioventricular block complete	1 (0.2)	1	0	0	1 (0.1)	1
Bundle branch block left	1 (0.2)	1	0	0	1 (0.1)	1
Cardiac arrest	0	0	1 (0.2)	1	1 (0.1)	1
Cardiac failure	2 (0.4)	2	3 (0.6)	4	5 (0.5)	6
Cardiac failure congestive	1 (0.2)	1	0	0	1 (0.1)	1
Cardiopulmonary failure	1 (0.2)	1	0	0	1 (0.1)	1
Cardiovascular insufficiency	1 (0.2)	1	0	0	1 (0.1)	1
Coronary artery disease	1 (0.2)	2	0	0	1 (0.1)	2
Left ventricular failure	0	0	1 (0.2)	2	1 (0.1)	2
Myocardial infarction	3 (0.6)	3	0	0	3 (0.3)	3
Pericardial effusion	3 (0.6)	3	1 (0.2)	1	4 (0.4)	4
Tachyarrhythmia	0	0	2 (0.4)	2	2 (0.2)	2
Tachycardia	1 (0.2)	1	0	0	1 (0.1)	1
Congenital, familial and genetic disorders	1 (0.2)	1	0	0	1 (0.1)	1
Tracheo-oesophageal fistula	1 (0.2)	1	0	0	1 (0.1)	1
Gastrointestinal disorders	41 (8.7)	69	24 (5.0)	36	65 (6.8)	105
Abdominal pain	1 (0.2)	1	3 (0.6)	3	4 (0.4)	4
Abdominal pain upper	1 (0.2)	1	1 (0.2)	1	2 (0.2)	2
Acute abdomen	0	0	1 (0.2)	2	1 (0.1)	2
Anal haemorrhage	1 (0.2)	1	0	0	1 (0.1)	1
Ascites	1 (0.2)	2	0	0	1 (0.1)	2
Constipation	1 (0.2)	1	1 (0.2)	1	2 (0.2)	2
Diarrhoea	22 (4.7)	27	5 (1.0)	7	27 (2.8)	34
Dysphagia	1 (0.2)	1	0	0	1 (0.1)	1
Gastric haemorrhage	2 (0.4)	2	0	0	2 (0.2)	2
Gastric perforation	0	0	1 (0.2)	2	1 (0.1)	2
Gastric ulcer haemorrhage	0	0	1 (0.2)	1	1 (0.1)	1
Gastritis	1 (0.2)	1	0	0	1 (0.1)	1
Gastrointestinal haemorrhage	2 (0.4)	2	0	0	2 (0.2)	2
Gastrointestinal pain	0	0	1 (0.2)	1	1 (0.1)	1
Haematemesis	2 (0.4)	3	1 (0.2)	1	3 (0.3)	4
Ileus paralytic	0	0	1 (0.2)	1	1 (0.1)	1
Lower gastrointestinal haemorrhage	1 (0.2)	1	0	0	1 (0.1)	1
Nausea	7 (1.5)	8	5 (1.0)	5	12 (1.3)	13
Pancreatitis	1 (0.2)	1	0	0	1 (0.1)	1

Table 11. Summary of Treatment-Emergent, All-Causality, Serious Adverse Events by Treatment, MedDRA System Organ Class and Preferred Term (Per-Protocol Set)

System Organ Class Preferred Term	Sunitinib + Erlotinib		Erlotinib		Total	
	Number (%) of Subjects	Number of Events	Number (%) of Subjects	Number of Events	Number (%) of Subjects	Number of Events
Peritonitis	1 (0.2)	1	0	0	1 (0.1)	1
Rectal haemorrhage	1 (0.2)	1	0	0	1 (0.1)	1
Small intestinal obstruction	0	0	1 (0.2)	2	1 (0.1)	2
Small intestinal perforation	1 (0.2)	1	0	0	1 (0.1)	1
Thrombosis mesenteric vessel	0	0	1 (0.2)	1	1 (0.1)	1
Vomiting	11 (2.3)	14	8 (1.7)	8	19 (2.0)	22
General disorders and administration site conditions	93(19.7)	110	77(16.1)	89	170(17.9)	199
Asthenia	11 (2.3)	12	4 (0.8)	4	15 (1.6)	16
Chest pain	0	0	4 (0.8)	4	4 (0.4)	4
Death	2 (0.4)	2	4 (0.8)	4	6 (0.6)	6
Disease progression	70 (14.8)	73	61 (12.8)	64	131 (13.8)	137
Euthanasia	0	0	1 (0.2)	1	1 (0.1)	1
Fatigue	5 (1.1)	5	1 (0.2)	1	6 (0.6)	6
General physical health deterioration	6 (1.3)	6	3 (0.6)	4	9 (0.9)	10
Irritability	1 (0.2)	1	0	0	1 (0.1)	1
Malaise	1 (0.2)	1	0	0	1 (0.1)	1
Mucosal inflammation	1 (0.2)	3	1 (0.2)	1	2 (0.2)	4
Oedema peripheral	1 (0.2)	1	1 (0.2)	1	2 (0.2)	2
Pyrexia	6 (1.3)	6	4 (0.8)	4	10 (1.1)	10
Sudden death	0	0	1 (0.2)	1	1 (0.1)	1
Hepatobiliary disorders	6 (1.3)	8	3 (0.6)	3	9 (0.9)	11
Bile duct stone	0	0	1 (0.2)	1	1 (0.1)	1
Cholecystitis	2 (0.4)	2	0	0	2 (0.2)	2
Cholelithiasis	1 (0.2)	1	1 (0.2)	1	2 (0.2)	2
Gallbladder perforation	1 (0.2)	1	0	0	1 (0.1)	1
Hepatic failure	0	0	1 (0.2)	1	1 (0.1)	1
Hepatic function abnormal	2 (0.4)	2	0	0	2 (0.2)	2
Hyperbilirubinaemia	1 (0.2)	2	0	0	1 (0.1)	2
Immune system disorders	0	0	1 (0.2)	1	1 (0.1)	1
Anaphylactic shock	0	0	1 (0.2)	1	1 (0.1)	1
Infections and infestations	31 (6.6)	38	28 (5.9)	32	59 (6.2)	70
Acute tonsillitis	0	0	1 (0.2)	1	1 (0.1)	1
Bronchitis	1 (0.2)	1	1 (0.2)	1	2 (0.2)	2
Bronchopneumonia	2 (0.4)	2	0	0	2 (0.2)	2
Clostridial infection	0	0	1 (0.2)	1	1 (0.1)	1
Clostridium difficile colitis	1 (0.2)	1	0	0	1 (0.1)	1
Device related infection	1 (0.2)	1	0	0	1 (0.1)	1
Empyema	1 (0.2)	2	0	0	1 (0.1)	2
Endocarditis	1 (0.2)	1	0	0	1 (0.1)	1
Erysipelas	1 (0.2)	1	1 (0.2)	1	2 (0.2)	2
Gastroenteritis	3 (0.6)	3	1 (0.2)	1	4 (0.4)	4
Hepatitis B	1 (0.2)	1	0	0	1 (0.1)	1
Herpes simplex	1 (0.2)	1	0	0	1 (0.1)	1
Herpes virus infection	1 (0.2)	1	0	0	1 (0.1)	1
Infection	2 (0.4)	2	1 (0.2)	1	3 (0.3)	3
Influenza	0	0	1 (0.2)	1	1 (0.1)	1
Lower respiratory tract infection	0	0	1 (0.2)	1	1 (0.1)	1
Lung abscess	1 (0.2)	1	0	0	1 (0.1)	1
Lung infection	0	0	2 (0.4)	2	2 (0.2)	2

Table 11. Summary of Treatment-Emergent, All-Causality, Serious Adverse Events by Treatment, MedDRA System Organ Class and Preferred Term (Per-Protocol Set)

System Organ Class Preferred Term	Sunitinib + Erlotinib		Erlotinib		Total	
	Number (%) of Subjects	Number of Events	Number (%) of Subjects	Number of Events	Number (%) of Subjects	Number of Events
Pneumonia	7 (1.5)	7	13 (2.7)	14	20 (2.1)	21
Pseudomembranous colitis	0	0	1 (0.2)	1	1 (0.1)	1
Pyonephrosis	0	0	1 (0.2)	1	1 (0.1)	1
Pyothorax	0	0	1 (0.2)	1	1 (0.1)	1
Respiratory tract infection	4 (0.8)	5	0	0	4 (0.4)	5
Sepsis	2 (0.4)	2	1 (0.2)	2	3 (0.3)	4
Septic shock	0	0	1 (0.2)	2	1 (0.1)	2
Streptococcal bacteraemia	1 (0.2)	1	0	0	1 (0.1)	1
Streptococcal sepsis	1 (0.2)	1	0	0	1 (0.1)	1
Urinary tract infection	4 (0.8)	4	1 (0.2)	1	5 (0.5)	5
Injury, poisoning and procedural complications	2 (0.4)	2	6 (1.3)	11	8 (0.8)	13
Accidental overdose	0	0	1 (0.2)	1	1 (0.1)	1
Ankle fracture	0	0	1 (0.2)	1	1 (0.1)	1
Fall	0	0	1 (0.2)	1	1 (0.1)	1
Hip fracture	0	0	1 (0.2)	1	1 (0.1)	1
Joint dislocation	0	0	1 (0.2)	3	1 (0.1)	3
Pelvic fracture	1 (0.2)	1	0	0	1 (0.1)	1
Road traffic accident	0	0	1 (0.2)	1	1 (0.1)	1
Spinal fracture	0	0	1 (0.2)	1	1 (0.1)	1
Subdural haemorrhage	0	0	1 (0.2)	2	1 (0.1)	2
Upper limb fracture	1 (0.2)	1	0	0	1 (0.1)	1
Investigations	5 (1.1)	6	3 (0.6)	6	8 (0.8)	12
Alanine aminotransferase increased	0	0	2 (0.4)	2	2 (0.2)	2
Aspartate aminotransferase increased	0	0	1 (0.2)	1	1 (0.1)	1
Blood bilirubin increased	1 (0.2)	1	1 (0.2)	1	2 (0.2)	2
Body temperature increased	1 (0.2)	1	0	0	1 (0.1)	1
General physical condition abnormal	1 (0.2)	1	0	0	1 (0.1)	1
Haemoglobin decreased	2 (0.4)	2	1 (0.2)	2	3 (0.3)	4
Hepatic enzyme increased	1 (0.2)	1	0	0	1 (0.1)	1
Metabolism and nutrition disorders	18 (3.8)	21	13 (2.7)	15	31 (3.3)	36
Decreased appetite	2 (0.4)	2	4 (0.8)	4	6 (0.6)	6
Dehydration	9 (1.9)	9	5 (1.0)	5	14 (1.5)	14
Hyperglycaemia	1 (0.2)	1	0	0	1 (0.1)	1
Hyperkalaemia	1 (0.2)	1	0	0	1 (0.1)	1
Hypocalcaemia	2 (0.4)	2	0	0	2 (0.2)	2
Hypokalaemia	2 (0.4)	3	1 (0.2)	3	3 (0.3)	6
Hypomagnesaemia	1 (0.2)	1	2 (0.4)	2	3 (0.3)	3
Hyponatraemia	1 (0.2)	1	1 (0.2)	1	2 (0.2)	2
Hypophagia	1 (0.2)	1	0	0	1 (0.1)	1
Musculoskeletal and connective tissue disorders	10 (2.1)	11	6 (1.3)	6	16 (1.7)	17
Arthralgia	0	0	1 (0.2)	1	1 (0.1)	1
Back pain	1 (0.2)	1	4 (0.8)	4	5 (0.5)	5
Flank pain	0	0	1 (0.2)	1	1 (0.1)	1
Muscle haemorrhage	1 (0.2)	1	0	0	1 (0.1)	1
Muscular weakness	1 (0.2)	1	0	0	1 (0.1)	1
Musculoskeletal chest pain	1 (0.2)	1	0	0	1 (0.1)	1

Table 11. Summary of Treatment-Emergent, All-Causality, Serious Adverse Events by Treatment, MedDRA System Organ Class and Preferred Term (Per-Protocol Set)

System Organ Class Preferred Term	Sunitinib + Erlotinib		Erlotinib		Total	
	Number (%) of Subjects	Number of Events	Number (%) of Subjects	Number of Events	Number (%) of Subjects	Number of Events
Musculoskeletal pain	1 (0.2)	2	0	0	1 (0.1)	2
Neck pain	1 (0.2)	1	0	0	1 (0.1)	1
Osteonecrosis of jaw	1 (0.2)	1	0	0	1 (0.1)	1
Pain in extremity	2 (0.4)	2	0	0	2 (0.2)	2
Pathological fracture	1 (0.2)	1	0	0	1 (0.1)	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (0.4)	2	3 (0.6)	3	5 (0.5)	5
Liposarcoma	0	0	1 (0.2)	1	1 (0.1)	1
Rectal cancer	0	0	1 (0.2)	1	1 (0.1)	1
Tumour haemorrhage	1 (0.2)	1	0	0	1 (0.1)	1
Tumour pain	1 (0.2)	1	1 (0.2)	1	2 (0.2)	2
Nervous system disorders	10 (2.1)	16	8 (1.7)	10	18 (1.9)	26
Ataxia	0	0	1 (0.2)	1	1 (0.1)	1
Cerebral infarction	2 (0.4)	2	0	0	2 (0.2)	2
Cerebral ischaemia	1 (0.2)	3	0	0	1 (0.1)	3
Cerebrovascular accident	3 (0.6)	3	1 (0.2)	1	4 (0.4)	4
Depressed level of consciousness	0	0	1 (0.2)	2	1 (0.1)	2
Haemorrhagic stroke	1 (0.2)	1	0	0	1 (0.1)	1
Hemiparesis	1 (0.2)	1	0	0	1 (0.1)	1
Hemiplegia	0	0	1 (0.2)	1	1 (0.1)	1
Ischaemic stroke	1 (0.2)	1	0	0	1 (0.1)	1
Lethargy	1 (0.2)	1	0	0	1 (0.1)	1
Loss of consciousness	1 (0.2)	1	0	0	1 (0.1)	1
Meningorrhagia	1 (0.2)	2	0	0	1 (0.1)	2
Monoparesis	0	0	1 (0.2)	1	1 (0.1)	1
Neuralgia	0	0	1 (0.2)	1	1 (0.1)	1
Neurological decompensation	0	0	1 (0.2)	1	1 (0.1)	1
Paralysis	0	0	1 (0.2)	1	1 (0.1)	1
Syncope	1 (0.2)	1	1 (0.2)	1	2 (0.2)	2
Psychiatric disorders	5 (1.1)	6	6 (1.3)	6	11 (1.2)	12
Aggression	1 (0.2)	1	0	0	1 (0.1)	1
Anxiety	0	0	1 (0.2)	1	1 (0.1)	1
Completed suicide	1 (0.2)	1	0	0	1 (0.1)	1
Confusional state	3 (0.6)	3	2 (0.4)	2	5 (0.5)	5
Mental status changes	1 (0.2)	1	0	0	1 (0.1)	1
Psychotic disorder	0	0	1 (0.2)	1	1 (0.1)	1
Sopor	0	0	1 (0.2)	1	1 (0.1)	1
Suicide attempt	0	0	1 (0.2)	1	1 (0.1)	1
Renal and urinary disorders	9 (1.9)	10	4 (0.8)	4	13 (1.4)	14
Anuria	1 (0.2)	1	0	0	1 (0.1)	1
Calculus ureteric	0	0	1 (0.2)	1	1 (0.1)	1
Focal segmental glomerulosclerosis	1 (0.2)	1	0	0	1 (0.1)	1
Haematuria	1 (0.2)	1	0	0	1 (0.1)	1
Nephrolithiasis	1 (0.2)	2	0	0	1 (0.1)	2
Renal failure	4 (0.8)	4	1 (0.2)	1	5 (0.5)	5
Renal failure acute	1 (0.2)	1	1 (0.2)	1	2 (0.2)	2
Urinary retention	0	0	1 (0.2)	1	1 (0.1)	1
Respiratory, thoracic and mediastinal disorders	49 (10.4)	62	58 (12.2)	71	107 (11.3)	133

Table 11. Summary of Treatment-Emergent, All-Causality, Serious Adverse Events by Treatment, MedDRA System Organ Class and Preferred Term (Per-Protocol Set)

System Organ Class Preferred Term	Sunitinib + Erlotinib		Erlotinib		Total	
	Number (%) of Subjects	Number of Events	Number (%) of Subjects	Number of Events	Number (%) of Subjects	Number of Events
Acute respiratory distress syndrome	0	0	1 (0.2)	1	1 (0.1)	1
Asphyxia	0	0	1 (0.2)	2	1 (0.1)	2
Atelectasis	0	0	1 (0.2)	1	1 (0.1)	1
Chronic obstructive pulmonary disease	2 (0.4)	2	2 (0.4)	2	4 (0.4)	4
Cough	0	0	1 (0.2)	1	1 (0.1)	1
Dyspnoea	17 (3.6)	22	21 (4.4)	22	38 (4.0)	44
Epistaxis	3 (0.6)	4	0	0	3 (0.3)	4
Haemoptysis	5 (1.1)	6	4 (0.8)	4	9 (0.9)	10
Hydrothorax	1 (0.2)	2	0	0	1 (0.1)	2
Interstitial lung disease	1 (0.2)	1	1 (0.2)	2	2 (0.2)	3
Lung disorder	0	0	2 (0.4)	3	2 (0.2)	3
Lung infiltration	1 (0.2)	1	0	0	1 (0.1)	1
Pleural effusion	5 (1.1)	5	4 (0.8)	4	9 (0.9)	9
Pneumonia aspiration	1 (0.2)	1	1 (0.2)	1	2 (0.2)	2
Pneumothorax	3 (0.6)	4	2 (0.4)	2	5 (0.5)	6
Pulmonary embolism	4 (0.8)	4	7 (1.5)	7	11 (1.2)	11
Pulmonary haemorrhage	1 (0.2)	1	3 (0.6)	3	4 (0.4)	4
Pulmonary infarction	1 (0.2)	1	0	0	1 (0.1)	1
Pulmonary oedema	1 (0.2)	1	0	0	1 (0.1)	1
Respiratory arrest	1 (0.2)	1	0	0	1 (0.1)	1
Respiratory disorder	0	0	1 (0.2)	1	1 (0.1)	1
Respiratory failure	5 (1.1)	6	12 (2.5)	14	17 (1.8)	20
Respiratory tract congestion	0	0	1 (0.2)	1	1 (0.1)	1
Skin and subcutaneous tissue disorders	5 (1.1)	7	1 (0.2)	1	6 (0.6)	8
Dermatitis acneiform	1 (0.2)	1	0	0	1 (0.1)	1
Palmar-plantar erythrodysaesthesia syndrome	1 (0.2)	1	0	0	1 (0.1)	1
Petechiae	0	0	1 (0.2)	1	1 (0.1)	1
Rash	3 (0.6)	3	0	0	3 (0.3)	3
Rash generalised	1 (0.2)	2	0	0	1 (0.1)	2
Vascular disorders	9 (1.9)	10	6 (1.3)	7	15 (1.6)	17
Aortic aneurysm rupture	1 (0.2)	2	0	0	1 (0.1)	2
Circulatory collapse	1 (0.2)	1	1 (0.2)	1	2 (0.2)	2
Deep vein thrombosis	3 (0.6)	3	2 (0.4)	2	5 (0.5)	5
Embolism	1 (0.2)	1	0	0	1 (0.1)	1
Hypertension	1 (0.2)	1	1 (0.2)	1	2 (0.2)	2
Hypovolaemic shock	0	0	1 (0.2)	1	1 (0.1)	1
Peripheral ischaemia	0	0	1 (0.2)	1	1 (0.1)	1
Peripheral vascular disorder	1 (0.2)	1	0	0	1 (0.1)	1
Phlebitis	1 (0.2)	1	0	0	1 (0.1)	1
Superior vena caval occlusion	0	0	1 (0.2)	1	1 (0.1)	1
Missing system organ class	2 (0.4)	2	2 (0.4)	2	4 (0.4)	4
Missing preferred term	2 (0.4)	2	2 (0.4)	2	4 (0.4)	4

Table 11. Summary of Treatment-Emergent, All-Causality, Serious Adverse Events by Treatment, MedDRA System Organ Class and Preferred Term (Per-Protocol Set)

System Organ Class Preferred Term	Sunitinib + Erlotinib		Erlotinib		Total	
	Number (%) of Subjects	Number of Events	Number (%) of Subjects	Number of Events	Number (%) of Subjects	Number of Events

All AEs 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.
% = (n/N) × 100.
MedDRA; version 13 dictionary applied.
AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects who received at least 1 dose of study treatment; n = number of subjects who had data for summary.

Treatment-Related SAEs: Diarrhea, vomiting, dehydration, and nausea were the only SAEs that were considered to be related to treatment in >1% of subjects in the sunitinib + erlotinib group; for the erlotinib group, no treatment related SAEs were reported for >1% of subjects. Table 12 presents treatment-emergent treatment-related SAEs reported during the study.

Table 12. Treatment-Emergent Treatment-Related (Erlotinib or Sunitinib/Placebo) Serious Adverse Events

Preferred Term	Sunitinib + Erlotinib (N=473)	Erlotinib (N=477)
Diarrhoea	21 (4.4)	3 (0.6)
Vomiting	7 (1.5)	3 (0.6)
Dehydration	6 (1.3)	1 (0.2)
Nausea	5 (1.1)	1 (0.2)
Fatigue	4 (0.8)	1 (0.2)
Anaemia	3 (0.6)	2 (0.4)
Asthenia	3 (0.6)	2 (0.4)
General physical health deterioration	3 (0.6)	0
Rash	3 (0.6)	0
Deep vein thrombosis	2 (0.4)	1 (0.2)
Epistaxis	2 (0.4)	0
Gastric haemorrhage	2 (0.4)	0
Haemoptysis	2 (0.4)	0
Hypocalcaemia	2 (0.4)	0
Hypokalaemia	2 (0.4)	1 (0.2)
Respiratory tract infection	2 (0.4)	0
Thrombocytopenia	2 (0.4)	0
Abdominal pain upper	1 (0.2)	0
Anal haemorrhage	1 (0.2)	0
Anuria	1 (0.2)	0
Blood bilirubin increased	1 (0.2)	1 (0.2)
Bundle branch block left	1 (0.2)	0
Cerebral infarction	1 (0.2)	0
Cholecystitis	1 (0.2)	0
Confusional state	1 (0.2)	0
Death	1 (0.2)	0
Dermatitis acneiform	1 (0.2)	0
Dyspnoea	1 (0.2)	0
Febrile neutropenia	1 (0.2)	0
Focal segmental glomerulosclerosis	1 (0.2)	0
Gallbladder perforation	1 (0.2)	0
Gastrointestinal haemorrhage	1 (0.2)	0
General physical condition abnormal	1 (0.2)	0
Haematuria	1 (0.2)	0
Haemoglobin decreased	1 (0.2)	1 (0.2)
Hepatic enzyme increased	1 (0.2)	0
Hepatic function abnormal	1 (0.2)	0
Herpes simplex	1 (0.2)	0
Hyperbilirubinaemia	1 (0.2)	0
Hypertension	1 (0.2)	1 (0.2)
Hypomagnesaemia	1 (0.2)	1 (0.2)
Hyponatraemia	1 (0.2)	0
Hypophagia	1 (0.2)	0
Infection	1 (0.2)	0
Ischaemic stroke	1 (0.2)	0
Lethargy	1 (0.2)	0
Loss of consciousness	1 (0.2)	0
Lung abscess	1 (0.2)	0
Meningorrhagia	1 (0.2)	0
Mucosal inflammation	1 (0.2)	1 (0.2)
Myocardial infarction	1 (0.2)	0
Osteonecrosis of jaw	1 (0.2)	0
Palmar-plantar erythrodysaesthesia syndrome	1 (0.2)	0
Pancreatitis	1 (0.2)	0
Pericardial effusion	1 (0.2)	0

Table 12. Treatment-Emergent Treatment-Related (Erlotinib or Sunitinib/Placebo) Serious Adverse Events

Preferred Term	Sunitinib + Erlotinib (N=473)	Erlotinib (N=477)
Pneumonia	1 (0.2)	0
Pulmonary embolism	1 (0.2)	1 (0.2)
Pyrexia	1 (0.2)	1 (0.2)
Rash generalised	1 (0.2)	0
Renal failure	1 (0.2)	1 (0.2)
Renal failure acute	1 (0.2)	1 (0.2)
Sepsis	1 (0.2)	0
Tumour haemorrhage	1 (0.2)	0
Acute tonsillitis	0	1 (0.2)
Alanine aminotransferase increased	0	1 (0.2)
Asphyxia	0	1 (0.2)
Ataxia	0	1 (0.2)
Decreased appetite	0	3 (0.6)
Gastric ulcer haemorrhage	0	1 (0.2)
Haematemesis	0	1 (0.2)
Interstitial lung disease	0	1 (0.2)
Lung disorder	0	1 (0.2)
Pseudomembranous colitis	0	1 (0.2)
Pulmonary haemorrhage	0	2 (0.4)
Subdural haemorrhage	0	1 (0.2)
Missing preferred term	1 (0.2)	0

All AEs that occurred on or after the first dose of the study treatment were included in the table.
% = (n/N) × 100.
MedDRA; version 13 dictionary applied.
AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; 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: The most common AEs leading to discontinuation were disease progression and diarrhea, each of which led to discontinuation of approximately 5% of subjects in the sunitinib + erlotinib group (Table 13). Discontinuation due to these AEs was lower for the erlotinib group (3.6% due to disease progression and 0.4% due to diarrhea). A similar trend was seen for AEs leading to discontinuation of sunitinib/placebo.

Table 13. Most Common (≥1%) Treatment-Emergent Adverse Events Associated With Discontinuation by Treatment and Preferred Term (Per Protocol Set)

Number (%) of Subjects	Sunitinib + Erlotinib (N=473)	Erlotinib (N=477)	Total (N=950)
Adverse Events Associated With Erlotinib Discontinuation			
Disease progression	26 (5.5)	17 (3.6)	43 (4.5)
Diarrhoea	24 (5.1)	2 (0.4)	26 (2.7)
Fatigue	10 (2.1)	4 (0.8)	14 (1.5)
Rash	9 (1.9)	5 (1.0)	14 (1.5)
Dyspnoea	5 (1.1)	4 (0.8)	9 (0.9)
Respiratory failure	3 (0.6)	5 (1.0)	8 (0.8)
Adverse Events Associated With Sunitinib/Placebo Discontinuation			
Disease progression	25 (5.3)	17 (3.6)	42 (4.4)
Diarrhoea	26 (5.5)	2 (0.4)	28 (2.9)
Fatigue	9 (1.9)	4 (0.8)	13 (1.4)
Rash	9 (1.9)	4 (0.8)	13 (1.4)
Dyspnoea	5 (1.1)	4 (0.8)	9 (0.9)
General physical health deterioration	5 (1.1)	3 (0.6)	8 (0.8)

Adverse events leading to erlotinib and sunitinib/placebo discontinuation reported for ≥1% of subjects in either group are presented, ranked in order of decreasing frequency in the sunitinib + erlotinib group.
N = number of subjects.

Temporary Discontinuations Due to AEs: The most common AEs leading to temporary stopping of administration of erlotinib and sunitinib/placebo were diarrhea and rash.

Deaths: Approximately 89% of subjects died (Table 14): 421/473 subjects (89.0%) and 428/477 subjects (89.7%) in the sunitinib + erlotinib and erlotinib groups, respectively, mainly due to the disease under study (ie, advanced/metastatic NSCLC; approximately 17% of subjects in each treatment group). A total of 3 subjects (0.6%) and 2 subjects (0.4%) in the sunitinib + erlotinib and erlotinib groups, respectively, died on-study due to treatment-related toxicity.

Table 14. Summary of Deaths by Treatment and Cause (Per Protocol Set)

	Sunitinib + Erlotinib (N=473) n (%)	Erlotinib (N=477) n (%)	Total (N=950) n (%)
Subjects who died	421 (89.0)	428 (89.7)	849 (89.4)
Subjects who died on-study[a]	100 (21.1)	103 (21.6)	203 (21.4)
Disease under study	83 (17.5)	82 (17.2)	165 (17.4)
Study treatment toxicity	3 (0.6)	2 (0.4)	5 (0.5)
Unknown	3 (0.6)	1 (0.2)	4 (0.4)
Other	14 (3.0)	18 (3.8)	32 (3.4)
Subjects who died during follow-up[b]	321 (67.9)	325 (68.1)	646 (68.0)
Disease under study	298 (63.0)	305 (63.9)	603 (63.5)
Study treatment toxicity	0	0	0
Unknown	14 (3.0)	11 (2.3)	25 (2.6)
Other	9 (1.9)	10 (2.1)	19 (2.0)

One subject who received sunitinib + erlotinib had a Grade 5 adverse event (AE) of death that occurred within 28 days of the last dose of study medication recorded on AE page. AE page stated that this Grade 5 AE was associated with study treatment and the Investigator term of the AE was "unknown cause of death." Notice of death stated that the cause of death was "unknown" for this subject. Therefore, the subject was summarized as a subject who died due to unknown reason on study in this table.

One subject who received erlotinib had a Grade 5 AE of pulmonary hemorrhage that occurred within 28 days of the last dose of study medication recorded on AE page. AE page stated that this Grade 5 AE was associated with the study treatment and the Investigator term of the AE was "death due to pulmonary haemorrhage." Notice of death stated that the cause of death was "other (pulmonary hemorrhage)" for this subject. Therefore, the subject was summarized as a subject who died due to other reasons on study in the table.

One subject who received erlotinib had a Grade 5 AE of lung disorder that occurred within 28 days of the last dose of study medication recorded on AE page. AE page stated that this Grade 5 AE was associated with the study treatment and the Investigator term of the AE was "interstitial pneumopathy." Notice of death stated that the cause of death was "other (interstitial pneumopathy)" for this subject. Therefore, stated that the cause of death was "other (interstitial pneumopathy)" for this subject. Therefore, the subject was summarized as a subject who died due to other reasons on study in the table.

N = number of subjects; n = number of subjects with specified criteria.

a. On-study deaths are those that occurred after the first dose of study drug and within 28 days of the last dose of study drug. Subjects could have more than 1 cause of death specified.

b. Follow-up deaths are those that occurred more than 28 days after the last dose of study drug. Subjects could have more than 1 cause of death specified.

Other Safety Related Findings: The most common Grade 3/4 laboratory abnormalities observed included lymphopenia and hypophosphatemia; the incidence of these abnormalities was higher in the erlotinib + sunitinib group. Overall, there were no clinically important trends in the clinical laboratory, vital signs, ECG, and LVEF evaluations.

CONCLUSIONS:

- There was no statistically significant prolongation in OS. Median OS was 9.0 months for sunitinib plus erlotinib and 8.5 months for erlotinib. Survival probability at 1 year was 40% for sunitinib plus erlotinib and 37% for erlotinib.

- There was a statistically significant prolongation in PFS. Median PFS was 15.5 weeks for sunitinib plus erlotinib and 8.7 weeks for erlotinib.

- A greater ORR (CR or PR) was observed in the sunitinib + erlotinib group versus the erlotinib group (10.6% versus 6.9%). Five subjects had a CR; all were in the sunitinib + erlotinib group.

- Median DR was 39.6 weeks for the sunitinib + erlotinib group and 32.3 weeks for the erlotinib group.

- The combination of erlotinib + sunitinib was well tolerated. The most common AEs reported for both treatment arms were diarrhea and rash – known toxicities of both sunitinib and erlotinib.

    - The incidence of diarrhea was markedly higher in the erlotinib + sunitinib arm compared to the erlotinb group (72.5% versus 39.6%).

    - While the overall incidence of rash was comparable between the 2 treatment groups, the incidence of Grade 3 rash was higher in the erlotinib + sunitinib arm (12.7% versus 6.1%).

- On-study deaths due to AEs that were considered to be related to erlotinib or sunitinib/placebo were reported for 4 subjects in the sunitinib + erlotinib group (unknown cause of death, meningeal hemorrhage, respiratory infection, unconsciousness) and 4 subjects in the erlotinib group (pulmonary hemorrhage, pulmonary interstitial disease, interstitial pneumopathy, and subdural hemorrhage).

- Excluding disease progression, the most common SAEs observed in both treatment arms included diarrhea, dyspnea, asthenia and vomiting.

- The most common Grade 3/4 laboratory abnormalities observed included lymphopenia and hypophosphatemia; the incidence of these abnormalities was higher in the erlotinib + sunitinib group.

- Overall, there were no clinically important trends in the clinical laboratory, vital signs, ECG, and LVEF evaluations.

- Mean EQ-5D health index scores in both the sunitinib + erlotinib and erlotinib treatment groups remained stable during treatment cycles compared to Baseline.