Name of Sponsor/Company: Astellas Pharma Global Development, Inc		
Name of Finished Product: OSI-906 Tablets		
Name of Active Ingredient: Linsitinib		

SYNOPSIS

Title of Study: A Randomized, Double-Blind, Placebo-controlled Phase 2 Study of Maintenance OSI-906 plus Erlotinib (Tarceva®), or Erlotinib plus Placebo in Patients with Nonprogression Following Four Cycles of 1st – line Platinum-based Chemotherapy for Advanced Non-small Cell Lung Carcinoma (NSCLC)

Investigators/Coordinating Investigator: [redacted] PhD, FRCP

Study Center(s): 80 in total in Brazil (15 sites), Canada (7), Germany (13), Poland (6), Romania (7), Russia (8), South Korea (8), United Kingdom (7), and the United States (9)

Publication Based on the Study: Not applicable

Study Period: Mar 2011 to Jul 2013

Study Initiation Date (Date of First Enrollment): 04 Mar 2011

Study Completion Date (Date of Last Evaluation): 01 Jul 2013

Phase of Development: Phase 2

Objectives: The primary objective of this study was to determine progression-free survival (PFS) of maintenance linsitinib plus erlotinib (Arm A), or placebo plus erlotinib (Arm B) in patients with nonprogression following 4 cycles of first-line platinum-based chemotherapy for advanced NSCLC.

The secondary objectives were to evaluate:

- Epidermal growth factor receptor (EGFR) mutation positive and EGFR mutation negative subsets
- PFS in the squamous and nonsquamous subsets
- Disease control rate (DCR)
- Response upgrade rate (RUR)
- Best overall response rate (ORR)
- Duration of response
- Overall survival (OS)
- The safety profile of OSI-906/erlotinib combination
- The pharmacokinetic (PK) profile of OSI-906/erlotinib combination
- Tissue analyses looking at protein expression – including the relationship between E-cadherin and vimentin expression and clinical outcomes (PFS and OS)
- Exploratory biomarkers and correlations with treatment outcome

Methodology: This multicenter, randomized, double-blind, placebo-controlled, phase 2 study evaluated the efficacy and safety of maintenance treatment of linsitinib in combination with erlotinib, in patients with nonprogression following 4 cycles of first-line platinum-based chemotherapy for advanced NSCLC. Adult patients were randomized 1:1 to receive either linsitinib 150 mg twice daily (bid) in combination with erlotinib

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150 mg once daily (qd) or placebo in combination with erlotinib 150 mg qd. Study patients were stratified according to 4 stratification factors: EGFR mutation status (wild-type vs. activating mutations - exon 19 deletion/exon 21 L858R point mutation), histology (squamous vs. nonsquamous), response to prior platinum-based chemotherapy (complete response [CR]/partial response [PR] vs. stable disease [SD]) and smoking history (never vs. former vs. current).

Number of Patients (Planned, Enrolled and Analyzed): The study planned to enroll 200 patients (100 per treatment arm). A total of 205 patients (103 in the placebo/erlotinib arm and 102 in the linsitinib/erlotinib arm) were enrolled in this study, randomized and included in the full analysis set (FAS), 201 of whom received at least 1 dose of study drug while in the study (101 in the placebo/erlotinib arm and 100 in the linsitinib/erlotinib arm) and comprised the safety analysis set. All 201 patients treated had at least 1 blood sample collected for pharmacokinetic analyses and comprised the pharmacokinetic analysis set.

Diagnosis and Main Criteria for Inclusion: Male or female patients ≥ 18 years old with histologically confirmed advanced or metastatic NSCLC stages IIIB or IV, and with confirmed EGFR mutation status. Eligible patients were to have CR, PR or SD following completion of 4 cycles of first-line platinum-based chemotherapy and were not to have disease progression at the time of entry. Patients with SD or PR were to have measurable disease according to the Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 criteria and an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 to 1. A maximum interval of 28 days between the last day of the treatment cycle and randomization was required. Previously completed first-line combination bevacizumab therapy was permitted; however, current use of maintenance bevacizumab was not permitted. Patients were to have recovered from prior chemotherapy-related toxicity to ≤ Grade 2. Previous adjuvant or neo-adjuvant treatment was permitted. The following laboratory results were also required for study inclusion: fasting glucose ≤ 150 mg/dL (8.3 mmol/L), neutrophil count ≥ $1.5x10^9$/L, platelet count ≥ $100x10^9$/L, bilirubin ≤ 1.5 x upper limit of normal (ULN), aspartate aminotransferase and alanine aminotransferase ≤ 2.5x ULN, or ≤ 5xULN if the patient had documented liver metastases, serum creatinine ≤ 1.5x ULN, potassium, magnesium and calcium within normal limits.

The main exclusion criteria for patients in this study included prior exposure to agents directed at the human EGFR axis; prior therapy with an insulin-like growth factor-1 receptor (IGF-1R); malignancies other than NSCLC within the past 3 years (excluding basal or squamous cell carcinoma of skin; locally advanced prostate cancer; ductal carcinoma in situ of breast; in situ cervical carcinoma and superficial bladder cancer if curatively treated); diabetes mellitus currently requiring insulinotropic or insulin therapy; concurrent use of maintenance bevacizumab or proton pump inhibitors such as omeprazole, but H2-receptor antagonists such as ranitidine were not excluded; symptomatic brain metastases that were not stable, required steroids or had required radiation and/or other related treatment (i.e., anti-epileptic medication) within 21 days prior to randomization; history of poorly controlled gastrointestinal disorders that could affect the absorption of study drug; history (within last 180 days) of significant cardiovascular disease unless the disease was well controlled; history of arrhythmia (multifocal premature ventricular contractions, bigeminy, trigeminy, ventricular tachycardia or uncontrolled

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atrial fibrillation) that was symptomatic or required treatment (≥ Grade 3), left bundle branch block or asymptomatic sustained ventricular tachycardia, but patients with atrial fibrillation controlled by medication were not excluded; mean Fredericia's corrected QT interval ≥ 450 msec at screening, and the use of drugs that had a known risk of causing Torsades de Pointes were prohibited within 14 days prior to randomization; use of potent cytochrome (CYP)1A2 inhibitors such as ciprofloxacin and fluvoxamine, but other less potent CYP1A2 inhibitors/inducers were not excluded; use of potent CYP3A4 inhibitors; a history of cerebrovascular accident within 180 days prior to randomization or that resulted in ongoing neurologic instability; active infection or a serious underlying medical condition (including any type of active seizure disorder within 12 months prior to randomization).

Test Product, Dose and Mode of Administration: The Sponsor supplied linsitinib as tablets containing 150, 100, or 25 mg of free base of linsitinib plus excipients in 60 cc high-density polyethylene bottles with induction seal liner and child resistant closure.

Patients in the linsitinib/erlotinib arm received linsitinib 150 mg bid administered orally in addition to the approved single agent dose of erlotinib, 150 mg qd, administered orally for 21 days in a treatment period (TP). Dose modifications of either linsitinib or erlotinib were allowed, at the discretion of the investigator. Following the recommendation of the Data Monitoring Committee (DMC), treatment with linsitinib was discontinued and patients continued on the label-recommended dose of 150 mg erlotinib qd, as clinically tolerated until the discontinuation criteria were met (as described in Duration of Treatment).

Duration of Treatment (or Duration of Study, if applicable): Treatment with the study drug was planned to continue until the stated objectives of the trial were able to be evaluated for the purpose of the final analysis, or until the patient met any of the criteria for discontinuation: disease progression as determined by radiologic evaluation or symptomatic progression, as assessed by the investigator; adverse event (AE) resulting in death or requiring withdrawal from the study; failure to recover from hematological and/or nonhematological toxicity despite a dosing interruption of up to 14 days; and/or medical or ethical reasons including noncompliance; patient request (for reasons other than AE).

Reference Product, Dose and Mode of Administration: Placebo tablets were supplied by the sponsor for oral administration made to the same formulation as the active tablets, with an equivalent amount of lactose replacing the active pharmaceutical ingredient. The placebo tablets and bottles in which they were supplied were identical in appearance to the active tablets.

Patients in the placebo/erlotinib arm received placebo administered orally bid in addition to the approved single agent dose of erlotinib, 150 mg qd, administered orally for 21 days in a TP. Dose modifications of either placebo or erlotinib were allowed, at the discretion of the investigator. Following the recommendation of the DMC, treatment with placebo was discontinued and patients continued on the label-recommended dose of 150 mg erlotinib qd, as clinically tolerated, until the discontinuation criteria were met (as described in Duration of Treatment). The intake of placebo tablets was stopped at this point in the placebo/erlotinib arm.

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Criteria for Evaluation: The primary efficacy variable was PFS, defined as the time from randomization to disease progression based on RECIST v1.1 as assessed by the investigator, or until death due to any cause, whichever occurred first. The secondary efficacy variables included OS, DCR, best ORR, RUR, and duration of response (CR/PR).

Pharmacokinetic data were evaluated from blood samples. Linsitinib, erlotinib and OSI-420 (a metabolite of erlotinib) plasma concentrations versus time profiles were summarized using descriptive statistics.

Exploratory biomarker analyses consisted of the evaluation of biomarkers including proteins and nucleic acids in tumor samples or protein expression from tumor samples that may be related to clinical outcomes. The following exploratory biomarkers were included: Kirsten rat sarcoma viral oncogene mutations (KRAS) and phosphatidylinositol-4, 5-bisphosphate 3-kinase, and catalytic subunit alpha (PIK3CA) mutations from plasma or tumor sample DNA. Exploratory analysis of tissue samples were also conducted to determine the relationships between expression of genes and proteins related to epithelial-to-mesenchymal transition (E-cadherin protein expression from tumor samples by means of immunohistochemistry) and insulin-like growth factor (IGF)-1 receptor signaling axes.

Safety was assessed based mainly on AEs, clinical laboratory, vital signs and physical examination, and electrocardiogram data. National Cancer Institute Common Terminology Criteria for Adverse Events v4.02 was used to evaluate and grade all AEs.

Statistical Methods: Analyses were performed using SAS® v9.1. The null hypothesis was that duration of PFS was equal between the 2 arms. The alternative hypothesis was that duration of PFS was prolonged in the linsitinib/erlotinib arm. The null hypothesis was tested using a 2-sided log-rank test at significance level 0.05 for the overall population. Kaplan-Meier survival plots were used to describe the primary endpoint of PFS in each treatment arm. Median PFS and 95% CI were estimated from the Kaplan-Meier curve. The hazard ratio (HR) of the treatment effect along with 95% confidence interval (CI) was calculated using a Cox proportional hazard model. Patients who had not progressed at the time of analysis were censored at the date of last tumor assessment where nonprogression (i.e., CR, PR or SD) was documented. PFS was also analyzed using log-rank stratified by EGFR mutation status (wild-type vs. active mutations) and histology (squamous vs nonsquamous). Hazard ratios of the treatment effect and 95% CI were calculated using Cox proportional hazard models with EGFR mutation status and histology. PFS in the squamous and nonsquamous subgroups were analyzed using the same statistical methods as those for the primary efficacy variable. OS was analyzed using the same statistical methods as those for the primary efficacy variable. Response rate variables (DCR, RUR and ORR) along with the 95% CI intervals estimated by Fisher's Exact Method were calculated for each treatment arm. Exploratory analysis was to be conducted for patient subgroups as defined by stratification factors, by biomarker data as well as by other patient baseline characteristics. The cut-off points for E-cadherin (e.g., above median, below median, highest or lowest quartile) were to be used to explore their association with

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clinical outcomes (PFS and OS). In each biomarker subgroup analysis the hazard ratio along with 95% CI was to be calculated using Cox proportional hazard models.

No formal interim analyses of efficacy were planned for this study. Safety data reviews during the trial were conducted on a periodic basis by the DMC. The DMC had reviewed unblinded safety and efficacy data 4 times and recommended continuation of the study. However, following completion of the fifth review on 17 Apr 2013, the DMC reviewed the median PFS data, at which point the median PFS of the linsitinib/erlotinib arm was 127 days and the PFS of the placebo/erlotinib arm was 124 days with a hazard ration of 1.004 and determined that there was no improvement in the linsitinib/erlotinib arm. The DMC recommended that all patients should be unblinded and discontinued from linsitinib or placebo treatment. All patients were to remain in the study continuing on the appropriate dose of erlotinib, and were to be followed up for safety according to the protocol. The DMC indicated that continuation of the combination of linsitinib plus erlotinib for individual patients would be reasonable if the patient and the physician believed there was benefit from the treatment and the maximum toxicity was no worse than Grade 2. The DMC did not identify any new safety concerns for patients being treated with linsitinib in this study. Following Astellas' review of all available data across all studies within the linsitinib program to date, the company recommended that individual patients not remain on the combination of linsitinib plus erlotinib.

Summary of Results/Conclusions: A total of 205 patients (103 in the placebo/erlotinib arm and 102 in the linsitinib/erlotinib arm) were enrolled and randomized. All but 4 patients (2 in each treatment arm) received study drug. The majority of patients in both treatment arms (86.3% of the linsitinib/erlotinib patients and 78.6% of placebo/erlotinib patients) discontinued treatment before completing the study, most (74.6% across both groups) due to disease progression. A similar proportion of patients had AEs as the primary reason for discontinuation (11.4% of linsitinib/erlotinib patients and 8.6% of placebo/erlotinib patients). In general, the baseline demographic and disease characteristics were similar between the 2 treatment arms. The majority of patients in this study were male (62.4%) and White (75.6%) or Asian (20%) with a median age of 61 years.

Efficacy/Pharmacokinetic/Pharmacodynamic Results: Overall, linsitinib in combination with erlotinib did not improve PFS or OS compared to placebo/erlotinib treatment in this study of patients with nonprogression following 4 cycles of 1st -line platinum-based chemotherapy for advanced NSCLC. No statistically significant differences were found between the 2 treatment arms in either the primary analysis of PFS, or in the secondary analyses of OS in the FAS. The ORR was slightly higher in the linsitinib/erlotinib arm (15.7%) compared with the placebo/erlotinib arm (11.7%). Among responders, the RUR was similar between treatment arms (11 [10.8%] linsitinib/erlotinib patients and 9 [8.7%] placebo/erlotinib patients).

Pharmacokinetic Results: Predose concentrations of erlotinib at steady state were similar in both the linsitinib and placebo arms. Plasma concentrations of linsitinib appeared to be similar to those in single agent studies. Overall, results from this study are consistent with previous observations from the phase 1 study OSI-906-103, indicating a lack of substantial PK drug-drug interaction between linsitinib and erlotinib.

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Pharmacodynamic Results: The analysis of E-cadherin levels showed they did not have any effect on the efficacy outcomes. In addition, the increases in plasma IGF-1 concentrations seen in this study suggest that concentrations of linsitinib sufficient to inhibit IGF-1R signaling were achieved in tissues involved in regulating IGF-1 expression in patients. Despite the increased plasma levels of IGF-1 in the linsitinib/erlotinib arm, this did not result in improved efficacy in this treatment arm. The limited numbers of KRAS and/or PIK3CA mutations and EGFR exon deletions present in the patients enrolled in this study precludes any potential analysis of the relationship of mutation status to patient outcomes.

Safety Results: At least 1 treatment-emergent adverse event (TEAE) was reported in 193 (96.0%) patients in the safety analysis set, with a similar proportion in both treatment arms. A higher proportion of linsitinib/erlotinib patients reported at least 1 drug-related TEAE (93.0% vs. 87.1% for placebo/erlotinib patients), serious TEAEs (36.0% vs. 28.7% placebo/erlotinib patients), drug-related serious TEAEs (15.0% linsitinib/erlotinib vs. 7.9% placebo/erlotinib), severe (Grade 3 or 4) TEAEs (49.0% linsitinib/erlotinib vs. 27.7% placebo/erlotinib), severe drug-related TEAEs (10.0% linsitinib/erlotinib vs. 4.0% placebo/erlotinib), or TEAEs leading to permanent discontinuation of study drug (15.0% linsitinib/erlotinib vs. 10.9% placebo/erlotinib).

Dose interruptions and dose reductions also occurred with a higher incidence in the linsitinib/erlotinib arm than in the placebo/erlotinib arm. A larger proportion of patients in the linsitinib/erlotinib arm than in the placebo/erlotinib arm had dose reductions of linsitinib (45.0% vs. 26.7% of placebo in the placebo/erlotinib arm) and erlotinib (24.0% vs. 12.9% in the placebo/erlotinib arm). In both treatment arms, dose reductions were made due to drug-related toxicity (TEAE), but the incidence was higher in the linsitinib/erlotinib arm (35.6% attributed to linsitinib and 83.3% attributed to erlotinib) than in the placebo/erlotinib arm (11.1% attributed to placebo and 69.2% attributed to erlotinib). A similar proportion of patients had interruptions in either linsitinib (52.0%) or placebo (49.5%) during the study, but erlotinib was interrupted in 55.0% of patients in the linsitinib/erlotinib arm compared to only 38.6% of patients in the placebo/erlotinib arm. Dose interruptions were made due to drug-related toxicity in both treatment groups, but the incidence was higher in the linsitinib/erlotinib arm (53.8% due to linsitinib and 56.4% due to erlotinib) than in the placebo/erlotinib arm (18.0% due to placebo and 33.3% due to erlotinib). Nonetheless, the median duration of exposure to active treatment was similar in the 2 treatment arms.

One patient in the linsitinib/erlotinib arm died during treatment in this study ([redacted]). A further 11 patients died within 30 days of the last dose of the study drug: 6 (6.0%) patients in the linsitinib/erlotinib arm and 5 (5.0%) patients in the placebo/erlotinib arm. None of the 12 deaths were considered to be related to the study drug by the investigator and were mainly due to disease progression and respiratory conditions.

The combination of linsitinib with erlotinib in this study resulted in a small increase in the incidence of hepatic toxicities compared to treatment with erlotinib alone. There was an increased incidence of clinically significant changes in hepatic function in the linsitinib/erlotinib arm compared to the placebo/erlotinib arm, and a larger

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proportion of linsitinib/erlotinib than placebo/erlotinib patients had clinically significant liver function test (LFT) results, namely alanine aminotransferase (ALT) or aspartate aminotransferase (AST) that was > 3xULN and/or total bilirubin (TBL) that was > 2xULN. However, there were only 3 patients (2 linsitinib/erlotinib, 1 placebo/erlotinib) who experienced TEAEs in the system organ class (SOC) of hepatobiliary disorders. Liver metastases were not reported at baseline or for any subsequent visits in these patients with clinically significant LFTs.

CONCLUSIONS: The study was stopped prematurely after the DMC reviewed the PFS and safety data, and determined that there was no improvement in patients in the linsitinib/erlotinib arm. At the recommendation of the DMC, patients were unblinded and discontinued from linsitinib treatment.

Overall, linsitinib in combination with erlotinib did not improve either the PFS or OS compared to placebo/erlotinib treatment, in this study of patients with NSCLC with nonprogression following 4 cycles of first-line platinum-based chemotherapy.

Generally, the TEAE profile in both treatment arms was consistent with what would be expected in a population of patients with advanced NSCLC being treated with erlotinib. While the proportion of patients with any TEAE was similar between the treatment arms, most other categories of TEAEs (drug-related, serious, severe, leading to permanent discontinuation of study drug) were reported by a higher proportion of patients in the linsitinib/erlotinib group than in the placebo/erlotinib group, including drug-related TEAEs that resulted in drug reductions or interruptions.

Thus, in conclusion, the combination of linsitinib with erlotinib in this study did not improve efficacy compared to erlotinib alone and was associated with a less favorable safety profile.

Date of Report: 25 Jun 2014

Table 1 Patient Disposition

Population	Number (%) of patients		
	Placebo/ Erlotinib	**Linsitinib/ Erlotinib**	**Total**
Full Analysis Set	103 (100)	102 (100)	205 (100)
Safety Analysis Set	101 (98.1)	100 (98.0)	201 (98.0)
Pharmacokinetic Analysis Set	101 (98.1)	100 (98.0)	201 (98.0)
Discontinued treatment (Full Analysis Set)	81 (78.6)	88 (86.3)	169 (82.4)
Primary reason for discontinuation			
Disease progression	63 (77.8)	63 (71.6)	126 (74.6)
Symptomatic progression	6 (7.4)	8 (9.1)	14 (8.3)
Adverse event	7 (8.6)	10 (11.4)	17 (10.1)
Withdrew consent	2 (2.5)	6 (6.8)	8 (4.7)
Medical or ethical reasons	3 (3.7)	1 (1.1)	4 (2.4)
Deaths			
Adverse event resulting in death	6 (5.8)	7 (6.9)	13 (6.3)
Death within 30 days of last treatment	5 (4.9)	7 (6.9)	12 (5.9)

Full Analysis Set includes all randomized patients. Safety Analysis Set includes all randomized patients who took at least 1 dose of study drug. Pharmacokinetic Analysis Set includes all randomized patients who received study drug and for whom at least 1 blood sample was collected for measurement of the plasma concentrations of linsitinib or erlotinib, and for whom the time of sampling and the time of dosing on the day of sampling is known.
Source: Table 12.1.1.1 and Table 12.1.1.3

Table 2 Demographic Characteristics (Full Analysis Set)

Characteristic	Placebo/ Erlotinib (N = 103)	Linsitinib/ Erlotinib (N = 102)	Total (N = 205)
Gender, n (%)			
Male	66 (64.1)	62 (60.8)	128 (62.4)
Female	37 (35.9)	40 (39.2)	77 (37.6)
Race, n (%)			
White	77 (74.8)	78 (76.5)	155 (75.6)
Black	1 (1.0)	4 (3.9)	5 (2.4)
Asian	24 (23.3)	17 (16.7)	41 (20.0)
Other	1 (1.0)	3 (2.9)	4 (2.0)
Age (years), n (%)			
≤ 65	72 (69.9)	64 (62.7)	136 (66.3)
> 65	31 (30.1)	38 (37.3)	69 (33.7)
Mean (standard deviation)	60.3 (8.93)	60.7 (9.92)	60.5 (9.42)
Median	60.0	62.0	61.0
Minimum – maximum	40 - 83	36 - 81	36 - 83
Weight (kg)			
Mean (standard deviation)	70.7 (15.22)	69.3 (15.12)	70.0 (15.15)
Median	68.0	69.7	68.6
Minimum – maximum	44 - 117	37 - 100	37 - 117
Height (cm)			
Mean (standard deviation)	167.8 (10.49)	167.1 (10.0)	167.5 (10.23)
Median	168.7	168.0	168.0
Minimum – maximum	146 - 190	144 - 191	144 - 191
ECOG PS, n (%)			
0	32 (31.1)	36 (35.3)	68 (33.2)
1	71 (68.9)	66 (64.7)	137 (66.8)
Cigarette smoking history, n (%)			
Former smoker	60 (58.3)	59 (57.8)	119 (58.0)
Never smoked	20 (19.4)	20 (19.6)	40 (19.5)
Current smoker	23 (22.3)	23 (22.5)	46 (22.4)

Full Analysis Set: all randomized patients
ECOG: Eastern Cooperative Oncology Group; N: total number of patients in Full Analysis Set; n: number of patients; PS: performance status.
Source: Table 12.1.2.1.2 and Table 12.1.1.2

Table 3 Efficacy Results (Full Analysis Set)

Efficacy Variables	Placebo/ Erlotinib (N =103)	Linsitinib/ Erlotinib (N =102)	Unstratified Analysis	
			Hazard Ratio † (95% CI)	p-value‡
PFS				
Number of patients with event, n (%)	75 (72.8)	74 (72.5)		
Median (days) [95% CI]	129 [88;158]	125 [88;167]	1.090 [0.788;1.507]	0.6014
25% and 75% Quartiles (days)	50;246	50;230		
OS				
Number of patients with events, n (%)	38 (36.9)	44 (43.1)		
Median (days) [95% CI]	421 [367;NE]	381 [316;672]	1.200 [0.777;1.853]	0.4094
25% and 75% Quartiles	235;NE	197;672		
ORR §				
Number of patients (%)	12 (11.7)	16 (15.7)		
[95% CI]	[6.17;19.47]	[9.24;24.22]		

CI: confidence interval; N: total number of patients in full analysis set; n: number of patients; NE: median OS not estimable; ORR: objective response rate; OS: overall survival; PFS: progression-free survival.
† Hazard ratio for linsitinib/erlotinib arm vs placebo/erlotinib arm estimated by Cox Proportional Harvard model. Assuming proportional hazards, a hazard ratio less than 1 indicates a reduction in hazard rate in favor of linsitinib.
‡ p-value calculated by log-rank test for PFS and OS.
§ Estimate; 95% CI based on Fisher's exact method.
Source: Table 12.3.1.1, Table 12.3.1.3, and Table 12.3.3

Table 4 Most Common Treatment-emergent Adverse Events Occurring in ≥ 10% Patients in Any Treatment Arm (Safety Analysis Set)

	Number (%) of Patients					
	Placebo/Erlotinib (N = 101)		Linsitinib/Erlotinib (N = 100)		Total (N = 201)	
Preferred Term †	**All Grades**	**Grade 3/4**	**All Grades**	**Grade 3/4**	**All Grades**	**Grade 3/4**
Drug eruption	59 (58.4)	4 (4.0)	67 (67.0)	8 (8.0)	126 (62.7)	12 (6.0)
Diarrhoea	33 (32.7)	2 (2.0)	44 (44.0)	5 (5.0)	77 (38.3)	7 (3.5)
Decreased appetite	21 (20.8)	1 (1.0)	30 (30.0)	3 (3.0)	51 (25.4)	4 (2.0)
Nausea	19 (18.8)	0	22 (22.0)	2 (2.0)	41 (20.4)	2 (1.0)
Vomiting	17 (16.8)	1 (1.0)	19 (19.0)	2 (2.0)	36 (17.9)	3 (1.5)
Cough	20 (19.8)	0	15 (15.0)	0	35 (17.4)	0
Pruritus	19 (18.8)	0	15 (15.0)	0	34 (16.9)	0
Fatigue	13 (12.9)	2 (2.0)	17 (17.0)	3 (3.0)	30 (14.9)	5 (2.5)
Dyspnoea	18 (17.8)	3 (3.0)	11 (11.0)	0	29 (14.4)	3 (1.5)
Hyperglycaemia	8 (7.9)	0	19 (19.0)	5 (5.0)	27 (13.4)	5 (2.5)
Dry skin	12 (11.9)	0	12 (12.0)	2 (2.0)	24 (11.9)	2 (1.0)
Alanine aminotransferase increased	9 (8.9)	2 (2.0)	14 (14.0)	4 (4.0)	23 (11.4)	6 (3.0)
Blood creatinine increased	10 (9.9)	0	11 (11.0)	1 (1.0)	21 (10.4)	1 (0.5)
Paronychia	12 (11.9)	0	9 (9.0)	2 (2.0)	21 (10.4)	2 (1.0)
Stomatitis	6 (5.9)	1 (1.0)	11 (11.0)	1 (1.0)	17 (8.5)	2 (1.0)
Asthenia	4 (4.0)	0	12 (12.0)	5 (5.0)	16 (8.0)	5 (2.5)
Dyspepsia	11 (10.9)	0	5 (5.0)	0	16 (8.0)	0

N: number of patients in the safety set analysis.
† Sorted in descending incidence in the Total, All Grades group.
Source: Table 12.6.1.6 and Table 12.6.1.2.

Table 5 Summary of Serious Treatment-emergent Adverse Events in ≥ 2 Patients (Safety Analysis Set)

Primary System Organ Class Preferred Term†	Number of Patients (%)		
	Placebo/Erlotinib (N = 101)	Linsitinib/Erlotinib (N = 100)	Total (N = 201)
All Systems, Any AE	29 (28.7)	36 (36.0)	65 (32.3)
Respiratory, thoracic and mediastinal disorders	7 (6.9)	8 (8.0)	15 (7.5)
Cough	2 (2.0)	0	2 (1.0)
Dyspnoea	5 (5.0)	1 (1.0)	6 (3.0)
Pulmonary embolism	0	2 (2.0)	2 (1.0)
Respiratory failure	1 (1.0)	2 (2.0)	3 (1.5)
Gastrointestinal disorders	3 (3.0)	10 (10.0)	13 (6.5)
Abdominal pain	1 (1.0)	1 (1.0)	2 (1.0)
Diarrhoea	0	3 (3.0)	3 (1.5)
Duodenal ulcer	1 (1.0)	1 (1.0)	2 (1.0)
Vomiting	1 (1.0)	1 (1.0)	2 (1.0)
Infections and infestations	6 (5.9)	7 (7.0)	13 (6.5)
Cellulitis	0	2 (2.0)	2 (1.0)
Pneumonia	1 (1.0)	1 (1.0)	2 (1.0)
Respiratory tract infection	1 (1.0)	1 (1.0)	2 (1.0)
Investigations	3 (3.0)	6 (6.0)	9 (4.5)
Alanine aminotransferase increased	1 (1.0)	2 (2.0)	3 (1.5)
Aspartate aminotransferase increased	1 (1.0)	1 (1.0)	2 (1.0)
Blood creatinine increased	1 (1.0)	3 (3.0)	4 (2.0)
Liver function test abnormal	1 (1.0)	1 (1.0)	2 (1.0)
Metabolism and nutrition disorders	4 (4.0)	10 (10.0)	14 (7.0)
Decreased appetite	3 (3.0)	7 (7.0)	10 (5.0)
Hyperglycaemia	0	3 (3.0)	3 (1.5)
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	5 (5.0)	4 (4.0)	9 (4.5)
Malignant neoplasm progression	2 (2.0)	1 (1.0)	3 (1.5)
Metastases to central nervous system	1 (1.0)	1 (1.0)	2 (1.0)
Metastatic pain	1 (1.0)	1 (1.0)	2 (1.0)
Nervous system disorders	4 (4.0)	1 (1.0)	5 (2.5)
Cerebrovascular accident	2 (2.0)	0	2 (1.0)
Vascular disorders	1 (1.0)	2 (2.0)	3 (1.5)
Deep vein thrombosis	1 (1.0)	1 (1.0)	2 (1.0)

AE: adverse event.
† Medical Dictionary for Regulatory Activities (MedDRA) v.13.1.
Within a System Organ Class, patients may have reported more than one type of AE. At each level of summarization, a patient was counted only once if one or more events were reported.
Source: Table 12.6.1.4