Name of Sponsor/Company: Astellas Pharma Global Development, Inc. on behalf of OSI Pharmaceuticals, LLC.		
Name of Finished Product: Tarceva®		
Name of Active Ingredient: Erlotinib		

SYNOPSIS

Title of Study: A Two-Stage Phase 1 Dose Escalation Pharmacokinetic Study of Tarceva® (erlotinib) in Patients with Stage IIIB/IV Non-Small Cell Lung Cancer who Continue to Smoke After Failure of One or Two Prior Chemotherapy Regimens

Investigators/Coordinating Investigator: This study was conducted by multiple investigators across the United States the United Kingdom. Dr [redacted] MBBS, MRCP, PhD served as a coordinating investigator for this study.

Study Center(s): The patients from this study were enrolled at 9 investigational sites, 7 in the UK and 2 in the US. UK sites included: [redacted]. US sites included: [redacted].

Publication Based on the Study:

Hughes AN, O'Brien M, Dunlop D, Petty W, Rankin E, Chick J et al. Phase I dose escalation pharmacokinetic study of erlotinib after failure of prior chemotherapy in patients with advanced NSCLC who continue to smoke. J Clin Oncol. 2007;25(18S):161s [Abstract 3597].

Woll P, Petty W, O'Brien M, Rankin E, Dunlop D, Hughes A et al. Randomized phase I pharmacokinetic study of two doses of erlotinib after failure of prior chemotherapy in patients with advanced NSCLC who continue to smoke. J Thorac Oncol. 2007;2(8 Suppl 4):S463 [Abstract PD3-2-3].

Study Period:

Part I: approximately 10 months

Part II: approximately 10 months

Extended treatment phase: from 15 to 315 days

Study Initiation Date (Date of First Patient Treated):

Part I: 31 Jan 2006

Part II: 01 Nov 2006

Extended treatment phase: 15 Nov 2006

Study Completion Date (Date Last Patient Registered or Randomized):

Part I: 17 Oct 2006

Part II: 03 Aug 2007

Extended treatment phase: 23 May 2014

Phase of Development: Phase 1

Objectives:

The primary objective of Part I of this study was to establish the maximum tolerated dose (MTD) of erlotinib in currently smoking patients with stage IIIB/IV non-small cell lung cancer (NSCLC).

The primary objective of Part II of this study was to evaluate the steady-state pharmacokinetics of erlotinib in currently smoking patients with stage IIIB/IV NSCLC when given erlotinib at the MTD as compared with 150 mg.

A secondary objective of Part II of this study was to evaluate the survival of currently smoking patients with stage IIIB/IV NSCLC when given erlotinib at the MTD and 150 mg.

Methodology:

This was a 2-part, multicenter, open-label, randomized, phase 1 study of escalating doses of erlotinib in patients with advanced (stage IIIB/IV) NSCLC who currently smoke cigarettes. Part I was a traditional 3 + 3 patient dose-escalation study to determine the MTD, while Part II was open-label and randomized between the MTD from Part I and 150 mg erlotinib daily. In order to have participated in the study, patients must have had a histologically or a cytologically confirmed diagnosis of stage IIIB/IV NSCLC and must have received 1 or 2 prior chemotherapy regimens for advanced NSCLC and had progressive disease. They must also have been a current cigarette smoker (minimum of 10 cigarettes per day for ≥ 1 year with a positive test for cotinine) despite advice and support to quit.

Safety was evaluated on days 7 (Part I patients only) and 14 (all patients). Laboratory abnormalities and all adverse events spontaneously reported, elicited, or observed by the investigator were recorded. A dose-limiting toxicity (DLT) was defined as any grade 3 related nonhematological toxicity that occurred within the first 14 days of treatment. The MTD was defined as the highest dose level achieved where < 2/6 patients experienced a DLT.

Once the MTD for current smokers was established, a pharmacokinetic element of the study (Part II) began. Patients who had not participated in Part I were randomized 1:1 to 2 treatment groups: Arm A or Arm B. Patients in Arm A were treated with the MTD of erlotinib established in Part I, while patients in Arm B were treated with erlotinib 150 mg/day. Patients in both Arms A and B were treated for 14 days and had pharmacokinetic samples collected on days 14 and 15 to determine the steady-state pharmacokinetics of erlotinib and its active metabolite OSI-420.

Upon completion of 14 days of erlotinib dosing, full evaluation of any toxicities, and all pharmacokinetic sampling (for patients entered into Part II), patients may have entered an extended treatment phase and continued to receive oral erlotinib at the investigator's discretion until disease progression, intolerable toxicity, patient request to discontinue therapy, or death. The extended phase erlotinib dose was determined at the Investigator's discretion.

At the time of the database lock (26 Sep 2007), 17 patients (1 from Part I and 16 from Part II) remained on study drug as described in the original clinical study report (CSR) (dated 02 Nov 2007). Data collected into the database subsequent to lock for the original CSR consisted of safety and survival data. All grade 3/4 AEs and all serious adverse events (SAEs) were to be reported via the ARGUS safety database for the extended and long-term follow-up periods rather than in the clinical database. Only AEs of grade 3 or 4 severity that were considered related to Tarceva treatment were to be reported during the extended treatment phase. The actual grade for each event was not captured.

No cleaning was performed on any of the data received subsequent to the database lock.

No conclusions in the original report have changed as a result of the additional analysis.

Number of Patients (Planned, Enrolled and Analyzed):

Part I: 15-22 patients planned; 22 analyzed

Part II: 44 (22/arm) planned; 35 (17/18) analyzed

Diagnosis and Main Criteria for Inclusion:

Eligible patients were current cigarette smokers with stage IIIB/IV NSCLC after failure of 1 or 2 prior chemotherapy regimens who continued to smoke throughout the study duration, had an Eastern Cooperative Oncology Group Performance Status (ECOG) PS of 0 or 1, had received no prior treatment with epidermal growth factor receptor (EGFR) inhibitor therapy, were not taking concurrent cytochrome P450 (CYP)3A4 or other CYP1A2 inducers and/or inhibitors, and were not receiving other concurrent anticancer therapy.

Test Product, Dose and Mode of Administration, Batch Numbers:

Erlotinib 100 mg and 150 mg tablets were used.
Part I: erlotinib 200, 250, 300, or 350 mg/day orally according to dose escalation
Part II: Arm A: erlotinib at the MTD determined in Part I; and Arm B: erlotinib 150 mg/day orally
Lot numbers: 100 mg ( ) and 150 mg ( )

Duration of Treatment (or Duration of Study, if applicable):

All patients were to receive erlotinib at the assigned dose for up to 14 days. Upon completion of 14 days of dosing, full evaluation of any toxicities, and all pharmacokinetic sampling (for patients entered into Part II), patients may have continued to receive erlotinib at the Investigator's discretion until disease progression, intolerable toxicity, patient request, or death.

Per the protocol and the statistical analysis plan, an exploratory overall survival (OS) analysis was to be performed to evaluate survival of the Part II patients, once all patients known to be alive had been followed for at least 6 months (from the first day of erlotinib treatment in the extended treatment phase). Although 1 patient each took study drug to day 14 and day 13 (Patients and respectively), all patients were included in the OS analysis. The OS was thus calculated from the first day of the initial 14 day treatment for pharmacokinetic analysis until death or last known alive date.

Of the 35 patients in Part II, 33 entered the extended treatment phase. As stated in [Section 11.2.6] of the original CSR, survival data were not sufficiently mature at the time of the database lock to warrant statistical analysis.

Reference Product, Dose and Mode of Administration, Batch Numbers:

Not applicable for this study

Criteria for Evaluation:

MTD

A DLT was defined as any ≥grade 3 erlotinib-related, nonhematological toxicity (excluding alopecia or unpremedicated or inadequately treated nausea, vomiting, or diarrhea) occurring within the first 14 days of treatment. The MTD was defined as the highest dose level achieved at which < 2/6 patients experienced a DLT. A minimum of 6 patients must have been treated at a particular dose level for it to be considered the MTD.

Safety

Patients who received at least 1 dose of erlotinib were included in the safety analyses. For all patients, safety was evaluated on Days 7 and 14. Laboratory abnormalities and all adverse events spontaneously reported, elicited, or observed by the investigator were recorded. Toxicity was graded using the National Cancer Institute Common Terminology Criteria for Adverse Events v3.0. During the extended treatment phase, only grade 3 or 4 adverse events that were considered to be related to erlotinib were documented (along with serious adverse events and adverse events resulting in study discontinuation).

Pharmacokinetics

Patients who completed 14 days of uninterrupted dosing during Part II, had a positive cotinine test on day 14, and had evaluable pharmacokinetic profiles were included in the pharmacokinetic analyses. A plasma sample was collected at day 14 (prior to the day 14 dose) in all patients for determination of AAG concentration. In addition, pharmacokinetic samples were collected during Part II on day 14: prior to erlotinib dosing, and at 1, 2, 4, 6, 8, and 24 hours after dosing. Erlotinib and its active metabolite OSI-420 in plasma samples were quantified using a validated liquid chromatography with tandem mass spectrometry (LC/MS/MS) assay. Plasma pharmacokinetic parameters for erlotinib and OSI-420 were calculated by noncompartmental methods using WinNonlin, v5.2. α-1 acid glycoprotein concentrations were determined by a validated turbidimetric method.

Survival

Survival was defined as the time from first study drug administration until the day death was documented. Patients who were still alive were censored at the last day known to be alive.

Statistical Methods:

The primary safety endpoint during Part I was the incidence of DLT by dose cohort. Other safety endpoints during each part of the study were the incidence of patients from each dose cohort with adverse events (including serious adverse events and discontinuations due to adverse events) and the incidence of patients with a shift from baseline in hematology or biochemistry variables. The safety of erlotinib in each cohort was characterized during the 14-day study and in the extended treatment phase, but no statistical comparisons among cohorts were performed.

In Part I and Part II, adverse event incidence rates were summarized overall and by severity grade for each preferred term and system organ class. Summary tables were also generated for patients with serious adverse events, patients with related adverse events, patients who died, and patients who discontinued due to adverse

events. In all adverse event tables, a combined term RASH was created during analysis that combined preferred terms deemed representative of skin rash.

Summary statistics for pharmacokinetic parameters for each Part II dose cohort were reported. Ninety percent confidence intervals for the ratio of geometric means of $AUC_{0\text{-}tau}$ and C_{max} were calculated to characterize the relative exposure of the MTD and 150 mg/day cohorts.

Summary of Results/Conclusions:

Pharmacokinetic Results:

Part II (at the time of the original CSR): Fifteen patients in the 150 mg cohort and 17 patients in the 300 mg (MTD) cohort were evaluable for pharmacokinetic analyses. Following oral administration of erlotinib on day 14, plasma concentrations of erlotinib peaked at a median T_{max} of 2 hours in both the 150 mg and 300 mg dose cohorts. The median plasma C_{max} of erlotinib was 2.16 and 3.86 µg/mL for the 150 mg and 300 mg dose cohorts, respectively. The corresponding median $AUC_{0\text{-}tau}$ values were 19.7 and 51.1 µg hr/mL. The median steady-state trough erlotinib plasma concentration (C_{24}) was 0.375 and 1.22 µg/mL for the 150 mg and 300 mg dose cohorts, respectively. Erlotinib exposure was dose-proportional within the dose range tested in currently smoking NSCLC patients.

Efficacy Results:

Additional Overall Survival Information: Exploratory analyses were performed to evaluate the survival of the Part II patients at least 6 months from their first day of treatment with erlotinib. A total of 35 patients (n = 18 and n = 17 in Arms A and B, respectively) were evaluated. The median follow-up time in Arms A and B was 20.7 and 12.5 months, respectively. Of the 18 patients randomized to Arm A, 14 (77.8%) died and 4 (22.2%) of patients were censored at the time of evaluation. The number of deceased and censored patients in Arm B was 12 (70.6%) and 5 (29.4%), respectively. Across both treatment arms, disease progression was the most common cause of death.

The median overall survival time was comparable between the 2 treatment arms. At the time of the 6 month estimate, 11 patients in Arm A and 9 patients in Arm B remained at risk and the event free rate in Arms A and B was 0.65 (95% CI: 0.430, 0.879) and 0.53 (95% CI: 0.292, 0.767) respectively [Table 5].

Safety Results:

Part I (at the time of the original CSR): Twenty-two patients received at least 1 dose of erlotinib on Days 1 through 14 and were included in the safety analyses: 200 mg (n = 3), 250 mg (n = 6), 300 mg (n = 8), and 350 mg (n = 5). No DLTs were observed in the 200 or 250 mg cohorts. One DLT of facial rash (grade 3) was observed in 1 of 6 evaluable patients at the 300 mg dose level. At the 350 mg dose level, 2 patients experienced DLTs: grade 3 fatigue and decreased performance status ([redacted]); and grade 3 facial rash ([redacted]). The MTD was determined to be 300 mg/day.

Overall, treatment was well tolerated with common CTCAE grade 1 and 2 adverse events deemed related to erlotinib being limited to RASH (59%), diarrhea (55%), and nausea, vomiting, and pruritus (each 14%). The incidence of gastrointestinal adverse events (eg, diarrhea and nausea) was generally greater in the higher dose cohorts. No grade 4 events were reported during the initial 14-day treatment period.

Five patients experienced at least 1 serious adverse event during the initial 14-day treatment period: grade 2 lower respiratory tract infection (2 patients); grade 3 hyperkalemia (1 patient); and grade 3 tooth abscess following a dental procedure (1 patient). One of the 6 patients (250 mg cohort) experienced serious adverse events considered to be erlotinib related (dehydration, diarrhea, nausea, and vomiting). No serious adverse events were reported among patients who received 200 mg. There were no notable differences in the frequency of serious adverse events reported among the 250 mg, 300 mg, and 350 mg cohorts.

Nineteen of the 22 patients continued to receive erlotinib during the Part I extended treatment phase at the following doses: 150 mg (n = 2); 200 mg (n = 3); 250 mg (n = 5); 300 mg (n = 7); and 350 mg (n = 2). Fifteen patients experienced at least 1 adverse event during the extended treatment phase or beyond day 14, 3 of whom experienced erlotinib-related events. No patients receiving erlotinib at 150, 200, or 250 mg experienced grade 3 or 4 erlotinib related adverse events beyond day 14. Thirteen patients experienced at least 1 serious adverse event during the extended treatment phase, none of which were considered to be erlotinib related. No single type of serious adverse event occurred in more than 1 patient.

Four patients died while on study or within 30 days of the last erlotinib dose. All 4 deaths were considered to be unrelated to erlotinib. Three patients died due to progressive disease and 1 patient, who did not continue into the extended treatment phase, died due to unrelated pneumonia.

No patient experienced a grade 3 or 4 hematology or blood chemistry laboratory value during the initial 14 days. Several patients experienced hematology and/or blood chemistry laboratory values outside the normal range during the study, but all were judged to be clinically insignificant.

Part II (at the time of the original CSR): Thirty-five patients received at least 1 dose of erlotinib on days 1 through 14 and were included in the safety analyses: 17 patients in the 150 mg cohort and 18 patients in the 300 mg cohort. There was a higher incidence of adverse events in the 300 mg cohort than in the 150 mg cohort. Common adverse events, generally regarded as related to erlotinib treatment, included RASH (29% in the 150 mg cohort; 67% in the 300 mg cohort), diarrhea (18% in the 150 mg cohort; 50% in the 300 mg cohort), and fatigue (35% in the 150 mg cohort; 28% in the 300 mg cohort). Adverse events were generally mild or moderate in severity, with no reports of grade 4 adverse events and only 4 patients experiencing a grade 3 adverse event. Two patients experienced serious adverse events, neither of which was considered to be erlotinib related.

Thirty-three of the 35 patients continued to receive erlotinib during the extended treatment phase of the study (categorized by the doses patients received on the first day of the extended treatment phase): 150 mg (n = 13); 250 mg (n = 2); and 300 mg (n = 18). During this phase of the study, only serious adverse events, grade 3 or 4 related events, and adverse events leading to withdrawal were to be reported. No patients experienced grade 4 adverse events; 2 patients experienced grade 3 events. Four patients died on treatment or within 30 days of the last erlotinib dose, all due to causes unrelated to treatment with erlotinib. Ten patients experienced at least 1 serious adverse event during the extended treatment phase or beyond day 14, none of which were considered to be erlotinib related.

No patient experienced a grade 3 or 4 hematology or blood chemistry laboratory value during the initial 14 days. Several patients experienced hematology and/or blood chemistry laboratory values outside the normal range during the study, but all were judged to be clinically insignificant.

Additional Safety Information: Since the time of the database lock (26 Sep 2007), 6 patients experienced SAEs, with the majority of patients experiencing at least 2 events each. Of the events considered to be serious, only chest infection was reported to occur in more than a single patient. The other SAEs (occurring in a single patient each) included muscle weakness, progressive lung cancer, confusion, disease progression, suspected pneumonitis, respiratory infection, cataract, dehydration, infective lung abscess, vomiting, and diarrhea.

Three additional patients reported AEs of diarrhea, fatigue, abdominal pain, decreased appetite and weight loss which were not considered to be serious by the Investigator. Of these, only events of diarrhea and fatigue were reported by more than a single patient. All AEs are summarized in Table 8. The majority of AEs resolved, resulted in drug interruption and were not considered to be related to erlotinib administration by the Investigator.

Three patients died since the time of the database lock.

CONCLUSIONS:

Part I of this 2-part study determined that the MTD of erlotinib in NSCLC patients who continue to smoke cigarettes after failure of 1 or 2 regimens of chemotherapy was 300 mg/day. Part II demonstrated that erlotinib exposure was dose-proportional within the dose range tested in currently smoking cancer patients and the steady-state trough plasma concentrations in smokers treated at 300 mg/day erlotinib in the current study were similar to those in never/former smokers treated at 150 mg/day in the pivotal phase 3 study BR.21. In addition, erlotinib at 300 mg/day was generally well tolerated in NSCLC patients who continue to smoke cigarettes. Based on these findings, higher doses of erlotinib up to 300 mg/day should be considered among patients who continue to smoke cigarettes, while monitoring patient safety.

Subsequent to the database lock (26 Sep 2007) for the CSR:

- Three patient deaths were reported that were both attributed to the patients' underlying lung cancer.

- Limited safety data were collected during the extended treatment phase. Thirteen SAEs, majority of which were assessed as unrelated to study drug, were reported in 6 patients. Per Investigator's assessment, cataract [redacted] in Patient [redacted] was the only drug-related SAE. Additionally, 3 patients reported 7 AEs which were not considered as serious by the Investigator. Review of these SAEs did not reveal any new safety signals.

- A prespecified exploratory analysis was performed to estimate OS at 6 months from first erlotinib dose in the 35 patients in Part II. Given the small numbers of patients (18 and 17 patients in Arms A and B, respectively) and limited erlotinib treatment duration (2 patients discontinued erlotinib on or before day 14), interpretation of the 6 month OS estimates are limited.

Date of Report: 31 Mar 2015

Table 1 Patient Disposition: Part 1

	200 mg (N = 3)	250 mg† (N = 6)	300 mg (N = 8)	350 mg (N = 5)	Total Erlotinib (N = 22)
	n (%)	n (%)	n (%)	n (%)	n (%)
Enrolled	3 (100)	6 (100)	8 (100)	5 (100)	22 (100)
Treated	3 (100)	6 (100)	8 (100)	5 (100)	22 (100)
Evaluable for DLT	3 (100)	3 (50)	6 (75)	5 (100)	17 (77)
Off Treatment	3 (100)	6 (100)	7 (88)	5 (100)	21 (95)
Disease Progression	3 (100)	2 (33)	6 (75)	3 (60)	14 (64)
AE	0	1 (17)	1 (12)	2 (40)	4 (18)
Medical/Ethical Reason	0	0	0	0	0
Patient Request	0	1 (17)	0	0	1 (5)
Patient Death‡	0	2 (33)	0	0	2 (9)

AE: adverse event; CSR: clinical study report; DLT: dose-limiting toxicity
†Patient [redacted] in the 250 mg cohort took an incorrect dose of 150 mg during the initial 14-day treatment period.
‡Only includes patients who discontinued due to death; there were 2 additional deaths that occurred after the patients discontinued.

Source: OSI-774-107 CSR, Table 10-1

Table 2 Patient Disposition: Part II

	150 mg (N = 17)	300 mg (N = 18)	Total Erlotinib (N = 35)
	n (%)	n (%)	n (%)
Enrolled	17 (100)	18 (100)	35 (100)
Treated	17 (100)	18 (100)	35 (100)
Evaluable for Pharmacokinetics	15 (88)	17 (94)	32 (91)
Off Treatment	10 (59)	9 (50)	19 (54)
Disease Progression	6 (35)	7 (39)	13 (37)
AE	1 (6)	0	1 (3)
Medical/Ethical Reason	0	0	0
Patient Request	2 (12)	1 (6)	3 (9)
Patient Death	1 (6)	1 (6)	2 (6)

AE: adverse event

Source: OSI-774-107 CSR, Table 11-1

Table 3 Demographic Characteristics Part I

Categorical Characteristics	200 mg (N = 3) n (%)	250 mg (N = 6) n (%)	300 mg (N = 8) n (%)	350 mg (N = 5) n (%)	Total Erlotinib (N = 22) n (%)
Gender					
Female	1(33)	3(50)	4 (50)	2 (40)	10 (45)
Male	2 (67)	3 (50)	4 (50)	3 (60)	12 (55)
Race					
White	3 (100)	6 (100)	8 (100)	4 (80)	21 (95)
Black	0	0	0	1 (20)	1 (5)
Age (Years)					
40-64	1 (33)	5 (83)	6 (75)	4 (80)	16 (73)
≥ 65	2 (67)	1 (17)	2 (25)	1 (20)	6 (27)

Continuous Characteristics	Parameter	200 mg (N = 3)	250 mg (N = 6)	300 mg (N = 8)	350 mg (N = 5)	Total Erlotinib (N = 22)
Age (Years)	Median	67	58	61	58	61
	Min - Max	62 - 69	50 - 66	45 - 65	48 - 65	45 - 69
Weight (kg)	Median	70	68	64	52	64
	Min - Max	66 - 70	58 - 76	48 - 108	50 - 83	48 - 108
Height (cm)	Median	163	164	167	172	167
	Min - Max	159 - 170	157 - 181	143 - 171	157 - 179	143 - 181

Source: OSI-774-107 CSR, Table 10-2

Table 4 Demographic Characteristics Part II

Characteristics		150 mg (N = 17) n (%)	300 mg (N = 18) n (%)	Total Erlotinib (N = 35) n (%)
Gender				
Female		9 (53)	10 (56)	19 (54)
Male		8 (47)	8 (44)	16 (46)
Race				
White		16 (94)	14 (78)	30 (86)
Black		1 (6)	4 (22)	5 (14)
Age (Years)				
40-64		9 (53)	11 (61)	20 (57)
≥ 65		8 (47)	7 (39)	15 (43)
Age (Years)	Median	63	61	61
	Min - Max	50 - 78	40 - 75	40 - 78
Weight (kg)	Median	60	67	62
	Min - Max	44 - 66	45 - 109	44 - 109
Height (cm)	Median	170	164	168
	Min - Max	154-180	153-193	153-193

Source: OSI-774-107 CSR, Table 11-2

Table 5 Summary of Overall Survival: Part II Patients Only

Parameter	Arm A (n = 18)	Arm B (n = 17)
Deaths, n (%)	14 (77.8%)	12 (70.6%)
Censored, n (%)	4 (22.2%)	5 (29.4%)
Duration of Overall Survival, Months†		
Median (95% CI)	8.4 (4.6, 12.9)	8.9 (3.0, 11.3)
1st Quartile (95% CI)	4.6 (1.5, 6.3)	3.2 (1.8, 5.5)
3rd Quartile (95% CI)	12.9 (8.4, -)	11.3 (8.9, -)
Range‡	1.5 – 38.2+	1.8 – 85.8+
Median Follow-up Time, Months§	20.7 (12.9, 38.2)	12.5 (8.9, 85.8)
Overall Survival Rate, % (95% CI)¶		
3 Months Estimate		
Patients remaining at risk	16	13
Event Free Rate	0.89	0.76
95% CI for Rate	(0.744, 1.000)	(0.563, 0.966)
6 Months Estimate		
Patients remaining at risk	11	9
Event Free Rate	0.65	0.53
95% CI for Rate	(0.430, 0.879)	(0.292, 0.767)

Note: '-' indicates that the upper confidence limit of the 3rd quartile was not estimable.

CI: confidence interval

†Based on Kaplan-Meier estimate.

‡Including censored observations, '+' indicates censored observations.

§Based on reverse Kaplan-Meier estimate.

¶Survival rate and 95% CI are estimated using Kaplan-Meier method and Greenwood formula.

Source: Table 11.15

Table 6 Incidence of Patients with Adverse Events, Regardless of Causality, by Preferred Term, System Organ Class During the Initial 14 Days of Dosing: Part I

	200 mg (N = 3)		250 mg (N = 6)		300 mg (N = 8)		350 mg (N = 5)		Total Erlotinib (N = 22)	
MedDRA System Organ Class Total Preferred Term	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Total Patients With Any AE	1	(33)	6	(100)	8	(100)	5	(100)	20	(91)
Gastrointestinal disorders	1	(33)	4	(67)	6	(75)	5	(100)	16	(73)
Diarrhoea	1	(33)	4	(67)	4	(50)	4	(80)	13	(59)
Nausea	0	(0)	1	(17)	0	(0)	2	(40)	3	(14)
Vomiting	0	(0)	2	(33)	0	(0)	1	(20)	3	(14)
Constipation	0	(0)	1	(17)	1	(12)	0	(0)	2	(9)
Dry mouth	0	(0)	0	(0)	1	(12)	1	(20)	2	(9)
Dyspepsia	0	(0)	0	(0)	1	(12)	1	(20)	2	(9)
Abdominal pain upper	0	(0)	0	(0)	0	(0)	1	(20)	1	(5)
Lip dry	0	(0)	1	(17)	0	(0)	0	(0)	1	(5)
Skin and subcutaneous tissue disorders	0	(0)	4	(67)	7	(88)	4	(80)	15	(68)
RASH	0	(0)	4	(67)	6	(75)	3	(60)	13	(59)
Rash	0	(0)	3	(50)	3	(38)	1	(20)	7	(32)
Dermatitis acneiform	0	(0)	0	(0)	2	(25)	2	(40)	4	(18)
Pruritus	0	(0)	0	(0)	1	(12)	2	(40)	3	(14)
Dry skin	0	(0)	0	(0)	1	(12)	1	(20)	2	(9)
Erythema	0	(0)	0	(0)	1	(12)	0	(0)	1	(5)
Petechiae	0	(0)	1	(17)	0	(0)	0	(0)	1	(5)
Rash erythematous	0	(0)	1	(17)	0	(0)	0	(0)	1	(5)
Swelling face	0	(0)	0	(0)	0	(0)	1	(20)	1	(5)
Infections and infestations	0	(0)	2	(33)	3	(38)	1	(20)	6	(27)
Lower respiratory tract infection	0	(0)	1	(17)	1	(12)	0	(0)	2	(9)
Nasopharyngitis	0	(0)	0	(0)	1	(12)	0	(0)	1	(5)
Oral candidiasis	0	(0)	0	(0)	1	(12)	0	(0)	1	(5)
Pneumonia	0	(0)	1	(17)	0	(0)	0	(0)	1	(5)
Tooth abscess	0	(0)	0	(0)	0	(0)	1	(20)	1	(5)
Metabolism and nutrition disorders	0	(0)	2	(33)	3	(38)	1	(20)	6	(27)
Anorexia	0	(0)	1	(17)	2	(25)	1	(20)	4	(18)
Cachexia	0	(0)	0	(0)	1	(12)	0	(0)	1	(5)
Dehydration	0	(0)	1	(17)	0	(0)	0	(0)	1	(5)
Hyperkalaemia	0	(0)	0	(0)	1	(12)	0	(0)	1	(5)
Respiratory, thoracic and mediastinal disorders	0	(0)	1	(17)	3	(38)	1	(20)	5	(23)
Dyspnoea	0	(0)	1	(17)	1	(12)	0	(0)	2	(9)
Epistaxis	0	(0)	0	(0)	1	(12)	0	(0)	1	(5)
Haemoptysis	0	(0)	0	(0)	1	(12)	0	(0)	1	(5)
Pharyngolaryngeal pain	0	(0)	0	(0)	0	(0)	1	(20)	1	(5)
Wheezing	0	(0)	0	(0)	1	(12)	0	(0)	1	(5)
Eye disorders	0	(0)	0	(0)	2	(25)	2	(40)	4	(18)
Eye pain	0	(0)	0	(0)	2	(25)	1	(20)	3	(14)
Foreign body sensation in eyes	0	(0)	0	(0)	0	(0)	1	(20)	1	(5)
Lacrimation increased	0	(0)	0	(0)	1	(12)	0	(0)	1	(5)
Musculoskeletal and connective tissue disorders	0	(0)	1	(17)	1	(12)	2	(40)	4	(18)
Arthralgia	0	(0)	0	(0)	1	(12)	2	(40)	3	(14)
Back pain	0	(0)	1	(17)	1	(12)	1	(20)	3	(14)
Myalgia	0	(0)	0	(0)	1	(12)	1	(20)	2	(9)
Nervous system disorders	0	(0)	1	(17)	2	(25)	1	(20)	4	(18)
Dizziness	0	(0)	1	(17)	1	(12)	0	(0)	2	(9)
Headache	0	(0)	0	(0)	0	(0)	1	(20)	1	(5)
Paraesthesia	0	(0)	0	(0)	1	(12)	0	(0)	1	(5)

Table continued on next page

	200 mg (N = 3)		250 mg (N = 6)		300 mg (N = 8)		350 mg (N = 5)		Total Erlotinib (N = 22)	
MedDRA System Organ Class Total Preferred Term	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
General disorders and administration site conditions	0	(0)	1	(17)	0	(0)	1	(20)	2	(9)
Fatigue	0	(0)	0	(0)	0	(0)	1	(20)	1	(5)
Influenza like illness	0	(0)	1	(17)	0	(0)	0	(0)	1	(5)
Performance status decreased	0	(0)	0	(0)	0	(0)	1	(20)	1	(5)
Cardiac disorders	0	(0)	0	(0)	1	(12)	0	(0)	1	(5)
Palpitations	0	(0)	0	(0)	1	(12)	0	(0)	1	(5)
Ear and labyrinth disorders	0	(0)	0	(0)	1	(12)	0	(0)	1	(5)
Hypoacusis	0	(0)	0	(0)	1	(12)	0	(0)	1	(5)

AE: adverse event

Note: Patient [redacted] in the 250 mg cohort received 150 mg in error.

Note: Excludes progressive disease

Source: Table 13-5

Table 7 Incidence of Patients with Adverse Events, Regardless of Causality, by Preferred Term, System Organ Class During the Initial 14 Days of Dosing: Part II

	150 mg (N = 17)		300 mg (N = 18)		Total Erlotinib (N = 35)	
MedDRA System Organ Class Total Preferred Term	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Total Patients With Any AE	14	(82)	18	(100)	32	(91)
Skin and subcutaneous tissue disorders	9	(53)	13	(72)	22	(63)
RASH	5	(29)	12	(67)	17	(49)
Rash	5	(29)	6	(33)	11	(31)
Pruritus	1	(6)	4	(22)	5	(14)
Dermatitis acneiform	0	(0)	4	(22)	4	(11)
Dry skin	3	(18)	1	(6)	4	(11)
Rash pustular	0	(0)	1	(6)	1	(3)
Rosacea	0	(0)	1	(6)	1	(3)
Scab	1	(6)	0	(0)	1	(3)
Skin fissures	0	(0)	1	(6)	1	(3)
Gastrointestinal disorders	8	(47)	13	(72)	21	(60)
Diarrhoea	3	(18)	9	(50)	12	(34)
Nausea	3	(18)	3	(17)	6	(17)
Constipation	1	(6)	2	(11)	3	(9)
Mouth ulceration	2	(12)	0	(0)	2	(6)
Stomatitis	1	(6)	1	(6)	2	(6)
Vomiting	1	(6)	1	(6)	2	(6)
Chapped lips	1	(6)	0	(0)	1	(3)
Dry mouth	0	(0)	1	(6)	1	(3)
Dysgeusia	1	(6)	0	(0)	1	(3)
Dyspepsia	0	(0)	1	(6)	1	(3)
Lip pain	0	(0)	1	(6)	1	(3)
Oral pain	0	(0)	1	(6)	1	(3)
Stomach discomfort	1	(6)	0	(0)	1	(3)
General disorders and administration site conditions	7	(41)	6	(33)	13	(37)
Fatigue	6	(35)	5	(28)	11	(31)
Asthenia	0	(0)	1	(6)	1	(3)
Chills	1	(6)	0	(0)	1	(3)
Feeling cold	1	(6)	0	(0)	1	(3)
Pyrexia	1	(6)	0	(0)	1	(3)
Thirst	0	(0)	1	(6)	1	(3)
Nervous system disorders	3	(18)	6	(33)	9	(26)
Dizziness	1	(6)	3	(17)	4	(11)
Headache	1	(6)	2	(11)	3	(9)
Neuropathy peripheral	2	(12)	0	(0)	2	(6)
Hypoaesthesia facial	0	(0)	1	(6)	1	(3)
Neuralgia	0	(0)	1	(6)	1	(3)
Paraesthesia	0	(0)	1	(6)	1	(3)
Somnolence	0	(0)	1	(6)	1	(3)
Tremor	1	(6)	0	(0)	1	(3)
Eye disorders	2	(12)	4	(22)	6	(17)
Eye pain	1	(6)	2	(11)	3	(9)
Lacrimation increased	0	(0)	3	(17)	3	(9)
Dry eye	1	(6)	1	(6)	2	(6)
Conjunctivitis	1	(6)	0	(0)	1	(3)
Musculoskeletal and connective tissue disorders	3	(18)	2	(11)	5	(14)
Arthralgia	1	(6)	1	(6)	2	(6)
Myalgia	1	(6)	1	(6)	2	(6)
Muscle twitching	0	(0)	1	(6)	1	(3)
Neck pain	1	(6)	0	(0)	1	(3)

Table continued on next page

	150 mg (N = 17)		300 mg (N = 18)		Total Erlotinib (N = 35)	
MedDRA System Organ Class Total Preferred Term	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Respiratory, thoracic and mediastinal disorders	4	(24)	1	(6)	5	(14)
Dyspnoea	2	(12)	0	(0)	2	(6)
Haemoptysis	1	(6)	1	(6)	2	(6)
Cough	1	(6)	0	(0)	1	(3)
Dyspnoea exertional	1	(6)	0	(0)	1	(3)
Nasopharyngitis	1	(6)	0	(0)	1	(3)
Rhinorrhoea	1	(6)	0	(0)	1	(3)
Wheezing	1	(6)	0	(0)	1	(3)
Metabolism and nutrition disorders	1	(6)	3	(17)	4	(11)
Anorexia	1	(6)	3	(17)	4	(11)
Hepatobiliary disorders	1	(6)	1	(6)	2	(6)
Hepatomegaly	1	(6)	0	(0)	1	(3)
Hyperbilirubinaemia	0	(0)	1	(6)	1	(3)
Infections and infestations	2	(12)	0	(0)	2	(6)
Lower respiratory tract infection	2	(12)	0	(0)	2	(6)
Vaginal candidiasis	1	(6)	0	(0)	1	(3)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	(0)	2	(11)	2	(6)
Cancer pain	0	(0)	2	(11)	2	(6)
Psychiatric disorders	2	(12)	0	(0)	2	(6)
Depression	1	(6)	0	(0)	1	(3)
Insomnia	1	(6)	0	(0)	1	(3)
Blood and lymphatic system disorders	0	(0)	1	(6)	1	(3)
Lymphadenopathy	0	(0)	1	(6)	1	(3)
Injury, poisoning and procedural complications	0	(0)	1	(6)	1	(3)
Skin laceration	0	(0)	1	(6)	1	(3)
Renal and urinary disorders	1	(6)	0	(0)	1	(3)
Proteinuria	1	(6)	0	(0)	1	(3)

AE: adverse event

Note: Excludes progressive disease

Source: Table 13-12

Table 8 Adverse Events Reported During the Extended Treatment Phase

Patient Number	Event†	Serious Adverse Event (Y/N)	Investigator Assessment of Relationship to Study Drug	Action Taken	Event Outcome
[redacted]	[redacted] (Asthenia)	Y	Not related	Drug interrupted	Event ongoing at time of discharge (D 46)
	[redacted] (Malignant neoplasm progression)	Y			Fatal
[redacted]	[redacted] (Fatigue)	N	Unknown	None	Resolved
	[redacted] (Decreased Appetite)	N			
	[redacted] (Weight Decreased)	N			
[redacted]	[redacted] (Lung abscess)	Y	Not related§	Drug interrupted	Resolved
	[redacted] (Vomiting)	Y			
	[redacted] (Diarrhoea)	Y			
	[redacted] (Respiratory tract infection)	Y		None	
	[redacted] (Lower respiratory tract infection)	Y			
[redacted]	[redacted] (Confusional state)	Y	Not related¶	Drug interrupted	Resolved
	[redacted] (Lower respiratory tract infection)	Y			Subject withdrawn due to PD
[redacted]	[redacted] (dehydration)	Y	Not related	Drug discontinued	Resolved
[redacted]	[redacted] (Fatigue)	N	Unknown	None	Not resolved
	[redacted] (Abdominal pain)	N			
	[redacted] (Diarrhoea)	N			
[redacted]	[redacted] (Interstitial lung disease)	Y	Not related	None	Event continued
	[redacted] (Cataract)	Y	Related		Unknown
[redacted]	[redacted] (Diarrhoea)	N	Unknown	None	Resolved
[redacted]	[redacted] (Disease progression)	Y	Not related	Drug discontinued	Fatal

Note: Per protocol, only AEs of grade 3 or 4 severity that were considered related to Tarceva treatment were to be reported during the extended treatment phase. The table reflects the data that were actually reported, including events that were considered not related to Tarceva. The actual grade for each event was not captured.

AE: adverse event; D: study day; N: no; PD: progressive (lung) disease; PT: preferred term; Y: yes

†Reported as verbatim term (PT)
‡Subject died

§The Sponsor assessed all AEs but [redacted] respiratory infections to be related to erlotinib exposure.

¶ The Sponsor assessed AE [redacted] infection to be related to erlotinib exposure.

Source: Listing of OSI-774-107 study cases initially received 01-Aug-07 thru 11-Sep-14