Clinical trial results:
An Open-label, Randomized Phase 3 Efficacy Study of ASP8273 vs Erlotinib or Gefitinib in First-line Treatment of Patients with Stage IIIB/IV Non-small Cell Lung Cancer Tumors with EGFR Activating Mutations

Summary

EudraCT number	2015-002894-39
Trial protocol	GB HU DE NL ES PT BE FR IT
Global end of trial date	21 December 2017

Results information

Result version number	v1
This version publication date	21 November 2018
First version publication date	21 November 2018

Trial information

Trial identification

Sponsor protocol code	8273-CL-0302

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02588261
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Astellas Pharma Global Development, Inc.
Sponsor organisation address	1 Astellas Way, Northbrook, Illinois, United States, 60062
Public contact	Clinical Trial Disclosure, Astellas Pharma Global Development, Inc., 1800 888-7704, astellas.resultsdisclosure@astellas.com
Scientific contact	Clinical Trial Disclosure, Astellas Pharma Global Development, Inc., 1800 888-7704, astellas.resultsdisclosure@astellas.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	21 December 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	21 December 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to evaluate the progression free survival (PFS), based on independent radiologic review (IRR) of ASP8273 compared to erlotinib or gefitinib in patients with locally advanced, metastatic or unresectable stage IIIB/IV adenocarcinoma non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) activating mutations.

Protection of trial subjects:

This clinical study was written, conducted and reported in accordance with the protocol, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) Guidelines, and applicable local regulations, including the European Directive 2001/20/EC, on the protection of human rights, and with the ethical principles that have their origin in the Declaration of Helsinki. Astellas ensures that the use and disclosure of protected health information (PHI) obtained during a research study complies with the federal, national and/or regional legislation related to the privacy and protection of personal information.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	11 February 2016
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	36 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 23
Country: Number of subjects enrolled	Belgium: 4
Country: Number of subjects enrolled	Canada: 6
Country: Number of subjects enrolled	Chile: 8
Country: Number of subjects enrolled	France: 19
Country: Number of subjects enrolled	Germany: 17
Country: Number of subjects enrolled	Hungary: 4
Country: Number of subjects enrolled	Italy: 37
Country: Number of subjects enrolled	Japan: 128
Country: Number of subjects enrolled	Korea, Republic of: 65
Country: Number of subjects enrolled	Malaysia: 42
Country: Number of subjects enrolled	Netherlands: 4
Country: Number of subjects enrolled	Peru: 7
Country: Number of subjects enrolled	Portugal: 3

Country: Number of subjects enrolled	Romania: 8
Country: Number of subjects enrolled	Russian Federation: 5
Country: Number of subjects enrolled	Singapore: 8
Country: Number of subjects enrolled	Spain: 21
Country: Number of subjects enrolled	Taiwan: 37
Country: Number of subjects enrolled	Thailand: 27
Country: Number of subjects enrolled	Ukraine: 6
Country: Number of subjects enrolled	United Kingdom: 5
Country: Number of subjects enrolled	United States: 46
Worldwide total number of subjects	530
EEA total number of subjects	122

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	530
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

First-line participants with locally advanced, metastatic or unresectable stage IIIB/IV adenocarcinoma NSCLC with EGFR activating mutation (exon 19 deletion or exon 21 L858R) with or without a T790M mutation who had not previously been treated with an EGFR inhibitors were enrolled in 201 sites in 23 countries.

Pre-assignment

Screening details:

Eligible participants were stratified according to the following: Eastern Cooperative Oncology Group (ECOG) performance status (0, 1 or 2), Epidermal growth factor receptor (EGFR) mutation status (exon 19 deletion or mutations in exon 21 [L858R]), Tyrosine kinase inhibitor (TKI) chosen (erlotinib or gefitinib) and race (Asian versus non-Asian).

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	ASP8273

Arm description:

Participants received 300 mg of ASP8273 orally once daily in 28-day cycles until one of the discontinuation criteria was met (developed radiological progressive disease, required to receive local or systemic anti-cancer treatment, developed unacceptable toxicity, participant pregnancy, investigator decision, required to receive significant surgical procedure, participant protocol deviation or noncompliance, participant decline of further treatment and participant lost to follow-up).

Arm type	Experimental
Investigational medicinal product name	ASP8273
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Participants received ASP8273 300 mg orally once daily on an empty stomach (no food for at least 2 hours before and 1 hour after taking drug) at approximately the same time every day.

Arm title	Erlotinib or Gefitinib

Arm description:

Participants received 150 mg of erlotinib or 250 mg of gefitinib orally once daily in 28-day cycles until one of the discontinuation criteria was met (developed radiological progressive disease, required to receive local or systemic anti-cancer treatment, developed unacceptable toxicity, participant pregnancy, investigator decision, required to receive significant surgical procedure, participant protocol deviation or noncompliance, participant decline of further treatment and participant lost to follow-up).

Arm type	Active comparator
Investigational medicinal product name	Erlotinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants received erlotinib 150 mg orally once daily on an empty stomach (no food for at least 2 hours before and 1 hour after taking drug) at approximately the same time every day. At the beginning

of the trial, prior to site initiation and shipment of study drug supplies, each investigator selected either erlotinib or gefitinib to be utilized for all participants randomized to the comparator arm at their site.

Investigational medicinal product name	Gefitinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants received gefitinib 250 mg was taken orally once daily with water, with or without food, at approximately the same time every day. At the beginning of the trial, prior to site initiation and shipment of study drug supplies, each investigator selected either erlotinib or gefitinib to be utilized for all participants randomized to the comparator arm at their site.

Number of subjects in period 1	ASP8273	Erlotinib or Gefitinib
Started	267	263
Completed	0	0
Not completed	267	263
Noncompliance with Study Drug	-	1
Adverse Event	29	24
Protocol Deviation	1	-
Death	1	2
Lost to Follow-up	1	-
Progressive Disease	61	82
Miscellaneous	5	4
Withdrawal by Patient	12	8
Study Terminated by Sponsor	157	142

Baseline characteristics

Reporting groups	
Reporting group title	ASP8273
Reporting group description:	
Participants received 300 mg of ASP8273 orally once daily in 28-day cycles until one of the discontinuation criteria was met (developed radiological progressive disease, required to receive local or systemic anti-cancer treatment, developed unacceptable toxicity, participant pregnancy, investigator decision, required to receive significant surgical procedure, participant protocol deviation or noncompliance, participant decline of further treatment and participant lost to follow-up).	
Reporting group title	Erlotinib or Gefitinib
Reporting group description:	
Participants received 150 mg of erlotinib or 250 mg of gefitinib orally once daily in 28-day cycles until one of the discontinuation criteria was met (developed radiological progressive disease, required to receive local or systemic anti-cancer treatment, developed unacceptable toxicity, participant pregnancy, investigator decision, required to receive significant surgical procedure, participant protocol deviation or noncompliance, participant decline of further treatment and participant lost to follow-up).	

Reporting group values	ASP8273	Erlotinib or Gefitinib	Total
Number of subjects	267	263	530
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	66.6	65.0	
standard deviation	± 10.6	± 11.5	-
Gender categorical Units:			
Male	96	110	206
Female	171	153	324
Race Units: Subjects			
White	89	88	177
Black or African American	3	0	3
Asian	162	163	325
American Indian or Alaska Native	3	1	4
Native Hawaiian or Other Pacific Islander	0	0	0
Other	1	3	4
Missing	9	8	17
Ethnicity Units: Subjects			
Hispanic or Latino	12	11	23
Not Hispanic or Latino	244	245	489
Missing	11	7	18
Race (Asian vs Non-Asian) at Randomization Units: Subjects			
Asian	163	162	325
Non-Asian	104	101	205

Investigator Prerandomization Selected TKI at Randomization Units: Subjects			
Erlotinib	153	151	304
Gefitinib	114	112	226
ECOG Performance Status at Randomization			
ECOG Performance Status is composed of 6 grades: 0 - Fully active, able to carry on all predisease performance without restriction; 1 - Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature; 2 - Ambulatory and capable of all self-care but unable to carry out any work activities, Up and about more than 50% of waking hours; 3 - Capable of only limited self-care, confined to bed or chair more than 50% of waking hours; 4 - Completely disabled, Cannot carry on any self-care, Totally confined to bed or chair; 5 - Dead.			
Units: Subjects			
Grade 0	103	103	206
Grade 1	155	152	307
Grade 2	9	8	17
EGFR Mutation Status at Randomization Units: Subjects			
Exon 19 Deletion	149	147	296
Exon 21 L858R	118	116	234

End points

End points reporting groups

Reporting group title	ASP8273

Reporting group description:

Participants received 300 mg of ASP8273 orally once daily in 28-day cycles until one of the discontinuation criteria was met (developed radiological progressive disease, required to receive local or systemic anti-cancer treatment, developed unacceptable toxicity, participant pregnancy, investigator decision, required to receive significant surgical procedure, participant protocol deviation or noncompliance, participant decline of further treatment and participant lost to follow-up).

Reporting group title	Erlotinib or Gefitinib

Reporting group description:

Participants received 150 mg of erlotinib or 250 mg of gefitinib orally once daily in 28-day cycles until one of the discontinuation criteria was met (developed radiological progressive disease, required to receive local or systemic anti-cancer treatment, developed unacceptable toxicity, participant pregnancy, investigator decision, required to receive significant surgical procedure, participant protocol deviation or noncompliance, participant decline of further treatment and participant lost to follow-up).

Primary: Progression Free Survival (PFS) as assessed by Independent Radiologic Review (IRR)

End point title	Progression Free Survival (PFS) as assessed by Independent Radiologic Review (IRR)

End point description:

PFS was defined as the time from the date of randomization until the date of radiological disease progression or until death due to any cause, based on the Response Evaluation Criteria in Solid Tumors (RECIST) v1.1, as assessed by IRR. Results are based Kaplan-Meier estimate. The analysis population was the full analysis set (FAS), which consisted of all participants who were randomized. If a participant had neither progressed nor died, who received any further anticancer therapy for the disease before radiological progression, the participant was censored at the date of last radiological assessment. If progression or death occurred after missing 2 scheduled radiological assessments, the participant was censored at the date of last radiological assessment or at the date of randomization if no post-baseline radiological assessment was available. Data could not be calculated due to low number of events, and is denoted as "99999."

End point type	Primary

End point timeframe:

From date of randomization up to data cut-off date 09 May 2017 (approximately 15 months)

End point values	ASP8273	Erlotinib or Gefitinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	267	263		
Units: months				
median (confidence interval 95%)	9.26 (5.62 to 11.07)	9.59 (8.77 to 99999)		

Statistical analyses

Statistical analysis title	Stratified Analysis

Statistical analysis description:

Comparison between ASP8273 and Erlotinib or Gefitinib treatment groups was performed using log-rank test stratified by ECOG (0 and 1 vs 2), EGFR mutation type (exon 19 deletion or exon 21 L858R) and TKI chosen by the site (erlotinib or gefitinib) before randomization. Comparison was tested at 1-sided significance level of 0.025. Hazard ratio based on Cox proportional hazards model. Assuming proportional hazards, HR < 1 indicated a reduction in hazard rate in favor of ASP8273 treatment group.

Comparison groups	ASP8273 v Erlotinib or Gefitinib
Number of subjects included in analysis	530
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.992
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.611
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.086
upper limit	2.391

Secondary: Percentage of Deaths

End point title	Percentage of Deaths

End point description:

All events of death after the first study drug administration were included. The analysis population was the safety analysis set (SAF), which consisted of all participants who took at least one dose of study drug.

End point type	Secondary

End point timeframe:

From date of randomization up to data cut-off date 21 Dec 2017 (approximately 22 months)

End point values	ASP8273	Erlotinib or Gefitinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	265	262		
Units: participants	39	35		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Objective Response (OR)

End point title	Percentage of Participants with Objective Response (OR)

End point description:

Percentage of participants with OR was defined as the proportion of participants with best overall response as complete response (CR) or partial response (PR) without confirmation based on the RECIST v1.1 as assessed by the blinded IRR. CR was defined as disappearance of all target and nontarget

lesions. Any pathological lymph nodes (whether target or nontarget) must have reduction in short axis to < 10 mm from baseline measurement. PR was defined as at least a 30% decrease in the sum of diameters (longest for nonnodal lesions, short axis for nodal lesions) of target lesions taking as reference to the baseline sum of diameters. The analysis population was the FAS.

End point type	Secondary

End point timeframe:

From date of first dose of study drug up to data cut-off date 09 May 2017 (approximately 15 months)

End point values	ASP8273	Erlotinib or Gefitinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	267	263		
Units: percentage of participants				
number (confidence interval 95%)	33.0 (27.4 to 39.0)	47.9 (41.7 to 54.1)		

Statistical analyses

Statistical analysis title	Stratified Analysis

Statistical analysis description:

Comparison between ASP8273 and Erlotinib or Gefitinib treatment groups was performed using stratified Cochran–Mantel–Haenszel (CMH) test, stratified by ECOG (0 and 1 vs 2), EGFR mutation type (exon 19 deletion or exon 21 L858R) and TKI chosen by the site (erlotinib or gefitinib) before randomization. Comparison was tested at 1-sided significance level of 0.025.

Comparison groups	ASP8273 v Erlotinib or Gefitinib
Number of subjects included in analysis	530
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1
Method	Cochran-Mantel-Haenszel

Secondary: PFS as Assessed by the Investigator

End point title	PFS as Assessed by the Investigator

End point description:

PFS was defined as the time from the date of randomization until the date of radiological disease progression or until death due to any cause, based on RECIST V1.1, as assessed by local investigator. Results are based Kaplan-Meier estimate. The analysis population was the FAS. If a participant had neither progressed nor died, who received any further anticancer therapy for the disease before radiological progression, the participant was censored at the date of last radiological assessment. If progression or death occurred after missing 2 scheduled radiological assessments, the participant was censored at the date of last radiological assessment or at the date of randomization if no post-baseline radiological assessment was available. Data could not be calculated due to low number of events, and is denoted as "99999."

End point type	Secondary

End point timeframe:

From date of randomization up to data cut-off date 09 May 2017 (approximately 15 months)

End point values	ASP8273	Erlotinib or Gefitinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	267	263		
Units: months				
median (confidence interval 95%)	7.43 (5.49 to 9.26)	10.12 (9.03 to 99999)		

Statistical analyses

Statistical analysis title	Stratified Analysis

Statistical analysis description:

Comparison between ASP8273 and Erlotinib or Gefitinib treatment groups was performed using log-rank test stratified by ECOG (0 and 1 vs 2), EGFR mutation type (exon 19 deletion or exon 21 L858R) and TKI chosen by the site (erlotinib or gefitinib) before randomization. Comparison was tested at 1-sided significance level of 0.025. Hazard ratio based on Cox proportional hazards model. Assuming proportional hazards, HR < 1 indicated a reduction in hazard rate in favor of ASP8273 treatment group.

Comparison groups	ASP8273 v Erlotinib or Gefitinib
Number of subjects included in analysis	530
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.998
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.674
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.165
upper limit	2.406

Secondary: Percentage of Participants with Disease Control

End point title	Percentage of Participants with Disease Control

End point description:

Percentage of participants with disease control was defined as the proportion of participants whose best overall response was rated as CR, PR or stable disease (SD) among all analyzed participants based on RECIST V1.1. CR was defined as disappearance of all target and nontarget lesions. Any pathological lymph nodes (whether target or nontarget) must have reduction in short axis to < 10 mm from baseline measurement. PR was defined as at least a 30% decrease in the sum of diameters (longest for nonnodal lesions, short axis for nodal lesions) of target lesions taking as reference to the baseline sum of diameters. SD was defined as neither sufficient decrease to qualify for PR nor sufficient increase to qualify
for progressive disease taking as reference the smallest sum of diameters while on study
drug. The analysis population was the FAS.

End point type	Secondary

End point timeframe:

From date of first dose of study drug up to data cut-off date 09 May 2017 (approximately 15 months)

End point values	ASP8273	Erlotinib or Gefitinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	267	263		
Units: percentage of participants				
number (confidence interval 95%)	62.2 (56.1 to 68.0)	66.2 (60.1 to 71.9)		

Statistical analyses

Statistical analysis title	Stratified Analysis

Statistical analysis description:

Comparison between ASP8273 and Erlotinib or Gefitinib treatment groups was performed using stratified Cochran–Mantel–Haenszel (CMH) test, stratified by ECOG (0 and 1 vs 2), EGFR mutation type (exon 19 deletion or exon 21 L858R) and TKI chosen by the site (erlotinib or gefitinib) before randomization. Comparison was tested at 1-sided significance level of 0.025

Comparison groups	ASP8273 v Erlotinib or Gefitinib
Number of subjects included in analysis	530
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.839
Method	Cochran-Mantel-Haenszel

Secondary: Duration of Response (DOR)

End point title	Duration of Response (DOR)

End point description:

DOR was defined as the time from the date of the first response CR/PR (whichever was first recorded) as assessed by IRR to the date of radiographical progression or date of censoring. If a participant had not progressed, the participant was censored at the date of last radiological assessment or at the date of first CR/PR if no post-baseline radiological assessment was available. Results are based Kaplan-Meier estimate. The analysis population was the FAS. Only participants with best overall response as CR or PR (without confirmation) were included in the analysis. Data could not be calculated due to low number of events, and is denoted as "99999."

End point type	Secondary

End point timeframe:

From date of first response up to data cut-off date 09 May 2017 (approximately 15 months)

End point values	ASP8273	Erlotinib or Gefitinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	88	126		
Units: months				
median (confidence interval 95%)	9.17 (5.45 to 99999)	9.03 (7.39 to 99999)		

Statistical analyses

Statistical analysis title	Stratified Analysis

Statistical analysis description:

Comparison between ASP8273 and Erlotinib or Gefitinib treatment groups was performed using log-rank test stratified by ECOG (0 and 1 vs 2), EGFR mutation type (exon 19 deletion or exon 21 L858R) and TKI chosen by the site (erlotinib or gefitinib) before randomization. Comparison was tested at 1-sided significance level of 0.025. Hazard ratio based on Cox proportional hazards model. Assuming proportional hazards, HR < 1 indicated a reduction in hazard rate in favor of ASP8273 treatment group.

Comparison groups	ASP8273 v Erlotinib or Gefitinib
Number of subjects included in analysis	214
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.78
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.298
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.661
upper limit	2.548

Secondary: Number of Participants with Adverse Events (AEs)

End point title	Number of Participants with Adverse Events (AEs)

End point description:

Safety was assessed by AEs, which included abnormalities identified during a medical test (e.g. laboratory tests, vital signs, electrocardiogram, etc.) if the abnormality induced clinical signs or symptoms, needed active intervention, interruption or discontinuation of study medication or was clinically significant. A treatment-emergent AE (TEAE) was defined as an AE observed after starting administration of the study drug. AEs were considered serious (SAEs) if the AE resulted in death, was life threatening, resulted in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions, resulted in congenital anomaly, or birth defect or required inpatient hospitalization or led to prolongation of hospitalization. The analysis population was the safety analysis set (SAF), which consisted of participants who took at least 1 dose of study drug.

End point type	Secondary

End point timeframe:

From first dose of study drug up to 30 days after last dose of study drug taken up to data cut-off 09 May 2017

End point values	ASP8273	Erlotinib or Gefitinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	265	262		
Units: participants				
number (not applicable)				
TEAE	251	261		
Drug-Related TEAE	235	246		
Serious TEAE	84	67		
Drug-Related Serious TEAE	46	18		
TEAE Leading to Death	14	17		
Drug-Related TEAE Leading to Death	1	1		
TEAE Leading to Treatment Withdrawal	39	28		
Drug-Related TEAE Leading to Treatment Withdrawal	27	17		
TEAE Leading to Dose Reduction	51	51		
Drug-Related TEAE Leading to Dose Reduction	51	50		
TEAE Leading to Dose Interruption	95	74		
Drug-Related TEAE Leading to Dose Interruption	83	55		
Death	39	35		

Statistical analyses

No statistical analyses for this end point

Secondary: Functional Assessment of Cancer Therapy – EGFR Inhibitors Subscale (FACT-EGFRI-18) Questionnaire

End point title	Functional Assessment of Cancer Therapy – EGFR Inhibitors Subscale (FACT-EGFRI-18) Questionnaire

End point description:

FACT-EGFRI-18 is an 18-item Likert-scaled questionnaire, used to assess the effect of EGFR inhibitors on quality of life (QoL). The questionnaire is arranged in three HRQL dimensions: physical (seven items), social/emotional (six items), and functional well-being (five items). The response scores ranged from 0 to 4, and the response categories include "not at all", "a little bit", "somewhat", "quite a bit", and "very much." Negatively worded items (e.g., "My skin bleeds easily "or "My skin condition affects my mood") are reverse-scored, so that participants who experience a higher impact of symptom burden on HRQL receive a lower score (range 0-72). The analysis population was the SAF.

End point type	Secondary

End point timeframe:

Day 1 of each cycle up to data cut off 09 May 2017 (approximately 15 months)

End point values	ASP8273	Erlotinib or Gefitinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[1]	0[2]		
Units: units on a scale				
arithmetic mean (standard deviation)	()	()		

Notes:

[1] - As the study was terminated and ASP8273 development was discontinued, QoL data was not analyzed.
[2] - As the study was terminated and ASP8273 development was discontinued, QoL data was not analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire - Lung Cancer 13 (EORTC-QLQ-LC13)

End point title	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire - Lung Cancer 13 (EORTC-QLQ-LC13)

End point description:

The EORTC-QLQ-LC13 is a validated module of the EORTC-QLQ-Core 30, which includes module items that evaluate symptoms such as cough, hemoptysis, shortness of breath, sore mouth or tongue, dysphagia, tingling hands or feet, hair loss and pain. The total score for the questionnaire ranges from 0 to 100. A high score for a functional scale represents a high/healthy level of functioning whereas a high score for a symptom scale or item represents a high level of symptomatology or problems. The analysis population was the SAF.

End point type	Secondary

End point timeframe:

Day 1 of each cycle up to data cut off 09 May 2017 (approximately 15 months)

End point values	ASP8273	Erlotinib or Gefitinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[3]	0[4]		
Units: units on a scale				
arithmetic mean (standard deviation)	()	()		

Notes:

[3] - As the study was terminated and ASP8273 development was discontinued, QoL data was not analyzed.
[4] - As the study was terminated and ASP8273 development was discontinued, QoL data was not analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: European Organisation for Research and Treatment of Cancer Core Quality of Life Questionnaire (EORTC-QLQ-C30)

End point title	European Organisation for Research and Treatment of Cancer Core Quality of Life Questionnaire (EORTC-QLQ-C30)

End point description:

EORTC-QLQ-LC13 is a 30-item cancer-specific questionnaire with multitrait scaling was used to create five functional domain scales: Physical, Role, Emotional, Social and Cognitive; two items evaluate global QoL; in addition, three symptom scales assess Fatigue, Pain and Emesis; and six single items assess other symptoms. The total score ranges from 0 to 100, with a high score for a functional scale representing a high/healthy level of functioning and a high score for a symptom scale or item representing a high level of symptomatology or problems. The analysis population was the SAF.

End point type	Secondary

End point timeframe:

Day 1 of each cycle up to data cut off 09 May 2017 (approximately 15 months)

End point values	ASP8273	Erlotinib or Gefitinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[5]	0[6]		
Units: units on a scale				
arithmetic mean (standard deviation)	()	()		

Notes:

[5] - As the study was terminated and ASP8273 development was discontinued, QoL data was not analyzed.
[6] - As the study was terminated and ASP8273 development was discontinued, QoL data was not analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: EuroQol 5-Dimension 5-Level Questionnaire (EQ-5D-5L)

End point title	EuroQol 5-Dimension 5-Level Questionnaire (EQ-5D-5L)

End point description:

The EQ-5D is a generic preference-based measure that indirectly measures the utility for health that generates an index-based summary score based upon societal preference weights. The EQ-5D-5L consists of 6 items that cover 5 main domains (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) and a general visual analog scale (VAS) for health status. Each item has 5 response levels ranging from level 1 (no problem or none) to level 5 (unable to perform activity). The VAS ranges from 0 (worst health status) and 100 (best health status). The analysis population was the SAF.

End point type	Secondary

End point timeframe:

Day 1 of each cycle up to data cut off 09 May 2017 (approximately 15 months)

End point values	ASP8273	Erlotinib or Gefitinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[7]	0[8]		
Units: units on a scale				
arithmetic mean (standard deviation)	()	()		

Notes:

[7] - As the study was terminated and ASP8273 development was discontinued, QoL data was not analyzed.
[8] - As the study was terminated and ASP8273 development was discontinued, QoL data was not analyzed.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose of study drug up to 30 days after last dose of study drug taken up to data cut-off 21 Dec 2017 (approximately 22 months)

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups

Reporting group title	Erlotinib or Gefitinib

Reporting group description:

Participants received 150 mg of erlotinib or 250 mg of gefitinib orally once daily in 28-day cycles until one of the discontinuation criteria was met (developed radiological progressive disease, required to receive local or systemic anti-cancer treatment, developed unacceptable toxicity, participant pregnancy, investigator decision, required to receive significant surgical procedure, participant protocol deviation or noncompliance, participant decline of further treatment and participant lost to follow-up).

Reporting group title	ASP8273

Reporting group description:

Participants received 300 mg of ASP8273 orally once daily in 28-day cycles until one of the discontinuation criteria was met (developed radiological progressive disease, required to receive local or systemic anti-cancer treatment, developed unacceptable toxicity, participant pregnancy, investigator decision, required to receive significant surgical procedure, participant protocol deviation or noncompliance, participant decline of further treatment and participant lost to follow-up).

Serious adverse events	Erlotinib or Gefitinib	ASP8273	
Total subjects affected by serious adverse events			
subjects affected / exposed	67 / 262 (25.57%)	84 / 265 (31.70%)	
number of deaths (all causes)	35	39	
number of deaths resulting from adverse events	17	14	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute myeloid leukaemia			
subjects affected / exposed	1 / 262 (0.38%)	0 / 265 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Bowen's disease			
subjects affected / exposed	1 / 262 (0.38%)	0 / 265 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant neoplasm progression			

subjects affected / exposed	8 / 262 (3.05%)	6 / 265 (2.26%)	
occurrences causally related to treatment / all	0 / 9	0 / 7	
deaths causally related to treatment / all	0 / 6	0 / 5	
Malignant pleural effusion			
subjects affected / exposed	0 / 262 (0.00%)	2 / 265 (0.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to central nervous system			
subjects affected / exposed	2 / 262 (0.76%)	1 / 265 (0.38%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Metastases to eye			
subjects affected / exposed	0 / 262 (0.00%)	1 / 265 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to meninges			
subjects affected / exposed	1 / 262 (0.38%)	2 / 265 (0.75%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 1	
Neoplasm malignant			
subjects affected / exposed	0 / 262 (0.00%)	1 / 265 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neoplasm skin			
subjects affected / exposed	1 / 262 (0.38%)	0 / 265 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour haemorrhage			
subjects affected / exposed	0 / 262 (0.00%)	2 / 265 (0.75%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypertension			

subjects affected / exposed	0 / 262 (0.00%)	1 / 265 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive crisis			
subjects affected / exposed	1 / 262 (0.38%)	0 / 265 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	0 / 262 (0.00%)	1 / 265 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 262 (0.38%)	2 / 265 (0.75%)	
occurrences causally related to treatment / all	0 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	0 / 262 (0.00%)	1 / 265 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	0 / 262 (0.00%)	1 / 265 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Fatigue			
subjects affected / exposed	0 / 262 (0.00%)	2 / 265 (0.75%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gait disturbance			
subjects affected / exposed	0 / 262 (0.00%)	1 / 265 (0.38%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiac chest pain			

subjects affected / exposed	0 / 262 (0.00%)	1 / 265 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	1 / 262 (0.38%)	3 / 265 (1.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Prostatitis			
subjects affected / exposed	1 / 262 (0.38%)	0 / 265 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			
subjects affected / exposed	0 / 262 (0.00%)	1 / 265 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory failure			
subjects affected / exposed	0 / 262 (0.00%)	1 / 265 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchospasm			
subjects affected / exposed	2 / 262 (0.76%)	0 / 265 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	2 / 262 (0.76%)	0 / 265 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cough			

subjects affected / exposed	1 / 262 (0.38%)	0 / 265 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	3 / 262 (1.15%)	5 / 265 (1.89%)	
occurrences causally related to treatment / all	0 / 4	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			
subjects affected / exposed	3 / 262 (1.15%)	1 / 265 (0.38%)	
occurrences causally related to treatment / all	0 / 5	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Interstitial lung disease			
subjects affected / exposed	4 / 262 (1.53%)	1 / 265 (0.38%)	
occurrences causally related to treatment / all	7 / 7	1 / 1	
deaths causally related to treatment / all	1 / 1	0 / 0	
Pharyngeal inflammation			
subjects affected / exposed	1 / 262 (0.38%)	0 / 265 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	1 / 262 (0.38%)	3 / 265 (1.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	2 / 262 (0.76%)	0 / 265 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	2 / 262 (0.76%)	0 / 265 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pulmonary hypertension			

subjects affected / exposed	1 / 262 (0.38%)	0 / 265 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	2 / 262 (0.76%)	2 / 265 (0.75%)	
occurrences causally related to treatment / all	0 / 6	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 1	
Psychiatric disorders			
Agitation			
subjects affected / exposed	0 / 262 (0.00%)	1 / 265 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Confusional state			
subjects affected / exposed	0 / 262 (0.00%)	1 / 265 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Delirium			
subjects affected / exposed	0 / 262 (0.00%)	1 / 265 (0.38%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			
subjects affected / exposed	0 / 262 (0.00%)	1 / 265 (0.38%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mental status changes			
subjects affected / exposed	1 / 262 (0.38%)	1 / 265 (0.38%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychotic disorder			
subjects affected / exposed	0 / 262 (0.00%)	1 / 265 (0.38%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			

Alanine aminotransferase increased			
subjects affected / exposed	3 / 262 (1.15%)	1 / 265 (0.38%)	
occurrences causally related to treatment / all	9 / 9	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	2 / 262 (0.76%)	0 / 265 (0.00%)	
occurrences causally related to treatment / all	6 / 6	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 262 (0.38%)	0 / 265 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 262 (0.00%)	2 / 265 (0.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral neck fracture			
subjects affected / exposed	0 / 262 (0.00%)	2 / 265 (0.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	1 / 262 (0.38%)	0 / 265 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural nausea			
subjects affected / exposed	0 / 262 (0.00%)	1 / 265 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural pain			
subjects affected / exposed	0 / 262 (0.00%)	1 / 265 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Radius fracture			
subjects affected / exposed	0 / 262 (0.00%)	1 / 265 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 262 (0.00%)	1 / 265 (0.38%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Angina pectoris			
subjects affected / exposed	0 / 262 (0.00%)	1 / 265 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial thrombosis			
subjects affected / exposed	1 / 262 (0.38%)	0 / 265 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial effusion			
subjects affected / exposed	2 / 262 (0.76%)	0 / 265 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Nervous system disorders			
Altered state of consciousness			
subjects affected / exposed	0 / 262 (0.00%)	1 / 265 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aphasia			
subjects affected / exposed	0 / 262 (0.00%)	1 / 265 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain oedema			
subjects affected / exposed	0 / 262 (0.00%)	1 / 265 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	

Depressed level of consciousness			
subjects affected / exposed	0 / 262 (0.00%)	1 / 265 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysarthria			
subjects affected / exposed	0 / 262 (0.00%)	1 / 265 (0.38%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolic stroke			
subjects affected / exposed	0 / 262 (0.00%)	1 / 265 (0.38%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Encephalopathy			
subjects affected / exposed	0 / 262 (0.00%)	1 / 265 (0.38%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epilepsy			
subjects affected / exposed	1 / 262 (0.38%)	0 / 265 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage intracranial			
subjects affected / exposed	0 / 262 (0.00%)	1 / 265 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Headache			
subjects affected / exposed	1 / 262 (0.38%)	0 / 265 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraesthesia			
subjects affected / exposed	0 / 262 (0.00%)	1 / 265 (0.38%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Partial seizures			

subjects affected / exposed	1 / 262 (0.38%)	0 / 265 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 262 (0.00%)	1 / 265 (0.38%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	0 / 262 (0.00%)	2 / 265 (0.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal cord compression			
subjects affected / exposed	1 / 262 (0.38%)	0 / 265 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	0 / 262 (0.00%)	1 / 265 (0.38%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 262 (0.00%)	2 / 265 (0.75%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Deafness unilateral			
subjects affected / exposed	1 / 262 (0.38%)	0 / 265 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Retinal artery occlusion			
subjects affected / exposed	0 / 262 (0.00%)	1 / 265 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 262 (0.00%)	2 / 265 (0.75%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	0 / 262 (0.00%)	1 / 265 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	1 / 262 (0.38%)	0 / 265 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	0 / 262 (0.00%)	1 / 265 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	2 / 262 (0.76%)	7 / 265 (2.64%)	
occurrences causally related to treatment / all	2 / 2	6 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis			
subjects affected / exposed	0 / 262 (0.00%)	1 / 265 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	0 / 262 (0.00%)	1 / 265 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 262 (0.00%)	1 / 265 (0.38%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intussusception			

subjects affected / exposed	0 / 262 (0.00%)	1 / 265 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	0 / 262 (0.00%)	2 / 265 (0.75%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophagitis			
subjects affected / exposed	0 / 262 (0.00%)	1 / 265 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	0 / 262 (0.00%)	1 / 265 (0.38%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Umbilical hernia			
subjects affected / exposed	0 / 262 (0.00%)	1 / 265 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 262 (0.00%)	2 / 265 (0.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 262 (0.00%)	3 / 265 (1.13%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Biliary colic			
subjects affected / exposed	1 / 262 (0.38%)	0 / 265 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug-induced liver injury			

subjects affected / exposed	0 / 262 (0.00%)	1 / 265 (0.38%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic failure			
subjects affected / exposed	0 / 262 (0.00%)	1 / 265 (0.38%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic function abnormal			
subjects affected / exposed	1 / 262 (0.38%)	0 / 265 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Drug eruption			
subjects affected / exposed	2 / 262 (0.76%)	0 / 265 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	2 / 262 (0.76%)	5 / 265 (1.89%)	
occurrences causally related to treatment / all	2 / 3	3 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic kidney disease			
subjects affected / exposed	0 / 262 (0.00%)	1 / 265 (0.38%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
subjects affected / exposed	0 / 262 (0.00%)	1 / 265 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal impairment			
subjects affected / exposed	1 / 262 (0.38%)	0 / 265 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			

subjects affected / exposed	0 / 262 (0.00%)	1 / 265 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthritis			
subjects affected / exposed	0 / 262 (0.00%)	1 / 265 (0.38%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	3 / 262 (1.15%)	1 / 265 (0.38%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc protrusion			
subjects affected / exposed	1 / 262 (0.38%)	0 / 265 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscular weakness			
subjects affected / exposed	1 / 262 (0.38%)	0 / 265 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bacteraemia			
subjects affected / exposed	1 / 262 (0.38%)	0 / 265 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	0 / 262 (0.00%)	1 / 265 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopneumonia			
subjects affected / exposed	1 / 262 (0.38%)	0 / 265 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Cellulitis			
subjects affected / exposed	3 / 262 (1.15%)	0 / 265 (0.00%)	
occurrences causally related to treatment / all	0 / 5	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Dengue fever			
subjects affected / exposed	0 / 262 (0.00%)	1 / 265 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea infectious			
subjects affected / exposed	1 / 262 (0.38%)	0 / 265 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia urinary tract infection			
subjects affected / exposed	0 / 262 (0.00%)	2 / 265 (0.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	0 / 262 (0.00%)	1 / 265 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	1 / 262 (0.38%)	2 / 265 (0.75%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pneumonia			
subjects affected / exposed	5 / 262 (1.91%)	11 / 265 (4.15%)	
occurrences causally related to treatment / all	1 / 5	2 / 15	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pulmonary tuberculosis			
subjects affected / exposed	1 / 262 (0.38%)	0 / 265 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			

subjects affected / exposed	1 / 262 (0.38%)	3 / 265 (1.13%)	
occurrences causally related to treatment / all	0 / 1	1 / 3	
deaths causally related to treatment / all	0 / 1	0 / 0	
Septic shock			
subjects affected / exposed	1 / 262 (0.38%)	2 / 265 (0.75%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Soft tissue infection			
subjects affected / exposed	1 / 262 (0.38%)	0 / 265 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal bacteraemia			
subjects affected / exposed	1 / 262 (0.38%)	0 / 265 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Superinfection fungal			
subjects affected / exposed	1 / 262 (0.38%)	0 / 265 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 262 (0.38%)	1 / 265 (0.38%)	
occurrences causally related to treatment / all	0 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection bacterial			
subjects affected / exposed	0 / 262 (0.00%)	1 / 265 (0.38%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection enterococcal			
subjects affected / exposed	1 / 262 (0.38%)	0 / 265 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Decreased appetite			

subjects affected / exposed	0 / 262 (0.00%)	3 / 265 (1.13%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	0 / 262 (0.00%)	1 / 265 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus			
subjects affected / exposed	0 / 262 (0.00%)	1 / 265 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoalbuminaemia			
subjects affected / exposed	0 / 262 (0.00%)	1 / 265 (0.38%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	0 / 262 (0.00%)	1 / 265 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	1 / 262 (0.38%)	2 / 265 (0.75%)	
occurrences causally related to treatment / all	0 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	1 / 262 (0.38%)	14 / 265 (5.28%)	
occurrences causally related to treatment / all	0 / 1	16 / 17	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Erlotinib or Gefitinib	ASP8273	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	253 / 262 (96.56%)	240 / 265 (90.57%)	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	51 / 262 (19.47%)	53 / 265 (20.00%)	
occurrences (all)	107	125	
Aspartate aminotransferase increased			
subjects affected / exposed	43 / 262 (16.41%)	36 / 265 (13.58%)	
occurrences (all)	88	67	
Blood bilirubin increased			
subjects affected / exposed	15 / 262 (5.73%)	4 / 265 (1.51%)	
occurrences (all)	28	4	
Platelet count decreased			
subjects affected / exposed	3 / 262 (1.15%)	18 / 265 (6.79%)	
occurrences (all)	5	25	
Weight decreased			
subjects affected / exposed	21 / 262 (8.02%)	17 / 265 (6.42%)	
occurrences (all)	27	17	
Nervous system disorders			
Dizziness			
subjects affected / exposed	11 / 262 (4.20%)	29 / 265 (10.94%)	
occurrences (all)	11	29	
Dysgeusia			
subjects affected / exposed	10 / 262 (3.82%)	30 / 265 (11.32%)	
occurrences (all)	10	35	
Headache			
subjects affected / exposed	23 / 262 (8.78%)	21 / 265 (7.92%)	
occurrences (all)	25	25	
Paraesthesia			
subjects affected / exposed	7 / 262 (2.67%)	19 / 265 (7.17%)	
occurrences (all)	7	22	
Peripheral sensory neuropathy			
subjects affected / exposed	2 / 262 (0.76%)	57 / 265 (21.51%)	
occurrences (all)	2	76	
Blood and lymphatic system disorders			

Anaemia			
subjects affected / exposed	17 / 262 (6.49%)	21 / 265 (7.92%)	
occurrences (all)	30	27	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	19 / 262 (7.25%)	31 / 265 (11.70%)	
occurrences (all)	28	39	
Fatigue			
subjects affected / exposed	30 / 262 (11.45%)	50 / 265 (18.87%)	
occurrences (all)	47	73	
Pyrexia			
subjects affected / exposed	17 / 262 (6.49%)	18 / 265 (6.79%)	
occurrences (all)	20	22	
Eye disorders			
Dry eye			
subjects affected / exposed	17 / 262 (6.49%)	7 / 265 (2.64%)	
occurrences (all)	21	8	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	24 / 262 (9.16%)	54 / 265 (20.38%)	
occurrences (all)	24	68	
Diarrhoea			
subjects affected / exposed	135 / 262 (51.53%)	161 / 265 (60.75%)	
occurrences (all)	224	255	
Dry mouth			
subjects affected / exposed	1 / 262 (0.38%)	30 / 265 (11.32%)	
occurrences (all)	1	31	
Nausea			
subjects affected / exposed	33 / 262 (12.60%)	66 / 265 (24.91%)	
occurrences (all)	41	85	
Stomatitis			
subjects affected / exposed	55 / 262 (20.99%)	18 / 265 (6.79%)	
occurrences (all)	70	21	
Vomiting			
subjects affected / exposed	26 / 262 (9.92%)	51 / 265 (19.25%)	
occurrences (all)	31	60	

Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	30 / 262 (11.45%)	25 / 265 (9.43%)	
occurrences (all)	41	28	
Dyspnoea			
subjects affected / exposed	16 / 262 (6.11%)	20 / 265 (7.55%)	
occurrences (all)	16	25	
Epistaxis			
subjects affected / exposed	15 / 262 (5.73%)	6 / 265 (2.26%)	
occurrences (all)	15	6	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	37 / 262 (14.12%)	8 / 265 (3.02%)	
occurrences (all)	42	8	
Drug eruption			
subjects affected / exposed	186 / 262 (70.99%)	32 / 265 (12.08%)	
occurrences (all)	377	34	
Dry skin			
subjects affected / exposed	66 / 262 (25.19%)	32 / 265 (12.08%)	
occurrences (all)	83	33	
Pruritus			
subjects affected / exposed	35 / 262 (13.36%)	12 / 265 (4.53%)	
occurrences (all)	44	13	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	17 / 262 (6.49%)	22 / 265 (8.30%)	
occurrences (all)	17	24	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	7 / 262 (2.67%)	14 / 265 (5.28%)	
occurrences (all)	7	16	
Back pain			
subjects affected / exposed	18 / 262 (6.87%)	14 / 265 (5.28%)	
occurrences (all)	22	16	
Infections and infestations			

Paronychia			
subjects affected / exposed	67 / 262 (25.57%)	5 / 265 (1.89%)	
occurrences (all)	106	6	
Upper respiratory tract infection			
subjects affected / exposed	18 / 262 (6.87%)	10 / 265 (3.77%)	
occurrences (all)	24	11	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	48 / 262 (18.32%)	56 / 265 (21.13%)	
occurrences (all)	64	73	
Hyponatraemia			
subjects affected / exposed	7 / 262 (2.67%)	64 / 265 (24.15%)	
occurrences (all)	13	134	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 February 2016	The changes include: revised the secondary objectives; increased the planned patient sample size; clarified the method of comparator selection, the study eligibility criteria and the criteria for treatment after disease progression; and updated the imaging and contraception requirements, dose modification guidelines and the concomitant medication restrictions.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The study was terminated due to Independent Data Monitoring Committee (IDMC) recommendation (after completion of a safety data review), due to excess toxicity with limited predicted efficacy of ASP8273 relative to erlotinib and gefitinib.

Notes: