



Clinical trial results:

A Randomized, Double-Blind, Placebo-Controlled, Phase III Study of First-Line Maintenance Tarceva® Versus Tarceva at the Time of Disease Progression in Patients With Advanced Non-Small Cell Lung Cancer (NSCLC) Who Have Not Progressed Following 4 Cycles of Platinum-Based Chemotherapy

Summary

EudraCT number	2010-024468-16
Trial protocol	SK HU CZ LV LT NL FR BG IT
Global end of trial date	22 January 2016

Results information

Result version number	v2
This version publication date	06 July 2016
First version publication date	01 May 2016
Version creation reason	• New data added to full data set Final CSR

Trial information

Trial identification

Sponsor protocol code	BO25460
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01328951
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	F. Hoffmann-La Roche AG
Sponsor organisation address	Grenzacherstrasse 124, Basel, Switzerland, CH-4070
Public contact	Roche Trial Information Hotline, F. Hoffmann-La Roche AG, +41 616878333, global.trial_information@roche.com
Scientific contact	Roche Trial Information Hotline, F. Hoffmann-La Roche AG, +41 616878333, global.trial_information@roche.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	26 February 2016
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	22 January 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The study evaluated the benefit of first-line maintenance erlotinib versus erlotinib at the time of disease progression in participants with advanced non-small cell lung cancer (NSCLC) who have not progressed following 4 cycles of platinum-based chemotherapy and whose tumor does not harbor an epidermal growth factor receptor (EGFR) activating mutation. The study included three periods: a Blinded Period (BP), an Open-Label Period (OLP) and a final Survival Follow-Up (SFU) period.

Protection of trial subjects:

The study was conducted in full conformance with the principles of the Declaration of Helsinki, or the laws and regulations of the country in which the research was conducted, whichever afforded greater protection to the participant. The study has fully adhered to the principles outlined in the Guideline for Good Clinical Practice (GCP) International Conference on Harmonisation (ICH) Tripartite Guideline (January 1997) or with local law if it afforded greater protection to the participant. For study sites in the European Union (EU)/European Economic Area (EEA), the study has also complied with the EU Clinical Trial Directive (2001/20/EC). For study sites in the United States (US) or under the US Investigational New Drug application (IND), the study has also adhered to the basic principles of GCP as outlined in the current version of 21 Code of Federal Regulations (CFR), subchapter D, part 312, "Responsibilities of Sponsors and Investigators"; part 50, "Protection of Human Subjects"; and part 56, "Institutional Review Boards". In other countries where Guidelines for GCP exist, the Sponsor and the investigators have strictly ensured adherence to the stated provision.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	06 July 2011
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	51 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Canada: 4
Country: Number of subjects enrolled	China: 61
Country: Number of subjects enrolled	Korea, Republic of: 4
Country: Number of subjects enrolled	Romania: 53
Country: Number of subjects enrolled	Thailand: 54
Country: Number of subjects enrolled	Taiwan: 18
Country: Number of subjects enrolled	Ukraine: 87
Country: Number of subjects enrolled	United States: 7
Country: Number of subjects enrolled	South Africa: 30

Country: Number of subjects enrolled	Brazil: 37
Country: Number of subjects enrolled	Netherlands: 7
Country: Number of subjects enrolled	Poland: 21
Country: Number of subjects enrolled	Slovakia: 13
Country: Number of subjects enrolled	Bulgaria: 80
Country: Number of subjects enrolled	Czech Republic: 32
Country: Number of subjects enrolled	France: 13
Country: Number of subjects enrolled	Hungary: 44
Country: Number of subjects enrolled	Italy: 43
Country: Number of subjects enrolled	Latvia: 7
Country: Number of subjects enrolled	Lithuania: 28
Worldwide total number of subjects	643
EEA total number of subjects	341

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)	420
From 65 to 84 years	220
85 years and over	3

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

The study consisted of three periods: a BP, an OLP, and final SFU. These periods were not necessarily sequential, because the OLP could be "skipped" in select participants. Therefore, the reasons for discontinuation are presented altogether within the Overall Study.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

Participants received double-blinded treatment during the BP; however, open-label treatment was administered during the OLP.

Arms

Are arms mutually exclusive?	Yes
Arm title	Late Erlotinib

Arm description:

Participants received blinded placebo tablets orally (PO) once daily during the BP in the maintenance setting until disease progression, death, or unacceptable toxicity. Those who demonstrated disease progression were unblinded and could receive second-line erlotinib tablets during the OLP as 150 milligrams (mg) PO once daily, provided by the Sponsor. This treatment continued until disease progression, death, or unacceptable toxicity. If disease progression or unacceptable toxicity occurred during the OLP, the participant entered a final SFU period. Participants could also enter the SFU period directly after the BP if they were unable to receive second-line treatment per protocol.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo was administered as film-coated tablets PO once daily during the BP until disease progression, death, or unacceptable toxicity.

Investigational medicinal product name	Erlotinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Erlotinib was administered during either the BP (for Early Erlotinib) or the OLP (for Late Erlotinib) as 150 mg PO once daily until disease progression, death, or unacceptable toxicity.

Arm title	Early Erlotinib
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Arm description:

Participants received blinded erlotinib tablets, 150 mg PO once daily during the BP in the maintenance setting until disease progression, death, or unacceptable toxicity. Those who demonstrated disease progression were unblinded and could receive an approved second-line therapy (but not EGFR targeted therapies) or best supportive care (BSC) as chosen by the investigator during the OLP. This treatment continued until disease progression, death, or unacceptable toxicity. If disease progression or

unacceptable toxicity occurred during the OLP, the participant entered a final SFU period. Participants could also enter the SFU period directly after the BP if they were unable to receive second-line treatment per protocol.

Arm type	Experimental
Investigational medicinal product name	Erlotinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Erlotinib was administered during either the BP (for Early Erlotinib) or the OLP (for Late Erlotinib) as 150 mg PO once daily until disease progression, death, or unacceptable toxicity.

Number of subjects in period 1	Late Erlotinib	Early Erlotinib
Started	321	322
Completed	0	0
Not completed	321	322
Disease progression	17	14
Death	243	258
Not specified	11	6
Adverse event	2	-
Lost to follow-up	6	7
Withdrawal by subject	6	6
Study closed by the Sponsor	36	31

Baseline characteristics

Reporting groups

Reporting group title	Late Erlotinib
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Reporting group description:

Participants received blinded placebo tablets orally (PO) once daily during the BP in the maintenance setting until disease progression, death, or unacceptable toxicity. Those who demonstrated disease progression were unblinded and could receive second-line erlotinib tablets during the OLP as 150 milligrams (mg) PO once daily, provided by the Sponsor. This treatment continued until disease progression, death, or unacceptable toxicity. If disease progression or unacceptable toxicity occurred during the OLP, the participant entered a final SFU period. Participants could also enter the SFU period directly after the BP if they were unable to receive second-line treatment per protocol.

Reporting group title	Early Erlotinib
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Reporting group description:

Participants received blinded erlotinib tablets, 150 mg PO once daily during the BP in the maintenance setting until disease progression, death, or unacceptable toxicity. Those who demonstrated disease progression were unblinded and could receive an approved second-line therapy (but not EGFR targeted therapies) or best supportive care (BSC) as chosen by the investigator during the OLP. This treatment continued until disease progression, death, or unacceptable toxicity. If disease progression or unacceptable toxicity occurred during the OLP, the participant entered a final SFU period. Participants could also enter the SFU period directly after the BP if they were unable to receive second-line treatment per protocol.

Reporting group values	Late Erlotinib	Early Erlotinib	Total
Number of subjects	321	322	643
Age categorical Units: Subjects			

Age continuous Units: years arithmetic mean standard deviation	60.6 ± 9.1	60.8 ± 8.8	-
Gender categorical Units: Subjects Female Male	77 244	84 238	161 482

End points

End points reporting groups

Reporting group title	Late Erlotinib
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Reporting group description:

Participants received blinded placebo tablets orally (PO) once daily during the BP in the maintenance setting until disease progression, death, or unacceptable toxicity. Those who demonstrated disease progression were unblinded and could receive second-line erlotinib tablets during the OLP as 150 milligrams (mg) PO once daily, provided by the Sponsor. This treatment continued until disease progression, death, or unacceptable toxicity. If disease progression or unacceptable toxicity occurred during the OLP, the participant entered a final SFU period. Participants could also enter the SFU period directly after the BP if they were unable to receive second-line treatment per protocol.

Reporting group title	Early Erlotinib
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Reporting group description:

Participants received blinded erlotinib tablets, 150 mg PO once daily during the BP in the maintenance setting until disease progression, death, or unacceptable toxicity. Those who demonstrated disease progression were unblinded and could receive an approved second-line therapy (but not EGFR targeted therapies) or best supportive care (BSC) as chosen by the investigator during the OLP. This treatment continued until disease progression, death, or unacceptable toxicity. If disease progression or unacceptable toxicity occurred during the OLP, the participant entered a final SFU period. Participants could also enter the SFU period directly after the BP if they were unable to receive second-line treatment per protocol.

Subject analysis set title	Placebo (Late Erlotinib)
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Subject analysis set type	Full analysis
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Subject analysis set description:

Participants received blinded placebo tablets PO once daily during the BP in the maintenance setting until disease progression, death, or unacceptable toxicity.

Subject analysis set title	Erlotinib (Early Erlotinib)
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Subject analysis set type	Full analysis
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Subject analysis set description:

Participants received blinded erlotinib tablets, 150 mg PO once daily during the BP in the maintenance setting until disease progression, death, or unacceptable toxicity.

Primary: Percentage of Participants Who Died During the Overall Study

End point title	Percentage of Participants Who Died During the Overall Study ^[1]
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End point description:

Participants were followed for survival until death or premature withdrawal. The percentage of participants who died during the Overall Study (BP, OLP, or SFU) was calculated. Intent-to-Treat (ITT) Population: All participants who were randomized to treatment.

End point type	Primary
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End point timeframe:

Up to approximately 3.5 years (visits at Baseline and Weeks 6, 12, and 18 and every 12 weeks until/at disease progression during BP; per local standards during OLP; then every 12 weeks during SFU until death)

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: This endpoint reflects the percentage of participants with the event of interest. Statistical analysis was performed on the time-to-event endpoint.

End point values	Late Erlotinib	Early Erlotinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	321	322		
Units: percentage of participants				
number (not applicable)	73.2	75.2		

Statistical analyses

No statistical analyses for this end point

Primary: Overall Survival (OS) as Median Time to Event During the Overall Study

End point title	Overall Survival (OS) as Median Time to Event During the Overall Study
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End point description:

Participants were followed for survival until death or premature withdrawal. OS was defined as the interval between date of randomization and date of death from any cause. Median time to event during the Overall Study (BP, OLP, or SFU) was estimated using the Kaplan-Meier method and expressed in months. ITT Population.

End point type	Primary
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End point timeframe:

Up to approximately 3.5 years (visits at Baseline and Weeks 6, 12, and 18 and every 12 weeks until/at disease progression during BP; per local standards during OLP; then every 12 weeks during SFU until death)

End point values	Late Erlotinib	Early Erlotinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	321	322		
Units: months				
median (confidence interval 95%)	9.46 (8.38 to 11.33)	9.72 (8.57 to 11.17)		

Statistical analyses

Statistical analysis title	Unstratified Analysis
Comparison groups	Late Erlotinib v Early Erlotinib
Number of subjects included in analysis	643
Analysis specification	Pre-specified
Analysis type	other ^[2]
P-value	= 0.8183
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.85
upper limit	1.22

Notes:

[2] - The HR and 95% confidence interval (CI) were estimated by Cox regression.

Statistical analysis title	Stratified Analysis
Statistical analysis description: Stratified according to tumor histology, stage of disease, objective response at Baseline, bevacizumab use, smoking status, and region of enrollment.	
Comparison groups	Late Erlotinib v Early Erlotinib
Number of subjects included in analysis	643
Analysis specification	Pre-specified
Analysis type	other ^[3]
P-value	= 0.5256
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.87
upper limit	1.32

Notes:

[3] - The HR and 95% CI were estimated by Cox regression.

Primary: Percentage of Participants Event-Free (Alive) at 1 Year During the Overall Study

End point title	Percentage of Participants Event-Free (Alive) at 1 Year During the Overall Study
End point description: Participants were followed for survival until death or premature withdrawal. The percentage of participants event-free (i.e., still alive) at 1 year during the Overall Study was calculated. ITT Population.	
End point type	Primary
End point timeframe: At 1 year	

End point values	Late Erlotinib	Early Erlotinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	321	322		
Units: percentage of participants				
number (confidence interval 95%)	41.75 (36.2 to 47.3)	42.15 (36.6 to 47.7)		

Statistical analyses

Statistical analysis title	Difference in Event-Free Rate
Comparison groups	Late Erlotinib v Early Erlotinib

Number of subjects included in analysis	643
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.9207
Method	Chi-squared
Parameter estimate	Difference in event-free rate
Point estimate	-0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.25
upper limit	7.45

Secondary: Percentage of Participants Who Died or Experienced Disease Progression During Blinded Treatment

End point title	Percentage of Participants Who Died or Experienced Disease Progression During Blinded Treatment
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End point description:

Tumor response was evaluated using Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Disease progression was defined as a greater than or equal to (\geq) 20 percent (%) and \geq 5-millimeter (mm) increase in the sum of target lesion diameters in reference to the smallest sum on study and/or substantial worsening in non-target disease. The percentage of participants who died or experienced disease progression during the BP was calculated. ITT Population.

End point type	Secondary
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End point timeframe:

Up to approximately 3.5 years (visits at Baseline and Weeks 6, 12, and 18 and every 12 weeks until/at disease progression during BP)

End point values	Placebo (Late Erlotinib)	Erlotinib (Early Erlotinib)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	321	322		
Units: percentage of participants				
number (not applicable)	95	94.1		

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-Free Survival (PFS) as Median Time to Event During Blinded Treatment

End point title	Progression-Free Survival (PFS) as Median Time to Event During Blinded Treatment
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End point description:

Tumor response was evaluated using RECIST version 1.1. Disease progression was defined as a \geq 20% and \geq 5-mm increase in the sum of target lesion diameters in reference to the smallest sum on study and/or substantial worsening in non-target disease. PFS was defined as the interval between date of

randomization and date of first documented death or disease progression. Median time to event during the BP was estimated using the Kaplan-Meier method and expressed in weeks. ITT Population.

End point type	Secondary
End point timeframe:	
Up to approximately 3.5 years (visits at Baseline and Weeks 6, 12, and 18 and every 12 weeks until/at disease progression during BP)	

End point values	Placebo (Late Erlotinib)	Erlotinib (Early Erlotinib)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	321	322		
Units: weeks				
median (full range (min-max))	12 (11.71 to 12.29)	13 (12.14 to 17.43)		

Statistical analyses

Statistical analysis title	Unstratified Analysis
Comparison groups	Placebo (Late Erlotinib) v Erlotinib (Early Erlotinib)
Number of subjects included in analysis	643
Analysis specification	Pre-specified
Analysis type	other ^[4]
P-value	= 0.4759
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.94
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.8
upper limit	1.11

Notes:

[4] - The HR and 95% CI were estimated by Cox regression.

Statistical analysis title	Stratified Analysis
Statistical analysis description:	
Stratified according to tumor histology, stage of disease, objective response at Baseline, bevacizumab use, smoking status, and region of enrollment.	
Comparison groups	Placebo (Late Erlotinib) v Erlotinib (Early Erlotinib)
Number of subjects included in analysis	643
Analysis specification	Pre-specified
Analysis type	other ^[5]
P-value	= 0.1635
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.87

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.72
upper limit	1.06

Notes:

[5] - The HR and 95% CI were estimated by Cox regression.

Secondary: Percentage of Participants Event-Free (Alive and No Disease Progression) at 6 Months During Blinded Treatment

End point title	Percentage of Participants Event-Free (Alive and No Disease Progression) at 6 Months During Blinded Treatment
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End point description:

Tumor response was evaluated using RECIST version 1.1. Disease progression was defined as a $\geq 20\%$ and ≥ 5 -mm increase in the sum of target lesion diameters in reference to the smallest sum on study and/or substantial worsening in non-target disease. The percentage of participants event-free (i.e., still alive and without disease progression) at 6 months during the BP was calculated. ITT Population.

End point type	Secondary
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End point timeframe:

At 6 months

End point values	Placebo (Late Erlotinib)	Erlotinib (Early Erlotinib)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	321	322		
Units: percentage of participants				
number (confidence interval 95%)	24.22 (19.5 to 28.94)	27.11 (22.19 to 32.02)		

Statistical analyses

Statistical analysis title	Difference in Event-Free Rate
Comparison groups	Placebo (Late Erlotinib) v Erlotinib (Early Erlotinib)
Number of subjects included in analysis	643
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.4069
Method	Chi-squared
Parameter estimate	Difference in event-free rate
Point estimate	-2.89
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.7
upper limit	3.93

Secondary: Percentage of Participants With Complete Response (CR) or Partial Response (PR) According to RECIST During Blinded Treatment

End point title	Percentage of Participants With Complete Response (CR) or Partial Response (PR) According to RECIST During Blinded Treatment
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End point description:

Tumor response was evaluated using RECIST version 1.1. CR was defined as disappearance of all target and non-target lesions and short-axis reduction to less than (<) 10 mm of any pathological lymph nodes. PR was defined as a $\geq 30\%$ decrease in the sum of target lesion diameters in reference to the Baseline sum. The percentage of participants with a best overall response of either CR or PR (i.e., the objective response rate [ORR]) during the BP was calculated, and corresponding 95% CI was constructed using the Pearson-Clopper method. ITT Population.

End point type	Secondary
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End point timeframe:

Up to approximately 3.5 years (visits at Baseline and Weeks 6, 12, and 18 and every 12 weeks until/at disease progression during BP)

End point values	Placebo (Late Erlotinib)	Erlotinib (Early Erlotinib)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	321	322		
Units: percentage of participants				
number (confidence interval 95%)	3.7 (1.95 to 6.44)	6.5 (4.08 to 9.8)		

Statistical analyses

Statistical analysis title	Difference in Response Rate
Comparison groups	Placebo (Late Erlotinib) v Erlotinib (Early Erlotinib)
Number of subjects included in analysis	643
Analysis specification	Pre-specified
Analysis type	other ^[6]
P-value	= 0.1097
Method	Chi-squared
Parameter estimate	Difference in response rate
Point estimate	2.78
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.78
upper limit	6.35

Notes:

[6] - The 95% CI for difference in response rates was constructed using the Anderson-Hauck method.

Statistical analysis title	Odds Ratio
Comparison groups	Placebo (Late Erlotinib) v Erlotinib (Early Erlotinib)

Number of subjects included in analysis	643
Analysis specification	Pre-specified
Analysis type	other ^[7]
Parameter estimate	Odds ratio (OR)
Point estimate	1.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.87
upper limit	3.72

Notes:

[7] - The 95% CI for OR was constructed using the Wald method.

Secondary: Percentage of Participants by Best Overall Response According to RECIST During Blinded Treatment

End point title	Percentage of Participants by Best Overall Response According to RECIST During Blinded Treatment
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End point description:

Tumor response was evaluated using RECIST version 1.1. CR was defined as disappearance of all target and non-target lesions and short-axis reduction to <10 mm of any pathological lymph nodes. PR was defined as a $\geq 30\%$ decrease in the sum of target lesion diameters in reference to the Baseline sum. Stable disease (SD) was defined as neither sufficient shrinkage in target lesions to qualify for PR nor sufficient growth to qualify for disease progression. Disease progression (progressive disease/PD) was defined as a $\geq 20\%$ and ≥ 5 -mm increase in the sum of target lesion diameters in reference to the smallest sum on study and/or substantial worsening in non-target disease. The percentage of participants with each level of best tumor response during the BP was calculated, and corresponding 95% CI was constructed using the Pearson-Clopper method. ITT Population.

End point type	Secondary
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End point timeframe:

Up to approximately 3.5 years (visits at Baseline and Weeks 6, 12, and 18 and every 12 weeks until/at disease progression during BP)

End point values	Placebo (Late Erlotinib)	Erlotinib (Early Erlotinib)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	321	322		
Units: percentage of participants				
number (confidence interval 95%)				
CR	0.6 (0.08 to 2.23)	0.9 (0.19 to 2.7)		
PR	3.1 (1.5 to 5.65)	5.6 (3.35 to 8.69)		
SD	55.5 (49.83 to 60.97)	54.7 (49.04 to 60.19)		
PD	38.6 (33.27 to 44.2)	32.3 (27.22 to 37.71)		
Missing	2.2 (0.88 to 4.44)	6.5 (4.08 to 9.8)		

Statistical analyses

Secondary: Percentage of Participants With CR, PR, or SD According to RECIST During Blinded Treatment

End point title	Percentage of Participants With CR, PR, or SD According to RECIST During Blinded Treatment
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End point description:

Tumor response was evaluated using RECIST version 1.1. CR was defined as disappearance of all target and non-target lesions and short-axis reduction to <10 mm of any pathological lymph nodes. PR was defined as a $\geq 30\%$ decrease in the sum of target lesion diameters in reference to the Baseline sum. SD was defined as neither sufficient shrinkage in target lesions to qualify for PR nor sufficient growth to qualify for disease progression. The percentage of participants with a best overall response of CR, PR, or SD (i.e., the disease control rate [DCR]) during the BP was calculated, and corresponding 95% CI was constructed using the Pearson-Clopper method. ITT Population.

End point type	Secondary
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End point timeframe:

Up to approximately 3.5 years (visits at Baseline and Weeks 6, 12, and 18 and every 12 weeks until/at disease progression during BP)

End point values	Placebo (Late Erlotinib)	Erlotinib (Early Erlotinib)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	321	322		
Units: percentage of participants				
number (confidence interval 95%)	59.2 (53.59 to 64.62)	61.2 (55.62 to 66.53)		

Statistical analyses

Statistical analysis title	Difference in Response Rate
Comparison groups	Placebo (Late Erlotinib) v Erlotinib (Early Erlotinib)
Number of subjects included in analysis	643
Analysis specification	Pre-specified
Analysis type	other ^[8]
P-value	= 0.6062
Method	Chi-squared
Parameter estimate	Difference in response rate
Point estimate	1.99
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.74
upper limit	9.72

Notes:

[8] - The 95% CI for difference in response rates was constructed using the Anderson-Hauck method.

Statistical analysis title	Odds Ratio
Comparison groups	Placebo (Late Erlotinib) v Erlotinib (Early Erlotinib)

Number of subjects included in analysis	643
Analysis specification	Pre-specified
Analysis type	other ^[9]
Parameter estimate	Odds ratio (OR)
Point estimate	1.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.79
upper limit	1.49

Notes:

[9] - The 95% CI for OR was constructed using the Wald method.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to approximately 4.5 years (visits at Baseline and Weeks 6, 12, and 18 and every 12 weeks until disease progression, death, or unacceptable toxicity during BP; per local standards and 28 days after last visit during OLP)

Adverse event reporting additional description:

Safety Population: All participants who received at least one dose of study treatment, according to the drug actually received. Only serious adverse events (AEs) were collected during OLP. Therefore, the numbers of subjects affected have been entered as 0 under "Non-Serious Adverse Events" with one exception (see "Rash").

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	18.0
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Reporting groups

Reporting group title	Placebo (Late Erlotinib)
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Reporting group description:

Participants received blinded placebo tablets PO once daily during the BP in the maintenance setting until disease progression, death, or unacceptable toxicity.

Reporting group title	Second-Line Erlotinib (Late Erlotinib)
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Reporting group description:

Participants who received blinded placebo and who demonstrated disease progression were unblinded and could receive second-line erlotinib as 150-mg tablets PO once daily, provided by the Sponsor. This treatment continued during the OLP until disease progression, death, or unacceptable toxicity.

Reporting group title	Second-Line Chemotherapy (Early Erlotinib)
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Reporting group description:

Participants who received blinded erlotinib and who demonstrated disease progression were unblinded and could receive an approved second-line therapy (but not EGFR targeted therapies) or BSC as chosen by the investigator. This treatment continued during the OLP until disease progression, death, or unacceptable toxicity.

Reporting group title	Erlotinib (Early Erlotinib)
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Reporting group description:

Participants received blinded erlotinib tablets, 150 mg PO once daily during the BP in the maintenance setting until disease progression, death, or unacceptable toxicity.

Serious adverse events	Placebo (Late Erlotinib)	Second-Line Erlotinib (Late Erlotinib)	Second-Line Chemotherapy (Early Erlotinib)
Total subjects affected by serious adverse events			
subjects affected / exposed	27 / 319 (8.46%)	23 / 248 (9.27%)	8 / 162 (4.94%)
number of deaths (all causes)	11	51	31
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Meningeal neoplasm			

subjects affected / exposed	0 / 319 (0.00%)	1 / 248 (0.40%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 319 (0.31%)	0 / 248 (0.00%)	1 / 162 (0.62%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			
subjects affected / exposed	1 / 319 (0.31%)	0 / 248 (0.00%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral ischaemia			
subjects affected / exposed	0 / 319 (0.00%)	1 / 248 (0.40%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Superior vena cava syndrome			
subjects affected / exposed	1 / 319 (0.31%)	0 / 248 (0.00%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombosis			
subjects affected / exposed	1 / 319 (0.31%)	0 / 248 (0.00%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Finger amputation			
subjects affected / exposed	0 / 319 (0.00%)	0 / 248 (0.00%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 319 (0.31%)	1 / 248 (0.40%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Death			
subjects affected / exposed	0 / 319 (0.00%)	1 / 248 (0.40%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Fatigue			
subjects affected / exposed	2 / 319 (0.63%)	0 / 248 (0.00%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperthermia			
subjects affected / exposed	0 / 319 (0.00%)	0 / 248 (0.00%)	1 / 162 (0.62%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Impaired healing			
subjects affected / exposed	0 / 319 (0.00%)	1 / 248 (0.40%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Perforated ulcer			
subjects affected / exposed	0 / 319 (0.00%)	1 / 248 (0.40%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	0 / 319 (0.00%)	1 / 248 (0.40%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Pneumonia aspiration			
subjects affected / exposed	0 / 319 (0.00%)	1 / 248 (0.40%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Chronic obstructive pulmonary disease			
subjects affected / exposed	3 / 319 (0.94%)	0 / 248 (0.00%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Dyspnoea			
subjects affected / exposed	0 / 319 (0.00%)	3 / 248 (1.21%)	1 / 162 (0.62%)
occurrences causally related to treatment / all	0 / 0	1 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Haemoptysis			
subjects affected / exposed	0 / 319 (0.00%)	1 / 248 (0.40%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Interstitial lung disease			
subjects affected / exposed	0 / 319 (0.00%)	0 / 248 (0.00%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	0 / 319 (0.00%)	1 / 248 (0.40%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleuritic pain			
subjects affected / exposed	1 / 319 (0.31%)	0 / 248 (0.00%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	0 / 319 (0.00%)	0 / 248 (0.00%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	1 / 319 (0.31%)	0 / 248 (0.00%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Psychiatric disorders			
Confusional state			
subjects affected / exposed	0 / 319 (0.00%)	0 / 248 (0.00%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Depression			

subjects affected / exposed	0 / 319 (0.00%)	0 / 248 (0.00%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Spinal compression fracture			
subjects affected / exposed	1 / 319 (0.31%)	0 / 248 (0.00%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subdural haematoma			
subjects affected / exposed	0 / 319 (0.00%)	0 / 248 (0.00%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tracheal obstruction			
subjects affected / exposed	1 / 319 (0.31%)	0 / 248 (0.00%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femur fracture			
subjects affected / exposed	1 / 319 (0.31%)	0 / 248 (0.00%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fracture			
subjects affected / exposed	0 / 319 (0.00%)	0 / 248 (0.00%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hip fracture			
subjects affected / exposed	1 / 319 (0.31%)	0 / 248 (0.00%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ilium fracture			
subjects affected / exposed	1 / 319 (0.31%)	0 / 248 (0.00%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Limb injury			

subjects affected / exposed	0 / 319 (0.00%)	0 / 248 (0.00%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 319 (0.00%)	1 / 248 (0.40%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arrhythmia			
subjects affected / exposed	0 / 319 (0.00%)	1 / 248 (0.40%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	0 / 319 (0.00%)	0 / 248 (0.00%)	1 / 162 (0.62%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure			
subjects affected / exposed	0 / 319 (0.00%)	1 / 248 (0.40%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Cardio-respiratory arrest			
subjects affected / exposed	0 / 319 (0.00%)	0 / 248 (0.00%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiopulmonary failure			
subjects affected / exposed	0 / 319 (0.00%)	0 / 248 (0.00%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	0 / 319 (0.00%)	0 / 248 (0.00%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericardial effusion			

subjects affected / exposed	1 / 319 (0.31%)	0 / 248 (0.00%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular extrasystoles			
subjects affected / exposed	0 / 319 (0.00%)	0 / 248 (0.00%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebral ischaemia			
subjects affected / exposed	1 / 319 (0.31%)	0 / 248 (0.00%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrovascular accident			
subjects affected / exposed	0 / 319 (0.00%)	0 / 248 (0.00%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dizziness			
subjects affected / exposed	0 / 319 (0.00%)	0 / 248 (0.00%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hydrocephalus			
subjects affected / exposed	1 / 319 (0.31%)	0 / 248 (0.00%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Hypoglycaemic coma			
subjects affected / exposed	0 / 319 (0.00%)	0 / 248 (0.00%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Paraparesis			
subjects affected / exposed	1 / 319 (0.31%)	0 / 248 (0.00%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			

subjects affected / exposed	0 / 319 (0.00%)	0 / 248 (0.00%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 319 (0.31%)	1 / 248 (0.40%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Leukopenia			
subjects affected / exposed	0 / 319 (0.00%)	0 / 248 (0.00%)	1 / 162 (0.62%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	0 / 319 (0.00%)	0 / 248 (0.00%)	1 / 162 (0.62%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Retinal artery occlusion			
subjects affected / exposed	0 / 319 (0.00%)	1 / 248 (0.40%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Gastric ulcer			
subjects affected / exposed	0 / 319 (0.00%)	2 / 248 (0.81%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis erosive			
subjects affected / exposed	0 / 319 (0.00%)	0 / 248 (0.00%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhoids thrombosed			
subjects affected / exposed	1 / 319 (0.31%)	0 / 248 (0.00%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Nausea			
subjects affected / exposed	0 / 319 (0.00%)	0 / 248 (0.00%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	0 / 319 (0.00%)	0 / 248 (0.00%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	0 / 319 (0.00%)	1 / 248 (0.40%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Jaundice			
subjects affected / exposed	0 / 319 (0.00%)	1 / 248 (0.40%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Liver injury			
subjects affected / exposed	0 / 319 (0.00%)	1 / 248 (0.40%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 319 (0.00%)	1 / 248 (0.40%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin mass			
subjects affected / exposed	0 / 319 (0.00%)	0 / 248 (0.00%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			

subjects affected / exposed	1 / 319 (0.31%)	0 / 248 (0.00%)	1 / 162 (0.62%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary retention			
subjects affected / exposed	1 / 319 (0.31%)	0 / 248 (0.00%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Musculoskeletal pain			
subjects affected / exposed	0 / 319 (0.00%)	1 / 248 (0.40%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteonecrosis of jaw			
subjects affected / exposed	0 / 319 (0.00%)	0 / 248 (0.00%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Abscess oral			
subjects affected / exposed	1 / 319 (0.31%)	0 / 248 (0.00%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Impetigo			
subjects affected / exposed	0 / 319 (0.00%)	1 / 248 (0.40%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lobar pneumonia			
subjects affected / exposed	1 / 319 (0.31%)	0 / 248 (0.00%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Peritonitis			
subjects affected / exposed	0 / 319 (0.00%)	0 / 248 (0.00%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Pharyngitis			
subjects affected / exposed	0 / 319 (0.00%)	0 / 248 (0.00%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	3 / 319 (0.94%)	2 / 248 (0.81%)	1 / 162 (0.62%)
occurrences causally related to treatment / all	0 / 3	1 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 1
Respiratory tract infection			
subjects affected / exposed	0 / 319 (0.00%)	0 / 248 (0.00%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 319 (0.00%)	0 / 248 (0.00%)	1 / 162 (0.62%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			
subjects affected / exposed	1 / 319 (0.31%)	0 / 248 (0.00%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	1 / 319 (0.31%)	1 / 248 (0.40%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 319 (0.31%)	1 / 248 (0.40%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetes mellitus			
subjects affected / exposed	1 / 319 (0.31%)	0 / 248 (0.00%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypokalaemia			

subjects affected / exposed	0 / 319 (0.00%)	0 / 248 (0.00%)	1 / 162 (0.62%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolic acidosis			
subjects affected / exposed	0 / 319 (0.00%)	0 / 248 (0.00%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Erlotinib (Early Erlotinib)		
Total subjects affected by serious adverse events			
subjects affected / exposed	36 / 322 (11.18%)		
number of deaths (all causes)	25		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Meningeal neoplasm			
subjects affected / exposed	0 / 322 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 322 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypotension			
subjects affected / exposed	0 / 322 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Peripheral ischaemia			
subjects affected / exposed	0 / 322 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Superior vena cava syndrome			

subjects affected / exposed	0 / 322 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Thrombosis			
subjects affected / exposed	0 / 322 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Finger amputation			
subjects affected / exposed	1 / 322 (0.31%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 322 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Death			
subjects affected / exposed	0 / 322 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Fatigue			
subjects affected / exposed	0 / 322 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hyperthermia			
subjects affected / exposed	0 / 322 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Impaired healing			
subjects affected / exposed	0 / 322 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Perforated ulcer				
subjects affected / exposed	0 / 322 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pyrexia				
subjects affected / exposed	0 / 322 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Pneumonia aspiration				
subjects affected / exposed	1 / 322 (0.31%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Chronic obstructive pulmonary disease				
subjects affected / exposed	0 / 322 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Dyspnoea				
subjects affected / exposed	0 / 322 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Haemoptysis				
subjects affected / exposed	2 / 322 (0.62%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 1			
Interstitial lung disease				
subjects affected / exposed	2 / 322 (0.62%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Pleural effusion				
subjects affected / exposed	1 / 322 (0.31%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Pleuritic pain			
subjects affected / exposed	0 / 322 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pulmonary embolism			
subjects affected / exposed	4 / 322 (1.24%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 3		
Respiratory failure			
subjects affected / exposed	0 / 322 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Confusional state			
subjects affected / exposed	2 / 322 (0.62%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Depression			
subjects affected / exposed	1 / 322 (0.31%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Spinal compression fracture			
subjects affected / exposed	0 / 322 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Subdural haematoma			
subjects affected / exposed	1 / 322 (0.31%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Tracheal obstruction			
subjects affected / exposed	0 / 322 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Femur fracture				
subjects affected / exposed	0 / 322 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Fracture				
subjects affected / exposed	1 / 322 (0.31%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hip fracture				
subjects affected / exposed	0 / 322 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ilium fracture				
subjects affected / exposed	0 / 322 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Limb injury				
subjects affected / exposed	1 / 322 (0.31%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Acute myocardial infarction				
subjects affected / exposed	0 / 322 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Arrhythmia				
subjects affected / exposed	0 / 322 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Atrial fibrillation				
subjects affected / exposed	0 / 322 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiac failure				

subjects affected / exposed	0 / 322 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardio-respiratory arrest			
subjects affected / exposed	1 / 322 (0.31%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Cardiopulmonary failure			
subjects affected / exposed	1 / 322 (0.31%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Myocardial infarction			
subjects affected / exposed	1 / 322 (0.31%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pericardial effusion			
subjects affected / exposed	0 / 322 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ventricular extrasystoles			
subjects affected / exposed	1 / 322 (0.31%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Cerebral ischaemia			
subjects affected / exposed	0 / 322 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cerebrovascular accident			
subjects affected / exposed	2 / 322 (0.62%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 1		
Dizziness			

subjects affected / exposed	1 / 322 (0.31%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hydrocephalus			
subjects affected / exposed	0 / 322 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypoglycaemic coma			
subjects affected / exposed	1 / 322 (0.31%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Paraparesis			
subjects affected / exposed	0 / 322 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Syncope			
subjects affected / exposed	1 / 322 (0.31%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 322 (0.62%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Leukopenia			
subjects affected / exposed	0 / 322 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Neutropenia			
subjects affected / exposed	0 / 322 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Eye disorders			

Retinal artery occlusion			
subjects affected / exposed	0 / 322 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Gastric ulcer			
subjects affected / exposed	0 / 322 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastritis erosive			
subjects affected / exposed	1 / 322 (0.31%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Haemorrhoids thrombosed			
subjects affected / exposed	0 / 322 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nausea			
subjects affected / exposed	1 / 322 (0.31%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	1 / 322 (0.31%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Diarrhoea			
subjects affected / exposed	2 / 322 (0.62%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Jaundice			
subjects affected / exposed	0 / 322 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Liver injury			
subjects affected / exposed	0 / 322 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 322 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Skin mass			
subjects affected / exposed	1 / 322 (0.31%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 322 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Urinary retention			
subjects affected / exposed	0 / 322 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Musculoskeletal pain			
subjects affected / exposed	0 / 322 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Osteonecrosis of jaw			
subjects affected / exposed	1 / 322 (0.31%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Abscess oral			

subjects affected / exposed	0 / 322 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Impetigo				
subjects affected / exposed	0 / 322 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lobar pneumonia				
subjects affected / exposed	0 / 322 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Peritonitis				
subjects affected / exposed	1 / 322 (0.31%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pharyngitis				
subjects affected / exposed	1 / 322 (0.31%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	4 / 322 (1.24%)			
occurrences causally related to treatment / all	1 / 6			
deaths causally related to treatment / all	0 / 2			
Respiratory tract infection				
subjects affected / exposed	1 / 322 (0.31%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Sepsis				
subjects affected / exposed	0 / 322 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Septic shock				

subjects affected / exposed	0 / 322 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			
subjects affected / exposed	0 / 322 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 322 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Diabetes mellitus			
subjects affected / exposed	0 / 322 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypokalaemia			
subjects affected / exposed	0 / 322 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metabolic acidosis			
subjects affected / exposed	1 / 322 (0.31%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		

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

Non-serious adverse events	Placebo (Late Erlotinib)	Second-Line Erlotinib (Late Erlotinib)	Second-Line Chemotherapy (Early Erlotinib)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	107 / 319 (33.54%)	1 / 248 (0.40%)	0 / 162 (0.00%)
General disorders and administration site conditions			
Chest pain			

subjects affected / exposed	11 / 319 (3.45%)	0 / 248 (0.00%)	0 / 162 (0.00%)
occurrences (all)	12	0	0
Fatigue			
subjects affected / exposed	20 / 319 (6.27%)	0 / 248 (0.00%)	0 / 162 (0.00%)
occurrences (all)	21	0	0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	14 / 319 (4.39%)	0 / 248 (0.00%)	0 / 162 (0.00%)
occurrences (all)	20	0	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	37 / 319 (11.60%)	0 / 248 (0.00%)	0 / 162 (0.00%)
occurrences (all)	40	0	0
Dyspnoea			
subjects affected / exposed	23 / 319 (7.21%)	0 / 248 (0.00%)	0 / 162 (0.00%)
occurrences (all)	25	0	0
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	3 / 319 (0.94%)	0 / 248 (0.00%)	0 / 162 (0.00%)
occurrences (all)	3	0	0
Rash	Additional description: Per protocol, only serious AEs were to be reported during the OLP. However, one non-serious AE was reported for a participant in the Second-Line Erlotinib (Late Erlotinib) arm and was therefore included in the analysis and coded with MedDRA (18.1).		
subjects affected / exposed	32 / 319 (10.03%)	1 / 248 (0.40%)	0 / 162 (0.00%)
occurrences (all)	33	1	0
Rash maculo-papular			
subjects affected / exposed	3 / 319 (0.94%)	0 / 248 (0.00%)	0 / 162 (0.00%)
occurrences (all)	4	0	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	11 / 319 (3.45%)	0 / 248 (0.00%)	0 / 162 (0.00%)
occurrences (all)	11	0	0

Non-serious adverse events	Erlotinib (Early Erlotinib)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	206 / 322 (63.98%)		
General disorders and administration site conditions			

Chest pain subjects affected / exposed occurrences (all)	17 / 322 (5.28%) 20		
Fatigue subjects affected / exposed occurrences (all)	21 / 322 (6.52%) 21		
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all)	78 / 322 (24.22%) 102		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	31 / 322 (9.63%) 33		
Dyspnoea subjects affected / exposed occurrences (all)	27 / 322 (8.39%) 28		
Skin and subcutaneous tissue disorders Pruritus subjects affected / exposed occurrences (all)	17 / 322 (5.28%) 20		
Rash	Additional description: Per protocol, only serious AEs were to be reported during the OLP. However, one non-serious AE was reported for a participant in the Second-Line Erlotinib (Late Erlotinib) arm and was therefore included in the analysis and coded with MedDRA (18.1).		
subjects affected / exposed occurrences (all)	127 / 322 (39.44%) 148		
Rash maculo-papular subjects affected / exposed occurrences (all)	17 / 322 (5.28%) 21		
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	21 / 322 (6.52%) 24		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 February 2013	The protocol was amended primarily to allow a lower dose of carboplatin in combination with pemetrexed during the screening phase. Additional minor updates/clarifications were provided for several aspects of the protocol including adverse event reporting, dose modification, administration and unblinding, data collection, and recruitment.

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.

Following the final analysis, the study was closed and all remaining participants were withdrawn from the study and considered "Not Completed" (as presented under Subject Disposition). However, the overall status of study was confirmed as completed.

Notes: