



Clinical trial results:

Phase 2, Open-Label, Single Arm Study of the Efficacy and Safety of PF-02341066 in Patients With Advanced Non-Small-Cell Lung Cancer (NSCLC) Harboring a Translocation or Inversion Involving the Anaplastic Lymphoma Kinase (ALK) Gene Locus

Summary

EudraCT number	2009-012504-13
Trial protocol	GB NL DE ES HU PL GR IT FR IE BG SE
Global end of trial date	29 December 2015

Results information

Result version number	v2 (current)
This version publication date	29 December 2016
First version publication date	01 April 2016
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	A8081005
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00932451
WHO universal trial number (UTN)	-
Other trial identifiers	EudraCT Number: 2009-012504-13

Notes:

Sponsors

Sponsor organisation name	Pfizer, Inc.
Sponsor organisation address	235 East 42nd Street, New York, United States, 10017
Public contact	Pfizer ClinicalTrials.gov Call Center, Pfizer, Inc., 001 18007181021 x, ClinicalTrials.gov_Inquiries@pfizer.com
Scientific contact	Pfizer ClinicalTrials.gov Call Center, Pfizer, Inc., 001 18007181021 x, ClinicalTrials.gov_Inquiries@pfizer.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	08 August 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	16 March 2015
Global end of trial reached?	Yes
Global end of trial date	29 December 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

1.) To assess the anti-tumor efficacy of oral single agent PF - 02341066 administered to patients with advanced NSCLC after failure of at least one line of chemotherapy and harbor a translocation or inversion event involving the ALK gene locus as measured by ORR; 2.) To assess the safety and tolerability of oral PF-02341066

Protection of trial subjects:

This study was conducted in compliance with the ethical principles originating in or derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonization Good Clinical Practice (GCP) Guidelines. In addition, all local regulatory requirements were followed; in particular, those affording greater protection to the safety of study participants.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	07 January 2010
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	6 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 17
Country: Number of subjects enrolled	Brazil: 11
Country: Number of subjects enrolled	Bulgaria: 3
Country: Number of subjects enrolled	Canada: 11
Country: Number of subjects enrolled	China: 190
Country: Number of subjects enrolled	France: 45
Country: Number of subjects enrolled	Germany: 45
Country: Number of subjects enrolled	Greece: 4
Country: Number of subjects enrolled	Hong Kong: 10
Country: Number of subjects enrolled	Hungary: 2
Country: Number of subjects enrolled	Ireland: 3
Country: Number of subjects enrolled	Italy: 82
Country: Number of subjects enrolled	Japan: 77
Country: Number of subjects enrolled	Korea, Republic of: 143
Country: Number of subjects enrolled	Netherlands: 5
Country: Number of subjects enrolled	Poland: 3

Country: Number of subjects enrolled	Russian Federation: 6
Country: Number of subjects enrolled	Spain: 52
Country: Number of subjects enrolled	Sweden: 3
Country: Number of subjects enrolled	Taiwan: 34
Country: Number of subjects enrolled	United Kingdom: 18
Country: Number of subjects enrolled	United States: 302
Worldwide total number of subjects	1066
EEA total number of subjects	265

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)	894
From 65 to 84 years	172
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 1069 participants were enrolled and 1066 participants received greater than or equal to 1 dose of crizotinib. The 3 participants who were enrolled and not treated were withdrawn from the study before receiving treatment because they were not eligible and were mistakenly entered into the interactive voice response system.

Pre-assignment

Screening details:

A total of 144 participants in study NCT00932893 were also enrolled in this study to receive treatment with crizotinib, including 143 participants randomized to the chemotherapy arm then crossed over in this study and 1 participant initially erroneously randomized in the crizotinib arm but not treated.

Period 1

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

Arms

Arm title	Crizotinib 250 mg BID
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Arm description:

Participants were administered crizotinib at a starting dose of 250 mg orally, BID on a continuous dosing period as two 100-mg tablets and one 50-mg tablet at approximately 12 hours apart the same time each day.

Arm type	Experimental
Investigational medicinal product name	Crizotinib
Investigational medicinal product code	
Other name	PF-02341066
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

starting dose 250 mg orally, BID, continuous dosing schedule

Number of subjects in period 1	Crizotinib 250 mg BID
Started	1066
Completed	244
Not completed	822
Consent withdrawn by subject	69
Death	726
Reason unspecified	5
Lost to follow-up	22

Baseline characteristics

Reporting groups

Reporting group title	Crizotinib 250 mg BID
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Reporting group description:

Participants were administered crizotinib at a starting dose of 250 mg orally, BID on a continuous dosing period as two 100-mg tablets and one 50-mg tablet at approximately 12 hours apart the same time each day.

Reporting group values	Crizotinib 250 mg BID	Total	
Number of subjects	1066	1066	
Age categorical Units: Subjects			
<65	894	894	
>=65	172	172	
Age Continuous Units: years arithmetic mean standard deviation	52.2 ± 12.3	-	
Gender, Male/Female Units: Participants			
Male	465	465	
Female	601	601	

Subject analysis sets

Subject analysis set title	ALK Positive by IUO
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Subject analysis set type	Full analysis
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Subject analysis set description:

Participants were administered crizotinib at a starting dose of 250 milligram [mg] orally, twice daily (BID) on a continuous dosing period as two 100-mg tablets and one 50-mg tablet at approximately 12 hours apart the same time each day.

Subject analysis set title	ALK positive by non-IUO only
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Subject analysis set type	Full analysis
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Subject analysis set description:

Participants were administered crizotinib at a starting dose of 250 milligram [mg] orally, twice daily (BID) on a continuous dosing period as two 100-mg tablets and one 50-mg tablet at approximately 12 hours apart the same time each day.

Subject analysis set title	Plasma concentrations of crizotinib (PF-02341066)
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Subject analysis set type	Safety analysis
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Subject analysis set description:

Participants were administered crizotinib at a starting dose of 250 mg orally, BID on a continuous dosing period as two 100-mg tablets and one 50-mg tablet at approximately 12 hours apart the same time each day.

Subject analysis set title	Plasma concentrations of crizotinib metabolite (PF-06260182)
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Subject analysis set type	Safety analysis
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Subject analysis set description:

Participants were administered crizotinib at a starting dose of 250 mg orally, BID on a continuous dosing period as two 100-mg tablets and one 50-mg tablet at approximately 12 hours apart the same time each day.

Subject analysis set title	Crizotinib 250 mg BID-ALT cases
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Subject analysis set type	Safety analysis
Subject analysis set description: Participants were administered crizotinib at a starting dose of 250 milligram [mg] orally, twice daily (BID) on a continuous dosing period as two 100-mg tablets and one 50-mg tablet at approximately 12 hours apart the same time each day.	
Subject analysis set title	Crizotinib 250 mg BID-ALT controls
Subject analysis set type	Safety analysis
Subject analysis set description: Participants were administered crizotinib at a starting dose of 250 milligram [mg] orally, twice daily (BID) on a continuous dosing period as two 100-mg tablets and one 50- mg tablet at approximately 12 hours apart the same time each day.	

Reporting group values	ALK Positive by IUO	ALK positive by non-IUO only	Plasma concentrations of crizotinib (PF-02341066)
Number of subjects	908	158	906
Age categorical Units: Subjects			
<65	393	72	
>=65	515	86	
Age Continuous Units: years arithmetic mean standard deviation	51.8 ± 12.05	54.3 ± 13.66	±
Gender, Male/Female Units: Participants			
Male	393	72	
Female	515	86	

Reporting group values	Plasma concentrations of crizotinib metabolite (PF-06260182)	Crizotinib 250 mg BID-ALT cases	Crizotinib 250 mg BID-ALT controls
Number of subjects	904	74	115
Age categorical Units: Subjects			
<65			
>=65			
Age Continuous Units: years arithmetic mean standard deviation	±	±	±
Gender, Male/Female Units: Participants			
Male			
Female			

End points

End points reporting groups

Reporting group title	Crizotinib 250 mg BID
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Reporting group description:

Participants were administered crizotinib at a starting dose of 250 mg orally, BID on a continuous dosing period as two 100-mg tablets and one 50-mg tablet at approximately 12 hours apart the same time each day.

Subject analysis set title	ALK Positive by IUO
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Subject analysis set type	Full analysis
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Subject analysis set description:

Participants were administered crizotinib at a starting dose of 250 milligram [mg] orally, twice daily (BID) on a continuous dosing period as two 100-mg tablets and one 50-mg tablet at approximately 12 hours apart the same time each day.

Subject analysis set title	ALK positive by non-IUO only
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Subject analysis set type	Full analysis
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Subject analysis set description:

Participants were administered crizotinib at a starting dose of 250 milligram [mg] orally, twice daily (BID) on a continuous dosing period as two 100-mg tablets and one 50-mg tablet at approximately 12 hours apart the same time each day.

Subject analysis set title	Plasma concentrations of crizotinib (PF-02341066)
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Subject analysis set type	Safety analysis
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Subject analysis set description:

Participants were administered crizotinib at a starting dose of 250 mg orally, BID on a continuous dosing period as two 100-mg tablets and one 50-mg tablet at approximately 12 hours apart the same time each day.

Subject analysis set title	Plasma concentrations of crizotinib metabolite (PF-06260182)
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Subject analysis set type	Safety analysis
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Subject analysis set description:

Participants were administered crizotinib at a starting dose of 250 mg orally, BID on a continuous dosing period as two 100-mg tablets and one 50-mg tablet at approximately 12 hours apart the same time each day.

Subject analysis set title	Crizotinib 250 mg BID-ALT cases
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Subject analysis set type	Safety analysis
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Subject analysis set description:

Participants were administered crizotinib at a starting dose of 250 milligram [mg] orally, twice daily (BID) on a continuous dosing period as two 100-mg tablets and one 50-mg tablet at approximately 12 hours apart the same time each day.

Subject analysis set title	Crizotinib 250 mg BID-ALT controls
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Subject analysis set type	Safety analysis
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Subject analysis set description:

Participants were administered crizotinib at a starting dose of 250 milligram [mg] orally, twice daily (BID) on a continuous dosing period as two 100-mg tablets and one 50- mg tablet at approximately 12 hours apart the same time each day.

Primary: Objective response rate

End point title	Objective response rate ^[1]
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End point description:

The objective response rate (ORR) as a measure of anti-tumor efficacy of oral PF-02341066 in participants with advanced NSCLC with an ALK gene translocation or inversion after failure of at least one line of chemotherapy. Response-evaluable populations: defined as participants in either the SA-ALK positive by IUO population or SA-ALK positive by non-IUO population, respectively, who had adequate baseline tumor assessment.

End point type	Primary
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End point timeframe:

6 years

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: Statistical analysis was not planned for the end point.

End point values	Crizotinib 250 mg BID			
Subject group type	Reporting group			
Number of subjects analysed	1066			
Units: Percentage				
number (confidence interval 95%)				
ALK Positive by IUO; N=908	54.1 (50.8 to 57.4)			
ALK Positive by non-IUO only, N= 158	40.5 (32.8 to 48.6)			

Statistical analyses

No statistical analyses for this end point

Primary: Number of participants with adverse events

End point title	Number of participants with adverse events ^[2]
End point description: Incidence of adverse events and laboratory abnormalities (severity graded by the National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE], version 4.0). The safety analysis population included all participants who were enrolled and received at least 1 dose of study medication (excluding day-7 pharmacokinetic [PK] dosing).	
End point type	Primary
End point timeframe: 6 years	

Notes:

[2] - 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: Statistical analysis was not planned for the end point.

End point values	Crizotinib 250 mg BID			
Subject group type	Reporting group			
Number of subjects analysed	1066			
Units: Percentage of Participants				
number (not applicable)				
Serious AEs (all causalities)	50.6			
Grade 3/4 AEs (all causalities)	65.6			
Grade 5 AEs (all causalities)	22.7			
Serious AEs (treatment related)	11.5			
Grade 3/4 AEs (treatment related)	40.2			
Grade 5 AEs (treatment related)	1.6			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of response (DR)

End point title	Duration of response (DR)
End point description: DR was defined as the time from the first documentation of objective tumor response (CR or PR) that was subsequently confirmed, to the first documentation of objective tumor progression or to death on study due to any cause, whichever occurred first. DR (in months) was calculated as (first date of PD or death – first date of CR or PR that was subsequently confirmed + 1)/30.4. Response-evaluable populations: defined as participants in either the SA-ALK positive by IUO population or SA-ALK positive by non-IUO population, respectively, who had adequate baseline tumor assessment.	
End point type	Secondary
End point timeframe: 6 years	

End point values	Crizotinib 250 mg BID			
Subject group type	Reporting group			
Number of subjects analysed	1066			
Units: Months				
median (confidence interval 95%)				
ALK Positive by IUO, N=491	11.8 (10.4 to 12.8)			
ALK Positive by non-IUO only, N=64	9.5 (6.9 to 15.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Tumor Response (TTR)

End point title	Time to Tumor Response (TTR)
End point description: TTR was defined as the time (in weeks) from the date of Cycle 1 Day 1 dose to first documentation of objective tumor response (CR or PR) that was subsequently confirmed. For participants proceeding from PR to CR, the onset of PR was taken as the onset of response. Response-evaluable populations: defined as participants in either the SA-ALK positive by IUO population or SA-ALK positive by non-IUO population, respectively, who had adequate baseline tumor assessment.	
End point type	Secondary
End point timeframe: 6 years	

End point values	Crizotinib 250 mg BID			
Subject group type	Reporting group			
Number of subjects analysed	1066			
Units: Weeks				
median (full range (min-max))				
ALK Positive by IUO (n=491)	6.1 (2.7 to 164)			
ALK Positive by non-IUO only (n=64)	6.3 (4.7 to 65.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Control Rate (DCR)

End point title	Disease Control Rate (DCR)
End point description: DCR at 6 and 12 weeks was defined as the percentage of participants with a confirmed CR, confirmed PR, or SD (according to RECIST v 1.1) at 6 weeks and 12 weeks, respectively. Response-evaluable populations: defined as participants in either the SA-ALK positive by IUO population or SA-ALK positive by non-IUO population, respectively, who had adequate baseline tumor assessment.	
End point type	Secondary
End point timeframe: 6 years	

End point values	Crizotinib 250 mg BID			
Subject group type	Reporting group			
Number of subjects analysed	1066			
Units: Percentage				
number (confidence interval 95%)				
ALK Positive by IUO at Week 6, N=908	81.7 (79 to 84.2)			
ALK Positive by IUO at Week 12, N=908	70.8 (67.7 to 73.8)			
ALK Positive by non-IUO at Week 6, N=158	69.6 (61.8 to 76.7)			
ALK Positive by non-IUO at Week 12, N=158	61.4 (53.3 to 69)			

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival (PFS)

End point title	Progression Free Survival (PFS)
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End point description:

PFS was defined as the time from the date of the Cycle 1 Day 1 dose to the date of the first documentation of objective tumor progression or death on study due to any cause, whichever occurred first. The safety analysis populations included all participants who received at least 1 dose of study medication (excluding day-7 pharmacokinetic [PK] dosing), and were ALK positive either by IUO (SA-ALK positive by IUO population) or by non-IUO (SA-ALK positive by non-IUO population), respectively.

End point type	Secondary
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End point timeframe:

6 years

End point values	Crizotinib 250 mg BID			
Subject group type	Reporting group			
Number of subjects analysed	1066			
Units: Months				
median (confidence interval 95%)				
ALK Positive by IUO , N= 908	8.4 (7.1 to 9.7)			
ALK Positive by non-IUO only , N=158	6.9 (5.6 to 9.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from Baseline in QLQ-C30 Global Quality of Life scores.

End point title	Mean change from Baseline in QLQ-C30 Global Quality of Life scores.
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End point description:

The EORTC QLQ-C30 consists of 30 questions which assess five functional domains (physical, role, cognitive, emotional, and social), global health status/quality of life, disease/treatment related symptoms (fatigue, pain, nausea/vomiting, dyspnea, appetite loss, sleep disturbance, constipation, and diarrhoea), and the perceived financial impact of disease. "n" is the number of participants who completed the scale at baseline and at the respective Cycles. The patient reported outcomes (PRO) evaluable population was defined as the participants from the safety analysis (SA) population who completed a baseline assessment and at least one post-baseline assessment.

End point type	Secondary
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End point timeframe:

6 years

End point values	Crizotinib 250 mg BID			
Subject group type	Reporting group			
Number of subjects analysed	976			
Units: Units on a scale				
arithmetic mean (standard deviation)				
CYCLE2/DAY1	7.9 (± 22.2)			
CYCLE3/DAY1	10.6 (± 23.7)			
CYCLE4/DAY1	12.2 (± 24.9)			

CYCLE5/DAY1	11.5 (± 23.9)			
CYCLE6/DAY1	11.9 (± 24.8)			
CYCLE7/DAY1	12.3 (± 24.7)			
CYCLE8/DAY1	12.3 (± 24.1)			
CYCLE9/DAY1	11.8 (± 23.5)			
CYCLE10/DAY1	11.5 (± 23.6)			
CYCLE11/DAY1	10.4 (± 23.9)			
CYCLE12/DAY1	10.1 (± 21.6)			
CYCLE13/DAY1	11 (± 24)			
CYCLE14/DAY1	10.4 (± 21.5)			
CYCLE15/DAY1	9.5 (± 23.9)			
CYCLE16/DAY1	7.4 (± 23.2)			
CYCLE17/DAY1	8 (± 24.3)			
CYCLE18/DAY1	7.8 (± 22)			
CYCLE19/DAY1	7.8 (± 23.1)			
CYCLE20/DAY1	9.1 (± 22.4)			
CYCLE21/DAY1	7.8 (± 22.5)			
CYCLE22/DAY1	5.9 (± 23.7)			
CYCLE23/DAY1	6.7 (± 24)			
CYCLE24/DAY1	6.4 (± 25)			
CYCLE25/DAY1	4.7 (± 23.3)			
CYCLE26/DAY1	8.3 (± 24.7)			
CYCLE27/DAY1	5.9 (± 23.2)			
CYCLE28/DAY1	6.7 (± 24.2)			
CYCLE29/DAY1	5.7 (± 23.3)			
CYCLE30/DAY1	6.4 (± 24.9)			
End of treatment	-1 (± 27.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change from Baseline of EORTC QLQ-C30 Functional and Symptom Scale Scores

End point title	Mean Change from Baseline of EORTC QLQ-C30 Functional and Symptom Scale Scores
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End point description:

The EORTC QLQ-C30 consists of 30 questions which assess five functional domains (physical, role, cognitive, emotional, and social), global health status/quality of life, disease/treatment related symptoms (fatigue, pain, nausea/vomiting, dyspnoea, appetite loss, sleep disturbance, constipation, and diarrhoea), and the perceived financial impact of disease. "n" is the number of participants who completed the scale at baseline and at the respective Cycles. The PRO evaluable population was defined as the participants from the SA population who completed a baseline assessment and at least one post-baseline assessment.

End point type	Secondary
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End point timeframe:

6 years

End point values	Crizotinib 250 mg BID			
Subject group type	Reporting group			
Number of subjects analysed	976			
Units: Units on a scale				
arithmetic mean (standard deviation)				
Physical Functioning (Cycle 2/Day 1) (N=936)	4.3 (± 17.1)			
Physical Functioning (Cycle 3/Day 1) (N=879)	6.6 (± 18.6)			
Physical Functioning (Cycle 4/Day 1) (N=836)	8.2 (± 19.1)			
Physical Functioning (Cycle 5/Day 1) (N=810)	8.8 (± 18.8)			
Physical Functioning (Cycle 6/Day 1) (N=778)	9.5 (± 18.6)			
Physical Functioning (Cycle 7/Day 1) (N=739)	10 (± 19.3)			
Physical Functioning (Cycle 8/Day 1) (N= 704)	10.1 (± 18.8)			
Physical Functioning (Cycle 9/Day 1) (N= 673)	10.5 (± 18.2)			
Physical Functioning (Cycle 10/Day 1) (N= 637)	9.5 (± 17.9)			
Physical Functioning (Cycle 11/Day 1) (N=577)	9.1 (± 17.9)			
Physical Functioning (Cycle 12/Day 1) (N=412)	8.2 (± 17.3)			
Physical Functioning (Cycle 13/Day 1) (N=517)	8.7 (± 18.1)			
Physical Functioning (Cycle 14/Day 1) (N=358)	8.2 (± 16.5)			
Physical Functioning (Cycle 15/Day 1) (N=466)	7.3 (± 19.2)			
Physical Functioning (Cycle 16/Day 1) (N=295)	6.3 (± 19.1)			
Physical Functioning (Cycle 17/Day 1) (N=424)	6 (± 18.9)			
Physical Functioning (Cycle 18/Day 1) (N=250)	6.1 (± 18.4)			
Physical Functioning (Cycle 19/Day 1) (N=380)	6.6 (± 16.8)			
Physical Functioning (Cycle 20/Day 1) (N=224)	5.1 (± 16.8)			
Physical Functioning (Cycle 21/Day 1) (N=346)	5.7 (± 17.6)			
Physical Functioning (Cycle 22/Day 1) (N=182)	3.8 (± 17)			
Physical Functioning (Cycle 23/Day 1) (N=311)	3.7 (± 17.1)			
Physical Functioning (Cycle 24/Day 1) (N=156)	2.4 (± 18.9)			
Physical Functioning (Cycle 25/Day 1) (N=296)	4 (± 18)			
Physical Functioning (Cycle 26/Day 1) (N=129)	5.3 (± 18.1)			
Physical Functioning (Cycle 27/Day 1) (N=275)	3.8 (± 16.1)			
Physical Functioning (Cycle 28/Day 1) (N=121)	3.6 (± 20.4)			

Physical Functioning (Cycle 29/Day 1) (N=251)	3.7 (± 15.8)			
Physical Functioning (Cycle 30/Day 1) (N=109)	2.8 (± 21.9)			
Physical Functioning (End of treatment) (N=451)	0.1 (± 25)			
Cognitive functioning (Cycle 2/Day 1) (N=930)	1 (± 18.4)			
Cognitive Functioning (Cycle 3/Day 1) (N=874)	2.1 (± 19.4)			
Cognitive Functioning (Cycle 4/Day 1) (N=829)	2.1 (± 18.6)			
Cognitive Functioning (Cycle 5/Day 1) (N=806)	2.3 (± 18.4)			
Cognitive Functioning (Cycle 6/Day 1) (N=773)	2.5 (± 18.2)			
Cognitive Functioning (Cycle 7/Day 1) (N=734)	3.2 (± 18.6)			
Cognitive Functioning (Cycle 8/Day 1) (N=699)	3.3 (± 18.5)			
Cognitive Functioning (Cycle 9/Day 1) (N=667)	3 (± 18.4)			
Cognitive Functioning (Cycle 10/Day 1) (N=632)	2.7 (± 19)			
Cognitive Functioning (Cycle 11/Day 1) (N=571)	3 (± 18.5)			
Cognitive Functioning (Cycle 12/Day 1) (N=411)	1.5 (± 17.1)			
Cognitive Functioning (Cycle 13/Day 1) (N=512)	2 (± 19.3)			
Cognitive Functioning (Cycle 14/Day 1) (N=352)	1.2 (± 17.8)			
Cognitive Functioning (Cycle 15/Day 1) (N=462)	1.3 (± 19.7)			
Cognitive Functioning (Cycle 16/Day 1) (N=294)	-0.1 (± 18.1)			
Cognitive Functioning (Cycle 17/Day 1) (N=419)	0 (± 19.4)			
Cognitive Functioning (Cycle 18/Day 1) (N=247)	0.1 (± 19.2)			
Cognitive Functioning (Cycle 19/Day 1) (N=376)	0.1 (± 19.2)			
Cognitive Functioning (Cycle 20/Day 1) (N=222)	0.9 (± 18.1)			
Cognitive Functioning (Cycle 21/Day 1) (N=340)	-0.1 (± 17.8)			
Cognitive Functioning (Cycle 22/Day 1) (N=179)	-1.1 (± 17.5)			
Cognitive Functioning (Cycle 23/Day 1) (N=305)	-0.3 (± 17.6)			
Cognitive Functioning (Cycle 24/Day 1) (N=154)	-3.6 (± 21.2)			
Cognitive Functioning (Cycle 25/Day 1) (N=293)	-1.3 (± 18.1)			
Cognitive Functioning (Cycle 26/Day 1) (N=127)	-0.3 (± 20.2)			
Cognitive Functioning (Cycle 27/Day 1) (N=269)	-0.9 (± 17.7)			
Cognitive Functioning (Cycle 28/Day 1) (N=120)	-0.6 (± 20.7)			
Cognitive Functioning (Cycle 29/Day 1) (N=247)	-0.2 (± 16)			

Cognitive Functioning (Cycle 30/Day 1) (N=106)	-2.5 (± 23.7)			
Cognitive Functioning (End of treatment) (N=449)	-2.3 (± 21.7)			
Emotional Functioning (Cycle 2/Day 1) (N=928)	5.5 (± 18.4)			
Emotional Functioning (Cycle 3/Day 1) (N=873)	6.8 (± 18.8)			
Emotional Functioning (Cycle 4/Day 1) (N=827)	8.2 (± 18.3)			
Emotional Functioning (Cycle 5/Day 1) (N=804)	7.8 (± 18.3)			
Emotional Functioning (Cycle 6/Day 1) (N=772)	8.6 (± 18)			
Emotional Functioning (Cycle 7/Day 1) (N=731)	8.3 (± 18.3)			
Emotional Functioning (Cycle 8/Day 1) (N=697)	9.2 (± 18.9)			
Emotional Functioning (Cycle 9/Day 1) (N=665)	8.7 (± 18.6)			
Emotional Functioning (Cycle 10/Day 1) (N=630)	8.5 (± 18.9)			
Emotional Functioning (Cycle 11/Day 1) (N=571)	8.5 (± 17.6)			
Emotional Functioning (Cycle 12/Day 1) (N=410)	8.4 (± 17.6)			
Emotional Functioning (Cycle 13/Day 1) (N=511)	8.5 (± 19.1)			
Emotional Functioning (Cycle 14/Day 1) (N=352)	7.9 (± 16.6)			
Emotional Functioning (Cycle 15/Day 1) (N=461)	8.3 (± 18.7)			
Emotional Functioning (Cycle 16/Day 1) (N=293)	7.5 (± 16.8)			
Emotional Functioning (Cycle 17/Day 1) (N=418)	6.9 (± 19.2)			
Emotional Functioning (Cycle 18/Day 1) (N=246)	7.5 (± 17.2)			
Emotional Functioning (Cycle 19/Day 1) (N=376)	7.4 (± 18.3)			
Emotional Functioning (Cycle 20/Day 1) (N=221)	7.4 (± 17.6)			
Emotional Functioning (Cycle 21/Day 1) (N=340)	6.7 (± 17.5)			
Emotional Functioning (Cycle 22/Day 1) (N=178)	5.2 (± 17.9)			
Emotional Functioning (Cycle 23/Day 1) (N=305)	6.6 (± 17.6)			
Emotional Functioning (Cycle 24/Day 1) (N=153)	4.4 (± 19.5)			
Emotional Functioning (Cycle 25/Day 1) (N=293)	6.2 (± 17.4)			
Emotional Functioning (Cycle 26/Day 1) (N=126)	7.5 (± 18.9)			
Emotional Functioning (Cycle 27/Day 1) (N=269)	6.3 (± 17.6)			
Emotional Functioning (Cycle 28/Day 1) (N=119)	4.1 (± 19.2)			
Emotional Functioning (Cycle 29/Day 1) (N=247)	5.9 (± 17.7)			
Emotional Functioning (Cycle 30/Day 1) (N=105)	3.2 (± 21.5)			

Emotional Functioning (End of treatment) (N=448)	1.9 (± 22.3)			
Role Functioning (Cycle 2/Day 1) (N=935)	4.2 (± 25)			
Role Functioning (Cycle 3/Day 1) (N=879)	7.3 (± 27.8)			
Role Functioning (Cycle 4/Day 1) (N=835)	9.3 (± 28.7)			
Role Functioning (Cycle 5/Day 1) (N=809)	9.5 (± 28.4)			
Role Functioning (Cycle 6/Day 1) (N=778)	10.5 (± 28.7)			
Role Functioning (Cycle 7/Day 1) (N=738)	10.4 (± 30.2)			
Role Functioning (Cycle 8/Day 1) (N=702)	10.8 (± 28.5)			
Role Functioning (Cycle 9/Day 1) (N=671)	10.9 (± 28.1)			
Role Functioning (Cycle 10/Day 1) (N=635)	10.8 (± 28.8)			
Role Functioning (Cycle 11/Day 1) (N=576)	10 (± 29)			
Role Functioning (Cycle 12/Day 1) (N=413)	8.4 (± 28)			
Role Functioning (Cycle 13/Day 1) (N=516)	9 (± 28.8)			
Role Functioning (Cycle 14/Day 1) (N=358)	8.4 (± 26.5)			
Role Functioning (Cycle 15/Day 1) (N=465)	8.8 (± 28.7)			
Role Functioning (Cycle 16/Day 1) (N=296)	6 (± 28.3)			
Role Functioning (Cycle 17/Day 1) (N=424)	6.1 (± 30.4)			
Role Functioning (Cycle 18/Day 1) (N=250)	5.2 (± 27.8)			
Role Functioning (Cycle 19/Day 1) (N=380)	8 (± 27.5)			
Role Functioning (Cycle 20/Day 1) (N=224)	5.8 (± 25.1)			
Role Functioning (Cycle 21/Day 1) (N=346)	5.3 (± 27.1)			
Role Functioning (Cycle 22/Day 1) (N=182)	4.1 (± 26.7)			
Role Functioning (Cycle 23/Day 1) (N=311)	3.2 (± 27.9)			
Role Functioning (Cycle 24/Day 1) (N=157)	2.7 (± 29.5)			
Role Functioning (Cycle 25/Day 1) (N=297)	2.2 (± 27.2)			
Role Functioning (Cycle 26/Day 1) (N=129)	6.1 (± 28)			
Role Functioning (Cycle 27/Day 1) (N=275)	2.4 (± 27.6)			
Role Functioning (Cycle 28/Day 1) (N=121)	1.5 (± 30)			
Role Functioning (Cycle 29/Day 1)(N=251)	1.6 (± 24.6)			
Role Functioning (Cycle 30/Day 1) (N=109)	1.1 (± 34)			
Role Functioning (End of treatment) (N=451)	-1.6 (± 31.9)			

Social Functioning (Cycle 2/Day 1) (N=928)	6.8 (± 25.9)			
Social Functioning (Cycle 3/Day 1) (N=872)	9.1 (± 26.2)			
Social Functioning (Cycle 4/Day 1) (N=828)	10.4 (± 27.2)			
Social Functioning (Cycle 5/Day 1) (N=805)	10.6 (± 26.7)			
Social Functioning (Cycle 6/Day 1) (N=773)	11.1 (± 27)			
Social Functioning (Cycle 7/Day 1) (N=733)	12.1 (± 26.5)			
Social Functioning (Cycle 8/Day 1) (N=698)	12.3 (± 26.4)			
Social Functioning (Cycle 9/Day 1) (N=666)	12 (± 26.4)			
Social Functioning (Cycle 10/Day 1) (N=631)	11.8 (± 26.1)			
Social Functioning (Cycle 11/Day 1) (N=570)	12.1 (± 27.3)			
Social Functioning (Cycle 12/Day 1) (N=410)	10.3 (± 26.3)			
Social Functioning (Cycle 13/Day 1) (N=512)	10.6 (± 27.3)			
Social Functioning (Cycle 14/Day 1) (N=352)	10.4 (± 25.1)			
Social Functioning (Cycle 15/Day 1) (N=462)	10.1 (± 28.1)			
Social Functioning (Cycle 16/Day 1) (N=293)	9 (± 26.4)			
Social Functioning (Cycle 17/Day 1) (N=418)	8.8 (± 26.9)			
Social Functioning (Cycle 18/Day 1) (N=246)	6.6 (± 25.4)			
Social Functioning (Cycle 19/Day 1) (N=376)	8 (± 25.6)			
Social Functioning (Cycle 20/Day 1) (N=221)	5.7 (± 23.9)			
Social Functioning (Cycle 21/Day 1) (N=340)	6.7 (± 26.6)			
Social Functioning (Cycle 22/Day 1) (N=178)	5.3 (± 22.7)			
Social Functioning (Cycle 23/Day 1) (N=305)	7 (± 24.9)			
Social Functioning (Cycle 24/Day 1) (N=153)	3.6 (± 26.5)			
Social Functioning (Cycle 25/Day 1) (N=293)	4.4 (± 25.8)			
Social Functioning (Cycle 26/Day 1) (N=126)	5.2 (± 26.6)			
Social Functioning (Cycle 27/Day 1) (N=269)	5.3 (± 26.4)			
Social Functioning (Cycle 28/Day 1) (N=119)	2.1 (± 31.4)			
Social Functioning (Cycle 29/Day 1) (N=247)	6.6 (± 24.1)			
Social Functioning (Cycle 30/Day 1) (N=105)	1.6 (± 29)			
Social Functioning (End of treatment) (N=449)	2.7 (± 31.2)			
Appetite loss (Cycle 2/Day 1) (N=936)	-2.1 (± 30.3)			
Appetite loss (Cycle 3/Day 1) (N=877)	-6.3 (± 31.7)			

Appetite loss (Cycle 4/Day 1) (N=833)	-9.1 (± 31.9)			
Appetite loss (Cycle 5/Day 1) (N=810)	-10.4 (± 31.9)			
Appetite loss (Cycle 6/Day 1) (N=778)	-11.4 (± 32.1)			
Appetite loss (Cycle 7/Day 1) (N=738)	-11.4 (± 32.4)			
Appetite loss (Cycle 8/Day 1) (N=704)	-11.5 (± 32.6)			
Appetite loss (Cycle 9/Day 1) (N=673)	-11.7 (± 32.5)			
Appetite loss (Cycle 10/Day 1) (N=637)	-11.9 (± 30.9)			
Appetite loss (Cycle 11/Day 1) (N=577)	-11.2 (± 30.4)			
Appetite loss (Cycle 12/Day 1) (N=413)	-9.1 (± 30.9)			
Appetite loss (Cycle 13/Day 1) (N=517)	-11.3 (± 29.8)			
Appetite loss (Cycle 14/Day 1) (N=358)	-9.9 (± 31.8)			
Appetite loss (Cycle 15/Day 1) (N=466)	-10.5 (± 30.6)			
Appetite loss (Cycle 16/Day 1) (N=296)	-10.4 (± 32.4)			
Appetite loss (Cycle 17/Day 1) (N=424)	-8.6 (± 29.5)			
Appetite loss (Cycle 18/Day 1) (N=250)	-10.1 (± 31.5)			
Appetite loss (Cycle 19/Day 1) (N=380)	-8.9 (± 30.9)			
Appetite loss (Cycle 20/Day 1) (N=224)	-12.8 (± 29)			
Appetite loss (Cycle 21/Day 1) (N=346)	-7.5 (± 30.6)			
Appetite loss (Cycle 22/Day 1) (N=181)	-9.2 (± 27.7)			
Appetite loss (Cycle 23/Day 1) (N=310)	-4.9 (± 28.5)			
Appetite loss (Cycle 24/Day 1) (N=157)	-10.9 (± 30.1)			
Appetite loss (Cycle 25/Day 1) (N=297)	-4.6 (± 29)			
Appetite loss (Cycle 26/Day 1) (N=129)	-12.1 (± 32.3)			
Appetite loss (Cycle 27/Day 1) (N=275)	-4.2 (± 29.4)			
Appetite loss (Cycle 28/Day 1) (N=121)	-6.6 (± 34.6)			
Appetite loss (Cycle 29/Day 1) (N=251)	-3.2 (± 27)			
Appetite loss (Cycle 30/Day 1) (N=109)	-7.6 (± 29.3)			
Appetite loss (End of treatment) (N=451)	0 (± 36.9)			
Constipation (Cycle 2/Day 1) (N=929)	15.4 (± 32.9)			
Constipation (Cycle 3/Day 1) (N=870)	10.9 (± 33.8)			
Constipation (Cycle 4/Day 1) (N=827)	7 (± 31)			
Constipation (Cycle 5/Day 1) (N=804)	5.5 (± 30.4)			
Constipation (Cycle 6/Day 1) (N=771)	5.4 (± 30.3)			
Constipation (Cycle 7/Day 1) (N=732)	4.7 (± 30.3)			
Constipation (Cycle 8/Day 1) (N=698)	4.5 (± 29.8)			
Constipation (Cycle 9/Day 1) (N=665)	5 (± 29.9)			
Constipation (Cycle 10/Day 1) (N=631)	3.8 (± 30)			
Constipation (Cycle 11/Day 1) (N=571)	5.2 (± 29.7)			
Constipation (Cycle 12/Day 1) (N=410)	6.4 (± 29.6)			
Constipation (Cycle 13/Day 1) (N=513)	5.2 (± 29)			
Constipation (Cycle 14/Day 1) (N=349)	5 (± 28.7)			
Constipation (Cycle 15/Day 1) (N=464)	6 (± 30.1)			
Constipation (Cycle 16/Day 1) (N=291)	4.4 (± 29.9)			
Constipation (Cycle 17/Day 1) (N=420)	8.3 (± 30.5)			
Constipation (Cycle 18/Day 1) (N=246)	6 (± 30.7)			
Constipation (Cycle 19/Day 1) (N=376)	7.4 (± 30.5)			
Constipation (Cycle 20/Day 1) (N=221)	5.9 (± 33.2)			
Constipation (Cycle 21/Day 1) (N=340)	7.7 (± 31.3)			
Constipation (Cycle 22/Day 1) (N=178)	6.2 (± 31.2)			
Constipation (Cycle 23/Day 1) (N=306)	9.7 (± 31.9)			
Constipation (Cycle 24/Day 1) (N=154)	9 (± 34.2)			

Constipation (Cycle 25/Day 1) (N=293)	10.9 (± 29.4)			
Constipation (Cycle 26/Day 1) (N=126)	5.6 (± 32)			
Constipation (Cycle 27/Day 1) (N=269)	8.3 (± 30.7)			
Constipation (Cycle 28/Day 1) (N=119)	9.8 (± 31.1)			
Constipation (Cycle 29/Day 1) (N=247)	7.8 (± 29.3)			
Constipation (Cycle 30/Day 1) (N=105)	11.7 (± 31.3)			
Constipation (End of treatment) (N=444)	8.9 (± 33)			
Diarrhea (Cycle 2/Day 1) (N=927)	11.4 (± 25.9)			
Diarrhea (Cycle 3/Day 1) (N=872)	12.8 (± 26.9)			
Diarrhea (Cycle 4/Day 1) (N=826)	11.7 (± 25.6)			
Diarrhea (Cycle 5/Day 1) (N=805)	12.6 (± 26.1)			
Diarrhea (Cycle 6/Day 1) (N=772)	11.6 (± 26.4)			
Diarrhea (Cycle 7/Day 1) (N=732)	10.9 (± 26.3)			
Diarrhea (Cycle 8/Day 1) (N=698)	9.8 (± 25.6)			
Diarrhea (Cycle 9/Day 1) (N=665)	10.5 (± 25.6)			
Diarrhea (Cycle 10/Day 1) (N=632)	11.1 (± 26.6)			
Diarrhea (Cycle 11/Day 1) (N=570)	10.1 (± 25.9)			
Diarrhea (Cycle 12/Day 1) (N=411)	8.1 (± 25.2)			
Diarrhea (Cycle 13/Day 1) (N=512)	8.8 (± 24)			
Diarrhea (Cycle 14/Day 1) (N=352)	10.1 (± 22.4)			
Diarrhea (Cycle 15/Day 1) (N=461)	8.5 (± 23.1)			
Diarrhea (Cycle 16/Day 1) (N=293)	10 (± 22.5)			
Diarrhea (Cycle 17/Day 1) (N=419)	8.6 (± 23.9)			
Diarrhea (Cycle 18/Day 1) (N=247)	7.4 (± 22.4)			
Diarrhea (Cycle 19/Day 1) (N=376)	7.8 (± 22.5)			
Diarrhea (Cycle 20/Day 1) (N=222)	6.8 (± 22.6)			
Diarrhea (Cycle 21/Day 1) (N=340)	6.6 (± 20.3)			
Diarrhea (Cycle 22/Day 1) (N=179)	6.8 (± 24.2)			
Diarrhea (Cycle 23/Day 1) (N=305)	8.7 (± 22.7)			
Diarrhea (Cycle 24/Day 1) (N=154)	6.4 (± 23.1)			
Diarrhea (Cycle 25/Day 1) (N=293)	10.1 (± 23.4)			
Diarrhea (Cycle 26/Day 1) (N=127)	5 (± 23.8)			
Diarrhea (Cycle 27/Day 1) (N=269)	8.3 (± 24.5)			
Diarrhea (Cycle 28/Day 1) (N=119)	5.6 (± 20.5)			
Diarrhea (Cycle 29/Day 1) (N=247)	9.7 (± 22.6)			
Diarrhea (Cycle 30/Day 1) (N=106)	10.1 (± 25.3)			
Diarrhea (End of treatment) (N=449)	5.9 (± 24.5)			
Dyspnoea (Cycle 2/Day 1) (N=933)	-9.8 (± 26.2)			
Dyspnoea (Cycle 3/Day 1) (N=876)	-11.4 (± 28.2)			
Dyspnoea (Cycle 4/Day 1) (N=834)	-12.3 (± 28.6)			
Dyspnoea (Cycle 5/Day 1) (N=808)	-12.2 (± 27.7)			
Dyspnoea (Cycle 6/Day 1) (N=776)	-13.7 (± 27.6)			
Dyspnoea (Cycle 7/Day 1) (N=737)	-13.8 (± 27.8)			
Dyspnoea (Cycle 8/Day 1) (N=702)	-13.8 (± 28.2)			
Dyspnoea (Cycle 9/Day 1) (N=671)	-13.3 (± 27.9)			
Dyspnoea (Cycle 10/Day 1) (N=635)	-13.4 (± 27.6)			
Dyspnoea (Cycle 11/Day 1) (N=575)	-15 (± 27.8)			
Dyspnoea (Cycle 12/Day 1) (N=411)	-13.1 (± 26.8)			
Dyspnoea (Cycle 13/Day 1) (N=515)	-13.1 (± 28.1)			
Dyspnoea (Cycle 14/Day 1) (N=356)	-12.7 (± 27.5)			
Dyspnoea (Cycle 15/Day 1) (N=463)	-12.6 (± 28.5)			

Dyspnoea (Cycle 16/Day 1) (N=295)	-12.2 (± 27.6)			
Dyspnoea (Cycle 17/Day 1) (N=421)	-11.8 (± 27.9)			
Dyspnoea (Cycle 18/Day 1) (N=248)	-11.5 (± 27.4)			
Dyspnoea (Cycle 19/Day 1) (N=377)	-14.2 (± 28)			
Dyspnoea (Cycle 20/Day 1) (N=222)	-9.2 (± 26.4)			
Dyspnoea (Cycle 21/Day 1) (N=344)	-13.4 (± 27.1)			
Dyspnoea (Cycle 22/Day 1) (N=181)	-8.8 (± 26.4)			
Dyspnoea (Cycle 23/Day 1) (N=309)	-10.9 (± 26.6)			
Dyspnoea (Cycle 24/Day 1) (N=156)	-8.5 (± 27.3)			
Dyspnoea (Cycle 25/Day 1) (N=295)	-10.5 (± 26.3)			
Dyspnoea (Cycle 26/Day 1) (N=129)	-10.1 (± 27.2)			
Dyspnoea (Cycle 27/Day 1) (N=273)	-9.3 (± 24.8)			
Dyspnoea (Cycle 28/Day 1) (N=121)	-12.1 (± 28.9)			
Dyspnoea (Cycle 29/Day 1) (N=249)	-8.8 (± 25.4)			
Dyspnoea (Cycle 30/Day 1) (N=109)	-11.6 (± 27.7)			
Dyspnoea (End of treatment) (N=450)	-4.2 (± 32.8)			
Fatigue (Cycle 2/Day 1) (N=936)	-4.8 (± 21.8)			
Fatigue (Cycle 3/Day 1) (N=879)	-8.9 (± 23.7)			
Fatigue (Cycle 4/Day 1) (N=836)	-11.4 (± 24.1)			
Fatigue (Cycle 5/Day 1) (N=810)	-12 (± 24.2)			
Fatigue (Cycle 6/Day 1) (N=778)	-13.7 (± 24.3)			
Fatigue (Cycle 7/Day 1) (N=739)	-14 (± 24.6)			
Fatigue (Cycle 8/Day 1) (N=704)	-15.3 (± 23.7)			
Fatigue (Cycle 9/Day 1) (N=671)	-14.9 (± 24)			
Fatigue (Cycle 10/Day 1) (N=637)	-14.4 (± 24.2)			
Fatigue (Cycle 11/Day 1) (N=577)	-13.7 (± 24.3)			
Fatigue (Cycle 12/Day 1) (N=413)	-12.2 (± 23.4)			
Fatigue (Cycle 13/Day 1) (N=517)	-13.4 (± 23.6)			
Fatigue (Cycle 14/Day 1) (N=358)	-13.2 (± 22.3)			
Fatigue (Cycle 15/Day 1) (N=466)	-13.1 (± 23.9)			
Fatigue (Cycle 16/Day 1) (N=296)	-11.3 (± 24.1)			
Fatigue (Cycle 17/Day 1) (N=424)	-11.3 (± 24.6)			
Fatigue (Cycle 18/Day 1) (N=250)	-10.4 (± 25.2)			
Fatigue (Cycle 19/Day 1) (N=380)	-11.9 (± 23.7)			
Fatigue (Cycle 20/Day 1) (N=224)	-10.6 (± 23.2)			
Fatigue (Cycle 21/Day 1) (N=346)	-11 (± 25)			
Fatigue (Cycle 22/Day 1) (N=182)	-8.4 (± 23)			
Fatigue (Cycle 23/Day 1) (N=311)	-8.7 (± 23.3)			
Fatigue (Cycle 24/Day 1) (N=157)	-6.7 (± 24.1)			
Fatigue (Cycle 25/Day 1) (N=297)	-7.9 (± 23.2)			
Fatigue (Cycle 26/Day 1) (N=129)	-12.1 (± 24.8)			
Fatigue (Cycle 27/Day 1) (N=275)	-7 (± 22.3)			
Fatigue (Cycle 28/Day 1) (N=121)	-6.7 (± 25.2)			
Fatigue (Cycle 29/Day 1) (N=251)	-7.1 (± 22.1)			
Fatigue (Cycle 30/Day 1) (N=109)	-7.2 (± 27)			
Fatigue (End of treatment) (N=451)	-5.3 (± 27.5)			
Financial Difficulties (Cycle 2/Day 1) (N=928)	-4.6 (± 24.1)			
Financial Difficulties (Cycle 3/Day 1) (N=871)	-4.2 (± 25.2)			
Financial Difficulties (Cycle 4/Day 1) (N=827)	-5.9 (± 25.7)			

Financial Difficulties (Cycle 5/Day 1) (N=803)	-5.1 (± 25.6)			
Financial Difficulties (Cycle 6/Day 1) (N=772)	-5.5 (± 25.4)			
Financial Difficulties (Cycle 7/Day 1) (N=732)	-6.2 (± 25.8)			
Financial Difficulties (Cycle 8/Day 1) (N=697)	-6.4 (± 26)			
Financial Difficulties (Cycle 9/Day 1) (N=663)	-5.8 (± 25.8)			
Financial Difficulties (Cycle 10/Day 1) (N=631)	-7.4 (± 25)			
Financial Difficulties (End of treatment) (N=447)	-2.2 (± 27.5)			
Financial Difficulties (Cycle 11/Day 1) (N=569)	-6.6 (± 25.4)			
Financial Difficulties (Cycle 12/Day 1) (N=410)	-4.8 (± 25.4)			
Financial Difficulties (Cycle 13/Day 1) (N=512)	-6.3 (± 25.8)			
Financial Difficulties (Cycle 14/Day 1) (N=352)	-5.8 (± 25.4)			
Financial Difficulties (Cycle 15/Day 1) (N=461)	-6.1 (± 26.7)			
Financial Difficulties (Cycle 16/Day 1) (N=294)	-4 (± 23.8)			
Financial Difficulties (Cycle 17/Day 1) (N=418)	-5.5 (± 26.8)			
Financial Difficulties (Cycle 18/Day 1) (N=247)	-3.8 (± 25.2)			
Financial Difficulties (Cycle 19/Day 1) (N=376)	-5.9 (± 26.8)			
Financial Difficulties (Cycle 20/Day 1) (N=220)	-5.2 (± 25.4)			
Financial Difficulties (Cycle 21/Day 1) (N=339)	-4.2 (± 25.9)			
Financial Difficulties (Cycle 22/Day 1) (N=177)	-2.1 (± 23.1)			
Financial Difficulties (Cycle 23/Day 1) (N=304)	-4.4 (± 24.9)			
Financial Difficulties (Cycle 24/Day 1) (N=153)	-2.8 (± 27.3)			
Financial Difficulties (Cycle 25/Day 1) (N=292)	-4.6 (± 24.8)			
Financial Difficulties (Cycle 26/Day 1) (N=126)	-2.9 (± 26)			
Financial Difficulties (Cycle 27/Day 1) (N=268)	-4.8 (± 25.5)			
Financial Difficulties (Cycle 28/Day 1) (N=119)	-4.2 (± 29.9)			
Financial Difficulties (Cycle 29/Day 1) (N=247)	-5.5 (± 25.2)			
Financial Difficulties (Cycle 30/Day 1) (N=105)	-3.5 (± 26.5)			
Insomnia (Cycle 2/Day 1) (N=934)	-7.6 (± 29.3)			
Insomnia (Cycle 3/Day 1) (N=878)	-11.3 (± 30.1)			
Insomnia (Cycle 4/Day 1) (N=833)	-13 (± 29.7)			
Insomnia (Cycle 5/Day 1) (N=808)	-12.8 (± 29.8)			
Insomnia (Cycle 6/Day 1) (N=778)	-13.3 (± 31.1)			
Insomnia (Cycle 7/Day 1) (N=739)	-13.9 (± 29.7)			
Insomnia (Cycle 8/Day 1) (N=703)	-12.6 (± 29.9)			

Insomnia (Cycle 9/Day 1) (N=673)	-13.2 (± 28.8)			
Insomnia (Cycle 10/Day 1) (N=637)	-13.2 (± 29.4)			
Insomnia (Cycle 11/Day 1) (N=576)	-12.2 (± 30)			
Insomnia (Cycle 12/Day 1) (N=413)	-11.3 (± 29.7)			
Insomnia (Cycle 13/Day 1) (N=516)	-13 (± 29.5)			
Insomnia (Cycle 14/Day 1) (N=358)	-11.7 (± 30.3)			
Insomnia (Cycle 15/Day 1) (N=464)	-12.4 (± 30)			
Insomnia (Cycle 16/Day 1) (N=296)	-10.9 (± 31.6)			
Insomnia (Cycle 17/Day 1) (N=424)	-10.8 (± 29.2)			
Insomnia (Cycle 18/Day 1) (N=250)	-10.4 (± 30.3)			
Insomnia (Cycle 19/Day 1) (N=379)	-12.6 (± 28.9)			
Insomnia (Cycle 20/Day 1) (N=224)	-11.5 (± 27.1)			
Insomnia (Cycle 21/Day 1) (N=346)	-10.2 (± 27.6)			
Insomnia (Cycle 22/Day 1) (N=182)	-7.9 (± 25.8)			
Insomnia (Cycle 23/Day 1) (N=311)	-10.5 (± 27.2)			
Insomnia (Cycle 24/Day 1) (N=157)	-5.7 (± 28)			
Insomnia (Cycle 25/Day 1) (N=296)	-7.7 (± 28.8)			
Insomnia (Cycle 26/Day 1) (N=129)	-10.9 (± 29.2)			
Insomnia (Cycle 27/Day 1) (N=274)	-10.1 (± 27.4)			
Insomnia (Cycle 28/Day 1) (N=121)	-6.9 (± 32.7)			
Insomnia (Cycle 29/Day 1) (N=251)	-8.4 (± 28.5)			
Insomnia (Cycle 30/Day 1) (N=109)	-11.3 (± 32.1)			
Insomnia (End of treatment) (N=451)	-5.7 (± 33.6)			
Nausea and Vomiting (Cycle 2/Day 1) (N=936)	6.2 (± 23.1)			
Nausea and Vomiting (Cycle 3/Day 1) (N=879)	2.4 (± 23.3)			
Nausea and Vomiting (Cycle 4/Day 1) (N=836)	0.3 (± 22.6)			
Nausea and Vomiting (Cycle 5/Day 1) (N=810)	-0.4 (± 21.1)			
Nausea and Vomiting (Cycle 6/Day 1) (N=779)	-1.6 (± 19.9)			
Nausea and Vomiting (Cycle 7/Day 1) (N=739)	-2.3 (± 21)			
Nausea and Vomiting (Cycle 8/Day 1) (N=704)	-1.9 (± 19.8)			
Nausea and Vomiting (Cycle 9/Day 1) (N=673)	-1.8 (± 21.2)			
Nausea and Vomiting (Cycle 10/Day 1) (N=637)	-1.4 (± 21.6)			
Nausea and Vomiting (Cycle 11/Day 1) (N=577)	-1.7 (± 20.9)			
Nausea and Vomiting (Cycle 12/Day 1) (N=413)	-1.5 (± 21.8)			
Nausea and Vomiting (Cycle 13/Day 1) (N=517)	-0.7 (± 21.2)			
Nausea and Vomiting (Cycle 14/Day 1) (N=358)	-0.4 (± 23.3)			
Nausea and Vomiting (Cycle 15/Day 1) (N=466)	-0.7 (± 21.2)			
Nausea and Vomiting (Cycle 16/Day 1) (N=296)	-0.8 (± 19.5)			
Nausea and Vomiting (Cycle 17/Day 1) (N=424)	-0.3 (± 20.2)			
Nausea and Vomiting (Cycle 18/Day 1) (N=250)	-0.9 (± 21.7)			

Nausea and Vomiting (Cycle 19/Day 1) (N=380)	-0.3 (± 20.1)			
Nausea and Vomiting (Cycle 20/Day 1) (N=224)	-2.3 (± 18.7)			
Nausea and Vomiting (Cycle 21/Day 1) (N=346)	-1.1 (± 18.6)			
Nausea and Vomiting (Cycle 22/Day 1) (N=182)	0.2 (± 19)			
Nausea and Vomiting (Cycle 23/Day 1) (N=311)	0.8 (± 17.4)			
Nausea and Vomiting (Cycle 24/Day 1) (N=157)	-1.3 (± 17.4)			
Nausea and Vomiting (Cycle 25/Day 1) (N=297)	0.6 (± 18)			
Nausea and Vomiting (Cycle 26/Day 1) (N=129)	-2.3 (± 20.2)			
Nausea and Vomiting (Cycle 27/Day 1) (N=275)	1.9 (± 17.5)			
Nausea and Vomiting (Cycle 28/Day 1) (N=121)	1.8 (± 19.7)			
Nausea and Vomiting (Cycle 29/Day 1) (N=251)	2.5 (± 18.9)			
Nausea and Vomiting (Cycle 30/Day 1) (N=109)	-0.5 (± 17.5)			
Nausea and Vomiting (End of treatment) (N=451)	4 (± 25.3)			
Pain (Cycle 2/Day 1) (N=935)	-13.1 (± 26.6)			
Pain (Cycle 3/Day 1) (N=880)	-16 (± 28)			
Pain (Cycle 4/Day 1) (N=836)	-15.7 (± 27.8)			
Pain (Cycle 5/Day 1) (N=810)	-15.5 (± 27.4)			
Pain (Cycle 6/Day 1) (N=779)	-15.5 (± 27.8)			
Pain (Cycle 7/Day 1) (N=739)	-16 (± 29)			
Pain (Cycle 8/Day 1) (N=705)	-15.9 (± 28.5)			
Pain (Cycle 9/Day 1) (N=673)	-15.5 (± 28.7)			
Pain (Cycle 10/Day 1) (N=637)	-15.1 (± 27.6)			
Pain (Cycle 11/Day 1) (N=577)	-14.6 (± 27.6)			
Pain (Cycle 12/Day 1) (N=414)	-13.6 (± 29.2)			
Pain (Cycle 13/Day 1) (N=517)	-13.8 (± 28)			
Pain (Cycle 14/Day 1) (N=357)	-13.9 (± 29.5)			
Pain (Cycle 15/Day 1) (N=466)	-12.1 (± 27)			
Pain (Cycle 16/Day 1) (N=296)	-12.5 (± 27.9)			
Pain (Cycle 17/Day 1) (N=424)	-10.6 (± 25.6)			
Pain (Cycle 18/Day 1) (N=250)	-11.1 (± 27.5)			
Pain (Cycle 19/Day 1) (N=380)	-10.8 (± 24.1)			
Pain (Cycle 20/Day 1) (N=224)	-11 (± 27.2)			
Pain (Cycle 21/Day 1) (N=346)	-10.1 (± 25.2)			
Pain (Cycle 22/Day 1) (N=182)	-7.7 (± 26.2)			
Pain (Cycle 23/Day 1) (N=311)	-7.4 (± 26)			
Pain (Cycle 24/Day 1) (N=157)	-8.8 (± 27.7)			
Pain (Cycle 25/Day 1) (N=297)	-8.8 (± 24.6)			
Pain (Cycle 26/Day 1) (N=129)	-12.5 (± 29.5)			
Pain (Cycle 27/Day 1) (N=275)	-7.6 (± 25.3)			
Pain (Cycle 28/Day 1) (N=121)	-7.9 (± 32.4)			
Pain (Cycle 29/Day 1) (N=251)	-8.1 (± 24.6)			
Pain (Cycle 30/Day 1) (N=109)	-7.5 (± 29.8)			
Pain (End of treatment) (N=451)	-5.3 (± 31.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change from Baseline of QLQ-LC13 Scale Scores

End point title	Mean Change from Baseline of QLQ-LC13 Scale Scores
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End point description:

The QLQ-LC13 consists of 1 multi-item scale and 9 single items that assess specific symptoms (dyspnoea, cough, hemoptysis, and site-specific pain), side effects (sore mouth, dysphagia, neuropathy, and alopecia), and pain medication use of lung cancer patients. "n" is the number of participants who completed the scale at baseline and at the respective Cycles. The PRO evaluable population was defined as the participants from the SA population who completed a baseline assessment and at least one post-baseline assessment.

End point type	Secondary
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End point timeframe:

6 years

End point values	Crizotinib 250 mg BID			
Subject group type	Reporting group			
Number of subjects analysed	976			
Units: Units on a scale				
arithmetic mean (standard deviation)				
Alopecia (Cycle 2/Day 1) (N=920)	-9.1 (± 29.6)			
Alopecia (Cycle 3/Day 1) (N=870)	-10.2 (± 31.6)			
Alopecia (Cycle 4/Day 1) (N=829)	-11.6 (± 30.7)			
Alopecia (Cycle 5/Day 1) (N=805)	-12.2 (± 32.3)			
Alopecia (Cycle 6/Day 1) (N=770)	-10.5 (± 30.9)			
Alopecia (Cycle 7/Day 1) (N=734)	-11.9 (± 32.3)			
Alopecia (Cycle 8/Day 1) (N=700)	-11.9 (± 33.2)			
Alopecia (Cycle 9/Day 1) (N=667)	-11.3 (± 34.7)			
Alopecia (Cycle 10/Day 1) (N=633)	-10.8 (± 33.9)			
Alopecia (Cycle 11/Day 1) (N=574)	-11.3 (± 34.8)			
Alopecia (Cycle 12/Day 1) (N=409)	-7.8 (± 34.8)			
Alopecia (Cycle 13/Day 1) (N=512)	-10.8 (± 35)			
Alopecia (Cycle 14/Day 1) (N=353)	-8.2 (± 36.4)			
Alopecia (Cycle 15/Day 1) (N=462)	-11.8 (± 34.3)			
Alopecia (Cycle 16/Day 1) (N=293)	-7.7 (± 34.1)			
Alopecia (Cycle 17/Day 1) (N=419)	-9.5 (± 32.9)			
Alopecia (Cycle 18/Day 1) (N=247)	-6.4 (± 31.3)			
Alopecia (Cycle 19/Day 1) (N=377)	-8.9 (± 34.1)			
Alopecia (Cycle 20/Day 1) (N=222)	-9 (± 30.7)			
Alopecia (Cycle 21/Day 1) (N=342)	-7.8 (± 32.9)			
Alopecia (Cycle 22/Day 1) (N=180)	-7.6 (± 35.6)			

Alopecia (Cycle 23/Day 1) (N=310)	-7 (± 33.2)			
Alopecia (Cycle 24/Day 1) (N=156)	-4.1 (± 34.1)			
Alopecia (Cycle 25/Day 1) (N=293)	-8.2 (± 31.8)			
Alopecia (Cycle 26/Day 1) (N=126)	-4.5 (± 31.1)			
Alopecia (Cycle 27/Day 1) (N=271)	-8.5 (± 31.5)			
Alopecia (Cycle 28/Day 1) (N=119)	-3.9 (± 33.1)			
Alopecia (Cycle 29/Day 1) (N=247)	-9.2 (± 28.3)			
Alopecia (Cycle 30/Day 1) (N=107)	-5 (± 31.7)			
Alopecia (End of treatment) (N=447)	-9.9 (± 35.3)			
Coughing (Cycle 2/Day 1) (N=926)	-12.9 (± 28.8)			
Coughing (Cycle 3/Day 1) (N=879)	-15.5 (± 31.8)			
Coughing (Cycle 4/Day 1) (N=832)	-17.7 (± 31.1)			
Coughing (Cycle 5/Day 1) (N=807)	-17.3 (± 31.8)			
Coughing (Cycle 6/Day 1) (N=775)	-18.3 (± 32.1)			
Coughing (Cycle 7/Day 1) (N=735)	-20.1 (± 32.2)			
Coughing (Cycle 8/Day 1) (N=703)	-20.8 (± 31.8)			
Coughing (Cycle 9/Day 1) (N=669)	-20.2 (± 30.9)			
Coughing (Cycle 10/Day 1) (N=636)	-19.9 (± 32)			
Coughing (Cycle 11/Day 1) (N=575)	-19.9 (± 31.6)			
Coughing (Cycle 12/Day 1) (N=414)	-19.2 (± 29.5)			
Coughing (Cycle 13/Day 1) (N=513)	-18.6 (± 32.6)			
Coughing (Cycle 14/Day 1) (N=355)	-17.9 (± 32.1)			
Coughing (Cycle 15/Day 1) (N=461)	-17.8 (± 31.7)			
Coughing (Cycle 16/Day 1) (N=294)	-17.3 (± 29.5)			
Coughing (Cycle 17/Day 1) (N=421)	-18.4 (± 32.5)			
Coughing (Cycle 18/Day 1) (N=249)	-16.9 (± 33.1)			
Coughing (Cycle 19/Day 1) (N=379)	-18.8 (± 30.3)			
Coughing (Cycle 20/Day 1) (N=222)	-18.3 (± 32.7)			
Coughing (Cycle 21/Day 1) (N=343)	-18 (± 31)			
Coughing (Cycle 22/Day 1) (N=181)	-16.7 (± 33.1)			
Coughing (Cycle 23/Day 1) (N=311)	-18.4 (± 32.1)			
Coughing (Cycle 24/Day 1) (N=155)	-18.9 (± 31.3)			
Coughing (Cycle 25/Day 1) (N=294)	-18.1 (± 31.3)			
Coughing (Cycle 26/Day 1) (N=125)	-21.9 (± 30.8)			
Coughing (Cycle 27/Day 1) (N=272)	-17.8 (± 32.2)			
Coughing (Cycle 28/Day 1) (N=119)	-19.6 (± 30.8)			
Coughing (Cycle 29/Day 1) (N=249)	-17.1 (± 31.3)			
Coughing (Cycle 30/Day 1) (N=106)	-16.7 (± 29.5)			
Coughing (End of treatment) (N=452)	-11.1 (± 33.5)			
Dysphagia (Cycle 2/Day 1) (N=926)	0 (± 19.6)			
Dysphagia (Cycle 3/Day 1) (N=879)	-1.1 (± 20.1)			
Dysphagia (Cycle 4/Day 1) (N=831)	-2.2 (± 20.8)			
Dysphagia (Cycle 5/Day 1) (N=807)	-2.3 (± 20)			
Dysphagia (Cycle 6/Day 1) (N=776)	-3 (± 19.9)			
Dysphagia (Cycle 7/Day 1) (N=737)	-3.1 (± 20.7)			
Dysphagia (Cycle 8/Day 1) (N=702)	-3.1 (± 18.6)			
Dysphagia (Cycle 9/Day 1) (N=670)	-2.7 (± 20.2)			
Dysphagia (Cycle 10/Day 1) (N=637)	-2.9 (± 19.4)			
Dysphagia (End of treatment) (N=449)	1.9 (± 23.5)			
Dysphagia (Cycle 11/Day 1) (N=577)	-3 (± 19.2)			
Dysphagia (Cycle 12/Day 1) (N=414)	-2.7 (± 18.1)			
Dysphagia (Cycle 13/Day 1) (N=513)	-3.1 (± 17.8)			

Dysphagia (Cycle 14/Day 1) (N=355)	-1.7 (± 18.2)			
Dysphagia (Cycle 15/Day 1) (N=463)	-2.8 (± 17.5)			
Dysphagia (Cycle 16/Day 1) (N=294)	-1.3 (± 20.1)			
Dysphagia (Cycle 17/Day 1) (N=422)	-2.2 (± 19)			
Dysphagia (Cycle 18/Day 1) (N=249)	-2.5 (± 18.4)			
Dysphagia (Cycle 19/Day 1) (N=378)	-2 (± 17.3)			
Dysphagia (Cycle 20/Day 1) (N=223)	-3.4 (± 18.5)			
Dysphagia (Cycle 21/Day 1) (N=344)	-2.5 (± 18.2)			
Dysphagia (Cycle 22/Day 1) (N=182)	-1.8 (± 19.7)			
Dysphagia (Cycle 23/Day 1) (N=311)	-3.4 (± 17)			
Dysphagia (Cycle 24/Day 1) (N=156)	-1.4 (± 16.5)			
Dysphagia (Cycle 25/Day 1) (N=295)	-2.8 (± 17.3)			
Dysphagia (Cycle 26/Day 1) (N=126)	-1.1 (± 15.7)			
Dysphagia (Cycle 27/Day 1) (N=274)	-1.6 (± 17.5)			
Dysphagia (Cycle 28/Day 1) (N=120)	-1.4 (± 16.4)			
Dysphagia (Cycle 29/Day 1) (N=248)	-1.5 (± 16.5)			
Dysphagia (Cycle 30/Day 1) (N=107)	-0.9 (± 18)			
Dyspnoea (Cycle 2/Day 1) (N=928)	-8 (± 19)			
Dyspnoea (Cycle 3/Day 1) (N=878)	-9.7 (± 21.5)			
Dyspnoea (Cycle 4/Day 1) (N=833)	-10.7 (± 21.7)			
Dyspnoea (Cycle 5/Day 1) (N=809)	-10.6 (± 21.4)			
Dyspnoea (Cycle 6/Day 1) (N=775)	-10.6 (± 21.7)			
Dyspnoea (Cycle 7/Day 1) (N=737)	-11.1 (± 21.1)			
Dyspnoea (Cycle 8/Day 1) (N=704)	-12 (± 20.7)			
Dyspnoea (Cycle 9/Day 1) (N=669)	-11 (± 20.7)			
Dyspnoea (Cycle 10/Day 1) (N=637)	-10.7 (± 21.1)			
Dyspnoea (Cycle 11/Day 1) (N=577)	-10.6 (± 20.8)			
Dyspnoea (Cycle 12/Day 1) (N=414)	-9 (± 20.2)			
Dyspnoea (Cycle 13/Day 1) (N=514)	-9.8 (± 21.1)			
Dyspnoea (Cycle 14/Day 1) (N=354)	-9.2 (± 20)			
Dyspnoea (Cycle 15/Day 1) (N=463)	-8.9 (± 21.6)			
Dyspnoea (Cycle 16/Day 1) (N=293)	-7.7 (± 21.3)			
Dyspnoea (Cycle 17/Day 1) (N=421)	-7.3 (± 20.5)			
Dyspnoea (Cycle 18/Day 1) (N=249)	-6.9 (± 21.3)			
Dyspnoea (Cycle 19/Day 1) (N=379)	-8.6 (± 19.7)			
Dyspnoea (Cycle 20/Day 1) (N=223)	-5.8 (± 19.8)			
Dyspnoea (Cycle 21/Day 1) (N=344)	-7.8 (± 19.5)			
Dyspnoea (Cycle 22/Day 1) (N=182)	-5.6 (± 18.3)			
Dyspnoea (Cycle 23/Day 1) (N=311)	-6.1 (± 19.3)			
Dyspnoea (Cycle 24/Day 1) (N=156)	-6.2 (± 18.3)			
Dyspnoea (Cycle 25/Day 1) (N=295)	-6.1 (± 19.7)			
Dyspnoea (Cycle 26/Day 1) (N=126)	-6.6 (± 19.3)			
Dyspnoea (Cycle 27/Day 1) (N=273)	-5.7 (± 19)			
Dyspnoea (Cycle 28/Day 1) (N=120)	-5.8 (± 19.5)			
Dyspnoea (Cycle 29/Day 1) (N=249)	-3.9 (± 19.2)			
Dyspnoea (Cycle 30/Day 1) (N=107)	-4.6 (± 17.5)			
Dyspnoea (End of treatment) (N=448)	-3 (± 25.7)			
Haemoptysis (Cycle 2/Day 1) (N=925)	-2.6 (± 12.6)			
Haemoptysis (Cycle 3/Day 1) (N=879)	-3 (± 12.6)			
Haemoptysis (Cycle 4/Day 1) (N=833)	-2.9 (± 12.7)			
Haemoptysis (Cycle 5/Day 1) (N=808)	-2.6 (± 12.9)			
Haemoptysis (Cycle 6/Day 1) (N=774)	-2.8 (± 12)			

Haemoptysis (Cycle 7/Day 1) (N=735)	-2.9 (± 12.7)			
Haemoptysis (Cycle 8/Day 1) (N=703)	-3.1 (± 11.9)			
Haemoptysis (Cycle 9/Day 1) (N=669)	-3 (± 11.7)			
Haemoptysis (Cycle 10/Day 1) (N=635)	-2.6 (± 11.7)			
Haemoptysis (Cycle 11/Day 1) (N=576)	-2.7 (± 11.6)			
Haemoptysis (Cycle 12/Day 1) (N=413)	-2.6 (± 10.3)			
Haemoptysis (Cycle 13/Day 1) (N=514)	-2.1 (± 12)			
Haemoptysis (Cycle 14/Day 1) (N=354)	-2.7 (± 11.3)			
Haemoptysis (Cycle 15/Day 1) (N=462)	-2.2 (± 10.8)			
Haemoptysis (Cycle 16/Day 1) (N=294)	-2.5 (± 11.4)			
Haemoptysis (Cycle 17/Day 1) (N=420)	-1.9 (± 11.4)			
Haemoptysis (Cycle 18/Day 1) (N=249)	-2.4 (± 12.1)			
Haemoptysis (Cycle 19/Day 1) (N=378)	-2.1 (± 11.5)			
Haemoptysis (Cycle 20/Day 1) (N=223)	-2.4 (± 13.6)			
Haemoptysis (Cycle 21/Day 1) (N=342)	-2.5 (± 11.5)			
Haemoptysis (Cycle 22/Day 1) (N=182)	-2.9 (± 11.2)			
Haemoptysis (Cycle 23/Day 1) (N=309)	-2.7 (± 12.5)			
Haemoptysis (Cycle 24/Day 1) (N=156)	-2.4 (± 12)			
Haemoptysis (Cycle 25/Day 1) (N=294)	-2.8 (± 12.4)			
Haemoptysis (Cycle 26/Day 1) (N=126)	-3.2 (± 12.9)			
Haemoptysis (Cycle 27/Day 1) (N=272)	-2.9 (± 11.4)			
Haemoptysis (Cycle 28/Day 1) (N=119)	-3.1 (± 12.3)			
Haemoptysis (Cycle 29/Day 1) (N=248)	-1.7 (± 12.1)			
Haemoptysis (Cycle 30/Day 1) (N=107)	-2.8 (± 11.3)			
Haemoptysis (End of treatment) (N=451)	-1.4 (± 15.9)			
Pain in Arm or Shoulder (Cycle 2/Day 1) (N=926)	-9.6 (± 26.9)			
Pain in Arm or Shoulder (Cycle 3/Day 1) (N=876)	-12.2 (± 27)			
Pain in Arm or Shoulder (Cycle 4/Day 1) (N=832)	-12.5 (± 28.2)			
Pain in Arm or Shoulder (Cycle 5/Day 1) (N=807)	-11.7 (± 27.1)			
Pain in Arm or Shoulder (Cycle 6/Day 1) (N=773)	-11.6 (± 26.3)			
Pain in Arm or Shoulder (Cycle 7/Day 1) (N=738)	-11.3 (± 28.1)			
Pain in Arm or Shoulder (Cycle 8/Day 1) (N=702)	-11.7 (± 28.5)			
Pain in Arm or Shoulder (Cycle 9/Day 1) (N=669)	-11.9 (± 28.5)			
Pain in Arm or Shoulder (Cycle 10/Day 1) (N=635)	-11.3 (± 28)			
Pain in Arm or Shoulder (Cycle 11/Day 1) (N=576)	-12.1 (± 27.3)			
Pain in Arm or Shoulder (Cycle 12/Day 1) (N=414)	-11 (± 27.7)			
Pain in Arm or Shoulder (Cycle 13/Day 1) (N=513)	-10.9 (± 27.2)			
Pain in Arm or Shoulder (Cycle 14/Day 1) (N=355)	-11.3 (± 27.3)			
Pain in Arm or Shoulder (Cycle 15/Day 1) (N=461)	-10.3 (± 25.6)			
Pain in Arm or Shoulder (Cycle 16/Day 1) (N=293)	-9.9 (± 28)			

Pain in Arm or Shoulder (Cycle 17/Day 1) (N=421)	-8.2 (± 26.5)			
Pain in Arm or Shoulder (Cycle 18/Day 1) (N=249)	-9.4 (± 27.6)			
Pain in Arm or Shoulder (Cycle 19/Day 1) (N=379)	-9.1 (± 26.5)			
Pain in Arm or Shoulder (Cycle 20/Day 1) (N=222)	-7.4 (± 27.3)			
Pain in Arm or Shoulder (Cycle 21/Day 1) (N=344)	-9 (± 27)			
Pain in Arm or Shoulder (Cycle 22/Day 1) (N=182)	-9 (± 29.1)			
Pain in Arm or Shoulder (Cycle 23/Day 1) (N=311)	-8.9 (± 25.5)			
Pain in Arm or Shoulder (Cycle 24/Day 1) (N=155)	-9.7 (± 30.6)			
Pain in Arm or Shoulder (Cycle 25/Day 1) (N=295)	-9.2 (± 26)			
Pain in Arm or Shoulder (Cycle 26/Day 1) (N=126)	-10.8 (± 33.7)			
Pain in Arm or Shoulder (Cycle 27/Day 1) (N=274)	-8.6 (± 26.5)			
Pain in Arm or Shoulder (Cycle 28/Day 1) (N=119)	-8.7 (± 29.6)			
Pain in Arm or Shoulder (Cycle 29/Day 1) (N=248)	-7.9 (± 27.2)			
Pain in Arm or Shoulder (Cycle 30/Day 1) (N=107)	-8.1 (± 30.3)			
Pain in Arm or Shoulder (End of treatment)(N=445)	-5.8 (± 30.7)			
Pain in Chest (Cycle 2/Day 1) (N=928)	-9.5 (± 23.4)			
Pain in Chest (Cycle 3/Day 1) (N=875)	-11.9 (± 25.1)			
Pain in Chest (Cycle 4/Day 1) (N=833)	-12.1 (± 26.1)			
Pain in Chest (Cycle 5/Day 1) (N=808)	-11.8 (± 25.8)			
Pain in Chest (Cycle 6/Day 1) (N=774)	-12.1 (± 25.3)			
Pain in Chest (Cycle 7/Day 1) (N=735)	-12.6 (± 25.4)			
Pain in Chest (Cycle 8/Day 1) (N=703)	-13.2 (± 25)			
Pain in Chest (Cycle 9/Day 1) (N=665)	-13.1 (± 25.8)			
Pain in Chest (Cycle 10/Day 1) (N=633)	-12.9 (± 26)			
Pain in Chest (Cycle 11/Day 1) (N=574)	-12 (± 25.5)			
Pain in Chest (Cycle 12/Day 1) (N=414)	-10.7 (± 25.5)			
Pain in Chest (Cycle 13/Day 1) (N=513)	-12.6 (± 24.5)			
Pain in Chest (Cycle 14/Day 1) (N=355)	-11.5 (± 24.4)			
Pain in Chest (Cycle 15/Day 1) (N=462)	-11.9 (± 24.7)			
Pain in Chest (Cycle 16/Day 1) (N=294)	-11 (± 23.4)			
Pain in Chest (Cycle 17/Day 1) (N=421)	-11.6 (± 23.8)			
Pain in Chest (Cycle 18/Day 1) (N=249)	-8 (± 23.1)			
Pain in Chest (Cycle 19/Day 1) (N=378)	-11.2 (± 23.8)			
Pain in Chest (Cycle 20/Day 1) (N=222)	-9.4 (± 24.3)			
Pain in Chest (Cycle 21/Day 1) (N=343)	-11.9 (± 23.5)			
Pain in Chest (Cycle 22/Day 1) (N=182)	-10.1 (± 21.9)			
Pain in Chest (Cycle 23/Day 1) (N=308)	-10.8 (± 24)			
Pain in Chest (Cycle 24/Day 1) (N=156)	-7.1 (± 26.8)			
Pain in Chest (Cycle 25/Day 1) (N=293)	-10.2 (± 22.3)			
Pain in Chest (Cycle 26/Day 1) (N=126)	-10.6 (± 25.2)			
Pain in Chest (Cycle 27/Day 1) (N=272)	-9.2 (± 22)			
Pain in Chest (Cycle 28/Day 1) (N=120)	-9.4 (± 26.7)			

Pain in Chest (Cycle 29/Day 1) (N=248)	-9.5 (± 24.4)			
Pain in Chest (Cycle 30/Day 1) (N=107)	-5.3 (± 26.8)			
Pain in Chest (End of treatment) (N=451)	-6.7 (± 28)			
Pain in Other Parts (Cycle 2/Day 1) (N=893)	-10 (± 31.3)			
Pain in Other Parts (Cycle 3/Day 1) (N=854)	-12 (± 31.9)			
Pain in Other Parts (Cycle 4/Day 1) (N=806)	-13.5 (± 31)			
Pain in Other Parts (Cycle 5/Day 1) (N=793)	-12.2 (± 30.2)			
Pain in Other Parts (Cycle 6/Day 1) (N=752)	-12.5 (± 30.9)			
Pain in Other Parts (Cycle 7/Day 1) (N=715)	-11.8 (± 30.3)			
Pain in Other Parts (Cycle 8/Day 1) (N=680)	-11.7 (± 30.5)			
Pain in Other Parts (Cycle 9/Day 1) (N=650)	-13.1 (± 29.9)			
Pain in Other Parts (Cycle 10/Day 1) (N=616)	-12.1 (± 30.4)			
Pain in Other Parts (Cycle 11/Day 1) (N=562)	-10.8 (± 29.3)			
Pain in Other Parts (Cycle 12/Day 1) (N=399)	-11.6 (± 30.9)			
Pain in Other Parts (Cycle 13/Day 1) (N=499)	-9.9 (± 30)			
Pain in Other Parts (Cycle 14/Day 1) (N=342)	-11.5 (± 31.3)			
Pain in Other Parts (Cycle 15/Day 1) (N=451)	-10.1 (± 28.9)			
Pain in Other Parts (Cycle 16/Day 1) (N=282)	-9.6 (± 30.3)			
Pain in Other Parts (Cycle 17/Day 1) (N=411)	-8.8 (± 28.1)			
Pain in Other Parts (Cycle 18/Day 1) (N=239)	-8.6 (± 31)			
Pain in Other Parts (Cycle 19/Day 1) (N=370)	-8.8 (± 29)			
Pain in Other Parts (Cycle 20/Day 1) (N=210)	-9.4 (± 31.3)			
Pain in Other Parts (Cycle 21/Day 1) (N=337)	-8.2 (± 28.6)			
Pain in Other Parts (Cycle 22/Day 1) (N=176)	-10.4 (± 30.2)			
Pain in Other Parts (Cycle 23/Day 1) (N=300)	-6.6 (± 29.2)			
Pain in Other Parts (Cycle 24/Day 1) (N=149)	-7.8 (± 35.2)			
Pain in Other Parts (Cycle 25/Day 1) (N=286)	-7.2 (± 30.2)			
Pain in Other Parts (Cycle 26/Day 1) (N=121)	-8.8 (± 34.6)			
Pain in Other Parts (Cycle 27/Day 1) (N=267)	-5.9 (± 29.5)			
Pain in Other Parts (Cycle 28/Day 1) (N=116)	-3.2 (± 34.6)			
Pain in Other Parts (Cycle 29/Day 1) (N=242)	-6.3 (± 27.1)			
Pain in Other Parts (Cycle 30/Day 1) (N=102)	-6.5 (± 34.8)			

Pain in Other Parts (End of treatment) (N=427)	-4.6 (± 34.8)			
Peripheral Neuropathy (Cycle 2/Day 1) (N=925)	0.6 (± 25.3)			
Peripheral Neuropathy (Cycle 3/Day 1) (N=876)	-0.4 (± 25.6)			
Peripheral Neuropathy (Cycle 4/Day 1) (N=833)	-1.7 (± 26.5)			
Peripheral Neuropathy (Cycle 5/Day 1) (N=807)	-1.2 (± 26.3)			
Peripheral Neuropathy (Cycle 6/Day 1) (N=775)	-1.4 (± 26.5)			
Peripheral Neuropathy (Cycle 7/Day 1) (N=737)	-2.6 (± 27.2)			
Peripheral Neuropathy (Cycle 8/Day 1) (N=703)	-2.1 (± 25.6)			
Peripheral Neuropathy (Cycle 9/Day 1) (N=668)	-1.8 (± 27.2)			
Peripheral Neuropathy (Cycle 10/Day 1) (N=635)	-1 (± 26.4)			
Peripheral Neuropathy (Cycle 11/Day 1) (N=575)	-1.6 (± 27.5)			
Peripheral Neuropathy (Cycle 12/Day 1) (N=413)	-0.8 (± 27.3)			
Peripheral Neuropathy (Cycle 13/Day 1) (N=512)	-1.5 (± 27)			
Peripheral Neuropathy (Cycle 14/Day 1) (N=354)	-2.1 (± 28.6)			
Peripheral Neuropathy (Cycle 15/Day 1) (N=462)	-0.7 (± 27.5)			
Peripheral Neuropathy (Cycle 16/Day 1) (N=294)	-1.5 (± 29.9)			
Peripheral Neuropathy (Cycle 17/Day 1) (N=418)	-0.3 (± 28.3)			
Peripheral Neuropathy (Cycle 18/Day 1) (N=249)	-0.7 (± 28.3)			
Peripheral Neuropathy (Cycle 19/Day 1) (N=378)	-1.5 (± 23.9)			
Peripheral Neuropathy (Cycle 20/Day 1) (N=221)	0 (± 28.1)			
Peripheral Neuropathy (Cycle 21/Day 1) (N=342)	0.2 (± 27.6)			
Peripheral Neuropathy (Cycle 22/Day 1) (N=182)	-3.7 (± 27.6)			
Peripheral Neuropathy (Cycle 23/Day 1) (N=310)	-1 (± 26.2)			
Peripheral Neuropathy (Cycle 24/Day 1) (N=156)	-1.7 (± 26.4)			
Peripheral Neuropathy (Cycle 25/Day 1) (N=295)	2.3 (± 25.5)			
Peripheral Neuropathy (Cycle 26/Day 1) (N=126)	-1.6 (± 24.9)			
Peripheral Neuropathy (Cycle 27/Day 1) (N=274)	2.1 (± 27.1)			
Peripheral Neuropathy (Cycle 28/Day 1) (N=119)	-0.6 (± 27.1)			
Peripheral Neuropathy (Cycle 29/Day 1) (N=249)	1.5 (± 26.3)			
Peripheral Neuropathy (Cycle 30/Day 1) (N=107)	-0.6 (± 28.2)			
Peripheral Neuropathy (End of treatment) (N=451)	-0.6 (± 26.6)			

Sore Mouth (Cycle 2/Day 1) (N=928)	1 (± 20)			
Sore Mouth (Cycle 3/Day 1) (N=879)	-0.2 (± 19.8)			
Sore Mouth (Cycle 4/Day 1) (N=834)	-0.6 (± 19.1)			
Sore Mouth (Cycle 5/Day 1) (N=808)	-1.3 (± 17.9)			
Sore Mouth (Cycle 6/Day 1) (N=776)	-1.8 (± 17.1)			
Sore Mouth (Cycle 7/Day 1) (N=738)	-1.2 (± 18.3)			
Sore Mouth (Cycle 8/Day 1) (N=704)	-2.2 (± 17)			
Sore Mouth (Cycle 9/Day 1) (N=669)	-2.1 (± 18.3)			
Sore Mouth (Cycle 10/Day 1) (N=636)	-1.7 (± 19.1)			
Sore Mouth (Cycle 11/Day 1) (N=577)	-1.8 (± 17.2)			
Sore Mouth (Cycle 12/Day 1) (N=414)	-1.9 (± 17.1)			
Sore Mouth (Cycle 13/Day 1) (N=514)	-1.5 (± 18)			
Sore Mouth (Cycle 14/Day 1) (N=354)	-1.3 (± 14.8)			
Sore Mouth (Cycle 15/Day 1) (N=463)	-0.9 (± 16.1)			
Sore Mouth (Cycle 16/Day 1) (N=294)	0.1 (± 16.6)			
Sore Mouth (Cycle 17/Day 1) (N=422)	-1.4 (± 17.6)			
Sore Mouth (Cycle 18/Day 1) (N=249)	-0.9 (± 18)			
Sore Mouth (Cycle 19/Day 1) (N=379)	-0.9 (± 17.3)			
Sore Mouth (Cycle 20/Day 1) (N=223)	-1.3 (± 17.7)			
Sore Mouth (Cycle 21/Day 1) (N=344)	-0.6 (± 18)			
Sore Mouth (Cycle 22/Day 1) (N=182)	-1.1 (± 14.8)			
Sore Mouth (Cycle 23/Day 1) (N=311)	0.3 (± 17.7)			
Sore Mouth (Cycle 24/Day 1) (N=156)	2.6 (± 17.2)			
Sore Mouth (Cycle 25/Day 1) (N=294)	-1.6 (± 17.6)			
Sore Mouth (Cycle 26/Day 1) (N=126)	-2.4 (± 14.7)			
Sore Mouth (Cycle 27/Day 1) (N=274)	-0.6 (± 18.4)			
Sore Mouth (Cycle 28/Day 1) (N=120)	-0.3 (± 15.3)			
Sore Mouth (Cycle 29/Day 1) (N=249)	-1.7 (± 16.4)			
Sore Mouth (Cycle 30/Day 1) (N=107)	-1.2 (± 12.9)			
Sore Mouth (End of treatment) (N=451)	-0.4 (± 20)			

Statistical analyses

No statistical analyses for this end point

Secondary: Patient reported outcomes (PROs) of health-related quality of life (HRQoL): Mean change from baseline of EQ-5D Visual Analog Score (VAS) Scale

End point title	Patient reported outcomes (PROs) of health-related quality of life (HRQoL): Mean change from baseline of EQ-5D Visual Analog Score (VAS) Scale
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End point description:

The EQ-5D descriptive system measured a patient's health state on 5 dimensions which included: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The respondent's self-rated health was assessed on a scale from 0 (worst imaginable health state) to 100 (best imaginable health state) by the EQ-VAS. "n" is the number of participants who completed the scale at baseline and at the respective Cycles. The PRO evaluable population was defined as the participants from the SA population who completed a baseline assessment and at least one post-baseline assessment

End point type	Secondary
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End point timeframe:

6 years

End point values	Crizotinib 250 mg BID			
Subject group type	Reporting group			
Number of subjects analysed	974			
Units: Units on a scale				
arithmetic mean (standard deviation)				
CYCLE 2/DAY 1 (N=926)	5.72 (± 17.51)			
CYCLE 3/DAY 1 (N=875)	8.57 (± 18.82)			
CYCLE 4/DAY 1 (N=836)	10.01 (± 19.73)			
CYCLE 5/DAY 1 (N=804)	10.38 (± 19.85)			
CYCLE 6/DAY 1 (N=771)	10.17 (± 20.38)			
CYCLE 7/DAY 1 (N=728)	10.17 (± 20.38)			
CYCLE 8/DAY 1 (N=693)	10.35 (± 19.22)			
CYCLE 9/DAY 1 (N=667)	10.69 (± 19.82)			
CYCLE 10/DAY 1 (N=633)	10.34 (± 19.15)			
CYCLE 11/DAY 1 (N=573)	10.09 (± 19.72)			
CYCLE 12/DAY 1 (N=409)	9.69 (± 18.81)			
CYCLE 13/DAY 1 (N=512)	9.74 (± 19.64)			
CYCLE 14/DAY 1 (N=351)	10.93 (± 18.67)			
CYCLE 15/DAY 1 (N=461)	8.71 (± 20.53)			
CYCLE 16/DAY 1 (N=289)	8.47 (± 20.66)			
CYCLE 17/DAY 1 (N=417)	7.99 (± 20.8)			
CYCLE 18/DAY 1 (N=244)	7.62 (± 19.86)			
CYCLE 19/DAY 1 (N=372)	8.17 (± 18.92)			
CYCLE 20/DAY 1 (N=219)	8.03 (± 18.45)			
CYCLE 21/DAY 1 (N=339)	6.96 (± 18.71)			
CYCLE 22/DAY 1 (N=179)	6.59 (± 18.97)			
CYCLE 23/DAY 1 (N=310)	5.53 (± 19.5)			
CYCLE 24/DAY 1 (N=154)	7.61 (± 19.58)			
CYCLE 25/DAY 1 (N=299)	4.97 (± 17.98)			
CYCLE 26/DAY 1 (N=128)	8.54 (± 18.97)			
CYCLE 27/DAY 1 (N=272)	5.24 (± 17.61)			
CYCLE 28/DAY 1 (N=120)	7.93 (± 19.53)			
CYCLE 29/DAY 1 (N=249)	5.05 (± 17.07)			
CYCLE 30/DAY 1 (N=108)	8.07 (± 19.95)			
End of Treatment (N=450)	0.09 (± 23.92)			

Statistical analyses

Secondary: Percentage of participants with Visual Symptom Assessment Questionnaire (VSAQ-ALK)

End point title	Percentage of participants with Visual Symptom Assessment Questionnaire (VSAQ-ALK)
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End point description:

The participants who responded to the question: "Have you experienced any visual disturbances?" Only the participants who answered yes were instructed to complete the rest of the questionnaire. "n" is the number of participants who completed the first question. The safety analysis population included all participants who were enrolled and received at least 1 dose of study medication (excluding day-7 pharmacokinetic [PK] dosing).

End point type	Secondary
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End point timeframe:

6 years

End point values	Crizotinib 250 mg BID			
Subject group type	Reporting group			
Number of subjects analysed	1066			
Units: Percentage of participants				
number (not applicable)				
Cycle 2/Day 1 (Yes) (N=798)	64.5			
Cycle 2/Day 1 (No) (N=798)	35.5			
Cycle 3/Day 1 (Yes) (N=768)	56.5			
Cycle 3/Day 1 (No) (N=768)	43.5			
Cycle 4/Day 1 (Yes) (N=754)	52.3			
Cycle 4/Day 1 (No) (N=754)	47.7			
Cycle 5/Day 1 (Yes) (N=743)	49.1			
Cycle 5/Day 1 (No) (N=743)	50.9			
Cycle 6/Day 1 (Yes) (N=731)	48.8			
Cycle 6/Day 1 (No) (N=731)	51.2			
Cycle 7/Day 1 (Yes) (N=699)	45.8			
Cycle 7/Day 1 (No) (N=699)	54.2			
Cycle 8/Day 1 (Yes) (N=670)	43.7			
Cycle 8/Day 1 (No) (N=670)	56.3			
Cycle 9/Day 1 (Yes) (N=653)	43.5			
Cycle 9/Day 1 (No) (N=653)	56.5			
Cycle 10/Day 1 (Yes) (N=621)	42.7			
Cycle 10/Day 1 (No) (N=621)	57.3			
Cycle 11/Day 1 (Yes) (N=565)	40.2			
Cycle 11/Day 1 (No) (N=565)	59.8			
Cycle 12/Day 1 (Yes) (N=403)	42.9			
Cycle 12/Day 1 (No) (N=403)	57.1			
Cycle 13/Day 1 (Yes) (N=507)	41.2			
Cycle 13/Day 1 (No) (N=507)	58.8			
Cycle 14/Day 1 (Yes) (N=354)	41.5			
Cycle 14/Day 1 (No) (N=354)	58.5			
Cycle 15/Day 1 (Yes) (N=468)	39.1			
Cycle 15/Day 1 (No) (N=468)	60.9			

Cycle 16/Day 1 (Yes) (N=296)	43.6			
Cycle 16/Day 1 (No) (N=296)	56.4			
Cycle 17/Day 1 (Yes) (N=418)	37.3			
Cycle 17/Day 1 (No) (N=418)	62.7			
Cycle 18/Day 1 (Yes) (N=249)	40.2			
Cycle 18/Day 1 (No) (N=249)	59.8			
Cycle 19/Day 1 (Yes) (N=378)	36.8			
Cycle 19/Day 1 (No) (N=378)	63.2			
Cycle 20/Day 1 (Yes) (N=221)	38.9			
Cycle 20/Day 1 (No) (N=221)	61.1			
Cycle 21/Day 1 (Yes) (N=344)	39			
Cycle 21/Day 1 (No) (N=344)	61			
Cycle 22/Day 1 (Yes) (N=181)	39.2			
Cycle 22/Day 1 (No) (N=181)	60.8			
Cycle 23/Day 1 (Yes) (N=312)	34.9			
Cycle 23/Day 1 (No) (N=312)	65.1			
Cycle 24/Day 1 (Yes) (N=155)	34.8			
Cycle 24/Day 1 (No) (N=155)	65.2			
Cycle 25/Day 1 (Yes) (N=302)	35.8			
Cycle 25/Day 1 (No) (N=302)	64.2			
Cycle 26/Day 1 (Yes) (N=130)	30.8			
Cycle 26/Day 1 (No) (N=130)	69.2			
Cycle 27/Day 1 (Yes) (N=276)	32.6			
Cycle 27/Day 1 (No) (N=276)	67.4			
Cycle 28/Day 1 (Yes) (N=118)	31.4			
Cycle 28/Day 1 (No) (N=118)	68.6			
Cycle 29/Day 1 (Yes) (N=249)	30.5			
Cycle 29/Day 1 (No) (N=249)	69.5			
Cycle 30/Day 1 (Yes) (N=106)	27.4			
Cycle 30/Day 1 (No) (N=106)	72.6			
End of Treatment (Yes) (N=428)	39.3			
End of Treatment (No) (N=428)	60.7			

Statistical analyses

No statistical analyses for this end point

Secondary: Molecular Profiling (ALK Status) Descriptive Statistics for ALK Percentage of Positive Cells by Central Laboratory Test (SA [ALK positive by IUO] Population)

End point title	Molecular Profiling (ALK Status) Descriptive Statistics for ALK Percentage of Positive Cells by Central Laboratory Test (SA [ALK positive by IUO] Population)
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End point description:

Molecular profiling outcomes included: Types of EML4-ALK fusion variants and ALK protein expression; Protein expression of identified biomarkers in serial tumor samples from surgery or biopsy, when available. The safety analysis population included all participants who received at least 1 dose of study medication (excluding day-7 pharmacokinetic [PK] dosing) and were ALK positive by IUO (SA-ALK positive by IUO population).

End point type	Secondary
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End point timeframe:

6 years

End point values	Crizotinib 250 mg BID			
Subject group type	Reporting group			
Number of subjects analysed	908			
Units: Percentage of cells				
median (full range (min-max))				
Descriptive statistics ALK positive-IUO population	60 (15 to 100)			

Statistical analyses

No statistical analyses for this end point

Secondary: Genotypes of alleles possibly associated with adverse hepatic drug reactions (Pharmacogenomic evaluable population)

End point title	Genotypes of alleles possibly associated with adverse hepatic drug reactions (Pharmacogenomic evaluable population)
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End point description:

Frequency of candidate gene alleles, HLA-DQA1*02:01, HLA-DQB1*02:02, HLA-DRB1*07:01 and TNXB/rs12153855, were measured in alanine transaminase (ALT) Cases and Controls to evaluate if there were statistically significant associations that would support/suggest any predictive (ie, diagnostic) value of these markers in identifying participants at increased risk for hepatic toxicity. Frequency of 2 additional HLA gene alleles, HLA-B*57:01 and HLA-DRB1*15:01, were also measured in ALT Cases and Controls. ALT Cases are participants with baseline ALT $\leq 1 \times$ ULN and at least one on-treatment ALT assessment $> 3 \times$ upper limit of normal (ULN); and ALT Controls are those with baseline and on-treatment assessments of ALT $\leq 1 \times$ ULN. All Genotyped Population was all participants in safety analysis population who had at least 1 genotype result. Pharmacogenomic Evaluable (PE) Population was participants in All Genotyped Population who had an HLA genotype result and were designated as ALT Case or Control.

End point type	Secondary
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End point timeframe:

6 years

End point values	Crizotinib 250 mg BID-ALT cases	Crizotinib 250 mg BID-ALT controls		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	74	115		
Units: Percentage of participants				
number (not applicable)				
HLA-DQA1*02:01	20.3	20		
HLA-DQB1*02:02	17.6	16.5		
HLA-DRB1*07:01	20.3	20		
TNXB/rs12153855	10.8	16.5		
HLA-B*57:01	2.7	4.3		

HLA-DRB1*15:01	17.6	20.9		
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Statistical analyses

No statistical analyses for this end point

Secondary: QTc prolongation in participants

End point title	QTc prolongation in participants
End point description: The number and percentage of participants with maximum post-dose QTcF/QTcB (<450, 450 - <480, 480 - <500, and ≥500 msec) were evaluated. Participants from the SA population who had a Baseline (last ECG [electrocardiogram] prior to Cycle 1 Day 1 dose) and ≥1 post Baseline ECG measurement and were not included in the ECG sub-study.	
End point type	Secondary
End point timeframe: 6 years	

End point values	Crizotinib 250 mg BID			
Subject group type	Reporting group			
Number of subjects analysed	999			
Units: Percentage				
number (not applicable)				
Maximum QTcF Interval (<450)	89.8			
Maximum QTcF Interval (450-<480)	7.7			
Maximum QTcF Interval (480 - <500)	1			
Maximum QTcF Interval (≥500)	1.5			
Maximum QTcB Interval (<450)	74.3			
Maximum QTcB Interval (450-<480)	21.2			
Maximum QTcB Interval (480-<500)	2.4			
Maximum QTcB Interval (≥500)	2.1			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)
End point description: OS was defined as the time from the Cycle 1 Day 1 dose to the date of death due to any cause. OS (in months) was calculated as (date of death – date of Cycle 1 Day 1 dose + 1)/30.4. The safety analysis populations included all participants who received at least 1 dose of study medication (excluding day-7 pharmacokinetic [PK] dosing), and were ALK positive either by IUO (SA-ALK positive by IUO population) or by non-IUO (SA-ALK positive by non-IUO population), respectively.	

End point type	Secondary
End point timeframe:	
6 years	

End point values	Crizotinib 250 mg BID			
Subject group type	Reporting group			
Number of subjects analysed	1066			
Units: Months				
median (confidence interval 95%)				
ALK-positive by IUO (N= 908)	21.8 (19.4 to 24)			
ALK-positive by non-IUO (N= 158)	16.9 (13.4 to 21.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: Probability of Survival

End point title	Probability of Survival
End point description:	
Six-month and 1-year survival probabilities were defined as the probabilities of survival at 6 months and 1 year, respectively, after the date of the Cycle 1 Day 1 dose based on the Kaplan-Meier estimate. The safety analysis populations included all participants who received at least 1 dose of study medication (excluding day-7 pharmacokinetic [PK] dosing), and were ALK positive either by IUO (SA-ALK positive by IUO population) or by non-IUO (SA-ALK positive by non-IUO population), respectively.	
End point type	Secondary
End point timeframe:	
6 years	

End point values	Crizotinib 250 mg BID			
Subject group type	Reporting group			
Number of subjects analysed	1066			
Units: Percentage				
number (confidence interval 95%)				
ALK positive by IUO at 6 Months	81.7 (79 to 84)			
ALK positive by non IUO at 6 Months	77.5 (70.1 to 83.3)			
ALK positive by IUO at 12 Months	66.5 (63.3 to 69.5)			
ALK positive by non IUO at 12 Months	62.4 (54.3 to 69.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma concentrations of crizotinib (PF-02341066) and its metabolite PF-06260182

End point title	Plasma concentrations of crizotinib (PF-02341066) and its metabolite PF-06260182
End point description: Plasma concentration of crizotinib (PF-02341066) and its metabolite PF-06260182. The method of dispersion is % coefficient of variation. All participants who have ≥ 1 measurement of PF-02341066 or PF-06260182 at the time of reporting are included in PK analysis. Concentration at Cycle 2 Day 1 and beyond are considered steady state, and only included those who received at least 14 continuous days of 250 mg BID dosing.	
End point type	Secondary
End point timeframe: 6 Years	

End point values	Plasma concentrations of crizotinib (PF-02341066)	Plasma concentrations of crizotinib metabolite (PF-06260182)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	906	904		
Units: ng/mL				
geometric mean (geometric coefficient of variation)				
Cycle 1 Day 1 (N= 13, 13)	1.95 (\pm 55)	0.00601 (\pm 167)		
Cycle 2 Day 1 (N=447, 431)	279 (\pm 46)	76.2 (\pm 79)		
Cycle 3 Day 1 (N=398, 385)	297 (\pm 44)	80.8 (\pm 58)		
Cycle 5 Day 1 (N=297, 290)	294 (\pm 48)	81.4 (\pm 61)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Active reporting period is from the time of informed consent until at least 28 days after study treatment last dose. For Serious adverse events: those with the possibility of being related to study drug must be reported as minimum thereafter.

Adverse event reporting additional description:

All causality (serious and non-serious) adverse events have been reported. Non-serious adverse events above the 5% threshold are reported herein. 15 fatalities causally related to crizotinib have been reported.

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	Crizotinib 250 mg BID
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Reporting group description:

Participants were administered crizotinib at a starting dose of 250 mg orally, BID on a continuous dosing period as two 100-mg tablets and one 50-mg tablet at approximately 12 hours apart the same time each day.

Serious adverse events	Crizotinib 250 mg BID		
Total subjects affected by serious adverse events			
subjects affected / exposed	539 / 1066 (50.56%)		
number of deaths (all causes)	241		
number of deaths resulting from adverse events	15		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	1 / 1066 (0.09%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Breast cancer			
subjects affected / exposed	1 / 1066 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gallbladder cancer			
subjects affected / exposed	1 / 1066 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		

Malignant melanoma			
subjects affected / exposed	2 / 1066 (0.19%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Metastases to meninges			
subjects affected / exposed	1 / 1066 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Neoplasm malignant			
subjects affected / exposed	1 / 1066 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Neuroendocrine tumour			
subjects affected / exposed	1 / 1066 (0.09%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Plasma cell myeloma			
subjects affected / exposed	1 / 1066 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Prostate cancer			
subjects affected / exposed	1 / 1066 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Small cell lung cancer			
subjects affected / exposed	1 / 1066 (0.09%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Squamous cell carcinoma of skin			
subjects affected / exposed	2 / 1066 (0.19%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			

Deep vein thrombosis				
subjects affected / exposed	14 / 1066 (1.31%)			
occurrences causally related to treatment / all	4 / 15			
deaths causally related to treatment / all	1 / 1			
Embolism				
subjects affected / exposed	1 / 1066 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Haematoma				
subjects affected / exposed	3 / 1066 (0.28%)			
occurrences causally related to treatment / all	1 / 3			
deaths causally related to treatment / all	0 / 0			
Hypotension				
subjects affected / exposed	1 / 1066 (0.09%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Hypovolaemic shock				
subjects affected / exposed	1 / 1066 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Orthostatic hypotension				
subjects affected / exposed	1 / 1066 (0.09%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Peripheral arterial occlusive disease				
subjects affected / exposed	1 / 1066 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Peripheral embolism				
subjects affected / exposed	2 / 1066 (0.19%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Phlebitis				

subjects affected / exposed	1 / 1066 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Superior vena cava syndrome			
subjects affected / exposed	4 / 1066 (0.38%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 1		
Thrombophlebitis			
subjects affected / exposed	1 / 1066 (0.09%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Thrombosis			
subjects affected / exposed	5 / 1066 (0.47%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 1		
Vasculitis			
subjects affected / exposed	1 / 1066 (0.09%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Vena cava thrombosis			
subjects affected / exposed	2 / 1066 (0.19%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Venous thrombosis			
subjects affected / exposed	4 / 1066 (0.38%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Pleural decortication			
subjects affected / exposed	1 / 1066 (0.09%)		
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	7 / 1066 (0.66%)			
occurrences causally related to treatment / all	0 / 9			
deaths causally related to treatment / all	0 / 0			
Chest discomfort				
subjects affected / exposed	2 / 1066 (0.19%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Chest pain				
subjects affected / exposed	5 / 1066 (0.47%)			
occurrences causally related to treatment / all	1 / 6			
deaths causally related to treatment / all	0 / 0			
Chills				
subjects affected / exposed	1 / 1066 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Condition aggravated				
subjects affected / exposed	2 / 1066 (0.19%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Death				
subjects affected / exposed	8 / 1066 (0.75%)			
occurrences causally related to treatment / all	3 / 8			
deaths causally related to treatment / all	6 / 6			
Device dislocation				
subjects affected / exposed	1 / 1066 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Disease progression				
subjects affected / exposed	135 / 1066 (12.66%)			
occurrences causally related to treatment / all	0 / 135			
deaths causally related to treatment / all	0 / 133			
Fatigue				

subjects affected / exposed	4 / 1066 (0.38%)		
occurrences causally related to treatment / all	1 / 4		
deaths causally related to treatment / all	0 / 0		
Gait disturbance			
subjects affected / exposed	1 / 1066 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General physical health deterioration			
subjects affected / exposed	9 / 1066 (0.84%)		
occurrences causally related to treatment / all	1 / 11		
deaths causally related to treatment / all	0 / 3		
Generalised oedema			
subjects affected / exposed	3 / 1066 (0.28%)		
occurrences causally related to treatment / all	2 / 3		
deaths causally related to treatment / all	0 / 0		
Mass			
subjects affected / exposed	1 / 1066 (0.09%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Multi-organ failure			
subjects affected / exposed	1 / 1066 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Oedema peripheral			
subjects affected / exposed	7 / 1066 (0.66%)		
occurrences causally related to treatment / all	5 / 8		
deaths causally related to treatment / all	0 / 0		
Pain			
subjects affected / exposed	1 / 1066 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pyrexia			

subjects affected / exposed	18 / 1066 (1.69%)		
occurrences causally related to treatment / all	0 / 19		
deaths causally related to treatment / all	0 / 0		
Thrombosis in device			
subjects affected / exposed	1 / 1066 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Contrast media allergy			
subjects affected / exposed	1 / 1066 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	1 / 1066 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pelvic pain			
subjects affected / exposed	1 / 1066 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			
subjects affected / exposed	1 / 1066 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Acute respiratory failure			
subjects affected / exposed	3 / 1066 (0.28%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 1		
Alveolitis			

subjects affected / exposed	1 / 1066 (0.09%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Asphyxia				
subjects affected / exposed	1 / 1066 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Atelectasis				
subjects affected / exposed	1 / 1066 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Bronchial hyperreactivity				
subjects affected / exposed	1 / 1066 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Chronic obstructive pulmonary disease				
subjects affected / exposed	1 / 1066 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Cough				
subjects affected / exposed	3 / 1066 (0.28%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Dyspnoea				
subjects affected / exposed	39 / 1066 (3.66%)			
occurrences causally related to treatment / all	8 / 46			
deaths causally related to treatment / all	2 / 8			
Epistaxis				
subjects affected / exposed	1 / 1066 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Haemoptysis				

subjects affected / exposed	3 / 1066 (0.28%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		
Hypoxia			
subjects affected / exposed	4 / 1066 (0.38%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 0		
Interstitial lung disease			
subjects affected / exposed	5 / 1066 (0.47%)		
occurrences causally related to treatment / all	2 / 6		
deaths causally related to treatment / all	1 / 2		
Lung infiltration			
subjects affected / exposed	1 / 1066 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Oropharyngeal pain			
subjects affected / exposed	1 / 1066 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pleural effusion			
subjects affected / exposed	14 / 1066 (1.31%)		
occurrences causally related to treatment / all	1 / 16		
deaths causally related to treatment / all	0 / 2		
Pleuritic pain			
subjects affected / exposed	1 / 1066 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia aspiration			
subjects affected / exposed	4 / 1066 (0.38%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 0		
Pneumonitis			

subjects affected / exposed	17 / 1066 (1.59%)		
occurrences causally related to treatment / all	18 / 21		
deaths causally related to treatment / all	4 / 4		
Pneumothorax			
subjects affected / exposed	8 / 1066 (0.75%)		
occurrences causally related to treatment / all	0 / 9		
deaths causally related to treatment / all	0 / 1		
Pulmonary arterial hypertension			
subjects affected / exposed	1 / 1066 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pulmonary artery thrombosis			
subjects affected / exposed	2 / 1066 (0.19%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Pulmonary embolism			
subjects affected / exposed	26 / 1066 (2.44%)		
occurrences causally related to treatment / all	5 / 30		
deaths causally related to treatment / all	1 / 7		
Pulmonary haemorrhage			
subjects affected / exposed	1 / 1066 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pulmonary oedema			
subjects affected / exposed	1 / 1066 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Pulmonary thrombosis			
subjects affected / exposed	1 / 1066 (0.09%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Rales			

subjects affected / exposed	2 / 1066 (0.19%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Respiratory failure			
subjects affected / exposed	17 / 1066 (1.59%)		
occurrences causally related to treatment / all	1 / 23		
deaths causally related to treatment / all	0 / 10		
Haemothorax			
subjects affected / exposed	1 / 1066 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Completed suicide			
subjects affected / exposed	1 / 1066 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Confusional state			
subjects affected / exposed	7 / 1066 (0.66%)		
occurrences causally related to treatment / all	1 / 7		
deaths causally related to treatment / all	0 / 0		
Depression			
subjects affected / exposed	3 / 1066 (0.28%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Disorientation			
subjects affected / exposed	1 / 1066 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Mania			
subjects affected / exposed	1 / 1066 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Mental status changes			

subjects affected / exposed	2 / 1066 (0.19%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Suicide attempt			
subjects affected / exposed	1 / 1066 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	5 / 1066 (0.47%)		
occurrences causally related to treatment / all	7 / 7		
deaths causally related to treatment / all	0 / 0		
Blood albumin decreased			
subjects affected / exposed	1 / 1066 (0.09%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Blood bilirubin increased			
subjects affected / exposed	1 / 1066 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood creatinine increased			
subjects affected / exposed	1 / 1066 (0.09%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Blood lactate dehydrogenase increased			
subjects affected / exposed	1 / 1066 (0.09%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
C-reactive protein increased			
subjects affected / exposed	1 / 1066 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Electrocardiogram QT prolonged			

subjects affected / exposed	1 / 1066 (0.09%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatic enzyme increased			
subjects affected / exposed	1 / 1066 (0.09%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Troponin I increased			
subjects affected / exposed	1 / 1066 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	2 / 1066 (0.19%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Bone fissure			
subjects affected / exposed	1 / 1066 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Craniocerebral injury			
subjects affected / exposed	1 / 1066 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Dislocation of vertebra			
subjects affected / exposed	1 / 1066 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Fall			
subjects affected / exposed	6 / 1066 (0.56%)		
occurrences causally related to treatment / all	0 / 6		
deaths causally related to treatment / all	0 / 0		
Femoral neck fracture			

subjects affected / exposed	4 / 1066 (0.38%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 0		
Femur fracture			
subjects affected / exposed	4 / 1066 (0.38%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Hip fracture			
subjects affected / exposed	1 / 1066 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Humerus fracture			
subjects affected / exposed	1 / 1066 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Joint dislocation			
subjects affected / exposed	1 / 1066 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lower limb fracture			
subjects affected / exposed	1 / 1066 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Overdose			
subjects affected / exposed	1 / 1066 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pelvic fracture			
subjects affected / exposed	1 / 1066 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Radiation necrosis			

subjects affected / exposed	1 / 1066 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Radiation pneumonitis			
subjects affected / exposed	1 / 1066 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Radius fracture			
subjects affected / exposed	2 / 1066 (0.19%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Road traffic accident			
subjects affected / exposed	2 / 1066 (0.19%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Spinal compression fracture			
subjects affected / exposed	2 / 1066 (0.19%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Subdural haemorrhage			
subjects affected / exposed	1 / 1066 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Traumatic haematoma			
subjects affected / exposed	1 / 1066 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Upper limb fracture			
subjects affected / exposed	1 / 1066 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Postoperative wound complication			

subjects affected / exposed	1 / 1066 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Wound dehiscence			
subjects affected / exposed	1 / 1066 (0.09%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	2 / 1066 (0.19%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Angina pectoris			
subjects affected / exposed	2 / 1066 (0.19%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Atrial fibrillation			
subjects affected / exposed	3 / 1066 (0.28%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		
Bradycardia			
subjects affected / exposed	1 / 1066 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac arrest			
subjects affected / exposed	2 / 1066 (0.19%)		
occurrences causally related to treatment / all	2 / 3		
deaths causally related to treatment / all	1 / 2		
Cardiac failure			
subjects affected / exposed	2 / 1066 (0.19%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 1		
Cardiac tamponade			

subjects affected / exposed	1 / 1066 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac failure congestive			
subjects affected / exposed	1 / 1066 (0.09%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Cyanosis			
subjects affected / exposed	1 / 1066 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Coronary artery stenosis			
subjects affected / exposed	1 / 1066 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Left ventricular failure			
subjects affected / exposed	1 / 1066 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Myocardial infarction			
subjects affected / exposed	2 / 1066 (0.19%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 2		
Myocarditis			
subjects affected / exposed	1 / 1066 (0.09%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Palpitations			
subjects affected / exposed	1 / 1066 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pericardial effusion			

subjects affected / exposed	7 / 1066 (0.66%)		
occurrences causally related to treatment / all	0 / 7		
deaths causally related to treatment / all	0 / 2		
Pericarditis			
subjects affected / exposed	1 / 1066 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Supraventricular tachycardia			
subjects affected / exposed	1 / 1066 (0.09%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Syncope			
subjects affected / exposed	6 / 1066 (0.56%)		
occurrences causally related to treatment / all	0 / 6		
deaths causally related to treatment / all	0 / 0		
Tachycardia			
subjects affected / exposed	2 / 1066 (0.19%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Angina unstable			
subjects affected / exposed	1 / 1066 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Aphasia			
subjects affected / exposed	2 / 1066 (0.19%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Ataxia			
subjects affected / exposed	1 / 1066 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Brain oedema			

subjects affected / exposed	3 / 1066 (0.28%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Cerebellar infarction			
subjects affected / exposed	1 / 1066 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cerebral haemorrhage			
subjects affected / exposed	4 / 1066 (0.38%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 4		
Cerebral infarction			
subjects affected / exposed	1 / 1066 (0.09%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Cerebrovascular accident			
subjects affected / exposed	1 / 1066 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Chorea			
subjects affected / exposed	1 / 1066 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Coma			
subjects affected / exposed	1 / 1066 (0.09%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Depressed level of consciousness			
subjects affected / exposed	1 / 1066 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Dizziness			

subjects affected / exposed	2 / 1066 (0.19%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Dysarthria				
subjects affected / exposed	2 / 1066 (0.19%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Generalised tonic-clonic seizure				
subjects affected / exposed	1 / 1066 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Haemorrhage intracranial				
subjects affected / exposed	1 / 1066 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Headache				
subjects affected / exposed	4 / 1066 (0.38%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Intracranial pressure increased				
subjects affected / exposed	1 / 1066 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ischaemic stroke				
subjects affected / exposed	1 / 1066 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Nervous system disorder				
subjects affected / exposed	2 / 1066 (0.19%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 1			
Neurological decompensation				

subjects affected / exposed	1 / 1066 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Paraplegia			
subjects affected / exposed	1 / 1066 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Peripheral motor neuropathy			
subjects affected / exposed	1 / 1066 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Peripheral sensorimotor neuropathy			
subjects affected / exposed	1 / 1066 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Peripheral sensory neuropathy			
subjects affected / exposed	1 / 1066 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pyramidal tract syndrome			
subjects affected / exposed	1 / 1066 (0.09%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Seizure			
subjects affected / exposed	9 / 1066 (0.84%)		
occurrences causally related to treatment / all	3 / 11		
deaths causally related to treatment / all	0 / 2		
Spinal cord compression			
subjects affected / exposed	2 / 1066 (0.19%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Transient ischaemic attack			

subjects affected / exposed	3 / 1066 (0.28%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Tremor			
subjects affected / exposed	1 / 1066 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vocal cord paralysis			
subjects affected / exposed	2 / 1066 (0.19%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	4 / 1066 (0.38%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Basophilia			
subjects affected / exposed	1 / 1066 (0.09%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Eosinophilia			
subjects affected / exposed	1 / 1066 (0.09%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Febrile neutropenia			
subjects affected / exposed	6 / 1066 (0.56%)		
occurrences causally related to treatment / all	4 / 6		
deaths causally related to treatment / all	0 / 0		
Leukocytosis			
subjects affected / exposed	1 / 1066 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Thrombocytopenia			

subjects affected / exposed	1 / 1066 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Monocytosis			
subjects affected / exposed	1 / 1066 (0.09%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Thrombocytosis			
subjects affected / exposed	1 / 1066 (0.09%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Cataract			
subjects affected / exposed	2 / 1066 (0.19%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Glaucoma			
subjects affected / exposed	1 / 1066 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Optic atrophy			
subjects affected / exposed	1 / 1066 (0.09%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Retinal detachment			
subjects affected / exposed	1 / 1066 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vision blurred			
subjects affected / exposed	1 / 1066 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vitreous haemorrhage			

subjects affected / exposed	1 / 1066 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	6 / 1066 (0.56%)		
occurrences causally related to treatment / all	0 / 6		
deaths causally related to treatment / all	0 / 0		
Abdominal wall haematoma			
subjects affected / exposed	1 / 1066 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ascites			
subjects affected / exposed	1 / 1066 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Colitis			
subjects affected / exposed	1 / 1066 (0.09%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Constipation			
subjects affected / exposed	3 / 1066 (0.28%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		
Diarrhoea			
subjects affected / exposed	4 / 1066 (0.38%)		
occurrences causally related to treatment / all	2 / 4		
deaths causally related to treatment / all	0 / 0		
Diarrhoea haemorrhagic			
subjects affected / exposed	1 / 1066 (0.09%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Dysphagia			

subjects affected / exposed	7 / 1066 (0.66%)		
occurrences causally related to treatment / all	0 / 8		
deaths causally related to treatment / all	0 / 0		
Gastric ulcer			
subjects affected / exposed	1 / 1066 (0.09%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastritis			
subjects affected / exposed	1 / 1066 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal haemorrhage			
subjects affected / exposed	3 / 1066 (0.28%)		
occurrences causally related to treatment / all	4 / 6		
deaths causally related to treatment / all	0 / 0		
Ileus			
subjects affected / exposed	3 / 1066 (0.28%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		
Intestinal obstruction			
subjects affected / exposed	1 / 1066 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Intestinal perforation			
subjects affected / exposed	1 / 1066 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nausea			
subjects affected / exposed	9 / 1066 (0.84%)		
occurrences causally related to treatment / all	4 / 10		
deaths causally related to treatment / all	0 / 0		
Oesophageal stenosis			

subjects affected / exposed	1 / 1066 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Oesophagitis			
subjects affected / exposed	2 / 1066 (0.19%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Pancreatic atrophy			
subjects affected / exposed	1 / 1066 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pancreatitis			
subjects affected / exposed	3 / 1066 (0.28%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Pancreatitis acute			
subjects affected / exposed	1 / 1066 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Peptic ulcer haemorrhage			
subjects affected / exposed	1 / 1066 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Peritoneal disorder			
subjects affected / exposed	1 / 1066 (0.09%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Retroperitoneal haemorrhage			
subjects affected / exposed	1 / 1066 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Small intestinal obstruction			

subjects affected / exposed	1 / 1066 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Subileus			
subjects affected / exposed	1 / 1066 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Upper gastrointestinal haemorrhage			
subjects affected / exposed	1 / 1066 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	6 / 1066 (0.56%)		
occurrences causally related to treatment / all	0 / 6		
deaths causally related to treatment / all	0 / 0		
Rectal haemorrhage			
subjects affected / exposed	1 / 1066 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	1 / 1066 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Drug-induced liver injury			
subjects affected / exposed	3 / 1066 (0.28%)		
occurrences causally related to treatment / all	4 / 4		
deaths causally related to treatment / all	0 / 0		
Hepatic failure			
subjects affected / exposed	2 / 1066 (0.19%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	1 / 1		
Hepatitis			

subjects affected / exposed	1 / 1066 (0.09%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatocellular injury			
subjects affected / exposed	1 / 1066 (0.09%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatotoxicity			
subjects affected / exposed	3 / 1066 (0.28%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Paraneoplastic pemphigus			
subjects affected / exposed	1 / 1066 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Rash			
subjects affected / exposed	1 / 1066 (0.09%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	5 / 1066 (0.47%)		
occurrences causally related to treatment / all	3 / 5		
deaths causally related to treatment / all	0 / 1		
Dysuria			
subjects affected / exposed	2 / 1066 (0.19%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Haematuria			
subjects affected / exposed	1 / 1066 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hydronephrosis			

subjects affected / exposed	2 / 1066 (0.19%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Nephrolithiasis			
subjects affected / exposed	2 / 1066 (0.19%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Renal cyst			
subjects affected / exposed	13 / 1066 (1.22%)		
occurrences causally related to treatment / all	20 / 20		
deaths causally related to treatment / all	0 / 0		
Renal cyst haemorrhage			
subjects affected / exposed	1 / 1066 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal failure			
subjects affected / exposed	1 / 1066 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ureteral polyp			
subjects affected / exposed	1 / 1066 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary retention			
subjects affected / exposed	2 / 1066 (0.19%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Urinary tract obstruction			
subjects affected / exposed	1 / 1066 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Arthralgia			

subjects affected / exposed	2 / 1066 (0.19%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Back pain			
subjects affected / exposed	5 / 1066 (0.47%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 0		
Bursitis			
subjects affected / exposed	1 / 1066 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Chest wall mass			
subjects affected / exposed	1 / 1066 (0.09%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Joint swelling			
subjects affected / exposed	1 / 1066 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lumbar spinal stenosis			
subjects affected / exposed	1 / 1066 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Muscular weakness			
subjects affected / exposed	2 / 1066 (0.19%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal pain			
subjects affected / exposed	3 / 1066 (0.28%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		
Myalgia			

subjects affected / exposed	1 / 1066 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Myopathy			
subjects affected / exposed	1 / 1066 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Neck pain			
subjects affected / exposed	2 / 1066 (0.19%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Osteoarthritis			
subjects affected / exposed	1 / 1066 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pain in extremity			
subjects affected / exposed	2 / 1066 (0.19%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Pathological fracture			
subjects affected / exposed	5 / 1066 (0.47%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 0		
Spinal column stenosis			
subjects affected / exposed	1 / 1066 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Spondylolisthesis			
subjects affected / exposed	1 / 1066 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Systemic lupus erythematosus			

subjects affected / exposed	1 / 1066 (0.09%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Abdominal abscess			
subjects affected / exposed	1 / 1066 (0.09%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Abscess limb			
subjects affected / exposed	1 / 1066 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Appendicitis			
subjects affected / exposed	8 / 1066 (0.75%)		
occurrences causally related to treatment / all	0 / 8		
deaths causally related to treatment / all	0 / 0		
Bacteraemia			
subjects affected / exposed	2 / 1066 (0.19%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Bone abscess			
subjects affected / exposed	1 / 1066 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bronchitis			
subjects affected / exposed	2 / 1066 (0.19%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Candiduria			
subjects affected / exposed	1 / 1066 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cellulitis			

subjects affected / exposed	13 / 1066 (1.22%)		
occurrences causally related to treatment / all	4 / 15		
deaths causally related to treatment / all	0 / 0		
Chest wall abscess			
subjects affected / exposed	1 / 1066 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Clostridium difficile infection			
subjects affected / exposed	1 / 1066 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cystitis			
subjects affected / exposed	1 / 1066 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Diverticulitis			
subjects affected / exposed	1 / 1066 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Empyema			
subjects affected / exposed	1 / 1066 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis			
subjects affected / exposed	6 / 1066 (0.56%)		
occurrences causally related to treatment / all	0 / 6		
deaths causally related to treatment / all	0 / 0		
Herpes zoster			
subjects affected / exposed	3 / 1066 (0.28%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Infection			

subjects affected / exposed	1 / 1066 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infectious pleural effusion			
subjects affected / exposed	2 / 1066 (0.19%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 1		
Infective spondylitis			
subjects affected / exposed	1 / 1066 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lower respiratory tract infection			
subjects affected / exposed	3 / 1066 (0.28%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Lung abscess			
subjects affected / exposed	1 / 1066 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Lung infection			
subjects affected / exposed	14 / 1066 (1.31%)		
occurrences causally related to treatment / all	4 / 20		
deaths causally related to treatment / all	2 / 5		
Meningitis			
subjects affected / exposed	1 / 1066 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metapneumovirus infection			
subjects affected / exposed	1 / 1066 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Oesophageal candidiasis			

subjects affected / exposed	2 / 1066 (0.19%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Osteomyelitis chronic				
subjects affected / exposed	1 / 1066 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Peritonitis				
subjects affected / exposed	1 / 1066 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	74 / 1066 (6.94%)			
occurrences causally related to treatment / all	7 / 99			
deaths causally related to treatment / all	4 / 20			
Pneumonia bacterial				
subjects affected / exposed	1 / 1066 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia fungal				
subjects affected / exposed	1 / 1066 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia staphylococcal				
subjects affected / exposed	1 / 1066 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Pyelonephritis				
subjects affected / exposed	1 / 1066 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Renal abscess				

subjects affected / exposed	2 / 1066 (0.19%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Renal cyst infection			
subjects affected / exposed	2 / 1066 (0.19%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Respiratory tract infection			
subjects affected / exposed	5 / 1066 (0.47%)		
occurrences causally related to treatment / all	0 / 6		
deaths causally related to treatment / all	0 / 0		
Sepsis			
subjects affected / exposed	8 / 1066 (0.75%)		
occurrences causally related to treatment / all	0 / 11		
deaths causally related to treatment / all	0 / 4		
Septic shock			
subjects affected / exposed	4 / 1066 (0.38%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 4		
Skin infection			
subjects affected / exposed	4 / 1066 (0.38%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Soft tissue infection			
subjects affected / exposed	1 / 1066 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Staphylococcal sepsis			
subjects affected / exposed	1 / 1066 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Upper respiratory tract infection			

subjects affected / exposed	7 / 1066 (0.66%)		
occurrences causally related to treatment / all	0 / 10		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			
subjects affected / exposed	7 / 1066 (0.66%)		
occurrences causally related to treatment / all	0 / 8		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection bacterial			
subjects affected / exposed	1 / 1066 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Viral infection			
subjects affected / exposed	1 / 1066 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Viral upper respiratory tract infection			
subjects affected / exposed	1 / 1066 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Wound infection			
subjects affected / exposed	2 / 1066 (0.19%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Lymphangitis			
subjects affected / exposed	1 / 1066 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	3 / 1066 (0.28%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		
Dehydration			

subjects affected / exposed	4 / 1066 (0.38%)		
occurrences causally related to treatment / all	2 / 4		
deaths causally related to treatment / all	0 / 0		
Failure to thrive			
subjects affected / exposed	2 / 1066 (0.19%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Fluid retention			
subjects affected / exposed	1 / 1066 (0.09%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Hypercalcaemia			
subjects affected / exposed	1 / 1066 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hyperglycaemia			
subjects affected / exposed	2 / 1066 (0.19%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Hyperkalaemia			
subjects affected / exposed	1 / 1066 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypoalbuminaemia			
subjects affected / exposed	1 / 1066 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypocalcaemia			
subjects affected / exposed	1 / 1066 (0.09%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hypoglycaemia			

subjects affected / exposed	1 / 1066 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypokalaemia			
subjects affected / exposed	5 / 1066 (0.47%)		
occurrences causally related to treatment / all	1 / 5		
deaths causally related to treatment / all	0 / 0		
Hypomagnesaemia			
subjects affected / exposed	1 / 1066 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hyponatraemia			
subjects affected / exposed	4 / 1066 (0.38%)		
occurrences causally related to treatment / all	4 / 6		
deaths causally related to treatment / all	0 / 0		
Hypophosphataemia			
subjects affected / exposed	1 / 1066 (0.09%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Crizotinib 250 mg BID		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1038 / 1066 (97.37%)		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	156 / 1066 (14.63%)		
occurrences (all)	241		
Chest pain			
subjects affected / exposed	105 / 1066 (9.85%)		
occurrences (all)	122		
Fatigue			

subjects affected / exposed	326 / 1066 (30.58%)		
occurrences (all)	528		
Oedema			
subjects affected / exposed	96 / 1066 (9.01%)		
occurrences (all)	125		
Oedema peripheral			
subjects affected / exposed	450 / 1066 (42.21%)		
occurrences (all)	758		
Pyrexia			
subjects affected / exposed	181 / 1066 (16.98%)		
occurrences (all)	290		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	260 / 1066 (24.39%)		
occurrences (all)	367		
Dyspnoea			
subjects affected / exposed	224 / 1066 (21.01%)		
occurrences (all)	315		
Haemoptysis			
subjects affected / exposed	55 / 1066 (5.16%)		
occurrences (all)	68		
Oropharyngeal pain			
subjects affected / exposed	75 / 1066 (7.04%)		
occurrences (all)	88		
Productive cough			
subjects affected / exposed	71 / 1066 (6.66%)		
occurrences (all)	99		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	76 / 1066 (7.13%)		
occurrences (all)	82		
Insomnia			
subjects affected / exposed	136 / 1066 (12.76%)		
occurrences (all)	171		

Investigations			
Alanine aminotransferase increased subjects affected / exposed occurrences (all)	302 / 1066 (28.33%) 736		
Aspartate aminotransferase increased subjects affected / exposed occurrences (all)	233 / 1066 (21.86%) 491		
Blood alkaline phosphatase increased subjects affected / exposed occurrences (all)	76 / 1066 (7.13%) 113		
Blood creatinine increased subjects affected / exposed occurrences (all)	105 / 1066 (9.85%) 165		
Blood lactate dehydrogenase increased subjects affected / exposed occurrences (all)	60 / 1066 (5.63%) 82		
Neutrophil count decreased subjects affected / exposed occurrences (all)	84 / 1066 (7.88%) 274		
Weight decreased subjects affected / exposed occurrences (all)	109 / 1066 (10.23%) 214		
Weight increased subjects affected / exposed occurrences (all)	98 / 1066 (9.19%) 203		
White blood cell count decreased subjects affected / exposed occurrences (all)	98 / 1066 (9.19%) 294		
Injury, poisoning and procedural complications			
Fall subjects affected / exposed occurrences (all)	59 / 1066 (5.53%) 70		
Cardiac disorders			

Bradycardia subjects affected / exposed occurrences (all)	93 / 1066 (8.72%) 115		
Nervous system disorders Dizziness subjects affected / exposed occurrences (all)	265 / 1066 (24.86%) 347		
Dysgeusia subjects affected / exposed occurrences (all)	213 / 1066 (19.98%) 253		
Headache subjects affected / exposed occurrences (all)	214 / 1066 (20.08%) 330		
Hypoaesthesia subjects affected / exposed occurrences (all)	65 / 1066 (6.10%) 84		
Paraesthesia subjects affected / exposed occurrences (all)	83 / 1066 (7.79%) 99		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	138 / 1066 (12.95%) 282		
Leukopenia subjects affected / exposed occurrences (all)	101 / 1066 (9.47%) 360		
Lymphopenia subjects affected / exposed occurrences (all)	71 / 1066 (6.66%) 159		
Neutropenia subjects affected / exposed occurrences (all)	180 / 1066 (16.89%) 770		
Eye disorders Photopsia			

subjects affected / exposed	96 / 1066 (9.01%)		
occurrences (all)	113		
Vision blurred			
subjects affected / exposed	80 / 1066 (7.50%)		
occurrences (all)	103		
Visual impairment			
subjects affected / exposed	460 / 1066 (43.15%)		
occurrences (all)	538		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	118 / 1066 (11.07%)		
occurrences (all)	148		
Abdominal pain upper			
subjects affected / exposed	106 / 1066 (9.94%)		
occurrences (all)	136		
Constipation			
subjects affected / exposed	475 / 1066 (44.56%)		
occurrences (all)	697		
Diarrhoea			
subjects affected / exposed	548 / 1066 (51.41%)		
occurrences (all)	1015		
Dyspepsia			
subjects affected / exposed	81 / 1066 (7.60%)		
occurrences (all)	96		
Dysphagia			
subjects affected / exposed	56 / 1066 (5.25%)		
occurrences (all)	72		
Nausea			
subjects affected / exposed	603 / 1066 (56.57%)		
occurrences (all)	1078		
Vomiting			
subjects affected / exposed	565 / 1066 (53.00%)		
occurrences (all)	1228		
Skin and subcutaneous tissue disorders			

Alopecia subjects affected / exposed occurrences (all)	67 / 1066 (6.29%) 75		
Pruritus subjects affected / exposed occurrences (all)	84 / 1066 (7.88%) 103		
Rash subjects affected / exposed occurrences (all)	134 / 1066 (12.57%) 173		
Musculoskeletal and connective tissue disorders			
Arthralgia subjects affected / exposed occurrences (all)	131 / 1066 (12.29%) 188		
Back pain subjects affected / exposed occurrences (all)	184 / 1066 (17.26%) 248		
Muscle spasms subjects affected / exposed occurrences (all)	79 / 1066 (7.41%) 103		
Muscular weakness subjects affected / exposed occurrences (all)	57 / 1066 (5.35%) 70		
Musculoskeletal pain subjects affected / exposed occurrences (all)	74 / 1066 (6.94%) 86		
Pain in extremity subjects affected / exposed occurrences (all)	137 / 1066 (12.85%) 183		
Infections and infestations			
Nasopharyngitis subjects affected / exposed occurrences (all)	113 / 1066 (10.60%) 188		
Upper respiratory tract infection subjects affected / exposed occurrences (all)	145 / 1066 (13.60%) 234		

Urinary tract infection subjects affected / exposed occurrences (all)	62 / 1066 (5.82%) 86		
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	326 / 1066 (30.58%) 497		
Hyperglycaemia subjects affected / exposed occurrences (all)	55 / 1066 (5.16%) 107		
Hypoalbuminaemia subjects affected / exposed occurrences (all)	98 / 1066 (9.19%) 224		
Hypocalcaemia subjects affected / exposed occurrences (all)	99 / 1066 (9.29%) 202		
Hypokalaemia subjects affected / exposed occurrences (all)	77 / 1066 (7.22%) 129		
Hyponatraemia subjects affected / exposed occurrences (all)	54 / 1066 (5.07%) 89		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 August 2009	Participants who were ineligible to enroll in Study A8081007 because they were treated with docetaxel as part of their platinum-based prior chemotherapy, yet had NSCLC that was predominantly squamous-cell carcinoma, and thus, were not eligible to be dosed with pemetrexed, were allowed to enroll in this study.
27 August 2009	The RECIST version was modified to Version 1.1, and participants with spinal cord compression, carcinomatous meningitis, or leptomeningeal disease were no longer excluded.
21 December 2009	The NCI CTCAE version was modified to version 4.0, the primary endpoint was modified to add safety as a co-primary endpoint, timing of tumor measurements was modified from a per cycle basis to a calendar basis, and the administration of crizotinib was allowed to be administered without regards to meals.
22 June 2010	The patient-reported VSAQ-ALK was included, additional ECG monitoring was added for participants with QTc >500 msec, modifications of the eligibility criteria (which included cutoffs for hemoglobin and platelet counts) were included, washout period for cardiovascular (CV) or cerebrovascular events was decreased, hypertension exclusion criteria was deleted, all available scans were required to be reviewed by a third-party radiology laboratory, a treatment delay to up to 42 days without requiring discontinuation was now allowed; and metabolites of crizotinib were to be evaluated, if possible.
05 August 2010	Additional safety monitoring for the potential AEs of pneumonitis were added and an exclusion criterion to exclude patients with known interstitial fibrosis or interstitial lung disease was added.
12 January 2011	Entry criteria changed to allow A8081007 eligible participants to enroll into this protocol once enrollment is closed in a specific country and approved by a site's IRB/IEC. Other entry criteria changed or updated: non-measurable disease now allowed, washout for palliative radiation changed, criteria for known brain metastases clarified, other ALK testing may be allowed after Sponsor review and approval. ECG substudy was added; sample size increased; dose modifications for PF-02341066 updated; PK analysis updated; endpoint descriptions updated; safety guidelines for potential cases of drug-induced liver injury added.
21 September 2011	Increase the number of participants to 800 in order to better evaluate possible genetic associations in patients with significant toxicities, especially those related to liver and kidney. Study objective and related endpoint for evaluation of pharmacogenetic markers of adverse hepatic and renal drug reactions were added. Monitoring guidance for the potential adverse hepatic and renal drug reactions were added. Entry criteria changed or updated: entry of participants with ALT/AST abnormalities expanded to x 5 ULN after agreement with Sponsor; entry of participants ineligible for Study A8081007 allowed if due to ECOG PS; once enrollment of the phase 3 A8081007 is closed, entry of participants receiving only one prior treatment for advanced NSCLC allowed. Dose administration modality as a oral solution allowed in participants unable to swallow the tablets, with agreement by the Sponsor. Visit frequency reduced for participants on study after 10 cycles; PK sampling collection not required any longer in participants newly enrolled; follow-up of visual symptoms, if present at end of treatment, added. Text modified is some sections following compliance with the Sponsor protocol template.

26 April 2012	The total number of participants enrolled was revised to manage country-specific regulatory requirements. Entry criteria changed to allow participants from the comparator arm of study A8081007 to enroll into this protocol once the study A8081007 has met the primary endpoint. Background safety information was updated. Dose modification rules were revised based on the updated safety information. Required imaging frequency was clarified. PK sampling collection required for ECG subgroup participants was clarified. Adverse event guidelines were updated to be consistent with Sponsor standards. Editing errors from prior Amendment were rectified.
18 December 2012	Inclusion criterion and related language elsewhere was modified to comply with the FDA requirement for all participants in the chemotherapy arm of Study A8081007 to have disease progression confirmed by independent radiology review (IRR) before they are allowed to cross over to receive crizotinib on Study A8081005. Detailed description of participants of childbearing potential language as an inclusion criterion and detailed contraception guidelines were introduced to ensure consistency with updated Pfizer protocol template. Text was added or replaced to ensure consistency with updated Pfizer protocol template language especially with respect to medication error, and serious adverse event reporting for Oncology studies after the active safety reporting period was clarified. Use of prophylactic antiemetics, prohibited medications by topical administration, and concomitant acetaminophen/paracetamol was clarified. Pregnancy testing in response to IRBs/IECs and/or local regulations was clarified. Reporting of local cardiologist manual ECG overread was clarified. Requirements for data retention were revised in consistency with the updated Pfizer protocol template language. Corrections of typographical errors and other administrative inconsistencies were made throughout the protocol.
26 November 2014	Blood samples for hematology and blood chemistries will now be collected also during the non-visit cycles after Cycle 10 to ensure consistency with the Investigator's Brochure. Dose modification and adverse event management guidances were revised for QTc prolongation, bradycardia, and pneumonitis based on the updated safety information for PF-02341066. Reduced Schedule of Activities was introduced for participants still ongoing after the Primary Completion Date. Text was added or replaced to ensure consistency with updated Pfizer protocol template language, especially with respect to contraception guidelines, pregnancy testing, and serious adverse event reporting for Oncology studies after permanent discontinuation of PF- 02341066 treatment. Corrections of typographical errors and other administrative inconsistencies were made throughout the protocol.

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.

Pharmacogenetic analysis of renal adverse events was not performed as no gene alleles have been identified with sufficient supportive data establishing an association with renal toxicity to support a case-control candidate gene assessment.

Notes: